Technology Guidance

Pembrolizumab

for treating high-risk early-stage triple-negative breast 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 as neoadjuvant treatment and then continued as adjuvant monotherapy after surgery, for treating high-risk, early-stage, triple-negative breast cancer. 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 claim limit for pembrolizumab are provided in the Annex.

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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, in combination with chemotherapy as neoadjuvant treatment, and then continued as adjuvant monotherapy after surgery, for treating high-risk, early-stage, triple-negative breast cancer (TNBC). The company's requested listing was in line with the HSA-approved indication for pembrolizumab.

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 200 patients are diagnosed with high-risk, early-stage TNBC each year in Singapore. The Committee noted the potential clinical need for effective treatment in this patient population, as they tend to be young and experience early disease recurrences.

2.2. In local practice, most patients with high-risk, early-stage TNBC receive neoadjuvant chemotherapy, which usually comprises 4 cycles of paclitaxel (with or without carboplatin) and 4 cycles of cyclophosphamide plus doxorubicin. In the adjuvant setting, patients without residual disease are actively monitored without systemic treatment, while patients with residual disease receive capecitabine. For a small group of patients with germline breast cancer gene (gBRCA) mutations, adjuvant olaparib may be considered.

2.3. The submission nominated standard-of-care chemotherapy and placebo as the comparators in the neoadjuvant and adjuvant phases, respectively. The Committee considered the nominated neoadjuvant comparator to be reasonable. However, the Committee considered it inappropriate that capecitabine was excluded as an adjuvant comparator for patients with residual disease, given it is routinely used in local practice, and there is evidence of survival benefits associated with its use.

2.4. The Committee considered 15 testimonials from local patient experts about living with early breast cancer and their experience with different treatments. They heard that breast cancer negatively impacted the daily lives of patients, physically, mentally and emotionally, especially during the first few years after diagnosis. The physical symptoms constrained patients' daily activities, and also caused low self-esteem and anxiety. The Committee noted that patients reported fear of disease recurrence and financial worries as their greatest concern. None of the patients had experience with pembrolizumab; however, they considered that any new treatments for breast cancer should have fewer side effects than current treatments, improve quality of life and enable them to return to work and undertake daily activities. The Committee noted that patients also valued treatments that are more affordable and can reduce the risk of disease recurrence.

Clinical effectiveness and safety

3.1. The Committee reviewed the clinical evidence from the company's submission, which was based on the fourth interim analysis (IA4) of an ongoing phase III randomised controlled trial (KEYNOTE-522) that compared neoadjuvant pembrolizumab plus chemotherapy, followed by adjuvant pembrolizumab monotherapy ("pembrolizumab plus chemotherapy") versus neoadjuvant chemotherapy, followed by adjuvant placebo ("chemotherapy only"). The Committee noted that the submission did not include a comparison that considered adjuvant capecitabine use.

3.2. At a median follow-up of 39.1 months (March 2021 data cut-off), pembrolizumab plus chemotherapy led to statistically significant improvements in event-free survival (EFS), compared with chemotherapy only (Table 1 and Figure 1). However, the Committee acknowledged that there was uncertainty in the long-term EFS benefit given that the EFS data was immature.

3.3. Pathological complete response (pCR) was not formally tested for statistical significance at IA4, as prespecified. However, the Committee noted that a statistically significant improvement with pembrolizumab plus chemotherapy was met at the first prespecified interim analysis, and that results at IA4 showed a point estimate difference of 7.5% between treatment arms.

3.4. The Committee noted that at IA4, the overall survival (OS) data was immature, with no statistically significant difference between treatment arms. In the absence of

mature OS data, the submission proposed EFS as a surrogate endpoint for OS. However, the Committee considered that the available evidence regarding the strength of the surrogacy relationship between pCR, EFS and OS was conflicting and agreed it was uncertain whether the improvements in pCR and EFS are expected to predict a clinically meaningful improvement in long-term survival.

Table 1: Results of pCR, EFS and OS in KEYNOTE-522 (ITT population) (IA4, data cut-off March 2021)

	Pembrolizumab + chemotherapy (N=784)	Chemotherapy only (N=390)
pCR rate (ypT0/Tis ypN0)		
Patients who achieved pCR, n	494	217
Proportion that achieved pCR, % (95% CI)	63.0 (59.5 to 66.4)	55.6 (50.6 to 60.6)
Rate difference (95% CI)	7.5 (1.6 to 13.4)[a]	
EFS		
Patients with event, n (%)	123 (15.7)	93 (23.8)
Median EFS, months (95% CI)	NE	NE
HR (95% CI), p-value	**0.63 (0.48 to 0.82), p=0.0003093**	
OS		
Patients with event, n (%)	80 (10.2)	55 (14.1)
Median OS, months (95% CI)	NE	NE
HR (95% CI), p-value	0.72 (0.51 to 1.02), p=0.0321377[b]	

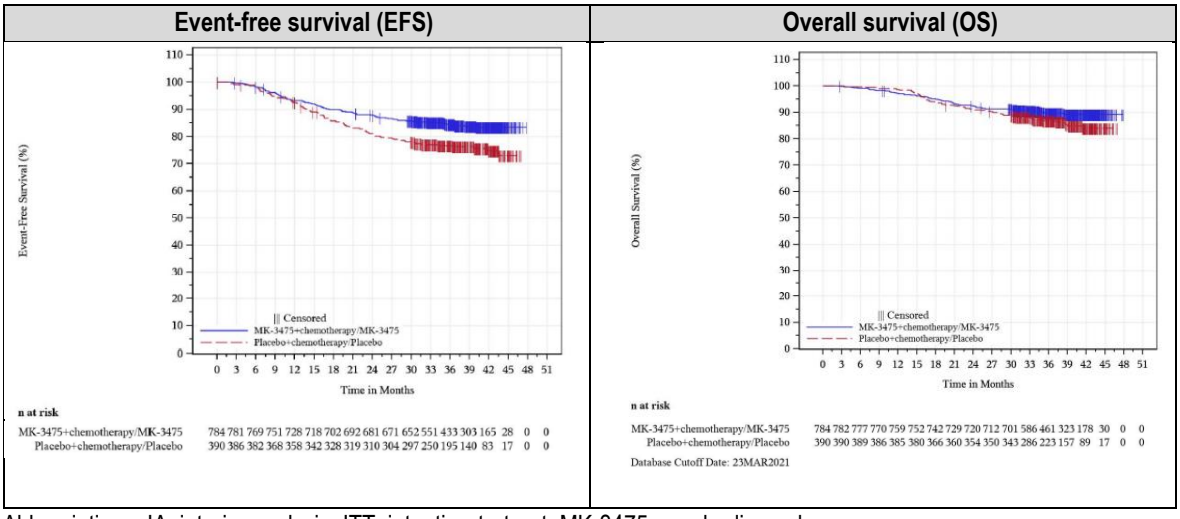
Abbreviations: CI, confidence interval; EFS, event-free survival; HR, hazard ratio; IA, interim analysis; ITT, intention-to-treat; NE, not evaluable; OS, overall survival; pCR, pathological complete response.

Bold indicates statistically significant result.

[a] Not formally tested at IA4 as a statistically significant improvement with pembrolizumab plus chemotherapy was met at the first pre-specified interim analysis.

[b] Does not meet the pre-specified statistical boundary of p=0.00085861.

Figure 1: Kaplan-Meier curves from KEYNOTE-522 (ITT population) (IA4, data cut-off March 2021)



Abbreviations: IA, interim analysis; ITT, intention-to-treat; MK-3475, pembrolizumab

3.5. The Committee heard that patients with residual disease in the chemotherapy-only arm of the KEYNOTE-522 trial were not permitted to receive adjuvant capecitabine treatment. Also, the submission stated that a comparison between pembrolizumab and adjuvant capecitabine in this subgroup of patients was not feasible due to heterogeneity of the study design, patient population, and outcomes between KEYNOTE-522 and CREATE-X (capecitabine trial). The Committee acknowledged that the evidence to inform this comparison was limited. However, given that adjuvant capecitabine treatment has been shown to improve disease-free survival and OS compared with placebo in this subgroup of patients, the Committee considered that the magnitude of treatment effect observed for pembrolizumab in KEYNOTE-522 was overestimated relative to local clinical practice.

3.6. The Committee heard that compared with chemotherapy only, a higher proportion of patients who received pembrolizumab plus chemotherapy experienced grade 3 to 5 treatment-related adverse events (TRAEs; 77.1% vs 73.3%), serious TRAEs (34.1% vs 20.1%) and discontinued treatment due to TRAEs (27.7% vs 14.1%).

3.7. The submission described pembrolizumab plus chemotherapy as superior in terms of effectiveness compared to chemotherapy only. Based on the evidence submitted, the Committee concluded that pembrolizumab plus chemotherapy was superior in terms of pCR rates and EFS, compared with chemotherapy only. However, the treatment effect observed in KEYNOTE-522 was overestimated relative to local clinical practice and the sustainability of the EFS benefit 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 concluded that pembrolizumab plus chemotherapy was inferior to chemotherapy only.

Cost effectiveness

4.1. The submission presented an economic evaluation for patients with high-risk, early-stage TNBC, based on the KEYNOTE-522 trial. Pembrolizumab plus chemotherapy was compared with chemotherapy only using a cost-utility analysis based on a semi-Markov state transition model with four health states. The analysis omitted adjuvant capecitabine. 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	High-risk, early-stage, triple-negative breast cancer patients
Outcomes	Total and incremental direct medical costs; total and incremental LY gained; total and incremental QALYs; ICER
Perspective	Singapore healthcare system
Type of model	Semi-Markov state transition model
Time horizon	15 years in the base case

Component	Description
Health states	• EFS: A health state where patients are free of disease recurrence (metastatic or non-metastatic disease). • DM: A health state where patients are suffering from a distant recurrence. • LRR: A health state where patients are suffering from a locoregional recurrence. • Death: An absorbing health state
Cycle length	1 week
Extrapolation methods used to generate results	Transition probabilities from EFS, LRR, and DM were informed by KN522 patient-level data. All-cause age-related mortality was informed by Singapore life tables. A piecewise approach was used to extrapolate EFS for both treatment arms. The submission informed the EFS using KM data from KN522 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, the cumulative hazard plots, and the Chow test. The submission selected a 50-week cut-off point based on plausible visual fit, a good balance of robust KM data, and sufficient data to fit the parametric curve. The submission stated that the proportional hazards assumption did not hold, and fitted the generalised gamma and the log-normal distributions to extrapolate EFS after 50 weeks in the pembrolizumab-plus-chemotherapy arm and chemotherapy-only arm, respectively. This selection was based on AIC/BIC statistics, visual fit, and clinical plausibility. Treatment effect waning and remission were not assumed in the base case. Approximately 90% of LYs and QALYs accrued and 22-33% of costs occurred in the extrapolated period.
Health-related quality of life	Utility values were informed by EQ-5D-5L data from KN522 using the UK algorithm and cross walked to EQ-5D-3L using van Hout (2012). • EFS on treatment = 0.795 • EFS off treatment = 0.803 • LRR = 0.738 • DM = 0.606 • Grade 3+ AE = -0.024
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; AIC, Akaike information criterion; BIC, Bayesian information criterion; DM, distant metastasis; EFS, event-free survival; EQ-5D-3L, EuroQoL 5 Dimension 3 Level; EQ-5D-5L, EuroQoL 5 Dimension 5 Level; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; KN522, KEYNOTE-522; LRR, locoregional recurrence; LY, life year; QALY, quality-adjusted life year.

4.2. The base-case incremental cost-effectiveness ratio (ICER) in the submission was between SG$15,000 and SG$45,000 per quality-adjusted life year (QALY) gained. However, the Committee considered the ICER to be highly uncertain and likely underestimated, in view of the following:

- The submission did not incorporate a remission point, which resulted in an overestimate of recurrences that favoured the pembrolizumab plus chemotherapy arm. With recurrences plateauing only after year 9, the model failed to reflect the known natural TNBC disease progression where recurrences are expected to plateau after year 5. Hence, the Committee agreed that this biased the result to favour pembrolizumab, as the chemotherapy-only arm continued to experience higher rates of recurrences beyond the point of remission. The Committee also noted that the model was highly sensitive to a 5-year remission time point.

- The submission assumed a sustained treatment effect beyond the median follow-up of 37 months in KEYNOTE-522, which resulted in an overestimation of the treatment effect of pembrolizumab plus chemotherapy. The Committee heard that data from CADTH's evaluation of this topic showed that the treatment effect of pembrolizumab plus chemotherapy declined after 24 months, once patients were no longer on pembrolizumab. Given the uncertainties associated with the long-term benefits of pembrolizumab beyond the median follow-up of the trial, the Committee considered that it was likely optimistic to assume that its treatment effect would be maintained in the long term.

- The extrapolations in the submitted model were overly optimistic by modelling a 20% survival benefit at 15 years for pembrolizumab plus chemotherapy. Modelling a substantial incremental benefit that predominately accrued over the extrapolated period was considered by the Committee to be unreasonable, given the lack of a statistically significant OS benefit in KEYNOTE-522 (2.8% difference between treatment arms at 36 months) and uncertain surrogacy relationship between EFS and OS for early-stage TNBC.

- The model underestimated the benefits of the chemotherapy-only arm as the use of adjuvant capecitabine was not allowed in KEYNOTE-522. Given the accepted effectiveness of adjuvant capecitabine in patients with residual disease, compared with placebo, the Committee expected that including adjuvant capecitabine in the economic model would decrease the incremental benefit of pembrolizumab plus chemotherapy.

4.3. The Committee considered the revised base case, which accounted for several uncertainties in the company's model. Key changes were the inclusion of a remission point at 5 years, incorporation of treatment waning, and choice of extrapolations that better reflected the uncertainties over long-term outcomes. These changes increased the ICER to between SG$45,000 and SG$75,000 per QALY gained. Furthermore, the Committee noted that the revised base case could not account for the use of adjuvant capecitabine in the chemotherapy-only arm and thus the ICER remains underestimated. Due to data limitations, the magnitude of this underestimation could not be established.

4.4. The Committee noted that, based on one-way sensitivity analysis of the revised base case, the incorporation of treatment waning and remission assumptions made the model less sensitive to the extrapolation function. This reduced the uncertainty in choice of extrapolations. The Committee also noted that the ICER remained between SG$45,000 and SG$75,000 per QALY gained in all scenarios presented.

4.5. Overall, the Committee considered that pembrolizumab did not represent a cost-effective use of healthcare resources for treating high-risk, early-stage TNBC 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 high-risk, early-stage TNBC.

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 between SG$1 million and SG$3 million in the first year, increasing to between SG$3 million and SG$5 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 as neoadjuvant treatment, and then continued as adjuvant monotherapy after surgery, for treating high-risk, early-stage TNBC. 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	MediShield Life claim limit per month (implementation date)
Pembrolizumab 100 mg/4 mL solution for infusion	Pembrolizumab in combination with chemotherapy as neoadjuvant treatment, and then continued as adjuvant monotherapy after surgery, for previously untreated high-risk, early-stage, triple-negative breast cancer. Treatment with pembrolizumab should be stopped after a maximum duration of 1 year across neoadjuvant and adjuvant phases, or earlier if disease progresses or recurs.	Not recommended for subsidy	$1800 (1 Mar 2024)

[5]