Clinician Group Input

Project Number: PC0469-000

Generic Drug Name (Brand Name): Trastuzumab Deruxtecan (ENHERTU)

Indication: Enhertu (trastuzumab deruxtecan for injection) in combination with pertuzumab is indicated for the first-line treatment of adult patients with unresectable or metastatic human epidermal growth factor 2 (HER2)-positive 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

Our members exchanged views in a sub-committee to review the evidence in HER2+ breast cancer. The sub-committee recommendations were then reviewed by the national nucleus committee. Finally, three rounds of Delphi consensus voting was conducted to determine our clinical recommendations for HER2+ advanced or metastatic breast cancer breast cancer, including the first-line use of trastuzumab deruxtecan (T-DXd) in patients with HER2-positive metastatic breast cancer. We compiled these recommendations to reflect our clinical opinion as breast cancer specialists on what we believe is best for our patients, as published in a peer-reviewed journal [1]. Our opinion is based on a literature review, level 1 data from clinical trials, and recent data releases from international congresses, as well as our collective clinical expertise.

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

3. Current Treatments and Treatment Goals

About HER2-Positive Metastatic Breast Cancer in Canada

Aggressiveness and outcomes: HER2-positive metastatic breast cancer is an aggressive disease subtype with rapid proliferation, high recurrence risk, and a propensity for visceral and central nervous system (CNS) metastases. Despite major improvements in HER2-targeted therapy, metastatic HER2-positive breast cancer remains an incurable condition for most patients, making disease control, preservation of quality of life, and prolongation of survival the main goals of treatment.

Treatment goals:

- **Efficacy:** Prolong overall survival (OS) and progression-free survival (PFS).
- **Durable Tumour Control:** Achieve deep and durable tumour responses and increase overall and complete response rates.
- **Tolerability & Safety:** Ensure that quality of life and functional status is maintained while minimizing treatment-related toxicity.

Current care standards and limitations: THP (a taxane chemotherapy plus trastuzumab and pertuzumab) has been the long-standing first-line standard of care, as established by the CLEOPATRA trial. CLEOPATRA demonstrated a median PFS of 18.7 months with THP versus 12.4 months with trastuzumab plus taxane alone (Δ 6.3

months; hazard ratio [HR] 0.68) and median OS of 56.5 months versus 40.8 months at long-term follow-up (Δ 15.7 months; HR 0.68) [2]. Despite this efficacy, THP has limitations in that many patients develop treatment resistance and disease progression. Also THP is associated with toxicities such as taxane-induced neuropathy, neutropenia, and diarrhea.

It is important to fully understand the CLEOPATRA study protocol and treatment regimen in order to appreciate the historical benchmark that is the current landscape. The CLEOPATRA regimen mandated at least 6 cycles of taxane (docetaxel) chemotherapy as the induction regimen followed by trastuzumab + pertuzumab maintenance therapy. In the CLEOPATRA trial, patients received a median number of docetaxel cycles of 8 and achieved a median PFS of 18.7 months [2].

An effectiveness study using US electronic databases quantified the median number of docetaxel cycles as 6 and the median real-world (rw) PFS as 15 months. The median number of cycles was 11 for paclitaxel/nab-paclitaxel and median rwPFS was 12.6 months [3]. This real world evidence is similar to what was seen in the CLEOPATRA trial for docetaxel and is similar to what we see in our practices in Canada.

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 Subgroups

Unmet need for more durable first-line disease control and improved survival and quality of life: Although THP has established first-line efficacy with an induction/maintenance regimen, metastatic HER2-positive breast cancer is an aggressive, mostly incurable disease with a high propensity for visceral and brain metastases [4,5]. There has not been a major change to standard first line therapy in 11 years, since the CLEOPATRA trial was reported in 2015. Real-world practice and the clinical trial evidence identify unmet needs under the current treatment paradigm as follows:

- **Patient Attrition Beyond First-Line Therapy:** A proportion of patients receiving first-line therapy never transition to second-line treatment due to rapid disease progression, visceral crisis, functional decline, or death, with Canadian attrition estimates ranging from 12% to 30% [5–7]. Since the first-line setting is where the largest degree of durable efficacy is experienced by patients, we recommend treatment strategies that offer longer periods of disease control. [1,5].
- **Toxicity Limitations:** Standard THP relies on cytotoxic taxane chemotherapy for a minimum of 6 cycles (docetaxel or paclitaxel). Taxane-associated neurotoxicity, diarrhea, and neutropenia results in taxane discontinuation in ~25% of patients [2].

5. Place in Therapy (Meeting the unmet need)

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

The treatment under review is trastuzumab deruxtecan (T-DXd) in combination with pertuzumab for use in the first-line setting for metastatic HER2+ breast cancer until disease progression. T-DXd plus pertuzumab was evaluated against THP in the DESTINY-Breast09 trial. T-DXd plus pertuzumab is a treatment that is given until disease progression or intolerance (and is not an induction/maintenance regimen like THP).

Key results of DESTINY-Breast09 are as follows [5]:

- **PFS:** 14-month improvement in median PFS over standard THP (40.7 months vs. 26.9 months by blinded independent central review [BICR]; HR 0.56, P < 0.00001) (see Figure 1).
- **Response rate:** Confirmed objective response in 85% of patients treated with TDXd + pertuzumab compared to 78.6% with THP. It is noteworthy that nearly twice as many patients experienced a complete response with T-DXd + pertuzumab compared to THP (15.1% vs. 8.5%).
- **Duration of response:** Median duration of response was 39.2 months with T-DXd + pertuzumab compared to 26.4 months with THP.

DESTINY-Breast09 is a randomized controlled Phase 3 trial with patients randomized to one of 3 arms; T-DXd monotherapy, T-DXd + pertuzumab, or THP induction/maintenance. The T-DXd monotherapy arm remains blinded until the final PFS analysis.

The control arm of DESTINY-Breast09 achieved a median PFS of 26.9 months, which is substantially higher than historical trial benchmarks and real-world data for induction/maintenance THP, as noted in section 3. While the DESTINY-Breast09 protocol was open-ended regarding the number of taxane cycles and permitted investigator-choice (docetaxel or paclitaxel) taxane continuation, the median number of taxane cycles actually delivered in the control arm was identical to standard practice and the CLEOPATRA protocol (median 8 cycles for docetaxel, 6 for paclitaxel). Therefore, the superior performance of the control arm in DESTINY-Breast09 cannot be attributed to extended cumulative taxane exposure. Instead, it reflects a combination of cross-era practice advances and trial-specific selection factors. On one hand, clinical practice has evolved over the >10 years since CLEOPATRA, including improved adjuvant/neoadjuvant HER2-targeted strategies, modern imaging surveillance, earlier detection of metastatic relapse, and greater use of concurrent endocrine therapy for HR+ metastatic disease during the maintenance phase. On the other hand, the DESTINY-Breast09 control arm's performance was likely optimized by protocol-specific criteria and baseline characteristics of the study population. DESTINY-Breast09 study population included a large de novo (i.e., treatment-naive) population (~50% of patients), and excluded patients who had disease relapse ≤6 months from adjuvant treatment in early-stage disease. Consequently, while modern practice improvements might be expected to elevate PFS beyond CLEOPATRA, the 26.9-month control-arm PFS likely represents a trial-specific modern THP benchmark rather than the expected outcome in unselected real-world practice.

Despite the control arm of DESTINY-Breast09 out-performing historical standards, (26.9 months vs 18.5 months in CLEOPATRA), T-DXd + pertuzumab still conferred a statistically significant and clinically meaningful 14-month PFS benefit over the current standard of care (40.7 vs 26.9 months; HR 0.56).

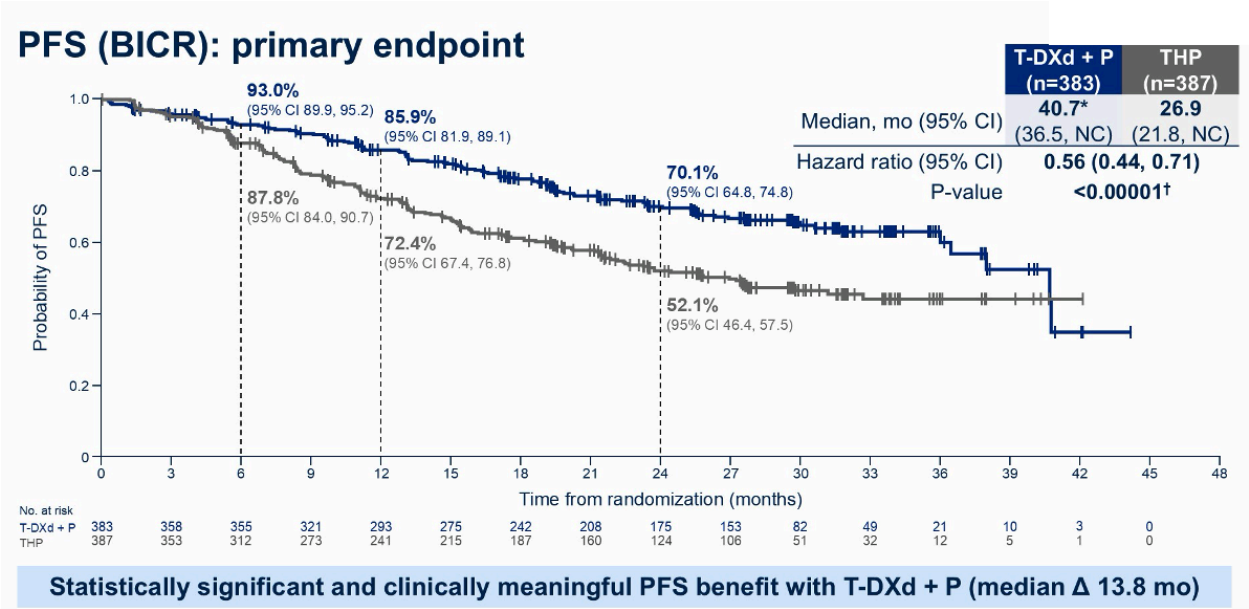

Figure 1: Progression-free survival by blinded independent central review [Tolaney, SM. Presented at ASCO 2025.]

Thus, based on these data, **T-DXD + pertuzumab is recommended as a first-line treatment option for patients with HER2+ metastatic breast cancer in REAL Alliance Recommendation 11** and the treatment algorithm (see Figure 2 and 3). Given the magnitude of the PFS benefit demonstrated in the pre-specified interim analysis, REAL Alliance issued a clinical recommendation in the 2025 update based on data available at publication. At the time of the initial Delphi voting, long-term quality of life (QoL) and functional impact data were unavailable, precluding a comprehensive tolerability review. Due to this and the pending Health Canada approval, REAL Alliance graded this consensus statement as a “Moderate Recommendation.” REAL Alliance continuously monitors evolving clinical data, regulatory, and HTA filings, and the subsequent release of DESTINY-Breast09 QoL data (collected after 27 three-week cycles). In accordance with our annual review process, this recommendation and its grading will be formally updated in 2026 to reflect the current body of evidence.

Recommendations for Metastatic Breast Cancer (Recommendations 10, 12, 15 Reprinted from Manna 2024 [1] with Permission)		REAL	ESMO [28,29]	ASCO [30,31]
11 Recommendation updated in 2025	*1L treatment de novo disease or late relapse* **For patients with HER2+ (HR±) metastatic breast cancer:** • **Who have not received prior HER2-directed therapy or chemotherapy (de novo);** • **Whose disease relapses >6 months after completion of (neo)adjuvant chemotherapy + HER2-directed therapy (late relapse),** treatment options include: (a) Trastuzumab + pertuzumab + taxane chemotherapy, followed by trastuzumab + pertuzumab +/− ET maintenance therapy, the current standard of care. (b) T-DXd * + pertuzumab could be considered using shared decision-making. * Pending Health Canada approval	Strong recommendation ●●●	✓	✓
		Moderate recommendation ●●	NC	NC

Figure 2: REAL Alliance Treatment Algorithm for HER2-positive metastatic stage [Kumar 2026]

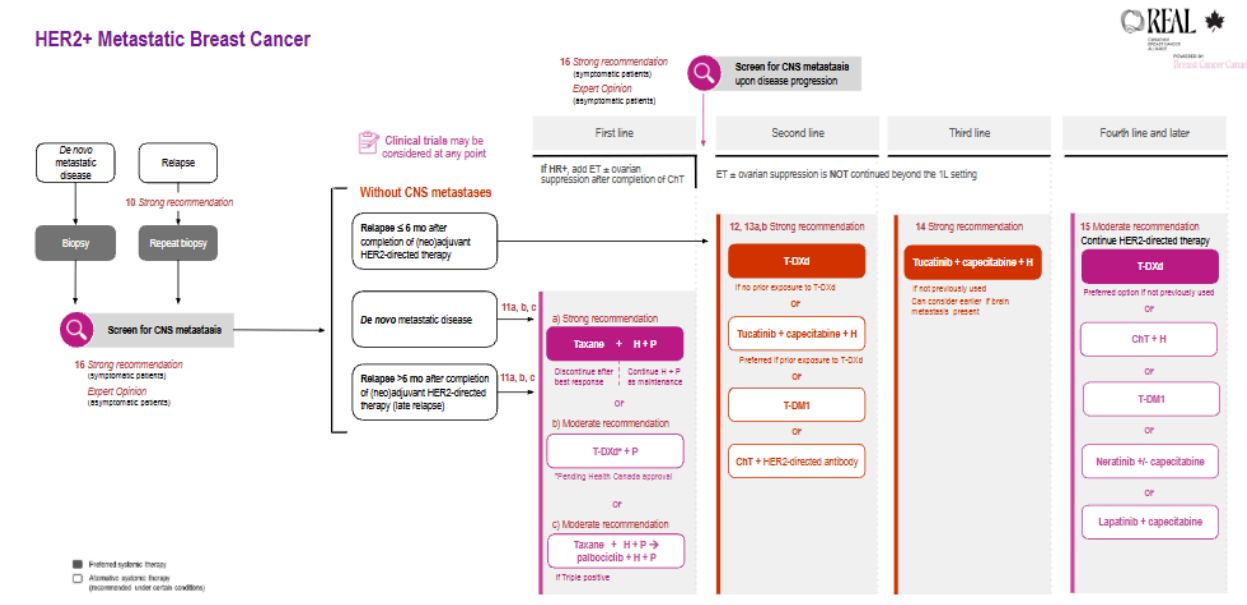

Figure 3: REAL Alliance Treatment Algorithm for HER2-positive metastatic stage [Kumar 2026]

Addressing the Unmet Need: DESTINY-Breast09 Clinical Trial

DESTINY-Breast09 randomised 1,157 patients with HER2-positive advanced/metastatic breast cancer who had not received prior systemic therapy for advanced disease to T-DXd plus pertuzumab (n=383), THP (n=387), or T-DXd monotherapy (n=387) [5]. (The T-DXd monotherapy arm remains blinded until the final PFS analysis.) The primary endpoint was PFS assessed by BICR; key secondary endpoints included OS, objective response rate, duration of response, PFS2, safety and quality of life treatment tolerability, pain and physical functioning.

Efficacy

As of the data cut-off on February 26, 2025, the median PFS, evaluated by BICR, was 40.7 months in the group receiving T-DXd plus pertuzumab as compared to 26.9 months in the THP group (HR 0.56; 95% confidence interval 0.44–0.71; P<0.00001). This result went beyond the pre-specified boundary for superiority and shows a 44% reduction in the risk of progression or death.

The rate of confirmed response was 85.1% with T-DXd + pertuzumab compared to 78.6% with THP. The rate of complete response was 15.1% compared to 8.5%, and the median duration of response was 39.2 months versus 26.4 months.

Subgroup analyses indicated consistent PFS benefit across hormone-receptor status, PIK3CA mutation status, and de novo versus recurrent disease. Overall survival results remain immature and will take many years given PFS2 in the TDX-d arm has not been reached after 3 year analysis.

Safety

The safety profile of T-DXd plus pertuzumab was consistent with the known toxicities of the individual agents. **Grade ≥3 adverse events occurred in 63.5% of patients receiving T-DXd plus pertuzumab and 62.3% receiving THP**. Common grade ≥3 events with T-DXd plus pertuzumab included neutropenia, hypokalemia, and anemia; with THP, neutropenia, leukopenia, and diarrhea were among the most common.

Interstitial lung disease/pneumonitis is a treatment-specific safety parameter of interest. Adjudicated drug-related ILD/pneumonitis occurred in 12.1% of patients receiving T-DXd plus pertuzumab, including 44 grade 1–2 events and two fatal grade 5 events, compared with 1.0% with THP, all grade 1–2. Canadian oncology clinics have implemented protocols to ensure baseline pulmonary assessment, symptom surveillance, prompt imaging when clinically indicated, and protocol-directed interruption/discontinuation guidance. **Given the clinical experience over the last several years, proper monitoring and surveillance is well incorporated into clinical practice.**

DESTINY-Breast09 reported a median treatment duration of 21.7 months for T-DXd plus pertuzumab versus 16.9 months for THP, indicating that patients stayed on treatment longer with the T-DXd regimen with 46% requiring a dose reduction but able to maintain treatment. The treatment duration of T-DXd is shorter than the median PFS because of discontinuation due to adverse events or patient preference. The proportion of patients who discontinued treatment due only to an adverse event was ~20% in the T-DXd arm compared with ~25% in the THP arm.

Quality of Life

T-DXd plus pertuzumab is associated with a higher early incidence of manageable gastrointestinal symptoms (nausea, constipation) during initial cycles. By Cycle 27, patients on T-DXd plus pertuzumab demonstrate a favorable long-term tolerability profile, particularly regarding skin and mucosal toxicities compared to THP, while maintaining high health-related quality of life and a higher rate of overall treatment retention (see Figure 4). Of note, pain, fatigue, physical function symptoms, and overall patient-reported treatment impact were similar between regimens.

Symptom (%)	**T-DXd + P**		**THP**	
EORTC QLQ-C30	**Cycle 2 (n=328)**	**Cycle 27 (n=187)**	**Cycle 2 (n=341)**	**Cycle 27 (n=166)**
Fatigue	41.2	38.0	41.9	35.5
Diarrhea	47.6	32.6	53.1	21.1
Nausea/vomiting	49.1	34.2	30.2	11.4
Constipation	24.1	23.0	15.5	8.4
Appetite loss	36.6	30.5	29.3	11.4
EORTC QLQ-BR45	**Cycle 2 (n=328)**	**Cycle 27 (n=187)**	**Cycle 2 (n=337)**	**Cycle 27 (n=165)**
'Skin mucosis' symptoms	22.9	37.4	33.5	41.8

Figure 4: DESTINY-Breast09 quality of life [Rimawi M et al. Abstract RF6-07 Presented at SABCS 2025]

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?

Best Suited: As noted in the REAL Alliance recommendation, T-DXd in combination with pertuzumab is a recommended treatment option in patients with HER2-positive metastatic breast cancer previously untreated de novo or those with relapse occurring after adjuvant HER2-based therapy [1].

Least Suitable: Patients who do not meet the eligibility criteria for DESTINY-Breast09 or those with contraindications to T-DXd, including pre-existing active interstitial lung disease (ILD)/pneumonitis or severe baseline pulmonary impairment [4,5].

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?

In clinical practice, treatment response is determined primarily by objective radiologic response (ORR) criteria (RECIST v1.1) categorizing response into complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Clinical symptom improvement, functional performance status, and scans/imaging are also critical indicators of therapeutic efficacy [1]. Radiologic disease response is assessed approximately every 12 weeks during active therapy as standard care, with re-evaluation recommended upon clinical suspicion of disease progression or new neurological symptoms to evaluate brain metastases [1,5].

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

Treatment discontinuation is driven primarily by objective radiologic or clinical disease progression. The onset of Grade ≥2 drug-related ILD/pneumonitis requires immediate, permanent discontinuation of T-DXd [4]. Additional key discontinuation factors include severe left ventricular dysfunction, unmanageable Grade 3/4 toxicities (e.g., severe fatigue, neutropenia), marked functional decline, or patient preference (11.1% in TDX-d arm compared to 7.3% in THP arm) regarding cumulative treatment burden.

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?

Treatment should be administered intravenously in an outpatient oncology clinic or specialised cancer treatment/infusion centre with personnel experienced in HER2-targeted systemic therapy and management of antibody-drug conjugate toxicities including T-DXd-associated ILD.

Finally, a medical oncologist or other qualified cancer specialist should oversee treatment selection and monitoring. The treating team should have established procedures for detecting and managing any possible toxicities and adverse effects associated with T-DXd and pertuzumab.

6. Additional Information

Key Takeaways:

1. HER2+ metastatic breast cancer is an aggressive disease requiring effective therapy to maximize disease control and maintain quality of life. There is an unmet need in the first-line setting for HER2+ metastatic breast cancer for treatments with improved efficacy and extended durable benefit because a proportion of patients never transition to second-line setting due to rapid disease progression, visceral crisis, functional decline, or death, with Canadian attrition estimates ranging from 12 to 30% [6,7]. DESTINY-Breast09 is the first phase III randomized trial in over a decade to demonstrate significant and clinically meaningful improvement in PFS in the first-line setting.

2. DESTINY-Breast09 met its primary endpoint of PFS with T-DXd + pertuzumab significantly prolonging median PFS to 40.7 months versus 26.9 months with THP (HR 0.56; 95% CI 0.44–0.71). OS data is immature with events in TDX-d arm not yet reached.
3. ILD/pneumonitis occurred in 12.1% with T-DXd + pertuzumab, including two fatal events, versus 1.0% with THP, with 6% of patients experiencing ILD discontinued treatment. In real-world clinical practice, T-DXd is a well-established therapy in metastatic breast cancer. The risk of ILD is not expected to increase with a longer duration of treatment given what is known about the typical timing of onset of ILD. Dose modification and treatment discontinuation for ILD is as per the Canadian product monograph.
4. Quality of life data support patient tolerance for TDX-d adverse events and duration of therapy of ≥18 months with no negative impact on physical function compared to current standard.
5. REAL Alliance 2025 recommendation 11 is a “Moderate Recommendation”. Additional data on long-term quality of life relevant to this treatment regimen was released after the REAL Alliance 2025 publication. This new data, coupled with a pending Health Canada regulatory review will be considered in REAL Alliance deliberations for the annual 2026 update. In accordance with our annual review process, this recommendation and its grading will be formally updated in 2026 to reflect the current body of evidence. REAL Alliance 2026 HER2 clinical recommendations update is planned for publication during this HTA review timeline.

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.

References

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. Swain SM, Baselga J, Kim SB, et al. Pertuzumab, Trastuzumab, and Docetaxel in HER2-Positive Metastatic Breast Cancer. *N Engl J Med*. 2015;372(8):724-734. doi:10.1056/NEJMoa1413513

3. Polito L, Shim J, Hurvitz SA, et al. Real-World First-Line Use of Pertuzumab With Different Taxanes for Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer: A Comparative Effectiveness Study Using US Electronic Health Records. *JCO Oncol Pract*. 2023;19(7):435-445. doi:10.1200/OP.22.00565

4. Li J, Hao C, Wang H, Pan Y, Jiang Z. DESTINY-Breast09, new breakthroughs in first-line therapy for HER2-positive advanced breast cancer. *Transl Breast Cancer Res*. 2025;6:28-28. doi:10.21037/tbcr-25-35

5. Tolaney SM, Jiang Z, Zhang Q, et al. Trastuzumab Deruxtecan plus Pertuzumab for HER2-Positive Metastatic Breast Cancer. *N Engl J Med*. 2026;394(6):551-562. doi:10.1056/NEJMoa2508668

6. Gambaro K, Groleau M, McNamara S, et al. Third-line treatment patterns in HER2-positive metastatic breast cancer: a retrospective analysis of real-world data in Canada. *J Pharm Pharm Sci*. 2023;26:12078. doi:10.3389/jpps.2023.12078

7. Seung SJ, Saherawala H, Moldaver D, Shokar S, Ammendolea C, Brezden-Masley C. Survival, treatment patterns, and costs of HER2+ metastatic breast cancer patients in Ontario between 2005 to 2020. *Breast Cancer Res Treat*. 2024;204(2):341-357. doi:10.1007/s10549-023-07185-7