CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

tucatinib (Tukysa)

Seagen Canada Inc.

Indication: Tucatinib is indicated in combination with trastuzumab and capecitabine for treatment of patients with locally advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received prior treatment with trastuzumab, pertuzumab, and trastuzumab emtansine, separately or in combination.

October 18, 2021

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0243-000
Brand name (generic)	Tukysa (tucatinib); Manufacturer: Seagen Canada Inc.
Indication(s)	Manufacturer reimbursement request: In combination with trastuzumab and capecitabine for treatment of patients with locally advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received prior treatment with trastuzumab, pertuzumab, and trastuzumab emtansine, separately or in combination.
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.

Re: *While patients enrolled in the HER2CLIMB trial were required to have an ECOG PS of 0 or 1, pERC agreed that clinicians may consider using tucatinib plus trastuzumab and capecitabine for patients with an ECOG PS of 2. The decision to use this treatment for patients with an ECOG PS of 2 should be based on the judgement of the treating physician.*

- The OH-CCO Breast DAC suggests removing numerical values re: PS. As patients with poor performance status whose conditions may be improved with treatment should be allowed for treatment based on the judgement of the treating physician.

Re: *pERC noted that, upon implementation of the tucatinib reimbursement, jurisdictions would need to fund trastuzumab, in the 3rd line setting, for patients who are eligible to receive tucatinib in combination with trastuzumab and capecitabine.* - The OH-CCO Breast DAC recognizes the importance of having funding in place for third-line trastuzumab for use with tucabinib combination treatment and supports the use of biosimilar trastuzumab.

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		
2. 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 support to the DAC.		
3. Did you receive help from outside your clincian 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		
4. 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 • Annie Ngan (pharmacist) • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*

☐	**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	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**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	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 3	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☒	**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	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 4	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**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	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 5	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**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	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0243
Name of the drug and Indication(s)	Tucatinib in combination with trastuzumab and capecitabine for the treatment of patients with locally advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received prior treatment with trastuzumab, pertuzumab, and T-DM1, separately or in combination
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
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
In Table 1. Reimbursement conditions and reasons, under the heading, Discontinuation, PAG is requesting a distinction be made between 5.1 and 5.2. Specifically, the combination of tucatinib, capecitabine and trastuzumab should be discontinued if 5.1 applies. PAG noted that 5.2 is a separate issue in that tucatinib alone may be discontinued and capecitabine/trastuzumab may be continued if there is unacceptable toxicity attributed solely to tucatinib.

c) Implementation guidance

In the implementation guidance section of the pERC recommendation, PAG is seeking pERC's stance on the following items:

- Time-limited funding for patients currently on systemic treatment whose disease has not progressed. Also, is this limited to patients on 3rd line options (vs. 3rd/later lines)?
- Continuing tucatinib if there are isolated brain metastases only.
- Patients who progressed on prior capecitabine or lapatinib.

In Table 2. Implementation Guidance from pERC, condition #1, PAG is seeking clarity whether pERC supports funding tucatinib-capecitabine-trastuzumab first line (for early relapsers of adjuvant TDM1) or is the intent to use tucatinib-trastuzumab-capecitabine second line for this scenario?

CADTH

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0243-000
Brand name (generic)	Tucatinib (Tukysa)
Indication(s)	In combination with trastuzumab and capecitabine for the treatment of patients with locally advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received prior treatment with trastuzumab, pertuzumab, and T-DM1, separately or in combination.
Organization	Seagen Canada Inc.
Contact information[a]	Name: [redacted] 2233 Argentia Road, Suites 302 & 302A, Mississauga, ON L5N 2X7 [redacted]

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

Seagen Canada Inc. (Seagen) agrees with CADTH's draft recommendation for tucatinib in combination with trastuzumab and capecitabine for the treatment of patients with locally advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received prior treatment with trastuzumab, pertuzumab, and trastuzumab emtansine (T-DM1), separately or in combination. Seagen supports conversion of the draft recommendation to a final recommendation.

Seagen also recognizes the feedback received from the provincial advisory group (PAG), clinicians and patient advocacy groups who have provided input and have all indicated that the reimbursement of tucatinib would fulfill a significant unmet need for a new treatment that can extend survival in heavily pre-treated patients with HER2+ metastatic breast cancer (MBC).

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	☐

Seagen fully agrees with the clinical considerations and patient-based values made by pERC while deliberating on tucatinib. Seagen specifically agrees with the following:

- Tucatinib plus trastuzumab and capecitabine was associated with statistically significant and clinically meaningful improvements in progression-free survival (PFS), including those with brain metastases, and overall survival (OS).
- Tucatinib provides an additional treatment option for patients with prolonged PFS and OS and no deterioration in quality of life and fulfills an unmet need for treatment of patients who have previously received trastuzumab, pertuzumab, and T-DM1.
- Combination therapy with tucatinib plus trastuzumab and capecitabine could fill a treatment gap in patients who cannot receive pertuzumab or T-DM1, due to contraindications or toxicity issues, and patients who relapse early on T-DM1 or trastuzumab in the adjuvant setting.
- It would be appropriate to offer the tucatinib combination for patients with an ECOG PS of 2, based on the judgement of the treating physician.

- It would be appropriate to offer the tucatinib combination to patients, otherwise eligible for HER2CLIMB criteria, who are currently receiving systemic therapy (e.g., capecitabine) with no evidence of progressive disease/intolerance

Regarding the pharmacoeconomic evaluation, Seagen would like to comment on the conclusions reached by CADTH on the economic models in the draft recommendation and the Pharmacoeconomic Review Report. Seagen believes that the ICER estimate provided by CADTH is likely overestimated due to a number of inputs and assumptions altered by CADTH and for which Seagen had provided feedback. Seagen respectfully reiterates the following:

- In response to CADTH's uses of survival curves from the HER2CLIMB data to inform the tucatinib-combination and hazard ratio (HR) estimates from the network meta-analysis (NMA) to inform the comparative effectiveness for other comparators, Seagen reiterates that comparative efficacy for all comparisons should be informed by the HRs used in the NMA to ensure a consistent approach across reviews for breast cancer products. To inform the comparisons across treatments, the CADTH re-analysis should use the same data source for comparative efficacy. This is in alignment with previous CADTH reviews in breast cancer (e.g., CDK 4/6 inhibitors) that have highlighted the importance of deriving comparative efficacy inputs from the same source.[1]
- In response to CADTH's use of 100% relative dose intensity (RDI) for all orally administered therapies (e.g., tucatinib, lapatinib, capecitabine), Seagen reiterates that the RDI provided in the submitted base case should be retained for all orally administered therapies in the economic model to ensure a consistent approach across previous CADTH reviews in breast cancer, and to reflect the results of published RCTs.[1]
- In response to CADTH's use of alternative assumptions for the OS efficacy curve (Gompertz), Seagen highlighted the difficulty in justifying the use of the Gompertz function for efficacy in terms of model fit and the long-term survival demonstrated by the tucatinib combination in HER2CLIMB and other trials.[2-4] Given that the Gompertz function provides a poor fit to the HER2CLIMB data and pessimistic predictions of the mean difference in survival between two arms, Seagen reiterates that the Weibull function should be used as the base case for the OS curve extrapolation.

Seagen also respectfully notes that the budget impact results by CADTH are likely overestimated, as it does not account for actual provincial utilization of prior therapies (e.g., T-DM1). These data would provide a more precise estimate of the true budget impact for tucatinib versus an epidemiological-based approach. Recent data suggest that the number of patients receiving T-DM1 (with prior exposure to trastuzumab and pertuzumab) is less than what CADTH has calculated.[5]

Notwithstanding the above economic comments, Seagen supports the conversion of the draft recommendation to a final recommendation to expedite access for patients with HER2+ MBC. Seagen is committed to working with all jurisdictions via the pCPA process to ensure that patients have timely access to tucatinib, which delivers an unprecedented OS benefit and a manageable safety profile, in patients with HER2+ MBC, including those with brain metastases who have received prior treatment with trastuzumab, pertuzumab and T-DM1.

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
Seagen is appreciative that the reasons for the recommendation are indeed clearly stated.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐

Seagen agrees that the reasons for the implementation issues are indeed clearly stated.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
Seagen is once again appreciative that the reimbursement criteria for the recommendation are indeed clearly stated.		

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

References:

1. CADTH. pan-Canadian Oncology Drug Review Final Economic Guidance Report. Abemaciclib (Verzenio) for Metastatic Breast Cancer. Published July 5, 2019. Accessed at: https://www.cadth.ca/sites/default/files/pcodr/Reviews2019/10161AbemaciclibMBC_fnEGR_NOREDACT-ABBREV_Post_05Jul2019_final.pdf.

2. Kaufman PA et al. Phase III open-label randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol. 2015 Feb 20;33(6):594-601.

3. Saura C et al. Neratinib plus capecitabine versus lapatinib plus capecitabine in HER2-positive metastatic breast cancer previously treated with ≥ 2 HER2-directed regimens: Phase III NALA trial. J Clin Oncol. 2020;37.

4. Urruticoechea A, Rizwanullah M, Im S-A, Sánchez Ruiz AC, Láng I, Tomasello G, et al. Randomized phase III trial of trastuzumab plus capecitabine with or without pertuzumab in patients with human epidermal growth factor receptor 2–positive metastatic breast cancer who experienced disease progression during or after trastuzumab-based therapy. J Clin Oncol. 2017 Sep 10;35(26):3030-8.

5. Ethier JL, Desautels D, Robinson A, et al. Practice Patterns and Outcomes of Novel Targeted Agents for the Treatment of ERBB2-Positive Metastatic Breast Cancer. JAMA Oncol. Published online July 8, 2021. Accessed at: https://jamanetwork.com/journals/jamaoncology/article-abstract/2781609.