Technology Guidance

Pembrolizumab

for treating resectable Stage II, IIIA, or IIIB (T3-4N2) 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 pembrolizumab for inclusion on the MOH List of Subsidised Drugs, when used in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, for the treatment of patients with resectable Stage II, IIIA, or IIIB (T3-4N2) non-small-cell lung cancer. The decision was based on the unfavourable cost-effectiveness of pembrolizumab compared with nivolumab, 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 for treating resectable Stage II, IIIA, or IIIB (T3-4N2) non-small-cell lung cancer (NSCLC) – used first in combination with platinum (Pt)-containing chemotherapy as neoadjuvant treatment and then continued as monotherapy as adjuvant treatment ("perioperative pembrolizumab"). 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 and patient experts from local patient and voluntary organisations assisted ACE in ascertaining 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. Lung cancer is the third most common malignancy in Singapore, with around 130 new cases of resectable Stage II, IIIA, or IIIB (T3-N4) NSCLC diagnosed annually. Around half of these patients do not have mutations in epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK), so they would be considered for treatment with anti-programmed death-ligand 1 (PD-L1) or programmed cell death protein 1 (PD-1) agents.

2.2. In local practice, patients with resectable Stage II NSCLC are generally treated with upfront surgical resection followed by adjuvant chemotherapy, with or without atezolizumab. Most patients with resectable Stage III NSCLC receive neoadjuvant nivolumab plus Pt-chemotherapy before surgical resection ("neoadjuvant nivolumab").

2.3. The submission nominated upfront surgery followed by adjuvant treatment as the main comparator, and neoadjuvant nivolumab plus chemotherapy as the secondary comparator. However, the Committee assessed that pembrolizumab is likely to replace neoadjuvant nivolumab for patients eligible for neoadjuvant therapy, with little impact on those receiving upfront surgery. Therefore, neoadjuvant nivolumab was deemed the most appropriate comparator.

2.4. The Committee also noted that more treatment options, including other PD-1/PD-L1 inhibitors are expected to receive regulatory approval for this indication. However, these near-market comparators were not addressed in the submission.

2.5. The Committee considered three testimonials from local patient experts and carers about their lived experiences with lung cancer and the treatments they have received. The Committee acknowledged that while the patient experts felt they were largely unaffected by their lung cancer, the treatment-associated side effects, such as fatigue and muscle weakness, significantly impacted their ability to carry out many daily activities.

2.6. The Committee heard that two patient experts were receiving treatment with targeted therapies and felt that they worked well, were easy to use and had manageable side effects. They noted that although none of the patient experts were familiar with pembrolizumab, most would be willing to accept side effects from a new treatment if it effectively reduced cancer recurrence without incurring higher costs. They considered that any new treatment for lung cancer should allow them to spend more time with family and friends, allow them to return to work, be more affordable, improve their quality of life, prolong their lifespan, and reduce the chance of cancer recurrence.

Clinical effectiveness and safety

3.1. The company requested a listing for patients with resectable Stage II, IIIA, or IIIB (T3-4N2) NSCLC. This was aligned with the approved HSA indication, and the population studied in the pivotal phase III randomised controlled trial, KEYNOTE-671. This trial compared perioperative pembrolizumab with neoadjuvant chemotherapy followed by surgery (“neoadjuvant chemotherapy”) and was provided as clinical evidence in the company’s submission.

3.2. The Committee noted that, at a median follow-up of 36.6 months in the KEYNOTE-671 trial, perioperative pembrolizumab was associated with a statistically significant improvement in the primary endpoints of overall survival (OS) and event-free survival (EFS) when compared to neoadjuvant chemotherapy (Table 1).

Table 1: Results of OS and PFS in KEYNOTE-671 trial (data cutoff 10 July 2023)

Parameter	Perioperative pembrolizumab (N=397)	Neoadjuvant chemotherapy (N=400)
OS		
Number of Events, n (%)	110 (27.7)	144 (36.0)
Median OS (95% CI), months	NR (NR to NR)	52.4 (45.7 to NR)
HR (95% CI), p value	**0.72 (0.56 to 0.93), p = 0.0057**	
EFS by investigator assessment		
Number of Events, n (%)	174 (43.8)	248 (62.0)
Median EFS (95% CI), months	47.2 (32.9 to NR)	18.3 (14.8 to 22.1)
HR (95% CI), p value	**0.59 (0.48 to 0.72), p<0.00001**	

Abbreviations: CI, confidence interval; EFS, event-free survival; HR, hazard ratio; NR, not reached; OS, overall survival.
Bold denotes a statistically significant result.

3.3. As neoadjuvant chemotherapy was not considered a relevant comparator and no direct comparative evidence was available for perioperative pembrolizumab versus neoadjuvant nivolumab, the submission included a Bayesian network meta-analysis (NMA) for the EFS endpoint. The NMA relied on EFS estimates from the KEYNOTE-671 trial (at a median follow up of 36.6 months) for perioperative pembrolizumab and from CheckMate 816 phase III randomised controlled trial (at a median follow up of 29.5 months) for neoadjuvant nivolumab. No adjustments were made for differences in treatment effect modifiers observed between the trials, including PD-L1 cut-off, region, disease stage, and EGFR or ALK status.

3.4. The Committee considered that the submission's claim that perioperative pembrolizumab is superior to neoadjuvant nivolumab was not supported, [redacted]. Bucher indirect treatment comparisons independently conducted by the evidence review centre also demonstrated no significant difference in EFS between the two treatments, further supporting the Committee's conclusion (Table 2).

Table 2: Results of NMA and ITC comparing EFS benefit of perioperative pembrolizumab to neoadjuvant nivolumab

Analysis	Within trial HR (95%CI) [analysis type]		Indirect comparison: pembrolizumab versus nivolumab: HR (95% CrI or CI)
	KN671	CM816	
NMA on EFS (in submission)	[redacted]	[redacted]	[redacted]
Bucher ITC on EFS Based on submission inputs	0.59 (0.48, 0.72) [IA]	0.68 (0.49, 0.93)[a] [BICR]	0.87 (0.55, 1.38)
Bucher ITC on EFS Based on BICR estimate for KN671	0.62 (0.51, 0.76) [BICR]	0.63 (0.44, 0.89)[b,c] [BICR]	0.98 (0.66, 1.48)
Bucher ITC on EFS Based on latest CM816 data	0.62 (0.51, 0.76) [BICR]	0.66 (0.49,0.90)[d] [BICR]	0.94 (0.65, 1.35)

Abbreviation: BICR, blinded independent central review; CM816, CheckMate 816; CI, confidence interval; CrI, credible interval; EFS, event-free survival; KN671, KEYNOTE-671; HR, hazard ratio; IA, investigator assessed; ITC, indirect treatment comparison; NMA, network meta-analysis; OS, overall survival.

[a] This estimate could not be verified in the evaluation.

[b] Forde 2022 (for CM816 trial) did not present 95% CI's but rather 97.38% CI's. consequently, the resulting indirect comparison result will likely not necessarily reflect a Bucher 95% CI. For the sake of simplicity, the Forde 2022 CI was assumed to be 95% CI.

[c] Based on median follow-up of 29.5 months for CM816 trial.

[d] Based on follow-up of 4 years for CM816 trial.

3.5. The Committee noted that the submission did not include any comparative safety information between perioperative pembrolizumab and neoadjuvant nivolumab. However, given similar rates of adverse events relative to chemotherapy were reported (for perioperative pembrolizumab (KEYNOTE-671) and neoadjuvant nivolumab (CheckMate 816), the Committee considered that both treatments have non-inferior and comparable safety profiles.

3.6. Overall, the Committee concluded that it would be appropriate to consider perioperative pembrolizumab to be non-inferior to neoadjuvant nivolumab in the treatment of resectable Stage II, IIIA, or IIIB (T3-4N2) NSCLC.

Cost effectiveness

4.1. Given the lack of evidence to support a claim of superiority for perioperative pembrolizumab over neoadjuvant nivolumab, the Committee agreed that a cost-minimisation analysis (CMA) would be more appropriate than the submission's cost-utility analysis (CUA) for assessing the cost-effectiveness of perioperative pembrolizumab in comparison to neoadjuvant nivolumab.

4.2. The evidence review centre conducted a CMA using the mean number of doses of perioperative pembrolizumab and neoadjuvant nivolumab administered in the KEYNOTE-671 and CheckMate 816 trials (11.29 and 2.91 doses respectively). Based on this CMA, the Committee noted that the total treatment cost of perioperative pembrolizumab was more than double that of neoadjuvant nivolumab.

4.3. Consequently, the Committee considered that, at the price proposed by the company, perioperative pembrolizumab was unlikely to represent a cost-effective use of healthcare resources for treating resectable Stage II, IIIA, or IIIB (T3-4N2) NSCLC.

Estimated annual technology cost

5.1. Using an epidemiological approach, the submission estimated that listing pembrolizumab on the MOH List of Subsidised Drugs for treating resectable Stage II, IIIA, or IIIB (T3-4N2) NSCLC would result in an annual cost impact to the public healthcare system ranging from less than SG$1 million in the first year to between SG$1 million and SG$3 million by the fifth year of listing.

5.2. The Committee considered that the submission's financial estimates were likely overestimated due to inappropriate model inputs, including the overestimation of the number of eligible patients 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.

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 the available evidence, the Committee recommended not listing pembrolizumab on the MOH List of Subsidised Drugs, for use in combination with Pt-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, for treating resectable Stage II, IIIA, or IIIB (T3-4N2) NSCLC. The decision was based on the unfavourable cost-effectiveness of pembrolizumab compared with nivolumab, 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 for the treatment of patients with resectable Stage II, IIIA, or IIIB (T3-4N2) NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery. Neoadjuvant treatment should be stopped after a maximum duration of 12 weeks or upon disease progression that precludes definitive surgery or unacceptable toxicity, whichever occurs first. The maximum duration of adjuvant treatment is 39 weeks post-surgery, or upon disease recurrence or unacceptable toxicity, whichever occurs first.	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 resectable Stage II, IIIA, or IIIB (T3-4N2) non-small-cell lung 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 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