Technology Guidance

Trastuzumab deruxtecan

for HER2-low unresectable and/or metastatic breast cancer after at least one prior line of chemotherapy

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 patients with human epidermal growth factor receptor 2 (HER2)-low unresectable and/or metastatic breast cancer who have received at least one prior line of chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. The decision was based on the unfavourable cost-effectiveness of T-DXd compared with chemotherapy, and the unacceptable price-volume agreement proposed by the company.

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

Updated: 13 September 2024

Factors considered to inform the recommendations for funding

Company-led submission

1.1. At the March 2024 meeting, the MOH Drug Advisory Committee ("the Committee") considered evidence submitted by the company and a review of the submission by an ACE evidence review centre for the technology evaluation of trastuzumab deruxtecan (T-DXd) for treating patients with human epidermal growth factor receptor 2 (HER2)-low unresectable and/or metastatic breast cancer (uBC and/or mBC), who have received at least one prior line of chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.

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 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 heard that approximately 317 patients are diagnosed with HER2-low uBC and/or mBC each year in Singapore. Most patients with disease progression during treatment or after one prior line of chemotherapy in the metastatic setting will receive single-agent chemotherapy (e.g. capecitabine, eribulin or gemcitabine).

2.2. The Committee considered testimonials from local patient experts about living with advanced or metastatic breast cancer and their experience with different treatments. They heard that breast cancer had negatively impacted their ability to carry out daily activities and the treatments caused several side effects. None of the patients had experience with T-DXd, but they considered that any new treatments for breast cancer should stop the cancer from worsening, have fewer side effects compared to current treatments, and improve their quality of life. The Committee noted that patients reported treatment affordability as the most important factor when considering a new treatment.

Clinical effectiveness and safety

3.1. The Committee noted that the company's requested listing was broader than the HSA approved indication. The criteria proposed by the company state that patients with hormone receptor (HR)positive breast cancer should have received or be ineligible for endocrine therapy. The HSA label states that patients with HR-positive breast cancer should have received at least one and be no longer considered eligible for endocrine therapy. The Committee agreed that any listing of T-DXd should align with the approved HSA indication.

3.2. The Committee reviewed the clinical evidence in the submission, which was based on a phase III randomised, open-label trial (DESTINY-Breast04) that compared T-DXd with treatment of physician's choice (TPC). The TPC chemotherapy agents included in the trial were capecitabine, eribulin, gemcitabine, nab-paclitaxel or paclitaxel. The Committee noted that the distribution of the chemotherapies in DESTINY-Breast04 differed from that in local clinical practice, thereby limiting the generalisability of the results. Further, no data were available about the comparative efficacy of T-DXd versus each chemotherapy, so the impact was unknown.

3.3. Compared with TPC, treatment with T-DXd was associated with a statistically significant improvement in progression-free survival (PFS) and OS (Table 1).

Table 1: Results for OS and PFS in DESTINY-Breast04 (FAS) (Jan 2022 data cut-off)

	T-DXd (n=373)	TPC (n=184)	Hazard ratio (95% CI), p-value
PFS by BICR			
Events, n (%) Progressive disease Death	243 (65.1) 208 (55.8) 35 (9.4)	127 (69.0) 117 (63.6) 10 (5.4)	-
Median PFS, months (95% CI)	9.9 (9.0, 11.3)	5.1 (4.2, 6.8)	**0.50 (0.40, 0.63), p<0.0001**
OS			
Events, n (%)	149 (39.9)	90 (48.9)	-
Median OS	23.4 (20.0, 24.8)	16.8 (14.5, 20.0)	**0.64 (0.49, 0.84), p=0.001**

Abbreviations: BICR, blinded independent central review; CI, confidence interval; FAS: full analysis set; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Bold indicates statistically significant result.

3.4. The Committee noted that the open-label design of Destiny-Breast04 could have led to bias. They noted that knowledge of treatment received may have influenced patients' responses to quality of life questionnaires and affected the investigator's assessment of the relationship between adverse events (AEs) and study treatment. For both treatment arms, the EuroQol 5-dimension 5-level (of severity) assessment (EQ-5D-5L) index score decreased between baseline and end of treatment. However, the change was not clinically meaningful and the difference between arms did not reach statistical significance.

3.5. In terms of safety, the Committee heard that more patients in the TPC arm experienced grade ≥3 treatment-emergent adverse events (TEAEs; 67.4% vs 52.6%) and grade ≥3 drug-related TEAEs (57.6% vs 41.5%) compared with patients in the T-DXd arm. However, patients receiving T-DXd had a greater risk of experiencing TEAEs leading to treatment discontinuation compared with TPC (16.2% vs 8.1%). The incidence of AEs of special interest was also higher in the T-DXd versus TPC arm, for example, interstitial lung disease (12.1% vs 0.6%) and left ventricular dysfunction (4.6% vs 0%).

3.6. The submission described T-DXd as superior in terms of effectiveness compared to TPC in patients with HER2-low uBC and/or mBC, who had been previously treated with at least one prior line of chemotherapy in the recurrent or metastatic setting. Based on the evidence submitted, the Committee considered that T-DXd was superior in terms of PFS and OS, compared with TPC. In terms of safety, the Committee considered that T-DXd was non-inferior compared with TPC, but with a different safety profile.

Cost effectiveness

4.1. The Committee considered the results of the submission's cost-utility analysis that compared T-DXd with TPC for HER2-low uBC and/or mBC after at least one prior line of chemotherapy, based on the DESTINY-Breast04 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-low uBC and/or mBC after at least one prior line of chemotherapy
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	17 years in the model base case based on a median follow-up of 18.4 months for OS in DB-04 trial
Health states	Pre-progression; post-progression; death
Cycle length	3 weeks (21 days)

Component	Description
Extrapolation methods used to generate results	Parametric models were selected based on the AIC/BIC values and clinical expert opinion. The parametric model fitted were: • PFS: dependent modelling, log normal distribution for T-DXd and TPC. • OS: dependent modelling, log-logistic distribution for T-DXd and TPC. • TTD: independent modelling, log-logistic distribution for T-DXd and TPC. Treatment waning was not assumed in the analysis.
Health-related quality of life	• Progression-free health state utilities were based on DB-04 = 0.850 (T-DXd) and 0.817 (TPC) • Post-progression health state utilities were based on DB-04 = 0.823 (T-DXd) and 0.785 (TPC)
Types of healthcare resources included	• Drug and drug administration • Disease management cost • Healthcare resource use • Subsequent treatment costs • AE management costs

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; DB-04, DESTINY-Breast04; ICER, incremental cost-effectiveness ratio; LY, life years; OS, overall survival; mBC, metastatic breast cancer; PD, progressed disease; PF, progression-free; PFS, progression-free survival; QALY, quality-adjusted life-year; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice; TTD, time to treatment discontinuation; uBC, unresectable breast cancer.

4.2. The base-case incremental cost-effectiveness ratio (ICER) in the submission was between SG$165,000 and SG$205,000 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 17 years in the base-case economic model based on clinical expert opinion. The Committee considered the time horizon to be optimistic, given the short median OS follow-up duration (18.4 months) in the DESTINY-Breast04 trial.

- The submission applied dependent log-logistic OS extrapolation to the OS curve of the T-DXd and TPC arms, which required the proportional hazards assumption to hold for OS throughout the time horizon. However, the Committee considered that this was uncertain as the log-log survival curves were not parallel in the first few months and the Schoenfeld residuals plot showed a non-zero slope over time. Furthermore, the submission did not apply a treatment waning effect which implied an ongoing treatment benefit associated with T-DXd over TPC which was modelled until the end of the 17-year time horizon. There was no evidence provided to support an ongoing treatment effect beyond the trial period. The Committee acknowledged the extrapolation of OS was uncertain and overly optimistic.

- The submission applied treatment-specific utility values for the progression-free (PF) and progressed disease (PD) health states despite no statistical differences observed in EQ-5D-5L data between the T-DXd and TPC arms in the DESTINY-Breast04 trial. The Committee considered it was more reasonable to apply pooled health state utility values. The Committee noted that the pooled utility value for the PF state derived from the trial appeared high, considering the background utility value of the general population for the corresponding age group. The small decrement between the PF and PD health state utility values from the trial also appeared implausible. This was likely due to the clinical trial collecting EQ-5D-5L data early in disease progression, which could not capture the utility of the PD health state until death. The Committee noted that the ICER was sensitive to utility values derived from various methods.

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, choice of OS extrapolation and applying alternative utility values. These changes 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 cost of T-DXd and health state utility values. When the model parameters were varied within their uncertainty ranges, the ICERs remained unfavourably high.

4.5. Overall, the Committee considered that T-DXd did not represent a cost-effective use of healthcare resources for previously treated HER2-low uBC and/or 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 be between SG$10 million and SG$15 million in the first year, and between SG$15 million and SG$20 million in the fifth year of listing T-DXd on the MOH List of Subsidised Drugs for patients with HER2-low uBC and/or mBC who have received at least one prior line of chemotherapy in the recurrent or metastatic setting.

5.2. The Committee considered that the submission's financial estimates and price-volume agreement (PVA) caps were high due to an overestimation in the number of vials per treatment course, an optimistic uptake rate for T-DXd, and an overestimation of patients treated in PHIs. 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 patients with HER2-low uBC and/or mBC who have received at least one prior line of chemotherapy in the recurrent or metastatic setting. The decision was based on the unfavourable cost-effectiveness of T-DXd compared with chemotherapy, and the unacceptable PVA proposed by the company.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Clinical indication	Subsidy class (implementation date)	MediShield Life claim limit per month (implementation date)
Trastuzumab deruxtecan 100 mg powder for concentrate for solution for infusion	Treatment of patients with HER2-low unresectable and/or metastatic breast cancer who have received at least one prior line of chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Patients with HR-positive breast cancer should have received at least one and be no longer considered eligible for endocrine therapy.	Not recommended for subsidy	$2400 (1 Nov 2024)

VERSION HISTORY

Guidance on trastuzumab deruxtecan for HER2-low unresectable and/or metastatic breast cancer after at least one prior line of chemotherapy

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	4 Jun 2024

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

Date of Publication	13 Sep 2024