Clinician Group Input

Project Number: PC0471-000
Generic Drug Name (Brand Name): Trastuzumab Deruxtecan (ENHERTU)

Indication: Enhertu (trastuzumab deruxtecan) followed by THP (a taxane, trastuzumab, and pertuzumab) is indicated for the neoadjuvant treatment of adult patients with HER2-positive Stage II or III breast cancer.

Name of Clinician Group: REAL Canadian Breast Cancer Alliance

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1. About Your Clinician Group

Research Excellence, Active Leadership Canadian Breast Cancer Alliance (REAL Alliance) is an equitable standing nucleus committee of multi-disciplinary, clinical-academic oncologists across Canada and Breast Cancer Canada, a patient advocacy 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

REAL Alliance exchanged views by first forming a sub-committee to review the evidence in this indication. Then the national nucleus committee reviewed the sub-committee recommendations. Finally three rounds of Delphi consensus voting was conducted. The role of trastuzumab deruxtecan (T-DXd) in the neoadjuvant treatment of patients with high-risk HER2-positive early-stage breast cancer was discussed, among other areas of HER2+ breast cancer. REAL Alliance has published current recommendations for neoadjuvant treatment in people diagnosed with HER2+ breast cancer [1]. Our clinical input for this submission is informed primarily by the phase III DESTINY-Breast11 trial and its published results [2].

DESTINY-Breast11 directly compared a neoadjuvant T-DXd-based strategy in patients with high-risk, early-stage HER2-positive breast cancer, which consisted of four cycles of T-DXd followed by four cycles of paclitaxel, trastuzumab, and pertuzumab (T-DXd-THP arm) compared to dose-dense doxorubicin plus cyclophosphamide followed by THP (ddAC-THP arm). The trial also evaluated T-DXd alone; however, enrolment to this arm was stopped early following an Independent Data Monitoring Committee recommendation because of a lower pathologic complete response (pCR) rate and a low likelihood that T-DXd alone would demonstrate superiority over the comparator. The decision was not based on a new safety finding.

The collective expertise from this national group of breast oncology experts equates to decades of clinical experience in the management of patients with breast cancer.

3. Current Treatments and Treatment Goals

About High-Risk HER2-Positive Early Breast Cancer in Canada

Aggressiveness and Outcomes: HER2-positive early breast cancer is a **biologically aggressive subtype**, particularly when patients present with l**arge primary tumours** and/or **lymph-node involvement.** These patients continue to be at **high risk of recurrence** despite modern HER2-directed treatment. Patients with larger tumours

(Stage ≥T3) or with nodal involvement (N1-3) must be treated with **neoadjuvant chemotherapy + HER2-targeted therapy** prior to surgery in order to shrink the tumour and downstage the axilla. The goal of such treatment is cure, with the intermediate goal being **pathological complete response (pCR)**. Patient outcomes are more favourable in those experiencing a pCR and many studies have shown that pCR is a surrogate endpoint of long-term efficacy [3–5].

Importance of Pathological Complete Response: Neoadjuvant treatment provides an opportunity to assess how effectively a tumour responds before surgery. pCR, defined as *no evidence of invasive tumour or nodal disease after neoadjuvant treatment as assessed by pathologic staging*, is an important endpoint in HER2-positive early breast cancer. It is well-established that achieving **pCR** is associated with **improved event-free survival (EFS)** for patients [3–5].

REAL Alliance stated the following in Kumar et al. 2026: *"pCR not only helps avoid the morbidity of axillary lymph node dissection but is also a clinically validated surrogate for long-term outcomes in HER2+ disease, including EFS and overall survival (OS). In practical terms, patients whose **disease achieves a pCR have substantially fewer recurrences and deaths,** making pCR a meaningful short-term treatment goal associated with favourable long-term outcomes."* Therefore, pCR serves as a critical prognostic tool in clinical practice and a recognized endpoint for evaluating neoadjuvant therapies in clinical trials [3–5]. However, there is a need for new neoadjuvant treatment options because only **39%-64% of patients have a pCR with current standard of care [2].** Furthermore, approximately **20% of patients** with HER2+ early-stage breast cancer who have residual disease (i.e., not pCR) after neoadjuvant treatment **will experience a recurrence** in their disease after 3 years [6].

Current Care Standards & Limitations - Efficacy: There has been some discussion about 6 cycles of docetaxel-carboplatin-trastuzumab-pertuzumab (TCHP) being a more contemporary/appropriate control arm for the DESTINY-Breast11 study. In trials such as KRISTINE, which evaluated non-anthracycline dual HER2-blockade regimens, TCHP achieved a pCR rate of 55.7%, comparable to the pCR rate observed with ddAC-THP in high-risk populations (56.3%) [2,7]. TCHP is associated with less risk of cardiotoxicity but is generally regarded as a treatment that is more difficult to tolerate than ddAC-THP (in the KRISTINE trial, ≥ grade 3 toxicity was 64%).

While non-anthracycline regimens (like TCHP) are sometimes chosen on a case-by-case basis to avoid cardiotoxicity, ddAC-THP represents the current standard benchmark in high-risk disease. Anthracycline-based regimens (like ddAC-THP) have historically yielded robust rates of pCR and long-term EFS and OS data in high-risk early HER2+ breast cancer [1,8]. Due to these long-term survival outcomes, anthracycline-containing sequential regimens became the standard priority recommendation in Canadian practice for high-risk, node-positive or large-tumour HER2+ early breast cancer and is the relevant comparator for contemporary clinical trials, like DESTINY-Breast11 discussed below.

Of note, the current standard treatment includes an adjuvant component after surgery. For the patient who experiences a pCR after neoadjuvant therapy based on pathological response, adjuvant treatment to complete trastuzumab for 1 year after surgery based on the HERA trial [9]. For patients who do not experience pCR, adjuvant treatment is with an anti-body drug conjugate, T-DM1, x 14 cycles based on the results of the KATHERINE trial [10].

Current Care Standards & Limitations - Toxicity: The adverse events associated with ddAC-THP include fatigue (54.8%) and neutropenia (44.2%; 34.6% for Grade ≥ 3). There is a risk of febrile neutropenia, necessitating routine primary G-CSF prophylaxis. Other common toxicities include stomatitis (27.6%) and peripheral neuropathy (20.8%) [2].

Adverse events that are particularly worrisome both for patients and clinicians are **cardiotoxicity** and **secondary malignancies**. Real-world pharmacovigilance data confirms early-stage anthracycline combination regimens (like ddAC-THP) carry **4 to 6 times higher odds of heart failure** than anthracycline-free regimens (see Figure 1) [11] .

Across large-scale breast cancer cohorts utilizing regimens like ddAC-THP, the long-term cumulative incidence of therapy-related myeloid neoplasms, including myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), stays low but significantly elevated at ~0.3% to 0.8% [12]. While the absolute risk is small, these secondary

malignancies have a notably poor prognosis, often carrying an overall survival timeline of just 8 to 10 months from diagnosis, severely altering long-term survivorship.

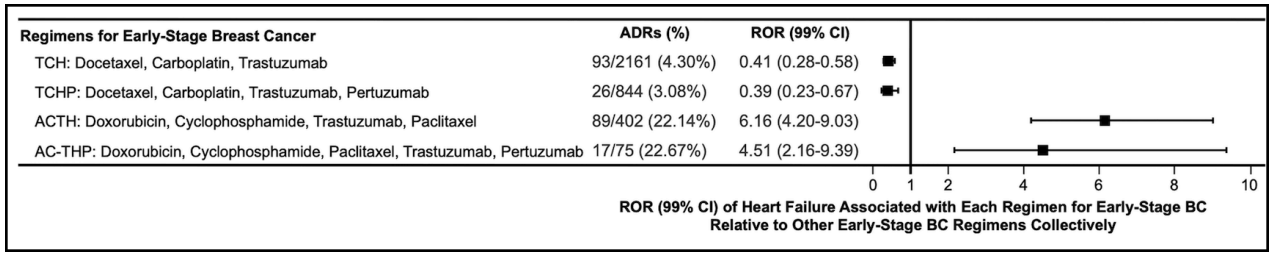


Figure 1: World Health Organization pharmacovigilance analysis for heart failure odds associated with chemotherapy and HER2-directed regimens for HER2+ breast cancer. Waliany S et al. JACC 2023 [11]

Treatment Goals: The main goal of treatment for Stage II-III HER2+ breast cancer is **cure.** This is achieved by neoadjuvant treatment before surgery, surgery, and adjuvant treatment based on the pathological response. Additional goals of curative-intent therapy include:

- **Maximizing Tumour Eradication and Recurrence-Free Survival**: Achieving a deep pathological response, reduces residual tumour burden and serves as a validated prognostic indicator for improved EFS [1,3–5].
- **Addressing Treatment Toxicity While Maintaining Efficacy**: Managing the toxicity associated with treatment is essential to reduce treatment interruptions and maintain curative-intent efficacy.
- **Preserving Surgical Readiness and Quality of Life**: Ensuring treatment tolerability such that patients proceed to definitive surgery without AE-related delay or cancellation, ideally within 4 to 6 weeks, and a maximum up to 8 weeks, of the last treatment dose. (Intervals longer than 8 weeks have been associated with worse survival outcomes, particularly in patients with residual disease [13–15].
- **Improvement in Surgical and Radiation Morbidity & Increase in Surgical Resectability:** Ensuring reduction of the extent of surgery and radiotherapy. Tumour and nodal downstaging after neoadjuvant therapy increases the eligibility of breast-conserving surgery and axillary surgical de-escalation, with omission of axillary lymph node dissection for those experiencing pCR [16; 17]. In the presence of a nodal complete response, axillary radiotherapy can often also be safely avoided [18]. Thus, a curative intent approach with the use of neoadjuvant therapy lowers the risk of lymphedema, neuropathy, and other arm comorbidities, without increasing the risk of other perioperative complications (i.e., hemorrhage, infections etc) [19].
- **Decreasing Toxicity of Additional Adjuvant Therapy:** The current standard of care for patients with residual disease after neoadjuvant therapy is to receive 10 months of T-DM1. This is associated with increased toxicity and cost compared to the approximately 6 months of adjuvant trastuzumab that is the current standard in the presence of pCR [10]. A neoadjuvant treatment that can increase pCR decreases the need for intensified therapy in the adjuvant 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.

Unmet Need in High-Risk Disease in the Neoadjuvant Setting

Unmet Need in High-Risk Subgroups:

Although taxane-anthracyline chemotherapy and HER2-targeted treatments can be effective, pCR is not achieved for all patients receiving current neoadjuvant treatment. Estimates note that historical pCR rates with standard neoadjuvant regimens have generally ranged from 39% to 64%, while ~20% of patients with residual disease after neoadjuvant therapy can expect to experience a recurrence at 3 years [2,6].

Furthermore, conventional chemotherapy regimens can add substantial toxicity, including (depending on the drug) risks such as cardiotoxicity, febrile neutropenia, surgical complications, neuropathy, and hematologic adverse events. Secondary malignancies are of concern as the life expectancy is often months after such a diagnosis [12].

For clinicians and patients, there is therefore an important unmet need for neoadjuvant approaches that can achieve a high rate of tumour eradication while reducing some of the toxicity associated with conventional chemotherapy.

5. Place in Therapy (Meeting the unmet need)

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

Addressing the Unmet Need: DESTINY-Breast11 Clinical Trial:

The drug under review is trastuzumab deruxtecan (T-DXd), which was evaluated in DESTINY-Breast11 phase III randomized clinical trial to address the unmet needs mentioned in Section 4.

DESTINY-Breast11 evaluated whether replacing the anthracycline-containing portion of neoadjuvant treatment with T-DXd could improve tumour eradication before surgery and reduce the toxicity burden associated with anthracycline-based neoadjuvant therapy [2].

Demographic and Clinical Risk Considerations: DESTINY-Breast11 specifically studied patients with previously untreated, locally advanced or inflammatory HER2-positive early breast cancer with ≥cT3 cN0 or any cT with cN1–3 disease. **This population represents patients for whom effective systemic treatment before surgery is particularly important because of the higher baseline risk associated with large primary tumours and/or nodal involvement.** The experimental treatment was T-DXd 5.4 mg/kg intravenously every 3 weeks x 4 cycles followed by paclitaxel, trastuzumab, and pertuzumab (THP) x 4 cycles, given prior to surgery, known as the **T-DXd-THP arm**. The comparator treatment was doxorubicin + cyclophosphamide x 4 cycles followed by THP x 4 cycles, given prior to surgery, known as the **ddAC-THP arm**.

A total of 927 patients were randomised. The median age was 50 years; 47.9% of patients were Asian, and 44.9% were White; 49.2% had stage II disease, and 50.4% had stage III disease. Most patients (72.9%) had hormone receptor-positive disease, while 26.8% had hormone receptor-negative disease. Importantly, 88.7% had node-positive disease, and 43.8% had cT3–4 tumours, reinforcing that DESTINY-Breast11 included a population with substantial clinical risk. Notably, DESTINY-Breast11 eligibility criteria also included those with inflammatory breast cancer (cT4d), a distinct group with a particularly poor prognosis.

DESTINY-Breast11 Efficacy:

Significantly Higher Pathological Complete Response:
The primary endpoint of the trial was pCR (defined as the complete absence of invasive cancer cells in the breast tissue and lymph nodes removed during surgery). As noted above, patient outcomes are more favourable in those experiencing a pCR and many studies have shown that pCR is a surrogate endpoint of long-term efficacy.

- **T-DXd-THP:** Achieved a 67.3% pCR rate
- **ddAC-THP:** Achieved a 56.3% pCR rate
- This represents a statistically and clinically meaningful absolute improvement of 11.2% (P=0.003)

In **HR-positive disease, pCR was 61.4% for T-DXd-THP versus 52.3% for ddAC-THP**; in **HR-negative disease, 83.1% for T-DXd-THP versus 67.1% ddAC-THP** (see Figure 1). [2]

Deeper Pathological Response (Residual Cancer Burden):
Residual cancer burden (RCB) is another parameter used in clinical trials and measures the volume of tumour left behind after neoadjuvant therapy. RCB-0 is the same as pCR. RCB-1 refers to minimal residual burden and is associated with excellent long-term outcomes [20]. Analysis of RCB, showed that patients on T-DXd-THP regimen had a deeper response prior to surgery.

- 81.3% of patients in the T-DXd-THP arm achieved an RCB 0 or 1 (meaning minimal to no residual disease at the time of surgery) compared to 69.1% in the ddAC-THP arm

Event-Free Survival:
The secondary EFS analysis was immature (4.5% maturity at the data cutoff), with an early hazard ratio of 0.56 (95% CI 0.26–1.17) and 2-year EFS rates of 96.9% versus 93.1%, respectively. These findings present a favourable trend with the use of T-Dxd-THP with mature 3-year data release anticipated during this HTA review period [2].

Overall, DESTINY-Breast11 demonstrated that T-DXd-THP can increase pathologic response before surgery compared with an anthracycline-containing neoadjuvant regimen in a high-risk HER2-positive population. The magnitude of pCR improvement was consistent across all subgroups (see Figure 2).

Given that approximately 90% of patients in DESTINY-Breast11 presented with node-positive disease, achieving a higher rate of pCR with neoadjuvant T-DXd-THP provides critical locoregional benefit by facilitating axillary downstaging and helping avoid the morbidity of formal axillary lymph node dissection. Furthermore, maximizing pCR reduces the proportion of patients requiring escalated adjuvant systemic therapy (i.e., T-DM1 or T-DXd), thereby minimizing treatment-related toxicity and cost during the adjuvant treatment phase.

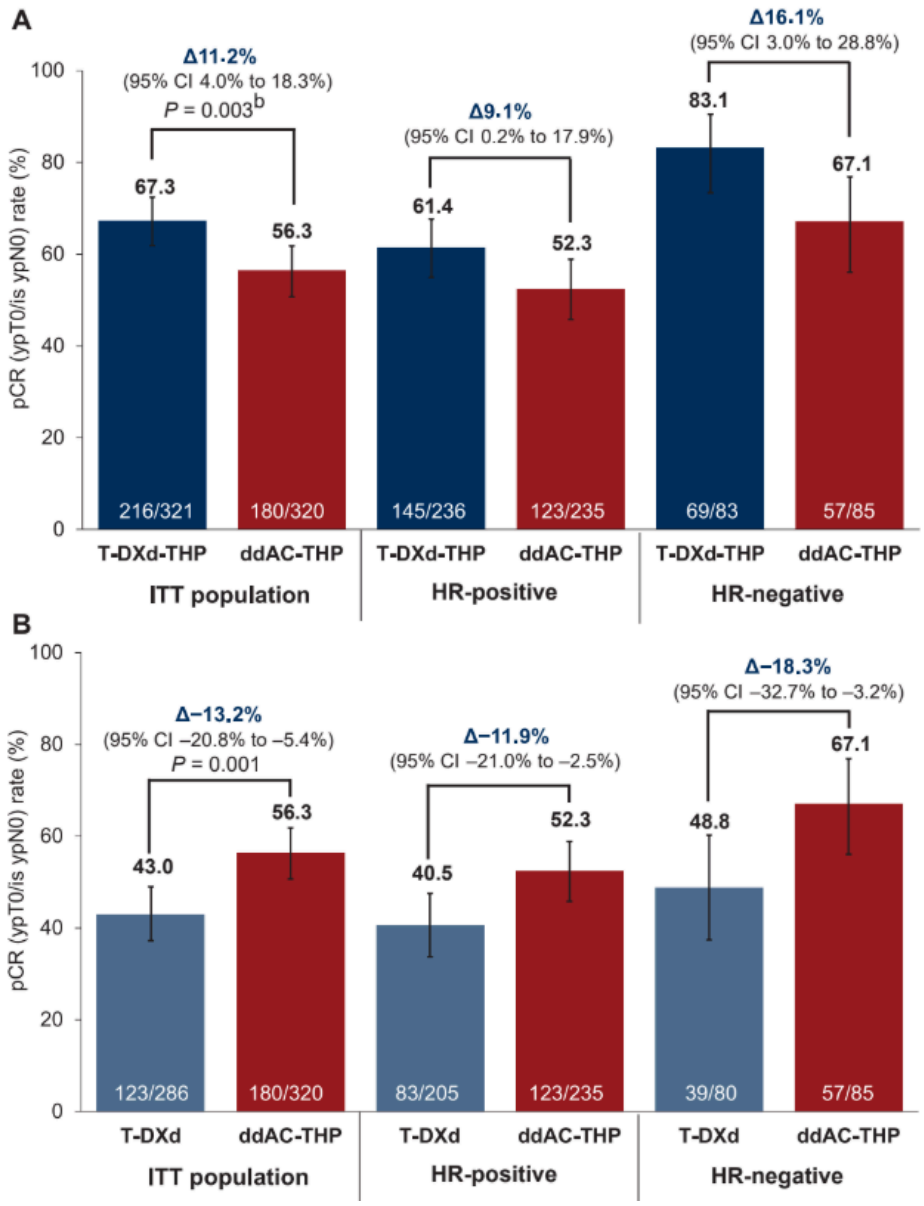


Figure 2 [2]: Pathological complete response rates in DESTINY-Breast11, T-DXd-THP versus ddAC-THP

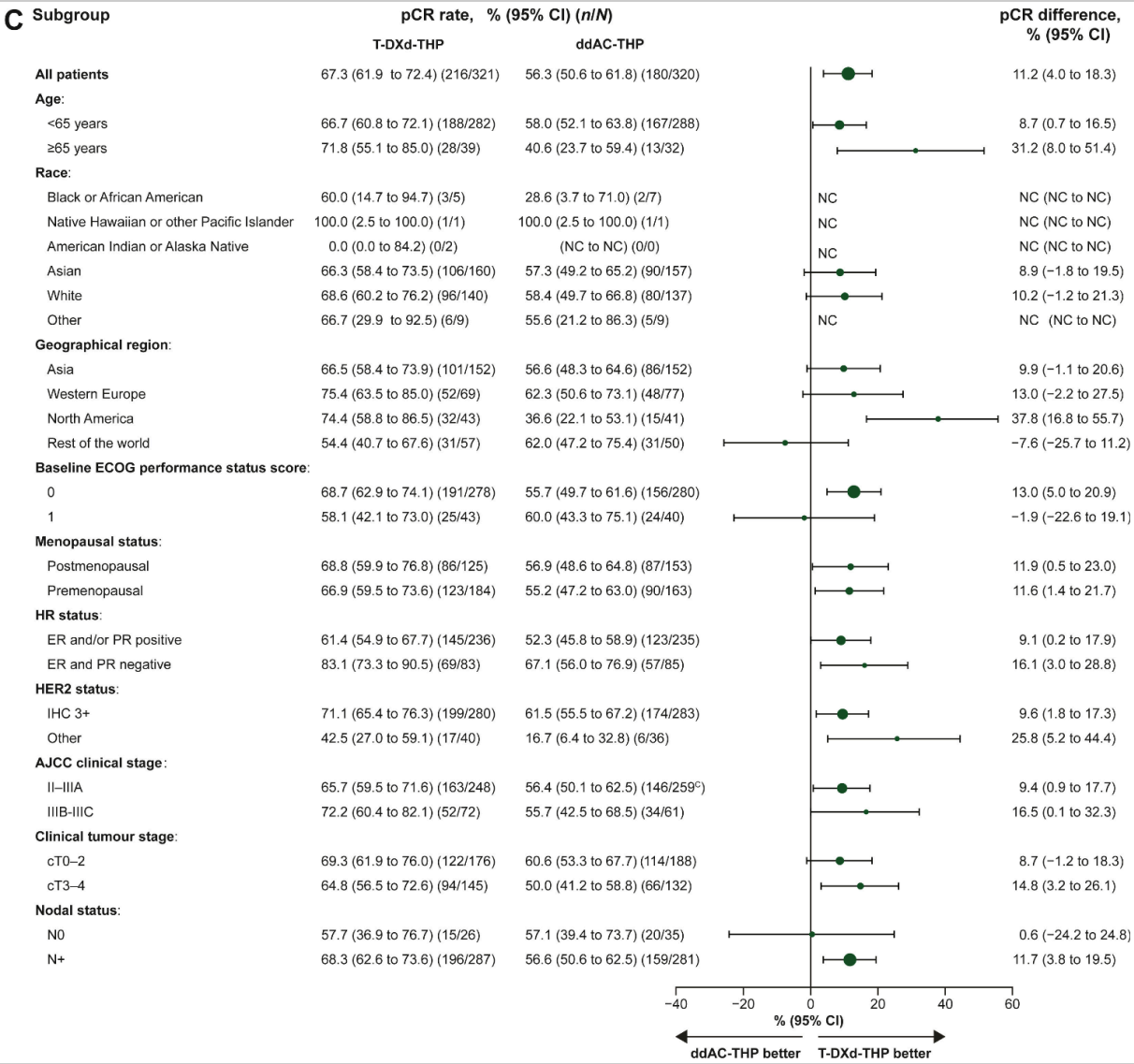


Figure 3 [2]: DESTINY-Breast11 trial subgroups pCR rate

Safety:

While ddAC-THP has historically served as the efficacy benchmark in high-risk early HER2+ breast cancer, the clinical utility is severely limited by substantial acute toxicity and long-term organ damage. DESTINY-Breast11 demonstrates that replacing the anthracycline component with four cycles of T-DXd (T-DXd-THP) not only increases complete pathologic response (pCR 67.3% vs. 56.3%), but also significantly improves overall patient safety and treatment tolerability.

Reduction in Severe Toxicities & Health Resource Utilization:

- **Fewer High-Grade Adverse Events:** Severe adverse events (Grade ≥ 3) occurred in **37.5%** of patients in the T-DXd-THP arm compared to **55.8%** in the ddAC-THP arm.
- **Halving of Serious Adverse Events:** Serious adverse events were reduced by nearly 50% in the T-DXd-THP arm (**10.6% vs. 20.2%**).
- **Fewer Treatment Interruptions:** Treatment interruptions due to adverse events occurred in **37.8%** of patients on T-DXd-THP versus **54.5%** on ddAC-THP, preserving treatment and thus efficacy.

Sparing Patients Irreversible Cardiotoxicity and Secondary Malignancies:

- **Cardiac Safety:** Left-ventricular dysfunction occurred in **1.3%** of patients receiving T-DXd-THP compared to **6.1%** with ddAC-THP. By eliminating anthracyclines, T-DXd-THP substantially reduces the lifelong risk of cumulative cardiomyopathy and heart failure.
- **Secondary Malignancy Risk:** Eliminating anthracyclines likely substantially reduces the established 0.3%–0.8% risk of therapy-related myeloid neoplasms (MDS/AML), preserving long-term survivorship.

Favourable Hematologic Profile:

- Rates of Grade ≥ 3 neutropenia were dramatically lower with T-DXd-THP (**13.8% vs. 34.6%** with ddAC-THP), as were Grade ≥ 3 anemia (**1.6% vs. 8.7%**) and leukopenia (**4.4% vs. 13.1%**). There is a cost-saving when hematological support (i.e., G-CSF) is not needed.

Manageable Interstitial Lung Disease (ILD) Risk:

- Adjudicated drug-related ILD/pneumonitis rates were low and comparable across arms (**4.4% for T-DXd-THP vs. 5.1% for ddAC-THP**), with Grade ≥ 3 events occurring in only **0.6%** of T-DXd-THP patients. Fixed 4-cycle neoadjuvant dosing minimizes cumulative exposure, making the safety profile predictable and manageable under the existing standard monitoring protocols already in place.

In addition to the above, we note that DESTINY-Breast11 reported 97.2% of patients in the T-DXd-THP arm successfully underwent surgery following neoadjuvant therapy, compared to 93.7% in the standard ddAC-THP group.

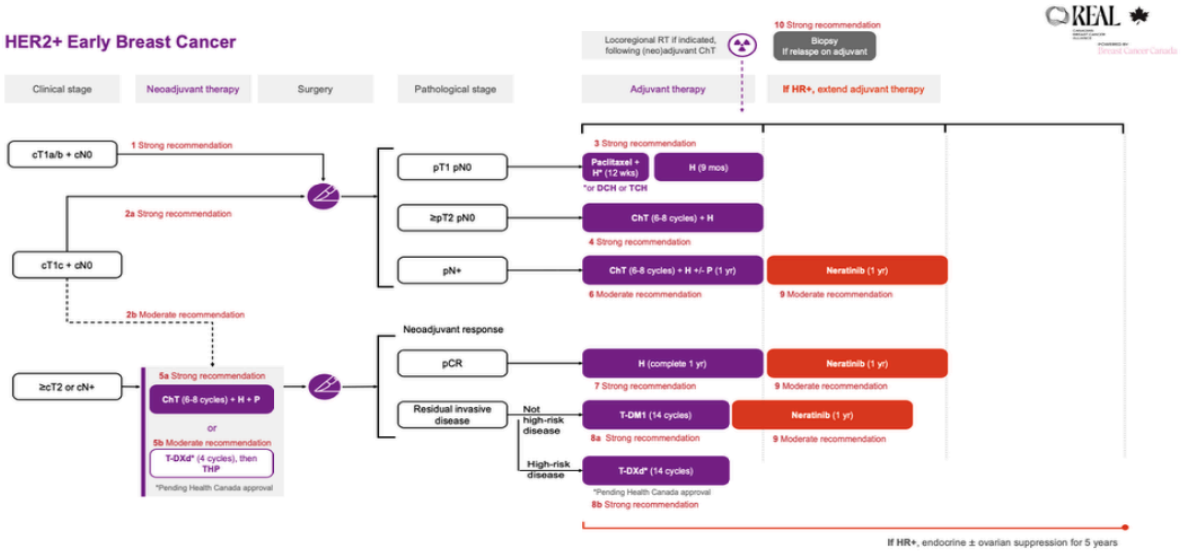
Adjuvant treatment is unchanged based on DESTINY-Breast11 and would be the same as noted in Section 3.

Place in therapy:

REAL Alliance highlights T-DXd-THP as a key neoadjuvant treatment option for patients with high-risk disease meeting the eligibility criteria of DESTINY-Breast11, as reflected in Recommendation 5 and the treatment algorithm of the 2025 update [clinical tumour stage of ≥cT3 and cN0-3, or primary tumour of any size with positive lymph node involvement (any cT and cN1-3)] [1]. REAL Alliance discussed the strength of the evidence and the group's confidence in application to clinical practice. The clinical magnitude of the pre-specified interim data release with significant surgical completion rates and pCR in notably higher-risk stage II/III patients (e,g. bulky disease, nodal involvement) is such that REAL Alliance agreed a clinical recommendation in the 2025 update was warranted based on conference-reported data. The grading of "Moderate Recommendation" was due to the fact that the reported data was in abstract form at the time of the REAL Alliance HER2 Update publication. Since then, the DESTINY-Breast11 full data set has been published in a peer-reviewed journal [2]. With the DESTINY-Breast11 publication, REAL Alliance continues to support the adoption of TDX-d in neoadjuvant therapy based on current peer-reviewed data. REAL Alliance conducts ongoing reviews to consider additional data releases, and global regulatory and HTA filings through 2026. REAL Alliance reviews and publishes updates to the recommendations on a yearly basis and thus this recommendation will be reviewed and revised according to the current body of evidence available in 2026.

5 **Recommendation updated in 2025**	*≥cT2 or cN+* **For patients with HER2+ early breast cancer with ≥cT2 or those with nodal disease (cN+),** the standard of care is neoadjuvant therapy. Treatment options are: (a) Trastuzumab + pertuzumab + chemotherapy (taxane backbone preferred); (b) For those meeting DESTINY-Breast11 criteria *, T-DXd † followed by trastuzumab + pertuzumab + taxane. * cT3 and cN0–3 or cT and cN1–3 † Pending Health Canada approval	Strong recommendation ●●● Moderate recommendation ●●

REAL Alliance: Kumar et al 2026 [1]



REAL Alliance: Kumar et al 2026 [1]

Take-home message on place in therapy:

T-DXd–THP represents an important advancement as an anthracycline-sparing alternative to standard ddAC-THP for curative-intent, high-risk HER2-positive early breast cancer while significantly improving surgical pCR rates and 2-year EFS efficacy outcomes and contributing favorable toxicity rates to current SOC.

The results of DESTINY-Breast11 show that a short four-cycle induction of T-DXd followed by THP delivers meaningfully higher pCR rates, rates of nodal clearance, and a more favourable overall toxicity profile than a current anthracycline-based standard. Importantly, this improvement in tumour eradication was achieved without compromising tolerability or treatment delivery. These findings support the conclusion that T-DXd followed by THP is not only a clinically practical and safe neoadjuvant treatment, but significantly more effective for patients with high-risk HER2-positive early breast cancer, offering a compelling opportunity to reduce the need for rescue adjuvant T-DM1 and improve long-term curative outcomes.

This represents a de-escalated treatment strategy that reduces toxicity and improves surgical outcomes without compromising curative efficacy.

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?

Patients best suited for T-DXd-THP are adults with previously untreated, high-risk HER2-positive early-stage breast cancer meeting the DESTINY-Breast11 clinical criteria (≥cT3 cN0 or cT0–4 cN1–3), for whom neoadjuvant systemic therapy is indicated.

Patients least suitable for T-DXd-THP include those who do not meet the high-risk population studied in DESTINY-Breast11, or those with contraindications or clinically significant intolerance to T-DXd or its components..

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

The primary treatment-response outcome in DESTINY-Breast11 was pCR (ypT0/is ypN0), assessed after completion of neoadjuvant therapy and before/at surgery. Clinicians should also consider residual cancer burden, clinical response, ability to proceed to surgery, treatment interruptions, and adverse events. DESTINY-Breast11 used a recommended surgery window of 3–6 weeks after the last neoadjuvant dose, with 6 weeks being comparable to CIHI and provincial targets in Canada.

During treatment, patients require regular clinical review and laboratory monitoring. DESTINY-Breast11 included assessment of physical examination, laboratory data, cardiac function, vital signs, ECOG performance status, and pulmonary monitoring for ILD/pneumonitis with high-resolution chest CT every 6 weeks during treatment. Standard scanning in the neoadjuvant setting would be adopted, different from the rigorous requirements of the clinical trial.

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

Treatment with T-DXd is given for a fixed number of 4 cycles prior to surgery. Treatment should be discontinued or interrupted for disease progression, or unacceptable toxicity, as per standard discontinuation protocols. In DESTINY-Breast11, potential ILD/pneumonitis prompted treatment interruption and full investigation, with independent adjudication of suspected cases. Low grade ILD/pneumonitis may have treatment with TDX-d resumed after resolution and safety considerations are clinically validated. High grade ILD/pneumonitis would discontinue TDX-d as per well-established standards with experience in the metastatic settings.

5.5 What settings are appropriate for treatment with T-DXd? Is a specialist required to diagnose, treat, and monitor patients who might receive T-DXd?

As is the current standard of 4 cycles of ddAC followed by 4 cycles of THP, T-DXd-THP is an intravenous neoadjuvant regimen delivered in an ambulatory out-patient oncology setting capable of administering systemic anticancer therapy and managing infusion-related, hematologic, gastrointestinal, cardiac, and pulmonary toxicities. T-DXd should be administered under the supervision of clinicians experienced in HER2-directed therapy, with access to appropriate monitoring and management of ILD/pneumonitis.
A multidisciplinary breast cancer team is appropriate for treatment planning, including medical oncology, breast surgery, radiology, pathology, and radiation oncology as indicated. Surgery is planned after completion of neoadjuvant therapy, with DESTINY-Breast11 recommending a 3–6-week interval after the final neoadjuvant dose. This is in keeping with the current standard of care for the use of neoadjuvant systemic therapy followed by surgical resection.

6. Additional Information

Key Takeaways:

1. **Unmet Need:** Although taxane-anthracyline chemotherapy and HER2-targeted treatments can be effective, pCR is not achieved for all patients receiving current neoadjuvant treatment. Estimates note that historical

pCR rates with standard neoadjuvant regimens have generally ranged from 39% to 64%, while ~20% of patients with residual disease after neoadjuvant therapy can expect to experience risk of recurrence at 3 years. The use of anthracycline agents in the curative-intent setting for breast cancer raises concerns about irreversible, lifelong cardiotoxicity and secondary malignancies, the latter of which often carries a life expectancy of only months after diagnosis. That said, while the non-anthracycline regimen, TCHP, is sometimes chosen on a case-by-case basis, TCHP is generally regarded as a treatment that is more difficult to tolerate than ddAC-THP.

2. **Clinically Meaningful Outcomes:** DESTINY-Breast11 provides further evidence that current standard anthracyclines are not more effective and are less safe in the treatment of high-risk early-stage, yet curable, breast cancer. T-DXd-THP represents an important advancement as an anthracycline-sparing alternative to standard ddAC-THP for curative-intent, high-risk HER2-positive early breast cancer while significantly improving surgical and event-free efficacy outcomes with fewer grade ≥3 adverse events, all-grade left-ventricular dysfunction, and similar numbers of adjudicated drug-related ILD/pneumonitis.
3. **Fixed number of T-DXd Cycles Produces Higher pCR:** TDX-d is given for a fixed (restricted) number of 4 cycles in the neoadjuvant setting. In addition, 11.2% more patients experience pCR with T-DXd-THP regimen than with ddAC-THP regimen and thus, they will not need antibody drug conjugate treatment, T-DM1, for 14 cycles (1 year) in the adjuvant setting. That represents a budget off-set for 11.2% more patients. The budget impact is neutral for the THP portion of the regimen as that is the current standard of care and will be publicly funded shortly across all provinces (CDA approval received in 2025 and pCPA pricing negotiations completed in 2026). There is a further budget offset with G-CSF as hematological support is not needed.
5. **Early EFS Signal:** The 2-year EFS rate was 96.9% with T-DXd-THP versus 93.1% with ddAC-THP, with a strong early EFS hazard ratio of 0.56 (95% CI 0.26–1.17 with 4.5% maturity at the pre-specified interim analysis). 3-year EFS results are anticipated for release during this HTA review timeframe.
   REAL Alliance Published Clinical Recommendation of DESTINY-Breast11: The clinical magnitude of the pre-specified interim data release with significant surgical completion rates and pCR in a notably higher-risk stage II/III patients (e,g. bulky disease, nodal involvement) is such that REAL Alliance agreed a clinical recommendation in the 2025 update was warranted based on conference-reported data. The peer-reviewed DESTINY-Breast11 data set was published after REAL Alliance 2025 clinical recommendation publication submission. This will contribute to REAL Alliance deliberations in the annual 2026 update and recommendation grading of the available evidence at time of publication submission.

Identical clinical input is submitted to CDA-AMC and INESSS, reflecting national expert consensus to promote equitable care across Canada. Thus, both logos appear in our submissions.

1. Kumar A, Jerzak KJ, Gelmon KA, et al. Guidance for Canadian Breast Cancer Practice: National Consensus Recommendations for the Systemic Treatment of Patients with HER2+ Breast Cancer in Both the Early and Metastatic Settings (2025 Update). *Curr Oncol*. 2026;33(4):200. doi:10.3390/curroncol33040200

2. Harbeck N, Modi S, Pusztai L, et al. Neoadjuvant trastuzumab deruxtecan alone or followed by paclitaxel, trastuzumab, and pertuzumab for high-risk HER2-positive early breast cancer (DESTINY-Breast11): a randomised, open-label, multicentre, phase III trial. *Ann Oncol*. 2026;37(2):166-179. doi:10.1016/j.annonc.2025.10.019

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