Canadian Journal of Health Technologies
July 2023 Volume 3 Issue 7

CADTH Reimbursement Recommendation

Trastuzumab Deruxtecan (Enhertu)

Indication: For the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH−) breast cancer who have received at least 1 prior line of chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Patients with hormone receptor positive breast cancer should have received at least 1 and be no longer considered for endocrine therapy.

Sponsor: AstraZeneca Canada Inc.

Final recommendation: Reimburse with conditions

ISSN: 2563-6596

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

Summary

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-low breast cancer if certain conditions are met.

Which Patients Are Eligible for Coverage?

Enhertu should only be covered to treat adult patients with HER2-low breast cancer that is unresectable (cannot be removed by surgery) or metastatic (has spread to other parts of the body) who have received a prior chemotherapy for metastatic disease or had their cancer come back after surgery within 6 months of completing adjuvant chemotherapy. If the patient is hormone receptor (HR)-positive, they should have been treated with at least 1 endocrine therapy (ET) and no longer be considered candidates for further ET treatment. Patients receiving Enhertu should be in relatively good health (i.e., have a good performance status, as determined by a specialist). Patients in whom the cancer has spread to the brain or spinal cord, for whom there is spinal cord compression causing symptoms, or those with interstitial lung disease or pneumonitis should not be eligible for coverage.

What Are the Conditions for Reimbursement?

Enhertu should only be reimbursed if prescribed by clinicians with experience and expertise in treating advanced breast cancer in centres, if it is not used with other cancer treatments, and if the cost of Enhertu is reduced. Patients who experience disease progression while taking Enhertu or who cannot tolerate the drug would not be eligible for continued coverage.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that Enhertu delays disease progression and extends life compared to physician's choice chemotherapy in patients with unresectable or metastatic HER2-low breast cancer.
- Enhertu meets patients' needs for new treatments for unresectable or metastatic HER2-positive breast cancer that have manageable side effects and can delay disease progression and extend life.
- 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. A price reduction is therefore required.

Summary

- Based on public list prices, Enhertu is estimated to cost the public drug plans approximately $211 million over the next 3 years. The size of this budget impact may create adoption issues for the drug plans.

Additional Information

What Is Metastatic HER2-Low Breast Cancer?

HER2-low breast cancer is a breast tumour containing low levels of the HER2 protein. Symptoms may include pain, fatigue, cognitive difficulties, and insomnia, and most patients will die within 5 years of diagnosis.

Unmet Needs in Metastatic HER2-Low Breast Cancer

Patients with HER2-low breast cancer have not previously had access to therapies that target the HER2 protein and would historically have been treated with chemotherapy. There is an unmet need for additional treatment options that can better delay disease progression and extend life.

How Much Does Enhertu Cost?

Treatment with Enhertu is expected to cost approximately $9,574 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-low (immunohistochemistry [IHC] 1+ or IHC 2+/in situ hybridization [ISH]–) breast cancer who have received at least 1 prior line of chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Patients with HR-positive breast cancer should have received at least 1 and be no longer considered for ET. This recommendation is dependent upon the conditions listed in Table 1 being met.

Rationale for the Recommendation

Evidence from 1 phase III, multicentre, open-label, randomized controlled trial (DESTINY-Breast04; N = 557) demonstrated that treatment with trastuzumab deruxtecan resulted in improved survival for adults with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH–) breast cancer who had previously received at least 1 prior line of chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Patients in the DESTINY-Breast04 trial with HR-positive breast cancer received at least 1 ET and were no longer considered for further ET. The DESTINY-Breast04 trial showed that, when compared to treatment of physician's choice (TPC), treatment with trastuzumab deruxtecan was associated with a statistically significant and clinically meaningful improvement in overall survival (OS) (full analysis set [FAS] median OS = 23.4 months and 95% confidence interval [CI], 20.0 to 24.8 versus FAS median OS = 16.8 months and 95% CI,14.5 to 20.0; P = 0.0010) and in progression-free survival (PFS) (full analysis set median PFS = 9.9 months and 95% CI, 9.0 to 11.3 versus full analysis set median PFS = 5.1 months and 95% CI, 4.2 to 6.8; P < 0.0001). Objective response rate (ORR) was higher in patients who received trastuzumab deruxtecan (52.3%) compared to patients who received TPC (16.3%), and 3.5% of the responses in the trastuzumab deruxtecan arm were complete responses compared to 1.1% in the TPC arm, notable in this population where complete response are rare. Trastuzumab deruxtecan was associated with a manageable toxicity profile.

Patients identified a need for new treatments targeting HER2-low breast cancer that control disease progression (i.e., extend life) and manage cancer-related symptoms (i.e., improve quality of life). pERC concluded that trastuzumab deruxtecan met disease progression and life extension needs as it provides a treatment option with improved OS and PFS with a manageable toxicity profile in this population. Health-related quality of life (HRQoL) outcomes were exploratory and therefore were uncertain due to an absence of prespecified statistical testing and potential for bias in an open-label trial.

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 $303,924 per quality-adjusted life-year (QALY) gained compared with TPC. At this incremental cost-effectiveness ratio, trastuzumab deruxtecan is not cost-effective at a $50,000 per QALY gained willingness-to-pay threshold for

the indicated population. A price reduction is required for trastuzumab deruxtecan to be considered cost-effective at a $50,000 per QALY gained threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH−) breast cancer who have all of the following: 1.1. treated with at least 1 prior line of chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy 1.2. patients who are hormone receptor positive must have been treated with at least 1 prior line of endocrine therapy and no longer be considered candidates for endocrine therapy 1.3. good performance status.	Evidence from the DESTINY-Breast04 trial demonstrated that trastuzumab deruxtecan resulted in a statistically and clinically significant improvement in progression-free survival and overall survival in patients with the characteristics listed in this condition. The CADTH review identified no evidence to demonstrate the benefit of trastuzumab deruxtecan in patients with an ECOG PS greater than 1. The DESTINY-Breast04 trial included patients with an ECOG PS of 0 or 1.	To ensure reliable differentiation of IHC 0 and IHC 1+ Canadian testing centres need to implement adequate education and training to ensure patients with HER2-low disease are correctly identified. 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 must not have any of the following: 2.1. symptomatic spinal cord compression 2.2. clinically active CNS metastases 2.3. current ILD or pneumonitis.	The CADTH review did not identify any evidence that patients with symptomatic spinal cord compression, active CNS metastases, or current ILD or pneumonitis would benefit from trastuzumab deruxtecan as they were excluded from the DESTINY-Breast04 trial.	—
Discontinuation		
3. Trastuzumab deruxtecan must be discontinued upon the occurrence of any of the following: 3.1. progressive disease per mRECIST v. 1.1 3.1.1. assessment for disease progression must be based on clinical and radiographic evaluation every 2 to 3 months, or as per physician's discretion 3.2. unacceptable toxicity.	The CADTH review identified no evidence that continuing treatment with trastuzumab deruxtecan in patients whose disease has progressed is effective. In the DESTINY-Breast04 trial, tumour response was assessed every 6 weeks until disease progression, and every 3 months thereafter. In the DESTINY-Breast04 trial, patients were monitored every 6 weeks with CT scans to detect ILD and pneumonitis.	—
Prescribing		
4. Trastuzumab deruxtecan must only be prescribed by clinicians with experience	This condition ensures that trastuzumab deruxtecan is prescribed only for appropriate	—

Reimbursement condition	Reason	Implementation guidance
and expertise in treating advanced breast cancer in centres with expertise in the administration of IV drugs.	patients, and that adverse effects are managed in an optimized and timely manner.	
5. Trastuzumab deruxtecan must not be used in combination with other cancer drugs.	Trastuzumab deruxtecan was administered as monotherapy in the DESTINY-Breast04 trial. The CADTH review identified no evidence on the safety and potential benefits of combining trastuzumab deruxtecan with any other treatments.	—
Pricing		
6. A reduction in price	The ICER for trastuzumab deruxtecan is $303,924 per QALY gained when compared with physician's choice chemotherapy. A price reduction of 75% would be required for trastuzumab deruxtecan to achieve an ICER of $50,000 per QALY gained compared to physician's choice chemotherapy.	—
Feasibility of adoption		
7. The feasibility of adoption of trastuzumab deruxtecan must be addressed.	At the submitted price, the incremental budget impact of trastuzumab deruxtecan is expected to be greater than $40 million in years 1, 2, and 3.	—

CNS = central nervous system; ECOG PS = European Cooperative Oncology Group Performance Status; ICER = incremental cost-effectiveness ratio; IHC = immunohistochemistry; ILD = interstitial lung disease; ISH = in situ hybridization; QALY = quality-adjusted life-year.

Discussion Points

- pERC acknowledged trastuzumab deruxtecan fulfills the need for a targeted therapy in patients with unresectable or metastatic HER2-low breast cancer who have received 1 or more prior lines of chemotherapy. Patients in this population have previously been considered HER2 negative and received single-agent chemotherapy. pERC discussed the impact that trastuzumab deruxtecan will have on the current treatment paradigm by providing an additional treatment option.
- pERC discussed the interim analysis of OS in the DESTINY-Breast04 trial. The results favoured trastuzumab deruxtecan over TPC. While it was noted that due to the nature of the interim analyses the results may be overestimated, this did not reduce pERC's confidence in the overall benefit of trastuzumab deruxtecan as shown in the DESTINY-Breast04 trial.
- The clinical experts and breast pathologist consulted by CADTH noted that there is existing HER2 testing infrastructure in Canada. Given HER2-low is a novel classification, the clinical experts suggested there may be interobserver discordance and lack of reproducibility when differentiating 0 and 1+ to determine HER2 IHC status, as historically, the interpretation of these 2 categories was less rigorous. pERC agreed with the clinical experts that with increased awareness and adequate training, pathologists and oncologists in Canada will be able to correctly identify patients with HER2-low

breast cancer. The pathologist indicated that it may be necessary to reread archival samples from before 2022 to differentiate between IHC 0 and IHC 1+. The pathologist also noted that the VENTANA testing kit may lead to different results than the Dako testing kit.

- pERC noted that the Health Canada indication includes the HR-negative subgroup and discussed the low sample size and exclusion from the statistical hierarchy. The clinical experts consulted by CADTH noted that trastuzumab deruxtecan is anticipated to have a similar benefit regardless of HR status given the consistency of data and because trastuzumab deruxtecan does not target the HR.
- pERC noted the relevance of sacituzumab govitecan as a comparator in the HR-negative HER2-low population considering sacituzumab govitecan in the triple-negative breast cancer indication. pERC discussed that a network meta-analysis comparing trastuzumab deruxtecan to sacituzumab govitecan was deemed infeasible and while a matching-adjusted indirect comparison may be feasible, the results would have been very uncertain due to the differences between the trials in patient characteristics and small sample sizes.
- pERC discussed the patient input that highlighted the need for treatment options that improve HRQoL. pERC noted the toxicity of trastuzumab deruxtecan relating to interstitial lung disease (ILD) and recognized the importance of routine imaging for early detection and management.
- pERC discussed the eligibility of patients who are HR-positive but are functionally HR-negative (HR-low). In this population, patients are generally treated as HR-negative and may not receive the required ET before initiating treatment with trastuzumab deruxtecan. Therefore, pERC agreed that treatment sequencing and national consensus is needed for the definition and management of these patients.

Background

Breast cancer is the most common cancer affecting females in Canada. In 2022, 28,600 new cases and 5,500 cancer-related deaths due to breast cancer were projected in Canada. Biologic testing is standard for determining standard treatment alongside disease staging. Breast cancer was historically classified as HER2-positive or HER2-negative based on the evidence or absence of HER2 amplification and/or overexpression and/or amplification based on IHC or ISH or fluorescence in situ hybridization. HER2-negative breast cancer was defined as IHC 0, IHC 1+, or IHC 2+/ISH−. Now, IHC scores of 1+, or 2+/ISH− are defined as HER2-low breast cancer. In Canada, prevalence estimates of HER2-low breast cancer show that HR-positive disease is predominant (89%) compared to HR-negative disease (11%). Patients who have been historically classified as HER2-negative HR-positive are recommended to receive first-line ET in combination with a cyclin-dependent kinase (CDK) 4 or CDK 6 inhibitor, upon progression, if refractory to ET, single-agent chemotherapy is recommended. In patients who have been historically classified as HER2-negative and HR-negative, the standard of care is sequential single-agent chemotherapy, with the addition of pembrolizumab depending on programmed cell death 1 ligand 1 (PD-L1) status.

The objective of CADTH's clinical review is to review and critically appraise the clinical evidence submitted by the sponsor of beneficial and harmful effects of trastuzumab deruxtecan (5.4 mg/kg IV every 3 weeks)

for the treatment of unresectable or metastatic HER2-low (IHC 1+ or IHC 2+ /ISH–) breast cancer. The target population consists of adults who have received at least 1 prior line of chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy; patients with HR+ breast cancer should have also received at least 1 ET and no longer be considered for further ET.

Trastuzumab deruxtecan has been approved by Health Canada for adults with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+ /ISH–) breast cancer who have received at least 1 prior line of chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Patients with HR-positive breast cancer should have received at least 1 ET and be no longer considered for ET. Trastuzumab deruxtecan is a HER2-targeted antibody drug conjugate that is available as an IV and the recommended dosage in the product monograph is 5.4 mg/kg every 3 weeks.

Sources of Information Used by the Committee

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

- a review of 1 randomized clinical study in patients with HER2-low breast cancer
- patient perspectives gathered by 2 patient groups, Rethink Breast Cancer (Rethink) and the Canadian Breast Cancer Network (CBCN)
- input from the public drug plans and cancer agencies that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with breast cancer
- 1 pathologist with expertise in breast cancer HER2 testing
- input from 1 clinician group, the Ontario Health-Cancer Care Ontario Breast Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Input from 2 patient groups, Rethink and the CBCN were summarized for this CADTH review. Input from Rethink was based on meetings with patients with breast cancer and results from an online survey of 78 patients with metastatic breast cancer (mBC) in Canada. Input received from the CBCN was obtained via online surveys that collected data from 50 patients who identified as having metastatic HER2-negative before the reclassification of HER2-low. Both patient groups highlighted that disease symptom burden due to metastasis negatively affects patient quality of life and noted that the disease restricts patient's employment and career opportunities, their ability to care for children and dependents, and their ability to be social and meaningfully participate in their community. Both groups highlighted the importance of treatments

that control disease progression (i.e., extend life) and manage cancer-related symptoms (i.e., improve quality of life).

Clinician Input

Input From Clinical Experts Consulted by CADTH

Two clinical experts with experience treating mBC highlighted the current unmet need for targeted therapies in the HER2-low population. The clinical experts agreed that standard outcome measures of treatment response, duration of response (DOR), survival statistics, toxicities, and quality of life measures are aligned with the outcomes used in the DESTINY-Breast04 clinical trial. The clinical experts suggested that trastuzumab deruxtecan be prescribed in a hospital setting or a specialty clinic that has expertise and staffing to administer chemotherapy and monitor and manage treatment-related toxicities. One expert pathologist indicated that with increased awareness and adequate training, pathologists and oncologists in Canada will be able to correctly identify patients with HER2-low disease.

Clinician Group Input

Input from 1 clinician group, the Ontario Health-Cancer Care Ontario Breast Cancer Drug Advisory Committee, was summarized for this review. The clinician group agreed broadly with the clinical experts consulted for this review, specifically in relation to the need for targeted treatments that patients can tolerate. The clinician group also highlighted the need for access to ILD monitoring, a safety issue associated with the use of Enhertu, and access to experts who can manage ILD for patients treated with trastuzumab deruxtecan.

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 relevant comparators
- considerations for initiation of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- potential need for a provisional funding algorithm
- care provision issues
- system and economic issues.

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

Drug program implementation questions	Response
Relevant comparators	
The DESTINY-Breast04 phase III study used physician's choice of chemotherapy for the standard arm, including capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel. In some provinces, nab-paclitaxel is restricted to use in patients who develop a severe hypersensitivity reaction to taxanes or have a contraindication to the premedications used with taxanes. Eribulin may be restricted to patients who have previously received both a taxane and an anthracycline. The rest of the comparators from the trial are funded in all provinces, but choice of chemotherapy regimen for subsequent lines depends on what was used as a first-line treatment for metastatic breast cancer, and usually involves a drug with a different mechanism or from a different class of drugs than that used in the first-line setting. HER2-negative, HR-positive mBC: • In absence of visceral crisis, standard of care first-line treatment is a CDK 4 or CDK 6 inhibitor plus an aromatase inhibitor; the second and subsequent lines include other endocrine therapies (e.g., fulvestrant, tamoxifen), and sequential use of chemotherapy (often single-agent), including anthracyclines (doxorubicin and epirubicin), taxanes (paclitaxel and docetaxel), antimetabolites (capecitabine and gemcitabine), microtubule inhibitors (eribulin and vinorelbine), and platinum drugs (cisplatin and carboplatin). HER2-negative, HR-negative mBC: • The standard of care is sequential single-agent chemotherapy, including those previously listed drugs; patients requiring a rapid response or with aggressive disease may have combination chemotherapy administered (e.g., platinum plus gemcitabine). • Although not funded at time of this input, sacituzumab govitecan has received a positive CADTH recommendation for unresectable locally advanced or metastatic triple-negative breast cancer in patients who have received 2 or more therapies.	This was a comment from the drug programs to inform pERC deliberations.
Considerations for initiation of therapy	
For historical cases, does HER2-low status need to be reconfirmed by pathology or can previously reported IHC and ISH scores be used to determine eligibility?	pERC agreed with the clinical experts consulted who noted that previously reported IHC and ISH scores can be used to determine HER2-low eligibility. The pathologist recommended that archival IHC 0 samples from before 2022 be reread, as this could identify patients who would be eligible for trastuzumab deruxtecan.

Drug program implementation questions	Response
In the DESTINY-Breast04 study, all patients must have had a recent tumour tissue sample after the most recent treatment regimen or agree to undergo a tissue biopsy before randomization. Is a recent tumour tissue sample required in real-world practice to determine eligibility for public funding?	The clinical experts consulted noted that it is common for retesting to occur when a patient transitions to metastatic disease and that HER2 status can change throughout the course of disease. pERC agreed that a requirement for recent testing or testing following each line of therapy, as was the case in the DESTINY-Breast04 study, is not aligned with clinical practice.
In the DESTINY-Breast04 study, patients must have been treated with at least 1, and at most 2, prior lines of chemotherapy in the recurrent or metastatic setting (if recurrence occurred within 6 months of (neo)adjuvant chemotherapy, (neo)adjuvant therapy would count as 1 line of chemotherapy). Is there a maximum number of previous lines of chemotherapy to determine eligibility for public funding? If there is a maximum number of previous lines of chemotherapy, should patients on active treatment be allowed to switch to trastuzumab deruxtecan due to the potential time-limited opportunity?	Provided that the patient is able to tolerate the treatment, the clinical experts suggested that access to trastuzumab deruxtecan not be limited by a maximum number of previous lines of chemotherapy. pERC acknowledged the time-limited need at the initial onset of reimbursement of trastuzumab deruxtecan and agreed with the clinical experts. Additionally, the experts noted that once trastuzumab deruxtecan becomes readily available, it is unlikely that patients would receive extended lines of chemotherapy before receiving trastuzumab deruxtecan. The experts agreed that patients should not switch from a treatment that is working to receive trastuzumab deruxtecan.
In the DESTINY-Breast04 study, patients who were HR-positive were eligible if considered refractory to endocrine therapy (which was defined as having progressed on at least 1 endocrine therapy) and the investigator determined that the patient would no longer benefit from further treatment with endocrine therapy. Should the same definition be used to determine eligibility for public funding for patients with HR-positive disease, or should all reasonable endocrine therapies be used in addition to receiving at least 1 line of chemotherapy before considering trastuzumab deruxtecan?	pERC agreed with the clinical experts consulted who noted that the definition used in the DESTINY-Breast04 trial is appropriate. Patients who are HR-positive must receive at least 1 line of endocrine therapy. In second-line and following lines of therapy, clinician judgment should be used to determine whether the patient is refractory. • pERC discussed the eligibility of patients who are HR-positive but are functionally HR-negative (HR-low). In this population, patients are generally treated as HR-negative and may not receive the required endocrine therapy before initiating treatment with trastuzumab deruxtecan. Therefore, pERC agreed that national consensus is needed for the definition, management, and treatment sequencing for these patients.
Pembrolizumab in combination with chemotherapy recently received a conditional positive pERC recommendation for first-line treatment of metastatic triple-negative breast cancer. Some of these patients may also be HER2-low, and therefore may also be eligible for trastuzumab deruxtecan. PAG would like confirmation on whether patients with breast cancer who were previously classified as triple-negative, but are also HER2-low would be eligible for trastuzumab deruxtecan following first-line treatment with pembrolizumab in combination with chemotherapy?	pERC agreed with the clinical experts consulted who noted that patients classified as having triple-negative breast cancer, but truly have HER2-low breast cancer, and who have received first-line pembrolizumab in combination with chemotherapy, should be eligible for second-line treatment with trastuzumab deruxtecan.
Generalizability	
In the DESTINY-Breast04 study, only patients with an ECOG PS of 0 to 1 were eligible. Should patients with an ECOG PS > 1 be considered eligible for public funding?	The clinical experts agreed that, in clinical practice, there will likely be patients with a borderline ECOG PS of 1 to 2 that will be considered by clinicians to be suitable for trastuzumab deruxtecan. pERC agreed with the clinical experts that the results of the DESTINY-Breast04 trial could be extended to patients with an ECOG PS of 2.

Drug program implementation questions	Response
Funding algorithm	
Clarification may be required on eligibility for drugs previously recommended by pERC for metastatic triple-negative breast cancer (e.g., pembrolizumab, sacituzumab govitecan) as some of these patients may now be classified as HER2-low, HR-negative instead of triple-negative. An updated algorithm for mBC would help clarify eligibility for all available treatments and sequences.	pERC acknowledged the input from the drug program. The clinical experts suggested that for patients with HER2-low breast cancer, the preferable second-line treatment may be trastuzumab deruxtecan over sacituzumab govitecan, as it is specifically targeted to the HER2 protein; however, there is no clear consensus of sequencing of these drugs. There is no direct comparative effectiveness data for trastuzumab deruxtecan vs. sacituzumab govitecan. pERC noted that there remains an evidence gap for the relative efficacy comparison against sacituzumab govitecan in the HR-negative cohort of patients. It is also worth noting that a small number of patients with HR-negative disease were included in the DESTINY-Breast04 study as opposed to the sacituzumab govitecan study, which was a randomized study in HR disease.
Care provision issues	
Trastuzumab deruxtecan is another look-alike, sound-alike member of the trastuzumab group (e.g., trastuzumab emtansine and trastuzumab). There is concern with operational issues to ensure all these drugs do not get inadvertently mixed up. Trastuzumab deruxtecan has a "black box" warning for potential medication errors related to this. The drug vials should be stored refrigerated and further diluted in D5W bags only (not normal saline). The drug should be administered only with an infusion set made of polyolefin or polybutadiene with a 0.2 micron or 0.22 micron inline polyethersulfone or polysulfone filter. 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, some drug wastage is anticipated. Given the potentially large patient population for this indication, the magnitude of drug wastage may be significant. Larger treatment centres may be able to mitigate some drug wastage by coordinating treatment appointments for patients at similar times and/or standardized days.	This was a comment from the drug programs to inform pERC deliberations.
System and economic issues	
Due to the potentially large patient population, a substantial budget impact is anticipated.	This was a comment from the drug programs to inform pERC deliberations.

CDK = cyclin-dependent kinase; D5W = dextrose 5% in water; ECOG PS = European Cooperative Oncology Group Performance Group; HR = hormone receptor; IHC = immunohistochemistry; ISH = in situ hybridization; mBC = metastatic breast cancer; PAG = provincial advisory group; pERC = CADTH pan-Canadian Oncology Drug Review Expert Review Committee; vs. = versus.

Clinical Evidence

Description of Studies

DESTINY-Breast04 was a randomized, double-arm, phase III, open-label, multicentre trial to compare the safety and efficacy of trastuzumab deruxtecan versus the TPC in patients with HER2-low, unresectable, and/or mBC. A total of 557 patients were randomized in a 2:1 ratio to receive open-label treatment with trastuzumab deruxtecan or TPC. Randomization was stratified by HER2 IHC status of tissue samples assessed by a central laboratory (HER2 IHC 1+ versus HER2 IHC 2+/ISH-negative), number of prior lines of chemotherapy (1 versus 2), HR or CDK status (HR-positive mBC with prior CDK 4 or CDK 6 inhibitor treatment versus HR-positive mBC without prior CDK 4 or CDK 6 inhibitor treatment versus HR-negative mBC). The primary objective was to compare the PFS benefit of trastuzumab deruxtecan to TPC in the cohort of patients with HER2-low, HR-positive mBC, based on blinded independent central review. Key secondary objectives were to compare the PFS benefit of trastuzumab deruxtecan to TPC in all randomized patients regardless of hormone receptor status (i.e., the FAS) based on blinded independent central review, to compare the OS benefit of trastuzumab deruxtecan to TPC in patients with HER2-low HR-positive mBC, and to compare the OS benefit of trastuzumab deruxtecan to TPC in the FAS. The mean age in both cohorts of the FAS was 56.5 (standard deviation [SD] = 10.58 in the trastuzumab deruxtecan arm and SD = 11.51 in the TPC arm). A small proportion of patients had baseline central nervous system metastasis — 6.4% in the FAS trastuzumab deruxtecan arm and 4.3% in the FAS TPC arm.

Efficacy Results

Overall Survival

In the HR-positive cohort, the median OS in the trastuzumab deruxtecan arm was 23.9 months (95% CI, 20.8 to 24.8), while in the TPC arm it was 17.5 months (95% CI, 15.2 to 22.4); P = 0.0028. The estimated hazard ratio comparing patients exposed to trastuzumab deruxtecan to patients receiving TPC was 0.64 (95% CI, 0.48 to 0.86).

In the FAS, the median OS in the trastuzumab deruxtecan arm was 23.4 months (95% CI, 20.0 to 24.8), while in the TPC arm it was 16.8 months (95% CI, 14.5 to 20.0); P = 0.0010. The hazard ratio was 0.64 (95% CI, 0.49 to 0.84).

Health-Related Quality of Life

HRQoL results were available for the HR-positive cohort. According to the global health status parameter of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), both treatment arms remained stable throughout the study. Mean baseline global health status in the trastuzumab deruxtecan arm was 36.26 (SD = 21.842) and 37.89 (SD = 22.511) in the TPC arm. Mean change from baseline was [redacted] in the trastuzumab deruxtecan arm and [redacted] in the TPC arm.

According to EORTC QLQ-BR45 (i.e., the updated version of the QLQ-BR23), the mean baseline breast symptoms score was [redacted] in the trastuzumab deruxtecan arm and [redacted] in the TPC arm, and mean change from baseline was [redacted] and [redacted] in the trastuzumab deruxtecan and TPC arms, respectively.

According to the 5-Level EQ-5D, the mean baseline index score was [redacted] in the trastuzumab deruxtecan arm and [redacted] in the TPC arm. Mean change from baseline to end of treatment was [redacted] and [redacted] in the trastuzumab deruxtecan and TPC arms, respectively.

Progression-Free Survival

In the HR-positive cohort, the median PFS in the trastuzumab deruxtecan arm was 10.1 months (95% CI, 9.5 to 11.5), while in the TPC arm it was 5.4 months (95% CI, 4.4 to 7.1); P < 0.0001. The hazard ratio was 0.51 (95% CI, 0.40 to 0.64).

In the FAS, the median PFS in the trastuzumab deruxtecan arm was 9.9 months (95% CI, 9.0 to 11.3), while in the TPC arm it was 5.1 months (95% CI, 4.2 to 6.8); P < 0.0001. The hazard ratio was 0.50 (95% CI, 0.40 to 0.63).

Objective Response Rate

The ORR of the 331 patients who received trastuzumab deruxtecan in the HR-positive cohort was [redacted], 3.6% of which were complete responses, while the 163 patients in the HR-positive cohort who received TPC had an ORR of [redacted], 0.6% of which were complete responses. In the FAS, the ORR of the 373 patients who received trastuzumab deruxtecan was 52.3% (95% CI, 47.1 to 57.4), 3.5% of which were complete responses, while the 184 patients who received TPC had an ORR of 16.3% (95% CI, 11.3 to 22.5), 1.1% of which were complete responses.

Duration of Response

In the HR-positive cohort, 176 patients received trastuzumab deruxtecan and recorded a complete or partial response, and the median DOR was 10.7 months [redacted] compared to 27 patients in the TPC arm with a median response of 6.8 months [redacted]. In the FAS, 196 patients in the trastuzumab deruxtecan arm recorded a complete or partial response, and the median DOR was 10.7 ([redacted]), compared to 30 patients in the TPC arm with a median response of 6.8 months ([redacted]).

Harms Results

In total, 99.5% of patients in the trastuzumab deruxtecan arm and 98.3% of patients in the TPC arm reported at least 1 adverse event (AE). Serious AEs of any grade were reported in 27.8% of patients in the trastuzumab deruxtecan arm and 25% of patients in the TPC arm. AEs leading to treatment discontinuation were reported in 16.2% of patients receiving trastuzumab deruxtecan and 8.1% in the TPC arm. Overall, [redacted] of patients in the trastuzumab deruxtecan arm and [redacted] of patients in the TPC arm had died by the January 11, 2022, data cut-off. The most common reasons leading to death in both arms were disease progression and AEs.

ILD and/or pneumonitis and left ventricular dysfunction were AEs of special interest and were more common in the trastuzumab deruxtecan arm (12.1% and 4.6%, respectively) than in the TPC arm (0.6% and 0%, respectively).

Critical Appraisal

Patients in the DESTINY-Breast04 trial were randomized according to appropriately chosen stratification factors. It should be noted that stratification was based on an interactive voice and web response system

(i.e., IXRS) at the time of randomization, which differed from the electronic data capture that corrected for mis-stratification at randomization. The overall number of patients who were mis-stratified with regards to hazard ratio status in the primary analysis was low and the impact on the conclusions of the trial is likely small. Primary and secondary end points were tested in a hierarchical sequence. OS analysis allowed for early stopping at the interim analysis. Early stopping rules preserve type I error rates of the OS significance test, but the analysis increases the possibility that benefits are overestimated. The open-label design may have resulted in an informative censoring mechanism in which certain patients exited the study before the first postbaseline tumour assessment. In the FAS analysis of PFS, [redacted] of patients in the TPC arm were censored due to no postbaseline tumour assessment, compared to only [redacted] in the trastuzumab deruxtecan arm. A post hoc sensitivity analysis was conducted to assess the impact of an alternative censoring strategy where patients with no postbaseline tumour assessment are assumed to have not experienced a progression event until the end of the study. Results of this post hoc sensitivity analysis were consistent with the primary analysis.

The DESTINY-Breast04 study population was considered by the clinical experts consulted by CADTH to be representative and generalizable to the Canadian population. The investigated dose of trastuzumab deruxtecan was 5.4 mg/kg, by IV, every 3 weeks, consistent with the expected Health Canada–approved dose. The clinical experts consulted suggested that the basket of chemotherapies used for the TPC arm of the DESTINY-Breast04 study was appropriate and representative of Canadian practice.

Long-Term Extension Studies

No long-term extension studies were submitted as part of this review.

Indirect Comparisons

The sponsor provided a feasibility assessment for conducting an indirect treatment comparison in the HR-negative population against the comparator sacituzumab govitecan. A network meta-analysis was deemed infeasible due to the major differences in the clinical trial characteristics and the small number of patients included. A matching-adjusted indirect comparison, while feasible, would likely produce biased and imprecise estimates due to the identified limitations.

Studies Addressing Gaps in the Pivotal and Randomized Controlled Trial Evidence

No studies addressing gaps were submitted as part of this review.

Conclusions

Evidence from the DESTINY-Breast04 trial showed a statistically significant and clinically meaningful benefit in PFS and OS with trastuzumab deruxtecan 5.4 mg/kg every 3 weeks compared to TPC in patients with unresectable or metastatic HER2-low breast cancer who had received at least 1 prior line of chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. HRQoL was identified from patient input as a key end point important to patients; however, the evidence provided by the DESTINY-Breast04 study was not sufficient for drawing conclusions on HRQoL. There remains an evidence gap for the relative efficacy comparison against sacituzumab govitecan in the

HR-negative cohort of patients, though the cohort of patients where this comparison is relevant is small compared to the overall patient population. The clinical experts consulted viewed the safety profile of trastuzumab deruxtecan as manageable and in line with their expectations.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Patients with HER2-low (IHC 1+ or IHC 2+/ISH−) unresectable and/or metastatic breast cancer who have been treated with at least 1 prior line of chemotherapy in the metastatic setting or have developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Patients with HR-positive breast cancer should have received at least 1 and be no longer considered eligible for ET.
Treatment	Trastuzumab deruxtecan
Dose regimen	5.4 mg/kg given as an IV infusion once every 3 weeks, until disease progression or unacceptable toxicity
Submitted price	Trastuzumab deruxtecan, 100 mg, vial: $2,440.00
Treatment costs	The cost of trastuzumab deruxtecan per 21-day cycle is $9,574 or $165,949 annually if patients remain on treatment for a full year
Comparators	Standard of care (consisting of choice of eribulin, capecitabine, vinorelbine, gemcitabine, or paclitaxel)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (12 years)
Key data source	DESTINY-Breast 04 trial
Key limitations	• The long-term clinical efficacy of trastuzumab deruxtecan in comparison with standard of care is uncertain. Approximately 51% of the benefit observed with trastuzumab deruxtecan was from the extrapolation period and the sponsor's base case predicted survival with trastuzumab deruxtecan beyond 10 years, which did not align with clinical expectations. • The sponsor's PSM approach produced estimates of patients who were progression free, but off treatment, which did not align with clinical expectations. The model predicted that eventually most patients would be off treatment but still benefiting from treatment. This led to an underestimation of drug acquisition costs in favour of trastuzumab deruxtecan. • The sponsor's model predicted that all progression events in the model beyond a certain time point only led to death. This is due to the PSM approach, which doesn't explicitly account for the relationship between PFS and OS. The clinical experts consulted by CADTH for this review indicated that the likelihood of a progression event being death or disease progression is not expected to change significantly over time. This led to an underestimation of subsequent treatment costs and QALYs for all therapies. • The sponsor's base case considered treatment-specific health utility values and did not include disutilities associated with AEs. This approach is not aligned with best practice guidelines, which

Component	Description
	recommend utilities specific to health states, and that disutilities related to events such as AEs should then be incorporated. This introduced uncertainty in treatment benefits estimated by the sponsor's submission. • The sponsor underestimated the proportion of patients who would receive subsequent therapy following progression from trastuzumab deruxtecan, which was lower than that expected for patients receiving standard of care. Patients treated with trastuzumab deruxtecan would be expected to have the same likelihood of receiving subsequent therapy as patients treated with standard of care, if not more likely, based on clinical expert feedback. This underestimated subsequent therapy costs with trastuzumab deruxtecan.
CADTH reanalysis results	• CADTH undertook reanalyses with the following changes to address limitations, where possible: shortening the time horizon to 10 years; basing treatment duration for the initial line of therapy in the model on PFS; using health state-based utilities and including disutilities for AEs; and setting the proportion of patients receiving subsequent therapy to be equal across all interventions. • In the CADTH base case, trastuzumab deruxtecan was associated with an ICER of $303,924 per QALY gained compared to standard of care (incremental costs = $168,104; incremental QALYs = 0.55). • For trastuzumab deruxtecan to be cost-effective compared to standard of care at a willingness-to-pay threshold of $50,000 per QALY gained, a price reduction of at least 75% is required.

AE = adverse event; ET = endocrine therapy; HR = hormone receptor; ICER = incremental cost-effectiveness ratio; IHC = immunohistochemistry; ISH = in situ hybridization; LY = life-year; PFS = progression-free survival; PSM = partitioned survival model; QALY = quality-adjusted life-year.

Budget Impact

CADTH identified the following key limitations: the proportions of patients with HR-positive disease who received a second and third line of chemotherapy and were refractory to prior ET were underestimated, the estimate of the proportion of patients receiving subsequent treatments following trastuzumab deruxtecan was underestimated, and market uptake of trastuzumab deruxtecan for the HR-negative cohort was uncertain. CADTH base-case revisions included increasing the proportions of patients with HR-positive disease who received a second and third line of chemotherapy and were refractory to prior ET, and increasing the proportion of patients receiving subsequent treatments after trastuzumab deruxtecan. The expected budget impact for funding trastuzumab deruxtecan is expected to be in $48,554,076 in year 1, $79,502,778 in year 2, and $83,912,162 in year 3, with a 3-year budget impact of $211,969,016 in the CADTH base case. From the health care payer perspective, the estimated budget impact of funding trastuzumab deruxtecan was $48,711,139, $79,763,181, and $84,149,672 for year 1, 2, and 3, respectively, for a 3-year total of $212,623,992. The results of CADTH's scenario analyses demonstrate that the estimated budget impact is sensitive to the proportion of patients with HR-positive disease receiving necessary prior therapy.

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: May 10, 2023

Regrets: One expert committee member did not attend.

Conflicts of interest: None