CADTH Reimbursement Review
Clinician Group Input Template

CADTH Project Number	**PC0247-000**
Generic Drug Name (Brand Name)	**Alpelisib (Piqray)**
Indication	**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**
Name of the Clinician Group	**The Ottawa Hospital Cancer Centre: Breast Medical Oncology group**
Author of the Submission	[redacted]
Contact information	[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

There are currently no specific treatments targeting the population of PIK3CA mutated metastatic hormone receptor positive Her2 negative breast cancer patients. Such mutations are common in the metastatic setting (especially 2nd line and later). PIK3CA mutations are found in approximately 40% of patients with metastatic HR+/HER2- breast cancers and are associated with poorer survival and are less sensitive to chemotherapy. In the first line setting, patients are treated with the combination of an aromatase inhibitor and a CDK 4/6 inhibitor (palbociclib, ribociclib or abemaciclib). On disease progression, patients receive chemotherapy if they have aggressive disease progression (especially if not responding to 1st line therapy) or significant visceral metastases (lung, liver); or, they may receive 2nd line endocrine therapy with fulvestrant (response rates <15%) or another single agent aromatase inhibitor (response rates <10%). Guidelines support up to 3 successive lines of endocrine therapy before moving on to chemotherapy, depending on the response to the previous line (and it's duration of benefit). There is no level I evidence showing survival prolongation with current "next line" therapies. Patients with actionable PIK3CA mutations have also been treated recently with combination fulvestrant/ alpelisib through the manufacturer's access program, but tumour testing for such mutations is not usually available. Molecular testing for cancers, to guide systemic therapies, remains challenging and woefully inaccessible in all parts of Canada outside of special programs, grants, or research protocols.

Supportive care approaches are pursued concomitantly, for symptom management and quality of life. These may include analgesics, radiation therapy and bone supportive therapies such as bisphosphonates or denosumab.

4. Treatment goals

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

Improved overall survival in this common disease setting. Maintained or improved quality of life compared with currently available treatments. Delay progression of cancer, improve or maintain organ function (eg. liver, bone, lungs), reduce cancer symptoms, and allow patients to be treated with oral therapy allowing gainful employment, and independence and preventing institutionalization.

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.

- Responses to current therapies in 2nd and later lines of therapy are disappointing
- Patients become more rapidly refractory to current therapies
- Current treatments have not been shown to improve overall survival
- Chemotherapy options are poorly tolerated, causing nausea, vomiting, alopecia, fatigue, cytopenias and sometimes dangerous adverse reactions

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

Of patients progressing after standard 1st line therapy (outlined above), the great unmet need for those with relevant PIK3CA mutations would be uniquely addressed by alpelisib (with fulvestrant). This would be a common subgroup of the metastatic 2nd (or later) line hormone receptor positive, Her2 negative population, representing > 1/3 of this group. In practice, alpelisib/ fulvestrant would be considered in a subgroup of eligible patients including

- Ability to understand and comply with the specific safety, monitoring and side effect management issues associated with the drug
- Postmenopausal (or treated with ovarian function suppression to achieve a menopausal state)
- ECOG performance status 0-1, or potentially ECOG PS 2 if fit with aggressive disease and felt unfit for chemotherapy
- Brain metastases if controlled or treated
- NOT having type 1 diabetes mellitus or poorly controlled type 2 diabetes mellitus (Hb A1c>6.4%)

6. Place in therapy

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

We would have to identify the PIK3CA mutation, and then add alpelisib to an established standard of care option, e.g. fulvestrant (500 mg im q 2 wk x 3 then q 4 wk). This would be a paradigm changing standard of care option in 2nd line, and considered a disease modifying approach. The numerical improvement demonstrated in the SOLAR-1 trial, with progression free survival lengthened by 5 months would be considered worthwhile by patients and clinicians. It's use there would be commensurate with current published international guidelines. Due to the timing of the trial when CDK4/6 inhibitors were not standard of care in the first line setting, only 5.9% or 20 patients on SOLAR-1 had prior treatment with CDK4/6 inhibitors. An additional trial ByLieve has reported activity of fulvestrant with alpelisib in a single-arm phase II trial in patients who had prior CDK4/6 inhibitors showing a progression-free survival of 7.3 months (95% CI: 5.6-8.3 months) but unfortunately there was no comparative arm with fulvestrant on this trial.

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.

It would be appropriate to use standard 1st line therapy (as above) before using fulvestrant/ alpelisib, in keeping with the studied population, SOLAR-1 trial design (eligibility criteria) and the indication being applied for. In SOLAR-1, only 5.9% of pts had preceding CDK 4/6 inhibitors however (now considered standard first line treatment). While we have insufficient data about the efficacy of alpelisib after CDK 4/6 inhibition, given their different targets and mechanism of actions, there is currently no biological rationale to suggest alpelisib would not be effective. We would only recommend chemotherapy beforehand in patients with life threatening visceral organ metastases ("visceral crisis").

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

This would replace fulvestrant monotherapy for those patients treated. Subsequent lines of therapy would include those used previously after fulvestrant, including multiple single agent chemotherapy drugs (sequentially) or clinical trials.

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

Patients meeting the eligibility criteria for SOLAR-1, and with activating mutations of PIK3CA. Patients would be eligible with or without visceral metastases, and should be of ECOG PS 0-1 with expected survival of > 3 months. They should not have type I diabetes mellitus or uncontrolled type 2 diabetes mellitus. Further trials are underway assessing efficacy after 1st line CDK 4/6 inhibitors.

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

We would require access to molecular testing for PIK3CA mutation status. Testing is not challenging but not routinely funded or accessible currently in Canada. It can be done by Canadian commercial laboratories or in the setting of academic hospital laboratories if funded.

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

ECOG PS 2-4. Type I or uncontrolled type 2 diabetes mellitus.

One contributor (to this input statement) felt that, without evidence, patients who had first line CDK 4/6 inhibitors would not be suitable for alpelisib, requiring another trial to clarify benefit there. Most of us felt that access and funding should not be withheld however for now.

Patients unable to understand the dosing and monitoring requirements and potential toxicities, or those non-compliant with follow up.

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

Patients with activating PIK3CA mutations are the ones who may benefit from treatment.

Clinical factors or patient subgroups otherwise cannot be used to select patients with a greater chance of benefit.

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

Responses are determined based on symptoms, laboratory markers, and radiographic scans and tumour measurements, with scans usually performed at least every 3 months initially. Treatment is continued if disease is either stable or responding by RECIST criteria radiographically.

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

- Reduction in the frequency or severity of symptoms (eg pain, dyspnea…)
- Improvement of organ function (bone, liver, lung)
- Stabilization of symptoms
- Maintenance or improvement of performance status

6.10. How often should treatment response be assessed?

At least every 3 months, with toxicity or symptom assessments more often early in treatment (every 2-4 weeks) or as needed.

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

- Disease progression
- Intolerable or dangerous toxicity, esp uncontrolled grade 3-4 hyperglycemia, rash or diarrhea
- Patient preference or refusal

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

Community setting, home (administration); hospital outpatient clinic or family doctors' offices (for fulvestrant injections).

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

Treatment should only be prescribed by certified medical oncologists or associated team physicians with expertise in cancer therapies and toxicity management.

7. Additional information

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

The benefits seen in the SOLAR-1 study are meaningful if applied to the studied population. Our group noted substantial discordance of opinion -- some felt that the benefits are uncertain in a current-day population treated with preceding 1st line CDK 4/6 inhibitors, that broader usage would be unlikely given the significant toxicities expected and that funding should not be granted for that population given scarce health care resources. One reviewer felt that the SOLAR-1 trial does not reflect our current practice and should not be used given the toxicities noted, and that capecitabine chemotherapy would likely yield a better therapeutic index. Others noted that there have not been advances in this niche for many years and that the documented benefits are commensurate with patient values and the toxicities, while substantial (76% grade 3 or 4 adverse events), are predictable and manageable by medical oncologists.

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 <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. Sandeep Sehdev*
Position	*Medical oncologist, The Ottawa Hospital Cancer Centre*
Date	*28-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	☐	☒	☐	☐
Pfizer	☐	☒	☐	☐
Lilly	☒	☐	☐	☐

Declaration for Clinician 2

Clinician Information	
Name	*Dr Mark Clemons*
Position	*Medical Oncologist, The Ottawa Hospital Cancer Centre*
Date	*3-MAY-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 Arif Awan*
Position	*Medical Oncologist, The Ottawa Hospital Cancer Centre*
Date	*07-MAY-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	☒	☐	☐	☐
Eli Lilly	☒	☐	☐	☐
Pfizer	☒	☐	☐	☐
Roche	☒			

Declaration for Clinician 4

Clinician Information	
Name	*Dr Amirrtha Srikanthan*
Position	*Medical Oncologist, The Ottawa Hospital Cancer Centre*
Date	*6-MAY-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 Moira Rushton-Marovac*
Position	*Medical Oncologist, The Ottawa Hospital Cancer Centre*
Date	*7-MAY-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	☐	☐	☐	☐

Declaration for Clinician 6

Clinician Information	
Name	*Dr Rakesh Goel*
Position	*Medical Oncologist, The Ottawa Hospital Cancer Centre*
Date	*9-MAY-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	☐	☐	☐	☐