CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

pertuzumab (Perjeta)

(Hoffman-La Roche Ltd.)

Indication: Early stage breast cancer

October 18, 2021

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0241
Name of the drug and Indication(s)	Pertuzumab in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either 2 cm in diameter or node positive)
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	PC0241-000
Brand name (generic)	Pertuzumab
Indication(s)	In combination with trastuzumab and chemotherapy for the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early-stage breast cancer (either 2 cm in diameter or node positive)
Organization	British Columbia Breast Tumour Group and Nova Scotia Breast Tumour Group
Contact information [a]	[redacted]

Stakeholder agreement with the draft recommendation

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

1. Multiple international guidelines clearly recommend neoadjuvant pertuzumab in this specific indication. Canada will clearly fall behind the stated standard of care in most jurisdictions in the world.
2. NeoSphere is underpowered for long term clinical outcomes. pCR was the primary endpoint of the trial to which the study was powered for. However both trial defined meta-analyses (FDA performed) and real-world evidence (from British Columbia) how shown achievement of a pCR clearly is associated with improved DFS and OS. Both of these studies are published in peer reviewed journals.
3. APHINITY, the adjuvant pertuzumab trial, met its primary endpoint of improved DFS. This is further evidence of efficacy of pertuzumab in the early stage setting. This adds to the whole body of evidence that dual anti-HER2 blockade synergizes with chemotherapy to improve efficacy.
4. It is unequivocal that assessment of neoadjuvant treatment in the pathological specimen is the key clinical decision point regarding adjuvant treatment(s). Increasing pCR with neoadjuvant pertuzumab will reduce the use of adjuvant T-DM1. This will reduce the increased toxicities to patients and reduce resource use and costs to society.

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	☒

- It is clear CADTDH did not acknowledge our input. All patients and breast cancer oncologists recognize and request neoadjuvant pertuzumab. This draft recommendation f**urther marginalizes patients** because those who have private insurance or the ability to pay out of pocket will receive better care than those who do not have those means. This is not in keeping with our assumed publicly funded health care system.

Clarity of the draft recommendation

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

Please look at the big picture. Not just at one trial's secondary endpoint which CADTDH acknowledges is under-powered. Look at the totality of evidence in this field. Please acknowledge that international guidelines and countries fund neoadjuvant pertuzumab for this specific indication. All future neoadjuvant trials in this HER2+ indication have pertuzumab in the standard of care arm. Thus the study that CADTH requests (a neoadjuvant trial of pertuzumab that has DFS as primary endpoint) will never be undertaken. This ruling will result in inferior care for our patients in Canada.		
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 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	*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 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	☐	☐	☐	☐

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.
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- 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.		
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: • Clinician 1 – Dr. Stephen Chia • Clinician 2 – Dr. Daniel Rayson • *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 3	
Name	*Dr Sandeep Sehdev*
Position	*Assistant Professor, U of Ottawa. Medical Oncologist, lead breast cancer group, The Ottawa Hospital Cancer Centre*
Date	*17-Oct-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

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**
Roche	☐	☒	☐	☐

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 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	PC0241-000
Brand name (generic)	Perjeta (Pertuzumab) – Roche
Indication(s)	**Manufacturer Requested Reimbursement Criteria[1]:** Pertuzumab in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either 2 cm in diameter or node positive). Patients should receive neoadjuvant treatment with pertuzumab in combination with trastuzumab and chemotherapy for three to six cycles depending on the regimen chosen. Patients who start pertuzumab in combination with trastuzumab and chemotherapy in the neoadjuvant setting and do not have residual disease following surgery should continue to receive adjuvant trastuzumab to complete one year of HER2-directed therapy.
Organization	Ontario Health (Cancer Care Ontario) Breast Cancer Drug Advisory Committee
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.		

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? The potential impact of higher pCR rate on the use of adjuvant TDM-1 was not examined. Neoadjuvant pertuzumab's cost-effectiveness may improve if biosimilar is available. Additionally, cost effectiveness may improve if pertuzumab is used with biosimilar trastuzumab. Pertuzumab is better tolerated vs TDM-1. Neoadjuvant pertuzumab may reduce the need for adjuvant TDM-1 and minimize TDM-1 related toxicities.		

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. Not applicable (Recommendation was “Do not Reimburse”)		
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. Not applicable (Recommendation was “Do not Reimburse”)		

[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.
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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. OH-CCO provided secretariat support to the DAC.		
2. 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		
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 • 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	PC0241-000
Brand name (generic)	Perjeta (pertuzumab)
Indication(s)	Pertuzumab in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either >2 cm in diameter or node positive). Patients should receive neoadjuvant treatment with pertuzumab in combination with trastuzumab and chemotherapy for three to six cycles depending on the regimen chosen.
Organization	Canadian Breast Cancer Network
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.

The Canadian Breast Cancer Network (CBCN) respectfully disagrees with the analysis put forth by the draft recommendation.

We raise concerns regarding the section which states "*Patients identified a need for new treatments that prevent recurrence and metastases, but pERC concluded there was uncertainty whether neoadjuvant pertuzumab meets this need given the limitations of the evidence on long-term outcomes,*" and,

"it is unclear whether the improvements in pCR observed with the addition of pertuzumab translate to clinically meaningful improvements in event-free or OS outcomes"

We would like to emphasize that this treatment is intended for HER2 positive breast cancer patients in the early-stage setting, who are at high-risk of recurrence. Accessing pertuzumab in the neoadjuvant setting, is especially important for these patients as the disease can be curable and often occurs in younger patients.

We note that from the patient perspective, uncertainty around evidence for achieving overall survival does not preclude the likelihood of benefit. The value of achieving pCR to both patients and clinicians should not be understated. As a clinical marker, pCR offers patients and clinicians important information not only about the patient's response to a given treatment, but also offers prognostic insights that can influence a patient's care. There is tremendous value to a patient in knowing that pCR has been achieved, and that they can have better outcomes and prognosis. This is particularly true in the case of high-risk, HER2-positive breast cancer patients. Knowing whether a patient has achieved pCR is extremely helpful to both the patient and the clinician and can avert systemic costs should a patient be found to have residual disease. The cost of providing a patient with 6 cycles of preoperative pertuzumab should be viewed as marginal when compared to the costs associated with providing a patient with residual disease 14 cycles of trastuzumab emtansine

The clinical utility of pCR is further demonstrated by its function in sparing patients and insurance providers unnecessary and costly treatments. Typically, patients who do not achieve pCR are often prescribed oral neratinib for one year. This treatment, is Health Canada approved, though not publicly reimbursed in Canada, and is widely accepted as standard of care for higher risk breast cancer patients who do not achieve pCR. Knowing whether a patient has achieved pCR is therefore of extreme value for a patient and their family, as it can spare them from continued therapy, and increased toxicities from treatment. It also offers a cost-saving benefit for both patients and insurers.

We strongly emphasize the need for Canadian treatment protocols to remain consistent with accepted international guidelines and standards, which are established by acknowledged experts in breast cancer (including ASCO and NCCN).

Neoadjuvant treatment with pertuzumab has become the standard of care for patients with HER2-positive, early-stage breast cancer globally. We note that NICE in the UK, the European Commission and the FDA in the US have all accepted the same clinical data featuring pathological complete response (pCR) as a relevant clinical endpoint. In these other jurisdictions, neoadjuvant treatment was approved and adopted as standard clinical practice to downsize the tumor and increase breast-conserving rates. The addition of targeted therapies to neoadjuvant chemotherapy has been shown to increase the proportion of patients who achieve pCR. It is well documented that patients who achieve pCR show better prognosis compared with those with residual disease following neoadjuvant therapy. We believe Canadian patients should be offered the same opportunities as our global counterparts to benefit from innovative and effective treatment options and we strongly urge CADTH to reconsider this recommendation.

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	☒

The draft recommendation states that "T*he most important outcomes to patients were the elimination of cancer cells, prevention of recurrence, and preventing metastases. Maintaining quality of life was also rated by the majority of patients as very important or important, as was managing adverse effects. Patients were clear that they were very willing to tolerate new adverse effects from drugs in order to extend life expectancy."*

CBCN notes that several other aspects of the patient experience mentioned in our submission were not referenced in the draft recommendation. We feel that these factors significantly impact the interpretation of the patient perspective of the disease and its management.

We discuss that while early-stage, HER2 positive patients are in the curative setting, patients have more limited treatment options available to them. The HER2-positive breast cancer subtype is traditionally associated with more aggressive cancers and a poor prognosis in the absence of HER2-directed therapy with a greater likelihood for central nervous system metastases. It is therefore of critical importance for patients to have targeted anti-HER2 therapies available to them to reduce the risk of disease recurrence. Even so, approximately 15 percent of patients treated with HER2-directed therapy continue to experience disease relapse.

We assert that the primary goal of neoadjuvant therapy is to target cancer cells in the body and that treatments that reduce tumour size may make the disease operable, and in other cases allow for breast-conserving surgery, thereby reducing the need for more complicated procedures like mastectomy and breast reconstruction and their associated risks. The value of this cannot be understated for the patient. We also include that preoperative therapy can also provide a real-time evaluation of tumor response to allow discontinuation of ineffective therapies, and can provide vital prognostic information as a supplement to conventional prognostic data (ie tumour staging, grade, receptor status etc). Thus, targeted neoadjuvant treatment offers patients and clinicians vital information and benefit beyond reducing the risk of recurrence.

There are also a number of patient values expressed within our submission that are not reflected in the draft recommendation. While quality of life and reducing the risk of recurrence were important considerations for patients surveyed by our organization, so too were other factors. Patients engaged by CBCN emphasized strong preferences for the following:

- Treatments that stabilize disease are extremely valued.
- Patients wish to avoid chemotherapy and other intensive treatments following surgery.

  "If I had to do it over again I would opt out of chemo"-Patient respondent

- Treatments with the *possibility* of reducing the risk of recurrence are valued.

  "I only wanted to reduce my risk of recurrence as much as possible. Everything else was secondary. "-Patient respondent

- Treatments that allow patients to live with minimal side effects are valued.
- Patients want to be aggressive in their treatment and do everything possible to get rid of the cancer.

  "I am a mother to 3 children. I wanted to be aggressive in order to increase my chances of survival. "-Patient respondent

- Many patients experience significant barriers to accessing private insurance or high out-of-pocket costs even with some private insurance coverage.

  "Regarding funding. Because even when they asked me for my group insurance, and they said my insurance would cover Perjeta 80 percent, and the other 20, I should cover myself. But the first dosage was double. It means one infusion is $3800-something. It means around $8000 I'm supposed to pay for the first infusion. And now I'm going to this treatment, there will be a total of 16 infusions. Every time I will pay $3800. It is a lot for one person to cover this every three weeks. " -Patient Respondent

- The patient community has expressed concern that treatments that are the international standard of care are not publicly accessible in Canada

  "Having just that additional little bit of peace of mind that I'm doing everything that I can. I'm pretty young. I've got a young family. I've got a three-year-old. So I need to be able to say that I've done everything that I possibly can to beat it. So having that peace of mind

that I'm getting the same care that others are getting elsewhere in the world, so I don't have to look at going somewhere else and all the costs and finances involved." Patient respondent

"The drug works and women should be able to get access to it. You know, there's been clinical trials that show its effectiveness, and it's so important that Canadians are getting the same treatment that others are getting elsewhere in the world" Patient respondent

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
We do not object to the language in the recommendation, but rather the recommendation itself.		
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	☒

While the language in the recommendation is clear, we remain uncertain as to how the committee came to this recommendation.

The draft recommendation states that "patients identified a need for new treatments that prevent recurrence and metastases, but pERC concluded there was uncertainty whether neoadjuvant pertuzumab meets this need given the limitations of the evidence on long-term outcomes." As mentioned above, we feel that the interpretation of the patient experience and values contained within our submission are not adequately reflected in the draft recommendation.

We note that patients and clinicians see value in the pCR endpoint for both treatment response and prognostic insights. Knowing whether a patient has achieved pCR is therefore of extreme value for a patient and their family, as it can also spare them from continued therapy, and increased toxicities from treatment. It also offers a cost-saving benefits for both patients and insurers. While we understand the committee's focus on overall survival and long-term outcomes, we must emphasize that a lack of evidence demonstrating overall survival does not preclude the likelihood of benefit for patients and clinicians.

We further reiterate the need for Canadian treatment protocols to remain aligned with accepted international guidelines and standards, which are established by acknowledged experts in breast cancer (including ASCO and NCCN).

We note that NICE in the UK, the European Commission and the FDA in the US have all accepted the same clinical data featuring pathological complete response (pCR) as a relevant clinical endpoint, and treatment with pertuzumab in the neoadjuvant setting is established as standard of care globally for high-risk, HER2-positive breast cancer patients. We believe Canadian patients should be offered the same opportunities as our global counterparts to benefit from innovative and effective treatment options and we strongly urge CADTH to reconsider this recommendation.

We thank you for your time and consideration and for the opportunity to continue sharing our input and working with CADTH to ensure that Canadian breast cancer patients are able to receive the best quality of care.

[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	*Niya Chari*
Position	*Director of Health Policy and Public Affairs*
Date	*October 14,2021*
☒	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	☐
CBCN did connect with our medical advisors to inform our understanding of this recommendation and its impact on clinical practice in Canada.		
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 Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0241-000
Brand name (generic)	Perjeta (Pertuzumab)
Indication(s)	In combination with trastuzumab and chemotherapy for the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either 2 cm in diameter or node positive)
Organization	Rethink Breast Cancer
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.

The draft commendation states on page 4 in bullet point 3: "Multiple meta-analyses have demonstrated an association between pCR and EFS or OS at the individual patient level based on responder analyses (i.e., comparisons of outcomes of patients with and without pCR irrespective of the neoadjuvant treatment received); however, at the trial level, there is insufficient evidence of an association and the magnitude of pCR improvement that is needed to predict long-term prognosis."

As noted by one of the patients we interviewed: "This is standard of care in so many places. It is a mystery to me that Canada has not recognized its contribution to improving Breast Cancer patients' survival rate."

CADTH has turned down the same data that had been accepted in dozens of other countries where neoadjuvant Perjeta has been used by medical oncologists for many years, including five years in the UK which is a jurisdiction we usually keep pace with regarding breast cancer treatment. CADTH's negative recommendation prompted our organization to review the recommendation for neoadjuvant Perjeta by NICE in the UK. After doing so, we are concerned that the Canadian appraisal process for innovative treatments remains too inflexible to cope with the complexities of modern cancer drugs.

Rethink believes it is important that the framework for data evaluated in a curative setting be aligned with the goals of patients who have the opportunity to live a cancer free life and avoid more toxic treatment down the road.

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 bullet point 5 on page 4 (Discussion section) of the draft recommendation notes, "Input from patient groups indicated that patients with early breast cancer desire new treatments that delay recurrence and the development of metastases while also maintaining quality of life. Based on the available evidence, pERC

concluded there was uncertainty whether neoadjuvant pertuzumab meets these patient needs given the limitations of the available evidence on long-term outcomes and the absence of data assessing its impact on patient quality of life. pERC noted that EFS and OS data from the PEONY trial are expected in the year 2022 and discussed that the long-term data from this trial could form the basis of a resubmission to CADTH."

35 of our 62 survey respondents matched the full indication for this review. When asked if they would recommend Perjeta to other patients with breast cancer, 100% of respondents who matched the full indication said that they would. And the outcomes reported by respondents who received Perjeta were overwhelmingly positive.

While the draft recommendation indicated a lack of quality of life evidence, our respondents said:

Perjeta improved the average quality of life for respondents in every listed category.

Respondents rated the side effects of Perjeta as the most tolerable of any therapy reviewed by Rethink Breast Cancer.

In the third last sentence on page 3, the draft recommendation states "it is unclear whether the improvements in pCR observed with the addition of pertuzumab translate to clinically meaningful improvements in event-free or OS outcomes."

This ignores the importance of preventing recurrence as demonstrated by our respondents:

- If Perjeta assists in eliminating HER2+ cancers and keeping them away, as I believe it has, I see it as a must for anyone facing these odds.
- The ultimate goal is CURE. With a pCR from the quadruplet, it makes it all worth it. A further decrease in risk of recurrence with very little added toxicity is also very important to reduce anxiety levels.
- Just for the fact that it is a drug that would add to preventing reoccurrence with minimal side effects I found it very beneficial.

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. Not applicable		

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

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- 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 Joanne DeCoteau
Position	Executive Director
Date	18/10/2021
☒	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.

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Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐