Canada's Drug and Health Technology Agency

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

TRASTUZUMAB DERUXTECAN (Enhertu)

(AstraZeneca Canada Inc.)

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

June 15, 2023

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0305-000
Brand name (generic)	Enhertu (Trastuzumab deruxtecan)
Indication(s)	As monotherapy for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Patients with hormone receptor positive (HR+) breast cancer should additionally have received or be ineligible for endocrine therapy.
Organization	Ontario Health (Cancer Care Ontario) Breast Cancer Drug Advisory Committee
Contact information[a]	Name: Dr. Andrea Eisen

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐
Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.		

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐
If not, what aspects are missing from the draft recommendation?		

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification. The DAC agrees with the CADTH pathology experts' recommendation that it is necessary to re-read archival samples from prior to 2022, for patients' whose result is IHC 0, by clinician request. The DAC is aware that some pathologists suggest there may be benefit in reviewing IHC 1+ cases, but the DAC is concerned about feasibility and access to treatment.		

In the DESTINY-Breast04 trial, patients were monitored every 6 weeks with CT scans for early detection of ILD/pneumonitis. There is guidance to suggest a less intense CT monitoring for ILD may be possible in keeping consistent with the typical schedule for monitoring therapeutic response.

Patients with low ER expression (IHC 1-10%) should be eligible for trastuzumab deruxtecan without having received prior endocrine therapy. [1]

1. D.A.A. Cameron, W. Jacot, T. Yamashita, M.J. Vidal Losada,et al. 92MO DESTINY-Breast04 subgroup analyses of trastuzumab deruxtecan (T-DXd) vs treatment of physician's choice (TPC) in patients (pts) with human epidermal growth factor 2 (HER2)-low, estrogen-receptor (ER) expression immunohistochemistry (IHC) 0-10% metastatic breast cancer (mBC), ESMO Open,2023, 8(1). DOI:https://doi.org/10.1016/j.esmoop.2023.101381

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒

If not, please provide details regarding the information that requires clarification.

The DAC agrees with the CADTH pathology experts' recommendation that it is necessary to re-read archival samples from prior to 2022, for patients' whose result is IHC 0, by clinician request. The DAC is aware that some pathologists suggest there may be benefit in reviewing IHC 1+ cases, but the DAC is concerned about feasibility and access to treatment.

In the DESTINY-Breast04 trial, patients were monitored every 6 weeks with CT scans for early detection of ILD/pneumonitis. There is guidance to suggest a less intense CT monitoring for ILD may be possible in keeping consistent with the typical schedule for monitoring therapeutic response.

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[a] CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- 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 feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please 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 declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☐
	Yes	☒
If yes, please detail the help and who provided it. OH-CCO provided secretariat function to the group.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
3. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☒
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Dr. Andrea Eisen • Dr Philip Blanchette		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Dr. Orit Freedman*
Position	*Member, OH-CCO Breast Cancer Drug Advisory Committee*
Date	*09-06-2023*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.
Conflict of Interest Declaration	

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.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	*Alaina Charlton*
Position	*Member, OH-CCO Breast Cancer Drug Advisory Committee*
Date	*09-06-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0305
Name of the drug and Indication(s)	Trastuzumab deruxtecan for unresectable or metastatic HER2-low breast cancer
Organization Providing Feedback	PAG

1. Recommendation revisions Please indicate if the stakeholder requires the expert review committee to reconsider or clarify its recommendation.		
Request for Reconsideration	**Major revisions:** A change in recommendation **category** or patient **population** is requested	☐
	Minor revisions: A change in reimbursement **conditions** is requested	☐
No Request for Reconsideration	**Editorial revisions:** Clarifications in recommendation **text** are requested	X
	No requested revisions	☐

2. Change in recommendation category or conditions Complete this section if major or minor revisions are requested
Please identify the specific text from the recommendation and provide a rationale for requesting a change in recommendation. N/A

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
Please provide details regarding the information that requires clarification. N/A
b) Reimbursement conditions and related reasons
Please provide details regarding the information that requires clarification. N/A
c) Implementation guidance
Please provide high-level details regarding the information that requires clarification. You can provide specific comments in the draft recommendation found in the next section. Additional implementation questions can be raised here.

A provisional funding algorithm (panel algorithm) is needed.

CADTH

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0305-000
Brand name (generic)	Enhertu (trastuzumab deruxtecan)
Indication(s)	unresectable or metastatic HER2-low breast cancer
Organization	Rethink Breast Cancer
Contact information[a]	Name: MJ DeCoteau

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☒

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

Overall, we were very pleased with the recommendation, especially that it includes both HR-positive and HR-negative patients and that those patients who had been previously classified as mTNBC and treated with Keytruda would be eligible for Enhertu. We are also very pleased to see that access is not limited by number of previous lines of chemotherapy.

Our concern is with wording regarding reimbursement condition 2.2 in Table 1 on page 4. We request the wording "uncontrolled" be changed to "symptomatic."

While most patients will have some form of control of brain metastasis with either surgery, stereotactic radiosurgery, whole-brain radiation or surgery, there will be some circumstances that individuals will want to delay these interventions. WBRT is especially something many patients in our community try to avoid or delay due to the associated cognitive decline and resources for interventions like Gamma Knife are not even across the country. If the patient is deemed asymptomatic, we would like to see them have Enhertu as an option.

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐

If not, what aspects are missing from the draft recommendation?

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☐
	No	☐

If not, please provide details regarding the information that requires clarification.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☐

If not, please provide details regarding the information that requires clarification.

	Yes	☐

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	No	☐

If not, please provide details regarding the information that requires clarification.

Our concern is with wording regarding reimbursement condition 2.2 in Table 1 on page 4. We request the wording “uncontrolled” be changed to "symptomatic."

While most patients will have some form of control of brain metastasis with either surgery, stereotactic radiosurgery, whole-brain radiation or surgery, there will be some circumstances that individuals will want to delay these interventions. WBRT is especially something many patients in our community try to avoid or delay due to the associated cognitive decline and resources for interventions like Gamma Knife are not even across the country. If the patient is deemed asymptomatic, we would like to see them have Enhertu as an option.

[a] CADTH may contact this person if comments require clarification.

Appendix 1. Conflict of Interest Declarations for Patient Groups

- 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 feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information	
Name	Mary Jo DeCoteau
Position	Executive Director
Date	June 14, 2023
☒	I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☐
	Yes	☒

D. New or Updated Conflict of Interest Declaration

3. 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.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0305
Brand name (generic)	Enhertu (trastuzumab deruxtecan)
Indication(s)	Enhertu for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received at least one prior line of chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Patients with hormone receptor positive (HR+) breast cancer should have received at least one and be no longer considered eligible for endocrine therapy.
Organization	AstraZeneca Canada Inc.
Contact information[a]	[redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

AstraZeneca (AZ) agrees with pERC's Draft Recommendation to reimburse Enhertu for adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer based on statistically significant and clinically meaningful improvements in both progression-free survival (PFS) and overall survival (OS) as demonstrated in the DESTINY-Breast04 (DB-04) trial.

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

If not, what aspects are missing from the draft recommendation?

- In Discussion Point #4 (page 5), the clinical experts consulted by CADTH noted that "*trastuzumab deruxtecan is anticipated to have a similar benefit regardless of HR status given the consistency of data and because trastuzumab deruxtecan does not target the hormone receptor*". AZ agrees with the clinical experts on this statement. However, the first key limitation on page 13 states "*There is also uncertainty with the treatment effect of T-DXd according to HR-status*"
    - **Due to the discrepancy between the clinical and economic sections of the draft recommendation, AZ proposes one of the following:**
        - The removal of the statement on page 13; or
        - Revising the statement on page 13 to align with the clinical experts consulted by CADTH – *"…As stated by clinical experts, the treatment effect of T-DXd is not expected to differ by HR-status"*

- Changes in the economic models are unlikely to reflect the value innovative medicines, like Enhertu, bring to HER2-low metastatic patients
    - AZ recognizes that the DB-04 trial was not powered to detect differences in HRQoL outcomes and that CADTH guidelines recommend against the use of treatment-state specific utilities values. However, the use of health state-specific utilities, as in the CADTH base-case, assumes that all patients that were progression-free/progressed had the same experience regardless of treatment.
    - In the DB-04 trial, Enhertu provided a statistically significant and clinically meaningful improvement in OS and PFS compared with TPC and this has translated to a benefit in HRQoL that extends beyond median PFS and treatment discontinuation. The time to definitive deterioration in patient-reported outcomes such as pain symptoms, physical functioning, emotional functioning, and social functioning were substantially longer than median PFS (12.8-19.2 months relative to 10.1 months mPFS). As such, health state-specific utilities are unlikely to capture these treatment-specific benefits in HRQoL.
    - Additionally, as highlighted by the clinical experts consulted by CADTH, *"The benefits seen in the DESTINY-Breast04 are meaningful and valuable, particularly because there has not been a therapy that has demonstrated this magnitude of survival benefit in the HER2-low patient population"* (Clinical Review Report, page 18). Seeing that there is no other treatment with comparable outcomes to what Enhertu showed in DB-04, it makes it difficult to validate the long-term extrapolation of the Enhertu OS results, which can be more than the conservative survival benefits estimated in the AZ base-case. As such, these economic models are unlikely to adequately capture the long-term benefits Enhertu provides and subsequently undervalues the true value of Enhertu to HER2-low patients.

- In CADTH's reanalysis of the budget impact model, "*CADTH changed the proportion of patients who were HR-positive who received second-line chemotherapy and were refractory to prior ET to 60%, and proportion of patients who received a third-line chemotherapy (i.e., eligible in 3rd line) and were refractory to prior ET to 90% (i.e., eligible in 4th line)*" based on clinical expert opinion (page 28 of the Pharmacoeconomic Review Report)
    - AZ's estimates of patients eligible in 3rd line and 4th line were informed by 45 Canadian medical oncologists and 171 patient charts across Canada.
    - While AZ appreciates CADTH acknowledging that the proportion of patients eligible for 3rd and 4th line Enhertu may vary due to jurisdictional differences in 2nd line ET funding across Canada, the proportions used by CADTH in their reanalysis are well above the jurisdictional averages observed across Canada. Based on market research, no region in Canada has proportions aligned to CADTH's assumptions and demonstrate significantly lower proportions for patients eligible in 3rd line and 4th line. The AZ submitted model is reflective of both the provisional funding algorithm for hormone receptor-positive breast cancer and the current treatment patterns in Canada.

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐

If not, please provide details regarding the information that requires clarification.

AZ agrees with pERC's conclusion that Enhertu provides a new treatment for the HER2-low population, regardless of hormone receptor status, that offers a statistically significant and clinically meaningful improvement in OS and PFS with a manageable toxicity profile.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐

If not, please provide details regarding the information that requires clarification.

AZ agrees with pERC that there are two outstanding issues that we await advice on from the CADTH Drug Implementation Advice Panel:

- *"The clinical experts suggested that for patients with HER2-low BC the preferable treatment in second line may be trastuzumab deruxtecan over sacituzumab govitecan, as it is specifically targeted to the HER2 protein, however there is no clear consensus of sequencing of these drugs"* (page 17 of the Clinical Review Report)
- *"pERC discussed the eligibility of patients that are HR-positive but are functionally HR-negative (HR-low). In this population, patients are generally treated as HR-negative and may not receive the required endocrine therapy prior to initiating treatment with trastuzumab deruxtecan. Therefore, pERC agreed that treatment sequencing and national consensus is needed for the definition and management of these patients"* (page 6 of the Draft Recommendation)

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒

If not, please provide details regarding the information that requires clarification.

- The wording of initiation criteria #2 reads "Patients must not have **had** any of the following" which could imply a history of these conditions (symptomatic spinal cord compression, uncontrolled CNS metastases, ILD/pneumonitis). This wording can cause confusion by excluding patients with previously uncontrolled conditions who are currently stable/controlled. Note, the DB-04 trial included patients with treatable brain metastases that were no longer symptomatic and who required no treatment with corticosteroids or anticonvulsants.
- AZ proposes to clarify initiation criteria #2 to reflect the exclusion criteria of the trial:
    - Patients must not have any of the following:
        - 2.1. symptomatic spinal cord compression
        - 2.2. clinically active CNS metastases
        - 2.3. current ILD/pneumonitis

[a] CADTH may contact this person if comments require clarification.