CADTH

CADTH REIMBURSEMENT REVIEW

Clinician Input

tucatinib (Tukysa)

Seagen Canada Inc.

Indication: Advanced or Metastatic Breast Cancer

April 23, 2021

CADTH Reimbursement Review
Clinician Group Input Template

CADTH Project Number	PC0243-000
Generic Drug Name (Brand Name)	**Tucatinib (Brand: Tukysa); Manufacturer: Seattle Genetics**
Indication	Manufacturer Requested Reimbursement Criteria[1]: **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.**
Name of the Clinician Group	**Ontario Health (Cancer Care Ontario) Breast Cancer Drug Advisory Committee**
Author of the Submission	**Dr. Andrea Eisen, Dr. Orit Freedman, Dr. Phillip Blanchette, Annie Ngan (pharmacist)**
Contact information	Name: Dr. Andrea Eisen Title: Ontario Cancer Lead Email: [redacted] Phone: NA

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

OH-CCO's Drug Advisory Committees provide timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs (PDRP) and the Systemic Treatment Program.

2. Information Gathering

Please describe how you gathered the information included in the submission.

Discussed jointly via emails and at a DAC meeting.

3. Current treatments

3.1. Describe the current treatment paradigm for the disease

Focus on the Canadian context.

Please include drug and non-drug treatments.

Drugs without Health Canada approval for use in the management of the indication of interest may be relevant if they are routinely used in Canadian clinical practice. Are such treatments supported by clinical practice guidelines?

Treatments available through special access programs are relevant.

Do current treatments modify the underlying disease mechanism? Target symptoms?

Response:

First line: trastuzumab, pertuzumab and taxane chemotherapy

Second line: trastuzumab emtansine

No third line anti-HER2 directed therapy is funded for HER2-positive metastatic breast cancer patients in Ontario and this is a huge unmet need. Currently there is no effective treatment for brain mets other than radiation.

4. Treatment goals

4.1. What are the most important goals that an ideal treatment would address?

Examples: Prolong life, delay disease progression, improve lung function, prevent the need for organ transplant, prevent infection or transmission of disease, reduce loss of cognition, reduce the severity of symptoms, minimize adverse effects, improve health-related quality of life, increase the ability to maintain employment, maintain independence, reduce burden on caregivers.

Response:

Tucatinib, capecitabine and trastuzumab as third line therapy provides a clinically meaningful and significant improvement in progression-free (PFS) and overall survival (OS). [N Engl J Med 2020;382:597-609]. In patients with central nervous system (CNS) metastasis, both survival and quality of life (QofL) outcomes were improved. [J Clin Oncol 38:2610-2619]

The side effect profile is favourable for tucatinib combination therapy.

5. Treatment gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

Examples:

- *Not all patients respond to available treatments*
- *Patients become refractory to current treatment options*
- *No treatments are available to reverse the course of disease*
- *No treatments are available to address key outcomes*
- *Treatments are needed that are better tolerated*

- *Treatment are needed to improve compliance*
- *Formulations are needed to improve convenience*

Response:

Tucatinib, capecitabine and trastuzumab provides a significant unmet need in treating advanced HER2-positive breast cancer as currently there is no available third line anti-HER2 directed treatments funded in the province. The treatment of CNS disease in HER2 positive metastatic breast cancer is also a large unmet need. Tucatinib has excellent CNS penetration and significantly improves PFS, OS and QofL in patient with CNS disease. [J Clin Oncol 38:2610-2619]

Patients who received adjuvant TDM-1 and relapsed within 6 months are currently not eligible for pertuzumab funding in Ontario and are left without anti-HER2 directed therapy. Although these patients were not eligible for tucatinib combination therapy in HER2CLIMB, funding should be extended to this population.

There is also a big unmet need in patients with aggressive brain mets who are not candidates for local therapies, as currently there are no other systemic therapy that has significant CNS activity. Tucatinib may be preferred in this patient population.

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

Would these patients be considered a subpopulation or niche population?

Describe characteristics of this patient population.

Would the drug under review address the unmet need in this patient population?

Response:

Patients with advanced HER2-positive breast cancer who have progressed on 1st line and 2nd line therapy do not have any provincially funded third line ant-HER2 directed therapy options. This advancement is also critical for patients with CNS metastasis as current available systemic therapies have poorer CNS penetration and activity.

6. Place in therapy

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

Is there a mechanism of action that would complement other available treatments, and would it be added to other treatments?

Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?

Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment?

Is the drug under review expected to cause a shift in the current treatment paradigm?

Response:

Tucatinib, capecitabine and trastuzumab would be added to existing therapy.

6.2. Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

If so, please describe which treatments should be tried, in what order, and include a brief rationale.

Response:

Eligible patients should have progressed on previous treatment with trastuzumab, pertuzumab and trastuzumab emtansine.

Patients who are not eligible for one of the above treatments for specific reasons should still be considered for treatment with tucatinib based on unmet need.

Although the trial excluded patients previously treated with capecitabine or lapatinib, these patients should be considered for tucatinib combination on a time-limited basis.

6.3. How would this drug affect the sequencing of therapies for the target condition?

If appropriate for this condition, please indicate which treatments would be given after the therapy has failed and specify whether this is a significant departure from the sequence employed in current practice.

Would there be opportunity to treat patients with this same drug in a subsequent line of therapy? If so, according to what parameters?

Response:

This treatment would not alter the sequencing of therapies for the treatment of HER2-positive breast cancer at present.

6.4. Which patients would be best suited for treatment with the drug under review?

Which patients are most likely to respond to treatment with the drug under review?

Which patients are most in need of an intervention?

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?

Response:

Patients with advanced breast carcinoma that had been determined to be HER2-positive on the basis of immunohistochemical analysis, in situ hybridization, or fluorescence in situ hybridization; had previously been treated with trastuzumab, pertuzumab, and trastuzumab emtansine.

6.5. How would patients best suited for treatment with the drug under review be identified?

Examples: *Clinician examination or judgement, laboratory tests (specify), diagnostic tools (specify)*

Is the condition challenging to diagnose in routine clinical practice?

Are there any issues related to diagnosis? (e.g., tests may not be widely available, tests may be available at a cost, uncertainty in testing, unclear whether a scale is accurate or the scale may be subjective, variability in expert opinion.)

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?

Should patients who are pre-symptomatic be treated considering the mechanism of action of the drug under review?

Response:

Patients must be determined to be HER2-positive on the basis of immunohistochemical analysis, in situ hybridization, or fluorescence in situ hybridization. This is standard testing in breast cancer care.

6.6. Which patients would be least suitable for treatment with the drug under review?

Response:

Patient previously treated with an anti-HER2 tyrosine kinase inhibitor, capecitabine (other than being considered on a time-limited basis) or patients with significant cardiac dysfunction.

6.7. Is it possible to identify those patients who are most likely to exhibit a response to treatment with the drug under review?

If so, how would these patients be identified?

Response:

No

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

Are the outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

Response:

Yes

6.9. What would be considered a clinically meaningful response to treatment?

Examples:

- *Reduction in the frequency or severity of symptoms (provide specifics regarding changes in frequency, severity, and so forth)*
- *Attainment of major motor milestones*
- *Ability to perform activities of daily living*
- *Improvement in symptoms*
- *Stabilization (no deterioration) of symptoms*

Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

Response:

A clinically meaningful response would mean improving progression-free, overall survival and quality of life of patients. This also includes improved control in CNS disease. HER2CLIMB trial demonstrated significant improvements in these areas compared with alternative treatments.

6.10. How often should treatment response be assessed?

Response:

Routine clinical and radiographic staging as per breast cancer guidelines

6.11. What factors should be considered when deciding to discontinue treatment?

Examples:

- *Disease progression (specify; e.g., loss of lower limb mobility)*
- *Certain adverse events occur (specify type, frequency, and severity)*
- *Additional treatment becomes necessary (specify)*

Response:

Treatment would be discontinued due to disease progression, toxicity, side effects, or patient or physician preference.

6.12. What settings are appropriate for treatment with the drug under review?

Examples: Community setting, hospital (outpatient clinic), specialty clinic

Response:

Treatment at specialized medical oncology cancer clinics. Tucatinib and capecitabine are oral take home cancer drugs.

Oral anti-cancer medication monitoring would be helpful.

6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?

If so, which specialties would be relevant?

Response:

NA

7. Additional information

7.1. Is there any additional information you feel is pertinent to this review?

Response:

Men were included in HER2CLIMB and should be eligible for tucatinib combination.

8. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

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

   OH-CCO provided secretariat support to the DAC in completing this input.

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

   No.

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. **Please note that this is required for <u>each clinician</u> that contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Clinician Information	
Name	*Dr. Andrea Eisen*
Position	*Ontario Cancer Lead; Medical oncologist, Odette Cancer Centre Sunnybrook Health Sciences Centre*
Date	*09-April-2021*
☒	**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				
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	☐	☐	☐	☐

Declaration for Clinician 2

Clinician Information	
Name	*Dr. Phillip Blanchette*
Position	*Medical Oncologist, London Regional Cancer Program*
Date	*01 April 2021*

☒	**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				
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	☐	☐	☐	☐

Declaration for Clinician 3

Clinician Information	
Name	*Dr. Orit Freedman*
Position	*Medical Oncologist, Durham Regional Cancer Centre*
Date	*06 April 2021*
☒	**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				
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	☐	☐	☐	☐

Declaration for Clinician 4

Clinician Information	
Name	*Annie Ngan*
Position	*Pharmacist, Odette Cancer Centre Sunnybrook Health Sciences Centre*
Date	*09 April 2021*
☒	**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				
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	☐	☐	☐	☐

Declaration for Clinician 5

Clinician Information	
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

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 Reimbursement Review
Clinician Group Input Template

CADTH Project Number	PC0243-000
Generic Drug Name (Brand Name)	**TUKYSA (tucatinib)**
Indication	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.
Name of the Clinician Group	**Ottawa Hospital Cancer Centre – medical oncology (breast disease site group)**
Author of the Submission	**Dr. Sandeep Sehdev**
Contact information	Name: Dr. Sandeep Sehdev Title: MD FRCPC, Assistant Professor Email: [redacted] Phone: [redacted]

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

We are members of the group of medical oncologists at the Ottawa Hospital Cancer Centre, affiliated with University of Ottawa, treating breast cancer. We are in an academic teaching hospital centre and we are all involved in the care of breast cancer patients. We offer routine standard of care treatments and access to promising treatments in the context of phase 1 to 3 clinical trials, and serve a large referral base from the Champlain LHIN in Ontario.

2. Information Gathering

Please describe how you gathered the information included in the submission.

Our members were canvassed electronically and in person for input and opinion, using this CADTH template, and the recommendations were condensed and coalesced into summary statements reflecting the breadth of opinions expressed. Our opinions were based on literature review, data from recent international congresses and publications.

3. Current treatments

3.1. Describe the current treatment paradigm for the disease

Focus on the Canadian context.

Please include drug and non-drug treatments.

Drugs without Health Canada approval for use in the management of the indication of interest may be relevant if they are routinely used in Canadian clinical practice. Are such treatments supported by clinical practice guidelines?

Treatments available through special access programs are relevant.

Do current treatments modify the underlying disease mechanism? Target symptoms?

Response:

Beyond current standard 1st line (taxane chemo + trastuzumab + pertuzumab) and 2nd line therapies (T-DM1, trastuzumab-emtansine), the standard of care is not well defined and usually further endocrine or chemotherapy agents are used as single agents sequentially. It is felt that further Her2 targeted agents should also be offered but they are not publically funded in Canadian jurisdictions. In other nations or for patients with private means, therapies can include:

Endocrine /Her2 targeted options such as fulvestrant/abemaciclb + trastuzumab; aromatase inhibitors or fulvestrant alone with trastuzumab; single agent chemotherapy (capecitabine or vinorelbine) with trastuzumab; dual Her2 targeted combination therapy (trastuzumab/lapatinib), or chemo/small molecule Her2 targeted approaches (capecitabine+lapatinib, capecitabine + neratinib). Clinical trials are recommended when available for eligible patients.

Choices of therapies are based on patient goals, performance status, symptoms, rapidity of disease progression, visceral organ involvement, and insurance coverage.

4. Treatment goals

4.1. What are the most important goals that an ideal treatment would address?

Examples: Prolong life, delay disease progression, improve lung function, prevent the need for organ transplant, prevent infection or transmission of disease, reduce loss of cognition, reduce the severity of symptoms, minimize adverse effects, improve health-related quality of life, increase the ability to maintain employment, maintain independence, reduce burden on caregivers.

Response:

Overall survival and quality of life are important goals. In this usually symptomatic patient population, improved response rates are also desirable in order to see more rapid symptom improvements. Given the lack of downstream available “next line” therapies, dramatic progression free survival benefits are also valuable, deferring the need for earlier use of potentially more toxic unproven future remedies. Further, there is a need to prevent/delay brain metastases, common in this disease, or to effectively treat them since other systemic therapies (in this line of treatment) have not been very effective.

Patients value OS, QoL, and PFS advantages when the toxicity trade offs are manageable and acceptable.

5. Treatment gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

Examples:

- *Not all patients respond to available treatments*
- *Patients become refractory to current treatment options*
- *No treatments are available to reverse the course of disease*
- *No treatments are available to address key outcomes*
- *Treatments are needed that are better tolerated*
- *Treatment are needed to improve compliance*
- *Formulations are needed to improve convenience*

Response:

Though ongoing Her2 targeting is a global standard of care, there are no funded, HER-2 targeted regimens in Canada beyond 2nd line TDM-1. Therefore large proportions of the population have no access to effective treatments following progression on TDM-1. This is partly because current treatments beyond second line treatment with TDM-1 in this population demonstrate some responses but do not have proven survival prolonging benefits. Brain metastases are common in this setting and current treatments do not effectively prevent those. Tucatinib, capecitabine, and trastuzumab thus fulfills a large unfilled need as a treatment that has shown improved survival, including in those with brain metastases. Given the lack of other options in this setting, this regimen is critically needed to improve both mortality and morbidity in this population of patients.

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

Would these patients be considered a subpopulation or niche population?

Describe characteristics of this patient population.

Would the drug under review address the unmet need in this patient population?

Response:

Since patients nowadays can do well initially with the above standard 1st and 2nd line treatments, a relatively large group are eligible for 3rd line therapy with this tucatinib based regimen. The benefits are felt to be ground-breaking. Also, 2nd line patients with: contraindications to trastuzumab-emtansine (eg persistent difficult residual peripheral neuropathy from preceding chemotherapy); recurrence or progression after preceding (neo)/adjuvant trastuzumab (+/- pertuzumab) or trastuzumab-emtansine; or active brain metastases (where the activity of trastuzumab-emtansine alone is modest) would also be eligible.

6. Place in therapy

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

Is there a mechanism of action that would complement other available treatments, and would it be added to other treatments?

Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?

Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment?

Is the drug under review expected to cause a shift in the current treatment paradigm?

Response:

It would fit in as a 3rd line of treatment, following the eligibility criteria of the referenced clinical trial (Her2CLIMB study), with allowances for additional exceptions as mentioned in #5.2 above.

Patients beyond 3rd line, treated before tucatinib became available, would also be good candidates for this approach as long as their disease had not progressed whilst on capecitabine chemotherapy.

6.2. Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

If so, please describe which treatments should be tried, in what order, and include a brief rationale.

Response:

Other available treatments do not have the level of evidence of benefit (OS, PFS) shown with Her2CLIMB even though is was a phase 2 randomized study. Other treatments which could be considered include clinical trials, or if not fitting eligibility criteria for Her2CLIMB or if having contraindications to either trastuzumab (cardiac ejection fraction low), capecitabine (ability to tolerate oral therapy, diarrhea, renal dysfunction); or based on patient preference or ability to comply. However, given the results of the Her2CLIMB study other treatment options, rather than tucatinib, unless driven by a lack of access to tucatinib (due to lack of funding) would not be appropriate based on the currently available evidence.

6.3. How would this drug affect the sequencing of therapies for the target condition?

If appropriate for this condition, please indicate which treatments would be given after the therapy has failed and specify whether this is a significant departure from the sequence employed in current practice.

Would there be opportunity to treat patients with this same drug in a subsequent line of therapy? If so, according to what parameters?

Response:

Other available treatments could be offered beyond progression, as they have been in the past. It is not expected that patients treated with tucatinib, capecitabine, and trastuzumab would be ineligible for subsequent treatment options. In light of expected attrition due to declining health and performance status, however, the number of subsequent lines would be fewer (in practice, 0-2 lines commonly).

6.4. Which patients would be best suited for treatment with the drug under review?

Which patients are most likely to respond to treatment with the drug under review?

Which patients are most in need of an intervention?

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?

Response:

Patients with metastatic Her2+ breast cancer (ASCO-CAP Her2 criteria), ECOG PS 0-2, previously treated with taxane chemo/trastuzumab/pertuzumab and trastuzumab-emtansine. Interceding use, for patients with more indolently behaving ER+ disease, of endocrine based regimens should not disqualify from eligibility.

6.5. How would patients best suited for treatment with the drug under review be identified?

Examples: *Clinician examination or judgement, laboratory tests (specify), diagnostic tools (specify)*

Is the condition challenging to diagnose in routine clinical practice?

Are there any issues related to diagnosis? (e.g., tests may not be widely available, tests may be available at a cost, uncertainty in testing, unclear whether a scale is accurate or the scale may be subjective, variability in expert opinion.)

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?

Should patients who are pre-symptomatic be treated considering the mechanism of action of the drug under review?

Response:

They would have been on active treatments, monitored closely by their medical oncologists, and identified on the basis of objective disease progression.

6.6. Which patients would be least suitable for treatment with the drug under review?

Response:

ECOG PS 3-4, expected survival < 3 months, dysfunctional gastrointestinal tracts, or those ineligible for trastuzumab (based on past severe infusion reactions or cardiac dysfunction) or capecitabine.

6.7. Is it possible to identify those patients who are most likely to exhibit a response to treatment with the drug under review?

If so, how would these patients be identified?

Response:

Response rates in the Her2CLIMB trial were 40.6% (by RECIST criteria) – all eligible patients should have the opportunity to benefit based on the inclusion/exclusion criteria above. No particular subgroups were found not to benefit.

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

Are the outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

Response:

Patients are evaluated prior to each cycle of treatment for efficacy and tolerability. Clinical examination, symptom improvement, biochemical parameters and periodic radiographic restaging (usually every 3-4 cycles) are all utilized.

6.9. What would be considered a clinically meaningful response to treatment?

Examples:

- *Reduction in the frequency or severity of symptoms (provide specifics regarding changes in frequency, severity, and so forth)*
- *Attainment of major motor milestones*
- *Ability to perform activities of daily living*
- *Improvement in symptoms*
- *Stabilization (no deterioration) of symptoms*

Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

Response:

Improvement in symptoms (varying depending on extent/location of metastatic involvement) or improvement of functional scores (ECOG PS, ESAS Edmonton Symptom Assessment Scale). Radiographic responses by RECIST criteria are also important, signifying a disease modifying effect that might imply longer PFS, delay to more toxic therapy, postponement of disability and improved survival.

6.10. How often should treatment response be assessed?

Response:

Radiographically, in practice, every 3-4 cycles.

6.11. What factors should be considered when deciding to discontinue treatment?

Examples:

- *Disease progression (specify; e.g., loss of lower limb mobility)*
- *Certain adverse events occur (specify type, frequency, and severity)*
- *Additional treatment becomes necessary (specify)*

Response:

Disease progression by radiographic RECIST criteria, intolerable or unmanageable toxicity (the usual spectrum of side effects of any of the 3 drugs used), patient preference,

6.12. What settings are appropriate for treatment with the drug under review?

Examples: Community setting, hospital (outpatient clinic), specialty clinic

Response:

The 2 oral therapies would be given at the patients' homes (or institutions) and the iv trastuzumab in the usual cancer clinic or infusion clinic environments.

6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?

If so, which specialties would be relevant?

Response:

Not applicable

7. Additional information

7.1. Is there any additional information you feel is pertinent to this review?
Response: This regimen fills an urgent unmet need. The magnitude of benefit warrants approval and use based on the large phase 2 trial referenced. The activity seen in controlling/improving brain metastases (even if active) is unprecedented.

8. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

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

No assistance was received in the completion of this report.

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

No assistance was received in collection or analysis of data to support this submission.

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. **Please note that this is required for each clinician that contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Clinician Information	
Name	*Dr Sandeep Sehdev*
Position	*Medical oncologist*
Date	*March 6 2021*
☒	**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	
Company	**Check Appropriate Dollar Range**

	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
AstraZeneca [advisory board/speaking fees]	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 2

Clinician Information	
Name	*Tina Hsu*
Position	*Medical oncologist; Assistant professor, University of Ottawa*
Date	*15-03-2021*
☒	**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

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Pfizer – ad board	☒	☐	☐	☐
Eisai – ad board	☒	☐	☐	☐
Genomic health – ad board	☒	☐	☐	☐

Declaration for Clinician 3

Clinician Information	
Name	*Dr Mark Clemons*
Position	*Medical Oncologist*
Date	*15-Mar-2021*
☒	**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

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Eli Lilly advisory board	☒	☐	☐	☐
Pfizer speakers bureau	☒	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 4

Clinician Information	
Name	*Dr. Terry Ng*
Position	*Medical oncologist, Assitant Professor, U of Ottawa*
Date	*15-Mar-2021*
☒	**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

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Takeda – medical education	☒	☐	☐	☐
Ariad – medical education	☒	☐	☐	☐
Boehringer-Ingelheim – advisory board	☒	☐	☐	☐

Declaration for Clinician 5

Clinician Information	
Name	*Dr. Sharon McGee*
Position	*Medical Oncologist*
Date	*15-Mar-2021*
☒	**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

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 6

Clinician Information	
Name	*Dr John Hilton*
Position	*Medical Oncologist*
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				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
AstraZeneca	☒	☐	☐	☐
Seattle Genetics	☒	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 7

Clinician Information	
Name	*Dr Xinni Song*
Position	*Medical Oncologist*
Date	*15-Mar-2021*
☒	**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				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Novartis	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 8

Clinician Information	
Name	*Dr Marie France-Savard*
Position	*Medical Oncologist*
Date	*15-Mar-2021*
☒	**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				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Pfizer	☒	☐	☐	☐
Amgen	☒	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 9

Clinician Information	
Name	*Dr. Amirrtha Srikanthan*
Position	*Medical Oncologist*
Date	*15-Mar-2021*
☒	**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				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐