CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

ALPELISIB (Piqray)

(Novartis Pharmaceuticals Canada Inc.)

Indication: Advanced or Metastatic Breast Cancer

October 18, 2021

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	**PC0247-000**
Brand name (generic)	**Alpelisib (Piqray)**
Indication(s)	**In combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor positive, Her2 negative, PIK3CA-mutated advanced or metastatic breast cancer after disease progression following a CDK4/6 inhibitor in combination with an endocrine-based regimen**
Organization	**Lead: The Ottawa Hospital Cancer Centre: Breast Medical Oncology group with additional affirmations by medical oncologists across Canada**
Contact information[a]	Name: Dr. Sandeep Sehdev Title: MD FRCPC, Assistant Professor Email: ssehdev@toh.ca Phone: 613-737-7700

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

"This population differs from the broader population of the Health Canada-approved indication for alpelisib in that it specifies that patients must have received a CDK4/6 inhibitor along with a previous endocrine-based regimen

- Standards of care evolve – 1st line CDK4/6 inhibition has become the standard of care in this disease setting and the application reflects this reality. There is no solid preclinical or biological rationale to suggest that PI3K inhibition would "not work" as well in this setting and patients should not be denied the opportunity to benefit from treatment arbitrarily based on their previous treatment. We do not deny them opportunities for specific chemotherapy drugs based on the lack of evidence beyond CDk4/6 inhibition.
- Only 1 of our group (Dr Clemons) felt that the committee's considerations were appropriate.

"The committee noted that the results from the entire PIK3CA mutant cohort, which consisted mostly of patients without prior CDK4/6 inhibitor treatment, could not be generalized to patients with prior CDK4/6 inhibitor treatment."

- There is no solid preclinical or biological rationale to suggest that PI3K inhibition would "not work" as well in this setting and patients should not be denied the opportunity to benefit from treatment arbitrarily based on their previous treatment. We do not deny them opportunities for specific chemotherapy drugs based on the lack of evidence beyond CDk4/6 inhibition.
- The data from the BYLieve study was intended to support this and was not painted as a definitive answer
- Ongoing studies are underway to confirm efficacy post CDK4/6 inhibition, as CADTH is aware
- Given the current state of evidence, eligible patients should not be denied access to alpelisib in the interim
- Consideration might be given to conditional approval (a newer CADTH mechanism applied previously for venetoclax) as clinicians would accept revocation if confirmatory trials should prove negative
- Only 1 of our group (Dr Clemons) felt that the committee's considerations were appropriate.

"…the drug's adverse effects were the same or worse than other treatments they had received."

- Clinicians (including us) have had the opportunity to use alpelisib in clinical trials and in practice. As with all new drugs, with experience our ability to minimize and manage toxicities has improved dramaticially with careful patient selection, dose adjustments, and prophylactic and supportive medications.
- Post CDK4/6 inhibition, the real world comparator would often be chemotherapy with often even greater toxicities

- Patients strongly prefer to avoid chemotherapy if possible, and prefer oral (home) medications, particularly in our Covid-19 era. Severe immunosuppression has not been a significant toxicity of alpelisib.

"A new phase III trial will be conducted for alpelisib plus fulvestrant in patients with prior CDK4/6 inhibitor treatment."

- Ongoing studies are underway to confirm efficacy post CDK4/6 inhibition, as CADTH is aware
- Given the current state of evidence, eligible patients should not be denied access to alpelisib in the interim
- Consideration might be given to conditional approval (a newer CADTH mechanism applied previously for venetoclax) as clinicians would accept revocation if confirmatory trials should prove negative
- Real world evidence (ByLieve, Flatiron) is supportive, suggesting similar benefits as seen in SOLAR-1. While not gold-standard comparative data, it is widely accepted as supportive of drug benefit and should not be downplayed.

"PIK3CA testing is not currently publicly funded in any jurisdictions in Canada."

- Access to required molecular testing for cancer patients is woefully limited across Canada. That is gradually being addressed through a combination of pharma supported funding for testing and new panel testing at academic centres.
- Health care funding in Canada remains terribly "siloed" but a refusal to approve in one silo (drug funding) should not be rationalized based on deficiencies in others
- PIK3CA testing will be widely available through public funding (for all patients in Ontario October) 2021, coordinated through Princess Margaret Cancer Centre
- Clinicians would only use alpelisib where a relevant PIK3CA mutation is identified

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 recommendation includes concerns we had about the toxicities and limitations acknowledged but does not factor in the potential benefits to select patients:

- Having access to another line of treatment. Historically, long term outcomes have been improving as patients have had access to increasing numbers of therapeutic options with differing mechanisms of actions
- Delay to requiring chemotherapy

Further the recommendation is not in line with international expert consensus (eg NCCN guideline listing alpelisib as preferred 2nd line therapy, category 1 evidence).

Only 1 of our group (Dr Clemons) felt that the committee's considerations were appropriate.

Clarity of the draft recommendation

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

Recommendations are clearly stated though, as noted, we feel they are not reasonable conclusions based on the totality of available evidence, experience and consensus

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

Not applicable

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

Not applicable

[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.

Declaration for Clinician 1

Clinician Information	
Name	*Dr. Sandeep Sehdev*
Position	*Medical oncologist, The Ottawa Hospital Cancer Centre*
Date	*13-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				
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	☐	☒	☐	☐
Pfizer	☐	☒	☐	☐
Lilly	☒	☐	☐	☐

Declaration for Clinician 2

Clinician Information	
Name	*Dr Mark Clemons*
Position	*Medical Oncologist, The Ottawa Hospital Cancer Centre*
Date	*13-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				
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	☐	☐	☐	☐

Declaration for Clinician 3

Clinician Information	
Name	*Dr Terry Ng*
Position	*Medical Oncologist, The Ottawa Hospital Cancer Centre*
Date	*13-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				
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	☐	☐	☐	☐

Declaration for Clinician 4

Clinician Information	
Name	*Dr Amirrtha Srikanthan*
Position	*Medical Oncologist, The Ottawa Hospital Cancer Centre*
Date	*13-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				
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	☐	☐	☐	☐

Declaration for Clinician 5

Clinician Information	
Name	*Dr John Hilton*
Position	*Medical Oncologist, Associate Prof, Lead (clinical trials program), Research Lead (breast program), The Ottawa Hospital Cancer Centre*
Date	*13-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

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	☒	☐	☐	☐

Declaration for Clinician 6

Clinician Information	
Name	*Dr Iqbal Nayyer, Professor (U of Saskatchewan) Medical Oncologist, Saskatoon Cancer Centre*
Position	*Medical Oncologist, The Ottawa Hospital Cancer Centre*
Date	*13-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

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	☒	☐	☐	☐
Novartis	☒	☐	☐	☐
Bristol Myers Squibb	☒	☐	☐	☐

Declaration for Clinician 7

Clinician Information	
Name	*Dr Jan-Willem Henning MBChB FRCPC*
Position	*Medical Oncologist, Tom Baker Cancer Centre, Calgary AB*
Date	*13-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

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	☐	☒	☐	☐
Pfizer	☒	☐	☐	☐
Lilly	☒	☐	☐	☐
AstraZeneca	☐	☐	☐	☐
None	☐	☒	☐	☐

Declaration for Clinician 8

Clinician Information	
Name	*Dr Karen Gelmon*
Position	*Medical Oncologist, Professor, Univ of British Columbia, BC Cancer Agency, Vancouver BC*
Date	*13-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

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	☐	☒	☐	☐
Lilly	☒	☐	☐	☐
Novartis	☐	☒	☐	☐
Pfizer	☒	☐	☐	☐
Roche	☒	☐	☐	☐
Merck	☒	☐	☐	☐
Seagen	☒	☐	☐	☐
Gilead	☒	☐	☐	☐
Ayala	☒	☐	☐	☐

Declaration for Clinician 9

Clinician Information	
Name	*Dr Pawel Zalewski*

Position	*Medical Oncologist, Lakeridge Cancer Centre, Oshawa ON*
Date	*13-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

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Lilly	☒	☐	☐	☐
Novartis	☒	☐	☐	☐
Pfizer	☒	☐	☐	☐

Declaration for Clinician 10

Clinician Information	
Name	*Dr Christine Brezden-Masley*
Position	*Medical Oncologist, Assoc Professor, Mt Sinai Hospital, Medical Director (Cancer Program, Sinai Health System), Director (Marvelle Koffler Breast Centre), Toronto ON*
Date	*13-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

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	☐	☒	☐	☐
Lilly	☐	☒	☐	☐
Novartis	☐	☒	☐	☐
Pfizer	☒	☐	☐	☐
Roche	☒	☒	☐	☐
Seagen	☒	☐	☐	☐
Gilead	☒	☐	☐	☐

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

1. 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	☐
3. Did you receive help from outside your clincian group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
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	☒

C. New or Updated Conflict of Interest Declarations

N/A

CADTH

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0247
Name of the drug and Indication(s)	Alpelisib in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor-positive, HER2-negative, PIK3CA-mutated advanced or metastatic breast cancer after disease progression following an endocrine-based regimen with a CDK 4/6 inhibitor
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	PC0247-000
Brand name (generic)	Piqray (alpelisib)
Indication(s)	Alpelisib in combination with fulvestrant for the treatment of postmenopausal women and men, with hormone receptor-positive, HER2-negative, PIK3CA mutated advanced or metastatic breast cancer after disease progression following an endocrine-based regimen with a CDK 4/6 inhibitor.
Organization	Canadian Breast Cancer Network
Contact information[a]	Name: Niya Chari

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

The Canadian Breast Cancer Network (CBCN) respectfully disagrees with CADTH's draft recommendation of Alpelisib in combination with fulvestrant for the treatment of postmenopausal women and men, with hormone receptor-positive, HER2-negative, PIK3CA mutated advanced or metastatic breast cancer after disease progression following an endocrine-based regimen with a CDK 4/6 inhibitor for the following reasons:

1. As a result of this recommendation, there remains an unmet need for patients with metastatic, HR-positive breast cancer harbouring PIK3CA mutations following disease progression on endocrine therapy. We believe that this decision is not the overall good of society, given that these patients have limited treatment options available to them.

2. From the patient perspective, uncertainty around evidence does not preclude the likelihood of benefit, particularly in the case of metastatic cancer. While we appreciate that data uncertainties exist around the extrapolation of benefit for patients following treatment with a CDK 4/6 inhibitor, there is robust data supporting the benefit of alpelisib for patients with known PIK3CA mutations which has served the basis of its approval and funding in several other global jurisdictions. CBCN believes that data uncertainties in this case could be resolved through the supplemental generation of real-world data rather than the blanket rejection of funding for this therapy.

3. There is a missed opportunity for the development of real-world evidence based on conditional approval. Specifically, this recommendation denies patients with metastatic disease whose cancers harbour the PIK3CA mutation, and have limited therapy options available to them, the opportunity to access effective and safe therapy. We note that metastatic patients in particular have urgent treatment needs and cannot await a recommendation from a resubmission in the future.

4. There remains a need for Canadian treatment protocols to remain consistent with accepted international guidelines and standards, which are established by acknowledged experts in breast cancer. We note that the European Commission and the FDA in the US have all accepted the same clinical data demonstrating the efficacy of alpelisib in this patient population. In these other jurisdictions, treatment was approved and adopted as standard clinical practice to reduce time to

disease progression. 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 "Patients expressed a desire for treatments that delay progression of their disease, prolong life without sacrificing quality of life, and have fewer adverse effects than current therapies."

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 patients with hormone-receptor positive breast, HER2 negative breast cancer make up approximately 70 percent of breast cancer cases. Endocrine therapy-including the use of cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors- are the standard treatment for patients with HR-positive, HER2 negative, advanced breast cancer. However, resistance to endocrine-based therapies remains a challenge. Approximately 40 percent of patients living with HR-positive, HER2-negative breast cancer have the PIK3CA mutated gene. These mutations are often associated with more aggressive tumour growth, resistance to endocrine treatment and a poor overall prognosis. As a result, there remains a current unmet need to provide alternative therapy options for metastatic HR-positive patients.

Further, we assert that for patients with advanced hormone-receptor positive, HER2-negative breast cancer initial treatment typically involves sequential use of multiple lines of endocrine-based therapy. Current front-line therapy is usually an aromatase inhibitor in combination with a CDK 4/6 inhibitor. If there is disease progression after this there is no specific standard of care therapy. As such, these patients are in particular need for therapeutic options following disease progression on standard endocrine therapy.

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 slowing progression of the disease 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 but are willing to tolerate adverse events for treatments that could offer benefits.

"70% of patients indicated that when it comes to pain, some or a moderate impact on one's quality of life would be considered acceptable, and 27% of patients indicated that a strong or debilitating impact would be considered acceptable"

"***I'm one of the administrators of a support group on Facebook of everyone who is on Piqray, and we have people in the group who were on the original trial. So it is a drug that people seem to be able to stay on for a good amount of time, despite the side effects and some of the difficulty in managing them. " -Patient Respondent***

– Treatments with the *possibility* of reducing progression of the disease are valued by metastatic patients.

"34% of respondents were willing to accept serious risk with treatment if it would control the disease • 45% of respondents were willing to accept some risk with treatment • 21% of respondents were very concerned and felt less comfortable with serious risks with treatment"

– Having choice in treatment options is valued by metastatic patients.

"I think patients (ESPECIALLY young patients) should be given more decision making power in terms of access to radical treatments to control disease. […] With two small I am determined to access any treatment that can extend my life and I hate struggling with doctors for this access." –

"Accessibility to new drugs- not limiting choices." – Patient Respondent
"Complete access to drug treatment choices and trials." – Patient Respondent

"It means that I have another option. it means that if my body doesn't respond to something else, Piqray is an option. Having something that targets a mutation, having something that targets something that is specific to my cancer makes it more likely that my cancer will respond. And that's the goal all the way around." -Patient Respondent

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

"I worry that in the future, a drug that may work for me won't be accessible to me based on provincial formulary." -Patient respondent

"It is expensive. Private insurance is working but not the answer." -Patient respondent "

"The lack of support is a Health Crisis - people are dying because the cost of treatment is not covered." -Patient respondent

- Access to precision oncology treatments are valued by metastatic breast cancer patients

"I think the biggest thing is having options that are specific to mutations equals longer lives for people with terminal cancer, and I think that that's really important." -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 "There is insufficient evidence that alpelisib meets an unmet therapeutic need in the patient population requested for reimbursement by the sponsor. Patients expressed a desire for treatments that delay progression of their disease, prolong life without sacrificing quality of life, and have fewer adverse effects than current therapies."

As mentioned above, we feel that the interpretation of the patient experience and values contained within our submission are not uniformly reflected in the draft recommendation.

We note that there remains an unmet need for treatment options for HR-positive breast cancer patients with disease progression following treatment with endocrine therapy. We acknowledge that data uncertainties exist around the extrapolation of benefit for patients following treatment with a CDK 4/6 inhibitor, however there is robust data supporting the benefit of alpelisib for patients with known PIK3CA mutations which has served the basis of its approval and funding in several other global jurisdictions.

CBCN believes that data uncertainties in this case could be resolved through the supplemental generation of real-world data based on conditional approval. This would allow metastatic breast cancer patients to benefit from effective therapy, while addressing the gaps in knowledge and data.

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

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- 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	☐
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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  - 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 • Clinician 2 • *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	☐	☐	☐	☐