Technology Guidance

Pembrolizumab

for the adjuvant treatment of renal cell carcinoma

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 for the adjuvant treatment of renal cell carcinoma in patients who are at increased risk of recurrence following nephrectomy or nephrectomy with resection of metastatic lesions. 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

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 for the adjuvant treatment of renal cell carcinoma (RCC) in patients who are at increased risk of recurrence following nephrectomy or nephrectomy with resection of metastatic lesions.

1.2. Expert opinion was obtained from the MOH Cancer Drug Subcommittee, who assisted ACE to ascertain 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. The Committee noted that approximately 440 patients are diagnosed with RCC each year in Singapore. The predominant histological subtype is clear cell RCC, accounting for majority of diagnoses. Around 30% of patients remain at an increased risk of disease recurrence after surgery (partial or radical nephrectomy).

2.2. The Committee noted that there is no established standard of care for the adjuvant treatment of RCC in local practice. Hence, patients are placed on routine surveillance following nephrectomy. The Committee noted the potential clinical need to consider pembrolizumab for funding, to improve treatment affordability and ensure appropriate patient care.

Clinical effectiveness and safety

3.1. The company requested a listing for patients with clear cell RCC, in line with the pivotal trial presented in their submission. The Committee heard local clinicians' inputs that the risk of inappropriate use outside of the trial population was low. Therefore, the Committee considered it was reasonable to consider listing of pembrolizumab in line with the approved HSA indication, which did not restrict the use of pembrolizumab according to histological subtype.

3.2. The Committee reviewed the clinical evidence from an ongoing phase III randomised controlled trial (KEYNOTE-564) that was referenced in the submission. The trial compared pembrolizumab with placebo in a cohort of patients with clear cell RCC who were at increased risk of recurrence following nephrectomy. At a median follow-up of 29.7 months (June 2021 data cut-off), pembrolizumab led to a statistically significant improvement in disease-free survival (DFS) by investigator assessment (IA), compared with placebo (Table 1 and Figure 1). However, DFS data was immature as median DFS was not reached in either treatment arm. The data immaturity introduced uncertainty as to whether the reported DFS benefit could be sustained beyond the trial duration.

3.3. The Committee noted that DFS by IA resulted in a greater magnitude of benefit compared to DFS assessed by blinded independent central review (BICR). The Committee acknowledged that (i) there were issues with the retrospective nature of the BICR analysis which could lead to informative censoring and (ii) the study was powered for DFS by IA, not for DFS by BICR. However, the Committee considered that assessments by BICR could mitigate potential detection bias and reduce measurement variability. On balance, the Committee agreed that DFS by BICR was more appropriate in assessing the clinical effectiveness of pembrolizumab, compared to placebo.

3.4. Overall survival (OS) data was immature, with no statistically significant difference between pembrolizumab and placebo. In the absence of mature survival data, the submission proposed DFS as a surrogate endpoint for OS in RCC. However, the Committee noted that the studies presented to support the surrogacy relationship did not investigate the correlation between the effects of adjuvant treatment on DFS and OS in RCC. Therefore, it was uncertain whether the improvements in DFS are expected to lead to a clinically meaningful gain in long-term survival.

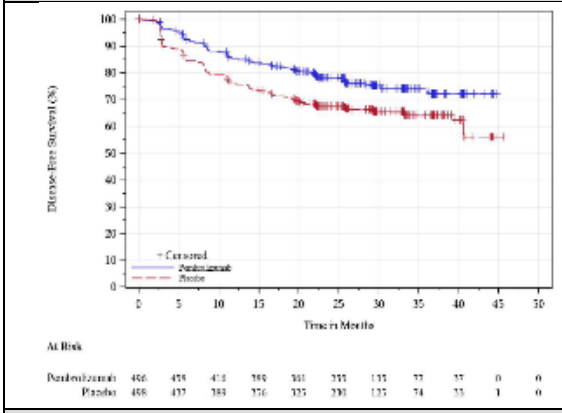
Table 1: Results of DFS and OS in KEYNOTE-564 trial

June 2021 data cut-off	Pembrolizumab (N=496)	Placebo (N=498)
DFS by investigator assessment		
DFS events, n (%)	114 (23.0)	169 (33.9)
Median DFS, months (95% CI)	NR (NR to NR)	NR (40.5 to NR)
HR (95% CI)	0.63 (0.50 to 0.80), p<0.0001 [a]	
DFS by blinded independent central review		
DFS events, n (%)	117 (23.6)	141 (28.3)
Median DFS, months (95% CI)	NR (NR to NR)	NR (NR to NR)
HR (95% CI)	0.78 (0.61 to 0.99), p=0.0212 [b]	
OS		
OS events, n (%)	23 (4.6)	43 (8.6)
Median OS, months (95% CI)	NR (NR to NR)	NR (NR to NR)
HR (95% CI)	0.52 (0.31 to 0.86), p=0.0047677 [c]	

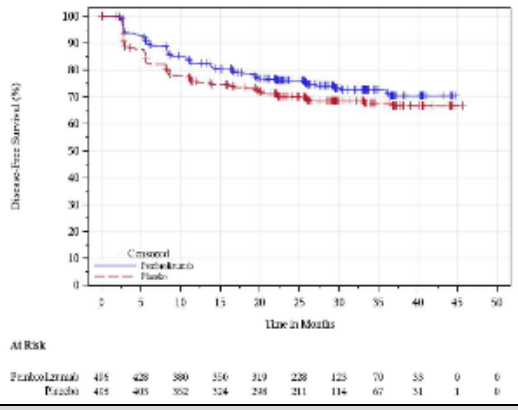
Abbreviations: CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; NR, not reached; OS, overall survival.
[a] While formal statistical testing was not performed in the updated analysis (June 2021 data cut-off), the primary endpoint was met in the interim analysis (December 2020 data cut-off).
[b] No formal statistical tests were performed.
[c] p-value did not cross the statistical hypothesis testing p-value boundary of 0.000095.

Figure 1: Kaplan-Meier curves from KEYNOTE-564 (data cut-off June 2021)

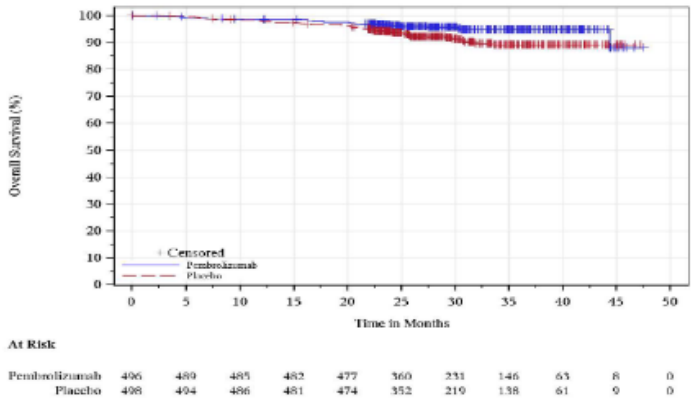
Disease-free survival by investigator assessment (DFS by IA)



Disease-free survival by blinded independent central review (DFS by BICR)



Overall survival (OS)



3.5. In terms of safety, the Committee heard that compared with placebo, pembrolizumab was associated with a higher incidence of grade ≥3 treatment-related adverse events (TRAEs; 18.6% vs 1.2%), serious TRAEs (12.1% vs 0.2%) and TRAEs leading to treatment discontinuation (18.2% vs 0.8%). The most common TRAEs reported with pembrolizumab included hypothyroidism, hyperthyroidism and pruritus.

3.6. The submission described pembrolizumab as superior, in terms of effectiveness, and similar, in terms of safety, compared with routine surveillance for patients with RCC following nephrectomy. Based on the available evidence, the Committee considered pembrolizumab to be superior in terms of DFS but the magnitude and sustainability of treatment effect remained uncertain. In addition, the Committee considered that there was significant uncertainty regarding the long-term survival benefit associated with pembrolizumab. In terms of safety, the Committee considered the safety of pembrolizumab to be inferior to routine surveillance.

Cost effectiveness

4.1. The Committee considered the results of the submission's cost-utility analysis, based on the KEYNOTE-564 trial, that compared pembrolizumab with routine surveillance in patients with RCC who are at increased risk of recurrence following nephrectomy. 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 renal cell carcinoma who have increased risk of recurrence following nephrectomy, with or without resection of metastatic lesions
Outcomes	Total and incremental direct medical costs; total and incremental LY gained; total and incremental QALYs; ICER
Perspective	Singapore healthcare system
Type of model	Markov state-transition model
Time horizon	15 years in the model base case, based on a median follow-up of 29.7 months in the KEYNOTE-564 trial
Health states	Disease-free (DF), locoregional recurrence (LR), distant metastases (DM), death
Cycle length	1 week

Component	Description
Extrapolation methods used to generate results	Transition probabilities starting from the DF state were estimated based on survival analyses of individual patient-level data from KEYNOTE-564. Among the different extrapolation methods considered in the submission, the company used proportional hazards modelling with one HR for the first year and then another HR for subsequent years in its base case, as it appeared to provide the best balance between goodness-of-fit with observed data and plausible long-term extrapolations in each arm. Gompertz distribution was used to model DF to DM transition, while exponential distribution was used for all other health state transitions. Approximately 90% of QALYs and 71 – 87% of costs occur after completion of adjuvant treatment. No treatment waning was applied in the base case.
Health-related quality of life	Utilities for DF and LR health states were informed by EQ-5D-5L data from KEYNOTE-564 and cross-walked to EQ-5D-3L using van Hout et al. algorithm. Utilities for DM health state were informed by EQ-5D-3L data from KEYNOTE-426, as it provided a larger sample of measurements within the DM state than KEYNOTE-564.[a] The values are stated as follows: • DF (without toxicity): 0.868 • LR: 0.839 • DM (pre-progression): 0.803 • DM (post-progression): 0.772 • Age-related disutility: regression coefficients from Ara et al. were applied • Grade 3+ AE-related disutility: -0.064, applied as a one-time QALY decrement in the first model cycle
Types of healthcare resources included	• Drug acquisition and drug administration costs • Disease management costs • Subsequent treatment costs • AE management costs • Terminal care costs

Abbreviations: AE, adverse event; DF, disease-free; DM, distant metastases; EQ-5D-3L, EuroQoL 5 Dimension 3 Level; EQ-5D-5L, EuroQoL 5 Dimension 5 Level; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LR, locoregional recurrence; LY, life year; QALY, quality-adjusted life year.

[a] The KEYNOTE-426 trial compared pembrolizumab + axitinib with sunitinib for untreated, advanced renal cell carcinoma.

4.2. Based on the submission's economic model, pembrolizumab was dominant over routine surveillance. However, the Committee considered the incremental cost-effectiveness ratio (ICER) to be uncertain and likely underestimated, given the following:

- The magnitude of DFS benefit was uncertain. While DFS by IA was used in the base case, the Committee considered DFS by BICR to be more methodologically robust in estimating the clinical effectiveness of pembrolizumab, as outlined in paragraph 3.3.

- The submission assumed that the treatment effect of pembrolizumab was sustained over the entire 15 years' time horizon even though treatment duration was about one year. The Committee considered this optimistic as both DFS and OS data were immature and most of the modelled benefits were accrued after completing adjuvant treatment. The Committee agreed that incorporating treatment waning in the base case was appropriate to reduce uncertainty associated with the limited evidence.

- The results were highly sensitive to the extrapolation method and choice of parametric distributions. The Committee considered that using standard parametric models fitted independently to pembrolizumab and placebo data from the trial was more methodologically robust and preferred over the use of proportional hazards. The Committee also considered that the chosen parametric distributions for the submission's base case (DFS by IA) were not appropriate for DFS by BICR, as they did not provide good statistical and visual fit with the observed disease-free (DF) transitions.

- The submission included palliative care costs in the DM health state where patients were receiving treatment for advanced RCC. The Committee noted that there could be double-counting as terminal care costs were also applied in the death state. The Committee considered that this overestimated the overall healthcare resource use and costs in the routine surveillance arm (where more life years were spent in the DM state).

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 choice of DFS assessment, extrapolation method and parametric distribution for DF transitions, applying treatment waning, and removing palliative care costs from the DM health state. These changes substantially increased the ICER to between SG$135,000 and SG$165,000 per quality-adjusted life-year gained.

4.4. The Committee noted that the one-way sensitivity analysis and scenario analyses of the revised base case resulted in a wide range of ICERs. The key model drivers were the choice of parametric distributions for DF transitions, time horizon and DFS assessment method. The Committee considered that this further highlighted the uncertainty associated with the magnitude of DFS benefit and the extrapolation of immature survival data.

4.5. Overall, the Committee considered that pembrolizumab did not represent a cost-effective use of healthcare resources for the adjuvant treatment of RCC 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$1 million and SG$3 million over the first five years of listing pembrolizumab on the MOH List of Subsidised Drugs for the adjuvant treatment of RCC in patients who are at increased risk of recurrence following nephrectomy with or without resection of metastatic lesions.

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

7.1. Based on the available evidence, the Committee recommended not listing pembrolizumab on the MOH List of Subsidised Drugs for the adjuvant treatment of RCC in patients who are at increased risk of recurrence following nephrectomy with or without resection of metastatic lesions. 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	Approved clinical indication	Subsidy class	Eligible for MediShield Life claims (implementation date)
Pembrolizumab 100 mg/4 mL solution for infusion	Adjuvant treatment of patients with renal cell carcinoma at increased risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions. Maximum duration of treatment: 12 months.	Not recommended for subsidy	Yes[1] (1 Mar 2024)

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

VERSION HISTORY

Guidance on pembrolizumab for the adjuvant treatment of renal cell carcinoma

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 reflect MediShield Life claims eligibility**

   Date of Publication 1 Jun 2026