CADTH Reimbursement Review
Clinician Group Input Template

Clinician Group Input

CADTH Project Number: PC0 401-000
Generic Drug Name (Brand Name): trastuzumab deruxtecan T-DXd (Enhertu)
Indication: For the treatment of adult patients with unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining) breast cancer who have received at least one endocrine therapy in the metastatic setting.

Name of Clinician Group: REAL Alliance
Author of Submission: Dr. Christine Brezden-Masley

1. About Your Clinician Group

The Research Excellence, Active Leadership (REAL) Canadian Breast Cancer Alliance is an equitable standing nucleus committee of multi-disciplinary, clinical-academic oncologists across Canada and Breast Cancer Canada, a patient organization. Formed in December 2023 in recognition that a national ecosystem of leadership should address evidence-based guidance and recommendations for equitable breast cancer clinical management. REAL Alliance publishes national clinical consensus recommendations, routinely updated, for timely health policy, funding, and consistent clinical adoption based on research evidence and medical specialty expertise to ensure optimal outcomes for breast cancer patients across all provinces and territories in Canada.

2. Information Gathering

Our members met virtually and exchanged views via email to discuss our clinical recommendations for trastuzumab deruxtecan (T-DXd) in patients with hormone receptor positive (HR+), HER-2 low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining) advanced or metastatic-breast cancer which has progressed on endocrine-based therapy (ET). Our recommendations were compiled to reflect our clinical opinion as medical specialists in breast cancer on what we believe is best for our patients. Our opinion is based on literature review, level 1 data from clinical trials, and recent data releases from international congresses, as well as our collective clinical expertise. We urge Canada's Drug Agency (CDA) to consider our clinical recommendation as per the evidence in this document along with the submissions put forward by patient advocacy groups to make an informed decision regarding the place in therapy for T-DXd in patients with HR+ HER2-low/ultralow advanced or metastatic breast cancer who are ET ineligible due to disease progression on endocrine-based therapy. The collective expertise from this group equates to decades of clinical experience in the management of patients with breast cancer.

3. Current Treatments and Treatment Goals

HER2-directed therapy is locked behind chemo for HER2-low patients.

Historically, HER2 status in breast cancer was viewed through a binary lens—either positive or negative. However, it is now recognized that HER2 expression exists on a continuum. Tumours classified as HER2-negative include both those with no detectable HER2

expression (HER2 0) and those with minimal or low levels of HER2 expression, a group now defined as HER2-ultralow and low. This phenotype is characterized by a HER2 immunohistochemistry (IHC) score of 1+ or 2+ without HER2 gene amplification by in situ hybridization (ISH) or in the case of HER2-ultralow, IHC 0 with ISH positive membrane staining. While approximately 80% of breast cancers are HER2-negative by traditional criteria, it is estimated that nearly 65% of these fall into the HER2-low category and 25% in the HER2-ultralow category with the vast majority being in the hormone receptor-positive (HR+) subtype [1–5].

In HR+ metastatic breast cancer with low expression of HER2, treatment is initially guided by hormone receptor status [6]. The standard of care begins with ET, often an aromatase inhibitor combined with a CDK4/6 inhibitor. Subsequent lines of treatment may include PARP inhibitors for BRCA-mutated disease or single agent selective estrogen receptor degraders (SERDs) like fulvestrant, sometimes in combination with targeted therapies such as alpelisib or capivasertib for PIK3CA-mutated tumours. However, resistance to ET-based therapy is inevitable, and once this occurs, evidence-based options become limited with a transition to chemotherapy-based treatment.

Once the breast cancer is ET ineligible, treatment goals in HR+ metastatic breast cancer are to prolong progression-free and overall survival, maintain quality of life, minimize treatment-related toxicity, and—where possible—delay the use of conventional generic chemotherapy associated with poor outcomes. However, following ET ineligibility, the first HER2-targeted therapies studied in HER2-low disease failed to show benefit, leading to limited optimism about this approach [7,8]. As such, up until recently, chemotherapy was the only available approach following ET ineligibility for patients harboring a disease with low expression levels of HER2. Oral agents like capecitabine are often used for their convenience and tolerability, while more aggressive intravenous chemotherapy is reserved for patients with visceral or rapidly progressing disease. Unfortunately, these regimens are frequently associated with only modest efficacy which results in poor disease control—leading to a higher symptom burden from cancer itself and reduced quality of life.

Fortunately, the emergence of more potent agents, particularly antibody-drug conjugates (ADCs), revived interest in targeting tumours with low levels of HER2 expression. This culminated with trastuzumab deruxtecan (T-DXd), a HER2-directed ADC, in the DESTINY-Breast04 trial which demonstrated a clear benefit in HR+ HER2-low heavily pre-treated metastatic breast cancer [9]. And now, DESTINY-Breast06 trial is expected to move T-DXd to an earlier place in therapy for the treatment of patients with HR+ HER2-low and ultralow disease after ET-based therapy has been exhausted in the metastatic setting.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Need for a HR+ HER2-low-directed therapy before conventional generic chemotherapy

Chemotherapy has long been the default option for HR+ metastatic breast cancer with low HER2 expression following ET ineligibility. However, this strategy remains suboptimal: response rates to chemotherapy in this setting are typically low with nearly no complete response rates [9–11]. This leaves patients with limited options. Even if T-DXd can be used to salvage this response in a later line of therapy, reserving it for later may serve as a disservice to the management of the tumour and symptom burden. This is particularly concerning in patients with visceral disease, where rapid control of tumour burden is critical[12]. Furthermore, most conventional generic chemotherapy lacks evidence to meaningful delay of disease progression or overall survival.

Need for a HR+ HER2-ultralow directed therapy

An emerging critical unmet need lies in the management of HER2-ultralow disease, which currently falls outside the eligibility criteria for HER2-directed therapies used in highly HER2 positive breast cancer [1–5]. Currently, these patients are left with chemotherapy as their only immediate post-ET option, even though they harbor a distinct, targetable biological profile. This gap highlights the need to broaden therapeutic access and better align treatment options with emerging molecular understanding.

Overall

Current treatment options fail to maximize disease control in HR+ HER2-low and ultralow metastatic breast cancer while preserving quality of life in the immediate post-ET setting (i.e. first introduction of chemotherapy phase of treatment), and this is the case especially for patients with visceral disease. HER2-directed treatment options are needed for these patients.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

T-DXd outperforms chemotherapy immediately following ET treatment exhaustion in HER2-low and ultralow HR+ metastatic breast cancer

T-DXd is poised to significantly shift the treatment paradigm for patients with HR+ HER2-low or HER2-ultralow metastatic breast cancer following exhaustion of ET-based therapy. The 2024 update of the DESTINY-Breast06 trial demonstrated that T-DXd outperforms standard chemotherapy options—capecitabine, nab-paclitaxel, or paclitaxel—when used after ET-based therapy (i.e. single agent or combined with CDK4/6 inhibitor) in the metastatic setting, including in patients who were chemotherapy-naïve [11,13].

In the intention-to-treat (ITT) population—which included both HER2-low (n=713) and HER2-ultralow (n=153) patients—T-DXd significantly extended median progression-free survival (PFS) to 13.2 months compared to 8.1 months with chemotherapy (HR: 0.63; 95% CI: 0.53–0.75; p < .0001), representing a clinically meaningful gain of delaying disease by over five months (Figure 1). This magnitude of benefit is consistent with the results of DESTINY-Breast04, which evaluated T-DXd in a later-line setting in more heavily pre-treated patients [9]. In the HER2-ultralow subgroup, a similar trend in PFS benefit was observed (T-DXd: 13.2 months [95% CI: 9.8–17.3] vs. chemotherapy: 8.3 months [95% CI: 5.8–15.2]), although statistical significance was not reached—likely due to the smaller sample size —the numerical difference still represents a clinically relevant signal that supports treatment benefit in this population (Figure 1). The consistency across settings supports the rationale for earlier use, when patients are more likely to be fit, able to tolerate therapy, and derive maximum clinical benefit. Delaying access to the most effective available option may reduce this opportunity, as treatment attrition and declining performance status can prevent some patients from benefiting to this therapy in later lines. Early disease control can also help preserve quality of life and may favorably influence long-term outcomes. Accordingly, while overall survival (OS) data from DESTINY-Breast06 remains immature at a median follow-up of 18.6 months, the sustained PFS benefit and limited number of OS events suggest a potential for longer-term survival benefit with T-DXd that may emerge with further follow-up.

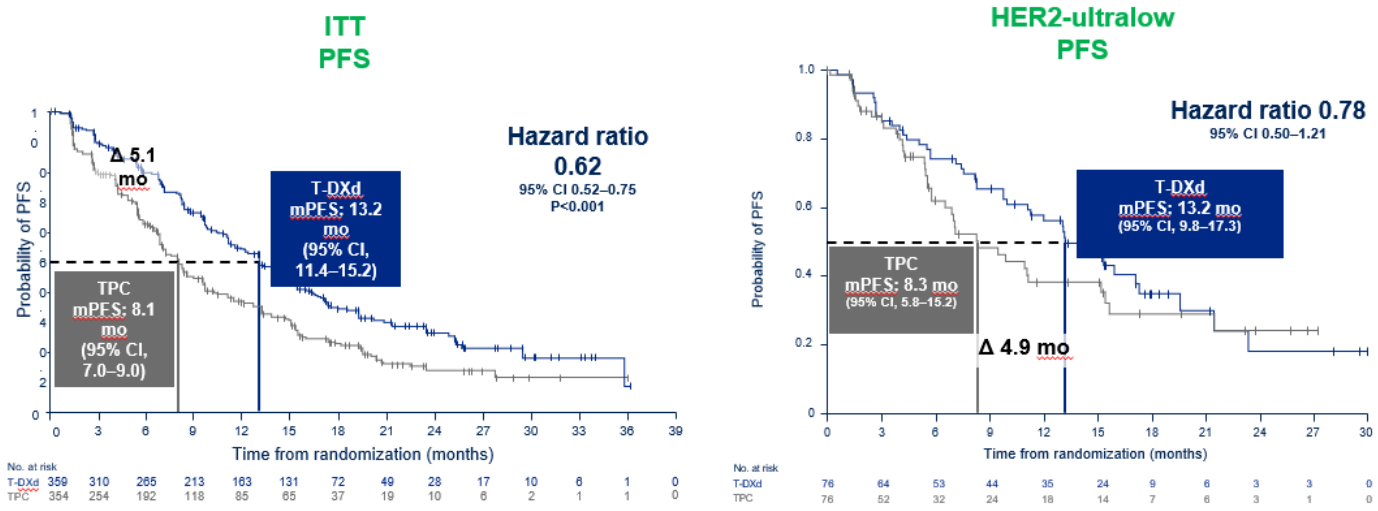

Figure 1. PFS in ITT (left) and HER2-ultralow (right) populations from DESTINY BREAST-06. For the HER2-ultralow data statistical significance was not tested, and the corresponding confidence interval for the hazard ratio was not adjusted for multiplicity. Figure adapted from *[11,13]*.

Importantly, **T-DXd nearly doubled the response rate compared to chemotherapy**, with a confirmed objective response rate (ORR) of 56.5% (95% CI: 51.2–61.7) versus 32.2% (95% CI: 27.4–37.3), respectively. These findings strongly support the early use of T-DXd immediately after endocrine therapy resistance, rather than defaulting to conventional generic chemotherapy.

Although overall survival (OS) data remains immature for DESTINY-Breast06 at the median follow-up of 18.6 months, the lack of early separation suggests patients who received T-DXd may be living longer.

T-DXd in patients with aggressive disease

Notably, **approximately 90% of the DESTINY Breast06 population had visceral disease**—a group historically underserved by existing chemotherapy options [11]. The improved PFS and higher ORR with T-DXd in this cohort highlight its potential to address this critical unmet need. In addition, the clinical benefits of T-DXd were also consistent across key subgroups, including those defined by the number of metastatic sites, time to progression on first-line ET, and type of endocrine resistance. These findings support consistent efficacy of T-DXd across diverse HR+ HER2-low/ultralow patient profiles.

Safety is as expected

From a safety standpoint, **no new concerns emerged in DESTINY Breast06 compared to previous trials using T-DXd**. Interstitial lung disease (ILD)/pneumonitis remains the most important adverse event of special interest. However, clinicians have increasing experience managing this risk given the broader use of T-DXd in HER2-positive disease. Furthermore, multiple international and country-specific guidelines—including Canadian-specific recommendations—are now available to support early recognition and management of ILD in clinical practice [14].

Overall

Overall, the DESTINY Breast06 results support the positioning of T-DXd as the preferred option over chemotherapy in HR+ HER2-low and ultralow disease immediately following ET-based therapy resistance, particularly in patients with visceral involvement with superior efficacy, manageable safety, and consistent benefit across subgroups compared to conventional generic chemotherapy. Reflecting this, **T-DXd has recently received expanded approval in both Europe [15] and the United States [16]** for use in the metastatic setting without the prior requirement of chemotherapy, and in both HER2-low and ultralow populations—further reinforcing its growing role in clinical practice.

Thus, based on the results of DESTINY-Breast-06 and our clinical experience, we recommend that T-DXd be made available as a treatment option immediately after endocrine therapy resistance in the transition to first chemotherapy treatment for patients with HR+/HER2-low or ultralow advanced or metastatic breast cancer [11].

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

We recommend T-DXd in patients with HR+/HER2-low or ultralow advanced or metastatic breast cancer who have exhausted endocrine-therapy having had at least one prior ET-based treatment in the advanced setting. This population has been shown to clearly derive PFS and ORR benefits [11]. We also recommend this target population where progression of disease is within 24 months on adjuvant ET.

Least suitable patient populations would include those ineligible for the DESTINY Breast06 study or whom have a contraindication to T-DXd. [11,17]

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Monitoring for recurrence would occur when clinically indicated, as per the current standard of care for post-ET setting.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

T-DXd therapy should be discontinued at the first evidence of disease progression or in the case of persistent toxicity, as per the product monograph.

5.5 What settings are appropriate for treatment with drug under review? Is a specialist required to diagnose, treat, and monitor patients who might receive drug under review?

Oncologists with experience in treating breast cancer patients are required for the treatment recommendation and monitoring of T-DXd therapy.

6. Additional Information

Scoring HER2 expression across the full spectrum (including HER2-low and ultralow)

The 2023 ASCO/CAP guideline update provides additional clarity for reporting HER2 IHC 1+, IHC 2+/ISH– results, and outlines best practices for distinguishing HER2-low and ultralow from truly HER2-negative disease [5]. While HER2-low tumors can often be inferred from current reporting, HER2-ultralow status is not routinely captured in clinical practice. The updated guidelines aim to support more precise classification by encouraging standardized scoring criteria and the adoption of higher-sensitivity assays. Importantly, these refinements can be integrated into existing pathology infrastructure, with the added emphasis on more sensitive and standardized interpretation—leveraging assays and scoring tools that are now available.

.

References

1. Chen, Z.; Jia, H.; Zhang, H.; Chen, L.; Zhao, P.; Zhao, J.; Fu, G.; Xing, X.; Li, Y.; Wang, C. Is HER2 Ultra-Low Breast Cancer Different from HER2 Null or HER2 Low Breast Cancer? A Study of 1363 Patients. *Breast Cancer Res. Treat.* **2023**, *202*, 313–323, doi:10.1007/s10549-023-07079-8.
2. Denkert, C.; Seither, F.; Schneeweiss, A.; Link, T.; Blohmer, J.-U.; Just, M.; Wimberger, P.; Forberger, A.; Tesch, H.; Jackisch, C.; et al. Clinical and Molecular Characteristics of HER2-Low-Positive Breast Cancer: Pooled Analysis of Individual Patient Data from Four Prospective, Neoadjuvant Clinical Trials. *Lancet Oncol.* **2021**, *22*, 1151–1161, doi:10.1016/S1470-2045(21)00301-6.
3. Schettini, F.; Chic, N.; Brasó-Maristany, F.; Paré, L.; Pascual, T.; Conte, B.; Martínez-Sáez, O.; Adamo, B.; Vidal, M.; Barnadas, E.; et al. Clinical, Pathological, and PAM50 Gene Expression Features of HER2-Low Breast Cancer. *NPJ Breast Cancer* **2021**, *7*, 1, doi:10.1038/s41523-020-00208-2.
4. Tarantino, P.; Hamilton, E.; Tolaney, S.M.; Cortes, J.; Morganti, S.; Ferraro, E.; Marra, A.; Viale, G.; Trapani, D.; Cardoso, F.; et al. HER2-Low Breast Cancer: Pathological and Clinical Landscape. *J. Clin. Oncol.* **2020**, *38*, 1951–1962, doi:10.1200/JCO.19.02488.
5. Wolff, A.C.; Somerfield, M.R.; Dowsett, M.; Hammond, M.E.H.; Hayes, D.F.; McShane, L.M.; Saphner, T.J.; Spears, P.A.; Allison, K.H. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: ASCO–College of American Pathologists Guideline Update. *J. Clin. Oncol.* **2023**, *41*, 3867–3872, doi:10.1200/JCO.22.02864.
6. Canada's Drug Agency Provisional Funding Algorithm Available online: https://www.cda-amc.ca/sites/default/files/DRR/2024/PH0053-HRPositive-HER2-Breast-Cancer.pdf.
7. Gianni, L.; Lladó, A.; Bianchi, G.; Cortes, J.; Kellokumpu-Lehtinen, P.-L.; Cameron, D.A.; Miles, D.; Salvagni, S.; Wardley, A.; Goeminne, J.-C.; et al. Open-Label, Phase II, Multicenter, Randomized Study of the Efficacy and Safety of Two Dose Levels of Pertuzumab, a Human Epidermal Growth Factor Receptor 2 Dimerization Inhibitor, in Patients with Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2010**, *28*, 1131–1137, doi:10.1200/JCO.2009.24.1661.
8. Fehrenbacher, L.; Cecchini, R.S.; Geyer, C.E.; Rastogi, P.; Costantino, J.P.; Atkins, J.N.; Crown, J.P.; Polikoff, J.; Boileau, J.-F.; Provencher, L.; et al. NSABP B-47/NRG Oncology Phase III Randomized Trial Comparing Adjuvant Chemotherapy With or Without Trastuzumab in High-Risk Invasive Breast Cancer Negative for HER2 by FISH and With IHC 1+ or 2. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2020**, *38*, 444–453, doi:10.1200/JCO.19.01455.
9. Modi, S.; Jacot, W.; Yamashita, T.; Sohn, J.; Vidal, M.; Tokunaga, E.; Tsurutani, J.; Ueno, N.T.; Prat, A.; Chae, Y.S.; et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. *N. Engl. J. Med.* **2022**, *387*, 9–20, doi:10.1056/NEJMoa2203690.

10. Jhaveri, K.; Marmé, F. Current and Emerging Treatment Approaches for Hormone Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer. *Cancer Treat. Rev.* **2024**, *123*, 102670, doi:10.1016/j.ctrv.2023.102670.
11. Bardia, A.; Hu, X.; Dent, R.; Yonemori, K.; Barrios, C.H.; O'Shaughnessy, J.A.; Wildiers, H.; Pierga, J.-Y.; Zhang, Q.; Saura, C.; et al. Trastuzumab Deruxtecan after Endocrine Therapy in Metastatic Breast Cancer. *N. Engl. J. Med.* **2024**, *391*, 2110–2122, doi:10.1056/NEJMoa2407086.
12. Mosele, F.; Stefanovska, B.; Lusque, A.; Tran Dien, A.; Garberis, I.; Droin, N.; Le Tourneau, C.; Sablin, M.-P.; Lacroix, L.; Enrico, D.; et al. Outcome and Molecular Landscape of Patients with PIK3CA-Mutated Metastatic Breast Cancer. *Ann. Oncol. Off. J. Eur. Soc. Med. Oncol.* **2020**, *31*, 377–386, doi:10.1016/j.annonc.2019.11.006.
13. Curigliano, G.; Hu, X.; Dent, R.A.; Yonemori, K.; Barrios, C.H.; O'Shaughnessy, J.; Wildiers, H.; Zhang, Q.; Im, S.-A.; Saura, C.; et al. Trastuzumab Deruxtecan (T-DXd) vs Physician's Choice of Chemotherapy (TPC) in Patients (Pts) with Hormone Receptor-Positive (HR+), Human Epidermal Growth Factor Receptor 2 (HER2)-Low or HER2-Ultralow Metastatic Breast Cancer (mBC) with Prior Endocrine Therapy (ET): Primary Results from DESTINY-Breast06 (DB-06). *J. Clin. Oncol.* **2024**, *42*, LBA1000–LBA1000, doi:10.1200/JCO.2024.42.17_suppl.LBA1000.
14. Henning, J.-W.; Brezden-Masley, C.; Gelmon, K.; Chia, S.; Shapera, S.; McInnis, M.; Rayson, D.; Asselah, J. Managing the Risk of Lung Toxicity with Trastuzumab Deruxtecan (T-DXd): A Canadian Perspective. *Curr. Oncol. Tor. Ont* **2023**, *30*, 8019–8038, doi:10.3390/curroncol30090582.
15. Enhertu Approved in the EU as First HER2-Directed Therapy for Patients with HR-Positive, HER2-Low or HER2-Ultralow Metastatic Breast Cancer Following at Least One Endocrine Therapy Available online: https://www.astrazeneca.com/media-centre/press-releases/2025/enhertu-approved-in-eu-in-post-et-breast-cancer.html (accessed on 14 May 2025).
16. Research, C. for D.E. and FDA Approves Fam-Trastuzumab Deruxtecan-Nxki for Unresectable or Metastatic HR-Positive, HER2-Low or HER2-Ultralow Breast Cancer. *FDA* **2025**.
17. AstraZeneca Canada Inc. ENHERTU (Trastuzumab Deruxtecan) Product Monograph. 2024.