CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

TRASTUZUMAB DERUXTECAN (Enhertu)

(AstraZeneca Canada Inc.)

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

September 16, 2022

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0285-000
Brand name (generic)	Trastuzumab deruxtecan
Indication(s)	HER2 mBC
Organization	Ontario Health (CCO) 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	☐

Table 1)
Initiation 2.0

The DAC agreed that there may be circumstances where prior antibody drug conjugates may have been used, and that patients may be considered for treatment. In this situation, the DAC favours a 6 month interval, and not the 12 mos recommended by pCODR. This is aligned with other treatment policies.

Prescribing 6.0

The DAC suggests that the statement "tras deruxtecan should not be given with other anti cancer drugs be modified to state …with other chemotherapy agents". There may be circumstances where patients should get endocrine therapy as well (eg mixed tumours, Her2 pos and ER pos).Clinicians should be able to use endocrine agents appropriate cases.
The DAC noted that there is a risk of pneumonitis, and that patients may not be symptomatic.. Access to experts who treating pneumonitis is important for toxicity management.

Implementation Q1) The DAC would like to support additional access to Kadcyla as an alternative to trastuzumab deruxtecan in some patients. There may be patients where Kadcyla would be a safer option in terms of toxicity than trastuzumab deruxtecan

The DAC considered the recommendation that TdxT could be given if patients had been exposed to prior antibody drug conjugate in the neo/adjuvant setting more that 12 mos prior to treatment. The DAC believes that this interval should be shortened to 6 mos, in alignment with other metastatic treatment policies.

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.		
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.		

[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	☒
Ontario Health provided secretariat function to the DAC.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
N/A		
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. Orit Freedman • Dr. Phillip Blanchette		

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0285-000
Brand name (generic)	Enhertu™ (Trastuzumab-deruxtecan)
Indication(s)	For the treatment of adult patients with unresectable or metastatic HER2 (human epidermal growth factor receptor 2)-positive breast cancer who have received a prior treatment with an anti-HER2-based regimen in the metastatic setting or developed disease recurrence during or within 6 months of completing neoadjuvant or adjuvant therapy
Organization	The Ottawa Hospital Cancer Centre – Breast Disease Site Group (medical oncology) and additional Canadian breast medical oncologists
Contact information[a]	Name: Dr Sandeep Sehdev

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

We agree with the clinical evidence based review.

- Table 1: item 2.1: Level 1 evidence has been reviewed from the DB-03 trial supporting this draft recommendation in the second line setting. However there is strong data supporting the value of trastuzumab-deruxtecan in later lines of therapy. The original phase 2 single arm DB-01 study demonstrated profound activity in even more heavily pre-treated patients in a setting of unmet need. Indeed the activity was impressive enough to achieve FDA approval and we have noted dramatic benefits in patients treated in later lines (even beyond trastuzumab emtansine and trastuzumab / tucatinib/ capecitabine ie the HER2CLIMB protocol) through the previous (now closed) compassionate access program. Another prospective randomized controlled trial is underway to confirm late line benefit and we would request expedited review of that indication when results become available.
- Table 1: item 7: ICERs of $50,000 per QALY remain arbitrary and based upon original cutoffs established in the 1980s and 1990s, for other non oncology diseases, unadjusted for inflation. While value for therapy remains important, access and approval should not be delayed for our patients and the acceptable ICER threshold should be actively reassessed (for all oncology drugs) with meaningful patient and stakeholder engagement, recognizing the increasing real world costs and complexity of drug development/discover, clinical research, and regulatory approval. Cancer is recognized as a unique condition, justifying special registries and government agencies (such as Cancer Care Ontario and pCODR) and cancer drugs should have different thresholds recognizing the grave and imminent danger to life posed by malignancies. Setting of prices is beyond the scope of CADTH.

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	☒

The reasons or evidence justifying the ICER threshold are not provided.

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.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒
The reasons or evidence justifying the ICER threshold are not provided.		

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

Appendix 1. Conflict of Interest Declarations for Patient Groups

Not applicable

Appendix 2. Conflict of Interest Declarations for Clinician Groups

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  - 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.		
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	☒
Dr. Sandeep Sehdev (Ottawa) Dr. Silvana Spadafora (Sault Ste Marie ON) Dr. Jan-Willem Henning (Calgary) Dr. Mark Clemons (Ottawa) Dr. Jawaid Younus (London) Dr. Amirrtha Srikanthan (Ottawa) Dr. Amy Groom (Halifax) Dr. Moria Rushton-Marovac (Ottawa) Dr. Karen Gelmon (Vancouver)		

C. New or Updated Conflict of Interest Declarations Not applicable

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0285
Name of the drug and Indication(s)	trastuzumab deruxtecan for metastatic HER2 positive BC
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	☐
	No requested revisions	X

2. Change in recommendation category or conditions Complete this section if major or minor revisions are requested
None.

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
None.
b) Reimbursement conditions and related reasons
None.
c) Implementation guidance
None.

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0285-000
Brand name (generic)	Enhertu (trastuzumab deruxtecan)
Indication(s)	Enhertu for the treatment of adult patients with unresectable or metastatic HER2 (human epidermal growth factor receptor 2)-positive breast cancer who have received at least one prior anti-HER2-based regimen either: (i) in the metastatic setting, or (ii) in the neoadjuvant or adjuvant setting and developed disease recurrence during or within 6 months of completing neoadjuvant or adjuvant therapy.
Organization	AstraZeneca Canada (sponsor)
Contact information[a]	[redacted]

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

AstraZeneca (AZ) agrees with pERC's Initial Recommendation to reimburse trastuzumab deruxtecan for adult patients with unresectable or metastatic HER2-positive breast cancer based on statistically significant and clinically meaningful improvements in progression-free survival (PFS) and manageable toxicity profile as demonstrated in the DESTINY-Breast03 (DB-03) trial. AZ also agrees with pERC's assessment that there is an unmet need for effective new therapies beyond first line of treatment in the metastatic HER2-positive breast cancer setting as most patients treated with currently available therapies experience disease progression and the long-term survival of patients in this setting remains poor (pg, 6).

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?

- Under 'Budget Impact' Section (pg, 14), CADTH indicated that the: *proportion of patients who received initial anti-HER2 regimen and the proportion of patients who received a second line therapy were underestimated by the sponsor*". However, AZ base-case assumption of the proportion of patients diagnosed with HER2+ mBC who receive a first-line therapy, and proportion of HER2+ mBC patients receiving a second-line therapy are grounded in Canadian real-world evidence (RWE) - provincial data (AHS & Ontario ICES). CADTH's re-analysis were based on clinician estimates, which are less reliable than two robust RWE studies, covering ~50% of the population of Canada. Please refer to the original submission or sponsor feedback on draft reports for percentages used in the AZ base-case.
- Additionally, the proportion of HER2+ mBC patients receiving second-line therapy and the market share for subsequent therapy with tucatinib + trastuzumab + capecitabine in the sponsor's base-case is also aligned to CADTH precedent established within the tucatinib review (where 40% of HER2+ mBC were receiving second-line therapy and tucatinib-combination therapy was estimated to have 60-70% market share in year 1 alone).

- CADTH included additional scenario analyses in the PE report to explore the uncertainty regarding the proportion of HER2+ mBC patients who received a first-line anti-HER2 therapy and the proportion of HER2+ mBC patients who received second-line therapy.

AZ Proposed changes to improve clarity:

- *"CADTH identified the following key limitations: proportion of patients who received initial anti-HER2 regimen and the proportion of patients who received a second line of therapy were **uncertain based on differences between sponsor submitted RWE (provincial data from Alberta and/or Ontario) and proportions provided by clinical experts consulted for this review**" (pg, 14; paragraph 1)*
- *Following the statement, "CADTH base-case case revisions included: increasing the proportion of patients who received initial anti-HER2 regimen……standard of care". AZ requests CADTH to consider adding the following statement "**Additional scenario analyses were conducted to explore the uncertainty regarding the proportion of patients who received initial anti-HER2 regimen and the proportion of patients who received a second line of therapy**." (pg, 14; paragraph 2)*

- Under the 'Economic Evidence' table (pg, 13), CADTH indicated that "t*he sponsor used OS data from EMILIA trial to extrapolate long-term OS estimate for T-DM1 beyond the DB-03 trial…Based on feedback from clinical experts, due to differences in patient populations in terms of prior treatment use, the results from EMILIA trial are not generalizable to the DESTINY-Breast03 trial population" (pg,13)* – Although the EMILIA trial is not Canadian, it is more mature than DB-03 trial data for the T-DM1 arm, and in the short-term DB-03 Kaplan-Meir (KM) curve is consistent with the EMILIA KM curve. As such, EMILIA trial provides a best estimate of long-term OS on T-DM1 to inform extrapolations, and aligns to other T-DM1 published KM curves (e.g. KATE2 trial).
- AZ also validated the base-case extrapolations against two Canadian RWE studies (Alberta O2 study and ICES Ontario study) to ensure generalizability of T-DM1 long-term OS estimates in our cost-effectiveness model to observed T-DM1 long-term OS among Canadian patients.

AZ Proposed changes to improve clarity:

- Under the 'Key Limitations' section of the Economic Evidence table; AZ requests CADTH to consider revising the sentence as such: "The sponsor's approach **may have** overestimated the OS benefit for T-DXd at the 25-year time point according to clinical experts consulted during this review" (pg, 13; bullet #2)
- Under the 'CADTH Reanalysis Results' section of the Economic Evidence table, AZ requests CADTH to consider adding the following statement: **"Additional scenario analyses were conducted to explore the uncertainty regarding the magnitude of OS benefit accrued with T-DXd**" (pg, 14; bullet #2)

Clarity of the draft recommendation

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

AZ agrees with pERC's conclusion that T-DXd provides an additional treatment option with statistically significant and clinically meaningful improvement in PFS relative to current standard of care.

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

- In Table 2 - Responses to Questions from Drug Programs under 'Funding Algorithm' section, pERC noted that '*patients should be able to switch from T-DXd to T-DM1 for toxicity reasons if there is no evidence of disease progression*'. AZ would like to request CADTH to provide

clarification on the reimbursement of T-DXd for patients that could not tolerate T-DM1 in the metastatic setting (pg, 9).

AZ proposed changes to improve clarity:

- *"patients should be able to switch from trastuzumab deruxtecan to trastuzumab emtansine,* ***and vice versa*** *for toxicity reasons if there is no evidence of disease progression"*

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

- Under Discussion Points, the committee noted possible sequencing of trastuzumab deruxtecan and trastuzumab emtansine (pg, 6; bullet #5). Similarly, under 'Budget Impact' section, the last sentence also alludes to the possibility of '*both therapies used in sequence*' (pg, 14; paragraph 3).
- Regarding the budget impact, AZ would like to clarify that the base-case assumption to not sequence T-DXd and T-DM1 is aligned to T-DXd's initiation criteria outlined by CADTH where patients should not have received prior treatment with an anti-HER2 antibody-drug conjugate (such as T-DM1) in the metastatic setting. As such, we expect T-DXd to displace T-DM1 as indicated by the clinical experts consulted by CADTH as well. Additionally, as indicated by CADTH, there is no evidence to support the use of T-DM1 post-T-DXd and no proven patient benefit.
- To derive CADTH base-case ICER and Budget Impact, revisions were made to the market shares for subsequent treatments based on expected accessibility for current treatments in Canadian practice, as well as input CADTH received from clinical experts and drug plans. In this revision, patients receiving T-DXd cannot receive T-DM1 as subsequent treatment and vice versa. This is aligned to the AZ base-case assumption to not sequence T-DM1 post T-DXd.

AZ proposed changes to improve clarity:

- As noted in the Pharmacoeconomic report (pg, 19; paragraph 4), AZ requests CADTH to add the following statement to the 'Discussion Points' or 'Budget Impact' section in the recommendation report **"*There has been no evaluation of this sequence of therapies, and therefore the benefit of following T-DXd treatment with T-DM1 in this population is unknown*"** or
- As noted in the Pharmacoeconomic Report (pg, 15; paragraph 1), AZ requests CADTH to add the following statement to the 'Discussion Points' or 'Budget Impact' section in the recommendation report **"*There is currently no robust evidence assessing the benefit of using of T-DM1 post T-DXd and the use in this manner is not aligned with how T-DM1 is currently funded in Canadian clinical practice"***

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