Technology Guidance

Datopotamab deruxtecan

for previously treated unresectable or metastatic HR-positive, HER2-negative breast cancer

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has not recommended datopotamab deruxtecan (Dato-DXd) for inclusion on the MOH List of Subsidised Drugs for treating patients with unresectable or metastatic hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer who have received prior endocrine-based therapy and chemotherapy for unresectable or metastatic disease. The decision was based on the unfavourable clinical and cost effectiveness of Dato-DXd compared with chemotherapy, at the price proposed by the company.

Clinical indication, subsidy class and MediShield Life claim limit for datopotamab deruxtecan are provided in the Annex.

Published: X September 2025

Company-led submission

1.1. At the June 2025 meeting, the MOH Drug Advisory Committee ("the Committee") considered the technology evaluation of datopotamab deruxtecan (Dato-DXd) for treating unresectable or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer in patients who had received prior endocrine-based therapy (ET) and chemotherapy. 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 Dato-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 each year in Singapore, approximately 203 new patients diagnosed with HR-positive, HER2-negative uBC or mBC require subsequent treatment after receiving ET and one additional line of chemotherapy.

2.2 The Committee noted that most patients with disease progression on ET and one prior line of chemotherapy will receive single-agent chemotherapy (e.g. capecitabine, eribulin, gemcitabine or vinorelbine). Hence, Dato-DXd is most likely to replace single-agent chemotherapy in clinical practice. The Committee acknowledged that the clinical need for Dato-DXd was not high, given that alternative treatment options to chemotherapy for certain patients with HR-positive, HER2-negative uBC or mBC are also available on the Cancer Drug List. These include trastuzumab deruxtecan (T-DXd) for a subset of patients with HER2-low disease who progressed on chemotherapy, and sacituzumab govitecan (SG) for patients with HR-positive, HER2-negative disease who progressed on ET and at least two additional systemic therapies in the metastatic setting.

2.3 The Committee considered 14 testimonials from local patient experts about living with advanced breast cancer and their experience with different treatments. They heard that breast cancer had negatively impacted their daily activities such as work and caring for their children, as well as their mental well-being due to living in fear about an uncertain future. The Committee noted that the financial burden of the treatments and the side effects that patients experienced strained family relationships. While none of the patient experts were familiar with Dato-DXd, the Committee acknowledged that patients would like new treatments for breast cancer to be more affordable, stop their cancer from worsening and prolong their time living with cancer.

Clinical effectiveness and safety

3.1. The Committee reviewed the clinical evidence, presented in the company's submission, from an ongoing phase III randomised controlled trial (RCT; TROPION-Breast01). The trial compared Dato-DXd with single-agent chemotherapy, including capecitabine, eribulin, gemcitabine, or vinorelbine, in patients with HR-positive, HER2-negative uBC or mBC who had progressed on ET and one or two lines of prior chemotherapy. In the absence of direct comparative evidence between Dato-DXd and SG, the Committee reviewed an indirect treatment comparison (ITC) presented in the company's submission. However, the submission did not include any relevant comparisons between Dato-DXd and T-DXd.

Dato-DXd versus single-agent chemotherapy

3.2. At a median follow-up of 10.8 months (July 2023 data cut-off) for progression-free survival (PFS), Dato-DXd showed a statistically significant improvement in median PFS compared with chemotherapy (Table 1). The Committee noted that it was unclear whether a 2-month improvement in median PFS was clinically meaningful, given a minimally clinically important difference for the PFS outcome was undefined. Moreover, at a median follow-up of 9.7 months (July 2023 data cut-off), the overall survival (OS) results did not show a statistically significant difference between Dato-DXd and chemotherapy.

3.3. The Committee heard that subsequent OS results from the second interim (April 2024 data cut-off) and final analyses (July 2024 data cut-off) became available following the company submission, and continued to show no statistically significant difference between Dato-DXd and chemotherapy (reduction in the difference in median OS from 0.8 to 0.3 months).

Table 1: Results of OS and PFS from TROPION-Breast01

Outcome	Dato-DXd (n=365)		Chemotherapy (n=367)		Difference in median, months	HR (95% CI), p-value
	n/N with event (%)	Median time to event, months (95% CI)	n/N with event (%)	Median time to event, months (95% CI)		
First interim analysis for OS and primary analysis for PFS (data cut-off 17 July 2023) – company-submitted results						
OS	80/365 (21.9)	16.1 (16.1 to NC)	91/367 (24.8)	NC (16.5 to NC)	0.8	0.84 (0.62 to 1.14), 0.2615
PFS by BICR	212/365 (58.1)	6.9 (5.7 to 7.4)	235/367 (64.0)	4.9 (4.2 to 5.5)	2.0	**0.63 (0.52 to 0.76), <0.001**
Second interim analysis (data cut-off 29 April 2024)						
OS	195/365 (53.4)	19.0 (17.4 to 20.2)	200/367 (54.5)	18.2 (17.3 to 19.9)	0.8	0.93 (0.76 to 1.13), 0.47
Final analysis (data cut-off 24 July 2024)						
OS	233/365 (63.8)	18.6 (17.3 to 20.1)	213/367 (58.0)	18.3 (17.3 to 20.5)	0.3	1.01 (0.83 to 1.22), 0.94

Abbreviations: BICR, blinded independent central review; CI, confidence interval; Dato-DXd, datopotamab deruxtecan; HR, hazard ratio; NC, not calculable; OS, overall survival; PFS, progression-free survival.
Bold indicates statistically significant results.

3.4. In terms of safety, the Committee noted that the incidence of adverse events (AEs) and AEs leading to treatment discontinuation were similar between both treatment arms. Compared with patients in the chemotherapy arm, Dato-DXd was associated with more treatment-related adverse events (TRAEs; 93.6% vs 86.3%), but a lower incidence of grade ≥3 AEs (32.5% vs 54.1%) and grade ≥3 TRAEs (20.8% vs 44.7%). The most frequently reported AEs with Dato-DXd were nausea, stomatitis, and alopecia.

3.5. The submission described Dato-DXd as superior in terms of effectiveness compared with chemotherapy, with a tolerable safety outcome for patients with HR-positive, HER2-negative uBC or mBC who had received prior systemic therapy. Based on the evidence submitted, the Committee concluded that the claim of superior clinical effectiveness was not supported. While the Committee agreed that Dato-DXd has a tolerable safety outcome, they noted that Dato-DXd had a different safety profile compared with chemotherapy.

Dato-DXd versus SG

3.6. The ITC compared two RCTs, TROPION-Breast01 for Dato-DXd and TROPiCS-02 for SG. TROPiCS-02 compared SG with chemotherapy in patients with HR-positive, HER2-negative uBC or mBC who had progressed after ET and two to four lines of prior chemotherapy. The results of the ITC showed no significant difference between Dato-DXd and SG in OS, PFS and objective response rate (ORR). However, Dato-DXd could not be interpreted as being non-inferior to SG due to the lack of defined non-inferiority margins for these outcomes. Moreover, the Committee considered that robust clinical conclusions could not be drawn from the ITC due to limitations such as differences between the trial populations that were not accounted for in the analysis.

3.7. In terms of safety, the ITC showed that Dato-DXd led to improved safety over SG, in terms of treatment-emergent adverse events (TEAEs) leading to death, grade ≥3 TEAEs, serious TEAEs and serious TRAEs. However, similar limitations to the ITC (paragraph 3.6) apply to the safety comparison, and no robust conclusions could be drawn.

3.8. Overall, the Committee considered the available evidence inadequate to support the company's claim of non-inferior effectiveness and superior safety for Dato-DXd versus SG.

Dato-DXd versus T-DXd

3.9. Given the submission did not include any relevant comparisons between Dato-DXd and T-DXd, their comparative efficacy and safety remain uncertain. The Committee acknowledged that Dato-DXd did not demonstrate a statistically significant OS benefit. However, the DESTINY-Breast04 trial showed that T-DXd led to statistically significant improvements compared with chemotherapy. Specifically, OS improved by 6.4 months and PFS by 4.7 months, in a subset of patients with HER2-low uBC or mBC who had progressed on one or two lines of prior chemotherapy. Local clinicians also considered the clinical benefit of T-DXd to be more meaningful than Dato-DXd.

Cost effectiveness

4.1. The Committee considered the results of the submission's cost-utility analysis that compared Dato-DXd with chemotherapy for treating HR-positive, HER2-negative uBC or mBC, based on the TROPION-Breast01 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	10 years in the model base case, based on a median follow-up of 9.7 months in the TROPION-Breast01 trial
Health states	Pre-progression; post-progression; death
Cycle length	3 weeks (21 days)
Extrapolation methods used to generate results	PFS: Dependent (within-trial) parametric curves (Dato-DXd, ICC =log-normal) OS: Independent parametric curves (Dato-DXd = constant HR TPP:0.84, ICC = Weibull) TTD: Independent parametric curves (Dato-DXd, ICC=Weibull) No treatment waning was applied in the base case. Sensitivity analysis assumed treatment waning to occur after 30 months.
Health-related quality of life	• Utilities for the pre-progression health state were treatment-specific utilities derived from cross-walked EQ-5D-3L data from TROPION-Breast01 trial (Dato-DXd = 0.760, ICC = 0.736) • Utilities for the post-progression health state were pooled utility value derived from the literature (=0.626)
Types of healthcare resources included	• Drug and drug administration • Disease management cost • Subsequent treatment costs • AE management costs • End-of-life care costs

Abbreviations: AE, adverse event; Dato-DXd, datopotamab deruxtecan; EQ-5D-3L, EuroQoL-5 Dimension-3 Level; HR, hazard ratio; ICC, investigators choice of chemotherapy; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; LY, life year; OS, overall survival; PFS, progression free survival; QALY, quality-adjusted life year; TPP, target product profile; TTD, time to treatment discontinuation.

4.2. The base-case incremental cost-effectiveness ratio (ICER) in the submission was between SG$205,000 and SG$245,000 per quality-adjusted life year (QALY) gained. However, the Committee considered the ICER to be uncertain and likely underestimated, given:

- The submission used an average weight of 55.4 kg and body surface area (BSA) of 1.57m^2, which were both lower than what is stated in the Singapore healthcare resource sheet. Using the higher weight of 60 kg and a BSA of 1.6m^2, as stated in the resource sheet, would result in a higher ICER.

- Inaccurate drug costs for both Dato-DXd and comparators were applied in the economic model, which underestimated the incremental costs of treatment with Dato-DXd, favouring the ICER.

4.3. The Committee considered the revised base case, which accounted for the abovementioned limitations in the company's model. Key changes to the economic model included standardising the patient weight and BSA, and applying accurate costs for Dato-DXd and comparators. These changes increased the ICER to between SG$285,000 and SG$325,000 per QALY gained.

4.4. The Committee noted that the key model drivers were the extrapolation of OS benefit for Dato-DXd compared to chemotherapy, the assumption of treatment waning, distribution of subsequent therapies and utility values in the progression-free health state. When these key drivers were varied in sensitivity analyses, the ICERs increased substantially to more than SG$365,000 per QALY gained.

4.5. Overall, the Committee considered that Dato-DXd did not represent a cost-effective use of healthcare resources for previously treated HR-positive, HER2-negative uBC 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 increase from between SG$1 million and SG$3 million in the first year, to between SG$3 million and SG$5 million in the fifth year of listing Dato-DXd on the MOH List of Subsidised Drugs for patients with HR-positive, HER2-negative uBC or mBC who had received prior ET and chemotherapy.

5.2. The Committee considered that the submission estimates and price-volume agreement (PVA) caps were uncertain and inadequate to manage the uncertainty in overall budget impact in the local setting.

Recommendations

6.1. Based on the evidence submitted, the Committee recommended not listing Dato-DXd on the MOH List of Subsidised Drugs for treating patients with HR-positive, HER2-negative uBC or mBC who have received prior ET and chemotherapy. The decision was based on the unfavourable clinical and cost effectiveness of Dato-DXd compared with chemotherapy, at the price proposed by the company.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Company-proposed clinical indication	Subsidy class	MediShield Life claim limit per month
Datopotamab deruxtecan powder for concentrate for solution for infusion 100 mg	Datopotamab deruxtecan for the treatment of adult patients with HR-positive, HER2-negative (IHC 0, IHC 1+ or IHC 2+/ISH-) breast cancer, who have received prior endocrine-based therapy and chemotherapy for unresectable or metastatic disease.	Not recommended for subsidy	Not recommended for MediShield Life claims

Abbreviations: IHC: immunohistochemistry; ISH: in situ hybridisation.