Technology Guidance

Trastuzumab deruxtecan

for previously treated HER2-positive metastatic breast cancer

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has not recommended trastuzumab deruxtecan (T-DXd) for inclusion on the MOH List of Subsidised Drugs for treating human epidermal growth factor receptor 2 (HER2)-positive unresectable or metastatic breast cancer after a prior anti-HER2-based regimen. The decision was based on the uncertain extent of clinical benefit and unfavourable cost-effectiveness of T-DXd at the price proposed by the company compared with alternative treatments.

Clinical indication, subsidy class and MediShield Life claim limit for T-DXd are provided in the Annex.

Updated: 1 September 2023

Factors considered to inform the recommendations for funding

Company-led submission

1.1. At the March 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 (ERCs) for the technology evaluation of trastuzumab deruxtecan (T-DXd) for treating human epidermal growth factor receptor 2 (HER2)-positive unresectable or metastatic breast cancer (mBC), after a prior anti-HER2-based regimen.

1.2. Expert opinion was obtained from the MOH Cancer Drug Subcommittee (CDS) and patient experts from local patient and voluntary organisations, who assisted ACE to ascertain the clinical value of T-DXd.

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 160 patients are diagnosed with HER2-positive unresectable or metastatic breast cancer each year in Singapore. Most patients with disease progression while on, or after, a prior anti-HER2-based regimen will receive trastuzumab emtansine (T-DM1) monotherapy. Others will receive trastuzumab plus chemotherapy. For patients who have received two or more prior anti-HER2 therapies, trastuzumab plus chemotherapy or lapatinib plus capecitabine are commonly used in local practice.

2.2. The Committee considered testimonials from local patient experts about living with breast cancer and their experience with different treatments. They heard that breast cancer had a significant negative impact on patients and their families. The physical symptoms constrained their daily activities, and some patients were unable to continue working. The Committee noted that patients also suffered from anxiety, a feeling of despair, hopelessness and uncertainty, with financial worries being their

greatest concern. They acknowledged that patients receiving T-DXd felt their treatment worked well to control the cancer but were concerned that it was expensive and had several side effects, including severe fatigue, nausea, constipation, bloatedness and decreased appetite. Patients considered that any new breast cancer treatments should be more affordable, have less side effects than current treatments, and be able to extend survival. The Committee noted that patients also valued treatments that improve quality of life, enabling them to return to work, live independently, and not be a burden to their families.

Clinical effectiveness and safety

3.1. The company requested a listing for patients with HER2-positive unresectable or metastatic breast cancer, who have received a prior anti-HER2-based regimen. This was aligned with the approved HSA indication, and the pivotal trial relied upon by the submission (i.e. DESTINY-Breast03, an ongoing phase III randomised controlled trial that compared T-DXd with T-DM1).

3.2. T-DXd versus T-DM1

Based on a median follow-up of 15.9 months (May 2021 data cut-off) in the DESTINY-Breast03 trial, T-DXd led to a statistically significant improvement in progression-free survival (PFS) compared with T-DM1 (Table 1). The results for overall survival (OS) suggested that T-DXd potentially reduced the risk of death versus T-DM1. However, OS data were immature (median OS was not reached for either treatment arm) and did not meet the pre-specified efficacy boundary (p value <0.000265).

Table 1: Results for PFS and OS in DESTINY-Breast03 trial

May 2021 data cut-off	T-DXd (N=261)	T-DM1 (N=263)	Absolute difference	HR (95% CI), p value
PFS based on blinded independent central review				
Patients with event, n (%) Progression Death	87 (33.3) 80 (30.7) 7 (2.7)	158 (60.1) 152 (57.8) 6 (2.3)	-26.8%	-
Median PFS, months (95% CI)	NE (18.5 to NE)	6.8 (5.6 to 8.2)	NE	**0.2840 (0.2165 to 0.3727), p<0.000001^**
OS				
Patients with event, n (%)	33 (12.6)	53 (20.2)	-7.6%	-
Median OS, months (95% CI)	NE	NE	NE	0.5546 (0.3587 to 0.8576), p=0.007172

Abbreviations: CI, confidence interval; HR, hazard ratio; NE, not evaluable; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; T-DM1, trastuzumab emtansine.

Bold indicates statistically significant result.

^ The actual p value was 7.8×10^{-22}.

3.3. In the absence of mature OS data, the submission proposed PFS as a surrogate endpoint for OS in HER2-positive mBC, based on results of a surrogate threshold effect (STE) analysis. However, the Committee considered the PFS-OS surrogacy relationship to be uncertain, with over one-third (eight out of 22) of the included studies exceeding the STE boundary. In addition, evidence from the literature provided only modest support for considering PFS as a surrogate for OS in HER2-positive mBC. Hence, definitive conclusions on the OS benefit provided by T-DXd could not be made.

3.4. In terms of safety, the Committee heard that T-DXd was associated with a higher incidence of grade ≥3 drug-related treatment-emergent adverse events (TEAEs; 45.1% vs 39.8%) and serious drug-related TEAEs (10.9% vs 6.1%), compared with T-DM1. More patients in the T-DXd arm also experienced drug-related TEAEs leading to study drug discontinuation (12.8% vs 5%), dose reduction (21.4% vs 12.6%) and interruption (35.4% vs 13%), compared with T-DM1. The most common grade ≥3 drug-related TEAEs reported with T-DXd were neutropenia, thrombocytopenia, leucopenia and nausea.

3.5. The submission described T-DXd as superior in terms of effectiveness and similar in terms of safety compared with T-DM1, for patients with previously treated HER2-positive mBC. Based on the evidence submitted, the Committee concluded that the extent of clinical benefit provided by T-DXd compared with T-DM1 was uncertain, due to immaturity of the OS data and uncertainty in the strength of the PFS-OS surrogacy relationship. In terms of safety, the Committee considered the safety of T-DXd to be inferior to T-DM1.

3.6. <u>T-DXd versus trastuzumab plus chemotherapy</u>
The submission also presented an indirect treatment comparison (ITC) between T-DXd and trastuzumab plus capecitabine. The results showed that the OS hazard ratio (HR) for T-DXd versus trastuzumab plus capecitabine had a wide confidence interval that included the null.

3.7. The submission described T-DXd as superior in terms of effectiveness compared with trastuzumab plus chemotherapy, for patients with previously treated HER2-positive mBC. However, the Committee considered the claim of superior clinical efficacy to be inappropriate, in view of the uncertain ITC results submitted.

3.8. In addition, the Committee noted that the submission had not adequately demonstrated the comparative efficacy of T-DXd versus standard of care in the third-line setting and beyond (trastuzumab plus chemotherapy, or lapatinib plus capecitabine). They acknowledged the company's response that an ongoing phase III trial (DESTINY-Breast02) would provide more evidence to assess the clinical effectiveness of T-DXd as a third- or subsequent-line treatment for HER2-positive mBC in patients previously treated with T-DM1.

Cost effectiveness

4.1. T-DXd versus T-DM1

The Committee considered the results of the submission's cost-utility analysis that compared T-DXd with T-DM1 for HER2-positive unresectable or metastatic breast cancer after a prior anti-HER2-based regimen, based on the DESTINY-Breast03 trial. 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 HER2-positive unresectable or metastatic breast cancer after a prior anti-HER2-based regimen
Outcomes	Total and incremental direct medical costs; total and incremental LY gained; total and incremental QALYs; ICER
Perspective	Singapore healthcare system
Type of model	Partitioned survival model
Time horizon	20 years in the model base case, based on a median follow-up of 15.9 months in the DB-03 trial
Health states	Pre-progression; post-progression; death
Cycle length	3 weeks (21 days)
Extrapolation methods used to generate results	Extrapolation of the PFS and TTD curves were informed by time-to-event data from DB-03 trial and fitted using standard parametric distributions in the base case: • PFS for both treatment arms = log normal distribution • TTD for both treatment arms = log normal distribution Extrapolation of the OS curves were performed using the 'KM + Tail' approach. KM data from DB-03 trial were applied until the curves plateaued (20 months for both treatment arms). Beyond 20 months, • OS for T-DM1 = log normal distribution (based on the EMILIA trial) • OS for T-DXd = fitted to the T-DM1 curve as a covariate and assumed proportional hazards. No treatment waning was applied in the base case. Sensitivity analysis assumed treatment waning to occur at eight years and end at 15 years in the model, however full convergence did not occur over the 20-year time horizon. 90% of the QALYs gained and 96% of the LYs gained occurred in the extrapolated period.
Health-related quality of life	• Utilities for the pre-progression health state were based on treatment specific DB-03 trial-based EQ-5D questionnaires. • Utilities for the post-progression health state were based on an algorithm (Lloyd et al, 2006)
Types of healthcare resources included	• Drug and drug administration • Disease management cost • Healthcare resource use • Subsequent treatment costs • AE management costs

Abbreviations: AE, adverse event; DB-03, Destinty-Breast03; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; LY, life year; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; T-DXd, trastuzumab deruxtecan; T-DM1, trastuzumab emtansine; TTD, time to treatment discontinuation.

4.2. The base-case incremental cost-effectiveness ratio (ICER) in the submission was between SG$105,000 and SG$135,000 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 applied a time horizon of 20 years in the base-case economic model. The Committee considered the time horizon to be optimistic, given the short median follow-up duration (15.9 months) and immature OS data in the DESTINY-Breast03 trial.

- The modelling of OS for both treatment arms was highly uncertain. The submission estimated the OS curve for T-DM1 using patient-level data from the DESTINY-Breast03 trial up to 20 months, and extrapolated long-term OS benefit by fitting parametric survival models based on OS data from the EMILIA trial[a]. The OS HR from DESTINY-Breast03 trial was then applied to this curve, to inform the long-term OS estimates for T-DXd. The Committee heard from local clinical experts that the results from the EMILIA trial were not generalisable to the DESTINY-Breast03 trial, due to important differences in the patient populations in terms of prior treatment use. Derivation of the OS curve for T-DXd also required the proportional hazards assumption to hold for OS throughout the time horizon; however, the Committee considered that this was uncertain based on the log-cumulative hazard plot and Schoenfeld residuals.

- The treatment effect of T-DXd compared with T-DM1 was assumed to be maintained over the entire time horizon. Although there was a separation in PFS favouring T-DXd over T-DM1 within the trial period, the Committee considered it optimistic to assume this treatment effect would be maintained indefinitely. A continued separation of OS curves may be implausible given the immature OS data and uncertain PFS-OS surrogacy relationship.

- In the base-case economic model, the submission calculated post-progression treatment costs on a per-cycle basis, with no stopping rule applied. The Committee noted this approach was inappropriate because it assumed that patients who progress and receive subsequent treatment would continue to accrue costs until death. Given that the model assumed a lower proportion of patients would receive subsequent treatment in the T-DXd arm, post-progression treatment costs were likely underestimated in favour of T-DXd.

- The model was highly sensitive to the distribution of subsequent treatments received in both treatment arms. The submission assumed that a substantial proportion of patients would receive T-DXd or T-DM1 as subsequent therapy after their initial treatment, which was not aligned with local clinical practice. Moreover, there is currently no robust evidence assessing the benefit of using T-DM1 and T-

[a] The EMILIA trial compared T-DM1 with lapatinib plus capecitabine in patients with HER2-positive unresectable, locally advanced, or metastatic breast cancer previously treated with trastuzumab and a taxane.

DXd sequentially. Given that OS benefit may be influenced by the subsequent treatments received, the timing of when they are received and the duration of treatment, the Committee considered it was more appropriate to apply the local distribution and duration of use of subsequent treatments in the economic 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 reducing the time horizon, applying treatment waning, and one-off post-progression treatment costs incorporating the local distribution and duration of use of subsequent treatments to reflect clinical practice. These changes substantially increased the ICER to between SG$245,000 and SG$285,000 per QALY gained.

4.4. The Committee noted that based on one-way sensitivity analysis of the revised base case, the key model drivers were the OS HR of T-DXd versus T-DM1, time horizon, and the cost of T-DXd. When the model parameters were varied within their uncertainty ranges, the ICERs remained unfavourably high.

4.5. <u>T-DXd versus trastuzumab plus chemotherapy</u>
The submission also presented a scenario analysis that compared T-DXd with trastuzumab plus capecitabine in patients with previously treated HER2-positive mBC, based on results of the ITC. Similar to the previously described base case, the Committee considered this ICER (between SG$165,000 and SG$205,000 per QALY gained) to be highly uncertain and likely underestimated, in view of uncertainties related to the ITC, time horizon, extrapolation method, and treatment effect waning.

4.6. The Committee considered the revised scenario analysis, which accounted for several uncertainties in the company's model. The revised ICER for T-DXd compared with trastuzumab plus capecitabine was between SG$205,000 and SG$245,000 per QALY gained.

4.7. Overall, the Committee considered that T-DXd did not represent a cost-effective use of healthcare resources for previously treated HER2-positive mBC 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 increase from less than SG$15 million in the first year, to more than SG$20 million in the fifth year of listing T-DXd on the MOH List of Subsidised Drugs for previously treated HER2-positive mBC.

5.2. The Committee considered that the submission estimates and price-volume agreement (PVA) caps were extremely high, due to an overestimation of treatment duration and an optimistic uptake rate for T-DXd. Based on the revised budget impact model, the annual cost impact to the public healthcare system was estimated to be between SG$5 million and SG$10 million in the first year, and between SG$10 million and SG$15 million in the fifth year of listing.

Recommendations

6.1. Based on the evidence submitted, the Committee recommended not listing T-DXd on the MOH List of Subsidised Drugs for treating HER2-positive unresectable or metastatic breast cancer after a prior anti-HER2-based regimen. The decision was based on the uncertain extent of clinical benefit and unfavourable cost-effectiveness of T-DXd at the price proposed by the company compared with alternative treatments.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Clinical indication	Subsidy class	MediShield Life claim limit per month (implementation date)
Trastuzumab deruxtecan 100 mg powder for concentrate for solution for infusion	Treatment of patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen.	Not recommended for subsidy	$2400 (1 Nov 2023)

VERSION HISTORY

Guidance on trastuzumab deruxtecan for previously treated HER2-positive metastatic breast 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 Jul 2023

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

   Date of Publication 1 Sep 2023