Canadian Journal of Health Technologies

CADTH

October 2022 Volume 2 Issue 10

CADTH Reimbursement Recommendation

# Trastuzumab Deruxtecan (Enhertu)

**Indication:** For the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received a prior treatment with an anti-HER2-based regimen in the metastatic setting or developed disease recurrence during or within 6 months of completing neoadjuvant or adjuvant therapy.

**Sponsor:** AstraZeneca Canada Inc.

**Final recommendation:** Reimburse with conditions

CADTH

**ISSN:** 2563-6596



**Funding:** CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

# Summary

CADTH

## What Is the CADTH Reimbursement Recommendation for Enhertu?

CADTH recommends that Enhertu be reimbursed by public drug plans for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer if certain conditions are met.

### Which Patients Are Eligible for Coverage?

Enhertu should only be covered to treat adult patients with HER2-positive breast cancer that is unresectable or metastatic (i.e., has spread beyond the initial tumour site) who have previously received trastuzumab and taxane for locally advanced or metastatic disease, or have tumours that progressed within 6 months of neoadjuvant or adjuvant therapy with trastuzumab and taxane. Patients must not have previously received an anti-HER2 antibody-drug conjugate in the metastatic setting.

### What Are the Conditions for Reimbursement?

Enhertu should only be reimbursed if prescribed without any other anticancer drugs by a clinician with expertise in treating advanced breast cancer and the cost of Enhertu is reduced.

### Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that Enhertu delayed disease progression compared to trastuzumab emtansine in patients with unresectable or metastatic HER2-positive breast cancer.
- Enhertu meets patients' needs for new treatments for unresectable or metastatic HER2-positive breast cancer that have acceptable toxicity profiles and can delay disease progression.
- Based on CADTH's assessment of the health economic evidence, Enhertu does not represent good value to the health care system at the public list price; therefore, a price reduction is required.
- Based on public list prices, Enhertu is estimated to cost the public drug plans approximately $181 million over the next 3 years. However, the actual budget impact is uncertain.

## Additional Information

### What Is Metastatic HER2-Positive Breast Cancer?

HER2-positive breast cancer is a breast tumour containing high levels of the HER2 protein. Symptoms may include pain, fatigue, cognitive difficulties, and insomnia, and most patients will die within 5 years. Approximately 562 patients with this type of cancer would be eligible for treatment with Enhertu in Canada every year.

### Unmet Needs in Metastatic HER2-Positive Breast Cancer

Many patients with metastatic HER2-positive breast cancer eventually develop resistance to available HER2-targeted drugs. Beyond the first line of treatment in the metastatic setting, responses are generally short-lived and progression usually occurs within months; there is an unmet need for additional treatment options that can more effectively delay disease progression and prolong survival.

### How Much Does Enhertu Cost?

Treatment with Enhertu is expected to cost approximately $9,017 per patient per 21-day cycle.

## Recommendation

The CADTH pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that trastuzumab deruxtecan be reimbursed for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received at least 1 prior anti–HER2-based regimen either in the metastatic setting, or in the neoadjuvant or adjuvant setting and developed disease recurrence during or within 6 months of completing neoadjuvant or adjuvant therapy only if the conditions listed in Table 1 are met.

## Rationale for the Recommendation

Evidence from 1 phase III, multicentre, open-label, randomized controlled trial (DESTINY-Breast03; N = 524) demonstrated that treatment with trastuzumab deruxtecan resulted in added clinical benefit for adult patients with unresectable or metastatic HER2-positive breast cancer who were previously treated with taxane chemotherapy plus trastuzumab. The DESTINY-Breast03 trial showed that, when compared with trastuzumab emtansine, treatment with trastuzumab deruxtecan was associated with statistically significant and clinically meaningful improvement in progression-free survival (PFS) (stratified hazard ratio [HR] = 0.2840; 95% confidence interval [CI], 0.2165 to 0.3727; P value < 0.0001). pERC was unable to reach a definitive conclusion about the relative impact of trastuzumab deruxtecan versus trastuzumab emtansine on overall survival (OS) due to immaturity of the OS data and non-statistically significant differences in OS at a prespecified boundary for the submitted interim analysis.

Patients identified a need for new treatments with acceptable toxicity profiles that can prolong survival, delay disease progression, control cancer symptoms, have an acceptable toxicity profile, and provide a good quality of life. pERC concluded that trastuzumab deruxtecan met some of these needs as it provides an additional treatment option with improved PFS and manageable toxicity. Conclusions on health-related quality of life (HRQoL) outcomes could not be drawn due to absence of formal statistical testing, potential for bias in an open-label trial, and high proportions of missing data.

Using the sponsor-submitted price for trastuzumab deruxtecan and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio for trastuzumab deruxtecan was $274,875 per quality-adjusted life-year (QALY) gained compared with trastuzumab emtansine. At this incremental cost-effectiveness ratio, trastuzumab deruxtecan is not cost-effective at a $50,000 per QALY willingness-to-pay threshold for adult patients with unresectable or metastatic HER2-positive breast cancer who have received at least 1 prior anti–HER2-based regimen either in the metastatic setting, or the neoadjuvant or adjuvant setting and developed disease recurrence during or within 6 months of completing neoadjuvant or adjuvant therapy. A reduction in price is required for trastuzumab deruxtecan to be considered cost-effective at a $50,000 per QALY threshold.

## Table 1: Reimbursement Conditions and Reasons

| Reimbursement condition | Reason | Implementation guidance |
|---|---|---|
| **Initiation** | | |
| 1. Treatment with trastuzumab deruxtecan should be initiated only in adult patients with unresectable or metastatic HER2-positve breast cancer who have all of the following:<br>1.1. have been previously treated with trastuzumab and taxane for locally advanced or metastatic breast cancer, or experienced disease progression within 6 months after neoadjuvant or adjuvant treatment involving a regimen including trastuzumab and taxane<br>1.2. good performance status. | Evidence from the DESTINY-Breast03 trial demonstrated that trastuzumab deruxtecan resulted in a statistically and clinically significant improvement in progression-free survival in patients with the characteristics listed in this condition.<br>The CADTH review identified no evidence to demonstrate the benefit of trastuzumab deruxtecan in patients with an ECOG PS greater than 1. The DESTINY-Breast03 trial included patients with an ECOG PS of 0 or 1. | Based on clinical expert input, selected patients with an ECOG PS of 2 could be considered for treatment at the discretion of the treating physician. |
| 2. Patients should not have received prior treatment with an anti-HER2 antibody-drug conjugate (such as trastuzumab emtansine) in the metastatic setting.<br>2.1. Prior treatment with an anti-HER2 antibody-drug conjugate in the adjuvant or neoadjuvant setting would be permitted if disease progression did not occur within 12 months of end of adjuvant therapy. | Patients who received prior treatment with an anti-HER2 antibody-drug conjugate were excluded from the DESTINY-Breast03 trial.<br>Consistent with the trial eligibility criteria, pERC concluded it appropriate to consider patients who have received HER2 antibody-drug conjugate in the adjuvant or neoadjuvant setting for eligibility, only if the patient has stayed free of disease progression within 12 months after completion of the adjuvant therapy. | — |
| **Discontinuation** | | |
| 3. Treatment with trastuzumab deruxtecan should be discontinued upon the occurrence of any of the following:<br>3.1. progressive disease per mRECIST v. 1.1<br>3.2. unacceptable toxicity. | The CADTH review identified no evidence that continuing treatment with trastuzumab deruxtecan in patients whose disease has progressed is effective.<br>Patients who are unable to complete treatment with trastuzumab deruxtecan due to unacceptable toxicity would likely not be able to receive further treatment with this drug. | — |
| 4. Assessment for disease progression should be based on clinical and radiographic evaluation every 2 to 3 months, or as per physician's discretion. | In DESTINY-Breast03, tumour response was assessed every 6 weeks until disease progression, and every 3 months thereafter. | According to the clinical experts, in clinical practice, imaging assessments would be performed every 2 to 3 months initially, and then at longer intervals depending on the patient's tolerance of the drug. |

| Reimbursement condition | Reason | Implementation guidance |
|---|---|---|
| **Prescribing** | | |
| 5. Trastuzumab deruxtecan should only be prescribed by clinicians with experience and expertise in treating advanced breast cancer in centres with expertise in the administration of IV drugs. | This condition ensures that trastuzumab deruxtecan is prescribed only for appropriate patients, and that adverse effects are managed in an optimized and timely manner. | — |
| 6. Trastuzumab deruxtecan should not be used in combination with other cancer drugs. | Trastuzumab deruxtecan was administered as monotherapy in the DESTINY-Breast03 trial. The CADTH review identified no evidence on the safety and potential benefits of combining trastuzumab deruxtecan with any other treatments. | — |
| **Pricing** | | |
| 7. A reduction in price | The ICER for trastuzumab deruxtecan is $274,875 when compared with trastuzumab emtansine.<br>A price reduction of at least 61% would be required for trastuzumab deruxtecan to be able to achieve an ICER of $50,000 per QALY compared to trastuzumab emtansine. | — |
| **Feasibility of adoption** | | |
| 8. The feasibility of adoption of trastuzumab deruxtecan must be addressed. | At the submitted price, the budget impact of trastuzumab deruxtecan is expected to be greater than $40 million in years 2 and 3.<br>At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate(s). | — |

ECOG PS = Eastern Cooperative Oncology Group Performance Status; ICER = incremental cost-effectiveness ratio; mRECIST v. 1.1 = modified Response Evaluation Criteria in Solid Tumours version 1.1; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; QALY = quality-adjusted life-year.

## Discussion Points

- The clinical experts consulted by CADTH noted that beyond the first line of treatment in the metastatic setting, responses to the currently available HER2-targeted therapies are generally short in duration, especially for patients who have had a disease recurrence within 6 months after completion of adjuvant therapy. The clinical experts highlighted that most patients treated with the available therapies experience disease progression and the long-term survival of patients in this setting remains poor. pERC agreed that there was an unmet need for effective treatment options that can improve long-term remission and survival in the patient population under review.
- Patients identified a need for effective and well-tolerated treatments that can prolong survival; delay disease progression; control cancer symptoms, especially those associated

with metastasis; have an acceptable toxicity profile; and provide a good quality of life. pERC agreed that trastuzumab deruxtecan met some of the needs identified by patients as it provides an additional treatment option with improved PFS. pERC was unable to make any firm conclusion about the HRQoL outcomes due to absence of formal statistical testing, potential for bias in an open-label trial, and high proportions of missing data.

- The interim analysis of OS data numerically favoured trastuzumab deruxtecan; however, pERC noted that the OS data were immature at the latest data cut-off date and the stratified log rank P value did not cross the prespecified boundary for the interim analysis. pERC additionally noted that imbalances between the study arms in terms of subsequent therapies and crossover from 1 arm to the other may have important impact on the OS results. Therefore, the committee was unable to make definitive conclusions regarding the treatment effect of trastuzumab deruxtecan versus trastuzumab emtansine on OS.
- In the DESTINY-Breast03 trial, serious adverse events (AEs) occurred at similar rates between patients treated with trastuzumab deruxtecan and those treated with trastuzumab emtansine; however, AEs leading to study drug interruption occurred in at higher rate in the trastuzumab deruxtecan arm than in the trastuzumab emtansine arm. Overall, the toxicity profile of trastuzumab deruxtecan was considered by the clinical experts to be manageable with appropriate supportive care. pERC considered the patient group input that indicated that patients would be willing to accept AEs from trastuzumab deruxtecan if there was a clinical benefit and the toxicity was tolerable.
- pERC additionally discussed the place of trastuzumab deruxtecan in therapy and agreed with the clinical experts that trastuzumab deruxtecan would likely displace trastuzumab emtansine as the second-line treatment of choice in the metastatic setting. However, due to the absence of evidence on sequencing of trastuzumab deruxtecan with currently available treatment options for patients with unresectable or metastatic HER2-positive breast, pERC was unable to make informed conclusions on the optimal sequencing of trastuzumab deruxtecan with trastuzumab emtansine, and with other post–second-line therapies, such as tucatinib plus capecitabine and trastuzumab, that may currently be available in some jurisdictions.
- pERC noted that trastuzumab deruxtecan is a costly treatment, and the estimated budget impact of reimbursing trastuzumab deruxtecan may have implications for the feasibility of adoption. The committee noted that the budget impact of reimbursing trastuzumab deruxtecan would be substantially greater if it is used in sequence with trastuzumab emtansine.

## Background

Breast cancer is the most common cancer and the leading cause of cancer mortality among women. Amplification and/or overexpression of the HER2 occurs in approximately 15% to 20% of breast cancers. The disease is most often detected at relatively early stages when cure is possible via surgical resection, radiation, chemotherapy, and HER2-targeted therapies. However, some patients treated at earlier stages of disease will relapse and others are diagnosed de novo with stage IV HER2-positive unresectable or metastatic breast cancer (MBC). Symptoms of MBC, including pain, fatigue, and insomnia, impose significant financial burdens as well as limitations on patients' activities of daily living. Especially in its later stages, HER2-positive MBC severely negatively impacts HRQoL due to the impacts of metastases. The sponsor estimated that approximately 562 patients per year would be

eligible for trastuzumab deruxtecan in Canada outside of Quebec. Median OS of patients with HER2-positive MBC is estimated to be approximately 4 to 6 years from diagnosis.

Trastuzumab deruxtecan is a HER2-targeted antibody-drug conjugate consisting of the humanized monoclonal antibody trastuzumab covalently linked to the topoisomerase I inhibitor deruxtecan. The relevant Health Canada indication for trastuzumab deruxtecan is for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received at least 1 prior anti-HER2-based regimen either in the metastatic setting, or in the neoadjuvant or adjuvant setting and developed disease recurrence during or within 6 months of completing neoadjuvant or adjuvant therapy. The drug is dosed at 5.4 mg/kg by IV infusion once every 3 weeks until disease progression or unacceptable toxicity.

## Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 phase III, multicentre, open-label randomized controlled trial in patients with HER2-positive MBC previously treated with taxane chemotherapy plus trastuzumab
- patients' perspectives gathered by 2 patient groups, the Canadian Breast Cancer Network (CBCN) and Rethink Breast Cancer (RBC)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- input form 2 clinical specialists with expertise diagnosing and treating patients with HER2-positive MBC
- input from 3 clinician groups, the Ontario Health-Cancer Care Ontario Breast Cancer Drug Advisory Committee, the RBC Scientific Advisory Committee, and a group of medical oncologists from the Ottawa Hospital Cancer Centre and across Canada
- a review of the pharmacoeconomic model and report submitted by the sponsor.

## Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient input and from clinical experts consulted by CADTH for the purpose of this review.

### Patient Input

Two patient groups, CBCN and RBC, provided input for this review. CBCN collected patient input via 2 online surveys (survey 1, 2017, n = 31 patients in Canada with HER2-positive MBC; survey 2, 2012, n = 71 patients in Canada and n = 16 caregivers of patients in Canada with MBC regardless of HER2 status; no respondents had direct experience with trastuzumab deruxtecan), telephone interviews with key informants (2021 and 2022, n = 7 patients in Canada with HER2-positive MBC who had direct experience with trastuzumab deruxtecan as third-line treatment in the metastatic setting), and a literature review. The input from RBC was based on general observations and insights gathered through various activities (e.g.,

patient blogs, virtual support groups, working groups, patient advisory boards, peer-support networks, Instagram, and scientific advisory committee meetings), email interviews (2022, n = 3 patients with HER2-positive MBC who had direct experience with trastuzumab deruxtecan), and written correspondence (2020, n = 1 patient with HER2-positive MBC seeking access to trastuzumab deruxtecan). Patients highlighted the negative impacts of HER2-positive MBC symptoms such as fatigue, insomnia, and pain, as well as the more severe symptoms associated with metastasis to the bones, lungs, liver, brain, and skin; together, these symptoms impose a heavy physical, emotional, psychosocial, and financial toll and negatively impact HRQoL. It was acknowledged in the input from patient groups that currently available treatments for HER2-positive MBC are only shown to prolong the progression-free period; the input also highlighted the decreasing response rates in later lines of therapy; while the disease will eventually progress, patients seek to live their remaining months and years with the best possible HRQoL. Patients identified an unmet need for new treatments for HER2-positive MBC that can prolong survival, delay disease progression, and control cancer symptoms (especially those associated with metastasis) while having an acceptable toxicity profile, although they indicated that they would be willing to tolerate treatment side effects for therapies that are effective in controlling disease. Patients who had direct experience with trastuzumab deruxtecan treatment felt that the drug had contributed to controlling their disease, improving their HRQoL, and had tolerable side effects such as nausea, vomiting, stomach pain or other stomach issues, loss of appetite, fatigue, and hair loss.

## Clinician Input

### Input From the Clinical Experts Consulted by CADTH

Two clinical specialists with expertise in the diagnosis and management of HER2-positive MBC provided input for this review. The clinical experts stated that although many patients with HER2-positive MBC will benefit from the available HER2-targeted therapies, response rates beyond the first line of treatment are generally low, with progression usually occurring within months. Although the available therapies for HER2-positive MBC are generally well tolerated, drugs with fewer toxicities would be highly desirable. The clinical experts stated that the most appropriate place in therapy for trastuzumab deruxtecan would be the position currently occupied by trastuzumab emtansine; displacement of trastuzumab emtansine by trastuzumab deruxtecan may therefore result in a shift in the current treatment paradigm of HER2-positive MBC in the metastatic setting. Thus, trastuzumab deruxtecan would be offered as second-line treatment in the metastatic setting after taxane chemotherapy plus trastuzumab and pertuzumab (for patients who have received no prior systemic therapy or if HER2-positive MBC occurs 6 months or longer after adjuvant or neoadjuvant therapy) or as first-line treatment in the metastatic setting (for patients who progress to MBC during or less than 6 months from adjuvant or neoadjuvant therapy). The clinical experts emphasized that for patients who progress following trastuzumab deruxtecan, optimal sequencing of subsequent therapies remains unclear; however, in the absence of contrary evidence, many clinicians would choose to use trastuzumab emtansine as third-line therapy in the metastatic setting following trastuzumab deruxtecan. The clinical experts clarified that currently, trastuzumab deruxtecan would not be used in the place of trastuzumab emtansine as adjuvant therapy for patients who have residual invasive disease at the time of surgery after systemic neoadjuvant therapy as the 2 drugs have not been compared in this setting. In patients who previously received adjuvant trastuzumab emtansine, the clinical experts acknowledged that the role of trastuzumab deruxtecan in the metastatic setting is unclear due to a lack of clinical trial evidence; however, the clinical experts believed that there is presently no reason to think that these patients would not derive benefit from trastuzumab

deruxtecan. Of note, in the DESTINY-Breast03 study, prior adjuvant or neoadjuvant treatment with trastuzumab emtansine was only allowed if disease progression had not occurred within 12 months of the end of adjuvant therapy.

The clinical experts relayed that the patients most likely to tolerate and respond to trastuzumab deruxtecan are those with good performance status (PS), no cardiovascular or pulmonary contraindications, and no active central nervous system (CNS) metastases. Response to trastuzumab deruxtecan would be assessed via serial radiological imaging (every 2 to 3 months) as well as via bloodwork and clinical evaluation (every 3 weeks or as needed). Clinically meaningful responses to treatment would be reflected by tumour shrinkage, stable metastatic disease, prolongation of survival, and improvement or stabilization of disease symptoms, PS, and HRQoL. Trastuzumab deruxtecan would be discontinued in patients who experience disease progression, who develop a serious toxicity (e.g., symptomatic interstitial lung disease) and are unable to tolerate the drug despite dose modifications, whose PS declines such that palliative care measures alone are required, and by patient preference.

### Clinician Group Input

Three clinician groups provided input for this review: the Ontario Health-Cancer Care Ontario Breast Cancer Drug Advisory Committee (3 medical oncologists), the RBC Scientific Advisory Committee (6 medical oncologists), and a group of medical oncologists from the Ottawa Hospital Cancer Centre and across Canada (11 medical oncologists). No major contrary views from those provided by the clinical experts consulted by CADTH for this review were presented. The clinician groups echoed the relatively low response rates of available treatment options for HER2-positive MBC beyond the first line in the metastatic setting and highlighted that with increasing use of HER2 drugs in the adjuvant or neoadjuvant settings, treatment resistance may develop rapidly in pretreated patients in the metastatic setting. Additional treatment options are needed in the second and subsequent lines in the metastatic setting, and trastuzumab deruxtecan could shift the current treatment paradigm by becoming the new standard second-line treatment.

## Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for trastuzumab deruxtecan: considerations for initiation of therapy, care provision issues, system and economic issues, and the potential need for a provisional funding algorithm. The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

## Table 2: Responses to Questions From the Drug Programs

| Implementation issues | Clinical experts' response |
|---|---|
| **Considerations for initiation of therapy** | |
| PAG noted that the DESTINY-Breast03 study included patients with an ECOG PS of 0 or 1 and excluded patients who had prior treatment with an anti-HER2 ADC.<br>1. Will patients who were treated with adjuvant trastuzumab emtansine (Kadcyla) be eligible for trastuzumab | The clinical experts consulted by CADTH noted that there is presently no reason to think that patients who received trastuzumab emtansine in the adjuvant or neoadjuvant setting would not be eligible for trastuzumab deruxtecan, acknowledging that the role of trastuzumab in the metastatic setting for these |

| Implementation issues | Clinical experts' response |
|---|---|
| deruxtecan?<br>2. Can the trial data be extended to patients with an ECOG PS > 1? | patients is currently uncertain due to a lack of clinical trial evidence. In the DESTINY-Breast03 study, prior adjuvant or neoadjuvant treatment with trastuzumab deruxtecan was only allowed if disease progression had not occurred within 12 months of the end of adjuvant therapy. However, no patients in the study had received anti-HER2 antibody-drug conjugates such as trastuzumab emtansine in the neoadjuvant or adjuvant setting.<br>The clinical experts stated that in clinical practice, trastuzumab deruxtecan would be administered to all patients with good PS at the discretion of the treating physician. pERC agreed with the clinical experts that the results of the DESTINY-Breast03 study could be extended patients with an ECOG PS of 2. |
| **Funding algorithm** | |
| PAG noted that the proposed place in therapy for trastuzumab deruxtecan is currently occupied by trastuzumab emtansine (Kadcyla).<br>1. Will trastuzumab deruxtecan potentially displace trastuzumab emtansine, or will clinicians choose between one or the other? | The clinical experts consulted by CADTH for this review responded that based on the results of the DESTINY-Breast03 study, trastuzumab deruxtecan would likely displace trastuzumab emtansine as the second-line treatment of choice for patients with no contraindications in the metastatic setting. pERC acknowledged that some patients may choose therapy with trastuzumab emtansine based on its toxicity profile. pERC also noted that patients should be able to switch from trastuzumab deruxtecan to trastuzumab emtansine for toxicity reasons if there is no evidence of disease progression. |
| **Care provision issues** | |
| PAG noted that drug vials should be stored refrigerated and that the drug should be diluted in D5W bags only (not normal saline). The drug should be administered only with an infusion set made of polyolefin or polybutadiene and a 0.2 or 0.22 micron in-line polyethersulfone or polysulfone filter.<br>After reconstitution, trastuzumab deruxtecan vials must be used immediately; thus, vial sharing is unlikely to be feasible. As vials are only available in 100 mg strength and the trastuzumab deruxtecan uses weight-based dosing, drug wastage is anticipated. | Comment from the drug programs to inform pERC deliberations. |
| PAG noted that trastuzumab deruxtecan carries 2 black box warnings for interstitial lung disease and embryofetal toxicity. | Comment from the drug programs to inform pERC deliberations. |
| PAG noted that trastuzumab deruxtecan is another look-alike, sound-alike member of the trastuzumab group. There was considerable concern with the first entry of trastuzumab emtansine (Kadcyla) and the same operational issues to ensure drugs do not get mixed up will be required for trastuzumab deruxtecan. ISMP has an excellent look-alike, sound-alike strategy table. The drug has a black box warning for medication errors. | Comment from the drug programs to inform pERC deliberations. |
| **System and economic issues** | |
| PAG noted that the sponsor anticipates that trastuzumab deruxtecan will take over the majority of the current market | Comment from the drug programs to inform pERC deliberations.<br>. |

| Implementation issues | Clinical experts' response |
|---|---|
| for trastuzumab emtansine (Kadcyla). The pan-Canadian 3-year drug cost is estimated to be $232 million. The sponsor also provided a 3-year incremental drug cost, which assumes that trastuzumab deruxtecan will replace trastuzumab emtansine. This may not be the case if there is interest in sequencing one after the other. | |
| PAG noted that the DESTINY-Breast03 study is ongoing, and the OS data are immature at this point. This adds considerable uncertainty to the budget impact. | Comment from the drug programs to inform pERC deliberations. |

ADC = antibody-drug conjugate; D5W = dextrose 5% in water; ECOG PS = Eastern Cooperative Oncology Group performance status; ISMP = Institute for Safe Medication Practices; OS = overall survival; PAG = Provincial Advisory Group; pERC = pan-Canadian Oncology Drug Review Expert Review Committee.

# Clinical Evidence

## Pivotal Studies and Protocol Selected Studies

### Description of Studies

One phase III, multicentre, open-label randomized controlled trial designed to compare the efficacy and safety of trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive MBC previously treated with taxane chemotherapy plus trastuzumab contributed evidence to this review (DESTINY-Breast03; N = 524). The primary objective of the study was to compare the PFS benefits per blinded independent central review (BICR) of trastuzumab deruxtecan versus trastuzumab emtansine in pretreated patients with HER2-positive MBC, and the key secondary objective (hierarchically tested) was to compare the OS benefits of the 2 drugs. Other secondary objectives included comparison of PFS per investigator assessment (IA), objective response rate (ORR) per BICR and IA, and duration of response (DOR) per BICR and IA, while changes in patient-reported HRQoL were evaluated as a Health Economics and Outcome Research (HEOR) analysis. Adult patients (age 18 years and older) with HER2-positive MBC that was previously treated with trastuzumab plus taxane chemotherapy in the metastatic setting (or who had progressed within 6 months after neoadjuvant or adjuvant treatment involving a regimen that included trastuzumab and taxane) were enrolled at 169 centres in 15 countries (1 site; n = 2 patients in Canada). Patients were randomized 1:1 to receive open-label trastuzumab deruxtecan (5.4 mg/kg by IV infusion every 21 days) or open-label trastuzumab emtansine (3.6 mg/kg by IV infusion every 21 days) until disease progression according to modified Response Criteria for Evaluation of Solid Tumours (RECIST) v. 1.1 or unacceptable toxicity. Randomization was stratified by hormone receptor status (i.e., positive or negative), prior treatment with pertuzumab (i.e., yes or no), and history of visceral disease (i.e., yes or no). Following treatment discontinuation, patients were followed for survival every 3 months until death.

Patients had to have an Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1 and adequate hematological and organ function; patients previously treated with an anti-HER2 antibody-drug conjugate were excluded (unless treatment was in the adjuvant or neoadjuvant setting and progression had not occurred within 12 months of the end of adjuvant therapy), as were patients with spinal cord compression or clinically active CNS metastases and patients with clinically significant cardiovascular or pulmonary disease. The mean age at study

was 54.4 years, approximately 60% of patients were Asian, and only 2 patients were male. Approximately 63% of patients had an ECOG PS of 0 and approximately 37% had an ECOG PS of 1. Approximately half of patients had hormone receptor positive disease (approximately half of patients had estrogen receptor positive disease, while approximately one-third had progesterone receptor positive disease). Approximately 73% and 70% of patients had visceral metastases at baseline or a reported history of visceral metastases, respectively, and approximately 16% and 22% of patients had CNS metastases at baseline or a reported history of CNS metastases, respectively. All patients had received at least 1 prior systemic therapy for breast cancer and the mean number of prior regimens received was 3.3 (standard deviation = 2.33 regimens). Approximately 60% of patients had received prior pertuzumab. Approximately 72% of patients had received less than 3 lines of prior systemic therapy excluding hormone therapies, while approximately 28% had received 3 lines of systemic therapy excluding hormone therapies or more. Approximately 40% of patients had received 1 prior line of therapy in the metastatic setting, while approximately 60% had received 2 or more prior lines in the metastatic setting; note that the definition of lines of prior systemic therapy in the metastatic setting included patients for whom the therapy was intended to treat locally advanced or metastatic or palliative disease and patients for whom the therapy was intended as neoadjuvant, adjuvant, or maintenance therapy and whose disease progressed within 6 months from the end of therapy (12 months for pertuzumab). Approximately 87% of patients had received prior systemic therapy with the intent to treat metastatic disease.

## Efficacy Results

### *Overall Survival*

As of the May 21, 2021, data cut-off, OS events had occurred in 33 (12.6%) patients in the trastuzumab deruxtecan arm and 53 (20.2%) patients in the trastuzumab emtansine arm. Median OS and its 95% CI could not be estimated in either treatment arm. The HR for OS comparing trastuzumab deruxtecan with trastuzumab emtansine was 0.5546 (95% CI, 0.3587 to 0.8576) in favour of trastuzumab deruxtecan; however, the stratified log rank P value of 0.007172 did not cross the prespecified boundary for the interim analysis ($P < 0.000265$) calculated based on 86 OS events.

### *Progression-Free Survival*

As of the May 21, 2021, data cut-off, PFS events per BICR had occurred in 87 (33.3%) patients in the trastuzumab deruxtecan arm and 158 (60.1%) patients in the trastuzumab emtansine arm. Median PFS per BICR had not yet been reached in the trastuzumab deruxtecan arm but the lower limit of the 95% CI was 18.5 months, while the median PFS per BICR was 6.8 months in the trastuzumab emtansine arm (95% CI, 5.6 to 8.2 months) ($P < 0.0001$). The HR for PFS per BICR comparing trastuzumab deruxtecan with trastuzumab emtansine was 0.2840 (95% CI, 0.2165 to 0.3727) in favour of trastuzumab deruxtecan.

As of the May 21, 2021, data cut-off, PFS events per IA had occurred in 78 (29.9%) patients in the trastuzumab deruxtecan arm and 168 (63.9%) patients in the trastuzumab emtansine arm. Median PFS per IA was 25.1 months (95% CI, 22.1 months to not estimable) in the trastuzumab deruxtecan arm and 7.2 months (95% CI, 6.8 to 8.3 months) in the trastuzumab emtansine arm. The HR for PFS per IA comparing trastuzumab deruxtecan with trastuzumab emtansine was 0.2649 (95% CI, 0.2011 to 0.3489) in favour of trastuzumab deruxtecan. Note that this analysis was not part of the statistical hierarchy and not adjusted for multiplicity.

*Health-Related Quality of Life*

Changes in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), EQ-5D 5-Levels, and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer 45 (EORTC QLQ-BR45) scores from baseline to the end of treatment were evaluated as a HEOR analysis. Interpretation of changes in patient-reported HRQoL outcomes was limited by high rates of missing data at later times post-baseline.

*Objective Response Rate*

The ORR per BICR was 79.7% (95% CI, 74.3% to 84.4%) in the trastuzumab deruxtecan arm and 34.2% (95% CI, 28.5% to 40.3%) in the trastuzumab emtansine arm. The ORR per IA was [redacted]% (95% CI, [redacted]% to [redacted]%) in the trastuzumab deruxtecan arm and [redacted]% (95% CI, [redacted]% to [redacted]%) in the trastuzumab emtansine arm. The difference in ORR per BICR was 45.5% (95% CI, 37.6% to 53.4%) in favour of trastuzumab deruxtecan. Note that this analysis was not part of the statistical hierarchy and not adjusted for multiplicity.

*Duration of Response*

Among patients who achieved objective responses to treatment, median DOR per BICR was not yet reached in either treatment arm (trastuzumab deruxtecan 95% CI, 20.3 months to not estimable; trastuzumab emtansine 95% CI, 12.6 months to not estimable). Among patients who achieved objective responses to treatment, median DOR per IA was not yet reached in either treatment arm (trastuzumab deruxtecan 95% CI, [redacted] months to not estimable; trastuzumab emtansine 95% CI, [redacted] months to not estimable). Note that this analysis was not part of the statistical hierarchy and not adjusted for multiplicity.

## Harms Results

Almost all patients treated with trastuzumab deruxtecan (99.6%) and trastuzumab emtansine (95.4%) experienced at least 1 AE. Serious AEs occurred overall at similar rates in patients treated with trastuzumab deruxtecan (19.1%) and trastuzumab emtansine (18.0%). Withdrawals due to AEs occurred in 13.6% of patients treated with trastuzumab deruxtecan and 7.3% of patients treated with trastuzumab emtansine. AEs leading to study drug interruption occurred in 44.0% of patients treated with trastuzumab deruxtecan and 23.4% of patients receiving trastuzumab emtansine. Five patients (1.9%) in each of the treatment groups had AEs associated with an outcome of death. The study protocol-defined AEs of special interest of interstitial lung disease, decreased left ventricular ejection fraction, and left ventricular dysfunction occurred more frequently in patients receiving trastuzumab deruxtecan (10.9%, 2.3%, and 0.4%, respectively) than in patients receiving trastuzumab emtansine (1.9%, 0.4%, and 0%, respectively).

## Critical Appraisal

A major limitation of the DESTINY-Breast03 study was immaturity of the OS analysis as of the May 21, 2021, data cut-off; only 86 OS events had been observed, and the prespecified boundary for statistical significance at the interim analysis was not crossed. In addition, analysis of OS did not take into account treatment switching and crossover, which were imbalanced between arms and may have important impacts on the results. Thus, no conclusions regarding the relative impacts of trastuzumab deruxtecan and trastuzumab emtansine on OS could be reached. Other potential limitations of the study included its open-label design and associated potential biases in outcome assessment due to knowledge of treatment allocation; although disease progression was objectively evaluated using

mRECIST 1.1 criteria per BICR, patients were discontinued from protocol therapy based on assignment of progressive disease per IA. Comparison of response evaluation per BICR and IA suggested that a subset of patients may have been selectively continued on trastuzumab deruxtecan post-progression per BICR and a subset of patients may have been discontinued from trastuzumab emtansine inappropriately due to an incorrect assignment of progressive disease per IA; this bias would be directional and in favour of trastuzumab deruxtecan, but according to the clinical experts consulted by CADTH for this review, would be unlikely to have major impacts on the PFS analysis. ORR, DOR, and HRQoL (evaluated as a HEOR analysis) were not part of the statistical hierarchy and statistical tests for these outcomes were not adjusted for multiplicity.

The DESTINY-Breast03 study excluded patients with active or symptomatic CNS metastases, and so provided no evidence as to the efficacy of trastuzumab deruxtecan in these patients. Only 6.5% of patients in the study were from North America and 59.9% of patients were Asian, which is not reflective of the patient population in Canada who have HER2-positive MBC. No patients previously exposed to anti-HER2 antibody-drug conjugates were included in the study, so the influence of use of these drugs for adjuvant or neoadjuvant therapy on responses in later lines was uncertain. Several of the subsequent therapies received in the study after discontinuation of protocol therapy are not available to patients in Canada who have HER2-positive MBC in this setting and may limit generalizability of the OS findings to Canadian practice.

### Indirect Comparisons

No indirect evidence was identified for this review.

### Other Relevant Evidence

No other relevant evidence was identified for this review.

## Economic Evidence

### Table 3: Cost and Cost-Effectiveness

| Component | Description |
|---|---|
| **Type of economic evaluation** | Cost-utility analysis<br>Partitioned survival model |
| **Target population** | Adult patients with unresectable or metastatic HER2-positive breast cancer who have received at least 1 prior anti–HER2-based regimen either in the metastatic setting, or in the neoadjuvant or adjuvant setting and developed disease recurrence during or within 6 months of completing neoadjuvant or adjuvant therapy |
| **Treatment** | T-DXd |
| **Submitted price** | T-DXd 100 mg vial: $2,440.00 |
| **Treatment cost** | At the sponsor's submitted price of $2,440.00 per 100 mg vial, the cost of T-DXd per 21-day cycle is $9,017 (calculated as cost per mg for 336.96 mg) or $153,289 annually if patients remain on treatment for a full year. |

| Component | Description |
|---|---|
| **Comparator** | T-DM1 |
| **Perspective** | Canadian publicly funded health care payer |
| **Outcomes** | QALYs, LYs |
| **Time horizon** | Lifetime (25 years) |
| **Key data source** | DESTINY-Breast03, a phase III, multicentre, randomized, open-label, active-controlled trial (T-DXd vs. T-DM1) |
| **Key limitations** | • OS data were immature in both T-DXd and T-DM1 arms at the data cut-off (May 21, 2021) from the DESTINY-Breast03 trial. Thus, no conclusions regarding OS differences between T-DXd and T-DM1 could be drawn.<br>• The sponsor used OS data from the EMILIA trial to extrapolate long-term OS estimates for T-DM1 beyond the DESTINY-Breast03 trial. The sponsor used immature data from the DESTINY-Breast03 trial to derive a hazard ratio for OS, which was then applied to a T-DM1 curve to generate OS estimates for T-DXd. Based on feedback from clinical experts, due to differences in patient populations in terms of prior treatment use, the results from the EMILIA trial are not generalizable to the DESTINY-Breast03 trial population. The sponsor's approach overestimated the OS benefit for T-DXd at the 25-year time point, according to the clinical experts consulted during this review.<br>• The sponsor overestimated the duration of treatment effect of T-DXd (up to 110 months), as there is no expectation that treatment benefits will be maintained once patients experience disease progression, according to the clinical experts consulted for this review.<br>• The trial-based utility value for PFS was higher than the general Canadian population normal value; thus, appeared to be overestimated.<br>• The sponsor underestimated the proportion of patients who would receive subsequent therapies in the T-DXd arm. The estimates used by the sponsor were based on data from the DESTINY-Breast03 trial with a median follow-up of approximately 16 months. Extrapolating this short-term data over the 25-year time horizon was considered inappropriate based on clinical expert feedback. Furthermore, the market shares of subsequent treatments submitted by the sponsor did not reflect generally available therapies in Canadian clinical practice.<br>• The submitted model lacked transparency and flexibility, including the inability to run probabilistic analysis when selecting alternate distributions pre-programmed in the sponsor's model. CADTH was unable to address these limitations and cautions that results from the submitted economic model could not be fully validated. |
| **CADTH reanalysis results** | • CADTH undertook reanalyses to address, as possible, limitations related to inappropriate OS extrapolation using data from EMILIA trial to inform long-term survival for T-DM1; overestimation of OS for T-DXd based on the sponsor's choice of distribution; overestimation of health-state utility values for the progression-free state; inappropriate incorporation of the proportion of patients receiving subsequent treatments; inappropriate incorporation of market shares for subsequent treatments; and use of RDI.<br>• In the CADTH base case, T-DXd for the proposed Health Canada indicated population was associated with an ICER of $274,875 per QALY compared to T-DM1 (incremental costs = $217,830; incremental QALYs = 0.79).<br>• For T-DXd to be cost-effective compared to T-DM1 at a willingness-to-pay threshold of $50,000 per QALY, a price reduction of 61% is required. |

ICER = incremental cost-effectiveness ratio; LY = life-year; RDI = relative dose intensity; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-year; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; vs. = versus.

## Budget Impact

CADTH identified the following key limitations: proportion of patients who received initial anti-HER2 regimen and the proportion of patients who received a second line of therapy

were underestimated, and market shares of subsequent treatments did not reflect Canadian clinical practice and were inappropriately incorporated into the budget impact analysis.

CADTH's base-case revisions included increasing the proportion of patients who received initial anti-HER2 regimen, increasing the proportion of patients who received a second line of therapy, and changing the market shares for subsequent treatments to align with Canadian standard of care.

Based on CADTH's base case, the expected budget impact for funding trastuzumab deruxtecan for the treatment of unresectable or metastatic HER2-positive breast cancer in those who have received a at least 1 prior anti–HER2-based regimen either in the metastatic setting or in the neoadjuvant or adjuvant setting, and have developed disease recurrence during or within 6 months of completing neoadjuvant or adjuvant therapy in the drug plan perspective is expected to be in $32,640,740 in year 1, $69,651,619 in year 2, and $78,936,706 in year 3, with a 3-year budget impact of $181,229,065. Results of CADTH's scenario analyses demonstrate that the estimated budget impact is sensitive to whether trastuzumab deruxtecan would displace trastuzumab emtansine in HER2-positive breast cancer or if trastuzumab emtansine would still be used as a subsequent (i.e., both therapies are used in sequence).

# pERC Information

## Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

**Meeting date**: August 9, 2022

**Regrets**: Two of the expert committee members did not attend.

**Conflicts of interest**: None