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CADTH Reimbursement Review

Trastuzumab Deruxtecan (Enhertu)

Sponsor: AstraZeneca Canada Inc.

Therapeutic area: Metastatic HER2-positive breast cancer

Clinical Review
Pharmacoeconomic Review
Stakeholder Input

CADTH

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

AE	adverse event
AESI	adverse event of special interest
BICR	blinded independent central review
CBC	complete blood count
CBCN	Canadian Breast Cancer Network
CI	confidence interval
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-BR45	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer 45
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EQ-5D-5L	5-Level EQ-5D
FAS	full analysis set
HEOR	health economics and outcome research
HER2	human epidermal growth factor 2
HR	hazard ratio
HRQoL	health-related quality of life
IA	investigator assessment
ILD	interstitial lung disease
KM	Kaplan-Meier
LV	left ventricular
MBC	metastatic breast cancer
MID	minimal important difference
mRECIST	modified Response Evaluation Criteria in Solid Tumours
OL	open label
ORR	objective response rate
OS	overall survival
PS	performance status
RBC	Rethink Breast Cancer
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
VAS	visual analogue scale
WDAE	withdrawal due to adverse event

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Introduction

Breast cancer is the most common cancer and the leading cause of cancer mortality among women.[2] Amplification and/or overexpression of the human epidermal growth factor 2 (HER2) occurs in approximately 15% to 20% of breast cancers.[3] The disease is most often detected at relatively early stages[4] when cure is possible via surgical resection, radiation, chemotherapy, and HER2-targeted therapies.[5] However, some patients treated at earlier stages of disease will relapse[6] and others are diagnosed de novo with stage IV HER2-positive unresectable or metastatic breast cancer (MBC).[7] Symptoms of MBC, including pain, fatigue, and insomnia, impose significant financial burdens as well as limitations on the activities of daily living.[8] Especially in its later stages, HER2-positive MBC severely negatively impacts health-related quality of life (HRQoL) due to the impacts of metastases.[9] The sponsor estimated that approximately 562 patients per year would be eligible for trastuzumab deruxtecan in Canada outside of Quebec.[1] Median overall survival (OS) of HER2-positive MBC is approximately 4 to 6 years from diagnosis.[10,11]

According to the clinical experts consulted by CADTH for this review, most patients who develop HER2-positive MBC have been previously diagnosed with an earlier stage of breast cancer and have previously received adjuvant or neoadjuvant systemic therapy consisting of chemotherapy plus trastuzumab (sometimes with pertuzumab added, if covered by private insurance). Patients who have residual invasive disease at the time of surgery are switched to adjuvant trastuzumab emtansine. For patients who have received no prior systemic therapy or if HER2-positive MBC occurs 6 months or longer after adjuvant or neoadjuvant therapy, the standard first-line treatment in the metastatic setting is taxane chemotherapy plus trastuzumab and pertuzumab. However, in patients who progress to MBC during or less

Table 1: Submitted for Review

Item	Description
Drug product	Trastuzumab deruxtecan (Enhertu) for injection, powder for concentrate for solution for infusion, 100 mg, IV infusion
Indication	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
Reimbursement request	As per indication
Health Canada approval status	NOC
Health Canada review pathway	Priority review; Project Orbis
NOC date	15 June 2022
Sponsor	AstraZeneca Canada Inc.

HER2 = human epidermal growth factor receptor 2; NOC = Notice of Compliance.
Source: Sponsor's drug reimbursement review submission for trastuzumab deruxtecan.[1]

than 6 months following adjuvant or adjuvant therapy, trastuzumab emtansine is given as the first line of treatment in the metastatic setting. A minority of patients may be considered for first-line endocrine therapy in the metastatic setting. According to the clinical experts, the standard second-line treatment in the metastatic setting is trastuzumab emtansine and, although not yet publicly funded and only accessible through patient access programs, the standard third-line treatment is likely to become tucatinib plus capecitabine and trastuzumab. There are no well-defined guidelines beyond these lines of therapy and options include chemotherapy alone or in combination with trastuzumab as well as other drugs, dependent on local funding. According to the clinical experts, the main goals of treatment of HER2-positive MBC are to prolong survival, delay disease progression, maintain or improve HRQoL, optimize performance status (PS), and minimize disease symptoms.

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.

The objective of this report was to perform a systematic review of the beneficial and harmful effects of trastuzumab deruxtecan (5.4 mg/kg by IV infusion every 21 days) 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 in the metastatic setting, or those who have received anti-HER2 therapies in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within 6 months of completing systemic neoadjuvant or adjuvant therapy.

Stakeholder Perspectives

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

Patient Input

Two patient groups, the Canadian Breast Cancer Network (CBCN) and Rethink Breast Cancer (RBC) provided input for this review. CBCN collected patient input via 2 online surveys (survey 1, 2017, n = 31 patients living 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, and that there are decreasing response rates with 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, including 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 in 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 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 [ILD]) 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

The Provincial Advisory Group identified the following jurisdictional implementation issues: considerations for initiation of therapy, funding algorithm, care provision issues, and system and economic issues. The clinical experts consulted by CADTH for this review weighed evidence from the included study and other clinical considerations to provide responses to the drug program's implementation questions.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

One phase III, multicentre, open-label (OL) 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).[12] The primary objective of the study was to compare the progression-free survival (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 including

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 OL trastuzumab deruxtecan (5.4 mg/kg by IV infusion every 21 days) or OL 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 (mRECIST) v. 1.1 or unacceptable toxicity. Randomization was stratified by hormone receptor status (positive or negative), prior treatment with pertuzumab (yes or no), and history of visceral disease (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 [SD] = 2.33 regimens). Approximately 60% of patients had received prior pertuzumab. Approximately 72% of patients had received fewer than 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 of therapy 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 and/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

Key efficacy results of the DESTINY-Breast03 study are summarized in Table 2.

Overall Survival

As of the May 21, 2021, data cut-off date, 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% confidence interval (CI) could not be estimated in either treatment arm. The hazard ratio (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 date, 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 months 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 date, 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 months 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), 5-Level EQ-5D (EQ-5D-5L), 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 an HEOR analysis. The 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 77.0% (95% CI, 71.4% to 82.0%) in the trastuzumab deruxtecan arm and 36.9% (95% CI, 31.0% to 43.0%) 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, 20.8 months to not estimable; trastuzumab emtansine 95% CI, 14.1 months to not estimable). Note that this analysis was not part of the statistical hierarchy and not adjusted for multiplicity.

Harms Results

Key harms results of the DESTINY-Breast03 study are summarized in Table 2. Almost all patients treated with trastuzumab deruxtecan (99.6%) and trastuzumab emtansine (95.4%) experienced at least 1 adverse event (AE). Serious AEs (SAEs) occurred overall at similar rates in patients treated with trastuzumab deruxtecan (19.1%) and trastuzumab emtansine (18.0%). Withdrawals due to AEs (WDAEs) 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 ILD, decreased left ventricular (LV) ejection fraction, and LV 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).

Table 2: Summary of Key Results From the DESTINY-Breast03 Study

Result	Trastuzumab deruxtecan FAS, N = 261; Safety, N = 257	Trastuzumab emtansine FAS, N = 263; Safety, N = 261
OS, months, FAS		
Events, n (%)	33 (12.6)	53 (20.2)
Median OS (95% CI)[a]	NE (NE to NE)	NE (NE to NE)
HR (95% CI)[b]	0.5546 (0.3587 to 0.8576)	
P value[b]	0.007172	
PFS per BICR, months, FAS		
Events, n (%)	87 (33.3)	158 (60.1)
Median PFS (95% CI)[a]	NE (18.5 to NE)	6.8 (5.6 to 8.2)
HR (95% CI)[b]	0.2840 (0.2165 to 0.3727)	
P value[b]	< 0.0001	
Harms, n (%), safety set		
AEs	256 (99.6)	249 (95.4)
SAEs	49 (19.1)	47 (18.0)
WDAEs	35 (13.6)	19 (7.3)
AEs associated with study drug interruption	113 (44.0)	61 (23.4)
AEs associated with dose reduction	55 (21.4)	33 (12.6)
AEs associated with an outcome of death	5 (1.9)	5 (1.9)
Notable harms, n (%), safety set		
ILD	28 (10.9)	5 (1.9)
Decreased LVEF	6 (2.3)	1 (0.4)
LV dysfunction	1 (0.4)	0

AE = adverse event; CI = confidence interval; CTCAE = Common Terminology Criteria for Adverse Events; FAS = full analysis set; HR = hazard ratio; ILD = interstitial lung disease; LV = left ventricular; LVEF = left ventricular ejection fraction; MedDRA = Medical Dictionary for Regulatory Activities; NE = not estimable; OS = overall survival; PFS = progression-free survival; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

Note: AEs were defined and graded using MedDRA version 23.0 and CTCAE version 5.0. All events are within 47 days of the last dose of the study drug unless otherwise indicated.

[a]From a Kaplan-Meier analysis.

[b]Two-sided P value is from the stratified log-rank test; HR and 95% CI are from the stratified Cox proportional hazards model with hormone receptor status, prior pertuzumab, and history of visceral disease stratification factors.

Source: DESTINY-Breast03 Clinical Study Report.[13]

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 consider 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 OL 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 per 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 an 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 as a result provided no evidence on the efficacy of trastuzumab deruxtecan in these patients. Only 6.5% of patients in the study were from North America and 59.9% of the patients were Asian, which is not reflective of the Canadian patient population with 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 with HER2-positive MBC in this setting and may limit the 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.

Conclusions

Evidence from the DESTINY-Breast03 study suggested that, compared with trastuzumab emtansine, administration of trastuzumab deruxtecan contributed to improved PFS per BICR among patients with HER2-positive MBC who had previously received taxane chemotherapy plus trastuzumab. Definitive conclusions could not be reached for OS due to immaturity of the data and non-statistically significant OS differences at a prespecified boundary for the interim analysis. Analyses of PFS per IA, ORR, and DOR also numerically favoured trastuzumab deruxtecan, although they were not part of the statistical hierarchy and were supportive of the primary analysis of PFS per BICR. Results for patient-reported HRQoL and symptom scores (i.e., EQ-5D-5L, EORTC QLQ-C30, and EORTC QLQ-BR45) could not be interpreted due to the absence of multiplicity control in formal statistical testing, the potential for bias in an OL trial,

and high rates of missing data at later time points post baseline. Dose interruption, dose reduction, treatment discontinuation, and ILD occurred more commonly in patients receiving trastuzumab deruxtecan than in those receiving trastuzumab emtansine. The observed PFS benefits, consistent numeric improvements in other efficacy outcomes, and toxicity profile considered manageable by clinical experts were aligned with outcomes identified as important to patients with HER2-positive MBC who are seeking additional treatment options to delay progression and prolong survival with an acceptable HRQoL.

Introduction

Disease Background

Breast cancer is the most common cancer and the leading cause of cancer mortality among women.[2] Amplification and/or overexpression of HER2 occurs in approximately 15% to 20% of breast cancers and contributes to an aggressive tumour phenotype characterized by rapid growth and spread, high rates of resistance to chemotherapies, and frequent visceral and CNS metastases.[3] The disease is most often detected at relatively early stages (approximately 29% in stage I, approximately 43% in stage II, and approximately 21% in stage III)[4] and in many of these patients, cure is possible via surgical resection, radiation, chemotherapy, and HER2-targeted therapies.[5] However, approximately 10% to 20% of patients diagnosed with early-stage HER2-positive breast cancer will experience recurrence within 5 years,[6] and approximately 5% of patients are diagnosed with stage IV HER2-positive unresectable breast cancer or MBC.[7] Symptoms including pain, fatigue, cognitive difficulties, and insomnia impose significant financial burdens as well as limitations on patients' ability to work, caregiving responsibilities, social activities, and ability to spend time with loved ones.[8] Especially in the later stages of disease, HER2-positive MBC severely negatively impacts HRQoL and can lead to a symptomatic death, often in younger women, due to the impacts of visceral and CNS metastases.[9]

Based on estimates of the incidence (21 to 23 cases per 100,000 population) and 10-year prevalence (552 cases per 100,000 population) of breast cancer, the proportion of tumours that are HER2-positive (14.3%), the proportion of patients who are diagnosed with MBC (4.9%), who progress to MBC from earlier stages of disease (5.7%), or who progress during or within 6 months of completing adjuvant or neoadjuvant therapy (2.8%) each year, and the proportions of patients who receive first-line (81.3%) and second-line (40.5%) treatment in the metastatic setting, the sponsor calculated that as of 2022, approximately 562 patients per year would be eligible for trastuzumab deruxtecan in Canada outside of Quebec.[1] Median OS of HER2-positive MBC is approximately 4 to 6 years from diagnosis,[10,11] which is made by a medical oncologist based on biopsy and imaging results as well as molecular testing for HER2 overexpression and/or amplification.

Standards of Therapy

According to the clinical experts consulted by CADTH for this review, most patients who develop HER2-positive MBC have been previously diagnosed with an earlier stage of breast cancer and have previously received adjuvant or neoadjuvant systemic therapy consisting of chemotherapy plus trastuzumab. The addition of pertuzumab to adjuvant or neoadjuvant therapy may improve rates of tumour pathologic complete responses without a clear survival

benefit; thus, the drug is not currently funded in the adjuvant or neoadjuvant settings in Canada, although some patients may receive it if covered by private medical insurance. The clinical experts relayed that patients who have residual invasive disease in the breast and/or axilla at the time of surgery are switched to adjuvant trastuzumab emtansine and in this group of patients, optimal first-line treatment following progression to MBC is unknown but the standard first-line treatment described in the following would be considered depending on the disease-free interval. For patients who have received no prior systemic therapy or if HER2-positive MBC occurs 6 months or longer after adjuvant or neoadjuvant therapy, the standard first-line treatment in the metastatic setting is taxane chemotherapy plus trastuzumab and pertuzumab. However, in patients who progress to MBC in 6 months or less from time of adjuvant or adjuvant therapy, trastuzumab emtansine is given as the first line of treatment in the metastatic setting. A minority of patients may be considered for first-line endocrine therapy in the metastatic setting (for instance, if they have hormone receptor positive disease and have contraindications to chemotherapy). According to the clinical experts, the standard second-line treatment in the metastatic setting is trastuzumab emtansine, and although not yet publicly funded and only accessible through patient access programs, the standard third-line treatment is likely to become tucatinib plus capecitabine and trastuzumab. There are no well-defined guidelines beyond these lines of therapy; options include chemotherapy alone or in combination with trastuzumab as well as other drugs (e.g., lapatinib, neratinib, margetuximab) dependent on local funding.

According to the clinical experts, the main goals of treatment of HER2-positive MBC are to prolong survival, delay disease progression, maintain or improve HRQoL, optimize PS, and minimize disease symptoms. The clinical experts relayed that the choice of systemic treatment for patients with HER2-positive MBC depends on PS, presence of comorbidities, previous treatments, the disease-free interval between adjuvant therapy and development of MBC, and patient preference.

Drug

The key characteristics of trastuzumab deruxtecan are shown in Table 3. Trastuzumab deruxtecan is dosed at 5.4 mg/kg by IV infusion once every 3 weeks until disease progression or unacceptable toxicity. 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. In 2021, the drug received a Notice of Compliance with Conditions from Health Canada for another indication (for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received prior treatment with trastuzumab emtansine) and has not been previously reviewed by CADTH. The mechanism of action of trastuzumab deruxtecan is binding to HER2, internalization, and inhibition of topoisomerase I leading to DNA damage and apoptotic cell death. The sponsor's reimbursement request is the same as the Health Canada indication. The drug is undergoing priority review at Health Canada under Project Orbis.

Table 3: Key Characteristics of Trastuzumab Deruxtecan and Trastuzumab Emtansine

Characteristic	Trastuzumab deruxtecan	Trastuzumab emtansine
Mechanism of action	Binding to HER2 followed by topoisomerase I inhibition, DNA damage, and apoptotic tumour cell death	Binding to HER2, inhibition of HER2 ECD shedding, inhibition of HER2 signalling, ADCC, inhibition of tubulin polymerization
Indication(s)[a]	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	• For the treatment of patients with HER2-positive metastatic breast cancer who received both prior treatment with trastuzumab and taxane, separately or in combination. Patients should have either received prior therapy for metastatic disease, or developed disease recurrence during or within 6 months of completing adjuvant therapy • For the adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease following neoadjuvant taxane and trastuzumab-based treatment
Route of administration	IV infusion	IV infusion
Recommended dose	5.4 mg/kg once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity	3.6 mg/kg once every 3 weeks (21-day cycle)
Serious adverse effects or safety issues	ILD, cardiac toxicity, neutropenia, infusion reactions	Hepatotoxicity, cardiac toxicity, hemorrhage, ILD, infusion reactions, peripheral neuropathy

ADCC = antibody-dependent cellular cytotoxicity; ECD = extracellular domain; HER2 = human epidermal growth factor 2; ILD = interstitial lung disease.

[a]Health Canada–approved indication or proposed Health Canada indication.

Sources: Product monograph for trastuzumab deruxtecan[14] and product monograph for trastuzumab emtansine.[15]

Stakeholder Perspectives

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups. The original patient group submissions can be found at the end of this report.

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 and 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, including 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

All CADTH review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by 2 clinical specialists with expertise in the diagnosis and management of HER2-positive MBC.

Unmet Needs

According to the clinical experts consulted by CADTH for this review, although many patients with HER2-positive MBC will benefit from the available HER2-targeted therapies, many eventually develop resistance to these drugs; moreover, beyond the first line of treatment in the metastatic setting, responses are generally short-lived and progression usually occurs within months. Although the available therapies for HER2-positive MBC are generally well tolerated, their toxicities (e.g., diarrhea, palmar-plantar erythrodysesthesia, ILD, cardiotoxicity) can be difficult for patients, and drugs with fewer toxicities would be highly desirable. The clinical experts highlighted that approximately half of patients with HER2-positive MBC will develop intracranial metastases and that while tucatinib can elicit tumour responses within the brain, there is an unmet need for additional drugs that can target CNS metastases (for instance, in patients with symptomatic brain metastases or leptomeningeal disease) in earlier lines of therapy.

Place in Therapy

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 would therefore result in a shift in the current treatment paradigm. 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) as well as first-line

treatment in the metastatic setting (for patients who progress to MBC during or less than 6 months after adjuvant or adjuvant therapy).

The clinical experts emphasized that in 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. However, the clinical experts also acknowledged that based on the results of the phase II DESTINY-Breast01 study,[16] use of trastuzumab deruxtecan as third-line treatment in the metastatic setting following trastuzumab emtansine appears to be associated with high ORRs and prolonged PFS; thus, patients who receive trastuzumab emtansine as second-line treatment in the metastatic setting are likely to derive clinical benefit from 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.

Patient Population

The clinical experts consulted by CADTH for this review relayed that the patients most likely to tolerate and respond to trastuzumab deruxtecan are those with good PS, no cardiovascular or pulmonary contraindications, and no active CNS metastases. Patients most in need of treatment (i.e., those with rapidly progressing, symptomatic MBC) would be identified by a medical oncologist. The only biomarker of response is HER2 expression status, which is routinely determined at the time of diagnosis.

Assessing Response to Treatment

According to the clinical experts consulted by CADTH for this review, response to trastuzumab deruxtecan would be assessed via serial radiological imaging, bloodwork, and clinical evaluation. 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. Imaging assessments would be conducted every 2 to 3 months, while clinical assessments would be performed more regularly (e.g., every 3 weeks) during early treatment or as needed.

Discontinuing Treatment

The clinical experts consulted by CADTH for this review stated that trastuzumab deruxtecan would be discontinued in patients who experience disease progression, who develop a serious toxicity (e.g., symptomatic ILD) 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.

Prescribing Conditions

According to the clinical experts consulted by CADTH for this review, trastuzumab deruxtecan would be administered in outpatient settings at facilities with those who have experience in the delivery of cancer therapies and that is equipped to monitor and manage AEs such as ILD and infusion reactions. Appropriate treatment settings would have access to a respirology service. However, the clinical experts emphasized that even in community settings, a medical oncologist would identify and monitor patients receiving trastuzumab deruxtecan.

Clinician Group Input

This section was prepared by CADTH staff based on the input provided by clinician groups. The original clinician group submissions can be found at the end of this report.

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 the 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

The drug programs provide input on each drug being reviewed through CADTH's reimbursement review processes by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted by CADTH are summarized in Table 4.

Table 4: Summary of Drug Plan Input and Clinical Expert Response

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. Will patients who were treated with adjuvant trastuzumab emtansine (Kadcyla) be eligible for trastuzumab deruxtecan? Can the trial data be extended to patients with an ECOG PS > 1?	The clinical experts consulted by CADTH for this review responded 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 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. The clinical experts stated that in real-world clinical practice, trastuzumab deruxtecan would be administered to all patients with good PS (as judged by the treating clinician) and no

Implementation issues	Clinical experts' response
	contraindications, which they expected would include some patients with an ECOG PS of 2. The clinical experts felt that the results of the DESTINY-Breast03 study could be extended to these patients.
Funding algorithm	
PAG noted that the proposed place in therapy for trastuzumab deruxtecan is currently occupied by trastuzumab emtansine (Kadcyla). 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. However, following progression during or after treatment with trastuzumab deruxtecan, clinicians would still likely access trastuzumab emtansine for later lines of treatment. The clinical experts were uncertain of the optimal sequencing of post–second-line therapies in patients receiving trastuzumab deruxtecan, which may include trastuzumab emtansine, tucatinib plus capecitabine and trastuzumab, and other options, depending on local funding. However, the clinical experts felt that most clinicians would choose to use trastuzumab emtansine as third-line therapy before other remaining options.
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 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 trastuzumab deruxtecan uses weight-based dosing, drug wastage is anticipated.	For pERC consideration.
PAG noted that trastuzumab deruxtecan carries 2 black box warnings for ILD and embryofetal toxicity.	For pERC consideration.
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.	For pERC consideration.
System and economic issues	
PAG noted that the sponsor anticipates that trastuzumab deruxtecan will take over the majority of the current market for trastuzumab emtansine (Kadcyla). The pan-Canadian 3-year drug cost is estimated at $232 million. The sponsor also provided a 3-year incremental drug cost, which assumes that trastuzumab deruxtecan will replace trastuzumab emtansine.	For pERC consideration.

Implementation issues	Clinical experts' response
This may not be the case if there is interest in sequencing one after the other.	
PAG noted that confidential pricing agreements are in place for relevant comparators for trastuzumab deruxtecan.	For pERC consideration.
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.	For pERC consideration.

ADC = antibody drug conjugate; D5W = dextrose 5% in water; ECOG = Eastern Cooperative Oncology Group; HER2 = human epidermal growth factor 2; ILD = interstitial lung disease; ISMP = Institute for Safe Medication Practices; OS = overall survival; PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review Expert Review Committee; PS = performance status.

Clinical Evidence

The clinical evidence included in the review of trastuzumab deruxtecan is presented a single section, the Systematic Review, which includes pivotal studies provided in the sponsor's submission to CADTH and Health Canada as well as those studies that were selected according to an a priori protocol. No indirect evidence was identified for this review. No additional studies contributing other relevant evidence that addressed important gaps in the evidence included in the systematic review were identified.

Systematic Review (Pivotal and Protocol Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of trastuzumab deruxtecan (5.4 mg/kg by IV infusion every 21 days) 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 in the metastatic setting, or those who have received an anti-HER2 treatment in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within 6 months of completing systemic neoadjuvant or adjuvant therapy.

Methods

Studies selected for inclusion in the systematic review will include pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those meeting the selection criteria presented in Table 5. Outcomes included in the CADTH review protocol reflect outcomes considered to be important to patients, clinicians, and drug plans.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the PRESS Peer Review of Electronic Search Strategies checklist.[17] Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid and Embase (1974–) via Ovid. All Ovid searches were run simultaneously as a multi-file search. Duplicates were removed using Ovid deduplication for multi-file searches, followed by manual deduplication in EndNote. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Enhertu and trastuzumab deruxtecan. The following clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, WHO's International Clinical Trials

Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, and the European Union Clinical Trials Register. No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. The initial search was completed on April 14, 2022. Regular alerts updated the search until the meeting of the CADTH pan-Canadian Oncology Drug Review Expert Committee (pERC) on August 10, 2022. Refer to Appendix 1 for the detailed search strategies.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the Grey Matters: A Practical Tool For Searching Health-Related Grey Literature resource.[18] Included in this search were the websites of regulatory agencies (US FDA and European Medicines Agency). Google was used to search for additional internet-based materials. Refer to Appendix 1 for more information on the grey literature search strategy.

Table 5: Inclusion Criteria for the Systematic Review

Criteria	Description
Patient population	Adult patients with unresectable or metastatic HER2-positive breast cancer who have received at least one prior anti-HER2-based regimen in the metastatic setting 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. Subgroups: • prior therapies • time from neoadjuvant or adjuvant therapy to development of MBC • hormone receptor status • visceral disease • brain metastasis
Intervention	Trastuzumab deruxtecan 5.4 mg/kg by IV infusion repeated every 21 days
Comparators	Trastuzumab emtansine
Outcomes	**Efficacy outcomes:** • OS[a] • PFS[a] • HRQoL[a] • ORR • DOR **Harms outcomes:** • AEs, SAEs, WDAEs, mortality • Notable harms: interstitial lung disease, pneumonitis, respiratory symptoms (e.g., cough, dyspnea, fever), LVEF decrease, myelosuppression (e.g., neutropenia and febrile neutropenia), infusion reactions
Study design	Published and unpublished phase III and IV RCTs

AE = adverse event; DOR = duration of response; HER2 = human epidermal growth factor receptor 2; HRQoL = health-related quality of life; LVEF = left ventricular ejection fraction; MBC = unresectable or metastatic breast cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a]These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies. Two CADTH clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least 1 reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Findings From the Literature

Two reports of a single study[12,13] were identified from the literature for inclusion in the systematic review (Figure 1). The included study is summarized in Table 6.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

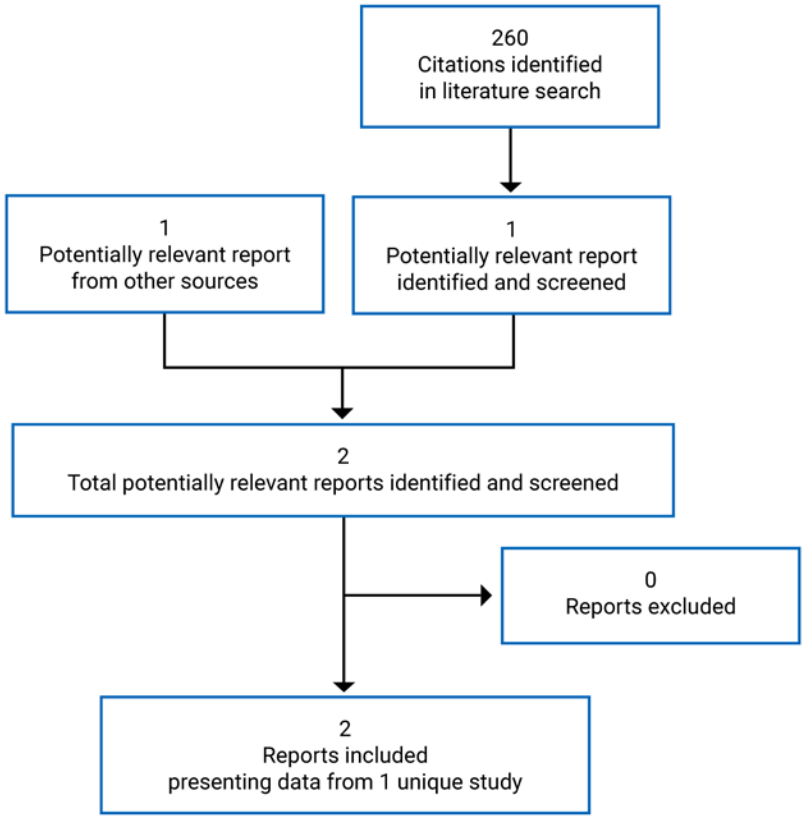


Table 6: Details of the Included Study

Detail	Destiny-Breast03
Designs and populations	
Study design	Phase III, multicentre, OL RCT
Locations	169 centres in 15 countries (Asia: Japan, Korea, China, Taiwan, Hong Kong; North America: US, Canada; Europe: France, Spain, Belgium, UK, Italy, Germany; rest of the world: Australia, Brazil)
Patient enrolment dates	July 20, 2018, to June 23, 2020[a]
Data cut-off date	May 21, 2021
Randomized (N)	524
Inclusion criteria	• Age ≥ 18 years • Pathologically documented breast cancer that was: ◦ unresectable or metastatic ◦ had confirmed HER2-positive expression according to ASCO-CAP guidelines evaluated at a central laboratory ◦ was previously treated with trastuzumab and taxane in the advanced or metastatic setting, or progressed within 6 months after neoadjuvant or adjuvant treatment involving a regimen including trastuzumab and taxane • Documented radiologic progression during or after most recent treatment or within 6 months after completing adjuvant therapy • Tumour was HER2 positive as confirmed by central laboratory assessment of most recent tumour tissue sample (if archived tissue unavailable, fresh biopsy required) • At least 1 measurable lesion per mRECIST v. 1.1 (brain lesions considered as non-target lesions only) • ECOG PS of 0 or 1 • Adequate bone marrow (ANC ≥ 1.5 × 10/L[b], platelets ≥ 100 × 10^9/L[c], and hemoglobin ≥ 9.0 g/dL[d]), renal (CrCL ≥ 30 mL per minute calculated using the Cockcroft-Gault equation), hepatic (TBIL ≤ 1.5 × ULN if no liver metastases or < 3 × ULN in the presence of documented Gilbert's syndrome or liver metastases at baseline), and blood clotting (INR or PT ≤ 1.5 × ULN and either PTT or aPTT ≤ 1.5 × ULN) function within 14 days before randomization • Adequate treatment washout period before randomization and/or enrolment, defined as chloroquine or hydroxychloroquine > 14 days
Exclusion criteria	• Prior treatment with an anti-HER2 ADC (such as trastuzumab emtansine) in the metastatic setting; prior treatment in the adjuvant or neoadjuvant setting was allowed if disease progression had not occurred within 12 months of end of adjuvant therapy • Uncontrolled or significant cardiovascular disease, including: ◦ history of myocardial infarction within 6 months before randomization ◦ history of symptomatic congestive heart failure (NYHA Class II to IV) ◦ troponin levels consistent with myocardial infarction within 28 days before randomization ◦ QTc prolongation to > 470 ms (women) or > 450 ms (men) based on average of screening triplicate 12-lead ECGs ◦ LV dysfunction < 50% within 28 days before randomization • History of ILD or pneumonitis that required steroids, current ILD or pneumonitis, or suspected ILD or pneumonitis that could not be ruled by imaging during screening • Spinal cord compression or clinically active CNS metastases, defined as untreated,

Detail	Destiny-Breast03
	symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control symptoms; patients with clinically inactive brain metastases were eligible, as were patients with treated brain metastases that were no longer symptomatic and did not require treatment if they had recovered from radiotherapy (minimum 2 weeks between end of whole brain radiotherapy and enrolment) • History of severe hypersensitivity reactions to components of trastuzumab deruxtecan or to other mAbs • Clinically significant cardiac disease, pulmonary disease, or psychological conditions • Uncontrolled infection requiring IV antibiotics, antivirals, or antifungals, HIV infection, or active HBV or HCV infection; patients positive for HCV antibody were eligible if PCR was negative for HCV RNA • Multiple primary malignancies within 3 years, except adequately resected non-melanoma skin cancer, curatively treated in situ disease, or contralateral breast cancer • Unresolved toxicities from previous anticancer therapies (other than alopecia) that had not yet resolved to grade ≤ 1 or returned to baseline levels; patients with chronic grade 2 toxicities (e.g., grade 2 chemotherapy-induced neuropathy) were eligible at investigator discretion in consultation with the sponsor • Therapeutic radiation or major surgery within 4 weeks before randomization or palliative stereotactic radiation therapy within 2 weeks before randomization • Systemic treatment with anticancer therapy (non-antibody-based immunotherapy, retinoid therapy, or hormonal therapy within 3 weeks before randomization; antibody-based anticancer therapy within 4 weeks before randomization; treatment with nitrosoureas or mitomycin C within 6 weeks before randomization; or treatment with small-molecule targeted drugs within 2 weeks or 5 half-lives before randomization, whichever was longer) • Participation in a therapeutic clinical study within 3 weeks before randomization (for small-molecule targeted drugs, the non-participation period was 2 weeks or 5 half-lives, whichever was longer) or current participation in other investigational procedures • Clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses including underlying pulmonary disorders (e.g., pulmonary emboli within 3 months of study enrolment, severe asthma, severe COPD, restrictive lung disease, pleural effusion), autoimmune, connective tissue or inflammatory disorders with pulmonary involvement (e.g., rheumatoid arthritis, Sjögren syndrome, sarcoidosis), or prior pneumonectomy
Drugs	
Intervention	Trastuzumab deruxtecan 5.4 mg/kg by IV infusion repeated every 21 days
Comparator	Trastuzumab emtansine 3.6 mg/kg by IV infusion repeated every 21 days
Duration	
Phase	
Screening	4 weeks
OL treatment	Until progressive disease per mRECIST v. 1.1, clinical progression per IA, unacceptable toxicity, treatment delay of ≥ 4 weeks, withdrawal of consent by patient, physician decision, or death, whichever occurred first
Long-term follow-up	Every 3 months until death, withdrawal of consent, loss to follow-up, or study closure, whichever occurred first

Detail	Destiny-Breast03
Outcomes	
Primary end point	PFS per BICR
Secondary and exploratory end points	**Key secondary:** • OS **Secondary:** • PFS per IA • ORR per BICR and IA • DOR per BICR and IA **Exploratory:** • CBR per BICR • PFS2 per BICR • TTR per BICR • Best percent change in the sum of the diameter of measurable tumours per BICR **Other:** • EORTC QLQ-C30 • EORTC QLQ-BR45 • EQ-5D-5L
Notes	
Publications	Cortés et al. (2022)[12]

ADC = antibody drug conjugate; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; ASCO = American Society of Clinical Oncology; BICR = blinded independent central review; CAP = College of American Pathologists; CBR = clinical benefit rate; CNS = central nervous system; COPD = chronic obstructive pulmonary disease; CrCL = creatinine clearance; DOR = duration of response; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-BR45 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer 45; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L = 5-Level EQ-5D; HBV = hepatitis B virus; G-CSF = granulocyte colony-stimulating factor; HCV = hepatitis C virus; HER2 = human epidermal growth factor receptor 2; IA = investigator assessment; ILD = interstitial lung disease; INR = international normalized ratio; LV = left ventricle; mAb = monoclonal antibody; mRECIST = modified Response Evaluation Criteria in Solid Tumours; NYHA = New York Heart Association; OL = open label; ORR = objective response rate; OS = overall survival; PCR = polymerase chain reaction; PFS = progression-free survival; PFS2 = progression-free survival on the next line of therapy; PS = performance status; PT = prothrombin time; PTT = partial thromboplastin time; QTc = corrected QT interval; RCT = randomized controlled trial; RNA = ribonucleic acid; TBIL = total bilirubin; TTR = time to response; ULN = upper limit of normal.

Note: One additional report was included (the DESTINY-Breast03 Clinical Study Report).

[a]The first informed consent was signed on 09 August 2018 according to the DESTINY-Breast03 Clinical Study Report.

[b]G-CSF administration was not allowed within 1 week of screening assessment.

[c]Platelet transfusion was not allowed within 1 week of screening assessment.

[d]Red blood cell transfusion was not allowed within 1 week of screening assessment.

Source: DESTINY-Breast03 Clinical Study Report.[13]

Description of Studies

The key characteristics of the DESTINY-Breast03 study are summarized in Table 6. DESTINY-Breast03 was a phase III, multicentre, OL randomized controlled trial (RCT) 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 (N = 524).[12] The primary objective of the study was to compare the PFS benefits per 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.

Following screening, adult patients (aged 18 years or 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 including trastuzumab and taxane) were enrolled from July 20, 2018, to June 23, 2020, at 169 centres in 15 countries (1 site, n = 2 patients in Canada). Patients were randomized on a 1:1 ratio using an Interactive Web and Voice Response System to receive OL trastuzumab deruxtecan (5.4 mg/kg by IV infusion every 21 days) or OL trastuzumab emtansine (3.6 mg/kg by IV infusion every 21 days) until disease progression or unacceptable toxicity. Randomization was stratified by hormone receptor status (positive or negative), prior treatment with pertuzumab (yes or no), and history of visceral disease (yes or no). Following treatment discontinuation, patients were followed for survival every 3 months until death. Enrolment was complete and the study was ongoing at the time this report was prepared; the data cut-off for the results presented in this report was May 21, 2021. The study was funded by Daiichi Sankyo, who jointly developed and commercialized the drug with the sponsor.

Populations

Inclusion and Exclusion Criteria

Key eligibility criteria for the DESTINY-Breast03 study are summarized in Table 6. Adult patients (age 18 years or older) with pathologically documented MBC that was HER2-positive according to American Society for Clinical Oncology-College of American Pathologists criteria and was previously treated with taxane chemotherapy plus trastuzumab in the metastatic setting (or progressed within 6 months of neoadjuvant or adjuvant therapy with taxane chemotherapy plus trastuzumab) were eligible if documented disease progression occurred during or after the most recent treatment (or within 6 months of completing adjuvant therapy), at least 1 measurable lesion was present, and the patient had an ECOG PS of 0 or 1, with adequate hematological, renal, and hepatic function. Patients who had previously been treated with an anti-HER2 antibody drug conjugate in the metastatic setting were excluded; however, prior treatment in the adjuvant or neoadjuvant setting was allowed if disease progression had not occurred within 12 months of the end of adjuvant therapy. Patients with spinal cord compression or clinically active CNS metastases (untreated, symptomatic, or requiring treatment with corticosteroids; patients with inactive or asymptomatic brain metastases were eligible) or a history of clinically significant cardiovascular disease or ILD were excluded.

Baseline Characteristics

The baseline demographic characteristics of patients in the DESTINY-Breast03 study are shown in Table 7. The mean age was 54.4 years (SD = 11.47 years), approximately 60% of patients were Asian, and only 2 patients were male. Only 6.5% of patients were from North America.

The baseline disease characteristics of patients in the DESTINY-Breast03 study are shown in Table 8. In the trastuzumab deruxtecan arm, 59.0% of patients had an ECOG PS of 0 and 40.6% had an ECOG PS of 1, while in the trastuzumab emtansine arm, 66.5% of patients had an ECOG PS of 0 and 33.1% of patients 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 60% of patients had received prior pertuzumab, approximately 73% and 70% had visceral metastases at baseline or a reported history of visceral metastases, respectively, and approximately 16% and 22% had CNS metastases at baseline or a reported history of CNS metastases, respectively. Approximately 90% of patients had 3 or higher HER2

expression by immunohistochemistry. Approximately 72% of patients had received 2 lines or fewer prior systemic therapies excluding hormone therapies, while approximately 28% had received 3 or more lines of systemic therapy.

A more detailed summary of prior systemic therapies for breast cancer in the DESTINY-Breast03 study are shown in Table 9. All patients had received at least 1 prior systemic therapy for breast cancer and the mean number of prior regimens received was 3.3 (SD = 2.33 regimens). 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 (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, 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 meant to treat metastatic disease.

Table 7: Summary of Baseline Demographic Characteristics in the DESTINY-Breast03 Study (FAS)

Characteristic	Trastuzumab deruxtecan (n = 261)	Trastuzumab emtansine (n = 263)	Total (N = 524)
Age, years			
Mean (SD)	54.5 (11.11)	54.2 (11.84)	54.4 (11.47)
Median (range)	54.3 (27.9 to 83.1)	54.2 (20.2 to 83.0)	54.3 (20.2 to 83.1)
Age group, n (%)			
18 to 39 years	[redacted]	[redacted]	[redacted]
40 to 64 years	[redacted]	[redacted]	[redacted]
65 to 74 years	[redacted]	[redacted]	[redacted]
≥ 75 years	[redacted]	[redacted]	[redacted]
Sex, n (%)			
Male	1 (0.4)	1 (0.4)	2 (0.4)
Female	260 (99.6)	262 (9.6)	522 (99.6)
Race, n (%)			
Asian	152 (58.2)	162 (61.6)	314 (59.9)
White	71 (27.2)	72 (27.4)	143 (27.3)
Black or African American	10 (3.8)	9 (3.4)	19 (3.6)
Multiple	2 (0.8)	0	2 (0.4)
Other	26 (10.0)	20 (7.6)	46 (8.8)
Region, n (%)			
Asia	149 (57.1)	160 (60.8)	309 (59.0)
Europe	54 (20.7)	50 (19.0)	104 (19.8)
Rest of World	41 (15.7)	36 (13.7)	77 (14.7)

Characteristic	Trastuzumab deruxtecan (n = 261)	Trastuzumab emtansine (n = 263)	Total (N = 524)
North America	17 (6.5)	17 (6.5)	34 (6.5)
BMI, kg/m^2			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Smoking status, n (%)			
Never	[redacted]	[redacted]	[redacted]
Former	[redacted]	[redacted]	[redacted]
Current	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]

BMI = body mass index; FAS = full analysis set; SD = standard deviation.

[a]Age in years was calculated using the date of birth and the date of informed consent.

Source: DESTINY-Breast03 Clinical Study Report.[13]

Table 8: Summary of Baseline Disease Characteristics in the DESTINY-Breast03 Study (FAS)

Characteristic	Trastuzumab deruxtecan (n = 261)	Trastuzumab emtansine (n = 263)	Total (N = 524)
Stratification factor: hormone receptors by IXRS, n (%)[a]			
Positive	131 (50.2)	134 (51.0)	265 (50.6)
Negative	130 (49.8)	129 (49.0)	259 (49.4)
Estrogen receptors: derived, n (%)[a]			
Positive	[redacted]	[redacted]	[redacted]
Negative	[redacted]	[redacted]	[redacted]
Indeterminate	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Progesterone receptors: derived, n (%)[a]			
Positive	[redacted]	[redacted]	[redacted]
Negative	[redacted]	[redacted]	[redacted]
Indeterminate	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Stratification factor: prior treatment with pertuzumab by IXRS, n (%)			
Yes	[redacted]	158 (60.1)	[redacted]
No	[redacted]	105 (39.9)	[redacted]
Stratification factor: prior history of visceral disease by IXRS, n (%)			
Yes	184 (70.5)	185 (70.3)	369 (70.4)
No	77 (29.5)	78 (29.7)	155 (29.6)

Characteristic	Trastuzumab deruxtecan (n = 261)	Trastuzumab emtansine (n = 263)	Total (N = 524)
Baseline visceral disease, n (%)[b]			
Yes	195 (74.7)	189 (71.9)	384 (73.3)
No	66 (25.3)	74 (28.1)	140 (26.7)
Reported history of CNS metastases, n (%)			
Yes	62 (23.8)	52 (19.8)	114 (21.8)
No	199 (76.2)	211 (80.2)	410 (78.2)
Baseline CNS metastases, n (%)			
Yes	43 (16.5)	39 (14.8)	82 (15.6)
No	218 (83.5)	224 (85.2)	442 (84.4)
HER2 expression (IHC): central, n (%)			
1+	1 (0.4)	0	1 (0.2)
2+	25 (9.6)	30 (11.4)	55 (10.5)
3+	234 (89.7)	232 (88.2)	466 (88.9)
Not evaluable	1 (0.4)	1 (0.4)	2 (0.4)
HER2 gene amplification (ISH): central, n (%)			
Amplified	[redacted]	[redacted]	[redacted]
Non-amplified	[redacted]	[redacted]	[redacted]
Missing[c]	[redacted]	[redacted]	[redacted]
Lines of prior systemic therapy excluding hormone therapies, n (%)			
< 3	188 (72.0)	191 (72.6)	379 (72.3)
≥ 3	73 (28.0)	72 (27.4)	145 (27.7)
Lines of therapy before pertuzumab, n (%)			
< 3	[redacted]	[redacted]	[redacted]
≥ 3	[redacted]	[redacted]	[redacted]
Renal function at baseline, n (%)[d]			
Within normal range	[redacted]	[redacted]	[redacted]
Mild impairment	[redacted]	[redacted]	[redacted]
Moderate impairment	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Hepatic function at baseline, n (%)[e]			
Within normal range	[redacted]	[redacted]	[redacted]
Mild impairment	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]

Characteristic	Trastuzumab deruxtecan (n = 261)	Trastuzumab emtansine (n = 263)	Total (N = 524)
ECOG PS, n (%)			
0	154 (59.0)	175 (66.5)	329 (62.8)
1	106 (40.6)	87 (33.1)	193 (36.8)
Missing	1 (0.4)	1 (0.4)	2 (0.4)
Time from initial histological diagnosis to study treatment, months			
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]

AST = aspartate transaminase; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; EDC = electronic data capture; FAS = full analysis set; HER2 = human epidermal growth factor receptor; IHC = immunohistochemistry; ISH = in situ hybridization; IXRS = interactive web/voice response system; PS = performance status; SD = standard deviation; ULN = upper limit of normal.

[a]Hormone receptors were classified as positive if estrogen receptors and/or progesterone receptors were positive; were classified as negative if estrogen receptors and progesterone receptors were negative; and were classified as indeterminate if neither estrogen receptors nor progesterone receptors were positive and either estrogen receptors or progesterone receptors were indeterminate. Derived data are those reported from EDC.

[b]Baseline visceral disease was determined with any target or non-target tumour in defined lesion locations.

[c]During tissue screening, tissue samples were first tested for HER2 IHC. Only samples with HER2 IHC 2 or higher were tested for HER2 gene amplification (ISH).

[d]Normal renal function was classified as creatinine clearance of 90 mL per minute or more; mild renal impairment was classified as creatinine clearance of 60 mL per minute or more but less than 90 mL per minute; moderate renal impairment was classified as creatinine clearance of 30 mL per minute or more but less than 60 mL per minute; severe renal impairment was classified as creatinine clearance of 15 mL per minute or more but less than 30 mL per minute; and end-stage renal disease was classified as creatinine clearance of less than 15 mL per minute.

[e]Normal hepatic function was classified as total bilirubin less than or equal to the ULN (and AST less than or equal to the ULN) except for patients with Gilbert syndrome, or total bilirubin less than or equal to 3.0 times the ULN (and AST less than or equal to the ULN) in patients with Gilbert syndrome; mild hepatic dysfunction was classified as total bilirubin greater than the ULN but less than or equal to 1.5 times the ULN (any AST) except for patients with Gilbert syndrome, or total bilirubin greater than the ULN but less than or equal to 3.0 times the ULN (and AST greater than the ULN) for patients with Gilbert syndrome, or total bilirubin less than or equal to the ULN (and AST greater than the ULN) regardless of Gilbert syndrome; moderate hepatic dysfunction was classified as total bilirubin greater than 1.5 times the ULN but less than or equal to 3.0 times the ULN (any AST) except for patients with Gilbert syndrome; and severe hepatic dysfunction was classified as total bilirubin greater than 3.0 times the ULN (and any AST) regardless of Gilbert syndrome.

Source: DESTINY-Breast03 Clinical Study Report.[13]

Table 9: Summary of Prior Breast Cancer Systemic Therapy in the DESTINY-Breast03 Study (FAS)

Characteristic	Trastuzumab deruxtecan (n = 261)	Trastuzumab emtansine (n = 263)	Total (N = 524)
Any prior systemic cancer therapy, n (%)			
Yes	[redacted]	[redacted]	[redacted]
No[a]	[redacted]	[redacted]	[redacted]
Number of prior regimens			
0, n (%)[a]	[redacted]	[redacted]	[redacted]
1, n (%)	[redacted]	[redacted]	[redacted]
2, n (%)	[redacted]	[redacted]	[redacted]
3, n (%)	[redacted]	[redacted]	[redacted]
4, n (%)	[redacted]	[redacted]	[redacted]
≥ 5, n (%)	[redacted]	[redacted]	[redacted]

Characteristic	Trastuzumab deruxtecan (n = 261)	Trastuzumab emtansine (n = 263)	Total (N = 524)
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Lines of prior systemic therapy in the metastatic setting, n (%)[b]			
0, n (%)[a]	[redacted]	[redacted]	[redacted]
1, n (%)	[redacted]	[redacted]	[redacted]
2, n (%)	[redacted]	[redacted]	[redacted]
3, n (%)	[redacted]	[redacted]	[redacted]
4, n (%)	[redacted]	[redacted]	[redacted]
≥ 5, n (%)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Lines of prior systemic therapy in the metastatic setting, not including hormone therapy, n (%)[b]			
0, n (%)[a]	2 (0.8)	3 (1.1)	5 (1.0)
1, n (%)	130 (49.8)	123 (46.8)	253 (48.3)
2, n (%)	56 (21.5)	65 (24.7)	121 (23.1)
3, n (%)	35 (13.4)	35 (13.3)	70 (13.4)
4, n (%)	15 (5.7)	19 (7.2)	34 (6.5)
≥ 5, n (%)	23 (8.8)	18 (6.8)	41 (7.8)
Mean (SD)	2.2 (1.85)	2.1 (1.69)	2.1 (1.77)
Median (range)	1 (0 to 16)	2 (0 to 14)	2 (0 to 16)
Intent of prior breast cancer therapy in the metastatic setting, n (%)[b,c]			
Neoadjuvant	[redacted]	[redacted]	[redacted]
Adjuvant	[redacted]	[redacted]	[redacted]
Locally advanced	[redacted]	[redacted]	[redacted]
Metastatic	[redacted]	[redacted]	[redacted]
Preventive	[redacted]	[redacted]	[redacted]
Maintenance	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Intent of prior cancer systemic therapy: trastuzumab, n (%)[d,e]			
Neoadjuvant	[redacted]	[redacted]	[redacted]
Adjuvant	[redacted]	[redacted]	[redacted]
Locally advanced	[redacted]	[redacted]	[redacted]
Metastatic	[redacted]	[redacted]	[redacted]
Preventive	[redacted]	[redacted]	[redacted]

Characteristic	Trastuzumab deruxtecan (n = 261)	Trastuzumab emtansine (n = 263)	Total (N = 524)
Maintenance	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]

FAS = full analysis set; SD = standard deviation.

[a]Prior cancer systemic therapy case report form pages were not completed for 2 patients who were mistakenly randomized but not treated.

[b]The definition of "lines of prior systemic therapy in the metastatic setting" included patients for whom the therapy was intended to treat locally advanced, metastatic, or "other" (palliative) disease and patients for whom the therapy was intended as neoadjuvant, adjuvant, or maintenance and whose disease progressed within 6 months from the end of therapy (12 months for pertuzumab), only if the date of the end of therapy and the date of progression were present after imputation.

[c]Patients may have received more than 1 type of therapy.

[d]Percentages are based on the number of patients with the corresponding prior cancer systemic therapy.

[e]Percentages are based on the number of patients who received trastuzumab as prior cancer systemic therapy.

Source: DESTINY-Breast03 Clinical Study Report.[13]

Interventions

Trastuzumab deruxtecan (starting dose 5.4 mg/kg) was administered as an IV infusion over 90 minutes for the first dose and over a minimum of 30 minutes for subsequent doses on day 1 of a 21-day treatment cycle. Trastuzumab emtansine (starting dose of 3.6 mg/kg) was administered in a similar manner. Treatment was continued until disease progression (per IA), unacceptable toxicity, treatment delay of 4 weeks or longer, withdrawal of consent, physician decision, or death, whichever occurred first.

Prophylactic treatment of drug-related nausea and vomiting was permitted at the investigator's discretion per institutional guidelines. It was recommended that patients receive prophylactic antiemetic drugs before infusion of trastuzumab deruxtecan and on subsequent days. Hematopoietic growth factors could be used for prophylaxis or treatment at the investigator's discretion. Use of other anticancer therapies (except for bisphosphonates or RANKL pathway inhibitors for the prevention or treatment of skeletal-related events), chloroquine or hydroxychloroquine, investigational drugs, radiotherapy (except for palliative radiation to metastatic sites if it did not affect response assessment or interrupt treatment for longer than 4 weeks), and long-term use of corticosteroids or other immunosuppressive medications were prohibited during the treatment period.

Guidelines for dose modification of trastuzumab deruxtecan due to toxicity are provided in Appendix 2. Does modifications of trastuzumab emtansine due to toxicity were made based on the locally approved label. Two dose reductions were permitted for each treatment arm (trastuzumab deruxtecan: starting dose of 5.4 mg/kg, first dose reduction to 4.4 mg/kg, second dose reduction to 3.2 mg/kg; trastuzumab emtansine: starting dose of 3.6 mg/kg, first dose reduction to 3.0 mg/kg, second dose reduction to 2.4 mg/kg). Once the dose of the study drug was reduced due to toxicity, all subsequent cycles were administered at that lower dose level unless further dose reduction was required. No dose re-escalations were allowed. If toxicity continued after 2 dose reductions, then the patient was withdrawn from the study drug. The dose could have been interrupted for up to 28 days from the planned date of administration. If a patient was assessed as requiring a dose delay of longer than 28 days, they were permanently discontinued from the study treatment.

Outcomes

A list of efficacy end points identified in the CADTH review protocol that were assessed in the clinical trial included in this review is provided in Table 10. These end points are further

summarized in the following text. A detailed discussion and critical appraisal of the outcome measures is provided in Appendix 3.

Table 10: Summary of Outcomes of Interest Identified in the CADTH Review Protocol

Outcome measure	DESTINY-Breast03	Definitions
OS	Key secondary	OS was defined as the time from the date of randomization to the date of death due to any cause. If no death was reported for a patient before the data cut-off, OS was censored at the last contact date at which the patient was known to be alive.
PFS per BICR	Primary	PFS was defined as the time from the date of randomization to the earliest date of the first objective documentation of radiographic disease progression per IA or BICR according to mRECIST v1.1 or death due to any cause. Patients who were alive with no objective documentation of (radiographic) disease progression by the data cut-off date were censored at the date of their last evaluable tumour assessment. Refer to Table 11 for PFS censoring rules.
PFS per IA	Secondary	
EORTC QLQ-C30	Other	NA
EORTC QLQ-BR45	Other	NA
EQ-5D-5L	Other	NA
ORR per BICR and IA	Secondary	ORR was defined as the proportion of patients who achieved a best overall response of CR or PR.
DOR per BICR and IA	Secondary	DOR was defined as the time from the date of the first documentation of objective response (CR or PR) to the date of the first documentation of disease progression based on BICR or IA or to the date of death due to any cause. DOR was measured only for patients with a response of CR or PR. Patients who were progression free at the time of the analyses were to be censored at the date of the last evaluable tumour assessment. Refer to Table 11 for DOR censoring rules.

BICR = blinded independent central review; CR = complete response; DOR = duration of response; EORTC QLQ-BR45 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer 45; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; IA = investigator assessment; mRECIST = modified Response Evaluation Criteria in Solid Tumours; NA = not applicable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response.

Source: DESTINY-Breast03 Clinical Study Report.[13]

OS, PFS, ORR, and DOR are standard and broadly accepted outcome measures in oncology trials for the treatment of MBC (refer to Table 10 and Table 11 for outcome definitions and censoring rules). Tumour assessment by CT/MRI of the chest, abdomen, pelvis, and any other sites of disease was performed during screening (within 4 weeks of cycle 1 day 1). CT or MRI of the brain was also performed during screening. During the treatment period, tumour imaging was performed every 6 weeks as well as within 1 week of study drug discontinuation; brain imaging was mandatory on the same schedule for patients with baseline stable brain metastases and was conducted if clinically indicated in other patients. Involvement of all sites of disease identified during screening and any additional newly suspected sites of progressive disease was assessed. For patients who discontinued treatment for reasons other than disease progression, tumour assessments were to be continued until disease progression. The same imaging modality was used for each patient throughout the study. Anonymized copies of all scans were sent for BICR.

Tumour response was assessed using mRECIST version 1.1.[19] Progressive disease was defined as a predefined increase in the sum of diameters of target lesions (at least 20%), taking as reference the smallest sum of diameters on study, in target lesions or the appearance of new non-target lesions; the sum must also have demonstrated an absolute increase of at least 5 mm. Partial response was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Complete response was defined as the disappearance of all target lesions with a reduction of the short axis of any pathological lymph nodes to less than 10 mm. Stable disease was defined as neither sufficient shrinkage (compared to baseline) to qualify for partial response nor sufficient increase (taking as reference the smallest sum of diameters while on study) to qualify for progressive disease. Under the mRECIST version 1.1 criteria, assessment of response by investigators was based on local imaging scans as well as clinical evaluation (e.g., using skin caliper measurements). An initial indication of response was confirmed at the next scheduled assessment.

Decisions to discontinue protocol therapy due to progressive disease were made by the investigator based on local imaging scans and clinical evaluation to assess clinical deterioration in the absence of radiological evidence. Patients who discontinued treatment without documented progressive disease continued to have radiological assessments every 6 weeks until progressive disease, death, or the date of study termination. Following disease progression, patients were followed up for survival every 3 months until death.

Patient-reported HRQoL was assessed using the EQ-5D-5L, EORTC QLQ-C30, and EORTC QLQ-BR45 instruments on day 1 of cycles 1, 2, 3, and then every 2 cycles thereafter as well as at the time of study drug discontinuation. For a detailed description of the measurement properties of these instruments, refer to Appendix 3. Neither the measurement properties nor the minimal important difference (MID) of these instruments have been specifically established in patients with HER2-positive MBC. However, differences in the EQ-5D-5L index score of approximately 0.037 to 0.056 in the general Canadian population, differences of approximately 7 to 12 points in the EQ visual analogue scale (VAS) among cancer patients, and differences of approximately 4 to 18 points in the EORTC QLQ-C30 individual items and scale scores among patients with MBC are typically considered significant. MIDs for EORTC QLQ-BR45 individual items and scale scores are uncertain.

- The EQ-5D-5L[20] is a generic, preference-based measure of HRQoL consisting of 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression; index scores range from 0 to 1, with 0 and 1 representing the health states "dead" and "perfect health," respectively, while EQ VAS scores range from 0 to 100, with 0 and 100 representing "worst imaginable health" and "best imaginable health," respectively.
- The EORTC QLQ-C30[21] is a multidimensional, cancer-specific, self-administered measure of HRQoL consisting of 30 questions across 5 multi-item functional scales, 3 multi-item symptom scales, 6 single-item symptom scales, and a 2-item global HRQoL scale. Each item is evaluated using 4- and 7-point Likert scales, raw scores for each scale are computed as the average of the items that contribute to a particular scale, and each raw scale score is converted to a standardized score that ranges from 0 to 100 using a linear transformation, with a higher score reflecting better function on the function scales, higher symptoms on the symptom scales, and better HRQoL on the global quality of life scale.
- The EORTC QLQ-BR45[22] is a 45-item patient-reported, breast cancer-specific, HRQoL questionnaire; each item is evaluated using 4-point Likert scales, where raw scores for each scale are computed as the average of the items that contribute to a particular scale,

and each raw scale score is converted to a standardized score that ranges from 0 to 100 using a linear transformation, with a higher score reflecting better function on the function scales, higher symptoms on the symptom scales, and better HRQoL on the global quality of life scale.

Harms outcomes included treatment-emergent AEs, SAEs, AEs requiring dose reduction, WDAEs, adverse events of special interest (AESIs), and deaths. AESIs were defined as ILD or pneumonitis and LV dysfunction. AEs that began or worsened on or after the start of protocol therapy until 47 days after the last dose of the study drug were captured. AEs were defined as any untoward medical occurrence and were coded according to Medical Dictionary for Regulatory Activities, version 23.0,[23] and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.[24]

Statistical Analysis

The statistical analysis of efficacy outcomes in the DESTINY-Breast03 study is summarized in Table 11. Randomization stratification factors were used in the primary efficacy analysis of PFS per BICR, sensitivity analyses of PFS per BICR, analysis of OS, analysis of PFS per IA, and analysis of ORR per BICR. In addition, the following key prognostic factors were used in a Cox regression model as covariates for PFS per BICR assessment as well as treatment arm: ECOG PS (0 or 1), lines of prior systemic therapy not including hormone therapy (< 3 or ≥ 3), clinically inactive CNS metastases at baseline (yes or no), and age (< 65 or ≥ 65 years). Missing or dropout data were not imputed unless otherwise specified.

Planned Analyses and Multiplicity Control

In the initial version of the protocol, the primary efficacy end point of PFS by BICR was to be analyzed when approximately 331 BICR-assessed PFS events had been observed. The primary efficacy end point, PFS, and the key secondary efficacy end point, OS, would be tested hierarchically to maintain the overall 2-sided type I error rate to 0.05 or less.

Protocol Changes

Based on emergent data from the DESTINY-Breast01 study,[16] the sponsor believed there was a strong rationale to evaluate the primary efficacy end point of PFS at an earlier time point. Therefore, the protocol was amended to add an interim analysis of PFS, which was to be conducted after approximately 234 BICR-assessed PFS events (70% information fraction) had been observed. If the study was not statistically significant at this interim analysis, the final PFS analysis was to be performed after observing 335 BICR-assessed PFS events. A group sequential design, using a 2-look Lan-DeMets alpha spending function with O'Brien-Fleming efficacy boundary, would be used to control the type I error rate for the primary efficacy analysis with an overall 2-sided significance level of 0.05.

To ensure that the study would be declared positive only if the results from the PFS interim analysis were robust enough to demonstrate not only statistical strength of evidence but also a highly clinically relevant magnitude of benefit compared with the control arm, the final version of the protocol changed the efficacy boundaries from the O'Brien-Fleming to the Haybittle-Peto efficacy boundaries with a 2-sided P value of 0.000204 for the interim analysis. A subsequent protocol change allowed up to 2 planned interim PFS analyses and a final analysis of OS, provided PFS was statistically significant. The final OS analysis was planned after approximately 250 OS events had been documented. A group sequential design, using a 3-look Lan-DeMets alpha spending function with an O'Brien-Fleming efficacy boundary, was used to construct the efficacy stopping boundaries for OS with an overall 2-sided significance

level of 0.05. If PFS was significant in the interim analysis for PFS, an interim analysis for OS was also to be performed. This guaranteed the protection of the overall significance level across the 2 hypotheses and the repeated testing of the OS hypotheses in the interim and the final analyses.

Power for Interim and Final Analyses

Assuming a median PFS of 9.6 months in the trastuzumab emtansine arm (based on the results of the EMILIA study[25]), it was hypothesized that treatment with trastuzumab deruxtecan would result in an HR of 0.7, corresponding to an improvement in median PFS from 9.6 months in the trastuzumab emtansine arm to 13.7 months in the trastuzumab deruxtecan arm under the exponential model assumption. A total of approximately 500 patients were planned to be randomized (250 patients to trastuzumab deruxtecan and 250 patients to trastuzumab emtansine). An interim analysis allowing the study to declare superiority for the primary PFS end point was planned after approximately 234 (70%) of the targeted PFS events were documented. The final PFS analysis would occur after approximately 335 PFS events had been documented, but only if superiority was not demonstrated at the interim analysis. With 335 PFS events, the study would have approximately 90.4% power to detect an HR of 0.70 in PFS at an overall 2-sided significance level of 0.05 to reject the null hypothesis (HR = 1) using a log-rank test and a 2-look group sequential design with Haybittle-Peto efficacy boundary.

OS would be compared between the 2 treatment groups provided that the test of the primary end point PFS was statistically significant at either the interim analysis or final analysis. Assuming a median OS of 29.9 months in the trastuzumab emtansine arm based on the results of the EMILIA study, it was hypothesized that treatment with trastuzumab deruxtecan would result in an HR of 0.7 for OS, corresponding to an improvement in median OS from 29.9 months in the trastuzumab emtansine to 42.7 months in the trastuzumab deruxtecan arm under the exponential model assumption. With 250 OS events, the study would have approximately 80% power (conditional on PFS being statistically significant) to detect an HR of 0.70 in OS at an overall 2-sided significance level of 0.05 to reject the null hypothesis (HR = 1) using a log-rank test and a 3-look group sequential design with Lan-DeMets alpha spending function with an O'Brien-Fleming efficacy boundary. If the true HR was 0.7, it was estimated that approximately 96 (38.4%) and 153 (61.2%) of the targeted OS events would be documented at the timing of the 2 OS interim analyses (when PFS interim and final analyses were performed).

Analytical Techniques

For the primary end point (PFS per BICR) and key secondary end point (OS), the trastuzumab deruxtecan and trastuzumab emtansine arms were compared using a 2-sided stratified log-rank test. The HR comparing treatment arms was calculated from stratified Cox proportional hazards model with treatment as the sole covariate. Stratification factors for these analyses were hormone receptor status, prior pertuzumab, and visceral disease. CIs adjusted for the corresponding significance level (95%) of the HR were calculated. The PFS and OS functions were estimated using the Kaplan-Meier (KM) product limit method; 2-sided 95% CIs for median survival were obtained by log-rank transformation. PFS and OS rates at fixed time points and their 95% CIs were derived from KM analysis. Analysis of PFS per IA as a secondary outcome and analysis of DOR was performed in the same manner as the primary analysis. Note that the primary analysis of PFS per BICR was not censored due to initiation of other anticancer therapy following study drug discontinuation (although censoring was incorporated in a sensitivity analysis of PFS per BICR). Similarly, OS was not censored at

the time of initiating new anticancer therapy following study drug discontinuation.ORR and its exact 95% CI was calculated in each treatment group using the Clopper-Pearson method. The differences in ORRs between treatment groups and corresponding 95% CIs were calculated using the Cochran-Mantel-Haenszel methodology adjusted by stratification factors used for randomization. Stratified ORs and their 95% CIs were calculated using the Mantel-Haenszel estimator. Patients who discontinued the study and tumour assessments before objective response were counted as nonresponders. Patient-reported HRQoL data (i.e., EQ-5D-5L index score, EQ VAS, EORTC QLQ-C30, and EORTC QLQ-BR45) were presented as descriptive and summary statistics.

Sensitivity analyses for the primary analysis of PFS per BICR included unstratified analysis with stratification factors as covariates, stratified analysis in the per-protocol set, analysis including censoring of PFS at the initiation of new anticancer therapy, analysis of PFS with back-dating progression for PFS events that occurred after the patient missed 1 or more tumour assessments, and multiple Cox regression analyses with additional covariates (set 1: age, ECOG PS, lines of prior systemic therapy not including hormone therapy, baseline CNS metastases; set 2: age, ECOG PS, lines of prior systemic therapy not including hormone therapy, history of CNS metastases).

Subgroup analyses of prespecified subgroups (by hormone receptor status, estrogen receptors, progesterone receptors, prior treatment with pertuzumab, lines of prior systemic therapy not including hormone therapy, renal impairment at baseline, hepatic impairment at baseline, baseline visceral disease, baseline lung metastases, baseline liver metastases, baseline CNS metastases, reported history of CNS metastases, age, race, region, and ECOG PS) were conducted per the primary analysis in exploratory fashion. The study was not specifically powered to evaluate outcomes in individual strata, and testing for interactions were not conducted.

Table 11: Statistical Analysis of Efficacy End Points in the DESTINY-Breast03 Study

End point	Position in hierarchy	Statistical model	Adjustment factors	Sensitivity analyses	Censoring rules	Handling of missing data
OS (key secondary)	2 (alpha = 0.05)	Per primary analysis of PFS per BICR (FAS)	Per primary analysis of PFS per BICR	Multiple Cox regression analysis with additional covariates (set 1: age, ECOG PS, lines of prior systemic therapy not including hormone therapy, baseline CNS metastases; set 2: age, ECOG PS, lines of prior systemic therapy not including hormone therapy, history of CNS metastases)	At the last contact date at which the patient was known to be alive; patients not known to have died were also censored if the interval between the last contact date and the data cut-off date was longer than the protocol-defined 3-month interval plus 2 weeks	Censoring
PFS per BICR (primary)	1 (alpha = 0.05)	Two-sided log-rank test stratified by randomization factors (FAS); KM analysis with median PFS and 95% CIs calculated via the Brookmeyer and Crowley method; PFS rates at fixed time points from KM analysis with 2-sided CIs; HRs and CIs calculated using stratified Cox proportional hazards model with treatment arm as the sole covariate	Stratification factors: • hormone receptor status • prior pertuzumab • history of visceral disease	• Unstratified analysis • Stratified analysis in the PP set • Analysis with censoring for new anticancer therapy • Analysis with back-dating progression for PFS events that occurred after the patient missed 1 or more tumour assessments • Multiple Cox regression analysis with additional covariates (set 1: age, ECOG PS, lines of prior systemic therapy not including hormone therapy, baseline CNS metastases; set 2: age, ECOG PS, lines of prior systemic therapy not	At date of randomization for patients with no baseline evaluable tumour assessment or patients with no post-baseline tumour assessment; at date of last evaluable tumour assessment before earliest of death or progression and data cut-off date for patients who had disease progression or death after missing ≥ 2 consecutive tumour assessments; or at date of last evaluable tumour assessment	Censoring

End point	Position in hierarchy	Statistical model	Adjustment factors	Sensitivity analyses	Censoring rules	Handling of missing data
				including hormone therapy, history of CNS metastases)	before the data cut-off date for patients with at least 1 post-baseline response assessment without death or objective documentation of radiographic disease progression	
PFS per IA (secondary)	Not included	Per primary analysis of PFS per BICR (FAS)	Per primary analysis of PFS per BICR	None	Per primary analysis of PFS per BICR	Censoring
EORTC QLQ-C30 (other)	Not included	Descriptive and summary statistics (FAS)	None	None	NA	Imputation according to EORTC QLQ-C30 manual
EORTC QLQ-BR45 (other)	Not included	Descriptive and summary statistics (FAS)	None	None	NA	Imputation according to EORTC QLQ-BR45 manual
EQ-5D-5L (other)	Not included	Descriptive and summary statistics (FAS)	None	None	NA	Imputation according to EQ-5D-5L manual
ORR per IA and BICR (secondary)	Not included	ORRs and 2-sided 95% CI scalculated using the Clopper-Pearson method; difference between ORRs and 95% CIs calculated using continuity correction; stratified 2-sided CMH test to compare ORRs (FAS)	Per primary analysis of PFS per BICR	None	None	CCA

End point	Position in hierarchy	Statistical model	Adjustment factors	Sensitivity analyses	Censoring rules	Handling of missing data
DOR per IA and BICR (secondary)	Not included	KM analysis with median PFS and 95% CIs calculated via the Brookmeyer and Crowley method (FAS)	None	None	Per primary analysis of PFS per BICR	Censoring

BICR = blinded independent central review; CCA = complete case analysis; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CNS = central nervous system; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-BR45 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer 45; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FAS = full analysis set; HR = hazard ratio; IA = investigator assessment; KM = Kaplan-Meier; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PP = per protocol; PS = performance status.

Source: DESTINY-Breast03 Clinical Study Report.[13]

Analysis Populations

The full analysis set (FAS) included all randomized patients; following the intent-to-treat principle, patients were analyzed according to the treatments and strata to which they were assigned at randomization. The per-protocol set included all patients from the FAS who complied sufficiently with the protocol with respect to exposure to study treatment, availability of tumour assessments, and absence of major protocol deviations likely to affect efficacy outcomes (requirements were to have received at least 1 dose of the study drug intended, as per randomization; at least 1 evaluable post-baseline tumour assessment per BICR or died within 14 weeks of first dose; absence of major protocol deviations). The safety analysis set included all randomized patients who received at least 1 dose of the study treatment; patients were summarized according to the treatment they actually received.

Results

Patient Disposition

Patient disposition in the DESTINY-Breast03 study is summarized in Table 12. A total of 699 patients were screened, of which 175 (25.0%) were categorized as screen failures. An analysis of reasons for screen failure was not provided. The remaining 524 patients were randomized to the trastuzumab deruxtecan (n = 261) and trastuzumab emtansine (n = 263) arms for OL treatment. The vast majority of participants (98% in the trastuzumab deruxtecan arm and 99.2% in the trastuzumab emtansine arm) received at least 1 dose of the study drug. The mean study duration was months (SD = [redacted] months) in the trastuzumab deruxtecan arm and [redacted] months (SD = [redacted] months) in the trastuzumab emtansine arm. As of the May 21, 2021, data cut-off, approximately 49% and 82% of patients in the trastuzumab deruxtecan and trastuzumab emtansine arms, respectively, had discontinued treatment. The most common reasons for treatment discontinuation were progressive disease (trastuzumab deruxtecan = 25.7%; trastuzumab emtansine = 60.5%) and AEs (trastuzumab deruxtecan = 13.6%; trastuzumab emtansine = 6.5%). In the trastuzumab deruxtecan arm, 5.1% of patients discontinued treatment due to patient withdrawal and 1.6% discontinued treatment due to clinical progression per IA, while in the trastuzumab emtansine arm, 4.2% of patients discontinued treatment due to patient withdrawal and 4.6% discontinued treatment due to clinical progression per IA.

Table 12: Patient Disposition in the DESTINY-Breast03 Study

Disposition	Trastuzumab deruxtecan	Trastuzumab emtansine
Screened, N	699	
Screen failures, n (%)	175 (25.0)	
Randomized, N (%)	261 (100.0)	263 (100.0)
Treated	257 (98.5)	261 (99.2)
Not treated	4 (1.5)	2 (0.8)
Study duration (months)[a]		
Mean (SD)	[redacted]	[redacted]
Median (range)	16.2 (0.0 to 32.7)	15.3 (0.0 to 31.3)

Disposition	Trastuzumab deruxtecan	Trastuzumab emtansine
Treatment status, n (%)[b]		
Ongoing on study drug	132 (51.4)	47 (18.0)
Discontinued study drug	125 (48.6)	214 (82.0)
Primary reason for discontinuation of study drug, n (%)		
Progressive disease per mRECIST v. 1.1	66 (25.7)	158 (60.5)
AE	35 (13.6)	17 (6.5)
Withdrawal by patient	13 (5.1)	11 (4.2)
Clinical progression per investigator	4 (1.6)	12 (4.6)
Death	3 (1.2)	3 (1.1)
Physician decision	2 (0.8)	8 (3.1)
Other	2 (0.8)[c]	5 (1.9)[d]
FAS, n (%)	261 (100.0)	263 (100.0)
PP set, n (%)	253 (96.9)	249 (94.7)
Safety set, n (%)	257 (98.5)	261 (99.2)

AE = adverse events; FAS = full analysis set; mRECIST = modified Response Evaluation Criteria in Solid Tumours; PP = per protocol; SD = standard deviation.

[a]Study duration (months) was defined as (end of study participation date – randomization date + 1)/365.25 × 12.

[b]The percentage was based on the number of patients in the safety analysis set (257 patients in the trastuzumab deruxtecan arm and 261 patients in the trastuzumab emtansine arm).

[c]Two patients were off the study drug for more than 28 days.

[d]One patient was noncompliant, 1 patient had a persistent tumour at the gamma knife site in the brain, 1 patient withdrew due to patient decision, 1 patient was off the study drug for more than 28 days, and 1 patient had hepatic failure.

[e]Patients withdrew consent for tumour assessments but were followed for survival.

Source: DESTINY-Breast03 Clinical Study Report.[13]

Major protocol deviations during the DESTINY-Breast03 study (those that had the potential to impact patient safety, substantially alter risks to patients, affect the integrity of study data, influence the conduct of the study, or affect the patient's willingness to participate in the study) are summarized in Table 13. Major protocol deviations occurred in 26 (10.0%) patients randomized to the trastuzumab deruxtecan arm and 22 (8.4%) patients randomized to the trastuzumab emtansine arm.

Exposure to Study Treatments

Treatment exposure in the DESTINY-Breast03 study is summarized in Table 14. Treatment compliance was assessed by site personnel during IV infusion of the study drug at each visit. As of the May 21, 2021, data cut-off date, the mean duration of treatment was [redacted] months (SD = [redacted] months) in the trastuzumab deruxtecan arm and [redacted] months (SD = [redacted] months) in the trastuzumab emtansine arm. The mean relative dose intensity approached 100% in both treatment arms.

Anticancer therapies received after discontinuation of the study treatment in the DESTINY-Breast03 study are summarized in Table 15. As of the May 21, 2021, data cut-off date, smaller proportions of patients randomized to the trastuzumab deruxtecan arm had initiated new radiation, surgery, or systemic therapy for cancer (3.8%, 0.8%, and 29.9%, respectively) following discontinuation of the study drug compared with the trastuzumab

emtansine arm (9.5%, 3.8%, and 62.4%, respectively). Following study drug discontinuation, higher proportions of patients randomized to receive trastuzumab deruxtecan received trastuzumab emtansine as subsequent therapy compared with patients randomized to receive trastuzumab emtansine (16.5% versus 6.5%). By contrast, following study drug discontinuation, lower proportions of patients randomized to receive trastuzumab deruxtecan versus trastuzumab emtansine received trastuzumab (8.8% versus 25.1%), trastuzumab deruxtecan (0% versus 11.4%), pertuzumab (4.2% versus 9.5%), taxane chemotherapy (1.9% versus 6.1%), taxane chemotherapy plus trastuzumab (1.1% versus 5.7%), other anti-HER2 drugs (6.1% versus 27.8%), hormone therapy (5.0% versus 8.0%), and other systemic therapy (15.3% versus 47.9%).

Table 13: Protocol Deviations in the DESTINY-Breast03 Study (FAS)

Protocol deviation	Trastuzumab deruxtecan (n = 261)	Trastuzumab emtansine (n = 263)	Total (N = 524)
Patients with any major protocol deviation, n (%)	[redacted]	[redacted]	[redacted]
Related to COVID-19	[redacted]	[redacted]	[redacted]
Type of major protocol deviation, n (%)			
Study procedures criteria	[redacted]	[redacted]	[redacted]
Related to COVID-19	[redacted]	[redacted]	[redacted]
Investigational product compliance	[redacted]	[redacted]	[redacted]
Eligibility criteria	[redacted]	[redacted]	[redacted]
Informed consent	[redacted]	[redacted]	[redacted]
Concomitant medication	[redacted]	[redacted]	[redacted]
Laboratory assessment criteria (results out of window)	[redacted]	[redacted]	[redacted]
Efficacy criteria	[redacted]	[redacted]	[redacted]
Serious adverse event reporting	[redacted]	[redacted]	[redacted]

FAS = full analysis set.

Note: For each category and deviation, patients were counted only once, regardless off the number of events in that category of deviation.

Source: DESTINY-Breast03 Clinical Study Report.[13]

Table 14: Treatment Exposure in the DESTINY-Breast03 Study (Safety Set)

Treatment exposure	Trastuzumab deruxtecan (n = 257)	Trastuzumab emtansine (n = 261)
Treatment duration, months[a]		
Mean (SD)	[redacted]	[redacted]
Median (range)	14.30 (0.7 to 29.8)	6.90 (0.7 to 25.1)
Duration of treatment as of data cut-off date, n (%)		
≤ 3 months	[redacted]	[redacted]
> 3 to 6 months	[redacted]	[redacted]
> 6 to 9 months	[redacted]	[redacted]
> 9 to 12 months	[redacted]	[redacted]
> 12 to 18 months	[redacted]	[redacted]
> 18 to 24 months	[redacted]	[redacted]
> 24 months	[redacted]	[redacted]
Dose intensity, mg/kg per 3 weeks[b]		
Mean (SD)	5.0 (0.56)	3.4 (0.30)
Median (range)	[redacted]	[redacted]
Relative dose intensity, %[c]		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]

SD = standard deviation.

[a]Treatment duration = (last dose date – first dose date + 21) × 12/365.25 (interruptions included).

[b]Dose intensity (mg/kg per 3 weeks) = total amount of drug taken / (treatment duration [days]/21).

[c]Relative dose intensity (%) = dose intensity/planned dose intensity × 100.

Source: DESTINY-Breast03 Clinical Study Report.[13]

Table 15: Subsequent Therapies in the DESTINY-Breast03 Study Received Following Study Drug Discontinuation (FAS)

Subsequent treatment, n (%)	Trastuzumab deruxtecan (n = 261)	Trastuzumab emtansine (n = 263)
Patients receiving radiation, n (%)	10 (3.8)	25 (9.5)
Patients receiving surgery, n (%)	2 (0.8)	10 (3.8)
Patients receiving ≥ 1 new systemic anticancer therapy, n (%)[a]	78 (29.9)	164 (62.4)
Types of new systemic anticancer therapies, n (%)[a]		
Trastuzumab	23 (8.8)	66 (25.1)
Trastuzumab deruxtecan	0	30 (11.4)
Trastuzumab emtansine	43 (16.5)	17 (6.5)

Subsequent treatment, n (%)	Trastuzumab deruxtecan (n = 261)	Trastuzumab emtansine (n = 263)
Pertuzumab	11 (4.2)	25 (9.5)
Taxane	5 (1.9)	16 (6.1)
Taxane plus trastuzumab	3 (1.1)	15 (5.7)
Other anti-HER2 agent	16 (6.1)	73 (27.8)
Anti-HER2 TKI	13 (5.0)	66 (25.1)
Other anti-HER2 antibody or ADC	3 (1.1)	13 (4.9)
Hormone therapy	13 (5.0)	21 (8.0)
Other systemic therapy	40 (15.3)	126 (47.9)

ADC = antibody drug conjugate; FAS = full analysis set; HER2 = human epidermal growth factor receptor 2; TKI = tyrosine kinase inhibitor.

[a]Denominator is the full analysis set.

Note: Patients may have received more than 1 subsequent treatment.

Source: Cortés et al. (2022).[12]

Note that the primary analysis of PFS per BICR was not censored due to initiation of other anticancer therapies following study drug discontinuation (although censoring was incorporated into a sensitivity analysis of PFS per BICR). Similarly, OS was not censored at the time of initiating a new anticancer therapy following study drug discontinuation. Crossover from trastuzumab deruxtecan to trastuzumab emtansine (trastuzumab deruxtecan arm = 16.5%), crossover from trastuzumab emtansine to trastuzumab deruxtecan (trastuzumab emtansine arm = 11.4%), and post-progression re-treatment with trastuzumab emtansine (trastuzumab emtansine arm = 6.5%) were imbalanced between treatment arms.

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported in the following. Refer to Appendix 3 for detailed efficacy data (sensitivity and subgroup analyses of PFS per BICR and OS).

Table 16: OS in the DESTINY-Breast03 Study (FAS)

Parameter	Trastuzumab deruxtecan (n = 261)	Trastuzumab emtansine (n = 263)
Patients with events (deaths), n (%)	33 (12.6)	53 (20.2)
Patients without events (censored), n (%)	228 (87.4)	210 (79.8)
Alive	215 (82.4)	192 (73.0)
Lost to follow-up	[redacted]	[redacted]
Median OS (95% CI), months[a]	NE (NE to NE)	NE (NE to NE)
Stratified log-rank P value[b]	0.007172	
Stratified Cox proportional HR (95% CI)[b]	0.5546 (0.3587 to 0.8576)	
Patients alive over time, % (95% CI)[a]		
3 months	[redacted]	[redacted]

Parameter	Trastuzumab deruxtecan (n = 261)	Trastuzumab emtansine (n = 263)
6 months	[redacted]	[redacted]
9 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]

CI = confidence interval; FAS = full analysis set; HR = hazard ratio; NE = not estimable; OS = overall survival.

[a]From Kaplan-Meier analysis.

[b]Two-sided P value is from the stratified log-rank test; HR and 95% CI are from the stratified Cox proportional hazards model with hormone receptor status, prior pertuzumab, and history of visceral disease stratification factors.

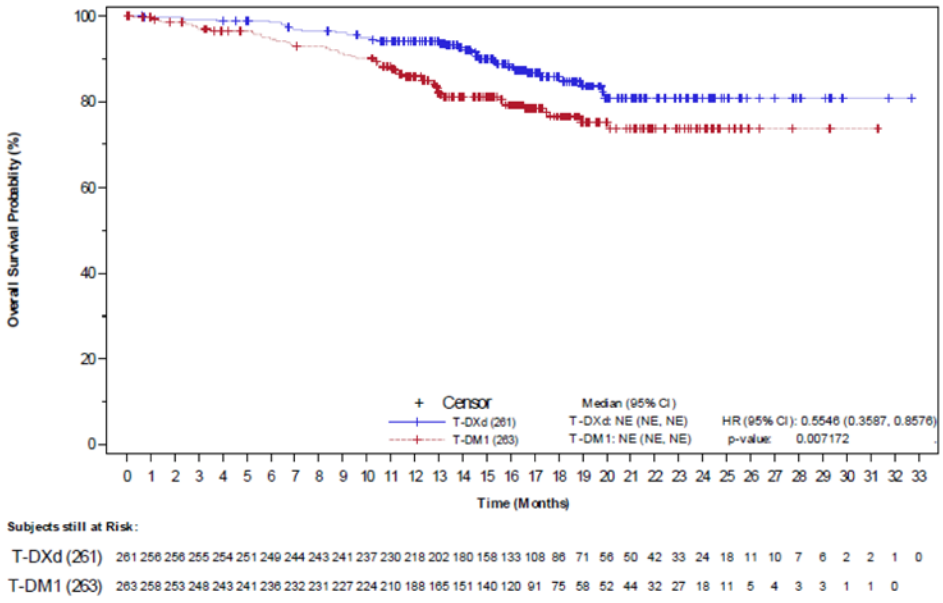
Source: DESTINY-Breast03 Clinical Study Report.[13]

Overall Survival

An analysis of the hierarchically tested key secondary outcome of OS in the DESTINY-Breast03 study is summarized in Table 16 and Figure 2. As of the May 21, 2021, data cut-off date, OS events had occurred in 33 (12.6%) patients in the trastuzumab deruxtecan arm and 53 (20.2%) patients in the trastuzumab emtansine arm. [redacted] patients [redacted] in the trastuzumab deruxtecan arm and [redacted] patients ([redacted]) in the trastuzumab emtansine arm had been lost to follow-up. 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. The 12-month OS rate was 94.1% (95% CI, 90.3% to 96.4%) in the trastuzumab deruxtecan arm and 85.9% (95% CI, 80.9% to 89.7%) in the trastuzumab emtansine arm.

Subgroup analyses of OS by hormone receptor status, estrogen receptors, progesterone receptors, prior treatment with pertuzumab, lines of prior therapy not including hormone therapy, baseline visceral disease, baseline CNS metastases, and history of CNS metastases were consistent with the main analysis across all strata (refer to Appendix 2). A subgroup analysis of OS by time from neoadjuvant or adjuvant therapy to development of MBC (less than 6 months versus 6 months or longer) was not conducted. Sensitivity analyses of OS were not conducted because the prespecified boundary for the interim analysis was not crossed. OS results from a more recent data cut were requested but not provided, although the sponsor confirmed that the trigger for the next interim analysis of OS (approximately 153 OS events) had not yet been reached.

Figure 2: Kaplan-Meier Plot of OS in the DESTINY-Breast03 Study (FAS)



CI = confidence interval; FAS = full analysis set; HR = hazard ratio; IA = investigator assessment; NE = not estimable; OS = overall survival; PFS = progression-free survival; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

Note: HR is from a stratified Cox proportional hazard model and P value is from the stratified log-rank test.

Source: DESTINY-Breast03 Clinical Study Report.[13]

Progression-Free Survival per Blinded Independent Central Review

Analysis of the primary outcome of PFS per BICR in the DESTINY-Breast03 study is summarized in Table 17 and Figure 3. 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. The most common reasons for censoring of PFS per BICR were treatment ongoing without event (49.0% and 18.6% of the trastuzumab deruxtecan and trastuzumab emtansine arms, respectively) and adequate tumour assessments no longer available (10.3% and 11.8% of the trastuzumab deruxtecan and trastuzumab emtansine arms, respectively). 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. The 12-month PFS per BICR rate was 75.8% (95% CI, 69.8% to 80.7%) in the trastuzumab deruxtecan arm and 34.1% (95% CI, 27.7% to 40.5%) in the trastuzumab emtansine arm.

Subgroup analyses of PFS per BICR by hormone receptor status, estrogen receptors, progesterone receptors, prior treatment with pertuzumab, lines of prior therapy not including hormone therapy, baseline visceral disease, baseline CNS metastases, and history of CNS metastases were consistent with the main analysis across all strata (refer to Appendix 3). In addition, a post- hoc subgroup analysis of PFS per BICR by time from neoadjuvant or

adjuvant therapy to development of MBC (less than 6 months versus 6 months or longer) was consistent with the main analysis across both strata. Sensitivity analyses of PFS per BICR, including an analysis with censoring at the time of initiating a new anticancer therapy if this occurred before progression per BICR, were consistent with the main analysis (refer to Appendix 2). Only [redacted] patients ([redacted] in the trastuzumab deruxtecan arm and [redacted] in the trastuzumab emtansine arm) had PFS censored due to initiation of a new anticancer therapy before progression per BICR.

Table 17: PFS per BICR in the DESTINY-Breast03 Study (FAS)

Parameter	Trastuzumab deruxtecan (n = 261)	Trastuzumab emtansine (n = 263)
Patients with events, n (%)	87 (33.3)	158 (60.1)
Progressive disease	80 (30.7)	152 (57.8)
Death	7 (2.7)	6 (2.3)
Patients without events (censored), n (%)	174 (66.7)	105 (39.9)
Ongoing without event	128 (49.0)	49 (18.6)
Adequate tumour assessment no longer available[a]	27 (10.3)	31 (11.8)
Event after missing 2 consecutive assessments	[redacted]	[redacted]
Withdrew consent	7 (2.7)	6 (2.3)
No post-baseline tumour assessment	3 (1.1)	7 (2.7)
No baseline evaluable tumour assessment	1 (0.4)	0
Median PFS (95% CI), months[b]	NE (18.5 to NE)	6.8 (5.6 to 8.2)
Stratified log-rank P value[c]	< 0.0001	
Stratified Cox proportional HR (95% CI)[b]	0.2840 (0.2165 to 0.3727)	
Patients alive and progression free over time, % (95% CI)[b]		
3 months	[redacted]	[redacted]
6 months	[redacted]	[redacted]
9 months	[redacted]	[redacted]
12 months	75.8 (69.8 to 80.7)	34.1 (27.7 to 40.5)
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]

BICR = blinded independent central review; CI = confidence interval; FAS = full analysis set; HR = hazard ratio; NE = not estimable; PFS = progression-free survival.

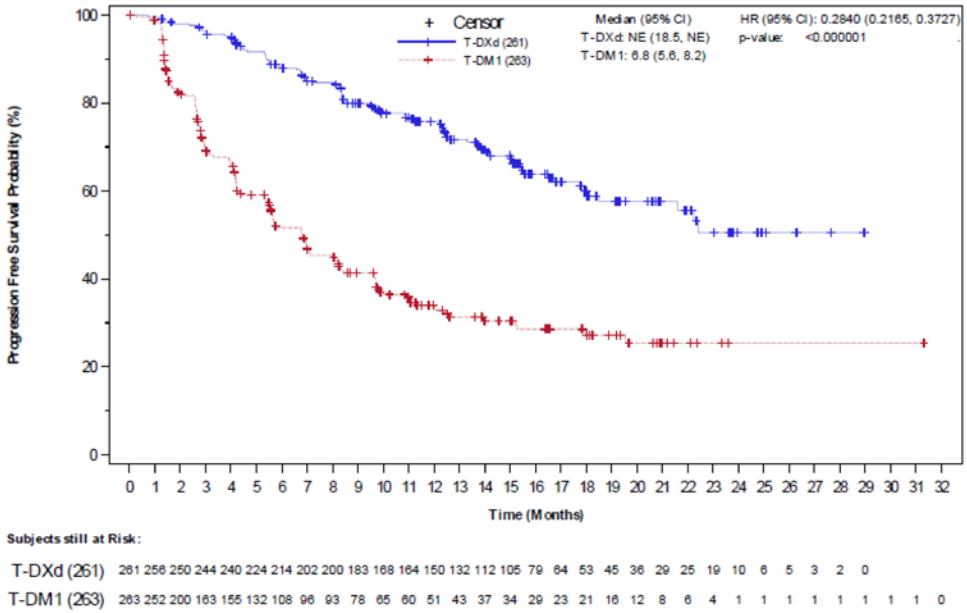
[a]Patients whose last tumour scan was more than 14 weeks before the data cut-off date.

[b]From a Kaplan-Meier analysis.

[c]Two-sided P value is from the stratified log-rank test; HR and 95% CI are from the stratified Cox proportional hazards model with hormone receptor status, prior pertuzumab, and history of visceral disease stratification factors.

Source: DESTINY-Breast03 Clinical Study Report.[13]

Figure 3: Kaplan-Meier Plot of PFS per BICR in the DESTINY-Breast03 Study (FAS)



BICR = blinded independent central review; CI = confidence interval; FAS = full analysis set; HR = hazard ratio; NE = not estimable; PFS = progression-free survival; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

Note: HR is from a stratified Cox proportional hazard model and P value is from the stratified log-rank test.

Source: DESTINY-Breast03 Clinical Study Report.[13]

Progression-Free Survival per Investigator Assessment

An analysis of the secondary outcome of PFS per IA in the DESTINY-Breast03 study is summarized in Table 18 and Figure 4. Note that this analysis was not part of the statistical hierarchy and not adjusted for multiplicity. As of the May 21, 2021, data cut-off date, PFS events per IA had occurred in [redacted] patients in the trastuzumab deruxtecan arm and [redacted] patients in the trastuzumab emtansine arm. The most common reasons for censoring of PFS per IA were treatment ongoing without event ([redacted] and [redacted] of the trastuzumab deruxtecan and trastuzumab emtansine arms, respectively) and adequate tumour assessments no longer available ([redacted] and [redacted] of the trastuzumab deruxtecan and trastuzumab emtansine arms, respectively). 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 months 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. The 12-month PFS per IA rate was 76.3% (95% CI, 70.4% to 81.2%) in the trastuzumab deruxtecan arm and 34.9% (95% CI, 28.8% to 41.2%) in the trastuzumab emtansine arm.

Table 18: PFS per IA in the DESTINY-Breast03 Study (FAS)

Parameter	Trastuzumab deruxtecan (n = 261)	Trastuzumab emtansine (n = 263)
Patients with events, n (%)	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Death	[redacted]	[redacted]
Patients without events (censored), n (%)	[redacted]	[redacted]
Ongoing without event	[redacted]	[redacted]
Adequate tumour assessment no longer available[a]	[redacted]	[redacted]
Event after missing 2 consecutive assessments	[redacted]	[redacted]
Withdrew consent	[redacted]	[redacted]
No post-baseline tumour assessment	[redacted]	[redacted]
No baseline evaluable tumour assessment	[redacted]	[redacted]
Median PFS (95% CI), months[b]	25.1 (22.1 to NE)	7.2 (6.8 to 8.3)
Stratified log-rank P value[c]	< 0.0001	
Stratified Cox proportional HR (95% CI)[c]	0.2649 (0.2011 to 0.3489)	
Patients alive and progression-free over time, % (95% CI)[b]		
3 months	[redacted]	[redacted]
6 months	[redacted]	[redacted]
9 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]

CI = confidence interval; FAS = full analysis set; HR = hazard ratio; IA = investigator assessment; NE = not estimable; PFS = progression-free survival.

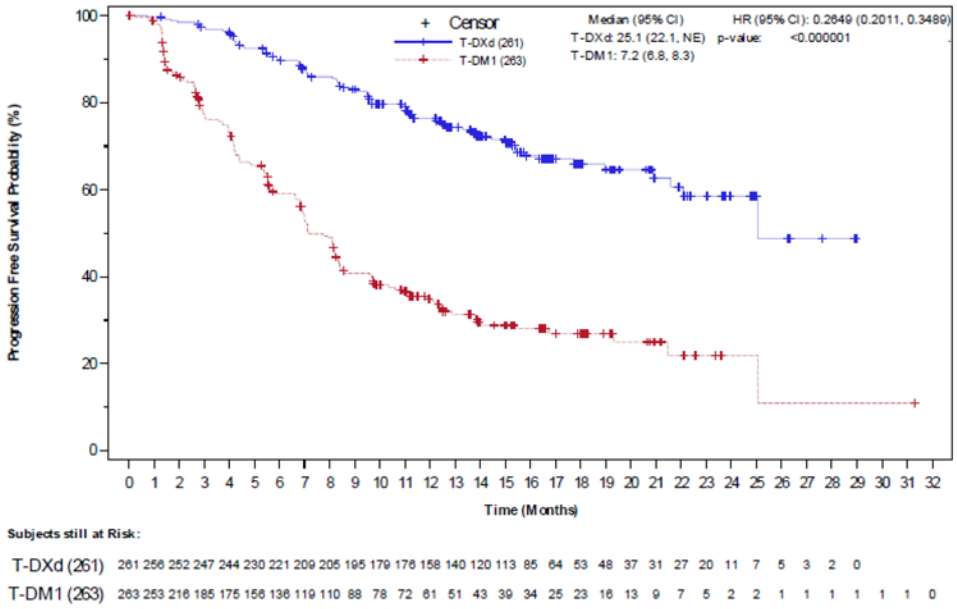
[a]Patients whose last tumour scan was more than 14 weeks before the data cut-off date.

[b]From a Kaplan-Meier analysis.

[c]Two-sided P value is from the stratified log-rank test (note that this test is outside the statistical hierarchy and the P value is not adjusted for multiplicity); HR and 95% CI are from the stratified Cox proportional hazards model with hormone receptor status, prior pertuzumab, and history of visceral disease stratification factors.

Source: DESTINY-Breast03 Clinical Study Report.[13]

Figure 4: Kaplan-Meier Plot of PFS per IA in the DESTINY-Breast03 Study (FAS)



CI = confidence interval; FAS = full analysis set; HR = hazard ratio; IA = investigator assessment; NE = not estimable; PFS = progression-free survival; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

Note: HR is from a stratified Cox proportional hazard model and P value is from the stratified log-rank test (note that this test is outside the statistical hierarchy and the P value is not adjusted for multiplicity).

Source: DESTINY-Breast03 Clinical Study Report.[13]

Health-Related Quality of Life

All patient-reported HRQoL instruments had completion rates of 82% or higher among patients still receiving protocol therapy in both treatment arms from cycles 3 to 27 (weeks 9 to 81).

An analysis of EORTC QLQ-C30 scores in the DESTINY-Breast03 study is summarized in Table 19. Among patients with available data in the trastuzumab deruxtecan arm, the mean changes from baseline to end of treatment in global health status, physical functioning, emotional functioning, and social functioning were 1.98 (SD = 21.340), [redacted], and [redacted] respectively. Among patients with available data in the trastuzumab emtansine arm, the mean changes from baseline to end of treatment in global health status, physical functioning, emotional functioning, and social functioning were 4.07 (SD = 22.048), [redacted], and [redacted], respectively.

An analysis of the EQ-5D-5L scores in the DESTINY-Breast03 study is summarized in Table 20. Among patients with available data in the trastuzumab deruxtecan arm, the mean changes from baseline to end of treatment in EQ-5D-5L index scores and EQ VAS scores were [redacted] and [redacted], respectively. Among patients with available data in the trastuzumab emtansine arm, the mean changes from baseline to end of treatment in EQ-5D-5L index scores and EQ VAS scores were [redacted] and [redacted], respectively.

An analysis of EORTC QLQ-BR45 breast symptoms scale scores in the DESTINY-Breast03 study is summarized in Table 21. Among patients with available data in the trastuzumab deruxtecan arm, the mean change from baseline to end of treatment was [redacted]. Among patients with available data in the trastuzumab emtansine arm, the mean change from baseline to end of treatment was [redacted].

Table 19: EORTC QLQ-C30 Scores in the DESTINY-Breast03 Study (FAS)

Parameter	Trastuzumab deruxtecan (n = 261)	Trastuzumab emtansine (n = 263)
Global health status		
Baseline		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
End of treatment		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Change from baseline to end of treatment		
n	[redacted]	[redacted]
Mean (SD)	1.98 (21.340)	4.07 (22.048)
Median (range)	0.00 (−50.0 to 66.7)	0.00 (−75.0 to 58.3)
Physical functioning		
Baseline		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
End of treatment		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Change from baseline to end of treatment		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]

Parameter	Trastuzumab deruxtecan (n = 261)	Trastuzumab emtansine (n = 263)
Emotional functioning		
Baseline		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
End of treatment		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Change from baseline to end of treatment		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Social functioning		
Baseline		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
End of treatment		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Change from baseline to end of treatment		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]

EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 ; FAS = full analysis set; SD = standard deviation.

Note: Linear transformations are applied to global health status and all subscales of the EORTC QLQ-C30. A high score for global health status represents a low HRQoL; a high score for a functional scale represents a low and/or unhealthy level of functioning; a high score for a symptom scale or item represents a high level of symptomatology or problems.

Source: DESTINY-Breast03 Clinical Study Report.[13]

Table 20: EQ-5D-5L Scores in the DESTINY-Breast03 Study (FAS)

Parameter	Trastuzumab deruxtecan (n = 261)	Trastuzumab emtansine (n = 263)
EQ-5D-5L index score		
Baseline		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
End of treatment		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Change from baseline to end of treatment		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
EQ VAS		
Baseline		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
End of treatment		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Change from baseline to end of treatment		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]

EQ-5D-5L = 5-Levels EQ-5D; FAS = full analysis set; SD = standard deviation; VAS = visual analogue scale.

Note: A linear transformation was applied to the health scale, which is measured according to a 0 mm to 100 mm VAS. A high VAS score represents worse overall self-rated health status.

Source: DESTINY-Breast03 Clinical Study Report.[13]

Table 21: EORTC QLQ-BR45 Breast Symptoms Scale Scores in the DESTINY-Breast03 Study (FAS)

Parameter	Trastuzumab deruxtecan (n = 261)	Trastuzumab emtansine (n = 263)
Breast symptoms		
Baseline		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
End of treatment		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Change from baseline to end of treatment		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]

EORTC QLQ-BR45 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer 45; FAS = full analysis set; SD = standard deviation.

Note: Linear transformations were applied to all subscales of the EORTC QLQ-BR45. A high score for a functional scale represents a low and/or unhealthy level of functioning; a high score for a symptom scale or item represents a high level of symptomatology or problems.

Source: DESTINY-Breast03 Clinical Study Report.[13]

Objective Response Rate per Blinded Independent Central Review and Investigator Assessment

Analysis of the secondary outcomes of ORR per BICR and per IA in the DESTINY-Breast03 study is summarized in Table 22. Note that this analysis was not part of the statistical hierarchy and not adjusted for multiplicity. 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 77.0% (95% CI, 71.4% to 82.0%) in the trastuzumab deruxtecan arm and 36.9% (95% CI, 31.0% to 43.0%) 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.

Table 22: ORR per BICR and IA in the DESTINY-Breast03 Study (FAS)

Parameter	Trastuzumab deruxtecan (n = 261)	Trastuzumab emtansine (n = 263)
BOR, n (%)		
Complete response	42 (16.1)[a], [redacted]	23 (8.7)[a], [redacted]
Partial response	166 (63.6)[a], [redacted]	67 (25.5)[a], [redacted]
Stable disease	44 (16.9)[a], [redacted]	112 (42.6)[a], [redacted]
Progressive disease	3 (1.1)[a], [redacted]	46 (17.5)[a], [redacted]
Not evaluable	6 (2.3)[a], [redacted]	15 (5.7)[a], [redacted]
ORR		
Responders, n (%)	208 (79.7)[a], 201 (77.0)[b]	90 (34.2)[a], 97 (36.9)[b]
95% CI[c]	74.3 to 84.4[a], 71.4 to 82.0[b]	28.5 to 40.3[a], 31.0 to 43.0[b]
P value[d]	< 0.0001[a], < 0.0001[b]	
Difference in ORR (95% CI)[c]	45.5 (37.6 to 53.4)[a]	

BOR = best overall response; BICR = blinded independent central review; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; FAS = full analysis set; IA = investigator assessment; NE = not estimable; ORR = objective response rate.

[a]Result per BICR. This test was outside of the statistical hierarchy and the P value was not adjusted for multiplicity.

[b]Result per IA. This test was outside of the statistical hierarchy and the P value was not adjusted for multiplicity.

[c]Based on the Clopper-Pearson method for single proportion and for the difference of 2 proportions with continuity correction.

[d]Based on the CMH test adjusted for hormone receptor status, prior treatment with pertuzumab, and history of visceral disease stratification factors.

Source: DESTINY-Breast03 Clinical Study Report.[13]

Duration of Response per Blinded Independent Central Review and Investigator Assessment

An analysis of the secondary outcomes of DOR per BICR and per IA in the DESTINY-Breast03 study is summarized in Table 23. Note that this analysis was not part of the statistical hierarchy and not adjusted for multiplicity. 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, 20.8 months to not estimable; trastuzumab emtansine 95% CI, 14.1 months to not estimable).

Table 23: DOR per BICR and IA in the DESTINY-Breast03 Study (FAS)

Parameter	Trastuzumab deruxtecan (n = 261)	Trastuzumab emtansine (n = 263)
Patients with CR or PR, n	208[a], 201[b]	90[a], 97[b]
Patients with events, n (%)[a]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Death	[redacted]	[redacted]
Patients without events (censored), n (%)[c]	[redacted]	[redacted]

Parameter	Trastuzumab deruxtecan (n = 261)	Trastuzumab emtansine (n = 263)
Event after missing 2 consecutive assessments	[redacted]	[redacted]
Withdrew consent	[redacted]	[redacted]
Ongoing without event	[redacted]	[redacted]
Adequate tumour assessment no longer available	[redacted]	[redacted]
Median DOR (95% CI), months[d]	[redacted]	[redacted]

BICR = blinded independent central review; CI = confidence interval; CR = complete response DOR = duration of response; FAS = full analysis set; IA = investigator assessment; NE = not estimable; partial response.

[a]Result per BICR.

[b]Result per IA.

[c]Percentage was calculated using the number of patients with CR and PR.

[d]From Kaplan-Meier estimate.

Source: DESTINY-Breast03 Clinical Study Report.[13]

Harms

Only those harms identified in the review protocol are reported in the following. Refer to Table 24 for detailed harms data.

Adverse Events

Almost all patients treated with trastuzumab deruxtecan (99.6%) and trastuzumab emtansine (95.4%) experienced at least 1 AE. Common AEs that occurred more frequently in patients receiving trastuzumab deruxtecan than in those receiving trastuzumab emtansine included nausea (75.9% versus 30.3%), fatigue (49.0% versus 34.5%), vomiting (49.0% versus 10.0%), neutropenia (42.8% versus 11.9%), alopecia (37.0% versus 3.1%), constipation (34.2% versus 19.5%), anemia (32.7% versus 17.2%), leukopenia (30.4% versus 8.4%), decreased appetite (29.2% versus 16.9%), diarrhea (29.2% versus 6.9%), abdominal pain ([redacted] versus [redacted]), stomatitis ([redacted] versus [redacted]), and weight loss ([redacted] versus [redacted]). Common AEs that occurred less frequently in patients receiving trastuzumab deruxtecan than in those receiving trastuzumab emtansine included increased aspartate transaminase (25.7% versus 40.2%) and thrombocytopenia (25.7% versus 53.3%).

Serious Adverse Events

SAEs occurred overall at similar rates in patients treated with trastuzumab deruxtecan (19.1%) and trastuzumab emtansine (18.0%). SAEs that occurred more frequently in patients receiving trastuzumab deruxtecan compared with trastuzumab emtansine included ILD ([redacted] versus [redacted]), vomiting ([redacted] versus [redacted]), and pyrexia ([redacted] versus [redacted]).

Withdrawals Due to Adverse Events

WDAEs occurred in 13.6% of patients treated with trastuzumab deruxtecan and 7.3% of patients treated with trastuzumab emtansine. The most common WDAE in patients receiving trastuzumab deruxtecan was ILD (8.2%).

AEs Leading to Dose Modification

AEs leading to study drug interruption occurred in 44.0% of patients treated with trastuzumab deruxtecan and 23.4% of patients receiving trastuzumab emtansine. The most common AEs leading to study drug interruption in patients receiving trastuzumab deruxtecan were neutropenia ([redacted]) and leukopenia ([redacted]). AEs leading to dose reduction occurred in 21.4% of

patients treated with trastuzumab deruxtecan and 12.6% of patients receiving trastuzumab emtansine. The most common AE leading to dose reduction in patients receiving trastuzumab deruxtecan was nausea ([redacted]).

Mortality

Five patients (1.9%) in each of the treatment groups had AEs associated with an outcome of death. In both treatment groups, the most common AEs associated with an outcome of death were disease progression ([redacted]) and COVID-19 ([redacted]).

Notable Harms

The study protocol-defined AESIs of ILD, decreased left ventricular ejection fraction, and LV 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). Among other notable harms specified in the CADTH review protocol, neutropenia and febrile neutropenia occurred more frequently in patients receiving trastuzumab deruxtecan (42.8% and 0.8%, respectively) than in patients receiving trastuzumab emtansine (11.9% and 0%, respectively).

Table 24: Summary of Harms in the Destiny-Breast03 Study (Safety Set)

Harm	Trastuzumab deruxtecan (n = 257)	Trastuzumab emtansine (n = 261)
Patients with ≥ 1 AE		
n (%)	256 (99.6)	249 (95.4)
Common AEs, n (%)[a]		
Nausea	195 (75.9)	79 (30.3)
Fatigue[b]	126 (49.0)	90 (34.5)
Vomiting	126 (49.0)	26 (10.0)
Neutropenia[c]	110 (42.8)	31 (11.9)
Alopecia	95 (37.0)	8 (3.1)
Constipation	88 (34.2)	51 (19.5)
Anemia[d]	84 (32.7)	45 (17.2)
Leukopenia[e]	78 (30.4)	22 (8.4)
Decreased appetite	75 (29.2)	44 (16.9)
Diarrhea	75 (29.2)	18 (6.9)
Increased AST	66 (25.7)	105 (40.2)
Thrombocytopenia[f]	66 (25.7)	139 (53.3)
Increased ALT	56 (21.8)	77 (29.5)
Headache[g]	56 (21.8)	42 (16.1)
Abdominal pain[h]	[redacted]	[redacted]
Stomatitis[i]	[redacted]	[redacted]
Decreased weight	[redacted]	[redacted]

Harm	Trastuzumab deruxtecan (n = 257)	Trastuzumab emtansine (n = 261)
Patients with ≥ 1 SAE		
n (%)	49 (19.1)	47 (18.0)
Common SAEs, n (%)[j]		
ILD	[redacted]	[redacted]
Vomiting	5 (1.9)	2 (0.8)
Pneumonia	4 (1.6)	5 (1.9)
Pyrexia	4 (1.6)	0
Patients with WDAEs		
n (%)	35 (13.6)	19 (7.3)
Common WDAEs, n (%)[k]		
ILD	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Patients with ≥ 1 AE associated with study drug interruption		
n (%)	113 (44.0)	61 (23.4)
Common AEs associated with study drug interruption, n (%)[l]		
Neutropenia[c]	[redacted]	[redacted]
Leukopenia[e]	[redacted]	[redacted]
Patients with ≥ 1 AE associated with dose reduction		
n (%)	55 (21.4)	33 (12.6)
Common AEs associated with study drug reduction, n (%)[m]		
Nausea	[redacted]	[redacted]
Patients with AEs associated with an outcome of death		
n (%)	5 (1.9)	5 (1.9)
Most common AEs associated with an outcome of death, n (%)[n]		
Disease progression	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Notable harms		
AESIs, n (%)		
ILD	28 (10.9)	5 (1.9)
Decreased LVEF	6 (2.3)	1 (0.4)
LV dysfunction	1 (0.4)	0
Other protocol-defined notable harms, n (%)		
Cough	27 (10.5)	26 (10.0)

Harm	Trastuzumab deruxtecan (n = 257)	Trastuzumab emtansine (n = 261)
Dyspnea	21 (8.2)	13 (5.0)
Pyrexia	27 (10.5)	39 (14.4)
Neutropenia[c]	110 (42.8)	31 (11.9)
Febrile neutropenia	2 (0.8)	0
Infusion reactions	[redacted]	[redacted]

AE = adverse event; AESI = adverse event of special interest; ALT = alanine aminotransferase; AST = asparagine aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; ILD = interstitial lung disease; LV = left ventricular; LVEF = left ventricular ejection fraction; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

Note: AEs were defined and graded using MedDRA version 23.0 and CTCAE version 5.0. All events are within 47 days of the last dose of the study drug unless otherwise indicated.

[a]AEs with frequency > 15% in either treatment arm are shown.

[b]Includes the preferred terms fatigue, asthenia, and malaise.

[c]Includes the preferred terms decreased neutrophil count and neutropenia.

[d]Includes the preferred terms hemoglobin decreased, decreased red blood cell count, anemia, and decreased hematocrit.

[e]Includes the preferred terms decreased white blood cell count and leukopenia.

fIncludes the preferred terms decreased platelet count and thrombocytopenia.

[g]Includes the preferred terms migraine, headache, and sinus headache.

[h]Includes the preferred terms abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and gastrointestinal pain.

[i]Includes the preferred terms stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosal blistering.

[j]SAEs occurring in 4 or more patients in either treatment arm are shown.

[k]WDAEs occurring in more than 1 patient in either treatment arm are shown.

[l]AEs leading to treatment interruption with frequency > 5% in either treatment arm are shown.

[m]AEs leading to dose reduction with frequency > 5% in either treatment arm are shown.

[n]AEs associated with an outcome of death occurring in more than 1 patient in either treatment arm or in exactly 1 patient in both treatment arms are shown.

Source: DESTINY-Breast03 Clinical Study Report.[13]

Critical Appraisal

Internal Validity

DESTINY-Breast03 was a large, phase III, randomized, OL, multicentre study comparing the efficacy and safety of trastuzumab deruxtecan and trastuzumab emtansine in patients with HER2-positive MBC who had been previously treated with taxane chemotherapy plus trastuzumab (N = 524).[12] In the study, randomization did not appear to adequately balance baseline demographic and disease characteristics between the trastuzumab deruxtecan and trastuzumab emtansine arms. No imbalances between the study arms of potential prognostic relevance were identified by the clinical experts consulted by CADTH for this review, although a slightly lower proportion of patients in the trastuzumab deruxtecan arm had an ECOG PS of 0 when compared with the trastuzumab emtansine arm (59.0% versus66.5%).

Many of the outcomes used in the DESTINY-Breast03 study (e.g., PFS, OS, ORR, DOR) are standard in oncology trials and tumour responses were objectively evaluated using mRECIST 1.1 per BICR. Neither the key secondary analysis of OS nor the primary analysis of PFS per BICR was censored for patients who initiated other anticancer therapies following the study's protocol therapy discontinuation. As of the May 21, 2021, data cut-off date, 29.9% and 62.4% of patients in the trastuzumab deruxtecan and trastuzumab emtansine arms, respectively, had initiated a new systemic anticancer therapy. Subsequent therapies received were imbalanced between the study arms and included crossover to trastuzumab emtansine (16.5% of the trastuzumab deruxtecan arm), crossover to trastuzumab deruxtecan (11.4% of the trastuzumab emtansine arm), re-treatment with trastuzumab emtansine (6.5% of the trastuzumab emtansine arm), trastuzumab (8.8% of the trastuzumab deruxtecan arm

and 25.1% of the trastuzumab emtansine arm), anti-HER2 tyrosine kinase inhibitors (5.0% of the trastuzumab deruxtecan arm and 25.1% of the trastuzumab emtansine arm), and other systemic therapies (15.3% of the trastuzumab deruxtecan arm and 47.9% of the trastuzumab emtansine arm). The clinical experts consulted by CADTH for this review agreed that imbalances in subsequent therapies, including crossover, may impact the OS analysis and were largely explained by the higher proportion of patients in the trastuzumab emtansine arm who experienced disease progression. Analytical approaches to analyze OS in the presence of treatment switching or crossover that can minimize potential biases (e.g., inverse probability of censoring weighting or the rank-preserving structural failure time model) were not conducted. A sensitivity analysis of PFS per BICR was conducted with censoring at the time of initiating new anticancer therapy and showed a similar result to the primary PFS analysis. Only [redacted] patients ([redacted] in the trastuzumab deruxtecan arm and [redacted] in the trastuzumab emtansine arm) had PFS censored due to initiation of a new anticancer therapy before progression per BICR.

The OL design of the DESTINY-Breast03 study had the potential to introduce bias in several forms, especially in the assessment of subjective outcomes, although the impacts of these biases were most likely minor, affecting small numbers of patients that were generally similar between arms. Rates of patient discontinuation from study therapy for reasons other than disease progression or toxicity were relatively low (patient withdrawal was [redacted] and [redacted] of the trastuzumab deruxtecan and trastuzumab emtansine arms, respectively; clinical progression per IA was [redacted] and [redacted] of the trastuzumab deruxtecan and trastuzumab emtansine arms, respectively; physician decision was [redacted] and [redacted] of the trastuzumab deruxtecan and trastuzumab emtansine arms, respectively), although the proportions of patients assessed with clinical progression per IA and those withdrawn from therapy due to physician decision were slightly higher in the trastuzumab emtansine arm. Likewise, similar proportions of patients in each arm were lost to follow-up in the OS analysis ([redacted] and [redacted] of the trastuzumab deruxtecan and trastuzumab emtansine arms, respectively), and similar proportions were censored from PFS analyses due to missing tumour assessments (PFS per BICR was 10.3% and 11.8% of the trastuzumab deruxtecan and trastuzumab emtansine arms, respectively; PFS per IA was [redacted] and [redacted] of the trastuzumab deruxtecan and trastuzumab emtansine arms, respectively). According to the clinical experts consulted by CADTH for this review, the impacts of any attrition biases and associated missing data were unlikely to be directional or to limit interpretation of the study results. Although the assessment of progression in the primary PFS analysis was per BICR, decisions to discontinue protocol therapy were made by investigators based on local imaging scans and clinical assessment, and bias for or against either study drug could have impacted these decisions. A higher proportion of patients in the trastuzumab deruxtecan arm were assessed as having disease progression per BICR (n = [redacted]) compared with IA (n = [redacted]), while a lower proportion of patients in the trastuzumab emtansine arm were assessed as having disease progression per BICR (n = [redacted]) compared with IA (n = [redacted]). Thus, 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 given the relatively small discordance between the BICR and IA assessments, this potential source of bias would be unlikely to have major impacts on the PFS analyses. Several statistical issues should be considered when interpreting the results of the DESTINY-Breast03 study. First, the OS data are still immature, and although numerically in favour of trastuzumab deruxtecan, 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. Thus, no

conclusions regarding OS differences between the trastuzumab deruxtecan and trastuzumab emtansine arms can yet be reached. Statistical tests were overall appropriate, and a hierarchical strategy was applied for multiplicity control of the primary PFS analysis and the key secondary OS analysis, as well as between interim and final analyses. However, analyses of ORR and DOR were not controlled for multiplicity. The primary PFS analysis was robust to an array of sensitivity analyses. Some subgroup analyses of interest to this review were specified a priori (i.e., hormone receptor status, estrogen receptors, progesterone receptors, prior treatment with pertuzumab, lines of prior systemic therapy not including hormone therapy, baseline visceral disease, baseline CNS metastases, history of CNS metastases), 2 of which were based on randomization stratification factors (i.e., hormone receptor status, prior treatment with pertuzumab, history of visceral disease). The study was not specifically powered to evaluate strata among subgroups, there were no tests for differences among subgroups, and subgroup analyses were not controlled for multiplicity.

Patient-reported HRQoL was analyzed as a HEOR outcome in the DESTINY-Breast03 study. The absence of multiplicity control in formal statistical comparisons and missing HRQoL data at later time points post baseline (due to variable completion rates as well as expected attrition of the study population) limited interpretation of potentially important changes in HRQoL outcomes, which were considered highly important by patients and clinical experts. Attrition in this population of patients with HER2-positive MBC was a major contributing factor to missing post-baseline HRQoL data, as all patient-reported HRQoL instruments had completion rates of 82% or higher among patients still receiving protocol therapy in both treatment arms from cycles 3 to 27 (weeks 9 to 81), while the median treatment duration was 14.3 months in the trastuzumab deruxtecan arm and 6.9 months in the trastuzumab emtansine arm. In addition, 51.4% of patients in the trastuzumab deruxtecan arm and 18.0% of patients in the trastuzumab emtansine arm were still receiving treatment at the data cut-off date, thus end-of-treatment HRQoL data have yet to be collected. Furthermore, measurement of patient-reported HRQoL outcomes may have been influenced to some degree by knowledge of treatment allocation. Moreover, although the measurement properties of instruments used (i.e., EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-BR45) have been studied in patients with MBC, MIDs specific to HER2-positive MBC were not available and MIDs for MBC were only identified for the EORTC QLQ-C30.

External Validity

According to the clinical experts consulted by CADTH for this review, the demographic and disease characteristics of the DESTINY-Breast03 study population were broadly reflective of the population of patients in Canada with HER2-positive MBC who would be candidates for trastuzumab deruxtecan. The clinical experts also felt that the eligibility criteria for the study would be expected to recruit a population of patients with characteristics similar to patients in Canada with HER2-positive MBC they treat in their practice. Although reasons for screen failure were not provided, the clinical experts felt that the final enrolled population generally reflected the patient population that they treat in their clinical practice. However, they emphasized that, as with most oncology trials, the eligibility criteria for the DESTINY-Breast03 study likely selected for a healthier cross section of the overall patient population with HER2-positive MBC who were more likely to tolerate and respond to therapy than the general patient population, as evidenced by the majority of enrolled patients (59% to 67%) having an ECOG PS of 0 at baseline (the inclusion criteria specified an ECOG PS of 0 or 1 only). Nevertheless, the clinical experts expected that in practice, some patients with an ECOG PS of 2 would receive trastuzumab deruxtecan and felt that the study results could be generalized to these patients. The clinical experts commented that relatively few patients in the study were from North

America (6.5%) and 59.9% of patients were Asian, which is not reflective of the population of patients in Canada with HER2-positive MBC; moreover, only 2 patients were male. Despite these factors, the clinical experts felt that the results of the study would be generalizable to all patients in Canada with HER2-positive MBC, including small subgroups.

The DESTINY-Breast03 study population included patients with a variety of treatment histories for HER2-positive MBC. Many patients were heavily pretreated (e.g., 52.6% of patients had received 2 or more lines of prior therapy in the metastatic setting, not including hormone therapy; 29.5% of patients had received 3 or more lines of prior therapy in the metastatic setting, not including hormone therapy) and received the study drug well beyond the second line in the metastatic setting; thus, the clinical experts consulted by CADTH for this review noted that the magnitudes of treatment effects would not be expected to directly translate to the intended second-line treatment setting for MBC. The clinical experts also noted that although the DESTINY-Breast03 study was not designed to focus solely on the second-line setting, therapies for HER2-positive MBC are generally expected to be more effective when used in earlier lines.

The eligibility criteria for the DESTINY-Breast03 study precluded prior treatment with an anti-HER2 antibody drug conjugate in the metastatic setting, but allowed for prior use of anti-HER2 antibody drug conjugates in the adjuvant or neoadjuvant setting if disease progression had not occurred within 12 months of 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. Thus, the generalizability of the study results to patients who have previously been exposed to trastuzumab emtansine (or to trastuzumab deruxtecan) in an earlier line of treatment was uncertain.

As of the May 21, 2021, data cut-off, 51.4% of patients in the trastuzumab deruxtecan arm and 18.0% of patients in the trastuzumab emtansine arm were still receiving protocol-assigned therapies. Discontinuations due to AEs were more frequent in the trastuzumab deruxtecan arm than in the trastuzumab emtansine arm (13.6% and 6.5%, respectively). According to the clinical experts consulted by CADTH for this review, discontinuations due to AEs may be expected to occur more frequently in the general population of patients with HER2-positive MBC compared with a trial population enriched for patients in better health and with better PS. The clinical experts commented that if discontinuations occurred more frequently in real-world practice, this could potentially limit the generalizability of the study results to the subset of patients who are likely to tolerate treatment, who could be identified by medical oncologists based on clinical evaluation.

The doses of trastuzumab deruxtecan and trastuzumab emtansine used in the DESTINY-Breast03 study were aligned with Health Canada–approved dosing and with clinical practice. However, the clinical experts consulted by CADTH for this review noted that many of the subsequent therapies received by patients in the study following progression are not generally available to patients with HER2-positive MBC in Canada after the second-line treatment setting in which trastuzumab deruxtecan would be used. The clinical experts felt that although use of these subsequent therapies may impact OS findings to some extent, the impacts would likely be minor as there are no well-defined guidelines beyond third-line treatment with tucatinib plus capecitabine and trastuzumab, and progression generally occurs rapidly. The clinical experts did not feel that uptake of subsequent therapies that are unavailable to patients in Canada with HER2-positive MBC would be an impediment to generalizing the study findings.

Several of the outcomes assessed in the DESTINY-Breast03 study, including OS, PFS, and HRQoL, were identified as clinically important by both patients and clinical experts. At the time this report was prepared, the duration of follow-up was adequate for assessing the primary efficacy end point of PFS per BICR, but inadequate for assessing OS. Although patients and clinical experts agreed that prolonging survival and delaying progression were the most important goals of treatment, maintaining HRQoL and controlling the symptoms of metastatic disease were also critical considerations. According to the clinical experts consulted by CADTH for this review, the HRQoL instruments used in the DESTINY-Breast03 study are important research tools but are not typically used in clinical practice. Thus, they were uncertain whether the patient-reported HRQoL and cancer symptom data from the study could be generalized to a broader context.

Indirect Evidence

No indirect evidence was identified for this review. No literature search for network meta-analyses was conducted because of the identification of a direct head-to-head comparison between trastuzumab deruxtecan and the only relevant comparator, trastuzumab emtansine, in the systematic review.

Other Relevant Evidence

No other relevant evidence was identified for this review.

Discussion

Summary of Available Evidence

One phase III, randomized, OL, multicentre study (DESTINY-Breast03, N = 524) contributed evidence to this report. The study was a head-to-head comparison of trastuzumab deruxtecan and trastuzumab emtansine in adult patients with HER2-positive MBC (with an ECOG PS of 0 or 1,and without symptomatic clinically active CNS metastases) previously treated with taxane chemotherapy plus trastuzumab in the metastatic setting or those who had progressed within 6 months after neoadjuvant or adjuvant treatment involving a regimen including trastuzumab and taxane. Patients were randomized 1:1 to receive OL trastuzumab deruxtecan (5.4 mg/kg by IV infusion every 21 days) or OL trastuzumab emtansine (3.6 mg/kg by IV infusion every 21 days) until disease progression or unacceptable toxicity, then followed for survival every 3 months until death. The primary outcome of the study was PFS per BICR and the key secondary objective (hierarchically tested) was OS. Other secondary objectives included comparison of PFS per IA, ORR per BICR and IA, and DOR per BICR and IA, while changes in patient-reported HRQoL were evaluated as a HEOR analysis.

According to clinical experts consulted by CADTH for this review, apart from a few important parameters (e.g., only 6.5% of patients were from North America and 59.9% of patients were Asian, which is not reflective of the population of patients in Canada with HER2-positive MBC), the baseline characteristics of the DESTINY-Breast03 study population were broadly representative of patients in Canada with HER2-positive MBC who would be candidates for trastuzumab deruxtecan. The mean age at study entry was 54.4 years, approximately 60% of patients were Asian, and only 2 patients were male. Approximately 73% of patients had

visceral metastases at baseline and approximately 22% had a reported a history of CNS metastases. Approximately 60% of patients had received prior pertuzumab. Approximately 72% of patients had received fewer than 3 lines or fewer of prior systemic therapy, excluding hormone therapies, while approximately 28% had received 3 lines or more of systemic therapy, excluding hormone therapies. The primary limitations of the study were its short follow-up as of the May 21, 2021, data cut-off and immaturity of the OS data, its OL design and potential biases in outcome assessment (including decisions to discontinue treatment) due to knowledge of treatment allocation, and assessment of HRQoL and cancer symptoms (evaluated as a HEOR analysis) outside of the formal statistical hierarchy. In addition, the study excluded patients with clinically active symptomatic CNS metastases, so the efficacy and safety of the drug in these patients was not evaluated.

Interpretation of Results

Efficacy

Administration of trastuzumab deruxtecan in the DESTINY-Breast03 study resulted in an HR for PFS per BICR of 0.28 (95% CI, 0.22 to 0.37) compared with trastuzumab emtansine. The median PFS per BICR in the trastuzumab deruxtecan arm had not been reached at the time of the analysis; however, the lower limit of the 95% CI was estimated at 18.5 months. The clinical experts consulted by CADTH considered this to be a clinically meaningful result compared with the median PFS per BICR of 6.8 months (95% CI, 5.6 to 8.2 months) in the trastuzumab emtansine arm, despite the preliminary nature of the data. Analysis of the secondary outcome of PFS per IA was consistent with the primary analysis of PFS per BICR in favour of trastuzumab deruxtecan (HR = 0.2649; 95% CI, 0.2011 to 0.3489). OS data were immature as of the May 21, 2021, data cut-off; although the interim analysis numerically favoured trastuzumab deruxtecan (HR = 0.5546; 95% CI, 0.3587 to 0.8576), 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. In addition, analysis of OS did not consider treatment switching and crossover, which were imbalanced between arms and may have important impacts on the results. Thus, definitive conclusions regarding the treatment effect of trastuzumab deruxtecan versus trastuzumab emtansine on OS are not possible. Multiple studies have suggested the PFS is a significant predictor and useful surrogate end point for OS in MBC, including HER2-positive MBC,[26-28] although the same studies also acknowledge that correlations between PFS and OS are imperfect (coefficient of determination ranging from 0.31 to 0.67) and that OS should be independently examined if possible.

Analyses of ORR per BICR (trastuzumab deruxtecan = 79.7%; 95% CI, 74.3% to 84.4%; trastuzumab emtansine = 34.2%, 95% CI, 28.5% to 40.3%), and analyses of ORR per IA (trastuzumab deruxtecan = 77.0%; 95% CI, 71.4% to 82.0%; trastuzumab emtansine = 36.9%; 95% CI, 31.0% to 43.0%) were outside the statistical hierarchy and not adjusted for multiplicity, but were supportive of the primary analysis of PFS per BICR. The clinical experts commented that the descriptive difference in ORR per BICR (45.5%; 95% CI, 37.6% to 53.4%) in favour of trastuzumab deruxtecan was clinically meaningful in second- and subsequent-line treatment of HER2-positive MBC, where response rates are generally low. Among patients who achieved objective responses to treatment, median DOR per BICR and per IA was not yet reached in either treatment arm.

Changes in EORTC QLQ-C30, EQ-5D-5L, and EORTC QLQ-BR45 scores from baseline to the end of treatment were evaluated as an HEOR analysis. Interpretation of changes in patient-

reported HRQoL and cancer symptoms was limited by high rates of missing data at later times post baseline and absence of multiplicity control.

Harms

The safety profile of trastuzumab deruxtecan in the DESTINY-Breast03 study was as expected by the clinical experts consulted by CADTH for this review based on prior experience with the drug. The AEs associated with trastuzumab deruxtecan treatment were not clinically insignificant but were considered by the clinical experts to be manageable with appropriate supportive care. WDAEs (13.6% versus 7.3%), AEs leading to dose interruption (44.0% versus 23.4%), AEs leading to dose reduction (21.4% versus 12.6%), ILD (10.9% versus 1.9%), decreased left ventricular ejection fraction (2.3% versus 0.4%), and LV dysfunction (0.4% versus 0%) occurred more commonly in patients receiving trastuzumab deruxtecan than in those receiving trastuzumab emtansine. Although the potential for ILD is a serious concern, the clinical experts consulted by CADTH for this review emphasized that most oncologists have extensive experience with managing patients who are receiving other drugs (such as immunotherapies and chemotherapies) that are also associated with a risk of ILD. As of the May 21, 2021, data cut-off date, 51.4% of patients in the trastuzumab deruxtecan arm and 18.0% of patients in the trastuzumab emtansine arm were still receiving their assigned protocol therapy; as the data mature, the relative rates of treatment discontinuation for toxicity between the 2 arms may become clearer, and may inform the group of patients most likely to benefit from treatment with trastuzumab deruxtecan.

Conclusions

Evidence from the DESTINY-Breast03 study suggested that, compared with trastuzumab emtansine, administration of trastuzumab deruxtecan improved PFS per BICR among patients with HER2-positive MBC who had previously received taxane chemotherapy plus trastuzumab. Definitive conclusions could not be reached for OS due to immaturity of the data and non-statistically significant OS differences at a prespecified boundary for the interim analysis. Analyses of PFS per IA, ORR, and DOR also numerically favoured trastuzumab deruxtecan, although they were not part of the statistical hierarchy and were supportive of the primary analysis of PFS per BICR. Results for patient-reported HRQoL and symptom scores (i.e., EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-BR45) could not be interpreted due to an absence of multiplicity control in formal statistical testing, potential for bias in an OL trial, and high rates of missing data at later time points post baseline. Dose interruption, dose reduction, treatment discontinuation, and ILD occurred more commonly in patients receiving trastuzumab deruxtecan than in those receiving trastuzumab emtansine. The observed PFS benefits, consistent numeric improvements in other efficacy outcomes, and toxicity profile considered manageable by clinical experts were aligned with outcomes identified as important to patients with HER2-positive MBC who are seeking additional treatment options to delay progression and prolong survival with an acceptable HRQoL.

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Appendix 1: Literature Search Strategy

Note that this appendix has not been copy-edited.

Clinical Literature Search

Overview

Interface: Ovid

Databases:

- MEDLINE All (1946-present)
- Embase (1974-present)
- **Note:** Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: April 14, 2022

Alerts: Bi-weekly search updates until project completion

Search filters applied: No filters were applied to limit the retrieval by study type

Limits: Conference abstracts: excluded

Table 25: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.dq	Candidate term word (Embase)
.rn	Registry number
.nm	Name of substance word (MEDLINE)
.yr	Publication year
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily
cctr	Ovid database code; Cochrane Central Register of Controlled Trials

Multi-Database Strategy

1. (trastuzumab deruxtecan* or famtrastuzumab deruxtecan* or Enhertu* or WHO10516 or WHO 10516 or T-DXd or DS8201* or DS-8201* or 5384HK7574).ti,ab,ot,kf,hw,nm,rn.
2. 1 use medall
3. *trastuzumab deruxtecan/
4. (trastuzumab deruxtecan* or famtrastuzumab deruxtecan* or Enhertu* or WHO10516 or WHO 10516 or T-DXd or DS8201* or DS-8201*).ti,ab,kf,dq.
5. 3 or 4
6. 5 use oemezd
7. 6 not (conference abstract or conference review).pt.
8. 2 or 7
9. remove duplicates from 8

Clinical Trials Registries

ClinicalTrials.gov

Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials.

Search -- Studies found for: deruxtecan | "Breast Neoplasms"

WHO ICTRP

International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials.

Search terms – deruxtecan AND breast

Health Canada's Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials.

Search terms – deruxtecan AND breast

EU Clinical Trials Register

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.

Search terms – trastuzumab deruxtecan AND breast

Grey Literature

Search dates: April 7-14, 2022

Keywords: Enhertu, trastuzumab deruxtecan, breast cancer, breast neoplasms, HER positive

Limits: None

Updated: Search updated prior to the completion of stakeholder feedback period

Relevant websites from the following sections of the CADTH grey literature checklist Grey Matters: A Practical Tool for Searching Health-Related Grey Literature were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trials Registries
- Databases (free)

Appendix 2: Detailed Outcome Data

Note that this appendix has not been copy-edited.

Table 26: Guidelines for Trastuzumab Deruxtecan Dose Modifications in the DESTINY-Breast03 Study

Worst toxicity grade[a]	Guidelines
No toxicity	Maintain dose and schedule
Infusion reactions	
Grade 1 (mild transient reaction; infusion interruption not indicated; intervention not indicated)	• If infusion related reaction (such as fever and chills, with and without nausea/vomiting, pain, headache, dizziness, dyspnea, or hypotension) is observed during administration, the infusion rate should be reduced by 50% and patients should be closely monitored • If no other reactions appear, the subsequent infusion rate could be resumed at the initial planned rate
Grade 2 (therapy or infusion interruption indicated but response promptly to symptomatic treatment with antihistamines, NSAIDs, narcotics, and IV fluids; prophylactic medications indicated for ≤24 hours)	• Administration of trastuzumab deruxtecan should be interrupted and symptomatic treatment started (e.g., antihistamines, NSAIDs, narcotics, IV fluids) • If event resolves or improves to Grade 1, infusion can be re-started at a 50% reduced infusion rate • Subsequent administrations should be conducted at the reduced rate
Grade 3 or 4 (prolonged or life-threatening consequences, urgent intervention indicated)	• Administration of trastuzumab deruxtecan should be discontinued immediately and permanently • Urgent intervention (antihistamines, steroids, epinephrine, bronchodilators, vasopressors, IV fluids, oxygen inhalation) should be administered
Hematologic toxicities	
Neutrophil count decreased and/or WBC count decreased	
Grade 3 (neutrophils <1.0 and ≥0.5×10^9/L, WBCs <2.0 and ≥1.0×10^9/L)	• Delay dose until resolved to Grade ≤2, then maintain dose
Grade 3 (neutrophils <0.5×10^9/L, WBCs <1.0×10^9/L)	• Delay dose until resolved to Grade ≤2 • Reduce dose 1 level[b]
Febrile neutropenia (ANC <1×10^9/L, fever >38.3°C or sustained temperature of ≥38°C for more than 1 hour)	• Delay dose until resolved • Reduce dose by 1 level
Lymphocyte count decreased	
Grade 1 to Grade 3	• No dose modification

Grade 4 (<0.2×10^9/L)	• Delay dose until resolved to Grade ≤2:
	  ◦ If resolved ≤14 days from onset, maintain dose
	  ◦ If resolved >14 days from onset, reduce dose 1 level

Anemia	

Worst toxicity grade[a]	Guidelines
Grade 3 (Hb <8.0 g/dL, transfusion indicated)	• Delay dose until resolved to Grade ≤2, then reduce dose 1 level
Grade 4 (Hb <8.0 g/dL, life threatening consequences, urgent intervention indicated)	• Delay dose until resolved to Grade ≤2, then reduce dose 1 level
Platelet count decreased	
Grade 3 (platelets <50 and ≥25×10^9/L)	• Delay dose until resolved to Grade ≤1: ◦ If resolved ≤7 days from onset, maintain dose ◦ If resolved >7 days from onset, reduce dose 1 level
Grade 4 (platelets <25×10^9/L)	• Delay dose until resolved to Grade ≤1, then reduce dose 1 level
Cardiac toxicity	
Symptomatic congestive heart failure	• Discontinue patient from study treatment
Decrease in LVEF of 10% to 20% (absolute value), but LVEF >45%	• Continue treatment with trastuzumab deruxtecan
LVEF 40% to ≤45% and decrease is <10% (absolute value) from baseline	• Continue treatment with trastuzumab deruxtecan • Repeat LVEF assessment within 3 weeks
LVEF 40% to ≤45% and decrease is 10% to 20% (absolute value) from baseline	• Interrupt trastuzumab deruxtecan dosing • Repeat LVEF assessment within 3 weeks • If LVEF has not recovered to within 10% (absolue value) from baseline, discontinue patient from study treatment • IF LVEF recovers to within 10% from baseline, resume study drug treatment and maintain dose
LVEF <40% or >20% (absolute value) drop from baseline	• Interrupt trastuzumab deruxtecan dosing • Repeat LVEF assessment within 3 weeks • If LVEF <40% or >20% drop from baseline is confirmed, discontinue patient from study treatment
ECG QT prolonged	
Grade 3 (average QTc >500 ms or >60 ms change from baseline)	• Delay dose until resolved to Grade ≤1 (QTc ≤480 ms); determine if another medication the patient as taking may be responsible and can be adjusted or if there any changes in serum electrolytes that can be corrected, then: ◦ If attributed to trastuzumab deruxtecan, reduce dose 1 level
Grade 4 (torsade to pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrythmia)	• Discontinue patient from study treatment
Troponin increased	
Grade 1 (levels above ULN and below the level of myocardial infarction as defined by the manufacturer	If troponin levels are above the upper limit of normal and below the level of myocardial infarction (CTCAE Grade 1) at baseline, no repeat testing is required if the troponin level is not Grade 3. For new diagnosed Grade 1 detected on study, repeat troponin testing at 3±1 hours after initial troponin test. • If repeat troponin at 3±1 hours rises significantly per institutional guidelines: ◦ Perform ECG in triplicate

Worst toxicity grade[a]	Guidelines
	◦ Repeat troponin testing at 6±1 hours • Follow institutional guidelines for management of detectable troponin testing • If repeat troponin level at 3±1 hours does not rise significantly per institutional guidelines: ◦ Repeat troponin testing 6±1 or 24±2 hours after initial troponin test ◦ Continue treatment with trastuzumab deruxtecan
Grade 3 (levels consistent with myocardial infarction as defined by the manufacturer)	• Perform ECG in triplicate • Repeat troponin testing at 6±1 hours and 12±1 hours after initial troponin test • Follow institutional guidelines for management of detectable troponin testing • If acute myocardial infarction is confirmed, discontinue patient from study treatment • Otherwise, delay dose until resolved to Grade ≤1: ◦ If resolved ≤7 days from onset, maintain dose ◦ If resolved >7 days from onset, reduce dose 1 level
Pulmonary toxicity	
General considerations	If a patient develops radiographic changes potentially consistent with ILD or develops acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough or fever, rule out ILD/pneumonitis. If the AE is confirmed to have an etiology other than ILD, pneumonitis, follow the management guidance outlined in the "Other non-laboratory adverse events" dose modification section below. If the AE is suspected to be ILD/pneumonitis, treatment with study drug should be interrupted pending further evaluations. Evaluations should include: • High resolution CT • Pulmonologist consultation (infectious disease consultation as clinically indicated) • Blood culture and CBC. Other blood tests could be considered as needed. • Consider bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible • Pulmonary function tests and pulse oximetry (SpO_2) • Arterial blood gases if clinically indicated • One blood sample collection for PK (central) analysis as soon as ILD/pneumonitis is suspected, if feasible Other tests could be considered as needed. Radiation applications utilized for the monitoring and management of potential ILD are not specific to this study; routine CT scans should be performed.

Worst toxicity grade[a]	Guidelines
	If the AE is confirmed to be ILD/pneumonitis, follow the management guidance as outlined below. All events of ILD regardless of severity of seriousness will be followed until resolution including after drug discontinuation.
Grade 1	Administration of trastuzumab deruxtecan must be interrupted for any ILD events regardless of grade. • Monitor and closely follow-up in 2 to 7 days for onset of clinical symptoms and pulse oximetry • Consider follow-up imaging in 1 to 2 weeks or as clinically indicated • Consider starting systemic steroids (e.g., at least 0.5 mg/kg/day prednisone or equivalent) until improvement, followed by gradual taper over at least 4 weeks • If worsening of diagnostic observations despite initiation of corticosteroids, then follow Grade 2 guidelines; if patient is asymptomatic, then they should be considered as Grade 1 even if steroid treatment is given For grade 1 events, trastuzumab deruxtecan can be restarted only if the event is fully resolved to Grade 0: • If resolved ≤28 days from onset, maintain dose • If resolved >28 days from onset, reduce dose 1 level However, if the Grade 1 ILD/pneumonitis occurs beyond cycle day 22 and has not resolved within 49 days from the last infusion, study treatment should be discontinued.

Grade 2	Permanently discontinue patient from study treatment.
	• Promptly start and treat with systemic steroids (e.g., at least 1 mg/kg/day prednisone or equivalent) for at least 14 days or until complete resolution of clinical and chest CT findings, then followed by a gradual taper over at least 4 weeks
	• Monitor symptoms closely
	• Re-image as clinically indicated
	• If worsening or no improvement in clinical or diagnostic observations in 5 days:
	  ◦ Consider increasing dose of steroids (e.g., 2 mg/kg/day prednisone or equivalent) and administration may be switched to intravenous (e.g., methylprednisolone)
	  ◦ Re-consider additional work-up for alternative etiologies as described above
	• Escalate care as clinically indicated

Grade 3 and 4	Permanently discontinued patient from study treatment. • Hospitalization required • Promptly initiate empiric high-dose methylprednisolone IV treatment (e.g., 500 to 1000 mg/day for 3 days), followed by at least 1 mg/kg/day of prednisone (or equivalent) for at least 14 days or until complete resolution of clinical and chest

Worst toxicity grade[a]	Guidelines
	CT findings, then followed by a gradual taper over at least 4 weeks • Re-image as clinically indicated • If still no improvement within 3 to 5 days, re-consider additional work-up for alternative etiologies as described above • Consider other immunosuppressants and/or treat per local practice
Ocular toxicity	
Grade 3	• Delay dose until resolved to Grade ≤1: ◦ If resolved ≤7 days from onset, maintain dose ◦ If resolved >7 days from onset, reduce dose 1 level
Grade 4	• Discontinue patient from study treatment
Blood creatinine increased	
Grade 3 (>3.0 to 6.0× ULN)	• Delay dose until resolved to ≤Grade 2 or baseline, then reduce dose 1 level
Grade 4 (>6.0× ULN)	• Discontinue patient from study treatment
Hepatic toxicity	
AST or ALT increased with simultaneous total bilirubin increased	
AST/ALT ≥3.0× ULN with simultaneous total bilirubin >2.0× ULN	• Delay study medication until drug-induced liver injury can be ruled out • If drug-induced liver injury is ruled out, the patients should be treated accordingly, and resumption of study treatment may occur after discussion between the investigator and the sponsor • If drug-induced liver injury cannot be ruled out from diagnostic work-up, permanently discontinue study treatment • Monitor AST/ALT and total bilirubin twice weekly until resolution or return to baseline
AST or ALT increased	
Grade 2 (>3.0 to 5.0× ULN if baseline was normal; >3.0 to 5.0× baseline if baseline was abnormal)	• No action
Grade 3 (>5.0 to 20.0× ULN if baseline was normal; >5.0 to 20.0× baseline if baseline was abnormal; applied in patients without liver metastases and patients with liver metastases and baseline level ≤3× ULN)	• Repeat testing within 3 days; delay dose until resolved to Grade ≤1 if baseline ≤3× ULN, otherwise delay dose until resolved to baseline and: ◦ If resolved ≤7 days from onset, maintain dose ◦ If resolved >7 days from onset, reduce dose 1 level
Grade 3 (>8.0 to 20.0× ULN if baseline was normal; >8.0 to 20.0× baseline if baseline was abnormal; applied in patients with liver metastases and patients with liver metastases and baseline level >3× ULN)	• Repeat testing within 3 days; delay dose to ≤baseline level and: ◦ If resolved ≤7 days from onset, maintain dose ◦ If resolved >7 days from onset, reduce dose 1 level

Worst toxicity grade[a]	Guidelines
Grade 4 (>20× ULN if baseline was normal; >20.0× baseline if baseline was abnormal)	• Discontinue patient from study treatment
Total bilirubin increased	
Grade 2 (>1.5 to 3.0× ULN if baseline was normal; >1.5 to 3.0× baseline if baseline was abnormal)	• If no documented Gilbert's syndrome or liver metastases at baseline, delay dose until resolved to Grade ≤1: ◦ If resolved ≤7 days from onset, maintain dose ◦ If resolved >7 days from onset, reduce dose 1 level • If documented Gilbert's syndrome or liver metastases at baseline, continue study treatment
Grade 3 (>3.0 to 10.0× ULN if baseline was normal; >3.0 to 10.0× baseline if baseline was abnormal)	• If no documented Gilbert's syndrome or liver metastases at baseline, repeat testing within 3 days; delay dose until resolved to Grade ≤1: ◦ If resolved ≤7 days from onset, reduce dose 1 level ◦ If resolved >7 days from onset, discontinue trastuzumab deruxtecan • If documented Gilbert's syndrome or liver metastases at baseline, repeat testing within 3 days; delay dose until resolved to Grade <2: ◦ If resolved ≤7 days from onset, reduce dose 1 level ◦ If resolved >7 days from onset, discontinue trastuzumab deruxtecan
Grade 4 (>10.0× ULN if baseline was normal; >10.0× baseline if baseline was abnormal)	• Discontinue patient from study treatment
Blood alkaline phosphatase increased	
Grade 3 (>5.0 to 20.0× ULN if baseline was normal; >5.0 to 20.0× baseline if baseline was abnormal)	• No modification unless determined by the investigator to be clinically significant or life-threatening
Grade 4 (>20.0× ULN if baseline was normal; >20.0× baseline if baseline was abnormal)	• No modification unless determined by the investigator to be clinically significant or life-threatening
Gastrointestinal toxicity	
Nausea	
Grade 3	• Delay dose until resolved to Grade ≤1: ◦ If resolved ≤7 days from onset, maintain dose ◦ If resolved >7 days from onset, reduce dose 1 level
Diarrhea/colitis	
Grade 3	• Delay dose until resolved to Grade ≤1: ◦ If resolved ≤3 days from onset, maintain dose ◦ If resolved >3 days from onset, reduce dose 1 level
Grade 4	• Discontinue patient from study treatment

Worst toxicity grade[a]	Guidelines
Other laboratory AEs	
Grade 3	• Delay dose until resolved to Grade ≤1 or baseline: ◦ If resolved ≤7 days from onset, maintain dose ◦ If resolved >7 days from onset, reduce dose 1 level
Grade 4	• Discontinue patient from study treatment
Other non-laboratory AEs	
Grade 3	• Delay dose until resolved to Grade ≤1 or baseline: ◦ If resolved ≤7 days from onset, maintain dose ◦ If resolved >7 days from onset, reduce dose 1 level
Grade 4	• Discontinue patient from study treatment

AE = adverse event; ALT = alanine aminotransferase; AST = asparagine aminotransferase; CBC = complete blood count; CT = computed tomography; ECG = electrocardiogram; Hb = hemoglobin; ILD = interstitial lung disease; IV = intravenous; LVEF = left ventricular ejection fraction; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSAID = non-steroidal anti-inflammatory drug; PK = pharmacokinetics; QTc = corrected QT interval; SpO_2 = oxygen saturation; ULN = upper limit of normal; WBC = white blood cell.

[a]Graded using NCI-CTCAE v. 5.0 unless otherwise specified.

[b]Dose levels were 3.6 mg/kg (starting dose), 3.0 mg/kg (dose reduction level 1), and 2.4 mg/kg (dose reduction level 2).

Source: DESTINY-Breast03 Clinical Study Report.[13]

Table 27: Sensitivity Analyses of PFS per BICR in the DESTINY-Breast03 Study

Analysis method	Number (%) of patients with events	Median PFS (95% CI), months	HR (95% CI)	Log-rank test P-value (2-sided)
FAS (primary analysis)				
Trastuzumab deruxtecan	87/261	NE (18.5, NE)	0.2840 (0.2165, 0.3727)	<0.0001[c]
Trastuzumab emtansine	158/263	6.8 (5.6, 8.2)		
Unstratified log-rank and Cox proportional hazards model				
Trastuzumab deruxtecan	87/261	NE (18.5, NE)	[redacted]	[redacted]
Trastuzumab emtansine	158/263	6.8 (5.6, 8.2)		
Analysis in the PP set				
Trastuzumab deruxtecan	[redacted]	[redacted]	[redacted]	[redacted]
Trastuzumab emtansine	[redacted]	[redacted]		
Analysis not censoring for missing two consecutive assessments				
Trastuzumab deruxtecan	95/261	22.2 (17.9, NE)	0.2946 (0.2273, 0.3820)	<0.0001[c]
Trastuzumab emtansine	171/263	6.9 (5.6, 8.3)		
Analysis censoring for new anticancer therapy[a]				
Trastuzumab deruxtecan	[redacted]	[redacted]	[redacted]	[redacted]
Trastuzumab emtansine	[redacted]	[redacted]		

Analysis method	Number (%) of patients with events	Median PFS (95% CI), months	HR (95% CI)	Log-rank test P-value (2-sided)
Analysis with back-dating of PFS[b]				
Trastuzumab deruxtecan	[redacted]	[redacted]	[redacted]	[redacted]
Trastuzumab emtansine	[redacted]	[redacted]		
Multiple Cox regression of PFS using covariate set 1				
NA	NA	NA	[redacted]	[redacted]
Multiple Cox regression of PFS using covariate set 2				
NA	NA	NA	[redacted]	[redacted]

BICR = blinded independent central review; CI = confidence interval; FAS = full analysis set; HR = hazard ratio; NA = not applicable; NE = not estimable; PFS = progression-free survival; PP = per protocol.

aFor patients who received new anticancer therapy, the censoring data was the date of the last evaluable tumour assessment prior to start of anticancer therapy.

[b]PFS event time was backdated in the case that PFS events occurred after the patient missed one or more tumour assessment. In such cases, the PFS event dat was considered to be 6 weeks after the last evaluable tumour assessment that occurred prior to progression/death.

[c]P-values are not adjusted for multiplicity and are descriptive only.

Note: see Table 11 for descriptions of sensitivity analyses.

Source: DESTINY-Breast03 Clinical Study Report.[13]

Table 28: Subgroup Analyses of PFS per BICR in the DESTINY-Breast05 Study (FAS)

Subgroup	Number of patients with events		Median PFS (95% CI), months		HR (95% CI)
	Trastuzumab deruxtecan	Trastuzumab emtansine	Trastuzumab deruxtecan	Trastuzumab emtansine	
Hormone receptor status					
Positive (n=272)	46/133	84/139	22.4 (17.7, NE)	6.9 (4.2, 9.8)	0.3191 (0.2217, 0.4594)
Negative (n=248)	41/126	73/122	NE (18.0, NE)	6.8 (5.4, 8.3)	0.2965 (0.2008, 0.4378)
Estrogen receptors					
Positive (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Negative (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progesterone receptors					
Positive (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Negative (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior treatment with pertuzumab					
Yes (n=320)	57/162	98/158	NE (18.5, NE)	6.8 (5.4, 8.3)	0.3050 (0.2185, 0.4257)
No (n=204)	30/99	60/105	NE (16.5, NE)	7.0 (4.2, 9.7)	0.2999 (0.1924, 0.4675)
Lines of prior systemic therapy not including hormone therapy					
<3 lines (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Subgroup	Number of patients with events		Median PFS (95% CI), months		HR (95% CI)
	Trastuzumab deruxtecan	Trastuzumab emtansine	Trastuzumab deruxtecan	Trastuzumab emtansine	
≥3 lines (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline visceral disease					
Yes (n=384)	72/195	123/189	22.2 (16.5, NE)	5.7 (4.2, 7.0)	0.2806 (0.2083, 0.3779)
No (n=140)	15/66	35/74	NE (NE, NE)	11.3 (6.8, NE)	0.3157 (0.1718, 0.5804)
History of CNS metastases					
Yes (n=114)	31/62	31/52	15.0 (12.6, 22.2)	5.7 (2.9, 7.1)	0.3796 (0.2267, 0.6357)
No (n=410)	56/199	127/211	NE (22.4, NE)	7.0 (5.5, 9.7)	0.2665 (0.1939, 0.3665)
Baseline CNS metastases					
Yes (n=82)	22/43	27/39	15.0 (12.5, 22.2)	3.0 (2.8, 5.8)	0.2465 (0.1341, 0.4529)
No (n=442)	65/218	131/224	NE (22.4, NE)	7.1 (5.6, 9.7)	0.2971 (0.2199, 0.4014)
Time from neoadjuvant or adjuvant therapy to development of MBC					
<6 months (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[3]6 months (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; CNS = central nervous system; FAS = full analysis set; HR = hazard ratio; MBC = metastatic breast cancer; NE = not estimable; PFS = progression-free survival.

Source: DESTINY-Breast03 Clinical Study Report.[13]

Table 29: Subgroup Analyses of OS in the DESTINY-Breast03 Study (FAS)

Subgroup	Number of patients with events		Median OS (95% CI), months		HR (95% CI)
	Trastuzumab deruxtecan	Trastuzumab emtansine	Trastuzumab deruxtecan	Trastuzumab emtansine	
Hormone receptor status					
Positive (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Negative (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estrogen receptors					
Positive (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Negative (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progesterone receptors					
Positive (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Subgroup	Number of patients with events		Median OS (95% CI), months		HR (95% CI)
	Trastuzumab deruxtecan	Trastuzumab emtansine	Trastuzumab deruxtecan	Trastuzumab emtansine	
Negative (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior treatment with pertuzumab					
Yes (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lines of prior systemic therapy not including hormone therapy					
<3 lines (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥3 lines (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline visceral disease					
Yes (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline CNS metastases					
Yes (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of CNS metastases					
Yes (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; CNS = central nervous system; FAS = full analysis set; HR = hazard ratio; NE = not estimable; OS = overall survival.
Source: DESTINY-Breast03 Clinical Study Report.[13]

Appendix 3: Description and Appraisal of Outcome Measures

Note that this appendix has not been copy-edited.

Aim

To describe the following outcome measures and review their measurement properties (validity, reliability, responsiveness to change, and MID):

- EQ-5D-5L
- EORTC QLQ-C30
- EORTC QLQ-BR45

Findings

Table 30: Summary of Outcome Measures and Their Measurement Properties

Type	Conclusions about Measurement Properties	MID
EQ-5D-5L index score: Generic, preference-based measure of HRQoL consisting of 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Scores range from 0 to 1 with higher scores indicating better health status.[20] EQ VAS: Generic, preference-based measure of HRQoL presented as a scale from 0 to 100 with 0 anchored as the worst possible health state and 100 as the best possible health state.[20]	**Validity:** Construct validity was assessed using the known-group approach. Patients presenting evidence of disease and receiving chemotherapy and/or radiotherapy showed significantly lower mean utility index as compared to their counterparts both in the English and Chinese samples.[29] Convergent validity: The EQ-5D-5L utility index and VAS were strongly correlated with the Functional Assessment of Cancer Therapy-Breast (FACT-B) total score [Spearman's correlation coefficient (r) ranging from 0.53 to 0.73] in patients with breast cancer.[29] **Reliability:** Test-retest reliability: The EQ-5D-5L index and VAS demonstrated substantial to almost perfect agreement[30] in English-speaking patients living with breast cancer and no history of brain metastasis based on an ICC of 0.81 (95% CI: 0.73 to 0.87) and 0.83 (95% CI, 0.76 to 0.89), respectively.[29] **Responsiveness:** Responsiveness was demonstrated in patients with breast cancer following curative treatment; however, small changes in health were not recognized as being meaningful.[31,32]	MID for the index score was estimated to range from 0.037 to 0.056 in the general Canadian population.[33] A MID specific to patients with breast cancer was not identified. MID for the EQ VAS was estimated to range from 7 to 12 in advanced cancer patients.[34]
A 30-item, patient-reported, cancer-specific, HRQoL questionnaire using 4- and 7-point Likert scales.[21]	**Validity:** Content validity: When mapping to the World Health Organization's ICF framework, 25 of the 30 items in the EORTC QLQ-C30 were endorsed by the experts.[35] Discriminant validity: As represented by correlation with external parameters such as ECOG performance status (Spearman's rank correlation	For patients with advanced breast cancer, MIDs for within-group changes ranged from 5 to 14 points for improvements and from −14 to −4 points for deterioration across the individual scales. For between-group differences, MIDs ranged from 4 to

Type	Conclusions about Measurement Properties	MID
	values ranging from 0.02 to 0.56) in patients with metastatic breast cancer.[36] Convergent validity: As represented by correlation with scores on the Profile of Mood States and Psychosocial Adjustment to Illness Scale, was also deemed to be acceptable (Spearman's rank correlation values ranging from 0.02 to 0.76) in patients with metastatic breast cancer.[36] **Reliability:** Inter-rater reliability: As represented by patient-observer agreement on the EORTC QLQ-C30 questionnaire, the median kappa coefficient for agreement across the 30 items in the EORTC QLQ-C30 was 0.86 with a range of 0.48 to 1.00 in patients with metastatic breast cancer, representing substantial to near-perfect agreement for most items.[30,37] **Responsiveness:** No literature was identified that assessed responsiveness in patients with breast cancer.	11 points for improvements and from −18 to −4 points for deterioration across the individual scales.[38] For patients with metastatic breast cancer, MIDs for within-group improvement varied from 7 to 15 and those for deterioration varied from −7 to −17. For between-group difference, MIDs varied from 5 to 11 for improvement and from −5 to −8 for deterioration across QLQ-C30 scales.[39]
A 45-item patient-reported, breast cancer-specific, HRQoL questionnaire using 4-point Likert scales. An updated version of the EORTC QLQ-BR23.[22]	**Validity:** Content (face) validity: All the newly added 22 items of the EORTC QLQ-BR45 fulfilled at least five of the eight prespecified inclusion criteria with a mean score greater than 1.5 in patients with breast cancer.[22] **Reliability:** Internal consistency reliability: All EORTC QLQ-BR45 subscales have demonstrated acceptable internal consistency by exceeding the accepted threshold of >0.70 Cronbach's alpha in patients with breast cancer.[22] **Responsiveness:** No literature was identified that assessed responsiveness in patients with breast cancer.	No literature was identified that estimated MIDs in patients with breast cancer.

ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = 5-Level EQ-5D; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-BR45 = The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer–Specific Quality of Life Questionnaire-45 item; EORTC QLQ-BR23 = The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer–Specific Quality of Life Questionnaire-23 item; HRQoL= health-related quality of life; ICC = intraclass correlation coefficient; ICF = International Classification of Functioning; MID = minimal important difference; VAS = visual analogue scale.

5-Level EQ-5D

Description and Scoring

The EQ-5D is a generic, self-reported, HRQoL instrument developed by the EuroQol Group that is applicable to a wide range of health conditions and treatments.[20] As a generic measure of HRQoL that can capture the net effect of treatment benefits and harms, the EQ-5D provides valuable information from the patient perspective. The EQ-5D-5L is an updated version of the original 3-level version of the EQ-5D (EQ-5D-3L).

The EQ-5D-5L consists of a descriptive system and the EQ VAS. The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is answered based on 5 levels, where 1 = "no problems", 2 = "slight problems", 3 = "moderate problems", 4 = "severe problems", and 5 = "extreme problems" or "unable to perform", which is the worst response in the dimension.[20] Respondents choose the level that reflects their health state for each of the 5 dimensions.

In total, there are 3,125 possible unique health states defined by the EQ-5D-5L, with 11111 and 55555 representing the best and worst health states, respectively. The numerical values assigned to levels 1 to 5 for each dimension reflect rank order categories of function. In terms of measurement properties, these are ordinal data and do not have interval properties, therefore, they should not be summed or averaged to, for example, produce a single dimension score. Results from the EQ-5D-5L descriptive system can be converted into a single index score using a scoring algorithm taking the local patient and population preferences into account. Therefore, the index score is a country-specific value and a major feature of the EQ-5D instrument.[40] The range of index scores will differ according to the scoring algorithm used; however, in all scoring algorithms of the EQ-5D-5L, a score of 0 represents the health state "dead" and 1.0 reflects "perfect health". Negative scores are also possible for those health states that society (not the individual patient) considers to be "worse than dead".

The EQ VAS records the respondent's self-rated health on a vertical VAS where the end points are labelled 0 ("the worst health you can imagine") and 100 ("the best health you can imagine"). Respondents are asked to mark a X on the point of the VAS that best represents their health on that day. The EQ-5D index and VAS scores can be summarized and analyzed as continuous data.[20]

Overall, the EQ-5D produces 3 types of data for each respondent:

- a profile indicating the extent of problems on each of the 5 dimensions represented by a 5-digit descriptor, such as 11121 or 21143,
- a population preference-weighted health index score based on the descriptive system,
- a self-reported assessment of health status based on the EQ VAS.

The EQ-5D-5L has been validated in terms of feasibility, ceiling effects, discriminatory power, and convergent validity in a diverse patient population from 6 countries with chronic conditions.[20]

Assessment of Validity, Reliability, and Responsiveness

Responsiveness of the EQ-5D-5L in 192 patients who were enrolled in a clinical trial investigating the cost-effectiveness of nurse-led telephone follow-up and an educational program after curative treatment for breast cancer. Anchor-based methods were used and the global health subscale of the EORTC QLQ-C30 was the anchor selected for clinical change. The global health subscale consists of two items: "how would you rate your physical condition during the past week?" and "how would you rate your overall quality of life during the past week?". Following demonstration of correlation to the EQ-5D-5L index and VAS, the use of the global health subscale as an anchor was deemed appropriate. Patients were classified into the following subgroups using the EORTC QLQ-C30: moderate-large deterioration, small deterioration, no change, a small improvement, moderate-large improvement in health status. Responsiveness was evaluated by calculating the standardized response mean (SRM) for the EQ-5D-5L index, VAS, and patient subgroups. The following benchmarks for effect sizes were used to interpret scores: 0.20 through 0.49 was interpreted as small, 0.50 through 0.79 as moderate and ≥ 0.80 as large.[41] Additionally, analysis of variance (ANOVA) procedures were used to determine the ability of the EQ-5D-5L to discriminate between subgroups. Overall, the EQ-5D-5L was able to detect improvements and deteriorations in health. Further, it demonstrated the ability to discriminate between patients with no change in health and patients with moderate-large changes in health; however, it was not able to differentiate between the "no change" subgroup and small improvements or a small or moderate-large deterioration.[31] Evidence of responsiveness for the EQ-5D-5L was also demonstrated in a study by Conner-Spady (2001). HRQoL was evaluated in 52 patients with stage II and III breast cancer at high risk of relapse following high dose chemotherapy with autologous blood stem cell transplantation. The Functional Living Index-Cancer (FLIC) was used as an anchor and the responsiveness of the EQ-5D-5L was assessed by effect size and ANOVA, which demonstrated responsiveness but a lack of sensitivity for smaller changes in HRQoL that are important to patients living with cancer.[32]

The validity and reliability of the English and Chinese versions of the EQ-5D-5L was evaluated in a study that recruited patients from a specialist outpatient clinic in Singapore. Adult English and/or Chinese-speaking patients with histologically confirmed breast cancer and no evidence of brain metastasis, psychosis, or severe depression were included.[29] The construct validity was assessed using the know-groups approach, patients presenting evidence of disease and receiving chemotherapy and/or radiotherapy showed significantly lower mean utility index as compared to their counterparts both in the English and Chinese samples. With regards to the convergent validity, both the English and Chinese version of the EQ-5D-5L utility index and VAS were strongly correlated with the Functional Assessment of Cancer Therapy-Breast (FACT-B) total score [Spearman's correlation coefficient (r) ranging from 0.53 to 0.73]. Test-retest reliability was assessed in patients that reported no change in performance status based on a 30-day follow-up period. The EQ-5D-5L index and VAS

demonstrated substantial to almost perfect agreement[30] among English-speaking patients (N = 169) based on an intraclass correlation coefficient of 0.81 (95% CI: 0.73 to 0.87) and 0.83 (95% CI, 0.76 to 0.89), respectively.

Minimal Important Difference

A Canadian-specific estimate of a MID for the EQ-5D-5L was generated by simulating the effects of single level transitions in each dimension.[33] The results yielded MIDs with a summarized mean of 0.056 (SD = 0.011), and a summarized median of 0.056 (interquartile range = 0.049 to 0.063).[33] A MID specific to patients with breast cancer was not identified. Pickard et al. (2007)[34] estimated the MID of the EQ-5D VAS based on cross-sectional data collected from 534 patients (mean 59 [SD 12] years, 52% male) in the United States with advanced (stage III or IV) cancer of the bladder, brain, breast, colon or rectum, head or neck, liver or pancreas, kidney, lung, lymphoma, ovary, or prostate.[34] MIDs for the EQ-5D VAS ranged from 8 to 12 based on the ECOG performance status, and from 7 to 10 based on Functional Assessment of Cancer Therapy HRQoL questionnaire quintiles.[34]

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30

Description and Scoring

The EORTC QLQ-C30 is one of the most used patient-reported outcome measures in oncology clinical trials. It is a multidimensional, cancer-specific, self-administered, measure of HRQoL.[21]

The EORTC QLQ-C30 is composed of both multi-item scales and single-item measures. These include 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea and vomiting), a global health status/HRQoL scale, and 6 single items assessing additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation and diarrhea) as well as perceived financial impact of the disease.[21]

The EORTC QLQ-C30 uses a 1-week recall period to assess functional status and symptoms. All scales and single-item measures are scored from 0 to 100. Most questions have 4 response options ("not at all", "a little", "quite a bit", "very much"), with scores on these items ranging from 1 to 4. For the 2 items that form the global HRQoL scale, the response format is a 7-point Likert-type scale with anchors at 1 = "very poor" and 7 = "excellent". Raw scores for each scale are computed as the average of the items that contribute to a particular scale. Scale sum scores are transformed such that a high score on the functional scales represents a high/healthy level of functioning, a high score on the symptom scales represents a high level of symptomatology, and a high score on the global health status/HRQoL scale represents a high HRQoL.[42]

According to the EORTC QLQ-C30 scoring algorithm, if there are missing items for a scale (i.e., the participant did not provide a response), the score for the scale can still be computed if there are responses for at least half of the items. The values for missing items are interpolated with the average of the respondent-completed items.[42]

Assessment of Validity, Reliability, and Responsiveness

One study[35] assessed the content validity of the EORTC QLQ-C30 based on the opinions of 21 experts. When mapping to the World Health Organization's International Classification of Functioning (ICF) framework, 25 of the 30 items in the EORTC QLQ-C30 were endorsed by the experts: 15 items mapping to impairment of body function, 7 mapping to activity limitations/participation restrictions, and 1 item mapping to both components. There were only 2 items of the EORTC QLQ-C30 tapped content outside of functioning: Item 29 mapping to perceived health and item 30 mapping to global quality of health. The authors stated that the fact that most items from the EORTC QLQ-C30 can be linked to the ICF framework means that the instrument's content reflects functioning, which is a key component of HRQoL.[35]

No studies were identified that investigated the validity, reliability, or responsiveness of the EORTC QLQ-C30 among patients with HER2-positive MBC. Among patients with MBC, a 1997 study investigated the inter-rater reliability using patient-observer agreement on the EORTC QLQ-C30 questionnaire. The median kappa coefficient for agreement across the 30 items in the EORTC QLQ-C30 was 0.86 with a range of 0.48 to 1.00,[37] representing substantial to near-perfect agreement for most items.[30] Another study[36] investigated the discriminative and convergent validity of the psychosocial subscales of EORTC QLQ-C30 in patients with breast cancer. The study found acceptable discriminative validity represented by correlation with external parameters such as ECOG performance status (Spearman's rank correlation values ranging from 0.02 to 0.56). A correlation of 0.2 represented significance at the 0.01 level. The

convergent validity, as represented by correlation with scores on the Profile of Mood States and Psychosocial Adjustment to Illness Scale, was also deemed to be acceptable (Spearman's rank correlation values ranging from 0.08 to 0.76).[36]

Minimal Important Difference

One study from 1998,[43] conducted in patients with breast cancer and small-cell lung cancer, estimated that a change in score on any scale of the EORTC QLQ-C30 of 10 points would be clinically significant. This estimate was based on an anchor-based approach to estimate the MID in which patients who reported "a little" change (for better or worse) on the subjective significance questionnaire (SSQ) had corresponding changes on a function or symptom scale of the EORTC QLQ-C30 of approximately 5 to 10 points. Patients who reported a "moderate" change had corresponding changes in the EORTC QLQ-C30 of about 10 to 20 points, and those who reported "very much" change had corresponding changes in the EORTC QLQ-C30 of more than 20 points.[43]

A more recent study from 2019[38] aimed to estimate the MID for the EORTC QLQ-C30 in patients with advanced breast cancer. This study used anchor-based and distribution-based approaches, utilizing performance status and selected AEs as the anchor variables. MIDs for within-group changes ranged from 5 to 14 points for improvements and from -14 to -4 points for deterioration across the individual scales. For between-group differences, MIDs ranged from 4 to 11 points for improvements and from -18 to -4 points for deterioration across the individual scales.[38] A 2011 report combined a systematic review, expert opinions, and meta-analysis to estimate large, medium and small differences for EORTC QLQ-C30 scores and recommended that small and medium differences corresponded with changes from 3 to 6 and 9 to 19 points, respectively, depending on the subscale.[44] In addition, A study from 2016[45] aimed to investigate the effect of response shift on MID over time for the EORTC QLQ-BR23 in patients with breast cancer or suspicious breast cancer. Three hundred eighty-one patients recruited from 4 hospitals and care centres participated in this study with a mean age of 58.4 years (SD = 11 years). This study used an anchor-based approach utilizing deterioration improvement as the anchor variables. The minimal of observed MID at 6 months (ranging from 0.5 to 10) was smaller in case of deterioration for EORTC QLQ-C30 compared to 3 months (ranging from 5 to 26). With regards to improvement, the observed MID at 6 months (ranging from 0.8 to 7) was similar to the observed MID at 3 months (ranging from 0.3 to 10).[45] Kawahara et al. obtained a dataset of 154 patients with MBC form the SELECT BC-CONFIRM RCT and calculated MIDs using an anchor-based approach.[39] The study utilized the patient's global rating of transition and change in ECOG PS as the anchor variables. MIDs were estimated in 8 of 15 scales of QLQ-C30. Estimated MIDs for within-group improvement varied from 7 to 15 and those for deterioration varied from − 7 to − 17. Estimated MIDs for between-group improvement varied from 5 to 11 and those for deterioration varied from − 5 to − 8 across QLQ-C30 scales.[39]

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer–Specific Quality of Life Questionnaire-45 Item

Description and Scoring

The EORTC QLQ-BR45 is a breast cancer-specific module, updated in 2020 from the EORTC QLQ-BR23 originally developed in 1996. The EORTC QLQ-BR45 contains a total of 45 items: 23 items from the QLQ-BR23 and 22 new items. The new additional items reflect side-effects and symptoms related to new BC therapies that have evolved since the development of the EORTC QLQ-BR23. The EORTC QLQ-BR45 items can be categorized into five functioning sub-scales (body image, future perspective, sexual functioning, sexual enjoyment, breast satisfaction), and seven symptom subscales (arm, breast, endocrine therapy, skin mucositis, endocrine sexual symptoms, systemic therapy side effects, and upset by hair loss). It also has three open-ended items to capture additional symptoms or problems not addressed by the previous items. All EORTC QLQ-BR45 items have the same four response options as the QLQ-C30 ("not at all", "a little", "quite a bit", "very much"), with scores ranging from 1 to 4.[22,46] A higher score indicates worse symptom experience.

Assessment of Validity, Reliability, and Responsiveness

The developers of the EORTC QLQ-BR45 recruited a total of 250 patients who were histologically confirmed diagnosis of breast cancer from 12 countries representing Northern, Central, Southern, Eastern, and English-speaking European regions and one non-European (Brazil) region to assess the content (face) and internal consistency reliability.[22] The EORTC QLQ-BR45 developers established 8 quantitative inclusion criteria for eligible items. All the newly added 22 items of the EORTC QLQ-BR45 fulfilled at least five of the prespecified inclusion criteria with a mean score greater than 1.5, which demonstrated adequate content validity. With regards to internal consistency reliability, all subscales have demonstrated acceptable internal consistency by exceeding the accepted threshold of > 0.70 Cronbach's alpha. In addition, the new items had no strong correlation with existing scales of the EORTC QLQ-BR 23, which indicated the necessity of new subscales to cover all side-effects of current breast cancer therapies.[22]

Minimal Important Difference

No relevant literature was identified that estimated the MIDs in patients with breast cancer.

CADTH

Pharmacoeconomic Review

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Abbreviations

AE	adverse event
BIA	budget impact analysis
CI	confidence interval
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
ICER	incremental cost-effectiveness ratio
OS	overall survival
PFS	progression-free survival
QALY	quality-adjusted life-year
RDI	relative dose intensity
T-DM1	trastuzumab emtansine
T-DXd	trastuzumab deruxtecan
TTD	time to treatment discontinuation
WTP	willingness-to-pay

Executive Summary

The executive summary comprises 2 tables (Table 1 and Table 2) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Trastuzumab deruxtecan (Enhertu), powder for reconstitution for IV infusion
Submitted price	Trastuzumab deruxtecan, 100 mg vial: $2,440.00
Indication	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.
Health Canada approval status	NOC
Health Canada review pathway	Priority review; Project Orbis
NOC date	June 15, 2022
Reimbursement request	As per indication
Sponsor	AstraZeneca Canada
Submission history	Previously reviewed: No

HER2 = Human epidermal growth factor receptor 2; NOC = Notice of Compliance.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis 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
Comparator	T-DM1
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, Lys
Time horizon	Lifetime (25 years)
Key data source	DESTINY-Breast 03, a phase III, multicentre, randomized, open-label, active-controlled trial (T-DXd vs. T-DM1)
Submitted results	ICER = $103,922 per QALY (incremental costs = $164,772 and incremental QALYs = 1.59)

Component	Description
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-Breast 03 trial. Thus, no conclusions regarding OS differences between T-DXd and T-DM1 could be drawn. • The sponsor used OS data from the EMILIA trial to extrapolate long-term OS estimates for T-DM1 beyond the DESTINY-Breast 03 trial. The sponsor used immature data from the DESTINY-Breast 03 trial to derive a hazard ratio for OS that was then applied to 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-Breast 03 trial population. The sponsor's approach overestimated the OS benefit for T-DXd at the 25-year time point, according to clinical experts consulted during this review. • 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 clinical experts consulted for this review. • The trial-based utility value for PFS was higher than the general Canadian population norm value; thus, appeared to be overestimated. • 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-Breast 03 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. • The submitted model lacked transparency and flexibility, including the inability to run probabilistic analysis when selecting alternate distributions pre-programmed within the sponsor's model. CADTH was unable to address these limitations and cautions that results from 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 the 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. • In the CADTH base case, for the proposed Health Canada–indicated population, T-DXd was associated with an ICER of $274,875 per QALY compared to T-DM1 (incremental costs = $217,830; incremental QALYs = 0.79). • 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.

HER2 = human epidermal growth factor receptor 2; ICER = incremental cost-effectiveness ratio; LY = life-year; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-year; RDI = relative dose intensity; T-DXd = trastuzumab deruxtecan; T-DM1 = trastuzumab emtansine; vs. = versus.

Conclusions

Based on the appraisal of the DESTINY-Breast 03 trial, the CADTH clinical review indicated that trastuzumab deruxtecan (T-DXd) may be associated with progression-free survival (PFS) benefits in adult patients with unresectable or metastatic HER2-positive breast cancer who have received at least 1 prior anti–human epidermal growth factor receptor 2 (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. No conclusions regarding overall survival (OS) differences between T-DXd and trastuzumab emtansine (T-DM1) can yet be reached. Notable harms were higher in the T-DXd group than in T-DM1 and the relative impact of T-DXd and T-DM1 on health-related

quality of life (HRQoL) was uncertain. It is important to note that, due to the relatively short duration of follow-up in this study (median of approximately 16 months), neither PFS data for T-DXd nor OS data for both T-DXd and T-DM1 were mature at the time of the trial data cut-off. Furthermore, the CADTH clinical review identified uncertainty regarding the impact of the potential imbalance of subsequent treatments used in the DESTINY-Breast 03 trial between treatments on OS given the data immaturity, the lack of censoring for treatment addition or switching, the open-label design of the trial, and the uncertainty associated with the efficacy of the subsequent treatments used. Additionally, CADTH highlighted uncertainty regarding the generalizability of the OS results as most of the subsequent treatments that were used in the DESTINY-Breast 03 trial are not generally available in the same setting in Canadian clinical practice. All these items limit the interpretation of the long-term survival benefits associated with T-DXd.

CADTH identified several limitations in the economic analyses submitted by the sponsor. The key limitations addressed by CADTH reanalysis included changes to the OS modelling approach, changes in health utility values for the progression-free state, changes in the proportion of patients receiving subsequent treatments, changes in market shares for subsequent treatments, and elimination of relative dose intensity (RDI). Based on the CADTH's base case, treatment with T-DXd is $217,830 more costly and yielded 0.79 more quality-adjusted life-year (QALYS), resulting in an incremental cost-effectiveness ratio (ICER) of $274,875 per QALY. A price reduction of at least 61% would be necessary to achieve an ICER of $50,000 per QALY. When considering the possibility of sequential treatment with T-DM1 after treatment with T-DXd, the ICER for T-DXd increased to $431,506 per QALY compared with T-DM1, as reported in the scenario analysis.

The cost-effectiveness of T-DXd compared to T-DM1 is dependent on the assumption that improvements in PFS lead to long-term improvements in OS, and that the treatment effect of T-DXd persists for years after discontinuation. Neither of these assumptions was supported by current evidence from the DESTINY-Breast 03 trial, adding considerable uncertainty to the cost-effectiveness results. The timing of subsequent treatments, duration of use, and clinical benefits associated with the use of T-DXd and T-DM1 have an impact that could not be fully addressed within the current review.

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups, registered clinicians, and drug plans that participated in the CADTH review process (specifically, information that pertains to the economic submission).

Two patient groups provided input for this review: the Canadian Breast Cancer Network and Rethink Breast Cancer Canadian. Patient input was based on focused conversations with the members from an advisory board, email interviews, phone interviews, and an online survey, all focused on patients with metastatic breast cancer in Canada. Most patients reported receiving 2 immunotherapy therapies (i.e., pertuzumab and trastuzumab) and chemotherapy that include a taxane. Patient feedback highlighted that most patients consider effectiveness of treatment as the most important factor about treatment, followed by prolonging life without sacrificing quality of life. Patients also indicated that they would consider it acceptable to have some side effects, including fatigue, nausea, depression, and others for 6

months of extended progression-free disease, but this tradeoff would not be acceptable if the side effect was pain. In addition, patient input identified loss of employed; costs of disease management, including managing side effects; and costs associated with travelling as having a significant impact in their lives. Ten patients had experience with T-DXd, and reported feeling good about the treatment, some with improvement in disease symptoms. Most patients reported nausea, stomach issues, fatigue, and hair loss with T-DXd treatment, all side effects deemed as manageable. One patient reported substantial side effects, resulting in hospital admission, including nausea, vomiting, and fatigue. These side effects were reported to be present for a week after each infusion.

Three clinician groups provided input for this review: the Ontario Health Cancer Care Ontario Breast Cancer Drug Advisory Committee, the Rethink Breast Cancer Scientific Advisory Committee, and a joint submission from the Ottawa Hospital Cancer Centre – Breast Disease Site Group (medical oncology) and additional breast medical oncologists in Canada. Clinician feedback indicated that trastuzumab emtansine is the current standard treatment for patients with HER2-positive metastatic breast cancer whose disease progresses after treatment with a combination of anti-HER2 antibodies and a taxane, as well as for patients who developed disease recurrence during or within 6 months of completing neoadjuvant or adjuvant therapy. Clinician input highlighted that the treatment goals for the indicated population include improvement of symptoms, maintenance, or improvement of quality of life compared with currently available treatments; maintenance or improvement of organ function; and improvement in OS and PFS, with acceptable toxicity. The clinician feedback raised concerns about the increased risk of pneumonitis, indicating the need of a risk-benefit assessment for the treatment of patients with severe underlying lung disease, especially underlying interstitial lung disease. It was noted that access to specialty services might be needed in the case of development of pneumonitis.

Drug plan input considered whether patients who were treated with adjuvant T-DM1 would be eligible for treatment with T-DXd. It was also noted that storage of T-DXd vials requires refrigeration, and after reconstitution, T-DXd vials must be used immediately; thus, vial sharing is unlikely to be feasible, which leads to drug wastage. The drug plans indicated that there is a considerable look-alike, sound-alike concern with correctly identifying another member of the trastuzumab group of treatments, which will require operational strategies to avoid confusion among treatments. Finally, the drug plans also noted that in the budget impact analysis (BIA), it was assumed that T-DXd would replace T-DM1, which might not be the case if both therapies are used in sequence.

Several of these concerns were addressed in the sponsor's model:

- In the sponsor's base case, the vial sharing was assumed to be 0%.
- The sponsor's submitted model accounted for quality of life and length of life by using QALYs as the primary outcome.

In addition, CADTH addressed the following concern:

- CADTH used scenario analyses to explore the impact of T-DM1 being used as a subsequent line of treatment instead of displacing T-DM1.

CADTH was unable to address the following concern raised from stakeholder input:

- Pneumonitis and pneumonitis management were included as a side effect in the model.

Economic Review

The current review is for T-DXd (Enhertu) 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.

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted a cost-utility analysis of T-DXd compared with trastuzumab entansine.[1] The model population comprised adult patients with unresectable or metastatic HER2-positive breast cancer who had 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, which aligns with the Health Canada–indicated population.

The recommended dosage of T-DXd is 5.4 mg/kg given as an IV infusion once every 3 weeks, until disease progression or unacceptable toxicity.[2] T-DXd should be administered over a 90-minute period initially, which may be reduced to 30 minutes for subsequent doses. 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. However, as wastage was incorporated by the sponsor using the method of moments approach, the actual cost per cycle was $9,760. The per 21-day cycle costs for T-DM1, the comparator treatment, was $5,070 (for a dose of 224.64 mg), and $7,380 per cycle when wastage was considered.

The clinical outcomes of interest were QALYs and life-years. The economic analysis was undertaken over a lifetime (25-year) time horizon from the perspective of a public health care payer in Canada. Discounting (1.5% per annum) was applied to both costs and outcomes.

Model Structure

The sponsor submitted a partitioned survival model with 3 health states: pre-progression, post-progression, and death (refer to Figure 1). All patients entered the model in the progression-free health state, where they receive either T-DM1 or T-DXd. Patients could remain progression-free, their disease could progress, or they could die. Post-progressed patients could either remain in the same state or move to death. The proportion of people who were progression-free and who had progressed disease for T-DXd was determined by fitting survival curves to PFS and OS data from the DESTINY-Breast 03 and EMILIA trials. In addition, following disease progression, patients could switch to a subsequent active treatment, modelled as a basket of treatments. Death was modelled as an absorbing state. The sponsor further divided the alive states by treatment status (on or off treatment) as time to treatment discontinuation (TTD) was modelled independent of PFS. The model assumed a cycle length of 3 weeks. The model did not stratify the population by patients who presented with unresectable HER2-positive breast cancer who developed disease recurrence during or within 6 months of completing neoadjuvant or adjuvant therapy, and patients who presented with metastatic HER2-positive breast cancer who had received a prior treatment with an anti-HER2-based regimen in the metastatic setting.

Model Inputs

The baseline population characteristics and clinical efficacy parameters in the model were characterized by the DESTINY-Breast 03 trial, a randomized, open-label, active-controlled, phase III study designed to evaluate the efficacy of T-DXd compared with T-DM1 in patients with unresectable or metastatic HER2-positive breast cancer previously treated with trastuzumab and a taxane. The sponsor assumed that the DESTINY-Breast 03 trial population (baseline characteristics: mean age = 54.4 years; 99.6% female; mean weight = 62.4 kg; mean body surface = 1.65 m^2) reflected the population in Canada.

Efficacy outcomes (i.e., OS, PFS, and TTD) for T-DXd were based on the DESTINY-Breast 03 trial. The PFS data for T-DXd and OS data for both treatments in the DESTINY-Breast 03 trial were not mature. Due to immaturity of the OS data, the sponsor estimated the OS curve for T-DM1 using patient-level data from DESTINY-Breast 03 trial up to 20 months and extrapolating benefit by fitting parametric survival models based on OS data from the EMILIA trial.[3] The EMILIA trial evaluated T-DM1 versus lapatinib and capecitabine in patients with HER2-positive unresectable, locally advanced, or metastatic breast cancer previously treated with trastuzumab and a taxane and reported a median OS of 29.9 months over a median follow-up of 47.8 months. The sponsor determined that the proportional hazards assumption held between T-DXd and T-DM1 for OS using the NICE Decision Support Unit and algorithm described by Guyot et al.[4] Based on this assumption, the OS curve for T-DXd was modelled by applying the OS hazard ratio (HR) of T-DXd versus T-DM1 from the DESTINY-Breast 03 clinical trial (HR = 0.56; 95% confidence interval [CI], 0.36 to 0.86) to the T-DM1 OS curve. The treatment effect was assumed to start waning after 110 months (9.6 years), at which time only 1% of patients receiving T-DXd were modelled to be in the PFS state. Selection of the parametric survival distributions was based on statistical goodness of fit measures (i.e., Akaike Information Criterion and the Bayesian Information Criterion) and clinical plausibility. PFS and TTD curves for T-DXd and T-DM1 were generated by fitting survival distributions to patient-level data from the DESTINY-Breast 03 trial. The TTD calculation was performed using the Kaplan–Meier methodology. Selection of the parametric survival distributions was based on statistical goodness of fit measures, visual inspection, and clinical plausibility. The sponsor chose a log-logistic function to extrapolate OS, and a gamma function to extrapolate PFS and TTD. Patients were censored at the last contact before data cut-off. As such, all-cause mortality was included in the model based on age- and sex-specific data from Canadian life tables, weighted to the gender distribution of patients in the DESTINY-Breast 03 study.

The grade 3 or greater AEs which occurred with a frequency of more than 1% (all grades) observed in the DESTINY-Breast 03 trial were incorporated into the model with an associated cost and disutility. These are applied as a 1-time cost and utility decrement in the first cycle of PFS state.

Health state utility values for the base-case PF health state were derived from the DESTINY-Breast 03 trial, and health utility values for the progressed states used another study from literature adjusted for patient characteristics based on DESTINY-Breast 03 trial.[5] Utility decrement for adverse events (AEs) were based on various sources in the literature and incorporated as a single disutility in the first cycle.

Costs in the model included the costs of drug acquisition, administration, AE, subsequent treatments, and treatment monitoring and disease management. To calculate T-DXd and T-DM1 costs, the sponsor considered the mean RDI from the DESTINY-Breast 03 trial (92.1% and 95.5% for T-DXd and T-DM1, respectively). Drug acquisition costs for comparators

were based on the IQVIA Delta PA database.[6] Wastage was calculated through a method of moments approach, based on patients' mean weight observed in the DESTINY-Breast 03 trial, assuming no vial sharing. Administration costs were obtained from the literature.[7] AE costs were derived from Ontario from the Ontario Case Costing Initiative for inpatient and ambulatory care, depending on the AE type.[8]

The sponsor assumed that patients would receive subsequent treatments in line with treatment options in the DESTINY-Breast 03 trial based on the available data cut-off date (median follow-up of 16 months), and that use of distinct treatments would differ depending on treatment arm. In the distribution of subsequent treatments, [redacted]% of patients who initially received T-DXd received T-DM1, while no patients were rechallenged with T-DXd. In the T-DM1 group, [redacted]% of patients received T-DXd as a subsequent treatment, while [redacted]% were rechallenged with T-DM1. Other treatments were used as subsequent treatments, including trastuzumab, pertuzumab, and capecitabine. The sponsor assumed that duration of subsequent treatment was until death. Subsequent treatment costs were obtained from the IQVIA Delta PA database and administration costs were sourced from the literature.[6,7]

For treatment monitoring costs and disease management, the sponsor used a macro costing approach based on predetermined Institute for Clinical Evaluative Sciences data categories for second- and third-line treatments for each health state. Progression-free state costs included laboratory, physicians, dialysis, emergency, inpatient, non-physician, drugs, outpatient, rehabilitation, same day surgery, and high-resolution CT and radiologist. Progressed state costs included all these, with the exception of CT and radiologist, as well as complex continuing care.

End of life costs were derived from the literature and were applied as off-off costs.[9]

Summary of Sponsor's Economic Evaluation Results

All analyses were run probabilistically (1,000 iterations for the base-case and scenario analyses). The deterministic and probabilistic results were similar.

Base-Case Results

In the sponsor's base-case analysis, treatment with T-DXd was associated with incremental costs of $164,772 and a gain of 1.59 QALYs compared with T-DM1 over the lifetime (25 year) analysis period, resulting in an ICER of $103,922 per QALY gained (refer to Table 3). The probability of T-DXd being cost-effective at a willingness-to-pay (WTP) threshold of $50,000 per QALY compared to T-DM1 was 4.8%. At the end of the 30-year time horizon, less than 1% of patients receiving T-DXd remained alive. CADTH noted that approximately 89% of the incremental QALYs in the sponsor's base case were accrued beyond 16 months, the median follow-up of the DESTINY-Breast 03 trial. The submitted analysis is based on the publicly available prices of all treatments, including subsequent therapies.

Table 3: Summary of the Sponsor's Economic Evaluation Results

Drug	Total costs ($)	Incremental costs ($)	Total QALYs	Incremental QALYs	ICER vs. T-DM1 ($/QALY)
T-DM1	366,097	Reference	2.25	Reference	Reference
T-DXd	530,869	164,772	3.84	1.59	103,922

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; vs. = versus.
Source: Sponsor's pharmacoeconomic submission.[1]

Sensitivity and Scenario Analysis Results

The sponsor assessed several model parameters in probabilistic scenario analyses. When a shorter (10-year) time horizon was selected, the ICER increased to $116,451. There were no other scenario analyses presented by the sponsor that drive the analysis.

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the economic analysis:

- **Long-term comparative efficacy is uncertain:** Although the results of the DESTINY-Breast 03 trial suggested that there may be a PFS benefit for T-DXd compared with T-DM1, it is unclear whether the magnitude of benefit observed in PFS translates into a similar magnitude of benefit in OS, or whether T-DXd merely delays the time to progression. The median OS was not reached in any of the treatment groups in the DESTINY-Breast 03 clinical trial by the data cut-off (May 21, 2021). Based on the CADTH clinical review, due to data immaturity at the current data cut, no conclusions regarding OS differences between the T-DXd and T-DM1 arms can be reached.

  The submitted model estimated the OS curve for T-DM1 using patient-level data from the DESTINY-Breast 03 trial up to 20 months and extrapolating OS benefit by fitting parametric survival models based on OS data from the EMILIA trial.[3] However, based on feedback from the clinical experts consulted for this review, the population of patients included in the EMILIA trial is not generalizable to the population included in the DESTINY-Breast 03 trial, as most of the patients in the EMILIA trial had not been treated with pertuzumab in the earlier course of their disease, and a lower proportion of patients in the EMILIA trial were treated with trastuzumab before T-DM1 in comparison with the DESTINY-Breast 03 trial. Furthermore, the OS curve for T-DXd was modelled by applying the OS HR of T-DXd versus T-DM1 from the DESTINY-Breast 03 clinical trial (HR = 0.56; 95% CI, 0.36 to 0.86), which is highly uncertain given the immaturity of data.

  The sponsor's approach resulted in 1% and 4% of patients alive after a time horizon of 25 years in the T-DM1 and T-DXd arms, respectively, and an incremental 2.24 life-years in patients treated with T-DXd. The difference in the proportion of patients alive at the 25-year time point was considered overestimated according to the clinical experts consulted during this review, given the great uncertainty around OS estimates.

  Furthermore, the OS benefit may be influenced by subsequent treatments that are received, the timing of when they are received, and the duration of treatment. In the DESTINY-Breast 03 trial, subsequent treatments varied greatly between treatment arms (as is noted in a later limitation) at the data cut-off date, including cross over from treatment arms, and were not aligned with treatment options generally available in current Canadian practice. The CADTH clinical review noted uncertainty regarding the impact of the potential imbalance on subsequent treatments used in DESTINY-Breast 03 trial on OS given the data immaturity, the lack of censoring for treatment addition or switching, the open-label design of the trial, and the uncertainty associated with the efficacy of the subsequent treatment used. As such, it is unclear whether the imbalance of subsequent treatments may confound any assessment of OS from the DESTINY-Breast 03 trial.

    - CADTH could not address the immaturity of data and potential confounding due to subsequent treatment use.
    - CADTH revised the method of OS extrapolation to independent distributions for each treatment arm. Data from DESTINY-Breast 03 alone were used for the extrapolation

of results in the T-DM1 and T-DXd arms, paired with an exponential and generalized gamma distribution, respectively. The choice of distributions was aligned with expected OS over time, including the same proportion of patients alive at 25 years (1%) in both arms.

- **Benefit of T-DXd for the subgroup of patients with unresectable HER2-positive breast cancer who developed disease recurrence during or within 6 months of completing neoadjuvant or adjuvant therapy is uncertain:** The DESTINY-Breast 03 study population comprised 2 subgroups: patients who presented with metastatic HER2-positive breast cancer who had received a prior treatment with an anti-HER2-based regimen in the metastatic setting and patients who received trastuzumab plus taxane intended as neoadjuvant or adjuvant therapy and then progressed to HER2-positive metastatic breast cancer during or within 6 months of completing neoadjuvant or adjuvant therapy (these patients received T-DXd as the first line of treatment in the metastatic setting). According to the clinical experts, the group of patients who progressed to HER2-positive metastatic breast cancer during or within 6 months of completing neoadjuvant or adjuvant therapy may differ prognostically from those who progress to HER2-positive metastatic breast cancer more slowly. Although a subgroup analysis for this patient population was provided to CADTH, these subgroup data were not incorporated within the sponsor-submitted model. CADTH observed that the subgroup results show a statistically significant treatment effect that is consistent with the analysis of the overall population, although the median PFS for T-DM1 is slightly shorter in those who relapsed early (5.5 months versus 7.0 months for those who relapsed early and late, respectively; with overlapping 95% CIs).
    - CADTH could not address this limitation as the model parameters were not reported or incorporated stratified by the 2 population subgroups. As such, the cost-effectiveness of T-DXd in this subgroup is uncertain.
- **Time to treatment effect waning is overestimated:** The model submitted by the sponsor assumed that patients receiving T-DXd would continuously benefit from the treatment up to 110 months (9.6 years), which the sponsor justified on the basis that at this time point, 1% of patients receiving T-DXd were modelled to remain in PFS. This estimation was calculated from the extrapolation of PFS data using gamma distribution, which resulted in a long-term tail. Although the primary PFS measure for the economic model (i.e., blinded independent central review) was not mature, thus, no median was available, the median PFS for T-DXd per investigator assessment was 25.1 months (95% CI, 22.1 months to not estimable) (equivalent to 2.1 years). According to clinical experts consulted for this review, the duration of treatment effect was overestimated, as there is no expectation that treatment benefits will be maintained once patients discontinue treatment and experience disease progression.
    - CADTH addressed this issue by changing the OS extrapolation to independent distributions for each treatment arm. A scenario analysis was conducted to explore the impact of changing the treatment waning effect to start after 25 months, given that the median PFS for T-DXd was 25.1 months and the upper bound 95% CI of treatment duration was 27 months.
- **Health utility values for the progression-free state were overestimated:** The model submitted by the sponsor included health utility values for progression-free and progressed states. The sponsor used 2 sources of health utility values, the DESTINY-Breast 03 trial for progression-free state and the Lloyd et al. study[5] for progressed disease state, though the sponsor indicated that Lloyd et al.'s values were adjusted for the DESTINY-Breast 03 population characteristics (Table 10). However, these sources are inherently different, as the DESTINY-Breast 03 trial sourced data from patients using the EQ-5D measure, while

Lloyd et al. elicited values from the general population. As such, values for the progression-free state differed substantially between the DESTINY-Breast 03 trial and the study by Lloyd et al. According to CADTH's economic evaluation guidelines, the selection of data sources for health state utility values should be based on their fitness for purpose, credibility, and consistency. In addition to the concerns with the consistency of values, CADTH noted that the mean health utility population norm available in Canada (0.84)[10] was lower than the health utility value obtained from the DESTINY-Breast 03 trial for progression-free state and appears to overestimate the HRQoL of patients with unresectable or metastatic HER2 breast cancer.

  - CADTH addressed this limitation by changing the source of the mean health utility values to those from the Lloyd et al. study[5] for the progression-free state, increasing consistency of health utility values given that they were obtained from the same source (refer to Table 14).

- **Estimates on the proportion of patients receiving subsequent treatments were inappropriately incorporated into the model:** The sponsor assumed that [redacted]% and [redacted]% of patients in the T-DXd and T-DM1 arms would receive subsequent treatments. These estimates were based on data from the DESTINY-Breast 03 trial, which had a median follow-up of approximately 16 months (May 21, 2021, data cut-off date). Given that the model accounts for a lifetime horizon and assumes that all patients are treated until death, the use of these estimates over the extended time horizon was inappropriate. The sponsor's approach resulted in a lower cost for subsequent treatments, favouring T-DXd.

  The values submitted by the sponsor presented differences in market shares for subsequent treatments between treatment groups (Table 11), which do not reflect expected use in Canadian clinical practice, according to the clinical experts consulted for this review. Furthermore, the type of treatments used did not appear to align with Canadian practice as several therapies are not expected to be available for use as subsequent treatment options if they were used in earlier treatment lines. In the DESTINY-Breast 03 trial, trastuzumab-based regimens (e.g., trastuzumab, trastuzumab plus taxanes, trastuzumab plus pertuzumab) were used by 99.6% of patients before treatment with T-DM1 or T-DXd, and the indication requires that patients have had at least 1 prior anti-HER2-based regimen. In addition, the sponsor assumed that a proportion of patients would receive T-DXd and/or T-DM1 as subsequent treatments after their initial T-DXd or T-DM1 treatment. There is currently no robust evidence assessing the benefit of using of T-DXd and T-DM1 sequentially, and their use in this manner is not aligned with how T-DM1 is currently funded in Canadian clinical practice.

  Furthermore, feedback from the clinical experts consulted for this review indicated that the use of each subsequent treatment is expected to be the same for both T-DXd and T-DM1.

  - CADTH addressed this limitation by changing the proportion of patients receiving subsequent therapies to 70% in both arms, based on input from the clinical experts.
  - The market shares were also revised based on availability of current treatments in Canadian clinical practice, as well as input from the clinical experts (refer to Table 15).[11] Of note, the changes made in CADTH's reanalysis only addressed limitations in the subsequent treatment costs, and not the effects that the types of subsequent treatment had on PFS, OS, or quality of life. Scenario analyses were performed to explore the impact of using T-DM1 as a subsequent therapy to T-DXd and the impact of reducing the proportion of patients receiving tucatinib plus trastuzumab plus capecitabine to 0% as the use of these therapies is still under review for funding.

- **RDI:** The sponsor's base case incorporated RDI for T-DM1 and T-DXd based on data from the DESTINY-Breast 03 trial. Consistent with previous reviews, given the inability to link reduced dose intensity with outcomes, the CADTH base case does not incorporate reduced dose intensity. A reduction in RDI can be derived from a delayed dose, a missed dose, or a reduction in dose. When considering wastage, each component can have a very different influence on drug costs. Likewise, it is unclear how treatment discontinuation influences RDI.
    - CADTH changed the RDI to 100%.
- **Lack of transparency and flexibility in the model:** Several limitations were observed in the submitted model, including that when independent distributions were selected by treatment, the probabilistic analysis reported results that lacked face validity, indicating an error in the coding. Other limitations noted by CADTH included a missing formula when choosing distribution in the T-DXd arm, as well as limiting the start of the waning effect to a minimum of 60 months in the excel spreadsheet; overall, the submitted model was not transparent and flexible to changes.
    - CADTH was unable to address these deficiencies, and cautions that the result from the submitted economic model could not be fully validated. Due to the inability to run probabilistic analysis, CADTH's base-case results were presented using deterministic analysis.

Additionally, the following key assumptions (refer to Table 4) were made by the sponsor and have been appraised by CADTH.

Table 4: Key Assumptions of the Submitted Economic Evaluation (Not Noted as Limitations to the Submission)

Sponsor's key assumption	CADTH comment
Costs and disutilities related to grade 3 or higher AEs with an incidence of at least 1% in the trial DESTINY-Breast 03 were included in the model.	Inappropriate. The sponsor selected an arbitrary threshold to capture the impact of treatment-related AEs rather than selecting the most clinically meaningful AEs to include within the model. CADTH's guidelines recommend that all AEs that have clinical or cost significance should be included in the model. As noted in the CADTH clinical review and the clinician input received by CADTH for this review, pneumonitis (all grades) was more common among patients who received T-DXd than T-DM1. The inclusion of only grade 3 or higher AEs in the pharmacoeconomic model may underestimate the cost of treatment associated with pneumonitis, as additional visits to a health care provider and drug treatments may be required.
Total management costs for AEs and disutilities related to AEs were applied as a one-time cost during the first model cycle, estimated as the sum of the costs and disutilities of the AE incidence.	Uncertain. This approach does not allow for discounting of AE costs or utilities as all are applied in the first cycle; it assumes that all AEs occur in the first cycle.
Treatment duration and PFS curves cross over during the first 3 and 5 cycles (2 and 3.5 months) in the T-DXd and T-DM1 arms, respectively.	Uncertain. The crossover of the curves indicated that the proportion of patients on treatment was higher than the proportion of patients in the progression-free state. Although according to the clinical experts consulted for this review, there would not be a clinical reason to maintain a patient on the same treatment after progression of disease, the use of

Sponsor's key assumption	CADTH comment
	PFS estimates from blinded independent central review instead of investigator assessment PFS could be the reason for the crossover of the curves.

AE = adverse event; PFS = progression-free survival; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

CADTH Reanalyses of the Economic Evaluation

Base-Case Results

CADTH's reanalysis addressed several limitations within the economic model. The CADTH base case was derived by making changes in model parameter values and assumptions, in consultation with clinical experts. Table 5 details each change made to derive the CADTH revised base case, which was conducted in a step-wise approach to highlight the impact of each change. The summary of results from the stepped reanalysis are presented in Table 6 and Table 16.

Results from the CADTH base case suggest that, compared to T-DM1, T-DXd was associated with higher costs ($217,830) and yielded more QALYs (0.79), resulting in an ICER of $274,875 per QALY (refer to Table 6). The estimated ICER was higher than the sponsor's base case, driven primarily by changes to the OS distributions, and changes to subsequent treatment assumptions. CADTH notes that due to the model structure, even after the CADTH analysis, T-DXd was associated with an incremental gain of 0.87 life-years compared with observation. CADTH noted that approximately 82% of the incremental QALYs in the sponsor's base case were accrued beyond 16 months, the median follow-up of the DESTINY-Breast 03 trial. This benefit should be interpreted with caution, given the lack of OS data to confirm this modelled benefit. Due to the lack of face validity in the sponsor's probabilistic analysis when revising the OS assumptions, CADTH could not calculate the probability that T-DXd is cost-effective at WTP threshold of $50,000 per QALY.

Table 5: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections[a] to sponsor's base case		
None	—	—
Changes to derive the CADTH base case		
1. Changes to OS modelling approach	OS extrapolation for T-DM1 was based on data from the DESTINY-Breast 03 and EMILIA trials and extrapolated using log-logistic distribution, while the T-DXd extrapolation curve was modelled by applying the OS hazard ratio of T-DXd vs. T-DM1 from the DESTINY-Breast 03 trial to the T-DM1 curve.	OS curves were modelled independently (distribution T-DXd = generalized gamma; distribution T-DM1 = exponential) based on the DESTINY-Breast 03 trial only for both treatments.
2. Health utility values for PFS state	Based on the DESTINY-Breast 03 trial.	Based on the Lloyd et al. study, and adjusted for patient's characteristics from the DESTINY-Breast 03 trial.
3. Change in proportion of patients receiving subsequent treatments	[redacted]% and [redacted]% of patients in the T-DXd and T-DM1 arms, respectively.	A total of 70% of patients for both arms.

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
4. Change in market shares for subsequent treatments	Market shares based on the DESTINY-Breast 03 trial with a median follow-up of 16 months, with different market shares depending on treatment arm.	Revised based on expected accessibility for current treatments in Canadian practice, as well as input from the clinical experts and drug plans, with the same market shares in both treatment arms. In this revision, patients receiving T-DXd cannot receive T-DM1 as subsequent treatment and vice versa.
5. Change in RDI	Assumed reduced dose intensity with T-DM1 and T-DXd therapies.	Assumed 100% dose intensity for T-DM1 and T-DXd.
CADTH base case	—	1 + 2 + 3 + 4 + 5

OS = overall survival; RDI = relative dose intensity; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; vs. = versus.

Table 6: Summary of the Stepped Analysis of the CADTH Reanalysis Results (Deterministic)

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER ($/QALY)
Sponsor's base case (deterministic)	T-DM1	374,430	2.29	Reference
	T-DXd	533,225	3.88	99,772
CADTH reanalysis 1: change in OS distributions	T-DM1	512,674	3.11	Reference
	T-DXd	544,180	4.00	35,385
CADTH reanalysis 2: changes in utilities	T-DM1	374,430	2.22	Reference
	T-DXd	533,225	3.72	106,311
CADTH reanalysis 3: change in the proportion of patients receiving subsequent treatment	T-DM1	400,520	2.29	Reference
	T-DXd	699,879	3.88	188,089
CADTH reanalysis 4: change in the market shares for subsequent treatments	T-DM1	165,966	2.29	Reference
	T-DXd	412,504	3.88	154,902
CADTH reanalysis 5: changes in RDI	T-DM1	374,669	2.29	Reference
	T-DXd	546,376	3.88	106,000
CADTH base case	T-DM1	375,334	3.05	Reference
	T-DXd	593,164	3.84	274,875

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; RDI = relative dose intensity; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

Scenario Analysis Results

CADTH undertook price reduction analyses based on the CADTH base case. These analyses demonstrated that a price reduction of at least 61% would be necessary to achieve cost-effectiveness at a WTP threshold of $50,000 per QALY (refer to Table 7).

Table 7: CADTH Price Reduction Analyses

Analysis	ICERs for T-DXd vs. T-DM1 ($/QALY)	
Price reduction	**Sponsor base case**	**CADTH reanalysis**
No price reduction	103,922	274,875
10%	87,558	238,741
20%	71,487	201,747
30%	55,415	164,754
40%	39,343	127,760
50%	23,272	90,767
60%	7,200	53,773
70%	T-DXd dominates	16,780
80%	T-DXd dominates	T-DXd dominates

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; vs. = versus.

In addition, CADTH conducted a series of exploratory analyses independently on the CADTH base case to determine the impact of alternative assumptions on the cost-effectiveness of T-DXd, which are outlined in the following:

1. Given the uncertainty associated with OS estimates, in this scenario analysis, CADTH re-applied the OS HR for T-DXd versus T-DM1 from the DESTINY-Breast 03 trial (HR = 0.5546) to the T-DM1 curve but maintained using data from the DESTINY-Breast 03 trial only for T-DM1 (i.e., excluding the EMILIA trial).
2. Given the assumption that T-DXd results in zero incremental benefit in the post-progression health state, CADTH conducted this scenario analysis by changing the OS HR for T-DXd versus T-DM1 to 0.6988, which was calculated as resulting in zero incremental benefit from T-DXd in the PP health state.
3. The assumption was made that treatment effect starts declining after 25 months (the approximate median PFS for T-DXd). As the sponsor's model was programmed such that a waning treatment effect (110 months in the sponsors base case) could only be applied to an HR in the model, in this scenario analysis, CADTH re-applied the OS HR for T-DXd versus T-DM1 from the DESTINY-Breast 03 trial to the T-DM1 curve but still used data from the DESTINY-Breast 03 trial only for T-DM1 (i.e., excluding the EMILIA trial).
4. The proportion of patients receiving T-DM1 as a subsequent treatment after receiving T-DXd is equal to 40%. According to the drug plans, clinical experts, and the DESTINY-Breast 03 trial, there is a possibility of T-DM1 being used as a subsequent therapy to T-DXd, instead of T-DXd only displacing T-DM1. The use of T-DXd as a subsequent treatment to T-DM1 was not considered as a scenario analysis as it did not represent current standard of practice and it is not funded or requested to be funded as a subsequent treatment to T-DM1.
5. The proportion of patients receiving tucatinib plus trastuzumab plus capecitabine is equal to 0% as the use of these therapies is still under review for funding.

The first 3 scenarios were undertaken to address the uncertainty associated with the OS estimates and the duration of treatment effect beyond the trial observational period, all using

a different approach than the base case (due in part to the sponsor's model parameters). In these scenarios, the ICER for T-DXd changed to $195,267 per QALY, $230,225 per QALY, and $299,829 per QALY compared with T-DM1 for scenarios 1, 2, and 3, respectively.

In the fourth scenario, in which CADTH considered the possibility of sequential treatment of T-DM1 after treatment with T-DXd, the ICER for T-DXd was $431,506 per QALY compared with T-DM1. Finally, when considering a scenario where the use of tucatinib plus trastuzumab plus capecitabine would not be available, the ICER for T-DXd was $303,344 per QALY compared with T-DM1. Full results for scenario analysis are reported in Table 17.

Issues for Consideration

- Stakeholder input noted that storage of T-DXd vials requires refrigeration, and after reconstitution, T-DXd vials must be used immediately; thus, vial sharing is unlikely to be feasible, which leads to drug wastage.
- The drug plans indicated that there is a considerable look-alike, sound-alike concern with correctly identifying another member of the trastuzumab group, which will require operational strategies to avoid confusion among treatments.

Overall Conclusions

Based on the appraisal of the DESTINY-Breast 03 trial, CADTH's clinical review indicated that T-DXd may be associated with PFS benefits in 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. However, it is important to note that, due to relatively short duration of follow-up in this study (median of 16 months), OS data for both T-DXd and T-DM1 were not mature at the time of the trial data cut-off. No conclusions regarding OS differences between the T-DXd and T-DM1 arms can yet be reached. Notable harms were higher in the T-DXd group than in T-DM1 and the relative impact of T-DXd and T-DM1 on HRQoL was uncertain.

Furthermore, the CADTH clinical review identified uncertainty regarding the impact of the potential imbalance of subsequent treatments used in the DESTINY-Breast 03 trial between treatments on OS given the data immaturity, the lack of censoring for treatment switching, the open-label design of the trial, and the uncertainty associated with the efficacy of the subsequent treatments used. Additionally, CADTH highlighted uncertainty regarding the generalizability of the OS results as most of subsequent treatments are not generally available in Canadian clinical practice in the setting used in the DESTINY-Breast 03 trial. All these items limit the interpretation of the long-term survival benefits associated with T-DXd.

CADTH identified several limitations in the economic analyses submitted by the sponsor, beyond the aforementioned uncertainty regarding the impact of T-DXd on long-term PFS and OS compared with T-DM1. These key limitations included OS extrapolation using data from EMILIA trial to inform long-term survival for T-DM1 despite the patient population from EMILIA being inherently different to the sponsor's DESTINY-Breast 03 trial, overestimation of OS for T-DXd based on the sponsor's choice of distribution, the sponsor's assumptions overestimating treatment effect, overestimation of health state utility values, inappropriate incorporation of the proportion of patients receiving subsequent treatments into the model, inappropriate incorporation of market shares for subsequent treatments, and dosing assumptions. CADTH conducted a reanalysis, which included changes to the OS modelling

approach; changes in the health utility values for PFS state; changes in the proportion of patients receiving subsequent treatments; changes in the market shares for subsequent treatments; and elimination of RDI. Based on the CADTH reanalysis, treatment with T-DXd is $217,830 more costly and yielded 0.79 more QALYS, resulting in an ICER of $274,875 per QALY. A price reduction of at least 61% would be necessary to achieve an ICER of $50,000 per QALY.

Despite the limitations regarding the comparative clinical evidence, CADTH reanalyses resulted in a modest relative benefit for T-DXd compared with T-DM1. Although there are concerns regarding the magnitude of benefit, the relative benefit associated with T-DXd compared with T-DM1 aligns with feedback from the clinical experts consulted by CADTH. Once the OS data from DESTINY-Breast 03 become mature, it is unclear what can be elucidated from it given the differences in the subsequent treatments given to patients in either arm or the effects these treatments may have on OS.

When considering the possibility of sequential treatment with T-DM1 after treatment with T-DXd, the ICER for T-DXd increased to $431,506 per QALY compared with T-DM1, as reported in the scenario analysis. There has been no evaluation of this sequence of therapies; therefore, the benefit of following the treatment with T-DXd with T-DM1 in this population is unknown.

The cost-effectiveness of T-DXd compared to T-DM1 is dependent on the assumption that improvements in PFS are associated with long-term improvements in OS, and that the treatment effect of T-DXd persists for years after discontinuation. Neither of these assumptions was supported by evidence from the DESTINY-Breast 03 trial, adding considerable uncertainty to the cost-effectiveness results. This lack of long-term evidence is particularly of note given that 82% of incremental estimated QALYs were generated in the post-trial period for which there is no direct comparative evidence, and where different assumptions about the pattern of long-term efficacy exert a notable influence on incremental effectiveness.

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Appendix 1: Cost Comparison Table

Note that this appendix has not been copy-edited.

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical expert(s) and drug plan. Comparators may be recommended (appropriate) practice or actual practice. Existing Product Listing Agreements are not reflected in the table and as such, the table may not represent the actual costs to public drug plans.

Table 8: CADTH Cost Comparison Table for HER2-Positive Metastatic Breast Cancer

Treatment	Strength / concentration	Form	Price	Recommended dosage	Daily cost	Average 28-day cost
Trastuzumab deruxtecan (T-DXd; Enhertu)	**100 mg**	**Vial for IV infusion (100mg)**	**2,440.0000[a]**	**5.4 mg/kg once every 3 weeks**	**464.76**	**13,013**
Immunotherapy						
Trastuzumab emtansine (T-DM1; Kadcyla)	100mg 160mg	**Vial for IV infusion (100mg and 160mg)**	2,128.9300 3,406.2800	3.6 mg/kg once every 3 weeks	263.58	7,380

Note: All prices are from the DeltaPA database[12] (accessed May 05, 2022), unless otherwise indicated, and do not include dispensing fees.

[a]Sponsor-submitted price.

[b]Weight based on trial 62.4 kg.

Appendix 2: Submission Quality

Note that this appendix has not been copy-edited.

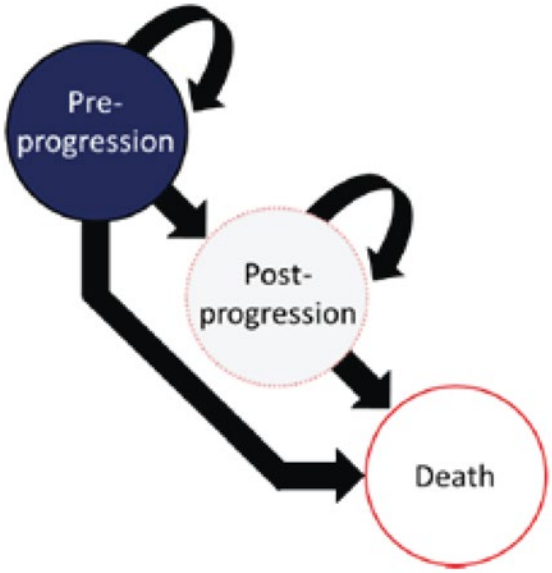
Table 9: Submission Quality

Description	Yes/No	Comments
Population is relevant, with no critical intervention missing, and no relevant outcome missing	No	See CADTH appraisal.
Model has been adequately programmed and has sufficient face validity	No	See CADTH appraisal. The submitted model considered distinct proportion of patients receiving subsequent treatments, distinct market shares by treatment arm, including therapies that would not be generally available in Canadian clinical practice.
Model structure is adequate for decision problem	Yes	No comment.
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis)	Yes	No comment.
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem	Yes	No comment.
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details)	No	See CADTH appraisal. Several limitations were observed in the submitted model, these included the inability to run probabilistic analysis when setting independent distributions per treatment arm, missing formula when choosing distribution in T-DXd arm, limiting start of waning effect to a minimum of 60 months in the excel spreadsheet, and overall, the submitted model was not transparent and flexible to changes.

Appendix 3: Additional Information on the Submitted Economic Evaluation

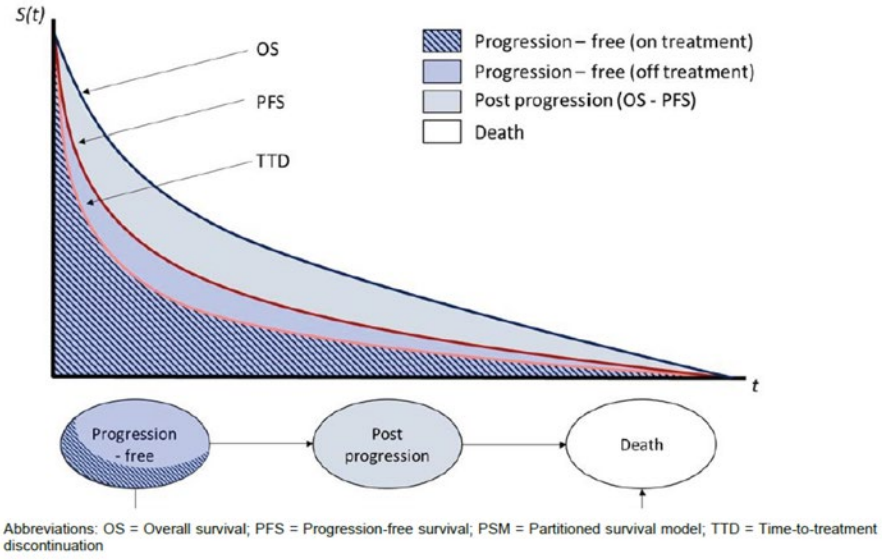
Note that this appendix has not been copy-edited.

Figure 1: Model Structure



Source: Sponsor's pharmacoeconomic submission.[1]

Figure 2: Transition Between the Health States in the Partition Survival Model



Abbreviations: OS = Overall survival; PFS = Progression-free survival; PSM = Partitioned survival model; TTD = Time-to-treatment discontinuation

Source: Sponsor's pharmacoeconomic submission.[1]

Detailed Results of the Sponsor's Base Case

Table 10: Health State Utility Values

Health state	DESTINY-Breast 03 trial	Lloyd et al.,[5] adjusted for patients' characteristics from DESTINY-Breast 03	Sponsor's Base Case Utility value
Progression free	[redacted]	0.787	[redacted] (DESTINY-Breast 03 trial)
Progressed	[redacted]	0.540	0.540 (Lloyd et al., adjusted for patients' characteristics from DESTINY-Breast 03)

Source: Sponsor's pharmacoeconomic submission.[1]

Table 11: Market Shares for Subsequent Treatments

Treatment	Proportion of patients with each subsequent treatment	
	T-DXd[a]	T-DM1[a]
Trastuzumab	[redacted]	[redacted]
T-DXd	[redacted]	[redacted]
T-DM1	[redacted]	[redacted]
Pertuzumab	[redacted]	[redacted]
Taxane (docetaxel)	[redacted]	[redacted]
Taxane + trastuzumab	[redacted]	[redacted]
Lapatinib	[redacted]	[redacted]
Hormone therapy	[redacted]	[redacted]
Capecitabine	[redacted]	[redacted]
Tucatinib + trastuzumab + capecitabine	[redacted]	[redacted]

T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

[a]Numbers were rounded in the table for simplicity.

Source: Sponsor's pharmacoeconomic submission.[1]

Table 12: Disaggregated Summary of Sponsor's Economic Evaluation Results (Probabilistic)

Parameter	T-DXd	T-DM1	Incremental
Discounted LYs			
Total	6.01	3.76	2.24
By health state or data source			
PF	2.36	0.94	1.42
PP	3.64	2.83	0.81
Discounted QALYs			
Total	3.84	2.25	1.59
By health state or data source			

Parameter	T-DXd	T-DM1	Incremental
PF	1.97	0.79	1.18
PP	1.87	1.47	0.40
Discounted costs ($)			
Total	530,869	366,096	164,772
PF			
Drug	280,070	67,505	212,564
Administration	6,313	2,713	3,600
Monitoring	50,121	20,437	29,684
AEs management	2,295	1,304	991
PP			
Monitoring	50,746	45,313	5,433
Subsequent treatment	121,898	208,304	-86,406
End of life	19,426	20,521	-1,095
ICER ($/QALY)	103,922		

T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.
Source: Sponsor's pharmacoeconomic submission.[1]

Table 13: Disaggregated Summary of Sponsor's Economic Evaluation Results (Deterministic)

Parameter	T-DXd	T-DM1	Incremental
Discounted LYs			
Total	6.08	3.84	2.24
By health state or data source			
PF	2.36	0.93	1.43
PP	3.72	2.91	0.81
Discounted QALYs			
Total	3.88	2.29	1.59
By health state or data source			
PF	1.97	0.78	1.19
PP	1.91	1.51	0.40
Discounted costs ($)			
Total	533,225	374,430	158,795
PF			
Drug	279,098	68,733	210,365
Administration	6,308	2,763	3,545
Monitoring	50,094	20,243	29,851

Parameter	T-DXd	T-DM1	Incremental
AEs management	2,300	1,310	989
PP			
Monitoring	51,722	46,648	5,074
Subsequent treatment	124,263	214,212	-89,949
End of life	19,440	20,521	-1,081
ICER ($/QALY)	99,772		

T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

Source: Sponsor's pharmacoeconomic submission.[1]

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

Note that this appendix has not been copy-edited.

Detailed Results of CADTH Base Case

Table 14: Health State Utility Values (CADTH Reanalysis)

Health state	DESTINY-Breast 03 trial	Lloyd et al., adjusted for patients' characteristics from DESTINY-Breast 03	CADTH's Base Case Utility value
Progression free	[redacted]	0.787	0.787 (Lloyd et al., adjusted for patients' characteristics from DESTINY-Breast 03)
Progressed	[redacted]	0.540	0.540 (Lloyd et al., adjusted for patients' characteristics from DESTINY-Breast 03)

Table 15: Market Shares for Subsequent Treatments (CADTH Reanalysis)

Treatment	Proportion of patients with each subsequent treatment	
	T-DM1[a]	T-DXd[a]
Trastuzumab	0%	0%
T-DXd	0%	0%
T-DM1	0%	0%
Pertuzumab	0%	0%
Taxane (docetaxel)	10%	10%
Taxane + trastuzumab	0%	0%
Lapatinib	0%	0%
Hormone therapy	12%	12%
Capecitabine	77%	77%
Tucatinib + trastuzumab + capecitabine	35%	35%

T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

[a]Numbers were rounded in the table for simplicity.

Table 16: Disaggregated Summary of CADTH's Economic Evaluation Results (Deterministic)

Parameter	T-DXd	T-DM1	Incremental
Discounted LYs			
Total	6.31	5.44	0.87
By health state or data source			
PF	2.36	0.93	1.43
PP	3.95	4.51	−0.56
Discounted QALYs			
Total	3.84	3.05	0.79
By health state or data source			
PF	1.81	0.71	1.18
PP	2.04	2.33	−0.30
Discounted costs ($)			
Total	593,165	375,334	217,830
PF			
Drug	292,249	67,452	220,277
Administration	6,308	2,763	3,545
Monitoring	50,094	20,243	29,815
AEs management	2,300	1,310	989
PP			
Monitoring	54,801	67,452	−12,651
Subsequent treatment	167,829	191,632	−23,803
End of life	19,584	19,962	−378
ICER ($/QALY)	274,875		

ICER = incremental cost-effectiveness ratio; LY= life-year; QALY = quality-adjusted life-year; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

Scenario Analyses

Table 17: Scenario Analysis

Stepped analysis	Comparator	Total costs ($)	Total QALYs	ICER ($/QALY)
CADTH's base case	T-DM1	375,334	3.05	Ref.
	T-DXd	593,164	3.84	274,875
CADTH scenario 1: Use of HR to model T-DXd's OS (HR = 0.5546)	T-DM1	375,334	3.05	Ref.
	T-DXd	670,545	4.56	195,267

Stepped analysis	Comparator	Total costs ($)	Total QALYs	ICER ($/QALY)
CADTH scenario 2: No incremental benefit in PP health state (HR = 0.6988)	T-DM1	375,334	3.05	Ref.
	T-DXd	623,568	4.13	230,225
CADTH scenario 3: Treatment effect of T-DXd starts to wane at month 25	T-DM1	375,334	3.05	Ref.
	T-DXd	587,893	3.79	285,252
CADTH scenario 4: Proportion of patients receiving T-DM1 after T-DXd equal to 30%	T-DM1	375,334	3.05	Ref.
	T-DXd	719,953	3.84	434,867
CADTH scenario 5: Proportion of patients receiving tucatinib + trastuzumab + capecitabine equal to 0%	T-DM1	193,702	3.05	Ref.
	T-DXd	434,093	3.84	303,344

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

Appendix 5: Submitted BIA and CADTH Appraisal

Note that this appendix has not been copy-edited.

Table 18: Summary of Key Take-Aways

Key Take-aways of the BIA
• 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 marker shares of subsequent treatments did not reflect Canadian clinical practice and were inappropriately incorporated into the BIA. • CADTH base-case 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 treatment to align with Canadian standard of care. • Based on CADTH's base-case, the expected budget impact for funding T-DXd for the treatment of unresectable or metastatic HER2-positive breast cancer who have received a at least one 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. In the health care payer perspective, the estimated budget impact of funding T-DXd was $33,337,456, $71,430,533, $81,218,128 for Year 1, 2, and 3, respectively. The 3-year total was $185,986,117. • Results of CADTH's scenario analyses demonstrate that the estimated budget impact is sensitive to whether T-DXd would displace T-DM1 in HER2 positive breast cancer or if T-DM1 would still be used as a subsequent (i.e., both therapies are used in sequence).

Summary of Sponsor's BIA

The sponsor submitted a BIA estimating the budget impact of introducing T-DXd as treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received a at least one 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.[13]

The analytic framework, which used a top-down epidemiology-based approach, leveraged data from multiple sources in the literature and assumptions based on clinical expert input to determine the estimated population size (Figure 7). The sponsor compared a reference scenario where T-DXd is not reimbursed as second-line therapy, with a new drug scenario, where T-DXd is funded as second-line therapy, as per the Health Canada indication. The current treatment available in the reference scenario was T-DM1 therapy.

The BIA base case was undertaken from a publicly funded drug plan perspective considering only drug costs over a 3-year time horizon. Additional health care costs were considered in health care payers perspective that included AE, administration, and high-resolution CT scans costs. Costs included that of second-line therapy and subsequent treatment regimens used among patients who progress. T-DXd costs were calculated by multiplying the recommended dosage (5.4 mg/kg) by an average patient weight of 62.4 kg, resulting in the need of 4 vials of 100 mg per patient. The sponsor assumed vials would not be shared among patients. Furthermore, T-DXd costs accounted for the duration of T-DXd therapy, data estimated from DESTINY-Breast 03 trial. The sponsor assumed that ||||% and ||||% of patients in the T-DXd and T-DM1 arms, respectively, would receive subsequent treatment based on data from DESTINY-Breast 03 trial (median follow-up of approximately 16 months). The sponsor also assumed that 75% of patients would receive tucatinib plus trastuzumab-capecitabine regimen, and 25% would receive evenly shares of other regimens including carboplatin, trastuzumab plus carboplatin, capecitabine, trastuzumab plus capecitabine, and lapatinib plus capecitabine. The sponsor also assumed a delay of one cycle between second-line treatment and subsequent treatments. The sponsor estimates that T-DXd will reach a market share of 90% after 3 years. Key inputs to the BIA are documented in Table 19.

Figure 3: Sponsor's Estimation of the Size of the Eligible Population

T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.
Note: This figure was redacted at the request of the sponsor.
Source: Sponsor's budget impact analysis submission.[13]

Table 19: Summary of Key Model Parameters

Parameter	Sponsor's estimate (reported as Year 1 / Year 2 / Year 3 if appropriate)
Target Population	
Number of patients eligible for drug under review	562 / 567 / 573
Metastatic HER2-positive breast cancer who have received a at least one prior anti-HER2-based regimen in the metastatic setting	493 / 498 / 503
Unresectable HER2-positive breast cancer who have received a at least one prior anti-HER2-based regimen in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within 6 months of completing neoadjuvant or adjuvant therapy.	69 / 69 / 70
Market Uptake (3 years)	
Uptake (reference scenario) T-DM1	 100% / 100% / 100%
Uptake (new drug scenario) T-DXd T-DM1	 85% / 90% / 90% 15% / 10% / 10%
Cost of treatment (per patient)	
Cost of treatment over [4-week cycle] T-DXd T-DM1	 $13,058 $7,406

T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.
Source: Sponsor's BIA submission.[13]

Summary of the Sponsor's BIA Results

In the drug plan perspective, the sponsor's estimated budget impact of funding T-DXd as treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received a at least one 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 was $18,917,473, $33,565,242, $26,508,113 for Year 1, 2, and 3, respectively. The 3-year total was $78,990,827.

In the health care payer perspective, the estimated budget impact of funding T-DXd was $19,359,626, $34,694,185, $27,955,958 for Year 1, 2, and 3, respectively. The 3-year total was $82,009,768.

CADTH Appraisal of the Sponsor's BIA

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the results of the BIA:

- **Proportion of patients who received initial anti-HER2 regimen and who received a second line of therapy are underestimated:** The sponsor assumed that the proportion of patients who received initial anti-HER2 regimen was [redacted]% and the proportion who received a second line of therapy was % based on data by Oncology Outcomes, analyzing data from the Alberta Health Services registry. According to clinical experts consulted for this review, these estimates might underestimate the expected proportion of patients who received initial anti-HER2 regimen since that is the current standard of care in Canada, and the proportion of patients that receive a second line treatment since most patients are eligible and choose to undergo subsequent treatment.
  - CADTH changed the proportion of patients who received initial anti-HER2 regimen to 90%, and proportion of patients who received a second line of therapy to 60% based on input from clinical experts.
- **Estimates on the proportion of patients receiving subsequent treatments were inappropriately incorporated into the BIA:** The sponsor assumed that [redacted]% and [redacted]% of patients in the T-DXd and T-DM1 arm would receive subsequent treatments. These estimates were based on data from DESTINY-Breast 03 trial, which had a median follow-up of approximately 16 months (data cut: 21 May 2021). The use of these estimates led to a higher proportion of each subsequent treatments to be weighted for the T-DM1 arm. Given the model accounts for a lifetime horizon and that treatment of metastatic stages of cancer can only increase the time to disease progression, the use of these estimates was inappropriate.
  - CADTH addressed this limitation by changing the proportion of patients receiving subsequent therapies to be equal weight in both treatment arms.
- **Differences in market shares for subsequent treatments between treatment arms do not reflect Canadian clinical practice and were inappropriately incorporated into the BIA:** The values submitted by the sponsor do not accurately reflect Canadian clinical practice. Several therapies are not expected to be available for use as subsequent treatment options if they were used in earlier treatment lines, including trastuzumab-based regimens (e.g., trastuzumab). In addition, the submitted BIA used distinct market shares than the ones submitted in the cost-utility analysis.
  - The market shares in the BIA were revised based on expected accessibility for current treatments in Canadian practice, as well as input from clinical experts and drug plan, in consistency with the market shares used in the CADTH's base case for the cost-utility analysis (Table 15).

Additional limitations were identified, but were not considered to be key limitations. These limitations include:

- **NIHB population was not submitted although subsequent treatment includes drugs funded by NIHB:** Subsequent treatments include drugs funded by NIHB. Therefore, the NIHB population should have been submitted to demonstrate the expected budget impact introduced by funding the drug under review.

CADTH Reanalyses of the BIA

CADTH' base-case case revised the proportion of patients who received initial anti-HER2 regimen, proportion of patients who received a second line of therapy, and the market shares for subsequent treatment.

Table 20: CADTH Revisions to the Submitted Budget Impact Analysis

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections[a] to sponsor's base case (None)		
Changes to derive the CADTH base case		
1. Change in proportion of patients who received initial anti-HER2 regimen	[redacted]%	90%
2. Change in proportion of patients who received a second line of therapy prior to T-DXd or T-DM1	[redacted]%	60%
3. Market shares for subsequent treatment	Market shares based on DESTINY-Breast 03 trial with a median follow-up of 16 months, with different market shares depending on treatment arm.	Revised based on expected accessibility for current treatments in Canadian practice, as well as input from clinical experts and drug plan, with same market shares in both treatment arms. In this revision, patients receiving T-DXd cannot receive T-DM1 as subsequent treatment and vice versa.
CADTH base case	1 + 2 + 3	

The results of the CADTH step-wise reanalysis are presented in summary format in Table 21 and a more detailed breakdown is presented in Table 22.

Based on CADTH's base-case, the expected budget impact for funding T-DXd for the treatment of unresectable or metastatic HER2-positive breast cancer who have received a at least one 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.

In the health care payer perspective, the estimated budget impact of funding T-DXd was $33,337,456, $71,430,533, $81,218,128 for Year 1, 2, and 3, respectively. The 3-year total was $185,986,117.

Table 21: Summary of the CADTH Reanalyses of the Budget Impact Analysis

Stepped analysis	Three-year total
Submitted base case	$78,990,827
CADTH reanalysis 1	$87,497,532
CADTH reanalysis 2	$112,436,699
CADTH reanalysis 3	$115,083,142
CADTH base case	$181,229,065

Table 22: Detailed Breakdown of the CADTH Reanalyses of the Budget Impact Analysis

Stepped analysis	Scenario	Year 0 (current situation)	Year 1	Year 2	Year 3	Three-year total
Submitted base case	T-DM1	$21,384,500	$57,909,790	$94,128,283	$124,606,258	$276,644,331
	T-DXd	$21,384,500	$76,827,263	$127,693,525	$151,114,371	$355,635,158
	Budget impact	**$0**	**$18,917,473**	**$33,565,242**	**$26,508,113**	**$78,990,827**
CADTH reanalysis 1	T-DM1	$23,687,446	$64,146,229	$104,265,175	$138,025,394	$306,436,798
	T-DXd	$23,687,446	$85,100,968	$141,445,135	$167,388,226	$393,934,329
	Budget impact	**$0**	**$20,954,739**	**$37,179,960**	**$29,362,832**	**$87,497,532**
CADTH reanalysis 2	T-DM1	$30,438,947	$82,429,507	$133,983,422	$177,366,271	$393,779,200
	T-DXd	$30,438,947	$109,356,888	$181,760,662	$215,098,349	$506,215,899
	Budget impact	**$0**	**$26,927,381**	**$47,777,240**	**$37,732,078**	**$112,436,699**
CADTH reanalysis 3	T-DM1	$19,702,801	$48,949,304	$76,169,606	$98,921,397	$224,040,307
	T-DXd	$19,702,801	$69,676,674	$120,399,429	$149,047,346	$339,123,449
	Budget impact	**$0**	**$20,727,370**	**$44,229,823**	**$50,125,949**	**$115,083,142**
CADTH base case	T-DM1	$31,027,250	$77,083,608	$119,949,227	$155,778,043	$352,810,878
	T-DXd	$31,027,250	$109,724,348	$189,600,846	$234,714,749	$534,039,943
	Budget impact	**$0**	**$32,640,740**	**$69,651,619**	**$78,936,706**	**$181,229,065**

T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

CADTH also conducted additional scenario analyses to address remaining uncertainty, using the CADTH base-case:

1. Proportion of patients receiving T-DM1 as a subsequent treatment after receiving T-DXd is equal to 40%. According to drug plan, clinical experts, and DESTINY-Breast 03 trial, there is a possibility of T-DM1 being used as a subsequent therapy to T-DXd, instead of T-DXd only displacing T-DM1. The use of T-DXd as a subsequent treatment to T-DM1 was not considered as a scenario analysis as it did not represent current standard of practice and it is not funded or requested to be funded as a subsequent treatment to T-DM1.
2. Proportion of patients receiving tucatinib + trastuzumab + capecitabine is equal to 0% as the use of these therapies is still under review for funding.
3. Reduced the price of T-DXd to the value in which it would be cost-effective at a $50,000 per QALY threshold (61%).
4. Proportion of patients treated with initial anti-HER2 regimen is equal to 81.3%.
5. Proportion of patients who received a second line of therapy prior to T-DXd or T-DM1 is equal to 40.5%.

Results are provided in Table 23. Results of CADTH's scenario analyses demonstrate that the estimated budget impact is highly sensitive to the changes in the proportion of patients receiving T-DM1 as a subsequent treatment after T-DXd treatment and changes in the proportion of patients receiving tucatinib + trastuzumab + capecitabine as subsequent treatment. In addition, treatment price reduction of 61% would result with BIA savings in the drug plan perspective. However, it is important to consider that that this analysis did not considered impacts on AEs, health care resource use, sequential treatment with T-DM1, and administration costs.

Table 23: Scenario Analysis

Stepped analysis	Scenario	Year 0 (current situation)	Year 1	Year 2	Year 3	Three-year total
CADTH's base case	T-DM1	$31,027,250	$77,083,608	$119,949,227	$155,778,043	$352,810,878
	T-DXd	$31,027,250	$109,724,348	$189,600,846	$234,714,749	$534,039,943
	Budget impact	**$0**	**$32,640,740**	**$69,651,619**	**$78,936,706**	**$181,229,065**
CADTH scenario 1: proportion of patients receiving T-DM1 after T-DXd equal to 40%	T-DM1	$31,027,250	$77,083,608	$119,949,227	$155,778,043	$352,810,878
	T-DXd	$31,027,250	$110,522,653	$196,204,286	$252,601,695	$559,328,634
	Budget impact	**$0**	**$33,439,044**	**$76,255,059**	**$96,823,652**	**$206,517,755**
CADTH scenario 2: proportion of patients receiving tucatinib + trastuzumab + capecitabine is equal to 0%	T-DM1	$23,590,523	$37,546,200	$40,750,832	$42,526,894	$120,823,926
	T-DXd	$23,590,523	$75,104,819	$132,613,504	$158,668,870	$366,387,193
	Budget impact	**$0**	**$37,558,619**	**$91,862,672**	**$116,141,976**	**$245,563,267**
CADTH scenario 3: price reduction of 61%	T-DM1	$31,027,250	$77,083,608	$119,949,227	$155,778,043	$352,810,878
	T-DXd	$31,027,250	$74,489,905	$113,433,517	$142,083,923	$330,007,345
	Budget impact	**$0**	**-$2,593,704**	**-$6,515,710**	**-$13,694,119**	**-$22,803,533**
CADTH scenario 4: proportion of patients treated with initial anti-HER2 regimen is equal to 81.3%	T-DM1	$28,707,657	$73,259,293	$115,623,125	$151,115,394	$339,997,812
	T-DXd	$28,707,657	$102,295,602	$176,504,996	$219,007,970	$497,808,569
	Budget impact	**$0**	**$29,036,309**	**$60,881,872**	**$67,892,577**	**$157,810,758**
CADTH scenario 5: proportion of patients who received a second line of therapy prior to T-DXd or T-DM1 is equal to 40.5%	T-DM1	$22,340,164	$57,010,013	$89,977,287	$117,597,109	$264,584,409
	T-DXd	$22,340,164	$79,605,908	$137,355,198	$170,430,661	$387,391,767
	Budget impact	**$0**	**$22,595,895**	**$47,377,911**	**$52,833,553**	**$122,807,358**

BIA = budget impact analysis; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

CADTH

Stakeholder Input

CADTH

List of Tables

Patient Input

Canadian Breast Cancer Network

About Canadian Breast Cancer Network

The Canadian Breast Cancer Network (CBCN) is a leading, patient-directed, national health charity committed to ensuring the best quality of care for all Canadians affected by breast cancer through the promotion of information, education, and advocacy activities. www.cbcn.ca

As a member of the Canadian Cancer Action Network, the Canadian Breast Cancer Network is committed to adhering to the Code of Conduct Governing Corporate Funding.

Information Gathering

Information for this submission was collected via:

- CBCN's 2017 Lived Experience Breast Cancer Patient Survey: An online survey was distributed in English and French to patients living with breast cancer. No patients surveyed had direct experience with the treatment under review. Survey questions comprised of a combination of scoring options and free form commentary. Patients were contacted through the membership databases of CBCN and other patient organizations.

Patient Respondents Profile:

- In this submission, CBCN specifically utilizes the data provided by the 31 patients from the survey who identified as being diagnosed with metastatic human epidermal growth factor receptor 2 (HER2) -positive breast cancer.
- The majority of these respondents were from Ontario (13). The rest of the respondents were from British Columbia (4), Alberta (4), Manitoba (2), Quebec (2), Saskatchewan (2), Nova Scotia (1), Prince Edward Island (1), and New Brunswick (1). 29 participants identified as female and 2 participants did not identify their sex. 26 participants identified as heterosexual, 1 participant identified as bisexual and 4 did not identify their sexual orientation. 26 participants identified English as their first language, while 3 identified French as their first language. 1 participant reported her first language as Afrikaans and 1 participant did not disclose their first language.
- Most of the respondents were first diagnosed with metastatic breast cancer when they were between the ages of 50 and 59 (13) and between the ages of 40 and 49 (8). 5 participants were diagnosed when they were between 30-39 years old, 3 were diagnosed between 60 to 69 years of age, 1 patient was between 20 and 29 years of age when they were diagnosed, and 1 respondent was diagnosed when they were 80 years or older.
- 25 participants reported that they were in a relationship, 4 reported that they were single and 2 did not disclose their relationship status. 81% of the respondents had children at the time of their diagnosis. At the time of their diagnosis, participants reported having a child or children that were between the ages of 2 and 5 (3), 6 and 12 (9), 13 and 19 (6) and 20 and older (12).

CBCN's 2012 Metastatic Breast Cancer Patient and Caregiver Survey Report: An online survey, conducted in collaboration with ReThink Breast Cancer, was distributed to patients living with metastatic breast cancer (mBC) and their caregivers. No patients surveyed had experience with the treatment under review. Survey questions comprised of a combination of scoring

options and free form commentary. Patients were contacted through the membership databases of CBCN and other patient organizations.

71 patients participated in the survey

16 caregivers participated in the survey

Key informant interviews: Phone interviews were conducted between November 2021 and February 2022 with 7 Canadian breast cancer patients living with metastatic HER2- positive breast cancer that had direct experience with the treatment under review. The 7 patients who were interviewed had experience with Enhertu as a third-line treatment.

Printed sources: A review was conducted of current studies and grey literature to identify issues and experiences that are commonly shared among many women living with breast cancer.

Disease Experience

Metastatic breast cancer is the spread of cancerous cell growth to areas of the body other than where the cancer first formed, and is often more severe than earlier stages of breast cancer. It is commonly spreads to the bones, but can include the lungs, liver, brain and skin. In our 2017 Lived Experience Breast Cancer Patient Survey (2017 Survey), the majority of metastatic HER2-positive breast cancer patients experienced metastases to their bones and liver: 58% reported metastases to their bones while 35% reported metastases to their liver. Metastatic HER2-positive breast cancer patients in our 2017 Survey also experienced metastases to their lungs (26% of patients) and brain (19% of patients). 19% of the metastatic HER2-positive patients also reported experiencing metastases to body parts other than the bones, brain, liver and lungs.

Current treatment options for metastatic breast cancer are only effective at prolonging progression-free disease, and most cases of advanced disease will progress and symptoms will worsen. Patients with a diagnosis of metastatic breast cancer understand the limitations of current treatment options and seek to live their remaining months and years with the best possible quality of life that they can achieve.

The HER2 gene creates HER2 proteins which control the growth of breast cells and also help to repair breast cells, however, an overexpression of the HER2 protein causes an uncontrollable reproduction of breast cells. Around 10 to 20% of breast cancers are HER2-positive (Treatments for Metastatic Breast Cancer. Susan G. Komen. Accessed March 12, 2022. https://www.komen.org/breast-cancer/treatment/by-diagnosis/metastatic/) and around 20% of metastatic breast cancers are HER2-positive (HER2-positive metastatic breast cancer. Breast Cancer Network Australia. Accessed March 12, 2022. https://www.bcna.org.au/media/7846/her2-positivembc-booklet_oct2019-web.pdf). HER2-positive breast cancer tends to be more aggressive than HER2-negative breast cancer (What Is HER2-Positive Breast Cancer? Understanding Your Outlook. healthline. Accessed March 12, 2022. https://www.healthline.com/health/breast-cancer/her2-positive-survival-rates-statistics) and has been associated with increased risk of brain metastases and a poor overall survival (OS) (Exman, P., & Tolaney, S. M. HER2-positive metastatic breast cancer: a comprehensive review. Clin Adv Hematol Oncol. 19(1), 40–50 (2021). https://pubmed.ncbi.nlm.nih.gov/33493147/). Younger women are more likely to be diagnosed with HER2- positive breast cancer (What Is HER2-Positive Breast Cancer? Understanding Your Outlook. healthline. Accessed March 12, 2022. https://www.healthline.com/health/breast-cancer/her2-positive-survival-rates-statistics). Other risk factors include being female, giving birth for the first time after 30 years

old, being overweight, having a sedentary lifestyle, using tobacco products, and having a history of receiving radiation therapy in the chest area (Ibid).

The Physical Impact of Metastatic Breast Cancer

How the disease presents itself through symptoms, how it progresses, and how it is experienced varies by patient, but many effects of metastatic breast cancer represent a significant or debilitating impact on their quality of life. In our 2012 Metastatic Breast Cancer Patient and Caregiver Survey (2012 Survey), patients were asked what impact cancer-related symptoms had on their quality of life:

- 54% of patients reported that fatigue resulted in a significant or debilitating impact, and 40% reported some or moderate impact;
- 39% of patients reported that insomnia resulted in a significant or debilitating impact, and 46% reported some or moderate impact;
- 37% of patients reported that pain resulted in a significant or debilitating impact, and 44% reported some or moderate impact.

These results were further reinforced in our 2017 Survey.

The Social Impact of Metastatic Breast Cancer

The impact of this disease touches all aspects of a patient's life, restricting an individual's employment and career, ability to care for children and dependents, and their ability to be social and meaningfully participate in their community. When asked in the 2012 Survey what kind of impact living with metastatic breast cancer has had on their quality of life:

- Among those who were employed, 71% of patients identified significant restrictions to their ability to work;
- Among those with children or dependents, 21% identified significant restrictions and 53% reported some or moderate restrictions to their caregiving responsibilities;
- 49% of patients identified significant restrictions and 38% identified some or moderate restrictions to their ability to exercise;
- 42% of patients identified significant restrictions and 42% identified some or moderate restrictions to their ability to pursue hobbies and personal interests;
- 41% of patients identified significant restrictions and 41% identified some or moderate restrictions to their ability to participate in social events and activities;
- 22% of patients identified significant restrictions and 52% identified some or moderate restrictions to their ability to spend time with loved ones.

Other experiences identified by patients included: guilt, the feeling of being a burden on caregivers, fear of death, poor body image, not knowing what functionality will be lost, fear of the impact of cancer and the loss of a parent on children, not knowing what will happen to children, the loss of support of loved ones, as well as marital stress/loss of fidelity and affection from husband.

Experiences With Currently Available Treatments

The Goals of Current Therapy

As with all treatment for metastatic breast cancer, the goal of treatment for metastatic HER2-positive breast cancer, is to control disease progression (extending life) and to manage cancer-related symptoms (extending or stabilizing quality of life). Treatment options for mBC

and their effectiveness vary among type of cancer, location of cancer, and how symptoms are experienced.

In the case of metastatic HER2-positive breast cancer, it is usually treated with HER2-targeted therapies, such as trastuzumab, in combination with chemotherapy (Treatments for Metastatic Breast Cancer. Susan G. Komen. Accessed March 12, 2022. https://www.komen.org/breast-cancer/treatment/by-diagnosis/metastatic/). Targeted treatments for HER2-positive breast cancer usually have less side effects than chemotherapy or radiation therapy because they target and attack a specific type of cancer cell without harming the body's non-cancerous cells (What Is HER2-Positive Breast Cancer? Understanding Your Outlook. healthline. Accessed March 12, 2022. https://www.healthline.com/health/breast-cancer/her2-positive-survival-rates-statistics). Immunotherapy drugs, which help the immune system attack cancer cells, may also be used in the treatment of HER2-positive breast cancer. The most used type of immunotherapy drugs in treating breast cancer are checkpoint inhibitors which override the natural limit the body imposes on the immune system controlling cancer cells (Treatments for Metastatic Breast Cancer. Susan G. Komen. Accessed March 12, 2022. https://www.komen.org/breast-cancer/treatment/by-diagnosis/metastatic/).

In the treatment of metastatic breast cancer, when a treatment regimen with chemotherapy does not work, a new regimen is used. Each new regimen is called a 'line'. As more lines of treatment are tried, the likelihood of the cancer to shrink becomes less. If the cancer does shrink, it is a short period of time until a new line is needed, with the time period getting shorter and shorter as more lines are used (Ibid).

Among the metastatic HER2-positive breast cancer patients in our 2017 Survey, 81% had undergone surgery, 58% had received radiation therapy, 97% had received chemotherapy and 61% reported receiving hormone therapy.

Key Factors for Decision-Making Around Treatment

Metastatic breast cancer patients in our 2017 Survey discussed the importance of the following factors in influencing their decision-making around treatments:

- Effectiveness of the treatment – how well the treatment stabilized their disease and delayed progression of their disease.
- Prolonging life without sacrificing quality of life – being able to maintain productive, active lives with minimal disruption to daily routines.
- Side effect management – minimizing risk while stabilizing their disease.
- Cost and accessibility of treatments – affordability and ease of accessing treatments.

Treatment efficacy

- 77% of metastatic HER2-positive breast cancer patients ranked treatment effectiveness as the most important factor when making decisions about treatment. Additionally, respondents talked about the importance of progression-free survival (PFS) in treatment decision making:
    - PFS of less than 3 months was rated as important by 23% of patients and very important by 61% of patients
    - PFS of 3 to 5 months was rated as important by 26% of patients and very important by 68% of patients

- PFS of 6 months or more was rated as important by 13% of patients and very important by 87% of patients

- When asked about OS, 10% and 84% of metastatic HER2-positive breast cancer patients indicated that it was important and very important, respectively, when considering treatment options.
- Metastatic patients with all types and subtypes of breast cancer in our 2017 Survey also spoke on the importance of treatment effectiveness in their decision-making anecdotally:

"The most important factors for me are progression free survival and quality of life." – mBC patient respondent

"Anything to prolong my survival and maintain quality of life." – mBC patient respondent

"Survival is of upmost importance to me." – mBC patient respondent

Quality of life

- Quality of life was routinely cited by patients as an important factor in making treatment decisions. In our 2017 Survey, quality of life was rated as important by 35% of metastatic HER2-positive patients and very important by 48% of metastatic HER2-positive patients. More specifically, patients reported on the importance of minimal side effects, mobility, and productivity when making decisions regarding treatment options. Among metastatic HER2-positive breast cancer patients in our 2017 Survey:
  - Minimal side effects was rated as important by 48% of patients and very important by 19% patients
  - Productivity was rated as important by 45% of patients, somewhat important by 45% of patients, and very important by 6% patients
  - Mobility was rated as important by 35% of patients and very important by 45% patients
- This concern was shared among all mBC respondents in our 2017 Survey:

"Quality of life over quantity." – mBC patient respondent

"Making sure I have some quality of life so I can [spend] as much time with my kids and family[.] I don't want them to watch me suffer" – mBC patient respondent

"Trying to balance the most effective treatment regime with the least impact on my day to day living/quality of life. Maintaining a certain level of independence is important to me." – mBC patient respondent

Patient willingness to tolerate treatment side effects

In our 2012 Metastatic Patient and Caregiver Survey, the responses to what level of side effects and how much impact on one's quality of life would be worth extending progression-free disease by six months was shown to be determined at the personal level.

- When asked to rate how much impact different symptoms of cancer and cancer treatment would be considered tolerable:
  - Almost two-thirds of patients indicated that when it comes to **fatigue, nausea, depression, problems with concentration, memory loss, diarrhea and insomnia**, some or a moderate impact on one's quality of life would be considered acceptable,

and approximately one quarter of patients indicated that a strong or debilitating impact would be considered acceptable.

- 70% of patients indicated that when it comes to **pain**, some or a moderate impact on one's quality of life would be considered acceptable, and 27% of patients indicated that a strong or debilitating impact would be considered acceptable.

- Among metastatic HER2-positive breast cancer patients in our 2017 Survey, when asked about the level of acceptable symptoms in exchange for 6 months or less of benefits from breast cancer treatment:
  - **Pain**, **nausea**, and **insomnia** were each rated as not acceptable by 10% of patients, somewhat acceptable by 55% of patients and very acceptable by 32% of patients.
  - **Fatigue** was rated as not acceptable by 3% of patients, somewhat acceptable by 23% of patients and very acceptable by 68% of patients.
  - **Depression** was rated as not acceptable by 29% of patients, somewhat acceptable by 48% of patients and very acceptable by 19% of patients.
  - **Lack of concentration** was rated as not acceptable by 10% of patients, somewhat acceptable by 58% of patients and very acceptable by 29% of patients.
  - **Memory loss** was rated as not acceptable by 26% of patients, somewhat acceptable by 48% of patients and very acceptable by 23% of patients.
  - **Diarrhea** was rated as not acceptable by 23% of patients, somewhat acceptable by 42% of patients and very acceptable by 32% of patients.
  - **Vomiting** was rated as not acceptable by 45% of patients, somewhat acceptable by 35% of patients and very acceptable by 16% of patients.
  - **Hair loss** was rated as somewhat acceptable by 29% of patients and very acceptable by 68% of patients.
- This willingness to tolerate side effects was also reflected anecdotally:

  "Definitely the balance of quality of life vs side effects with the [effectiveness]." – mBC patient respondent

  "Mom so just want to live – high tolerance for SE as long as management options provided." – metastatic HER2-positive breast cancer patient respondent

The financial burden of treating and managing breast cancer

- The financial burden associated with living with metastatic breast cancer extends far beyond any loss of income during a temporary or permanent absence from employment. In addition to the loss of income during illness, metastatic breast cancer patients can incur substantial costs associated with treatment and disease management. Research on the financial impact of breast cancer on patients identified the following (Janet Dunbrack, Breast Cancer: Economic Impact and Labour Force Re-entry. Canadian Breast Cancer Network, 2010):
  - 80% of breast cancer patients report a financial impact due to their illness.
  - 44% of patients have used their savings, and 27% have taken on debt to cover costs.
- These findings were consistent with the responses in our 2012 Survey:
  - Nearly one-third of patients indicated that the **cost of medication, the cost of alternative treatments (i.e. massage, physiotherapy, etc.) to manage symptoms**

and side effects, and the time required to travel to treatment had a significant or debilitating impact on their quality of life.

- 24% of patients indicated that the **costs associated with travel** had a significant or debilitating impact on their quality of life, and 41% of patients indicated that it had some or moderate impact on their quality of life.

In our 2017 Survey, metastatic HER2-positive breast cancer patients reported that their diagnosis had some (39%) or a very large (42%) impact on their finances.

In addition to this, 68% and 58% of metastatic HER2-positive breast cancer patients indicated that the **time required to travel to treatment** and the **cost to travel to treatment**, respectively, had some or a significant impact of their quality of life. 48% and 65% of metastatic HER2-positive breast cancer patients reported the same in regard to the **cost of prescription medications** and the **cost of other treatments** (i.e., massage, physiotherapy, etc.), respectively. 35% of metastatic HER2-positive breast cancer patients indicated that the **cost of devices** had some or a significant impact of their quality of life.

The financial impacts of a metastatic breast cancer diagnosed was also reiterated anecdotally by respondents in our 2017 Survey:

> "Always a concern as you never know if the next drug will be covered or how long it takes to get approval from private coverage. Many times, it delays treatment and this weighs on one's mind." – metastatic HER2-positive breast cancer patient respondent

> "If my community did not raise the money for my [treatment] I would likely not be here today. When I contacted every group or charity NOONE offered financial assistance for treatment." – metastatic HER2-positive breast cancer patient respondent

> "Many of the next step treatments are very expensive [and not covered by government programs] and it is a HUGE struggle to get [coverage]. […] When dealing with an incurable disease the last thing you want to have to do is spend time on a letter writing campaign to argue about whether or not you should receive the drugs [recommended by your physician]. At about $1500.00 a week, I don't know many who can afford that." – mBC patient respondent

> "I wanted to try [immunotherapy], but it is [$]7500.00 every 3 weeks not covered by private insurance, now will probably have to go on chemo again, and the last ones were very hard on me causing toxicity and having to get blood transfusions." – mBC patient respondent

> "Just because I am not in the lowest income bracket does not mean I don't need assistance. I am excluded from all programs I have tried to access." – mBC patient respondent

Other financial barriers that metastatic breast cancer patients mentioned include not qualifying for insurance at work, inability to change employers due to loss of insurance, and the prohibitive cost of new treatment options.

Patient Access to Local Resources and Supports During Treatment

When living with cancer, many patients experience significant barriers and challenges around availability of health care services and quality childcare in their community. In response to the

2012 Survey questions about the availability of supports such as childcare, transportation and alternative treatments in their community:

- Among patients with children or other dependents, 53% indicated that there is minimal or no access **to appropriate care for their loved ones** when they are experiencing debilitating symptoms related to their cancer, and 40% identified barriers to accessing quality care during cancer treatment.

In our 2017 Survey among metastatic HER2-positive breast cancer patients with children at the time of their diagnosis:

- 32% of patients reported that finding **appropriate care for their children/dependents when experiencing side effects** of cancer treatments was not accessible.
- 35% patients indicated that finding **appropriate care for their children/dependents during cancer treatment** was not accessible.
- Among all metastatic HER2-positive breast cancer patients from our 2017 Survey:
    - 29% indicated that finding transportation to appointments was not accessible
    - 52% indicated that finding mental health supports was somewhat accessible
    - 29% indicated that finding cancer treatment in or close to their community was somewhat accessible
    - 13% indicated that finding symptom management options in or close to their community was not accessible, 42% indicated that it was somewhat accessible

Patient Willingness to Tolerate Risk

When asked in the 2012 Survey about their willingness to tolerate risk with a new treatment:

- 34% of respondents were willing to accept serious risk with treatment if it would control the disease
- 45% of respondents were willing to accept some risk with treatment
- 21% of respondents were very concerned and felt less comfortable with serious risks with treatment

Need for Personal Choice

The open-ended questions and the key informant interviews showed that it is imperative that women with metastatic breast cancer have access to, and the option of what drugs they take. Most patients are well aware of the adverse effects of treatment up front and they want to make a personal choice that works for them. 68% of metastatic HER2- positive breast cancer patients in our 2017 Survey expressed being very comfortable participating in treatment decisions. Metastatic breast cancer patients expressed the need for personal choice and autonomy in our 2012 Survey as well as in the 2017 Survey:

> "I think patients (ESPECIALLY young patients) should be given more decision-making power in terms of access to radical treatments to control disease. […] With two small [children] I am determined to access any treatment that can extend my life and I hate struggling with doctors for this access." – 2012 Survey

> "I believe that I would prefer to tolerate severe restrictions in the quality of my life, if it meant that I would be able to have a longer period without progression." – 2012 Survey

"It would be nice to have more choices and more information about them. I was lucky to get on a clinical trial perhaps because my oncologist was a research oncologist and involved in many. While I knew friend and acquaintances that had Stage IV BC and never informed of clinical trials, and sadly several did not survive the disease." – 2017 Survey mBC patient respondent

"I am frustrated that ALL the treatment choices aren't given to me... I am told what I am taking next with no option or discussion on other options. My oncologist has assured me there are many treatments available, but have never shared which, so I have to turn to Facebook groups for guidance." – 2017 Survey mBC patient respondent

"I wish my doctor would present me with options." – 2017 Survey mBC HER2-positive breast cancer respondent

"Accessibility to new drugs- not limiting choices." – 2017 Survey mBC patient respondent

"Complete access to drug treatment choices and trials." – 2017 Survey mBC patient respondent

Improved Outcomes

For metastatic patients, extension of progression-free survival (PFS) is of critical concern. Like any other treatment for metastatic breast cancer, patients have an expectation that trastuzumab deruxtecan (Enhertu) will extend their PFS with good quality of life when first-line therapies stop working.

DESTINY-Breast03 (Cortés, M. D. et al. Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. N Engl J Med. 386, 1143- 1154 (2022). https://doi.org/10.1056/NEJMoa2115022) is a phase III, global, multicenter, clinical trial exploring the efficacy and safety of trastuzumab deruxtecan (T-DXd) versus trastuzumab emtansine (T-DM1) among individuals with metastatic or unresectable HER2-positive breast cancer that had progressed during or after being treated with trastuzumab and a taxane or patients that had progressed within 6 months following neoadjuvant or adjuvant treatment with trastuzumab and a taxane. 524 breast cancer patients from North America, South America, Europe, Asia, and Oceania were randomized into one of two groups at a 1:1 ratio. Patients were stratified by hormone receptor status (positive or negative), prior use of pertuzumab, and history of visceral disease. Patients were either administered T-DXd every 3 weeks (n = 261), or they were administered T-DM1 every 3 weeks (n = 263). The primary endpoint for this study was PFS as per blinded independent central review (BICR). Secondary endpoints were OS, overall response rate (complete or partial, as per BICR and investigator review), PFS as per investigator review, and safety.

Table 1: Key Characteristics of Patients in DESTINY-Breast03 at Baseline

Characteristic	Trastuzumab deruxtecan (n = 261)	Trastuzumab emtansine (n = 263)
Median age	**54.3 years old**	**54.2 years old**
HR-positive	131 (50.2%)	134 (51.0%)
HR-negative	130 (49.8)	129 (49.0%)
Stable brain metastases	62 (23.8%)	52 (19.8%)
Visceral disease	184 (70.5%)	185 (70.3%)
Prior use of pertuzumab	62.1%	60.1%
1 line of prior therapy	130 (49.8%)	123 (46.8%)
2 lines of prior therapy	56 (21.5%)	65 (24.7%)
3 lines of prior therapy	35 (13.4%)	35 (13.3%)
4 lines of prior therapy	15 (5.7%)	19 (7.2)
5 or more lines of prior therapy	23 (8.8)	18 (6.8)

Median follow-up from the DESTINY-Breast03 study was at around 16 months for trastuzumab deruxtecan and around 15 months for trastuzumab emtansine. Results from the first interim analysis showed that median PFS was not reached in the trastuzumab deruxtecan arm but was 6.8 months in the trastuzumab emtansine arm (95% confidence interval [CI], 5.6 to 8.2) with a hazard ration (HR) of 0.2840, p<0.001. Investigator review showed that estimated median PFS in the trastuzumab deruxtecan arm was 25.1 months (95% CI, 22.1 to unknown) and 7.2 months in the trastuzumab emtansine arm (95% CI, 6.8 to 8.3) with an HR of 0.26 (95% CI, 0.20 to 0.35; p<0.001).

An overall response (complete or partial) was observed in 79.7% (95% CI, 74.3 to 84.4) of the patients who were administered trastuzumab deruxtecan and in 34.2% (95% CI, 28.5 to 40.3) of those who were administer trastuzumab emtansine. In the trastuzumab deruxtecan arm, 16.1% of patients had a complete response (CR) and in the trastuzumab emtansine arm, 8.7% had a CR. Disease control rate was 96.6% for those who received trastuzumab deruxtecan and 76.8% for those who received trastuzumab emtansine.

The benefits of trastuzumab deruxtecan were observed across all prespecified subgroups, including patients with brain metastases or the presence of visceral disease, use of pertuzumab, and those defined by hormone receptor status. Overall, the risk of disease progression or death was found to be lower in the trastuzumab deruxtecan arm than in the trastuzumab emtansine arm. Compared to trastuzumab emtansine, the hazard ratios of all reviews (BICR, subgroup analyses, and investigator review) showed that trastuzumab deruxtecan led to an approximate 70% reduction in the risk of disease progression or death for patients in this study.

Adverse Effects

Median treatment duration for trastuzumab deruxtecan was 14.3 months (range, 0.7 months to 29.8 months) compared to 6.9 months with trastuzumab emtansine (range, 0.7 months to 25.1 months).

Incidence of adverse events was similar in both the trastuzumab deruxtecan group (99.6%) and the trastuzumab emtansine group (95.4%). The rate of adverse events that were of grade 3 of higher was also similar in both treatment groups: 52.1% in the trastuzumab deruxtecan arm and 48.3% in the trastuzumab emtansine arm. Serious adverse effects occurred in 19.1% of patients receiving trastuzumab deruxtecan and in 18.0% of patients receiving trastuzumab emtansine. Incidence of adverse events severe enough to lead to treatment discontinuation was higher in the trastuzumab deruxtecan group (13.6%) than in the trastuzumab emtansine group (7.3%).

The rate of treatment-related adverse effects (TRAEs) of any grade were observed in 98.1% patients who received trastuzumab deruxtecan and in 86.6% of patients who received trastuzumab emtansine. Those of grade 3 or higher occurred in 45.1% of patients who received trastuzumab deruxtecan and in 39.8% of patients who received trastuzumab emtansine. No patients, regardless of treatment administered, experienced a TRAE of grade 5.

The most common TRAEs of any grade amongst patients who were administered trastuzumab deruxtecan were nausea (72.8%, compared to 27.6% in those who were administered T-DM1), fatigue (44.7%, compared to 29.5% in those who were administered T-DM1), and vomiting (44.0%, compared to 5.7% in those who were administered T-DM1). The most common TRAE of grade 3 or 4 amongst patients who were administered trastuzumab deruxtecan were neutropenia (19.1% versus 3.1% in the T-DM1 group), thrombocytopenia (7.0% versus 24.9% in the T-DM1 group), leukopenia (6.6% versus 0.4% in the T-DM1 group), and nausea (6.6% versus 0.4% in the T-DM1 group). Drug-related alopecia of any grade was reported in 36.2% of patients who were administered trastuzumab deruxtecan and in 2.3% of those who were administered trastuzumab emtansine.

10.5% of patients in the trastuzumab deruxtecan arm and 1.9% of patients in the trastuzumab emtansine arm had adjudicated drug-related interstitial lung disease (ILD), with none being a grade 4 or 5. In the trastuzumab deruxtecan arm, the median time to onset of ILD or pneumonitis was 168 days (ranging from 33 days to 507 days) with 3 patients who had more than one event (all grade 2 or less). Treatment discontinuation due to ILD or pneumonitis occurred in 21 patients (8.2%) who received trastuzumab deruxtecan and in 3 patients (1.1%) who received trastuzumab emtansine.

At the first interim analysis, 94.1% (95% CI, 90.3 to 96.4) of patients in the trastuzumab deruxtecan arm and 85.9% (95% CI, 80.9 to 89.7) of patients in the trastuzumab emtansine arm were alive at 12 months. This difference did not reach the prespecified boundary for significance (P<0.000265) (HR for death, 0.55; 95% CI, 0.36 to 0.86; p = 0.007). 75.8% (95% CI, 69.8 to 80.7) of patients who were administer trastuzumab deruxtecan were alive without disease progression at 12 months; for those administered trastuzumab emtansine, this number was 34.1% (95% CI, 27.7 to 40.5) (hazard ratio for progression or death from any cause, 0.28; 95% CI, 0.22 to 0.37; P<0.001). 33 of the 261 patients who received trastuzumab deruxtecan and 53 of 263 of the patients who received trastuzumab emtansine had died as of the date of data cutoff.

Overall, DESTINY-Breast03 shows that trastuzumab deruxtecan is tolerable and has a manageable toxicity profile.

Impact of Treatment Options to Patients

By delaying the progression of the disease, trastuzumab deruxtecan can relieve cancer-related symptoms, and improve a patient's quality of life. Analyzed data from the DESTINY-

Breast03 clinical trial showed a statistically significant improvement in PFS with the treatment of trastuzumab deruxtecan compared to trastuzumab emtansine as a second-line therapy for patients with unresectable or metastatic HER2-positive breast cancer who had been previously treated with a taxane and trastuzumab. Results from this study show strong support for trastuzumab deruxtecan to become the standard of care as a second-line treatment for this patient population.

When living with no or with minimal cancer-related symptoms, and with minimal side effects from treatment, patients are able to reduce the impact of cancer on their ability to care for children and dependents, continue with their employment and earn income, spend time with loved ones and participate in their life in a meaningful way by engaging in social activities, travelling, maintaining friendships, and pursuing personal interests.

Value to Patients

The value to patients of extending the time that their cancer is progression-free cannot be overestimated. Patients living with metastatic breast cancer are aware that their advanced disease will progress with worsening symptoms until death, and embrace opportunities to try new treatments, even if benefits may be as little as a six-month extension of progression-free disease. It is also very important for patients to have good quality of life when receiving treatment for metastatic disease. Patients that we speak to on a regular basis acknowledge the importance to have the energy to attend their children's activities and to spend time with family and friends.

Experience With Drug Under Review

Patient Profiles

CBCN connected with 7 Canadian patients who had experience with the treatment in the third-line setting.

Patient 1: Is 54 years old and is living with metastatic HER2-positive breast cancer. She was diagnosed in 2019 and in addition to being treated with Enhertu, she has been treated with AC chemotherapy, atezolizumab, paclitaxel, Perjeta, Herceptin and Tukysa. She was also enrolled in a clinical trial for zanidatamab just before starting Enhertu. She accessed this drug through the patient assistance program offered by AstraZeneca after learning about it from a Facebook group.

Patient 2: Was diagnosed with breast cancer in 2014 and is living with metastatic HER2-positive invasive ductal carcinoma (IDC). When she was first diagnosed, her cancer was between stages II and III, eventually metastasizing to her brain and bones and becoming stage IV. She is 34 years old, and her cancer has been previously treated with chemotherapy, including capecitabine, as well as Perjeta, Herceptin, Kadcyla, and tucatinib. She accessed Enhertu via a compassionate care program.

Patient 3: Is 66 years old and was diagnosed in 2016. She is living with metastatic HER2-positive breast cancer and has previously been treated with chemotherapy, pertuzumab, lapatinib, and Herceptin. She has access to this treatment at the recommendation of her oncologist and through private donations.

Patient 4: Was diagnosed 4 and a half years ago and at 68 years old, is living with metastatic HER2-positive breast cancer. Other than Enhertu, she has also been on Taxol, Herceptin, and Kadcyla. She is accessing this treatment via compassionate access.

Patient 5: Is living with metastatic HER2-positive IDC. She is 32 years old and was diagnosed in 2020. She was treated with docetaxel, pertuzumab and Herceptin in the first-line setting. She is not sure of what treatments she received in the second-line setting.

Patient 6: Is 59 years old. When she was diagnosed in 2017, she was diagnosed as stage III which has since spread. She is now living with metastatic HER2-positive breast cancer with bone and lung metastases. Her previous treatments include a double mastectomy, chemotherapy, radiation, Perjeta, Herceptin, Kadcyla, and zoledronic acid for her bones.

Patient 7: Is 63 years old, was diagnosed in 2016, and is living with metastatic inflammatory HER2-positive breast cancer. She has been treated with trastuzumab, pertuzumab, paclitaxel, capecitabine, gemcitabine and tucatinib. Her treatment of pertuzumab stopped working in June of 2020 and she had a recurrence. She had a seizure in September of 2020 and another in January of 2021. She has also had a blood test which showed that her tumors changed to being HER2-positive to HER2-negative. She was interviewed alongside her husband.

The Impact of the Treatment on the Disease

While patients had not yet had a scan or gotten the results of scans if they had had them, at the time of the interview, they were confident that the treatment was working. Reasons for believing it was working included feeling better, having small tumor markers, having more energy, being able to physically feel their tumors, and more.

> "I had progression in my bone metastases on my last scan, but my tumour markers are better. They keep getting better and better. Lower and lower. So, we've decided to continue and do another bone scan in March to see what's going on." – Patient 1
>
> "I haven't had a scan yet, so I don't know. But I have been feeling pretty good. I think it's working." – Patient 2
>
> "I noticed a difference right away with how well it's working on my tumours." – Patient 3
>
> "I have a tumour in my left breast and one under my armpit on my left side in my lymph nodes. Just being able to feel them, they're softer, much better." – Patient 3
>
> "I only had three cycles, though, and everything seems to have stopped around that time, so we'll see. But I'm hopeful with this one." – Patient 5
>
> "I'm not sure. I'm waiting for another CT scan to see how things are doing for me. I'm feeling good." – Patient 6"
>
> From our perspective and dealing with this for the past number of years, [her] change is dramatic." – Patient 7's husband

Patient 7 and her husband were particularly in awe of how quickly and well the treatment seemed to be working based on her energy levels as well as test results. Having been on multiple lines, gone through many treatments, and having various health complications, they were able to see a clear difference in how she was responding to Enhertu compared to other treatments that she had been on. While she also had not had the progression of her cancer assessed at the time of the interview, all other tests and scans that she had received up to this point were looking positive.

> "It's amazing the difference in how I feel. And I can't thank them enough because it was not coming to the end of the road, but we didn't know where we were going to turn. So, I really do feel my energy coming back. My appetite is coming back. So, I really do feel that it has turned it around for me. So, I'm very grateful. Very thankful." – Patient 7

> "[Before Enhertu] her right lung was starting to gain quite a bit of fluid because the lung was one of the metastases. So, she had a drainage tube put in and it was monitored by the VON. I think her first drainage was 8500 mL. It was almost the equivalent of a two litre of milk in volume that came out. Then continuously it dropped to 200 mL, dropped to 100 mL. That tube was put in on the 18th of August. And for the past three weeks there has been zero drainage from the lung. The accumulation of the fluid has stopped. Obviously, she feels a whole lot better just from that alone. So, at this particular point the lung has completely stopped draining." – Patient 7's husband

> "Energy is back, appetite is back. Her blood work is showing perfect. Her MUGA scan has come back very positive." – Patient 7's husband

Assessing Risks Associated with the Treatment

The most common side effects mentioned among patients that we interviewed included nausea (mentioned by 3 patients), stomach pain or other stomach issues (mentioned by 3 patients), having little to no appetite (mentioned by 3 patients), fatigue (mentioned by 4 patients), and hair loss (mentioned by 4 patients). For most patients, these were experienced at manageable or controllable levels. The side effect of nausea, vomiting, and other stomach or bowel issue were the ones that usually needed medication to treat and were also the ones that most patients mentioned as being hard to tolerate. While fatigue was mentioned by many patients (4), patients did not mention needed medication to address it.

Patient 1 iterated that none of the side effects that she was experiencing were unacceptable to her. Her symptoms included: nausea, fatigue, brittle nails, and nosebleeds. She also has aches and pains in her bone and muscles but is unable to say that the treatment is solely responsible because she has bone lesions. She finds the nausea to be the most difficult to tolerate. While she would appreciate getting the nosebleeds under control, the rest of her side effects are low-grade, manageable, and well-controlled. She is taking Olanzapine for the nausea, Dilaudid for the bone pain, and Tylenol for other aches and pains; these all seem to be working well. Her nosebleeds are the only thing she and her doctors have not been able to find a solution for.

> "Everything is acceptable. Even this nausea if it continues as a low nausea." – Patient 1

> "The fatigue is not too bad. I guess that's acceptable. At the moment everything is well-controlled, and I guess it's acceptable. I would love to get the nosebleeds under control. That would be helpful." – Patient 1

Patient 2 only experienced fatigue and hair loss, both low-grade, which she is able to address without the need for medications. While she has not experienced nausea, she was warned that she could get nausea, this is one of the few side effects that she seems to be unacceptable. The hair loss is also difficult to deal with as she was not prepared for it to happen, but other than that, the fatigue is manageable as it is a normal side effect that she has experienced from chemotherapy.

> "They kept talking to me about bad nausea and diarrhea. So, I waited for that to happen, but it didn't." – Patient 2

> "This is a pretty good treatment. I haven't had many side effects. I lost my hair. That's one thing. They told me I wasn't going to lose it, but I did. And I just have fatigue. I'm really sleepy, really tired. That's pretty much it." – Patient 2

> "I rest when I'm tired. I lay down. I nap when I feel like I should." – Patient 2

Like patient 1, patient 3 also experienced nausea, and like patient 2, she also experienced hair loss. Additionally, her side effects from treatment included vomiting, constipation, and a headache when she is nauseous. Her side effects that relate to her stomach and bowels seem to operate on a cycle and she finds these to be debilitating, to the time where she is unable to work or do anything. She does note that she is on painkillers which she states may be to blame for the bowel problems she is experiencing, which differ in manageability day-to-day. To manage the side effect of nausea, she takes Zofran and Metonia, however, she finds that while she is on the pills she has an upset stomach, feels nauseous, her stomach feels full and she's ready to vomit but when not on the pills, she ends up vomiting.

> "Side effects I'm finding are quite harsh, actually. About a week after I had my treatments, I'm very nauseous and sick. And I was vomiting quite a bit. The oncologist has been working with me to get different pills to stop the vomiting. So the last treatment wasn't as bad as the one before. I'm also losing my hair. It's another side effect. I'm not happy with that. It's working, though. I do notice it in my tumours, definitely." – Patient 3

In addition to experiencing fatigue and nausea, patient 4 also experiences dehydration. The fatigue causes her to sleeps for long hours and to take naps in the afternoon. She takes pills for the nausea, and is able to manage the fatigue and dehydration, though the hydration has been a bit harder to deal with.

> "Acceptable is the fatigue, but the dehydration, I have to say, it's a little bit hard to get all the water. You have to drink a lot of water and I can't. Maybe I don't get enough electrolytes, I find. It hasn't been a major issue, but from the blogs I read, most women have that." – Patient 4

Patient 5 experiences nausea and having no appetite. While she sometimes needs ondansetron and dexamethasone for the nausea, she finds all her side effects to be easy to handle.

> "I think they're all pretty acceptable. It doesn't seem to be as bad as some [chemotherapies], so I'd say it's a little bit better than most." – Patient 5

Patient 6 mentioned experiencing hair loss, loss of appetite, fatigue, specific food cravings, constipation, and stomach pains, all of which are very mild, stating that her body seems to be tolerating the treatment very well. She needs to take naps due to the fatigue, required stool softeners to address the constipation she experienced in the beginning, and takes Tylenol for the stomach pains. She was on also on steroids from the stomach pains which helped her sleep better as the pains kept her awake at night.

> "I don't have much reaction with this drug. Also, I lost my hair in two infusions. That losing hair—this is the third time—to me that's nothing. And my brain is kind of clear compared to previous treatments. I'm not foggy, or something like that." – Patient 6

Patient 7 described her side effects from Enhertu as "almost non-existent" and being much less than the side effects she experienced from other therapies. While she did have hair loss, like patients 2, 3, and 6, she pointed out that her hair loss had begun even before she started on Enhertu. She addressed her hair loss by purchasing "some wigs and some hats". Like other patients, she also had a loss of appetite which her doctor prescribed half a milligram of dexamethasone to help with. Lastly, patient 7 mentioned being on a kind of antacid for stomach issues she experiences. Other than the breast cancer, patient 7 had suffered from seizures over the years and is on 100 mg of lamotrigine and 50 milligrams of brivaracetam to address it. Overall, patient 7 expressed that her side effects were much less than those she experienced while other treatments, they were less than she expected and anticipated, and were more than tolerable.

> "If I didn't know I was on this drug, I probably wouldn't even take notice to it. Because I can't say that there have been any side effects that have stopped me or that I have noticed. Other than the hair loss, and that really doesn't bother me. But other than that, I really wouldn't know I was taking a drug. Honestly. It's just amazing that you can take something like this and feel as good as you do. So, I have no complaints at all." – Patient 7

Alternatives to the Treatment

For many of the patients that we interviewed, Enhertu was their last option, being that this was their third line of treatment. This meant that they were very grateful to have been able to access it and they were happy that so far, the treatment appeared to be working. This was expressed when asked about why they chose this treatment:

> "I think I had taken all of the other drugs that were available at the time." – Patient 1

> "I don't have very many options left. Probably one of the last ones for me." – Patient 2

> "It was just something that my doctor read about. She said that there were very positive results. She thought it would be a good match for me. So, I just went with her recommendation." – Patient 3

> "No other options." – Patient 4

> "I'm fortunate to be selected to try this drug […] And I'm willing to try anything. I feel there's not much options there for me and what am I going to lose in my situation right now? Nothing." – Patient 6

Enhertu being their last option was reiterated when many of the patients that we interviewed were asked about what alternatives they would have gone with, had Enhertu not been available.

> "I have no idea. I'm just praying this treatment works." – Patient 1

> "There is none right now on the market. Maybe Tukysa. I think it's available in pill form. But it made me very sick when I tried capecitabine or whatever it's called, so I don't think that's an option. There's no options. This is it." – Patient 4

> "I don't know. They just recommend whatever they recommend." – Patient 6

While most patients did not know what alternatives they could be on and had to just wait for whatever becomes available or what their oncologist is able to find, patient 2 was the only patient who had a specific alternative treatment that she was open to trying.

> "I don't know. Probably traditional medicine. I'm First Nations. I'll probably go with traditional medicine." – Patient 2

When answering this question, patient 3 mentioned being limited in treatment choice by what she could afford.

> "I'm not in a financial position to choose all kinds of alternative treatments that people choose. I'm not in a financial position to choose any of those. Those are way out of my budget. So, I'm just at the mercy of whatever my oncologist is able to find for me that is either covered by donations like this one or [provincial] health care. And I've gone through a couple of those already, and I know you can't go backwards." – Patient 3

Patients also spoke about and compared the side effects from Enhertu to the side effects from other treatments and therapies that they had received in the past. For some the side effects were more difficult or debilitating in comparison to those from other treatments:

> "Initially it was more difficult compared to certain other treatments but now it's improving a bit. I have a better quality of life now." – Patient 1

> "More tired, more fatigued. More thirsty: dehydration." – Patient 4

> "This one, I kind of got really sick with. It was worse than all the other ones I've had." – Patient 5

For patients 6 and 7, the side effects were a lot more manageable:

> "This drug is different. The side effects are very mild. And I'm not a very big person. I'm five feet and I'm 100 pounds. And my body is tolerating this drug compared with the previous drug. The previous drug, I'm bleeding, it affects my platelets. I have two blood infusions. This Enhertu is doing much better. Before I started this treatment, my skin turned black, my nails turned black. My face was blistering. And with this, no. Nothing like that. If you see me right now, you can't tell that I'm sick, that I have cancer." – Patient 6

> "The side effects have been almost non-existent. I know there was a list that we both watched for. I wouldn't know I was taking it, compared to the other drugs, where there were quite a few side effects." – Patient 7

> "Back when she initially started treatment five, six years ago the cancer drugs, the chemo affected the blood pressure. Right now, [she] has not had blood pressure medication since August 20, and it started to come down. When she started the Enhertu, her blood pressure right now is always between 120 and 125 over 68 to 72. And that's no medication. That's fantastic. We're just elated." – Patient 7's husband

The Social and Financial Impact of the Treatment

A few patients spoke about the social impact of Enhertu in terms of their quality of life while on the treatment. Overall, when asked to rate their quality of life, patients rated it as medium to high.

> "Currently it's good. But the first three treatments, I would rate it as quite low because the nausea, the fatigue, they were quite debilitating. […] At the moment as we speak, it's good. It's a seven, six, seven [out of ten]. [Before] it was a three or four." – Patient 1

> "Maybe a five or six out of ten." – Patient 2

> "I take it every three weeks, so for most of the time, well, I would say about half of the time now, a week or 10 days, I am sick, so it's very different. When I'm not sick—like today I'm not sick—I'm pretty good. I'm about seven or eight out of ten. When I'm sick, it's gone down to about a four or five." – Patient 3

> "Same as before with the other drugs. Seven or eight out of ten." – Patient 4 "It's okay. Probably a seven out of ten." – Patient 5

> "I think I'm back to 80 percent." – Patient 6

> "I would say six, maybe seven. I would say now we're getting out and about. Of course, with COVID, I limit my travel. But if my husband is going anywhere, I will say I'm going to go in the car with you for the drive, and just sort of make my way out without being among people. So, I'm enjoying life now back again. It's not 100 percent, but it is something that is satisfying." – Patient 7

Patients also spoke about their productivity and mobility which differed from patient to patient. For patient 2 and 3, productivity and mobility were quite low:

> "Barely able to do things around the house. I can't wash dishes and sweep. I can't get out of the tub if I have a bath. I can't use a knife or scissors. I can't go up the stairs. I could cook, but with help." – Patient 2

> "On the days that I'm sick, I have to take those days off, a few days. There's been a couple of days when I got sick in my car while I'm working. So not great. I deliver food, so I'm in the car quite a bit. So, in making my deliveries, I have to stop, get sick, and then keep going again." – Patient 3

Patients 4 and 5 found their productivity levels to be unchanged from past treatments and they were able to get some things done.

> "Not different. I still have energy to help around the house. I stay in my chair watching TV." – Patient 4

> "It's about the same. I'm a little bit more tired sometimes. But it's not that bad." – Patient 5

A few patients found that their energy levels had changed for the better and they were able to get things done more often and easily.

> "I'm starting to have a bit more energy and starting to be a bit more active. I can cook and do some dishes. Light housekeeping." – Patient 1

> "If I didn't have to visit the oncology department, I would have a hard time to believe that I am as sick as I am, because knock wood, I do feel very good. […] I'm back doing things around the house because I don't go out a lot of course. And we have a home office here. So, I try not to go into it too deep. I don't want to tire myself out. But as far

> as around the house, I'm back to [doing] things all of the time. People are a little more cautious of me than I am of myself. They don't want me to overwork myself. But I enjoy getting up and moving around and I can do that again. So, it's great therapy for me. Very positive." – Patient 7

Patient 6 was especially grateful for the increase in productivity and energy levels afforded to her from the treatment. She's gained her sense of independence since being on Enhertu, walking 5KM, shovelling snow, driving 600KM, and resuming her daily activities. Her energy levels have been so impactful that she started socializing again and those around her are noticing the positive difference.

> "One thing I don't get right now is shortness of breath. I have energy that I can't explain. It seems I'm back to my old self before. I just don't want to push it too much. It's not 100 percent, but I'm getting there. My mind is more clear compared to the previous treatments I have. I know someone who explained that chemo will affect your mental capacity. But I'm okay. I can navigate the city. I can drive myself. And I can do much of the shopping, going to the stores. Previously I could only do a little of this. That's why at my next appointment I'm going to ask my doctor to put me back to work. I think I am adapting to Enhertu very well." – Patient 6

In terms of the impact that access to Enhertu had on their family, Patient 1 spoke about needing to rely on her family for getting to appointments and getting help around the house when she first began treatment, while the other patients were about to manage fairly well independently. For patient 4, Enhertu meant the "ability to be here with the family" and for patient 5, it also meant getting time to spend with her family.

> "It means I get to watch my babies grow up a little bit longer." – Patient 5

The hope that the effectiveness brought to patient 7 and her family could not be overstated.

> "As far as myself and our son are concerned, the drug Enhertu has given us a whole lot of positive outlook that a few short months ago we didn't seem to have. [She] was in a wheelchair because of the progression of the cancer. In terms of [her] and I, we have been married for 41 years, so it's pretty damn good and we're really thankful to be where we are at this point. And I have to attribute that to the Enhertu drug. There's just nothing else that I can see that made such a dramatic change in [her]. And she's been going through this since last September, a year from September past, I should say. Yeah, it's been very positive, and it has made us positive and has given us an outlook that we can take every day and be thankful. – Patient 7's husband

Patients also all positively spoke about what being able to access Enhertu mean to them personally.

> "It could possibly save my life. It's a big deal for me. I just hope it works for me." – Patient 1

> "It's important to me because it's keeping me alive. So, a chance at more life. More longevity." – Patient 2

> "Pretty much everything at this point." – Patient 3 "Everything. Extension of life." – Patient 4

> "Everything. We're so grateful that this was attainable. I can't even put it into words. I'm very grateful and to have the success up to this point, I can't even explain it." – Patient 7

For many of the patients that we interviewed, while they did not discuss experiencing financial challenges accessing Enhertu, they had access to Enhertu through some sort of financial assistance. Patient 1 mentioned that she "joined the patient assistance program" through the drug manufacturer. Patient 2 mentioned being approved for "approved for compassionate care". While patient 3 did not experience any financial challenges, she spoke about not knowing how she would have accessed Enhertu, had it not been financed through "private donations".

> "If it wasn't for that, there would be no way. I'm not in a position to buy the drug. I don't know what the cost is but I'm sure it's more than I can afford. I'm not in a good financial position." – Patient 3

Patient 4 did express having financial challenges and that she had to "put a request for compassion funding". Patient 5 was not sure how her access was financed but she stated that had she had to pay out-of-pocket, she "definitely wouldn't have been able to pay for it." Similarly, patient 6 is not sure how she is accessing this treatment, whether through her private insurance of the drug manufacturer, and is not sure she could afford the treatment.

> "I'm on disability and I can't afford the drug. And they told me they will give it to me." – Patient 6

As the other patients, patient 7 is also not financially able to access the treatment if she were to have to pay-out-of-pocket.

> "The doctor asked what our position was financially. We are self-employed. And the past two years with COVID we have been without employment. We've been surviving on our savings. And we don't have private insurance. He reached out to the company and a gentleman […] called. He asked us our position. 'Do we have private insurance?' I said, 'No, we don't'. And they supplied it to the doctor." – Patient 7's husband

Overall, Enhertu meant a great deal to the patients that we interviewed, and they were grateful to be able to access a treatment that showed promising results.

> "I think it's a good treatment. It's been good for me so far. I would really recommend it." – Patient 2

> "It's a life-saving drug and it's given me the chance to be here with the family again. I'm very grateful for being on it. Makes me happy. And I'm hoping to be on it for a long time. I'm grateful to be on it and to tolerate it well and to be here with the family. It's like a saviour drug to me and the family. So, I'm very grateful to be on it." – Patient 3

> "I just hope that for as many people as possible they make it accessible. Especially at my stage. But it makes a difference in the world." – Patient 7

Companion Diagnostic Test

Not applicable

Anything Else?

Not applicable

Conflict of Interest Declaration — Canadian Breast Cancer Network

Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

CBCN did connect with the manufacturer, AstraZeneca, to identify clinicians that could connect us with patients with experience on the treatment.

All other research, interviews and outreach to patients was conducted independently by the Canadian Breast Cancer Network, as was the compilation of information and data for the writing of this submission.

As a member of the Canadian Cancer Action Network, the Canadian Breast Cancer Network is committed to adhering to the Code of Conduct Governing Corporate Funding.

Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

No. The Canadian Breast Cancer Network compiled and wrote this submission independently.

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Table 2: Financial Disclosure for the Canadian Breast Cancer Network

	Check Appropriate Dollar Range			
Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Astra Zeneca Canada	—	—	—	X

Rethink Breast Cancer

About Rethink Breast Cancer

Rethink Breast Cancer (Rethink) is a Canadian charity known for making positive change. Rethink educates, empowers and advocates for system changes to improve the experience and outcomes of those with breast cancer, focusing on historically underserved groups: people diagnosed at a younger age, those with metastatic breast cancer and people systemically marginalized due to race, income or other factors. We foster spaces to connect, listen, empower, and rethink breast cancer, together. Rethink's strategic priorities and organizational direction are guided by the unique, unmet needs identified by breast cancer patients and their families.

Programs and Activities:

- Rethink Breast Cancer builds community, bringing patients with all stages of breast cancer together through our private and public social spaces as well as in-person events
- Rethink runs patient retreats and facilitates peer-support
- Rethink creates and runs education forums and conferences
- Rethink creates support and education tools, resources and content
- Rethink funds and supports breast cancer research

You can find out more by visiting: Rethink Breast Cancer Instagram and Rethink Breast Cancer Website

Information Gathering

For over 20 years, Rethink has been working closely with breast cancer patients in Canada. We learn from and listen to the community to understand their values, priorities and pain points to help drive change and system improvements. We learn from the 40 individuals that we work extremely closely with as key patient advisors; the 100 patients that share their stories on our blog; the 500 patients that participate in our virtual support groups; the 1,600 members of our private peer-support network; the 30,000 people that have joined our Instagram community; and the 150,000 individuals reached each month through that channel. We listen, learn, engage and have conversations in all these spaces.

Rethink Breast Cancer has several important patient advisory boards and working groups that offer experience-focused insights on issues related to those affected by and concerned about breast cancer, including:

- Metastatic Breast Cancer Advisory Board
- Early Breast Cancer Advisory Board
- Equity, Diversity and Inclusion working group
- Triple Negative Breast Cancer working group (all stages).

Rethink also benefits from regular knowledge exchange with our Scientific Advisory Committee, which includes some of the leading clinician scientists in Canada who treat breast cancer.

For this submission, we have drawn on our general observations and insights regarding the experience of metastatic HER2 positive breast cancer patients gathered through programming and meetings as described above. Rethink has a long history of developing resources for the HER2 positive breast cancer community, including producing an award-winning documentary About Her screened at film festivals along with a television broadcast on W Network. Our information gathering for this survey includes focused conversations with our Metastatic Breast Cancer Advisory Board, which includes three HER2 positive members. Rethink also conducted email interviews this March with three patients who have experience with Enhertu through AstraZeneca's patient support program. Finally, we have revisited written correspondence from fall 2020 with a patient involved in our organization who was desperately asking Rethink to collaborate on advocacy to make Enhertu available faster in Canada. Our hearts went out to her but knowing where Enhertu was in the HTA progress, we knew that effective advocacy options did not exist. She decided to go the Go Fund Me route and hoped to raise enough to travel across the border in the height of a global pandemic to pay for treatment with Enhertu in Buffalo, NY.

Disease Experience

Most people in the Rethink community are diagnosed at a younger age. When young people get breast cancer it may be more aggressive, which can lead to tougher treatments. In addition, those diagnosed in their 20s, 30s and early 40s face age-specific issues such as fertility or family-planning challenges, diagnosis during pregnancy, childcare, impact on relationships, body image, dating and sexuality, feeling isolated from peers who don't have cancer, career hiatuses, and financial insecurity. The physical and emotional toll that a breast cancer diagnosis and treatment takes on a young person's life is devastating and traumatic.

Of all breast cancers diagnosed in Canada, up to 15% will have a subtype known as HER2 positive breast cancer that is a more aggressive form, often occurring in young people, and has a high risk of recurrence or presentation as Stage IV at diagnosis. While anti-HER2 treatments in the early setting means fewer people are relapsing, there are still many in our community with recurrent HER2 positive metastatic breast cancer or de novo HER2 positive metastatic disease who need treatment. This stage of disease is not curable, and the median life expectancy following a diagnosis of metastatic HER2 positive breast cancer is 5 years once metastases have been diagnosed.

Processing this reality of a life-limiting diagnosis is extremely difficult, especially for the young patients in our community and the emotional impacts on quality of life cannot be understated. Moreover, many develop brain metastatis, which is difficult to treat and has a heavy symptom burden with both physical impacts and often changes in mood, personality and thinking. These cognitive and psychosocial challenges negatively impact both the patients and their caregivers who often have to take on an overwhelming number of responsibilities. Other symptoms of advanced HER2 positive metastatic breast cancer depend on the sites of the metastasis and include fatigue, shortness of breath for lung metastatis, pain and bone fractures for bone mets as well as nausea, headache and of course challenges doing normal daily activity. Our MBC Advisory Board strongly believes in the benefit of metastatic patients accessing palliative/supportive care services early to help address these symptoms.

Experiences With Currently Available Treatments

Metastatic HER2 positive breast cancer is usually treated with pertuzumab, trastuzumab and a taxane. One of the patients we interviewed who recently started Enhertu received her metastatic diagnosis in 2016. At that time, treatment started with having her ovaries removed and taking letrazole. Her tumors reduced and were stable for around 3 years. With progression in 2019, she received Perjeta and Herceptin, then Herceptin, then Kadcyla. She had this to say about the regimen of treatments she received from the time of her initial MBC diagnosis in 2016 to having progression in 2021:

> "I was able to improve and be stable for a good time and have received one chemo and two immunotherapies in this time. I was very scared because the very advanced stage of the mets, but fortunately they stayed in the lungs and have not gone anywhere else so far. Chemo treatments are very scary, and I was very nervous about how much I would not been able to do for my family because of treatment. The first chemo was ok, no big side effects apart from thinning of the hair, I think all the work to stay strong paid, I kept being me despite the chemo. Inmunotherapies were easy on me." –Mary F.

Improved Outcomes

Each individual patient brings their own personal values and goals to their discussions with their oncology team. Communication and trust in their team is essential. It's important that patients have a clear understanding of trade-offs and are well prepared for common side-effects of a given treatment. One of the patients we interviewed who was on Enhertu did not know hair loss was a factor with Enhertu until treatment was underway. While she expressed that the trade-off to shrink the tumour is worth it, she would have coped better with that side effect had she been prepared and could have explored cold capping to try and minimize hair loss.

In our experience working closely with many young metastatic breast cancer patients, we find most are willing to trade toxicity to control their cancer. In other words, they will

choose to endure additional side-effects and impacts on quality of life from the toxicity of a stronger therapy to ensure they are doing everything they can to treat what they know is an aggressive form of breast cancer. Rachel M., a patient in our community who was raising funds to pay out of pocket to access Enhertu in Buffalo in 2020 had this to say at that time regarding trade-offs:

> "I've learned that there is no 'worst'. There is no 'nothing left'. I used to think that when I would start needing oxygen tanks carted around with me or attached to me 24/7 in my home that it would be the worst. It's not, since it allows me to keep breathing and living.
>
> I thought that when I heard the words, "it has metastasized to your brain", it would be game over. It wasn't. It isn't. I had two spots in my brain this time last year that we resolved with a special radiation. I thought when I heard the words, 'you have three to six months and there's only a few drug options available that have a 10% chance', that I would just curl into a ball and pray I heard wrong. I didn't. I took those words, one year ago. The meds I decided to take that had a 10% efficacy rate were working. The lung disease is heavily burdensome, and I now have about fifty per cent of both lungs covered in tumors. We are buying time. There are also tumors in my lymph nodes, liver and spine, all of which are small, asymptomatic and don't require radiation.
>
> I have continued to live a pretty normal life. As my mantra goes, I'm the healthiest I can be. I'm not that girl with cancer even though my face and body have started to betray me due to some medication I am forced to take in order to help me breathe. While depressing to watch at first, I now say that I don't care what I look like, just keep me here, Lord. Every night, I give thanks for making it through, pray to wake up in the morning, and ask so humbly, for another day.
>
> So long as I can move and get around, I will wash Marin's hair in the bath, I will help prepare meals, I will make 60 jars of jam."

Experience With Drug Under Review

Rethink conducted email interviews in March 2022 with three patients with metastatic HER2 positive breast cancer who have experience with Enhertu. All three expressed gratitude that they had access through a patient support program.

Patient 1: Mary F.

> I am 48 years old, was diagnosed at 38 with stage 2b, P+, E+ and Her2- (I think it was kind of border line). There was no lymph nodes involved and further testing determined that my risk for recurrence was low so I went with lumpectomy and radiotherapy only. At 42 my lung mets were discovered, I don't think my doctors were very optimistic, but they did not say so. With lots of patient, a great healthcare team and God's help I was able to improve and be stable for a good time and have received one chemo and two immunotherapies in this time. When December 2021 brought news of some met advance my doctor recommended Enhertu. He has mentioned before that he was excited about this new treatment.
>
> The diagnosis of MBC gave my life a due date, it became very real. I was super afraid since my kids aged 9 and 13 at that time still needed time with me. I have had 4 treatments of Enhertu so far, apart some Nausea, which was stronger the first 2 treatments and some fatique, I have had no side effects. I keep working full time, today I went to my dance class

4 hours after finished my Enhertu infusion! I read the latest data on Enhertu and I am very optimistic that I will live long enough to try the new big thing coming to help me live with cancer as we do with other chronic diseases. I am looking forward to seeing my daughter graduate from High School and son from college. I believe Enhertu will help me get there!

I was very scared to not be able to access this med. Was not sure if insurance would cover it, and for sure did not have the resources for paying for it. I hope that Canada starts paying for it very soon.

This medication side effects have been very mild to none. It is probably too early to say, but I think the benefits will greatly surpass the negative side effects. I would definitely say you should try. The mechanism of action is very smart, making sure the medication enters where it should enter.

Patient 2: Liz B

I have had breast cancer for about 7 years. I had one beast removed, followed by chemo and radiation. A few years later it had metastasized to my liver. That was a very difficult moment. That led to a new round of chemo with all the dreadful side effects. About a year later I had a lesion in my hip bone which was successfully radiated and a year later a lesion in my brain again successfully radiated (cyber knife). Each time there is the dreadful progression, the chemo is changed. Before Enhertu I was on a trial drug for about a year before I had 'progression'. The Ontario Health System has given me outstanding treatment, for which I am very, very, thankful.

I have only been on Enhertu for a short time. I have yet to have tests to evaluate the effectiveness of the drug for me. I am very grateful to the company for providing me with the drug and I am obviously hopeful it works for me. I will know better in the coming weeks/ months. My oncologist has a lot of faith in this drug, so I have my fingers crossed that it is as good as he thinks it is.

Patient 3: Debbie B

I was diagnosed in 2016 and I'm 66 years old.

I started out with surgery on my breast, just the tumor removal. Then another surgery about a month later, on my auxillary lymph nodes. The cancer metastasized and spread into my brain, liver and again into my left breast and lymph nodes. I had a tumor removal surgery on my brain in 2017. Since then, I have been on various different chemos, blockers and radiation as the cancer has now spread to my spine as well.

I wanted to try Enhertu because my Oncologist Dr. had read and heard about it and she felt it might be a good fit for me. I had heard nothing about it myself, but she had and told me it had a good success rate in the trials. So, I decided to try it. There was a lack of communication and some problems though between the Enhertu booking dept., which resulted in a delay of 6 weeks. At that time, I could feel my left breast increased and hardened by quite a bit as well as, a tumor in my left arm pit also grew.

Since being on the treatment, which I take every 3 weeks now, the tumors have definitely decreased. I am waiting to find out from my Dr. as to how much, but I can see and feel, they have gone down by quite a bit. So, the drug does seem to be working. The side effects are terrible though. I did not know when I started it would cause me to lose my hair

again, and I am unfortunately losing it. Also, approximately a week after each treatment I am really sick. I didn't expect this for the first dosage, and I was vomiting several times a day for around three days. Even had to go to the hospital. Since that time, I have been working with my Dr. who has prescribed a few different anti-nausea medications, so I am prepared. They are working. Another terrible side effect during that time is Fatigue. I find it is very, very hard to do anything. I end up, basically in bed for a few days. Unable to work or do anything. My Dr. has since decreased my dosage. The first treatment didn't seem to make much of a difference, but I just had another treatment and the fatigue this time was definitely there, but not as severe.

I would recommend the Enhertu to other patients. Especially because I can see and feel the shrinking in a couple of my tumors and without the drug, they had increased quite a bit. So, I am able to see it is working. I would definitely let the other patients know about the bad side effects though.

I do feel all patients should have access from the Gov. to this treatment. I feel very fortunate to be able to try it and would hope the same for anybody in my situation. It would be absolutely impossible for me to have access through my own finances, and I can't imagine there are too many people who could afford it themselves. Which is so unfair already.

Companion Diagnostic Test

Nothing to report on this topic.

Anything Else?

As we ponder "anything else," we think about the MBC community that we know so well—and their loved ones. We think about those we've lost and those who are running out of options. We also think about the MBC community that we see currently thriving. We want more Canadians with HER2 positive metastatic breast cancer to have the opportunity to thrive for longer by having access to the most effective treatment as a second line option. It's hard to re-read Rachel M.'s emails, knowing that she'd run out of time to benefit from Enhertu. Rachel was diagnosed with Stage 1 HER2 positive breast cancer in 2013, when she was eight months pregnant. She became metastatic in 2017 and got involved in our education and advocacy campaigns. Unfortunately, she progressed and in late 2020, out of options in Canada, she and her husband travelled to Roswell Park in Buffalo, NY to line up treatment with Enhertu. They were raising funds to pay for it, but she died before reaching her fundraising goal. A young mom gone too soon. But that's the unmet need. And that's why two members of our MBC Advisory Board currently on their first line of treatment are advocating hard for Enhertu – they want a second line treatment that gives them, and others like then, the best possible outcome. Suzanne has young kids and was diagnosed de novo; Margaret, diagnosed with MBC early in pregnancy, has a toddler. These women need treatments that will keep their cancer stable for as long as possible. The stakes are incredibly high.

We ask a few more minutes of your time to read their stories, which are included as Appendix B.

Conflict of Interest Declaration — Rethink Breast Cancer

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for

participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

No.

Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

No.

List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 3: Financial Disclosures for Rethink Breast Cancer

	Check Appropriate Dollar Range			
Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
AstraZeneca 2022	–	–	–	X
AstraZeneca 2021	–	–	–	X

Testimonials of the Unmet Need

I am currently 42 (43 in May). I was diagnosed at 40 with Stage 1 Triple Positive breast cancer while pregnant but before I could start chemotherapy, it was discovered that the cancer was already well metastisized to my bones. I am 3+ her2 positive based on the initial biopsy. I live in Toronto with my husband and 2-year-old daughter. I was working on getting a regulatory affairs certification when diagnosed. I currently work part time as a tutor at a private girls school teaching math and science.

After my lump was diagnosed as cancer, I had the lumpectomy, and this was followed by A/C chemo (4 rounds) and after my daughter was born, I was able to finally get on targeted treatment (Herceptin + Perjeta) and hormone blocking treatment. In terms of health, I would say that so far after the diagnosis my health has very slowly been improving with the current treatment. This means that my pain slowly disappeared and other side effects are slowly being dealt with (thanks to the palliative care team).

Enhertu has been on my radar from the very beginning of my diagnosis. From what I know from different MBC groups, this is a very effective treatment for many patients. Many patients share that this treatment has allowed them to be NED or NEAD. Even though so far, my treatment has been working, I feel much more confident about my health knowing that at least there is an effective line of treatment coming up. I am most interested in the effectiveness of Enhertu to work in her2 low patients. I am very anxious about the cancer changing to less her2+ which happens quite often. I understand that there are some more potential side effects with Enhertu (diarrhea, etc) but this is something I already deal with in my current treatment. Patients on Enhertu really describe it as miracle drug and I would definitely like to have access to effective treatment the same as in the US. I also mentally am not prepared for weekly chemo which will absolutely destroy my QoL.

I think if how it stands now, my next line of treatment would be TDM1 (Kadcyla) but this doesn't have much success for many patients (OS improvement is short). After TDM1, normally Enhertu is given (in the US). This is very real looming anxiety for all MBC patients. And this is only two lines away. Knowing that Kadcyla isn't so effective especially after long Herceptin use, the next line really comes up quick. If this isn't covered, I would definitely figure out a way to get this paid for as this would be my best chance at an effective response.

I think Enhertu should be funded because it is proven to be an extremely effective treatment for her2+ and even for her2 low patients and currently there isn't anything else on the market other than very harsh chemotherapies that extremely reduce the quality of life for MBC patients.

MBC is a difficult diagnosis to receive and a difficult disease to live with. The uncertainty of whether or not your treatment will work, what the side effects may be and what your quality of life is all cause a great amount of anxiety for the patient and the patient's family. Fortunately, Margaret has responded well to targeted therapy which has allowed us to have precious time together as a family with her quality of life being reasonably good (all things considered). The biggest worry is the dreaded moment that we have progression and the disease no longer responds to the current line of therapy. The unknowns here are terrifying.

Enhertu is such an important treatment option for HER2+ MBC patients as other therapies (such as TDM1) are not as effective and non-targeted therapies have a very negative impact on quality of life (and survival). I am a member of an Enhertu clinical trial group on Facebook. The experiences of the women in this group are dramatic. Most of the women have had 2nd and 3rd line treatments fail, have had recurrence and have exhausted other targeted treatment modalities. For these women Enhertu is one of the final options to effectively stave off progression of their disease. Enhertu for the most part seems to be well tolerated (as well tolerated as treatment can be) and the response from treatment for the most part seems incredible (tumor reductions, total regression, etc.). I think if you were to ask the women on Enhertu in this group they would all agree that the treatment has been a life saver. If Enhertu is not funded by the government, we would try to pay out-of-pocket or travel to the US to participate in a clinical trial. Not all women would be in a position to do this - making government funding all the more important. We would not be able to sustain out-of-pocket costs for long, as the treatment is expensive ($10k+ per month) - but what is the value of a life? It would be a significant hardship, but we would have to try and make it work. It is imperative that the government fund this treatment NOW. Enhertu is a life-extending drug for HER2+ MBC patients who have had other lines of treatment fail. It is highly effective and allows women to have a reasonable quality of life while on treatment; it literally keeps HER2+ MBC patients alive and there is no other treatment like it. HER2+ MBC patients need more FUNDED tools to manage their disease and Enhertu is one of the gold standards of late-line treatment.

I was diagnosed in December 2016 with HER2+ metastatic breast cancer de novo at 47. I live in Toronto, Ontario and worked for 20+ years as an educator and administrator in the public-school board.

A diagnosis with MBC means living with cancer for the rest of my life. There is a constant worry that the current treatment I am on will stop working one day. As an MBC patient every treatment line is vital for my survival. The goal is to stay on whatever treatment that

works for as long as possible. Enhertu is another possible lifeline of treatment for me. I have heard that many in the US have had success with it. I would like it to be a part of my future treatment plan when I need it. I would also like further drug support for all of us living with Her2+ MBC. We are the group currently dying from cancer. If this treatment can prolong my life, then I want it. I want to see my children grow and live the best life that I can. While I understand that everyone reacts to treatment differently, another chance to live with a good quality of life is important to me. I want to be given the chance to try Enhertu and hopefully live as long and as well as possible with my family and friends. I will continue to advocate for myself and others. People with Her2+ metastatic breast cancer deserve more. I can safely say that most Canadians, including myself, want to support those with cancer.

As we learn how to treat cancer better, we also need to support that need for all Canadians. Safe and good treatments should be available to all who are eligible regardless of age, gender, race and socioeconomic status.

Rob and I travelled to Roswell Park 2 weeks ago to learn about it and I wrote about it in my blog and go fund me page. The drug is called Enhertu. The cost for me as a Canadian is $26,000 per infusion with a minimum of 3 if not 6 infusions to gather any meaningful response results. I'm not sure if we will entertain the total of over $300,000 (no way really my god, I could by a house), but maybe just 3 and see how that works. We are taking it day by day on that front with a great go fund me campaign and will cross the Buffalo bridge (literally) when it's right.

In the meantime, I am starting some radiation for some side effects I am finally starting to feel with my breathing, as the lungs are the pesky buggers (along with 11 spots in the brain that I just had Gamma Knife radiation on in October. They were almost undetectable so I'm hopeful there. It wiped the two I had in the brain last year so everyone feels this will be the same.

Tucatinib worked for about six months for me. Shrunk the lung tumours and bought more time. Then we switched when we saw resistance and I've been going down the lines ever since. One year ago exactly, Dr. B. gave me 3-6 months and I said well that's not going to happen and what other drugs are there? There were only 3 he suggested and had a 10% chance of working. I chose an old treatment of oral chemo call Cyclophosphamide and Methotrexate. That has worked until my last scans in late Aug where things showed some growth and some stability. We opted to stay on these meds while he told me about Enhertu and Roswell. So off on that mission, we went. The doctors there are supportive of my candidacy for the drug and were ready to start that day (of course when you're a golden egg of CDN cash).

Now I am doing some radiation on my spine thinking some small tumours are pressing on the nerves of the airway that's causing pressure and side effects in my chest and back. I've been asymptomatic for so long that this is all new for me. My breathing started getting tougher in May, hence starting the Dexamethasone and gaining 50 lbs.

I will also switch to a new chemo that is by infusion called Carboplatin that I have not had before. Combined with Herceptin again which I will be paying for although the wonderful insurance liaisons have been wonderful with finding compassionate programs or working through my insurance to help with the costs at the private clinic).

We are going to keep fundraising for Enhertu - it's going overwhelmingly well so far. I want to be the first person on the list the second Health Canada approves Enhertu and we can start the bridging program.

Tell me what I can do now or in the near future to stay as close to this as possible. I will do anything you suggest as will my family and network.

Clinician Input

Medical Oncologists From The Ottawa Hospital Cancer Centre and Across Canada

About Medical Oncologists From The Ottawa Hospital Cancer Centre and Across Canada

We are medical oncologists treating breast cancer at the Ottawa Hospital Cancer Centre, Cross Cancer Institute (Edmonton), London Health Science Centre, Sault Area Hospital (Sault Ste Marie ON), St Joseph's Health Centre (Toronto), Tom Baker Cancer Centre (Calgary), Dalhousie University Halifax NS, Memorial University St John's NL.

Information Gathering

Ongoing review of emerging data relevant to this file, including from ASCO, ESMO, and SABCS conferences in 2021, and the associated publication of the Destiny Breast 03 data. Local and regional consensus meetings/rounds and shared input into this submission's content.

Current Treatments and Treatment Goals

Current Canadian treatment paradigm: Patients with metastatic or locoregionally advanced unresectable metastatic Her2+ breast cancer are treated:

- In the first line, previously untreated setting: dual Her2 antibody treatment with trastuzumab and pertuzumab together with chemotherapy (usually a taxane, weekly paclitaxel or q3wk docetaxel) until intolerance, disease progression or, sometimes, sustained complete remission
- If previous (neo)/adjuvant systemic therapy (including a taxane and trastuzumab) received over 6 months prior, a similar approach as in (1) unless there are persistent toxicities from previous treatment that may be limiting
- Upon disease progression post (1) or (2), next line systemic therapy is offered with trastuzumab-emtansine (T-DM1, Kadcyla™). Subsequent lines of therapy, it is widely agreed, should include a Her2 targeting agent with another systemic therapy agent (chemotherapy drug or endocrine agent if ER positive). Examples: capecitabine/tucatinib/trastuzumab (Her2 Climb protocol), capecitabine/lapatinib, capecitabine/neratinib, trastuzumab/endocrine combinations (aromatase inhibitor, fulvestrant). See attached guideline.
- If previous (neo)/adjuvant systemic therapy (including a taxane and trastuzumab) received within 6 months prior, then first line treatment for metastatic relapse would jump to trastuzumab-emtansine (T-DM1, Kadcyla™), as per the Health Canada approved indication, followed by subsequent options as in (3).
- For any line, participation in relevant and applicable clinical trials is always considered.

- Treatment goals: The most important goals of treatment would include: improved overall survival; maintained or improved quality of life compared with currently available treatments; delay of progression of cancer, improvement or maintenance of organ function (eg. liver, bone, lungs); and reduction of cancer symptoms.

Treatment Gaps (Unmet Needs)

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

Overall response and duration of response to currently available therapies after taxane/trastuzuamb/pertuzumab are disappointing. Patients are quick to develop treatment resistance. There is greater propensity for Her2+ patients to develop visceral crises and/or brain metastases in pretreated patients. While trastuzuamb-emtansine has demonstrated benefits in, the improvements beyond pertuzumab/trastuzumab/chemo combinations are modest (the original trastuzumab-emtansine data was based largely on 2nd line use in patients who had not had pertuzumab previously, which is now standard of care) and long term survival remains quite poor. There is no defined optimal standard of care after past exposure to trastuzumab-emtansine.

Place in Therapy

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

Trastuzumab-deruxtecan would replace trastuzumab-emtansine, filling it's previous niche, as per the requested indication and as supported by the Destiny Breast 03 trial. It would be offered in a second line setting, post taxane/trastuzumab/pertuzumab, or as a first line treatment for patients developing metastatic disease within 6 months of completion of adjuvant/neoadjuvant taxane/trastuzumab based therapy with curative intent. It would not complement or be added to other treatment simultaneously. It would address the underlying disease, not just symptoms, and meaningfully improve survival outcomes. The impressive response rates would be reasonably expected to translate to more effective symptom relief. When viewed not only in isolation, but in the context of multiple lines of therapy proven to benefit survival, it will further improve the chance for long (sometimes years) term survival.

This would imply a major shift in our current treatment paradigm. Based on the Destiny Breast 03, barring contraindications it would not be reasonable to offer other treatments before trastuzumab-deruxtecan in the requested setting.

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

Patients most likely to respond: Her2+ metastatic or locoregionally advanced/unresectable disease patients, with Her positivity as defined by accepted ASCO-CAP criteria. This would not differ based on disease symptoms, distribution of disease or other disease characteristics (ER status, for example). Eligible patients would be identified based on evidence of metastatic progression (clinical findings, radiographic investigations) and demonstration of Her2 positivity would be required, based on archival tissue or on repeat biopsy of metastatic disease (only where felt appropriate by the clinician).

Patients with severe underlying lung disease, especially underlying interstitial lung disease, depending on the expected risk:benefit profile, might not be candidates for trastuzumab-deruxtecan given the possibility of pulmonary toxicity (ILD, pneumonitis). As is the case for

many cancer drugs with risks of specific toxicities, however, this would not be an absolute contraindication since clinicians have become adept at toxicity monitoring and early interventions/ drug cessation where needed and as informed by the product monograph.

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

Responses are determined based on symptoms, laboratory markers, and radiographic scans and tumour measurements, with scans usually performed at least every 3 months initially. Treatment is continued if disease is either stable or responding by RECIST criteria radiographically. Clinically meaningful responses would be suggested by:

Reduction in the frequency or severity of symptoms (e.g., pain, dyspnea, etc.); Improvement of organ function (bone, liver, lung); Stabilization of symptoms; Maintenance or improvement of performance status; Tumour radiographic response with either stabilization of disease or response by RECIST criteria.

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

Disease progression; Intolerable or dangerous toxicity, esp uncontrolled grade 3-4 rash or diarrhea or grade 2-4 pneumonitis; Patient preference or refusal

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

Hospital setting or specialty clinic that has expertise and staffing (chemotherapy nurses, oncology pharmacists) to administer chemotherapy and monitor / manage treatment-related toxicities

Additional Information

The benefits seen in the DESTINY BREAST 03 study are meaningful and practice changing. The overall survival results are particularly striking when compared to TDM-1, the relevant comparator in the trial and current Canadian standard of care. At the time of data cutoff for the interim analysis, the survival difference did not meet the pre-specified cutoff for significance ($p<0.000265$) but the hazard ratio for death was 0.55. A total of 33 of the 261 patients (12.6%) in the trastuzumab deruxtecan group and 53 of the 263 patients (20.2%) in the trastuzumab emtansine group had died. The percentage of patients who were alive at 12 months was 94.1% (95% CI, 90.3 to 96.4) with trastuzumab deruxtecan and 85.9% (95% CI, 80.9 to 89.7) with trastuzumab emtansine.

Access to Trastuzumab-Deruxtecan for Canadian patients is critical due to current limitation in access to other meaningful Her2- based therapies in many provinces and territories. The survival outcomes in the DESTINY BREAST 03 trial are unprecedented in this patient population with prior Her2-based therapy in the adjuvant and 1st-line metastatic disease setting. The documented benefits are commensurate with patient values and the toxicities are predictable and manageable by medical oncologists and their care teams.'

Conflict of Interest Declarations — Medical Oncologists From The Ottawa Hospital Cancer Centre and Across Canada

Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

No

Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

No

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Declaration for Clinician 1

Name: Dr Sandeep Sehdev, MD FRCPC

Position: Medical Oncologist, Assistant Professor, The Ottawa Hospital Cancer Centre, lead of breast cancer disease site group

Date: April 12, 2022

Table 4: Conflict of Interest Declaration for Medical Oncologists from The Ottawa Hospital Cancer Centre and Across Canada — Clinician 1

Company	Check Appropriate Dollar Range			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
AstraZeneca	—	X	—	—

Declaration for Clinician 2

Name: Dr Silvana Spadafora

Position: Regional Lead for Systemic Therapy for North East, Ontario Health, Medical Oncology, Algoma District Cancer Program (Sault Ste Marie)

Date: April 12, 2022

Table 5: Conflict of Interest Declaration for Medical Oncologists from The Ottawa Hospital Cancer Centre and Across Canada — Clinician 2

Company	Check Appropriate Dollar Range			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Pfizer, Merck, Novartis, Gilead, Bayer, AstraZeneca, Lilly	X each	—	—	—

Declaration for Clinician 3

Name: Dr Dorothy Lo

Position: Medical Oncologist, St Joseph's Health Centre, Toronto ON. Lead, COMET (Community Oncologists of Metropolitan Toronto)

Date: April 12, 2022

Table 6: Conflict of Interest Declaration for Medical Oncologists from The Ottawa Hospital Cancer Centre and Across Canada — Clinician 3

Company	Check Appropriate Dollar Range			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
AstraZeneca	X	–	–	–

Declaration for Clinician 4

Name: Dr Jan-Willem Henning

Position: Medical Oncologist, Breast and Sarcoma Tumour Groups, Tom Baker Cancer Centre, Calgary AB, Cumming School of Medicine, U of Calgary. Medical Co-Lead, Sarcoma Tumour Group and Adolescent and Young Adult Southern Alberta Program, Alberta Health Services, Cancer Care Alberta

Date: April 12, 2022

Table 7: Conflict of Interest Declaration for Medical Oncologists from The Ottawa Hospital Cancer Centre and Across Canada — Clinician 4

Company	Check Appropriate Dollar Range			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Merck	X	–	–	–

Declaration for Clinician 5

Name: Dr Mark Clemons

Position: Medical Oncologist, Ottawa Hospital Cancer Centre, Professor U of Ottawa

Date: April 12, 2022

Table 8: Conflict of Interest Declaration for Medical Oncologists from The Ottawa Hospital Cancer Centre and Across Canada — Clinician 5

Company	Check Appropriate Dollar Range			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
No COI	–	–	–	–

Declaration for Clinician 6

Name: Dr Anil Joy

Position: Medical Oncologist, Cross Cancer Institute, Edmonton AB. Professor, U of Alberta. Previous consultant for Medical Council of Canada, grant reviewer for Cdn Breast Cancer

Foundation and NCIC (National Cancer Institute of Canada). Medical Director (Edmonton) of Alberta Cancer Research Biobank.

Date: April 12, 2022

Table 9: Conflict of Interest Declaration for Medical Oncologists from The Ottawa Hospital Cancer Centre and Across Canada — Clinician 6

Company	Check appropriate dollar range			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Merck	X	—	—	—

Declaration for Clinician 7

Name: Dr Jawaid Younus

Position: Medical Oncologist, London Regional Cancer Centre, London ON. Assistant Prof, Western University.

Date: April 12, 2022

Table 10: Conflict of Interest Declaration for Medical Oncologists from The Ottawa Hospital Cancer Centre and Across Canada — Clinician 7

Company	Check appropriate dollar range			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
AstraZeneca	X	—	—	—

Declaration for Clinician 8

Name: Dr Amirrtha Srikanthan

Position: Medical Oncologist, Ottawa Hospital Cancer Centre, Assistant Professor U of Ottawa

Date: April 12, 2022

Table 11: Conflict of Interest Declaration for Medical Oncologists from The Ottawa Hospital Cancer Centre and Across Canada — Clinician 8

Company	Check appropriate dollar range			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
No COI	—	—	—	—

Declaration for Clinician 9

Name: Dr Amy Groom, MD, FRCPC

Position: Medical Oncologist, Saint John Regional Hospital, Assistant Professor of Medicine Dalhousie University, Assistant Professor of Medicine, Memorial University

Date: April 12, 2022

Table 12: Conflict of Interest Declaration for Medical Oncologists from The Ottawa Hospital Cancer Centre and Across Canada — Clinician 9

Company	Check appropriate dollar range			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
AstraZeneca	X	—	—	—

Declaration for Clinician 10

Name: Dr Terry Ng, MD FRCPC

Position: Assistant Professor, U of Ottawa, Medical Oncologist (Ottawa Hospital Cancer Centre)

Date: April 12, 2022

Table 13: Conflict of Interest Declaration for Medical Oncologists from The Ottawa Hospital Cancer Centre and Across Canada — Clinician 10

Company	Check appropriate dollar range			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Knight	X	—	—	—
Novartis	X	—	—	—
ARIAD/Takeda	X	—	—	—
Boehringer-Ingelheim	X	—	—	—

Declaration for Clinician 11

Name: Dr Daniel Rayson

Position: Medical Oncologist, Professor of Medicine, Dalhousie University

Date: April 12, 2022

Table 14: Conflict of Interest Declaration for Medical Oncologists from The Ottawa Hospital Cancer Centre and Across Canada — Clinician 11

Company	Check appropriate dollar range			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
AstraZeneca	X	—	—	—

Declaration for Clinician 12

Name: Dr Marie-France Savard, MD FRCPC

Position: Assistant Professor, U of Ottawa, Medical Oncologist (Ottawa Hospital Cancer Centre)

Date: April 12, 2022

Table 15: Conflict of Interest Declaration for Medical Oncologists from The Ottawa Hospital Cancer Centre and Across Canada — Clinician 12

Company	Check appropriate dollar range			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
AstraZeneca	X	—	—	—

Declaration for Clinician 13

Name: Dr Moira Rushton-Marovac, MD FRCPC, Investigator, Canadian Cancer Trials Group

Position: Assistant Professor, U of Ottawa, Medical Oncologist (Ottawa Hospital Cancer Centre). Senior investigator, Canadian Cancer Trials Group

Date: April 12, 2022

Table 16: Conflict of Interest Declaration for Medical Oncologists from The Ottawa Hospital Cancer Centre and Across Canada — Clinician 13

Company	Check appropriate dollar range			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
No COI	—	—	—	—

Ontario Health-Cancer Care Ontario Breast Cancer Drug Advisory Committee

About Ontario Health-Cancer Care Ontario Breast Cancer Drug Advisory Committee

OH-CCO's Drug Advisory Committees provide timely evidence-based clinical and health system guidance on drug- related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs (PDRP) and the Systemic Treatment Program.

Information Gathering

Discussed jointly at a DAC meeting.

Current Treatments and Treatment Goals

Trastuzumab emtansine is the current standard treatment for patients with human epidermal growth factor receptor 2 (HER2)– positive metastatic breast cancer whose disease progresses after treatment with a combination of anti-HER2 anti-bodies and a taxane. The standard of practice is to continue HER2 directed therapy for these patients.

Treatment goals would be prolonged life and delayed disease progression, with acceptable toxicity.

Treatment Gaps (Unmet Needs)

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

HER2-targeted therapies are not curative for locally advanced or metastatic disease and most patients will have disease progression, especially patients that recur within 6 months after receiving adjuvant treatment.

Place in Therapy

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

The standard treatment for newly diagnosed HER2-positive metastatic breast cancer is pertuzumab and trastuzumab in combination with a taxane. For patients who progress, the standard second-line is trastuzumab emtansine. Trastuzumab deruxtecan would be an optimal option to trastuzumab emtansine. The HER2-positive metastatic breast pathway supports a third line option (tucatinib, trastuzumab, capecitabine) after progression on TDM-1 and we expect third line options to be maintained for patients after trastuzumab deruxtecan.

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

Patients with HER2–positive metastatic breast cancer whose disease progresses after treatment with a combination of anti-HER2 anti-bodies and a taxane would be best suited for treatment.

Patients least suitable would align with the exclusion criteria of the clinical trial (ie, patients who have higher risk of interstitial lung disease/pneumonitis event and patients with poor performance status).

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

Clinical and radiographic response as per standard of care.

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

Disease progression, toxicity or patient preference.

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

Clinician with experience in treating breast cancer in an outpatient setting. The DAC is concerned about the risk on pneumonitis and the intensity of monitoring that was part of the study protocol. The clinician should have access to specialty services in the case of ILD.

Additional Information

We strongly believe that patients who failed TDM-1 should have access to trastuzumab deruxtecan.

Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation.

Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the Procedures for CADTH Drug Reimbursement Reviews (section 6.3) for further details.

Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

OH-CCO provided secretariat support to the DAC in completing this input.

Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

No

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.

Declaration for Clinician 1

Name: Dr. Andrea Eisen

Position: OH-CCO Breast Cancer Drug Advisory Lead

Date: 8/4/2022

Table 17: Conflict of Interest Declaration for Ontario Health-Cancer Care Ontario Breast Cancer Drug Advisory Committee — Clinician 1

	Check appropriate dollar range			
Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
No COI	—	—	—	—

Declaration for Clinician 2

Name: Dr. Orit Freedman

Position: OH-CCO Breast Cancer Drug Advisory Committee Member

Date: 8/4/2022

Table 18: Conflict of Interest Declaration for Ontario Health-Cancer Care Ontario Breast Cancer Drug Advisory Committee — Clinician 2

	Check appropriate dollar range			
Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
No COI	—	—	—	—

Declaration for Clinician 3

Name: Dr. Phillip Blanchette

Position: OH-CCO Breast Cancer Drug Advisory Committee Member

Date: 8/4/2022

Table 19: Conflict of Interest Declaration for Ontario Health-Cancer Care Ontario Breast Cancer Drug Advisory Committee — Clinician 3

	Check appropriate dollar range			
Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
No COI	–	–	–	–

Rethink Breast Cancer Scientific Advisory Committee

About Rethink Breast Cancer Scientific Advisory Committee

This submission is from a group of medical oncologists from across Canada who are also voluntary members of the Scientific Advisory Committee to Rethink Breast Cancer, a leading national breast cancer organization. The oncologists who contributed have extensive experience treating persons with breast cancer, including those with advanced HER2 positive breast cancer as well as experience with new drug development and approvals. We voluntarily wished to advocate for metastatic HER2 positive breast cancer.

Information Gathering

The information in this document has been gathered from scientific papers and studies of the treatment of HER2 positive breast cancer, which has been a very well documented area of oncology since the 1990s. The data described and summarized is from international, phase III randomized clinical trials and meta-analyses, which represents the highest and strongest level of evidence possible. In addition, the information summarized also represents the real world first-hand experience of the medical oncologists who have contributed to this document and who have treated thousands of persons with this disease. Finally, the patient voice has been an important and valued source of information as Rethink Breast Cancer has significant experience with hearing from and working with young women with HER2 positive breast cancer.

Current Treatments and Treatment Goals

The subject that we are discussing is HER2 positive advanced breast cancer (ABC) which is also known as Stage IV breast cancer or metastatic breast cancer. All these terms are interchangeable. Approximately 15% of newly diagnosed breast cancers overexpress the HER2 gene, which leads to a more aggressive cancer with a higher rate of stage IV disease at diagnosis. It also has a higher incidence in younger patients where effective therapies,, which provide prolongation of good quality survival are very important.

Since the advent of antiHER2 treatments in the early setting the number of persons relapsing has decreased but there are still a large number of persons with either recurrent HER2 positive ABC or de novo disease who need treatment. Treatment for this cancer has been more successful than some other types of breast cancer such as triple negative breast cancer but it remains an incurable disease with a life expectancy of a median of 5

years once metastases have been diagnosed. As well, over 50% of persons with HER2 ABC develop central nervous system (CNS) metastases that are difficult to treat, often causing a markedly shorter survival and often associated with devastating symptoms. The goals of treatments are to decrease the bulk of the disease with the hopes of relieving symptoms and prolonging survival.

First line treatment for HER2 positive ABC is usually with pertuzumab, trastuzumab and a taxane which are all given intravenously every three weeks or occasionally with weekly taxane. This regimen (known as the CLEOPATRA regimen) was reported to show both a benefit in progression free survival (PFS) and overall survival (OS) and has activity. However, only 18% of the patients in this trial had prior exposure to trastuzumab and none had prior pertuzumab. With the use of trastuzumab (and occasionally pertuzumab) in the neo 'and adjuvant settings the response with this regimen is less, as shown by data including population data from Alberta.

Second line treatment has been with T-DM1, which was shown to be more effective than a prior regimen of lapatinib /capecitabine in the EMILIA trial. Although this is an active regimen, contemporary use of adjuvant T-DM1 (approved recently by Health Canada and CADTH) affects the efficacy of this second line therapy.

Third line and beyond therapies have not been funded in the past in Canada despite good evidence that continued antiHER2 therapy was of benefit. Traditionally either non HER2 related chemotherapy was used or antiHER2 therapy was given in provinces with funding or for those patients who could self-fund. The regimens included lapatinib /capecitabine, trastuzumab/vinorelbine, or trastuzumab/capecitabine. Recently there has been impressive survival data including for patients with active brain metastases with tucatinib/trastuzumab and capecitabine and this regimen is considered third line therapy particularly as the study included patients with contemporary treatment including exposure to trastuzumab, pertuzumab and T-DM1.

Other agents that are also considered include neratinib plus capecitabine which has activity but considerable toxicity with diarrhea but this is not funded in Canada. As well, symptom management with supportive medications is important.

The symptoms of advanced HER2 positive cancers depend on the sites of metastases. Common sites include the brain, lungs, liver, bones as well as nodes and other areas such as intrabdominal. The symptoms are commonly fatigue, shortness of breath, pain, fracture of bones, nausea, headache, vomiting and difficulty doing normal activities. Without treatment, these symptoms cause significant decline in overall quality of life, and are challenging to palliate often requiring additional complex local therapies.

The goals of treatment are to improve symptoms and restore good quality of life as much as possible with the ultimate goal of prolonging good quality survival. The most important characteristics of a treatment include efficacy in terms of tumour response, minimal toxicity with good tolerance of the treatment, and ideally a convenient schedule for the patient. As responding patients may be on the effective therapy for a long time, manageable toxicity is an important factor as well as convenience.

Treatment Gaps (Unmet Needs)

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

The current treatments are all palliative, not curative and patients develop progressive disease and ultimately die of their HER2 positive ABC. The cancers become refractory to the treatments over time, so having more options and more effective options is important. Many of the treatments that we use for HER2 positive ABC at this time were developed before we had the current adjuvant treatments for early disease. Therefore the results achieved with these regimens cannot be assumed to be as efficacious for our current patient population. Prior exposure to drugs often causes resistance. Indeed, population studies that involve our contemporary patients report inferior outcomes than the initial studies. We need treatments that are both more effective and well tolerated. Schedules that do not involve frequent visits, long infusions or complicated polypharmacy are more convenient for the patient and improve compliance.

Place in Therapy

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

The efficacy of T-DXd has surprised everyone. The results of the studies are far superior to any other anti HER2 drug especially in the context of the comparison with an active drug, and not a placebo. The first studies with T-DXd in the later lines of therapy demonstrated an impressive 60% response rate. The randomized study, DESTINY 03, that compared T-DXd to T-DM1 were significant as T-DM1 is currently our standard of care in this setting and as the patients in the trial generally had been exposed to prior active therapies. The PFS with a hazard ratio (HR) of 0.28 was remarkable. The 12-month PFS of 75% for T-DXd compared to 34% for the T-DM1 was very impressive. The Forest Plot showed that all subgroups significantly benefited from the new agent. Although OS at 12 months was 94.1% for TDX-d compared to 85.9% for T-DM1 with a HR of 0.58. Although the p value did not cross the prespecified level for significance it is early, these patients live for some years and we are waiting for further follow-up. There were many more responses with TDXd with a complete response (CR), partial response (PR) and stable (SD) rate of 96.6% vs 76. 8% for T-DM1. In this trial, 99% of patients had received prior trastuzumab and over 60% had prior exposure to pertuzumab. Despite this pretreatment, the drug was very effective suggesting that the mechanism of action can overcome resistance to other drugs. These results clearly show that it is more effective than our current treatment with T-DM1 and it would replace this drug as second line therapy. With this activity, there may also be a role in first line therapy for persons with an early relapse, that is within 12 months of adjuvant therapy as these persons are often very refractory to treatment. This would be especially important in persons exposed to pertuzumab, trastuzumab and potentially T-DM1 in the early setting. The level of activity seen with TDX-d suggests that it should supplant TDM1 in advanced HER2 positive breast cancer.

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

All patients with biopsy proven, HER2 positive ABC, as determined either at their initial diagnosis or with a biopsy of the advanced disease would be potentially eligible and most in need for an intervention. With a drug showing this level of activity the rate of progressive disease would be lower and those events would occur later. With control of systemic disease, brain metastases would occur less frequently. Furthermore, in the trial, those patients with a history of established brain metastases had an equal response to TDX-d.

Patients best suited for therapy will be identified by their treating medical oncologist as these patients are all in the care of oncology clinics. The diagnosis of HER2 advanced cancer is very

straightforward with well validated pathology testing. There is unlikely to be a misdiagnosis with the quality control of our laboratories and with good diagnostic imaging. The patients who are most likely to exhibit a response would be like those in the DESTINY03 trial, i.e. persons with advanced HER2 positive cancer, with a good performance status. Over 70% of the patients had visceral disease, similar to the patients in we see in our clinics. Both estrogen positive and estrogen negative cancers responded to the treatment. (NEJM 2022; 386: 1143-1154.)

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

In clinical practice the most important outcome to follow is a decrease in the symptoms related to the disease. That is if the person has symptomatic lung metastases, a decrease cough and/or shortness of breath. If they have bone involvement, an improvement in pain and avoidance of complications such as pathological fractures. As well as improvement of symptoms, patients with advanced cancer have regular physical examinations to assess response. The most important follow-up however is diagnostic imaging with CT, MRI, ultrasounds or PET scans, which are done at regular intervals to assess the amount of cancer and the response to therapy. These are standardly done with all metastatic breast cancer and are very important especially in the first few months of therapy to assess the efficacy of the treatment.

An improvement in the scans is usually associated with an improvement in PFS and ultimately in OS but these outcomes can usually only be measured over time and the first indications of a successful treatment are the improvement of symptoms and burden of metastatic disease by examination and imaging. Blood parameters, and in particular improvement in liver enzymes if they were elevated, initially can also be assessed.

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

The most common reason to discontinue a drug is lack of efficacy. Eventually the treatment no longer controls the growth of the cancer because it develops resistance to the drug. Another reason to discontinue the drug is toxicity. With TDX-d the most worrisome toxicity is interstitial lung disease (ILD) which is a serious but relatively uncommon. Although 10.5% of persons had ILD only 7.8% had to stop the TDX-d because of this particular complication. Overall, 13.6% of persons in the DESTINY03 trial did stop the drug compared to 7.3% of persons on T-DM1. Finally in clinical care some persons choose to stop therapy for personal reasons, but this is rare if the treatment is effective.

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

The treatment should be given under the care of a medical oncologist who is experienced in the treatment of cancer and can assess both response and toxicity. The medical oncologist should know what to look for in terms of toxicity and do careful assessments to ensure the best care of the patient. In Canada we are fortunate that our cancer care is centralized so that the care of patients is generally in specialized clinics where appropriate precautions are done.

Additional Information

Many patients with HER2 positive advanced breast cancer are young and the opitimal treatments improve their outcomes, enable them to live longer with good quality of life, and allow them to be around for their families. This drug has significant activity and has been shown in a scientifically sound trial to be more effective than our standard therapy. This drug should be available to persons in Canada with advanced HER2 positive cancer to provide optimal care.

Conflict of Interest Declarations — Rethink Breast Cancer Scientific Advisory Committee

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation.

Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the Procedures for CADTH Drug Reimbursement Reviews (section 6.3) for further details.

Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

We did not receive outside help.

Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

We did not receive outside help.

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.

Declaration for Clinician 1

Name: Karen A Gelmon

Position: Professor of Medicine, UBC

Date: 13-04-2022

Table 20: Conflict of Interest Declaration for Rethink Breast Cancer Scientific Advisory Committee — Clinician 1

Company	Check appropriate dollar range			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
AstraZeneca	–	X	–	–
Seagen	X	–	–	–
Roche	X	–	–	–
Pfizer	–	X	–	–
Novartis	–	X	–	–
Lilly	X	–	–	–
Merck	–	X	–	–
Gilead	X	–	–	–
Ayala	–	X	–	–

Declaration for Clinician 2

Name: Christine Brezden- Masley

Position: Associate Professor U of T, Medical Director Cancer Program Sinai Health

Date: 13-04-2022

Table 21: Conflict of Interest Declaration for Rethink Breast Cancer Scientific Advisory Committee — Clinician 2

Company	Check appropriate dollar range			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Amgen	X	–	–	–
Astrazeneca	–	–	X	–
Agendia	X	–	–	–
Bristol Myers	X	–	–	–
Eisai	X	–	–	–
Gilead	X	–	–	–
Knight	X	–	–	–
Merck	X	–	–	–
Pfizer	–	–	X	–
Novartis	–	–	X	–
Eli Lilly	X	–	–	–
Taiho	–	X	–	–
Myriad	X	–	–	–

Company	Check appropriate dollar range			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Mylan	X	–	–	–
Seagen	X	–	–	–
Sanofi	X	–	–	–

Declaration for Clinician 3

Name: Tamara Shenkier

Position: Clinical Professor, UBC

Date: 13-04-2022

Table 22: Conflict of Interest Declaration for Rethink Breast Cancer Scientific Advisory Committee — Clinician 3

Company	Check appropriate dollar range			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
No COI	–	–	–	–

Declaration for Clinician 4

Name: Christine Simmons

Position: Clinical Associate Professor

Date: 13-04-2022

Table 23: Conflict of Interest Declaration for Rethink Breast Cancer Scientific Advisory Committee — Clinician 4

Company	Check appropriate dollar range			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
AstaZeneca	X	–	–	–
Amgen	X	–	–	–
Pfizer	X	–	–	–
Novartis	X	–	–	–
Lilly	–	X	–	–
Knight	–	X	–	–
Merck	X	–	–	–
Roche	X	–	–	–
Mylan	X	–	–	–

Declaration for Clinician 5

Name: Stephen Chia

Position: Professor of Medicine, UBC

Date: 13-04-2022

Table 24: Conflict of Interest Declaration for Rethink Breast Cancer Scientific Advisory Committee — Clinician 5

Company	Check appropriate dollar range			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
AstraZeneca	—	X	—	—
Gilead	—	X	—	—
Novartis	—	X	—	—
Pfizer	—	X	—	—
Merck	X	—	—	—
Eli Lilly	X	—	—	—

Declaration for Clinician 6

Name: Caroline Lohrisch

Position: Clinical Professor of Medicine, UBC

Date: 13-04-2022

Table 25: Conflict of Interest Declaration for Rethink Breast Cancer Scientific Advisory Committee — Clinician 6

Company	Check appropriate dollar range			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
AstraZeneca	X	—	—	—
Pfizer	X	—	—	—
Veracyte	—	—	X	—
ALApharma Canada	X	—	—	—