Canada's Drug Agency
L'Agence des médicaments du Canada

Reimbursement Recommendation

Reimbursement Recommendation

(Draft)

Trastuzumab Deruxtecan (Enhertu)

Indication: As monotherapy, is indicated for the treatment of adult patients with unresectable, locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen

Sponsor: AstraZeneca Canada Inc.

Recommendation: Time-limited reimbursement
This recommendation is time-limited and contingent on a reassessment of additional evidence.

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Recommendation

The CDA-AMC pCODR Expert Review Committee (pERC) recommends that trastuzumab deruxtecan be reimbursed as monotherapy, for the second-line treatment of adult patients with unresectable, locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior anti-HER2-based regimen for a time-limited period while additional evidence is generated and only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from 1 phase II, single-arm, open-label trial (DESTINY-Gastric02, N = 79) demonstrated that treatment with trastuzumab deruxtecan may result in added clinical benefit for patients (≥ 18 years) who had unresectable or metastatic, centrally confirmed human epidermal growth factor receptor 2 (HER2)-positive gastric or GEJ cancer who have experienced disease progression during or after first line therapy with a trastuzumab-containing regimen. The confirmed objective response rate (ORR) per ICR, the primary efficacy endpoint of the DESTINY-Gastric02 trial, was 41.8% (95% CI, 30.8 to 53.4) with 5.1% of the patients having complete response (CR). Additionally, the DESTINY-Gastric02 trial showed that treatment with trastuzumab deruxtecan may result in a clinically meaningful improvement in overall survival (OS) and progression-free survival (PFS). After a median follow-up of 10.2 (range, 0.7 to 22.1) months, the median OS was 12.1 months (95% confidence interval [CI], 9.4 to 15.4); and the probability of being alive was 77.8% (95% CI, 66.8 to 85.6) at 6 months, 50.6% (95% CI, 38.4 to 61.5) at 12 months, and 35.1% (95% CI, 22.1 to 48.4) at 18 months. The median PFS per independent central review (ICR) was 5.6 months (95% CI, 4.2 to 8.3); and the probability of being progression-free was 48.9% (95% CI, 36.6 to 60.2) at 6 months and 20.0% (95% CI, 9.4 to 33.3) at 12 months. In the sponsor submitted indirect treatment comparisons (ITC), the treatment effect estimates for OS and PFS favoured trastuzumab deruxtecan over all other comparators (i.e., ramucirumab plus paclitaxel, paclitaxel, FOLFIRI, irinotecan, and docetaxel); however, the ITC evidence was associated with high uncertainty due to several limitations in the design and methods (e.g., heterogeneity in study design, statistical analyses, geographical regions, and ethnicity distribution across studies included in the evidence network).

Patients identified a need for new treatments with equitable access that can prolong survival, control cancer symptoms, reduce risk of recurrence, improve quality of life, and have an acceptable toxicity profile. Based on the evidence reviewed, pERC concluded that trastuzumab deruxtecan met some of these needs as it provides an alternative treatment option with potential to improve OS and PFS.

Using the sponsor submitted price for trastuzumab deruxtecan and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for trastuzumab deruxtecan is $242,356 per quality-adjusted life-year (QALY) gained compared with ramucirumab plus paclitaxel. These results are largely based on a survival benefit of 0.41 life-years; the magnitude of benefit associated with trastuzumab deruxtecan is highly uncertain. A price reduction is required for trastuzumab deruxtecan to be considered cost-effective at a $50,000 per QALY gained threshold. As the comparative clinical evidence is highly uncertain and there is a negotiated price for ramucirumab, a higher price reduction may be required to achieve cost-effectiveness at the aforementioned threshold.

pERC noted that Health Canada has mandated the sponsor complete the ongoing DESTINY-Gastric04 phase III, randomized open-label study and confirm that trastuzumab deruxtecan improves the OS of patients with HER2-positive metastatic or unresectable Gastric or GEJ adenocarcinoma who have progressed on or after a trastuzumab-containing regimen, compared to ramucirumab plus paclitaxel. Given the considerable uncertainty in the magnitude of clinical benefit and cost-effectiveness, pERC recommends time-limited reimbursement of trastuzumab deruxtecan, with a reassessment of the comparative efficacy and cost-effectiveness when the results of the phase III DESTINY-Gastric04 trial are available from the sponsor. pERC noted that this approach would help facilitate equitable and timely access to promising treatments for patients while ensuring that treatments considered for public reimbursement adhere to a level of rigour that sufficiently demonstrates effectiveness, safety, and cost-effectiveness. The time-limited reimbursement strategy allows the integration of future clinical trial evidence to help shape stronger health policy and drug funding decisions where longer-term follow-up data are required. The sponsor has confirmed that the DESTINY-Gastric04 trial results will be filed with CDA-AMC in accordance with the timelines and requirements for a reassessment as described in the Procedures for Time-Limited Reimbursement Recommendations (September 2023 version).

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Trastuzumab deruxtecan should be initiated as second line treatment for patients who have all of the following: 1.1. 18 years of age or older 1.2. unresectable, locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma 1.3. received a prior trastuzumab -based regimen in the first line treatment setting 1.4. good performance status	Evidence from the DESTINY-Gastric02 trial demonstrated that trastuzumab deruxtecan has a clinical benefit in patients (≥ 18 years) who had unresectable or metastatic, centrally confirmed HER2-positive gastric or GEJ cancer who have experienced disease progression during or after first line therapy with a trastuzumab-containing regimen. The DESTINY-Gastric02 trial included patients with an ECOG PS of 0 or 1.	HER2-positive was defined as IHC 3+ or IHC 2+ followed by ISH+ in the DESTINY-Gastric02 trial. pERC agreed with the clinical experts that selected patients with an ECOG PS more than 1 may be treated at the discretion of the treating physician.
2. Patients must not have any of the following: 2.1. symptomatic spinal cord compression 2.2. clinically active CNS metastases 2.3. current ILD or pneumonitis	The CDA-AMC review did not include any evidence to demonstrate the benefit of trastuzumab deruxtecan in patients with symptomatic spinal cord compression, active CNS metastases, or current ILD or pneumonitis as these patients were excluded from the DESTINY-Gastric02 trial.	—
Discontinuation		
3. Treatment with trastuzumab deruxtecan should be discontinued upon the occurrence of any of the following: 3.1. objective disease progression 3.2. unacceptable toxicity	In the DESTINY-Gastric02 trial, treatment with trastuzumab deruxtecan continued until disease progression (per RECIST V1.1), unacceptable toxicity, withdrawal of consent, physician decision, or death, whichever occurred first.	—
Prescribing		
4. Trastuzumab deruxtecan should only be prescribed by clinicians with experience and expertise in treating gastric or GEJ adenocarcinoma.	This condition ensures that trastuzumab deruxtecan is prescribed only for appropriate patients, and that adverse effects are managed in an optimized and timely manner.	—
5. Trastuzumab deruxtecan should not be reimbursed in combination with other anticancer drugs.	Trastuzumab deruxtecan was administered as monotherapy in the DESTINY-Gastric02 trial. No evidence on the safety and potential benefits of combining trastuzumab deruxtecan with any other treatments was included in this CDA-AMC review.	—
Pricing		
6. A reduction in price	The ICER for trastuzumab deruxtecan is $242,356 per QALY gained when compared with ramucirumab plus paclitaxel. This is based on a survival benefit which is associated with uncertainty.	—

Reimbursement condition	Reason	Implementation guidance
	A price reduction of 31% would be required for trastuzumab deruxtecan to achieve an ICER of $50,000 per QALY compared to ramucirumab plus paclitaxel.	
Time-limited reimbursement		
7. A recommendation in favour of reimbursement is time-limited and contingent on a future reassessment of additional evidence that addresses the uncertainty.	Uncertainty in current phase II evidence must be adequately addressed in the upcoming confirmatory phase III, DESTINY-Gastric04 randomized trial. Specifically, evidence from the DESTINY-Gastric04 trial needs to ascertain a clinically meaningful survival benefit of trastuzumab deruxtecan relative to the comparator treatment as well as present an acceptable safety profile.	The sponsor has stated that the primary completion of the DESTINY-Gastric04 trial is estimated to occur in the fourth quarter of 2025. The sponsor has confirmed that the phase III DESTINY-Gastric04 trial results will be filed with CDA-AMC in accordance with the timelines and requirements for a reassessment as described in the *CDA-AMC Procedures for Time-Limited Reimbursement Recommendations,* which require the reassessment to be filed with CDA-AMC no later than 270 calendar days after the completion date of the phase III trial. In accordance with CDA-AMC's procedures, the sponsor must keep CDA-AMC informed of any revisions to the anticipated timelines for the DESTINY-Gastric04 trial.

CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group Performance Status; GEJ = gastroesophageal junction; HER2 = human epidermal growth factor 2; ICER = incremental cost-effectiveness ratio; IHC = immunohistochemistry; ILD = interstitial lung disease; ISH = in situ hybridization; QALY = quality-adjusted life year; RECIST V1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1.

Discussion Points

- **Unmet needs:** pERC noted that HER2 overexpression in patients with gastric or GEJ adenocarcinomas may be associated with poorer outcomes and more aggressive disease. Aligned with the input from the patient group and clinicians, pERC acknowledges that there is an unmet need for effective and safe anti-HER2 therapy options in the second line treatment setting for the requested patient population. In line with the clinical experts' opinions, pERC considered that currently available evidence from the DESTINY-Gastric02 trial reasonably demonstrates the potential of trastuzumab deruxtecan in improving OS and PFS with clinical meaningfulness.
- **Certainty of evidence**: pERC noted that the certainty of evidence in the phase II DESTINY-Gastric02 trial was very low due to the absence of a comparator group. In the absence of direct evidence comparing trastuzumab deruxtecan to other treatments currently used in Canada in the second line treatment setting for patients with unresectable, locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma , pERC discussed the evidence from the sponsor submitted ITCs which consisted of an unanchored matching adjusted indirect comparison (MAIC) and a network meta-analysis (NMA)unanchored MAIC and a NMA and which compared trastuzumab deruxtecan to relevant comparators in the second line setting including ramucirumab plus paclitaxel, paclitaxel, FOLFIRI, irinotecan, and docetaxel. Although the ITC treatment effect estimates for OS and PFS favoured trastuzumab deruxtecan over all other comparators, pERC noted that that the ITCs were associated with several major limitations in the design and methods that precluded any definitive conclusion about the magnitude of effect against other comparators. pERC concluded that a reassessment of comparative evidence from a

properly designed and executed phase III confirmatory clinical trial would be required to ascertain the existence of the benefits and to determine the magnitude of such benefits. pERC acknowledged that the sponsor is currently conducting a phase III DESTINY-Gastric04 trial with the aim to evaluate the efficacy and safety of trastuzumab deruxtecan relative to ramucirumab plus paclitaxel in the second line treatment setting for the patient population under review.

- **Side effects**: pERC discussed the safety profile of trastuzumab deruxtecan and noted that conclusions on the comparative safety profile of trastuzumab deruxtecan could not be drawn due to absence of formal statistical testing, potential for bias in an open-label trial, and the absence of harms outcomes in the submitted ITC. However, pERC agreed with the clinical experts consulted by CDA-AMC that trastuzumab deruxtecan associated lung toxicity – i.e., interstitial lung disease (ILD), is a key safety concern. However, the clinical experts noted that the incidence of ILD in the DESTINY-Gastric02 trial was consistent with the ILD rates reported in studies of trastuzumab deruxtecan in patients with breast cancer, the ILD events are typically of low grade (Grade 1 or 2), and that trastuzumab deruxtecan could be safely administered in a hospital or outpatient clinics specialized in the management of immunotherapy related side-effects, including ILD.
- **Health-related quality of life (HRQoL)**: pERC noted that patients and clinicians highlighted improvement in quality of life as an important outcome and treatment goal for patients with unresectable, locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma. No within-group improvement was observed in the Functional Assessment of Cancer Therapy-Gastric (FACT-Ga) total score, at the end of treatment, in the DESTINY-Gastric02 trial. pERC agreed with the clinical experts that this finding would be expected in the single arm trial as patients ended typically end trastuzumab deruxtecan treatment due to disease progression or intolerable side effects, which would negatively impact a patients' HRQoL. There were no HRQoL outcomes evaluated in the ITCs. Therefore, the comparative effect of trastuzumab deruxtecan on HRQoL versus other active treatments for second line treatment of patients with unresectable, locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinomas remains unknown.
- **Prior anti-HER2-based regimen**: pERC noted that the Health Canada indication (Notice of Compliance with Conditions [NOC/c]) is for adult patients with unresectable, locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma who have received a prior trastuzumab-based regimen, while the reimbursement request proposed by the sponsor is for the second line treatment of patients who have received any prior anti-HER2-based regimen. The clinical experts noted that trastuzumab-based regimen is currently the only authorized anti-HER2-based regimen that for the first line treatment of gastric or GEJ adenocarcinoma in Canada. However, a small number of patients may get access to other anti-HER2-based regimens through participation in clinical trials or special access programs. The clinical experts additionally noted that there may be a relatively small number of patients who are currently on second or later lines of therapy with available treatments and have not previously received trastuzumab deruxtecan. pERC agreed that these two groups of patients may be eligible to receive trastuzumab deruxtecan in third or subsequent lines of therapy, on a time limited basis, if they otherwise meet the eligibility criteria.
- **Economic evaluation**: pERC discussed the sponsor-submitted economic evaluation for trastuzumab deruxtecan and noted concerns with the sponsor's modelling approach, in addition to the limitations that were previously identified with the indirect comparative clinical effectiveness estimates. These concerns with the modelling approach, along with the uncertainty associated with the comparative clinical efficacy, subsequent treatments, and time to treatment discontinuation led to uncertainty associated with the incremental cost-effectiveness estimates of trastuzumab deruxtecan. pERC noted there is a negotiated price for ramucirumab, part of the key comparator regimen (ramucirumab plus paclitaxel) for trastuzumab deruxtecan. While CDA-AMC reported a 31% price reduction is required for trastuzumab deruxtecan to achieve an ICER of $50,000 per QALY gained, pERC noted that a higher price reduction may be required to achieve cost-effectiveness when taking into account these other factors. As commented earlier, pERC considered a time-limited recommendation for the use of trastuzumab deruxtecan in third line and later out of scope; no economic evidence provided for the third line and later setting.
- **Considerations for a time-limited reimbursement recommendation**: Based on the preliminary assessment by CDA-AMC, trastuzumab deruxtecan met the criteria to be considered by pERC for a time-limited reimbursement recommendation. In accordance with the Procedures for Time-Limited Reimbursement Recommendations(September 2023 version), pERC deliberated on the existing gaps in the evidence and the sponsor's evidence generation plans; and given the considerable uncertainty in the comparative clinical- and cost-effectiveness of trastuzumab deruxtecan versus relevant comparators, pERC concluded that a time-limited recommendation for trastuzumab deruxtecan would help facilitate equitable and timely access to promising treatments for patients while ensuring that treatments considered for public reimbursement meet rigorous standards of evidence-based decision-making. pERC noted, according to the information provided in the sponsor submission, primary completion of the ongoing confirmatory trial (DESTINY-Gastric04) is expected in the fourth quarter of 2025. Acknowledging that the current CDA-AMC Procedures for Time-Limited Reimbursement Recommendations (September 2023 version) allows for a reassessment request to be submitted within up within 270 calendar days after the

completion date of the phase III trial, pERC strongly encourages the sponsor to file for a reassessment as early as possible after the confirmatory DESTINY-Gastric04 trial are available to address existing uncertainties.

Background

Gastric cancer is the fifth most common cancer and the fifth leading cause of cancer mortality worldwide, with approximately 968,000 incident cases and 659,853 associated deaths in 2022 (equating to 6.8% of all cancer-related deaths). Gastric adenocarcinoma is the most common histological type of gastric cancer, accounting for over 95% of gastric cancer cases. In the clinical trials, patients with advanced gastroesophageal junction (GEJ) adenocarcinoma are often included alongside patients with advanced gastric adenocarcinoma because of the similarities in the tumour growth and patterns of disease spread between the two patient popualitons. In fact, GEJ adenocarcinoma and gastric adenocarcinoma have often been reviewed, investigated, or presented together in literature reviews, clinical trials, and clinical management guidelines. The projected incident rate of gastric cancer in Canada is 8.3 per 100,000 adults in 2024 with an estimated 1,400 cases in females and 2,600 cases in males. Signs and symptoms of gastric cancer include abdominal pain, heart burn, loss of appetite, bloating, nausea, vomiting, difficulty swallowing, blood in the stool, anemia, fatigue, ascites, and jaundice. The overall 5-year survival for all patients with gastric cancer is estimated to be 29% and patients with distant metastasis experience even worse outcomes, with an estimated 5-year relative survival rate of 7%. Compared to patients with gastric adenocarcinoma, patients with GEJ adenocarcinoma might have worse disease-specific survival with an approximately 10% higher cumulative incidence of recurrence.16 The prognostic role of human epidermal growth factor 2 (HER2) in gastric cancer remains controversial due to conflicting evidence. In a Canadian population, an estimated 21% of all gastric cancers and GEJ cancers showed HER2 positive. All patients with advanced or metastatic gastric cancer or GEJ cancer, including patients with both gastric and gastroesophageal adenocarcinomas, should undergo HER2 testing. HER2-positive is confirmed when the test results show immunohistochemistry (IHC) 3+ or IHC 2+ followed by in situ hybridization (ISH)+. HER2 testing may be repeated if there is a need for revaluation due to disease progression, or development of metastases.

According to the clinical experts consulted by the review team, most patients with locally advanced unresectable or metastatic HER2 positive gastric or GEJ cancers are treated with palliative intent, and the treatment goals of all therapies in this setting are to prolong overall survival and improve quality of life. The clinical experts consulted by the review team noted that the cornerstone of treatment for patients with locally advanced unresectable or metastatic HER2 positive gastric or GEJ cancers involves sequential use of the best available systemic therapies. In the first line treatment setting, the clinical experts consulted by the review team noted that the standard of care for patients with locally advanced or metastatic HER2 positive gastric or GEJ cancers and with a programmed death ligand 1 (PD-L1) combined positive score (CPS) < 1 includes a fluoropyrimidine/platinum doublet chemotherapy (e.g., FOLFOX, CAPOX, or cisplatin plus capecitabine) in combination with trastuzumab. In the second line treatment setting, according to the clinical experts consulted by the review team, the standard of care for locally advanced or metastatic HER2 positive gastric or GEJ cancers is treatment with ramucirumab plus paclitaxel, or ramucirumab alone. However, the clinical experts consulted by the review team noted that single agent ramucirumab is not reimbursed in many jurisdictions across Canada such as Ontario. The clinical experts consulted by the review team also noted that the second line treatment of HER2 positive gastric or GEJ cancers is identical to that of HER2 negative gastroesophageal at present. The sponsor noted that single agent chemotherapy options such as irinotecan, paclitaxel, or docetaxel have been suggested in guidelines for patients who are not eligible for ramucirumab plus paclitaxel.25,26 Furthermore, according to the sponsor, relevant guidelines also suggest the use a fluoropyrimidine/platinum combination, such as FOLFOX (fluorouracil + oxaliplatin + leucovorin) or CAPOX (capecitabine + oxaliplatin) for patients previously treated with FOLFIRI in the first line setting. In the third line setting, the clinical experts consulted by the review team noted that the treatment options for patients with locally advanced or metastatic HER2 positive gastric or GEJ cancers include trifluridine/tipiracil (i.e., TAS-102), nivolumab, and pembrolizumab.

Trastuzumab deruxtecan, as monotherapy, has received a NOC/c from Health Canada for the treatment of adult patients with unresectable, locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen. Trastuzumab deruxtecan is a HER2 targeted antibody drug conjugate. It is available as powder for concentrate for solution for infusion/100 mg/vial, and the dosage recommended in the product monograph is 6.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity for unresectable locally advanced or metastatic gastric and GEJ cancer.

Sources of Information Used by the Committee

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

- a review of 1 Phase II, single-arm, open-label study identified in systematic review (DESTINY-Gastric02) for patients (≥ 18 years) with unresectable or metastatic, centrally confirmed HER2-positive gastric or GEJ cancer who have experienced disease progression during or after first-line therapy with a trastuzumab-containing regimen; 1 indirect treatment comparison; and 1 Phase II, randomized controlled trial (DESTINY-Gastric01) included in the 'Other Evidence' section
- patients' perspectives gathered by 1 patient group, My Gut Feeling - Stomach Cancer Foundation of Canada
- 1 input from public drug plans that participate in the reimbursement review process
- 2 clinical specialists with expertise diagnosing and treating patients with gastric and GEJ cancer
- input from 2 clinician group(s), the Ontario Health (OH) Cancer Care Ontario (CCO) Gastrointestinal Cancer Drug Advisory Committee, the ad hoc group of adenocarcinoma-treating physicians and the Canadian Gastrointestinal Oncology Evidence Network (CGOEN)
- a review of the pharmacoeconomic model and report submitted by the sponsor

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

One input from My Gut Feeling - Stomach Cancer Foundation of Canada was received for this review. My Gut Feeling – Stomach Cancer Foundation of Canada is a non-profit organization in Canada, dedicated to providing support, awareness, education, information and advocacy to gastroesophageal cancer patients, survivors and caregivers. The patient group gathered information from thirty respondents (75% patients, 25% caregivers) via an online survey which was conducted in September 2024.

According to the patient group input, 95% of respondents felt that the cancer diagnosis had a significant impact on their quality of life, and cancer and its treatment affected their physical health, mental health, ability to eat, work, finances, social life, identity, psychosocial well-being, and personal image. Many respondents reported concerns over finances due to inability to work due to the diagnosis and/or treatment for cancer. Based on the input, patients and caregivers commented on the time and money spent for cancer treatment appointments, medications, driving and parking costs, and the costs of eating at the hospital as financial stressors.

The important outcomes reported by the respondents included quality of life, treatment side effects, cost of treatment, convenience of treatment, treatment access, duration of treatment and the survival benefits.

My Gut Feeling – Stomach Cancer Foundation of Canada stated that there is an unmet patient and caregiver need to receive equitable access to therapies that may prolong life, improve symptoms, reduce risk of recurrence and improve treatment tolerability; and noted that 4 respondents who had experience with traztuzumab deruxtecan were satisfied because traztuzumab deruxtecan had fewer side effects, was easier to tolerate, improved their quality of life, and better controlled cancer.

Clinician Input

Input From Clinical Experts Consulted for This Review

According to the clinical experts consulted by the review team, the goals for the treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma who have received a prior anti-HER2-based regimen are to prolong overall survival and improve quality of life. The clinical experts consulted by the review team noted that there was a considerable unmet need in terms of lacking effective anti-HER2 therapy beyond the first line treatment setting for patients with locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma.

According to the clinical experts consulted by the review team, following disease progression on first line HER-2 directed therapy, the current standard of care in the second line setting for patients with HER2 negative gastric or GEJ adenocarcinoma is treatment with either ramucirumab in combination with paclitaxel or ramucirumab alone. The clinical expects consulted by the review team noted that trastuzumab deruxtecan may cause a shift in the current treatment paradigm in adult patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma who have received a prior trastuzumab-based regimen, and all other current second line treatment regimens would shift to the third and subsequent lines.

According to the clinical expects consulted by the review team, aligned with the eligible participants in the sponsor submitted DESTINY-Gastric02 trial, the patients best suited for the treatment with trastuzumab deruxtecan in the second line treatment setting would be those who have all of the following conditions, including unresectable or metastatic gastric or GEJ cancer with progressive disease on or after first-line therapy with a trastuzumab-containing regimen, a HER2 positive gastric or GEJ cancer (defined as IHC 3+ or IHC 2+/ISH+) confirmed by a repeat biopsy, a preserved Eastern Cooperative Oncology Group Performance Status (ECOG PS), and a preserved cardiac ejection.

According to the clinical experts consulted by the review team, key factors to determine response to treatment included patient reported symptoms, side effects, or cross-sectional imaging (e.g. computed tomography [CT] scan and/or magnetic resonance imaging [MRI]).

According to the clinical experts consulted by the review team, patient reported symptoms, side-effects and the overall well-being of patients, in conjunction with assessment of treatment response, would be the major determinants for discontinuing treatment. In terms of toxicities, the clinical experts consulted by the review team noted that interstitial lung disease (ILD) is one of the most important AEs to be aware of.

According to the clinical experts consulted by the review team, trastuzumab deruxtecan should only be prescribed by or under the supervision of a specialist in medical oncology with expertise in the diagnosis and management of immunotherapy related side-effects, including ILD. The clinical experts consulted by the review team noted that trastuzumab deruxtecan could be safely administered in a hospital or an outpatient clinic.

Clinician Group Input

CDA-AMC received inputs from 2 clinician groups, the Ontario Health (OH) Cancer Care Ontario (CCO) Gastrointestinal Cancer Drug Advisory Committee, with contribution of 5 clinicians, and the ad hoc group of adenocarcinoma-treating physicians & the Canadian Gastrointestinal Oncology Evidence Network (CGOEN), with contribution of 15 clinicians.

According to the clinician groups, the goals of treatment include to improve symptoms, response rates, quality of life, and overall survival. Based on both clinician inputs there is a gap in treatment of patients with HER2+ mGC/GEJC where their disease progress after first-line standard therapy, and trastuzumab deruxtecan should be considered in the second line setting. CGOEN added that efficacy outcomes such as objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) along with safety and toxicity outcomes and quality of life are important to assess response to treatment. OH CCO believes that response to treatment should be assessed every 2 to 3 months.

According to the clinician inputs, factors to be considered to discontinue treatment would include disease progression and intolerance. Further, the outpatient setting under the care of a health care provider with training in oncology is appropriate for treatment.

Drug Program Input

The clinical experts consulted for the review provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions from the Drug Programs

Drug program implementation questions	Clinical expert response
Relevant comparators	
DESTINY-Gastric01 evaluated the safety and efficacy of trastuzumab deruxtecan versus physician choice (single agent irinotecan or paclitaxel) while DESTINY-Gastric02 was a single arm trial of trastuzumab deruxtecan. Funded comparators include ramucirumab-paclitaxel, FOLFIRI, irinotecan, paclitaxel. **Question:** How does trastuzumab deruxtecan compare against ramucirumab plus paclitaxel, FOLFIRI?	The sponsor submitted an ITC that aimed to determine the efficacy of trastuzumab deruxtecan relative to other second line treatments currently available in Canada, including ramucirumab plus paclitaxel, paclitaxel, FOLFIRI, irinotecan, and docetaxel. The ITC treatment effect estimates for OS and PFS favoured trastuzumab deruxtecan over all other comparators; however, pERC was unable to make any definitive conclusion about the magnitude of effect due to several major methodological limitations. PERC noted that the sponsor's upcoming confirmatory phase III, DESTINY-Gastric04 trial, That compares efficacy and safety of trastuzumab deruxtecan relative to the comparator treatment is expected to help address some of existing uncertainties.
Considerations for initiation of therapy	
The DESTINY-Gastric01 trial included patients who had progressed on or after at least 2 prior regimens which included a fluoropyrimidine, a platinum, and a (brand or approved biosimilar) trastuzumab-based regimen. The trastuzumab did not have to be the most recent regimen. The DESTINY-Gastric02 trial included patients who had progressive disease on or after a first line (brand or approved) biosimilar trastuzumab-containing regimen." In both trials, prior adjuvant therapy can be counted as a line of therapy if disease progression occurred on or within 6 months of completing adjuvant therapy. The manufacturer's submission is specific to the use of trastuzumab deruxtecan as a second line option only (after failure of a trastuzumab-based therapy). **Question**: Should trastuzumab deruxtecan be considered for third or subsequent lines?	According to the clinical experts consulted by the review team, if reimbursed, trastuzumab deruxtecan is expected to become the standard of care in the second line setting for patients with HER2 positive gastric and GEJ cancer, and trastuzumab deruxtecan will not be rechallenged in the third line and later settings when there is disease progression. However, the clinical experts consulted by the review team noted that for a small number of patients who are on currently available second line or later lines of therapy and have never received trastuzumab deruxtecan between present and the time when trastuzumab deruxtecan becomes available in the second line setting, trastuzumab deruxtecan can be used for these patients in third line and later settings. Patients who have experienced treatment failure on trastuzumab deruxtecan in previous lines of therapy should not be rechallenged. pERC agreed with the clinical experts.
Question: Should trastuzumab deruxtecan be considered for patients with advanced HER2 positive esophageal adenocarcinoma who have received prior anti-HER2 targeted therapy?	pERC agreed with the clinical experts consulted by the review team that any patient with esophageal, gastric, or GEJ adenocarcinoma whose tumour is HER2 positive should be eligible for trastuzumab deruxtecan if they otherwise meet the eligibility criteria outlined in this recommendation. The clinical experts noted that the classification of "esophageal" versus "GEJ" is somewhat arbitrary, and that there is no pre-clinical or clinical rationale to suggest that the biology of HER2 positive disease or the response to HER2-directed therapies differ based on whether the disease is in the esophagus proper or the GEJ. According to the clinical experts consulted by the review team, an estimated 20% of all esophageal cancers (based on clinical experience in Ontario) would consist of adenocarcinomas. The clinical experts additionally noted that the distribution of adenocarcinoma versus squamous cell carcinoma may differ between patient populations with different risk factors (e.g.

Drug program implementation questions	Clinical expert response
	patients with smoking and/or alcohol exposure are more likely to present with squamous cell carcinoma histology; patients with obesity, reflux, or metabolic syndrome are more likely to present with adenocarcinoma histology).
Considerations for discontinuation of therapy	
In DESTINY-Gastric01/02, patients were allowed to continue the study drug even if discontinuation criteria had been met provided that there is evidence of benefit (and after approval from the trial sponsor). **Question:** When should trastuzumab deruxtecan be discontinued?	pERC agreed with the clinical experts consulted by the review team that trastuzumab deruxtecan should be discontinued when there is disease progression or significant toxicity.
Considerations for prescribing of therapy	
The recommended dose for trastuzumab deruxtecan is 6.4mg/kg every 3 weeks, which is different from the starting dose for breast cancer (5.4mg/kg); caution is needed to ensure that the appropriate dosing is given.	This is a comment from the drug plans to inform pERC deliberations.
Generalizability	
Question: Are the following patients eligible for trastuzumab deruxtecan? • ECOG PS > 1 • Prior treatment with trastuzumab deruxtecan (e.g., for breast cancer)	ECOG PS > 1 – The DESTINY-Gastric02 trial included patients with an ECOG PS of 0 or 1. However, pERC agreed with the clinical experts that selected patients with an ECOG PS more than 1 could be considered for treatment at the discretion of the treating physician. Prior treatment with trastuzumab deruxtecan – According to the clinical experts consulted by the review team, the scenario in which patient has received trastuzumab deruxtecan for other types of cancer (e.g., breast cancer) and later developed gastric or GEJ cancer is very rare. pERC was unable to comment on the effectiveness of trastuzumab deruxtecan in this scenario, as it did not review any evidence that supported the use trastuzumab deruxtecan in patients who have a history of previously receiving this treatment for another cancer site. However, pERC agreed with the clinical experts that patients with HER2-positive advanced or metastatic gastric or GEJ adenocarcinoma who discontinue trastuzumab deruxtecan due to disease progression should not be rechallenged with this drug in subsequent lines of treatment.
Questions: • Should patients currently on another second line regimen be eligible to switch to trastuzumab deruxtecan? • Should patients on subsequent lines (after second line) be considered for trastuzumab deruxtecan?	pERC agreed with the clinical experts consulted by the review team that patients who are currently on other treatment regimens in the second or later lines of therapy, and have not previously been treated with trastuzumab deruxtecan, would be considered for treatment with trastuzumab deruxtecan, if they otherwise meet the eligibility criteria outlined in this recommendation. PERC also agreed with the clinical experts that patients who are currently on other treatment regimens in the second line of therapy would be considered, on a limited time basis, to switch to treatment with trastuzumab deruxtecan, especially if they experience serious adverse events on their current treatment in the second line.
Funding algorithm (oncology only)	
Request an initiation of a rapid provisional funding algorithm. Note that if the final reimbursement recommendation for this	This is a comment from the drug plans to inform pERC deliberations.

Drug program implementation questions	Clinical expert response
drug under review is “Do not Reimburse”, the project will be suspended indefinitely.	
Drug may change place in therapy of comparator drugs	This is a comment from the drug plans to inform pERC deliberations.
Drug may change place in therapy of drugs reimbursed in subsequent lines	This is a comment from the drug plans to inform pERC deliberations.
Question: For patients with HER2 positive disease, under what circumstances would trastuzumab deruxtecan be preferred over ramucirumab-paclitaxel and vice-versa? For patients who receive 2nd line trastuzumab deruxtecan, what therapies would be funded in subsequent lines?	According to the clinical experts consulted by the review team, once reimbursed, trastuzumab deruxtecan will likely become the standard of care in the second line setting for adult patients with HER2 positive gastric and GEJ adenocarcinoma. The clinical experts anticipated that all therapies currently being used in the second line setting would be moved to the third line and those currently in the third line to the fourth line, and so on, before considering trifluridine-tipiracil as the last resort. However, pERC noted that no evidence was included in this review to support comparative efficacy and safety of trastuzumab deruxtecan versus ramucirumab-paclitaxel in second line setting for patients with HER2 positive disease. pERC noted that the sponsor is currently conducting a phase III DESTINY-Gastric04 trial that is expected to answer this question. The committee was also unable to comment on the sequencing of the subsequent lines after trastuzumab deruxtecan and considered this issue out of the scope of this review. Nevertheless, pERC agreed with the clinical experts that patients who experience disease progression on trastuzumab deruxtecan in the second line should not be rechallenged with this drug in subsequent lines of treatment.
Care provision issues	
For dose reductions, the product monograph allows for a maximum of 2 dose reductions. Dose re-escalation after a dose reduction is not recommended.	This is a comment from the drug plans to inform pERC deliberations.
Question: Is re-testing of the tumour post trastuzumab progression needed to confirm HER2 positivity (IHC3+, IHC2+ and ISH+) in order to be eligible for trastuzumab deruxtecan?	According to the clinical experts consulted by the review team, a re-biopsy of the tumour post trastuzumab progression to confirm HER2 positivity is typically used to determine trastuzumab deruxtecan is the best available treatment option for a patient; However, re-testing should not be considered mandatory to determine eligibility for trastuzumab deruxtecan, especially when there is no safe and easily accessible site to biopsy. pERC agreed with the clinical experts.
System and economic issues	
A confidential negotiated price exists for ramucirumab.	This is a comment from the drug plans to inform pERC deliberations.

ECOG PS = Eastern Cooperative Oncology Group performance status; ESS = effective sample size; FOLFIRI = irinotecan plus leucovorin plus 5-fluorouracil; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; ISH = in-situ hybridization; ITC = indirect treatment comparison; MAIC = matching adjusted indirect comparison; NMA = network meta-analysis; OS = overall survival; PFS = profession-free survival.

Clinical Evidence

Description of Studies

One relevant sponsor conducted pivotal study, DESTINY-Gastric02 (N = 79), was included in the systematic review of this clinical report. The DESTINY-Gastric02 trial was a Phase II, single-arm, open-label study investigating the use of trastuzumab deruxtecan

as monotherapy for the treatment of patients (≥ 18 years) who had unresectable or metastatic, centrally confirmed HER2-positive gastric or GEJ cancer who have experienced disease progression during or after first-line therapy with a trastuzumab-containing regimen. Patients enrolled in the DESTINY-Gastric02 trial were from Europe and North America (no patients in Canada). The primary objective of the DESTINY-Gastric02 trial was to assess the efficacy of trastuzumab deruxtecan based on the confirmed ORR per independent central review (ICR) assessment (primary outcome). OS, PFS, health-related quality of life (HRQoL) outcomes (e.g., Functional Assessment of Cancer Therapy-Gastric [FACT-Ga]), and harms (e.g., ILD) were also assessed in the DESTINY-Gastric02 trial.

The median age of the DESTINY-Gastric02 trial population was 60.7 years (range, 20.3 to 77.8), with 58.5% of the patients being younger than 65 years. The majority of the trial population was male (72.2%), White (87.3%), with an ECOG PS of 1 (63.3%), with GEJ as the cancer location (65.8%), and having a HER2 status of IHC 3+ (86.1%). Almost all the patients (78 out of 79 patients) had a histological subtype of adenocarcinoma.

Efficacy Results

Results submitted by the sponsor were from 2 data cut-off dates, April 9, 2021, and November 8, 2021. The median duration of follow-up was 5.9 months (range: 0.7 to 15.4) as of the data cut-off date of April 9, 2021, and 10.2 months (range, 0.7 to 22.1) as of the data cut-off date of November 8, 2021.

OS

As of the data cut-off date of November 8, 2021, the proportion of patients in the full analysis set (FAS) who had OS events was 58.2%. The median OS was 12.1 months (95% confidence interval [CI], 9.4 to15.4). The probability of being alive was 77.8% (95% CI, 66.8 to 85.6) at 6 months, 50.6% (95% CI, 38.4 to 61.5) at 12 months, and 35.1% (95% CI, 22.1 to 48.4) at 18 months.

PFS per ICR assessment

As of November 8, 2021, the proportion of patients in the FAS who had PFS events as determined by PFS was 64.6%. The median PFS was 5.6 months (95% CI, 4.2 to 8.3). The probability of being progression-free was 70.5% (95% CI, 58.7 to 79.5) at 3 months, 48.9% (95% CI, 36.6 to 60.2) at 6 months, 36.3% (95% CI, 24.5 to 48.1) at 9 months, and 20.0% (95% CI, 9.4 to 33.3) at 12 months.

Confirmed ORR per ICR assessment

As of November 8, 2021, the proportion of patients in the FAS who achieved confirmed ORR per ICR assessment was 41.8% (95% CI, 30.8 to 53.4). There were 4 (5.1%) patients who achieved a best overall response of confirmed complete response (CR), and 29 (36.7%) who achieved confirmed partial response (PR). The results of subgroup analyses on ORR were generally consistent with the results in the FAS.

FACT-Ga total score

A higher FACT-Ga total score indicates a better outcome. As of the data cut-off date of April 9, 2021, the mean FACT-Ga total score at baseline was [redacted]). The mean FACT-Ga total score at the end of treatment was [redacted]), with a mean change of [redacted]).

Harms Results

Treatment emergent adverse events (TEAEs)

The most commonly reported TEAEs in the DESTINY-Gastric02 trial were nausea (67.1%), followed by fatigue (57.0%), vomiting (44.3%), and anemia (38.0%). The proportion of patients who had any TEAE of grade 3 and higher was 55.7%. The most commonly reported TEAE of grade 3 and higher was anemia (13.9%), followed by neutropenia (12.7%).

Treatment emergent serious adverse events (TESAEs)

The proportion of patients who had any TESAE was 41.8%. The most commonly reported TESAE was nausea (5.1%), followed by pneumonitis (3.8%) and vomiting (3.8%).

Treatment discontinuation due to TEAEs

The proportion of patients who discontinued trastuzumab deruxtecan was 19.0%. Discontinuation due to pneumonitis or ILD occurred in 7.6% and 2.5% of the trial population, respectively.

Mortality

As of the data cut-off date of November 8, 2021, the number of patients who had any TEAE associated with an outcome of death was 11 (13.9%), among whom 1 (1.3%) died due to ILD and 1 (1.3%) due to pneumonitis.

Notable Harms

As of the data cut-off date of November 8, 2021, the proportion of patients who had ILD was [redacted]%, and 10.5% of patients had a Grade 2 left ventricular (LV) dysfunction (defined as resting left ventricular ejection fraction [LVEF] from 50% to 40%; 10% to 19% LVEF decrease from baseline). As of the data cut-off date of April 9, 2021, the proportion of patients who had infusion related reaction (IRR) was 5.1%. QT prolongation was not reported in the DESTINY-Gastric02 trial.

Critical Appraisal

Overall, the absence of an internal comparison group in the single-arm DESTINY-Gastric02 trial is a key limitation. Moreover, a comparison between the trastuzumab deruxtecan group in the DESTINY-Gastric02 trial versus an external control (e.g., a target value or historical study control) was also not available. Lacking comparative data prevents the demonstration of the advantage of trastuzumab deruxtecan over current therapies available in the second line setting, and inferences about the efficacy and safety of trastuzumab deruxtecan are challenging and cannot be established with certainty. The selection of the primary efficacy endpoint, confirmed ORR (defined as sum of CR or PR as determined by ICR based on Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST v1.1]), was necessary for the single-arm DESTINY-Gastric02 trial for regulatory approval as a direct measure of a drug antitumor activity which can be assessed in a single-arm study. As ORR does not always capture the effects of a treatment on patient survival and may not always correlate with symptoms or function, the DESTINY-Gastric02 trial addressed this limitation by examining time-to-event outcomes as secondary endpoints in the trial, including OS which was considered as the most important efficacy outcome for the trial population by the clinical experts consulted by the review team. Although OS was included in the statistical analysis plan and controlled for multiplicity, this outcome can be sensitive to natural history and progression of the disease as well as heterogeneity of patient characteristics; therefore, inference of treatment efficacy based on the reported OS results in the absence of a comparator can be prone to bias.

The DESTINY-Gastric02 trial targeted a second line treatment setting for patients with HER2 positive gastric or GEJ cancer, which aligns with the treatment setting in the reimbursement request submitted by the sponsor. The Health Canada indication, however, targets not only patients in the second line treatment setting but also patients in the third line and later setting. The DESTINY-Gastric02 trial population does not align with the patients in the third line and later setting as described by the proposed Health Canada indication. That being said, results from the DESTINY-Gastric02 trial may not be generalizable to the patients in the third and subsequent lines setting, and there remains a gap in evidence. According to the clinical experts consulted by the review team, the eligibility criteria of the DESTINY-Gastric02 trial were in general aligned with the selection criteria in the Canadian setting when identifying eligible patients with HER2 positive gastric or GEJ cancer for the second line use of trastuzumab deruxtecan.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and randomized controlled trials (RCTs) identified in the sponsor's systematic review, GRADE (Grading of Recommendations Assessment, Development and Evaluation) was used to assess the certainty of the evidence for outcomes considered most relevant to inform expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

Although GRADE guidance is not available for noncomparative studies, the review team assessed pivotal single-arm trials for study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias to present these important considerations. Because the lack of a comparator arm does not allow for a conclusion to be drawn on the effect of the intervention versus any comparator, the certainty of evidence for single-arm trials started at very low certainty with no opportunity for rating up.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null.

Certainty of evidence was summarized narratively for OS, PFS, ORR, FACT-Ga total score, and harms due to lack of comparators.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- OS
- PFS per ICR assessment
- Confirmed ORR per ICR assessment
- HRQoL outcomes: FACT-Ga total score
- Harms: ILD

Results of GRADE Assessments

Table 3 presents the GRADE summary of findings for trastuzumab deruxtecan for the treatment of adult patients with unresectable or metastatic HER2 positive gastric or GEJ cancer who had disease progression during or after first-line therapy with a trastuzumab-containing regimen.

Table 3: Summary of Findings for Trastuzumab Deruxtecan for the Second line Treatment of Adult Patients with Unresectable or Metastatic HER2 Positive Gastric or GEJ Cancer

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
OS (Data Cut-Off Date: November 8, 2021)				
OS Median follow-up duration (months): 10.2 (range, 0.7 to 22.1)	N = 79 (1 single arm study)	Probability of being alive at 6 months • Probability of being alive at 6 months: 77.8% (95% CI, 66.8 to 85.6) • Probability of being alive at 12 months: 50.6% (95% CI, 38.4 to 61.5) • Probability of being alive at 18 months: 35.1% (95% CI, 22.1 to 48.4)	Very Low[a]	The evidence is uncertain about the effect of trastuzumab deruxtecan on unresectable or metastatic HER2 positive gastric or GEJ cancer in the second line treatment setting.
PFS per ICR assessment (Data Cut-Off Date: November 8, 2021)				
PFS per ICR assessment Median follow-up duration (months): 10.2 (range, 0.7 to 22.1)	N = 79 (1 single arm study)	• Probability of being progression free at 6 months: 48.9% (95% CI, 36.6 to 60.2) • Probability of being progression free at 12 months: 20.0% (95% CI, 9.4 to 33.3)	Very Low[a]	The evidence is uncertain about the effect of trastuzumab deruxtecan on unresectable or metastatic HER2 positive gastric or GEJ cancer in the second line treatment setting.
ORR (Data Cut-Off Date: November 8, 2021)				
Confirmed ORR per ICR assessment Median follow-up duration (months): 10.2 (range, 0.7 to 22.1)	N = 79 (1 single arm study)	As of the data cut-off date, the confirmed ORR per ICR assessment was 41.8% (95% CI, 30.8 to 53.4), of which 5.1% of the patients had CR.	Very Low[a]	The evidence is uncertain about the effect of trastuzumab deruxtecan on unresectable or metastatic HER2 positive gastric or GEJ cancer in the second line treatment setting.
HRQoL (Data Cut-Off Date: April 9, 2021)				
FACT-Ga total score Median follow-up duration (months): 5.9 (range, 0.7 to 15.4)	N = 27 (1 single arm study)	At the end of treatment, the mean change from baseline in the FACT-Ga total score was [redacted]).	Very Low[a]	The evidence is uncertain about the effect of trastuzumab deruxtecan on unresectable or metastatic HER2 positive gastric or GEJ cancer in the second line treatment setting.
Harms (Data Cut-Off Date: November 8, 2021)				
ILD Median follow-up duration (months): 10.2 (range, 0.7 to 22.1)	N = 79 (1 single arm study)	The proportion of patients who had ILD was [redacted]%.	Very Low[a]	The evidence is uncertain about the harms effect of trastuzumab deruxtecan on patients with unresectable or metastatic HER2 positive gastric or GEJ cancer.

CI = confidence interval; CR = complete response; FACT-Ga = Functional Assessment of Cancer Therapy-Gastric; GEJ = gastroesophageal junction; HER2 = human epidermal growth factor receptor 2; HRQoL = health-related quality of life; ICR = independent central review; ILD = interstitial lung disease; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; SD = standard deviation

[a] In absence of a comparator arm, certainty of evidence started at very low. There were no observed criteria that would warrant rating up.

Long-Term Extension Studies

No long-term extension studies were submitted by the sponsor for this review.

Indirect Comparisons

Description of Studies

In the absence of direct evidence comparing trastuzumab deruxtecan to other second line treatments (i.e., ramucirumab plus paclitaxel, paclitaxel, FOLFIRI, irinotecan, and docetaxel) currently available in Canada, an indirect treatment comparison (ITC) was submitted by the sponsor to inform this gap. The sponsor submitted ITC consisted of an unanchored matching adjusted indirect comparison (MAIC) and a network meta-analysis (NMA). The unanchored MAIC was used to connect the single-arm pivotal DESTINY-Gastric02 trial into the evidence network of the NMA. The relative treatment effect estimates between trastuzumab deruxtecan and ramucirumab plus paclitaxel were generated based on this unanchored MAIC, while the relative treatment effect estimates between trastuzumab deruxtecan versus other relevant comparators including paclitaxel, FOLFIRI, irinotecan, and docetaxel were generated from the NMA.

Efficacy Results

OS

Generated from the MAIC, the hazard ratio (HR) for OS was [redacted]) between trastuzumab deruxtecan versus ramucirumab plus paclitaxel.

In the fixed-effects (FE) model of the NMA, the estimated base case HRs for OS were [redacted]) between trastuzumab deruxtecan versus paclitaxel, [redacted]) between trastuzumab deruxtecan versus FOLFIRI, [redacted]) between trastuzumab deruxtecan versus irinotecan, and [redacted]) between trastuzumab deruxtecan versus docetaxel.

PFS

Generated from the MAIC, the HR for PFS was [redacted]) between trastuzumab deruxtecan versus ramucirumab plus paclitaxel.

In the FE model of the NMA, the estimated base case HRs for PFS were [redacted]) between trastuzumab deruxtecan versus paclitaxel, [redacted]) between trastuzumab deruxtecan versus FOLFIRI, [redacted]) between trastuzumab deruxtecan versus irinotecan, and [redacted]) between trastuzumab deruxtecan versus docetaxel.

Harms Results

Harms were not addressed in the sponsor submitted ITC.

Critical Appraisal

Through MAIC, the comparison was established between the cohort of patients treated with trastuzumab deruxtecan in the DESTINY-Gastric02 trial and the cohort of patients treated with ramucirumab plus paclitaxel in the RAINBOW trial. There are concerns regarding patient comparability between the DESTINY-Gastric02 trial and the RAINBOW trial. There were differences in some of the important patient characteristics (e.g., HER2 status, time-on-first treatment) that were not involved in the weighting process due to lack of information or insufficient sample size. Currently, the prognostic role of HER2 in gastric cancer remains controversial due to conflicting evidence. With HER2 status being unavailable in the RAINBOW trial, there is increased uncertainty about the treatment effect estimates between trastuzumab deruxtecan versus ramucirumab plus paclitaxel, but the direction of bias is unclear. Additionally, only 5 out of 16 potential prognostic factors and treatment effect modifiers were involved in the propensity score weighting. Exclusion of potentially relevant prognostic factors from the analysis could bias the results, although the magnitude of the residual bias in the relative treatment effect estimates remains uncertain. Furthermore, after reweighting, apparent differences were identified between the DESTINY-Gastric02 trial or the RAINBOW trial in some of the patient characteristics such as time to progressive disease on first line therapy, histological subtype, and number of metastases sites, suggesting the possible existence of

inadequate balance and increases the uncertainty of the findings. After reweighting, there was also a marked reduction in effective sample size (ESS), from [redacted] to [redacted], indicating that the weights might be highly variable due to a lack of population overlap and that the treatment effect estimates yielded via the MAIC approach might be unstable. Other than heterogeneity in patient characteristics, there were significant design and methodological heterogeneity between the DESTINY-Gastric02 (i.e., Phase II, single-arm study without a hypothesis specified a priori or a statistical test) and RAINBOW trials (Phase III, double-blind, RCT with formal hypothesis testing). The MAIC approach can only correct for bias directly related to differences in baseline patient characteristics and does not correct heterogeneity cause by between-trial differences in study design or methods.

The limitations of the MAIC analyses also contributed to the uncertainty of the NMA findings because the NMA evidence network was constructed based on the MAIC which connected the single-arm DESTINY-Gastric02 trial and the RAINBOW trial. On top of the sources of heterogeneity existing the MAIC analyses, additional sources of heterogeneity might have introduced uncertainty to the NMA estimates. For instance, in the MAIC, the sponsor assumed that geographical region and ethnicity were important prognostic factors and that Asian patients had a better prognosis than patients from the Western countries. Subsequently, to limit the number of Asian patients in the MAIC, the sponsor only selected patients from Europe, Israel, Australia, and the United States from the RAINBOW trial, and compared them with the study population of the DESTINY-Gastric02 trial of which the majority were white (87.3%). However, in the NMA network, all included studies did not report on the distribution of ethnicity except for the DESTINY-Gastric02 trial and the RAINBOW trial. Moreover, KSCG/ST10-01, Sym et al. (2013), and WJOG 4007 were conducted in Asia, while Roy et al. (2013) was conducted in both Western and Asian countries. Under the assumption made by the sponsor about geographic region and ethnicity being important prognostic factors, the potential heterogeneity regarding differences in geographical regions and ethnicity in the NMA network could not be ignored, although the degree of uncertainty remains unknown. The rationale of reporting the results of a FE model is justified when estimation of between-study variance using the random-effects (RE) model is very imprecise and unstable in situations that consider only a few studies. However, the FE model does not sufficiently account for heterogeneity between studies, leading to overly precise and narrow CI. Given that there were various sources of heterogeneity existing in the sponsor submitted ITC (described above), use of the FE model introduced uncertainty in the NMA treatment effect estimates.

Other Evidence

Description of Studies

The DESTINY-Gastric01 trial, conducted in Asia (i.e., Japan and South Korea), enrolled 188 patients with HER2-positive advanced gastric or GEJ adenocarcinoma who had progressed on or after at least 2 prior regimens including a fluoropyrimidine agent, a platinum agent, and a trastuzumab-containing regimen (i.e., in the third line and later setting). The primary objective of the DESTINY-Gastric01 trial was to compare the efficacy of trastuzumab deruxtecan versus the physician's choice of treatment (i.e., irinotecan 150 mg/m^2 intravenously every 2 weeks or paclitaxel 80 mg/m^2 intravenously every week), as measured by ORR per ICR assessment. Secondary endpoints included OS, PFS, FACT-Ga, and harms.

Rationale of Inclusion of DESTINY-Gastric01

The DESTINY-Gastric01 trial population is not aligned with the population described in sponsor's reimbursement request because the DESTINY-Gastric01 trial focused on the third line and later treatment settings, while the sponsor's funding request is limited to the second line treatment setting. Therefore, the DESTINY-Gastric01 trial was considered to be out of the scope for the present Clinical Review Report.

Of note, the DESTINY-Gastric01 trial population (patients who received ≥ 2 prior regimens including an anti-HER regimen) would be relevant for a group of patients who are implied in the broader indication for trastuzumab deruxtecan that is currently under review by Health Canada, which is for use "as monotherapy in adult patients with unresectable locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma who have received a prior trastuzumab-based regimen". According to the clinical experts consulted by the review team, this group of patients who have received ≥ 2 prior regimens is small in number in the real-world setting, and will mainly include those patients who are on a currently available second or later lines of therapy and may miss the window of opportunity for being consider eligible for treatment with trastuzumab deruxtecan under the current funding request for the second line setting. Therefore, results from the DESTINY-Gastric01 trial were considered supplementary evidence and are summarized below.

Efficacy Results

OS

As of the data cut-off date of June 3, 2020, the proportion of patients in the intention to treat (ITT) population who had OS events in the DESTINY-Gastric01 trial was 67.2% for the trastuzumab deruxtecan group and 79.0% for the physician's choice group. The median OS was 12.5 months (95% CI, 10.3 to 15.2) for the trastuzumab deruxtecan group and 8.9 months (95% CI, 6.4 to 10.4) for the physician's choice group. The adjusted HR was 0.60 (95% CI, 0.42 to 0.86).

PFS per ICR assessment

As of June 3, 2020, the proportion of patients in the ITT population who had PFS events was 65.1% for the trastuzumab deruxtecan group and 58.1% for the physician's choice group. The median PFS was 5.6 months (95% CI, 4.3 to 6.9) for the trastuzumab deruxtecan group and 3.5 months (95% CI, 2.0 to 4.3) for the physician's choice group. The adjusted HR was 0.47 (95% CI, 0.31 to 0.71).

Confirmed ORR per ICR assessment

The confirmed ORR per ICR assessment in the ITT population was [redacted]) for the trastuzumab deruxtecan group and 11.3% (95% CI, 4.7 to 21.9) for the physician's choice group. The proportion of patients who achieved a best overall response of confirmed CR in the trastuzumab deruxtecan group was 7.9%, while no patients achieved CR in the physician's choice group.

FACT-Ga total score

As of the data cut-off date of November 8, 2019, the mean FACT-Ga total score at the end of treatment was [redacted]) for the trastuzumab deruxtecan group and [redacted]) for the physician's choice group, with a mean change of [redacted]) and [redacted]), respectively.

Harms Results

The data- cut-off date for the harms data was June 3, 2020.

TEAEs

All of the patients in the trastuzumab deruxtecan group while 98.4% of the patients in the physician's choice group had TEAEs. The most commonly reported TEAE was neutropenia, with a 64.8% in the trastuzumab deruxtecan group versus 35.5% in the physician's choice group.

The proportion of patients who had any TEAE of grade 3 and higher was 85.6% in the trastuzumab deruxtecan group, higher than 56.5% reported in the physician's choice group. The most commonly reported TEAE of grade 3 and higher was neutropenia (51.2% in the trastuzumab deruxtecan group versus 24.2% in the physician's choice group), followed by anemia (38.4% in the trastuzumab deruxtecan group versus 22.6% in the physician's choice group).

TESAEs

The proportion of patients who had any TESAE was 44.8% in the trastuzumab deruxtecan group, higher than 25.8% reported in the physician's choice group. The most commonly reported TESAE was decreased appetite (10.4% in the trastuzumab deruxtecan group versus 1.6% in the physician's choice group), followed by ILD (5.6% in the trastuzumab deruxtecan group versus 0 in the physician's choice group), anemia (3.2% in the trastuzumab deruxtecan group versus 3.2% in the physician's choice group), and dehydration (3.2% in the trastuzumab deruxtecan group versus 0 in the physician's choice group).

Treatment discontinuation due to TEAEs

The proportion of patients who discontinued study treatment was 17.6% in the trastuzumab deruxtecan group and 6.5% in the physician's choice group. Discontinuation due to ILD occurred in 6.4% in the trastuzumab deruxtecan group versus 0 in the physician's choice group.

Mortality

The proportion of patients who had any TEAE associated with an outcome of death was 6.4% in the trastuzumab deruxtecan group, higher than 3.2% reported in the physician's choice group.

Notable Harms

The proportion of patients who had ILD was 12.8% in the trastuzumab deruxtecan group, of which 5.6% occurred as TESAEs. No patients in the physician's choice group had ILD. The proportion of patients who had IRR was 6.4% in the trastuzumab deruxtecan group and 3.2% in the physician's choice group. The proportion of patients who had Grade 2 LV dysfunction (defined as resting LVEF from 50% to 40%; 10% to 19% LVEF decrease from baseline) was 9.4% in the trastuzumab deruxtecan group. The proportion of patients who had QT prolongation events was 0.8% in the trastuzumab deruxtecan group and 3.2% in the physician's choice group.

Critical Appraisal

The DESTINY-Gastric01 trial enrolled 188 patients with 126 and 66 patients being randomized to the trastuzumab deruxtecan group and the physician's choice group (2:1 randomization), respectively. The randomization was done using an interactive web/voice response system and stratified based on region (Japan or Korea), ECOG PS (0 or 1), and HER2 status (IHC 3+ or IHC 2+/ISH +) to minimize potential imbalances between the study groups that might bias the results. Despite the relatively small sample size, the distribution of patients in baseline characteristics was in general balanced between the trastuzumab deruxtecan group and the physician's choice group, indicating a low risk of bias in the randomization process. Despite the open-label study design, the review team determined that there is a low risk of detection bias in PFS or ORR, but still there is an increased uncertainty of the treatment efficacy in this setting. Results of both PFS per ICR assessment and PFS per investigator assessment (data not shown) were consistent in general, and so were the findings from unconfirmed ORR and confirmed ORR. However, there is a notable risk of performance bias for the HRQoL – FACT-Ga, which was associated to the open-label design and the subjective nature of the measure. The DESTINY-Gastric01 trial reported OS, which was considered by the clinical experts consulted by the review team as the most important outcome for the study population. Multiplicity adjustment was carried out for unconfirmed ORR (i.e., primary endpoint of the trial) and OS to control for type I error; however, all the remaining efficacy endpoints (e.g., PFS, FACT-Ga) was not adjusted for multiplicity.

There are some concerns regarding whether the patient population in the DESTINY-Gastric01 trial was representative of the corresponding patient population in Canada. According to clinical experts consulted by the review team, the inclusion and exclusion criteria of DESTINY-Gastric01 trial were generally appropriate in terms of selecting eligible patients, however, the efficacy observed in the trastuzumab deruxtecan group and in the physician's choice group were both higher than they would expect or have seen in real-world third line and later settings where patients usually are of poor status and efficacy, suggesting the potential differences between the trial population and the real-world population in Canada.

In addition to the concerns regarding the difference in lines of treatment, there are additional issues related to the generalizability of the results from the DESTINY-Gastric01 trial population to the DESTINY-Gastric02 trial population due to obvious differences in patient characteristics. For instance, 87.3% of the patients in the DESTINY-Gastric02 trial were White from North America, whereas all the patients in the DESTINY-Gastric01 trial were Asian from Japan and South Korea. As noted in the sponsor submitted ITC, geographical region and ethnicity were important prognostic factors and that Asian patients had a different prognosis from patients from the Western countries. Second, in the DESTINY-Gastric02 trial 34.2% of the patients had gastric cancer and 65.8% had GEJ cancer, whereas in the DESTINY-Gastric01 trial 87.2% of the patients had gastric cancer and 12.8% had GEJ cancer. These differences in patient characteristics may introduce treatment heterogeneity that increases our uncertainty of the results and their generalizability to the Canadian context.

The clinical experts consulted by the review team noted that the use of irinotecan or paclitaxel as comparator in the DESTINY-Gastric01 trial does not accurately reflect of the current clinical practice in Canada. T the clinical experts noted that at the time of designing the DESTINY-Gastric01 trial irinotecan and paclitaxel were commonly used in the third line and later setting, but in current clinical practice irinotecan and paclitaxel are rarely used; and when they are used, it is typically for a very small group of patients, such as those who have developed serious neuropathy from previous lines of therapy.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis PSM
Target population	As second-line treatment in adult patients with HER2-positive locally advanced or metastatic gastric or GEJ adenocarcinoma who have progressed on or after one anti-HER2-containing regimen.[a]
Treatment	Trastuzumab deruxtecan
Dose regimen	6.4 mg/kg every 21 days until disease progression or unacceptable toxicity
Submitted price	Trastuzumab deruxtecan: $2,440.00 per 100 mg single-use vial for intravenous infusion
Submitted treatment cost	$13,083.50 every 21-days (considers wastage, relative dose intensity, and average dose assumptions)
Comparator	Ramucirumab plus paclitaxel[b]
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	5 years
Key data sources	Sponsor-submitted MAIC in which efficacy inputs for trastuzumab deruxtecan were informed by DESTINY-Gastric02, (NCT04014075; data cut-off date: November 2021), a phase 2, open-label, single-arm trial and RAINBOW (NCT01170663) for ramucirumab plus paclitaxel.[c]
Key limitations	• While the proposed Health Canada indication is for use in the second-line or later setting, the submitted economic evidence is only for use in the 2L setting (i.e., not subsequent lines). The cost-effectiveness of trastuzumab deruxtecan in the 3L or later treatment is unknown. • The comparative efficacy of trastuzumab deruxtecan with other 2L treatments (i.e., ramucirumab plus paclitaxel, paclitaxel, FOLFIRI, irinotecan, and docetaxel) is highly uncertain owing to a lack of head-to-head trials and several major limitations with the sponsor's MAIC and NMA, which preclude any definitive conclusion about the magnitude of effect • The use of a PSM introduces structural assumptions about the relationship between PFS and OS that likely do not accurately reflect causal relationships within the disease pathway. In the sponsor's base case, these assumptions produced a post-progression survival benefit that favored trastuzumab deruxtecan for which there was no evidence to support. • The sponsor selected OS and PFS extrapolations that allowed PFS to exceed OS, and it is clinically implausible for more patients to be at-risk of progression than alive. As a result, the modelled clinical outcomes lack face validity and the modelled output (QALYs and LYs) is associated with substantial uncertainty. • Subsequent therapy costs are highly uncertain as published literature highlighted a wide potential range in the proportion of patients treated with 3L therapy (6% to 50%). Clinical expert input noted currently that only a small proportion of patients are treated with subsequent lines of therapy. That proportion may increase depending on the effectiveness of trastuzumab deruxtecan. • The derived utility values from the DESTINY-Gastric02 trial suggested there was little difference in terms of QoL between the average Canadian and patients receiving a 2L treatment for HER2-positive locally advanced or metastatic gastric or GEJ adenocarcinoma. Clinical expert input indicated the utility values from the RAINBOW trial to be more reflective of QoL for the indicated population. • TTD is uncertain as the sponsor's approach assumes patients discontinue treatment before experiencing disease progression. Clinical expert input stated majority of patients will discontinue treatment due to progression.

Component	Description
	• CADTH identified several discrepancies in drug acquisition costs stemming from incorrect drug unit costs, and inappropriate dosing and wastage assumptions.
CADTH reanalysis results	• The CADTH base case was derived by assuming TTD equals PFS for all treatments; excluding subsequent therapy costs; adopting health state utility values from the RAINBOW trial; and, correcting unit drug costs and the dose of fluorouracil, and assuming bulk pharmacy vials are shared. • Trastuzumab deruxtecan was associated with an ICER of $242,356 per QALY gained relative to ramucirumab plus paclitaxel (incremental costs = $69,457; incremental QALYs = 0.29). • A price reduction for trastuzumab deruxtecan of approximately 31% would be required to achieve an ICER of $50,000 per QALY gained relative to ramucirumab plus paclitaxel. However, this assumes that there is a notable clinical benefit (0.41 life-years gained) associated with trastuzumab deruxtecan. As the comparative clinical evidence is highly uncertain and there is a negotiated price for ramucirumab, a higher price reduction may be required to achieve cost-effectiveness.

2L = second-line; 3L = third-line; FOLFIRI = folinic acid, fluorouracil, and irinotecan; GEJ = gastroesophageal junction; HER2 = human epidermal growth factor receptor 2; ICER = incremental cost-effectiveness ratio; LY = life-year; MAIC = matching-adjusted indirect comparison; NMA = network meta-analysis; OS = overall survival; PFS = progression-free survival; PSM = partitioned survival model; QALY = quality-adjusted life-year; QoL = quality-of-life; TTD = time to treatment discontinuation.

[a] In line with the sponsor's reimbursement request, and rationale for going through the Time Limited Recommendation process, the sponsor's economic analysis was restricted to the 2L population and thus did not consider evidence from the DESTINY-Gastric01 trial.

[b] The sponsor included comparisons of trastuzumab deruxtecan with paclitaxel, docetaxel, irinotecan, and FOLFIRI in scenario analyses. Ramucirumab plus paclitaxel was considered standard of care by the sponsor was deemed to be the primary comparator.

[c] The comparisons of trastuzumab deruxtecan with paclitaxel, docetaxel, irinotecan, and FOLFIRI was derived through a sponsor-submitted NMA, in which trastuzumab deruxtucan was incorporated into the NMA via the adjusted results from the MAIC.

[d] Scenario analysis results suggested that trastuzumab deruxtecan is associated with more QALYs and more costs compared with each of paclitaxel, docetaxel, irinotecan, and FOLFIRI. The pairwise ICERs for trastuzumab deruxtecan vs. each comparator range from $228,558 per QALY gained to $302,654 per QALY gained.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the number of eligible patients is likely underestimated, time to discontinuation is uncertain, drug acquisition costs are uncertain, the market uptake of trastuzumab deruxtecan is likely underestimated, and subsequent therapy costs are uncertain.

The limitations identified by CADTH had minimal impact on the results of the BIA. Furthermore, in the absence of more reliable estimates to inform the key parameters of the BIA (i.e., the number of eligible patients), the sponsor's submitted base case was maintained.

The sponsor estimated that the 3-year budget impact of reimbursing trastuzumab deruxtecan for the 2L treatment of adults with HER2-positive locally advanced or metastatic gastric or GEJ adenocarcinoma who have progressed on or after receiving a trastuzumab-containing regimen to be $22,572,044 (Year 1: $4,518,314; Year 2: $8,704,420; Year 3: $9,349,311).

Clinical experts stated that the absolute number of patients eligible for trastuzumab deruxtecan may be underestimated and the number of eligible patients could be several times greater than estimated by the sponsor. However, CADTH was unable to identify alternative sources of information to validate this estimate. As such, the 3-year budget impact is uncertain.

pERC Information

Members of the Committee:

Dr. Catherine Moltzan (Chair), Dr. Philip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung, Dr. Michael Crump, Annette Cyr, Dr. Jennifer Fishman, Dr. Jason Hart, Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Aly-Khan Lalani, Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Pierre Villeneuve, and Danica Wasney.

Meeting date: February 12, 2025

Regrets:

One expert committee member did not attend.

Conflicts of interest:

None