CADTH

CADTH Reimbursement Review

Patient Input

alpelisib (Piqray)

(Novartis Pharmaceuticals Canada Inc.)

Indication: Advanced or Metastatic Breast Cancer

CADTH received patient input from:

Canadian Breast Cancer Network

CanCertainty

Rethink Breast Cancer

May 14, 2021

CADTH

CADTH Reimbursement Review
Patient Input Template

Name of the Drug and Indication	Piqray (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 a CDK4/6 inhibitor in combination with an endocrine-based regimen.
Name of the Patient Group	Canadian Breast Cancer Network
Author of the Submission	[redacted]
Name of the Primary Contact for This Submission	[redacted]
Email	[redacted]
Telephone Number	[redacted]

1. About Your Patient Group

The Canadian Breast Cancer Network (CBCN) is a leading, patient-directed, national health charity committed to ensuring the best quality of care for all Canadians affected by breast cancer through the promotion of information, education and advocacy activities. www.cbcn.ca

The Canadian Breast Cancer Network is committed to strict adherence to the Code of Conduct Governing Corporate Funding.

2. Information Gathering

Information for this submission was collected via:

CBCN's 2017 Metastatic Lived Experience Breast Cancer Patient Report: An online survey was distributed in English and French to patients living with breast cancer. No patients surveyed had direct experience with the treatment under review. Survey questions comprised of a combination of scoring options and free form commentary. Patients were contacted through the membership databases of CBCN and other patient organizations.

Patient Respondents Profile:

180 metastatic, breast cancer patients responded to the survey in English and French.

In this submission, CBCN specifically utilizes the data provided by 90 Canadian, metastatic, hormone receptor (HR)-positive, HER2-negative breast cancer patients who responded to our survey.

The respondents all identified as female and primarily (58) spoke English as a first-language, with 16 speaking French as a first language, and 5 respondents selecting other as their first language (split between Hungarian, Russian, German, Dutch and Serbo-Croatian), with 10 respondents undeclared. The majority of respondents were from Ontario (33) and 16 from Quebec, British Columbia (7), Alberta (7), Saskatchewan (6), (4) from Manitoba, , 1 from Nova Scotia, 1 from New Brunswick, and 1 from Newfoundland and Labrador. The remainder did not specify their province of residence.

Most of the respondents (31) were between the ages of 40-49 when diagnosed, 21 respondents were in the 50-59 age range, 15 were between 60-69 years of age and 14 were between 30-39 years, 3 were between 20-29, and the remainder were undisclosed.

Most respondents were in a relationship (60), while 16 declared themselves as single, and the rest did not specify their relationship status. Most of the patients (60) had children, with the majority (39) with children 20 years or older, 17 had children between the ages of 13-19, 14 had children between 6-12 years of age, 5 had children 2-5 years of age, and 1 had children below 1 year.

CBCN's 2012 Metastatic Breast Cancer Patient and Caregiver Survey Report: An online survey, conducted in collaboration with ReThink Breast Cancer, was distributed to patients living with metastatic breast cancer and their caregivers. No patients surveyed had experience with the treatment under review. Survey questions comprised of a combination of scoring options and free form commentary. Patients were contacted through the membership databases of CBCN and other patient organizations.

• 71 patients participated in the survey

• 16 caregivers participated in the survey

Key informant interviews: Phone interviews were conducted in May 2021 with a metastatic breast cancer patient living with hormone receptor-positive, HER2-negative, PIK3CA- mutated breast cancer and had direct experience with the treatment under review.

Printed sources: A review was conducted of current studies and grey literature to identify issues and issues and experiences that are commonly shared among many women living with breast cancer.

3. Disease Experience

Metastatic breast cancer is the spread of cancerous cell growth to areas of the body other than where the cancer first formed, and is often more severe. It is most commonly spread to the bones, but can include the lungs, liver, brain and skin. Current treatment options for metastatic breast cancer are only effective at prolonging progression-free disease, and most cases of advanced disease will progress and symptoms will worsen. Patients with a diagnosis of metastatic breast cancer understand the limitations of current treatment options and seek to live their remaining months and years with the best possible quality of life that they can achieve.

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. [1]

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. [2]

The Physical Impact of Metastatic Breast Cancer

How the disease presents itself through symptoms, how it progresses, and how it is experienced varies by patient, but many effects of metastatic breast cancer represent a significant or debilitating impact on their quality of life. In our 2012 Metastatic Breast Cancer Patient and Caregiver Survey (2012 Survey), patients were asked what impact cancer-related symptoms had on their quality of life:

· 54% of patients reported that fatigue resulted in a significant or debilitating impact, and 40% reported some or moderate impact;

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[1] Veronica Wendy Setiawan, Kristine R. Monroe, Lynne R. Wi kens, Laurence N. Kolonel, Malcolm C. Pike, Brian E. Henderson, Breast Cancer Risk Factors Defined by Estrogen and Progesterone Receptor Status: The Multiethnic Cohort Study, *American Journal of Epidemiology*, Volume 169, Issue 10, 15 May 2009, Pages 1251–1259, https://doi.org/10.1093/aje/kwp036

[2] Lea Mollon, Alejandra Aguilar, Elizabeth Anderson, Joni Dean, Lisa Davis, Terri Warholak, AyalA. Aizer, Emma Platt, Aditya Bardiy and Derek Tang
Abstract 1207: A systematic literature review of the prevalence of PIK3CA mutations and mutation hotspots in HR+/HER2- metastatic breast cancer
Cancer Res July 1 2018 (78) (13 Supplement) 1207; **DOI:** 10.1158/1538-7445.AM2018-1207

· 39% of patients reported that insomnia resulted in a significant or debilitating impact, and 46% reported some or moderate impact;

· 37% of patients reported that pain resulted in a significant or debilitating impact, and 44% reported some or moderate impact.

These results were further reinforced in our 2017 Metastatic Breast Cancer Patient Survey (2017 Survey).

The Social Impact of Metastatic Breast Cancer

The impact of this disease spreads across all aspects of a patient's life, restricting an individual's employment and career, ability to care for children and dependents, and their ability to be social and meaningfully participate in their community. When asked in the 2012 Survey what kind of impact living with metastatic breast cancer has had on their quality of life:

• Among those who were employed, 71% of patients identified significant restrictions to their ability to work;

• Among those with children or dependents, 21% identified significant restrictions and 53% reported some or moderate restrictions to their caregiving responsibilities;

• 49% of patients identified significant restrictions and 38% identified some or moderate restrictions to their ability to exercise;

• 42% of patients identified significant restrictions and 42% identified some or moderate restrictions to their ability to pursue hobbies and personal interests;

• 41% of patients identified significant restrictions and 41% identified some or moderate restrictions to their ability to participate in social events and activities;

• 22% of patients identified significant restrictions and 52% identified some or moderate restrictions to their ability to spend time with loved ones.

Other experiences identified by patients included: guilt, the feeling of being a burden on caregivers, fear of death, poor body image, not knowing what functionality will be lost, fear of the impact of cancer and the loss of a parent on children, not knowing what will happen to children, the loss of support of loved ones, as well as marital stress/loss of fidelity and affection from husband.

4. Experiences With Currently Available Treatments

The Goals of Current Therapy

The goals of current treatment options for metastatic breast cancer include controlling the progression of the disease (extending life), and reducing cancer-related symptoms (extending or stabilising quality of life). Treatment options and effectiveness vary among type of cancer, location of cancer, and how symptoms are experienced.

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. Current clinical practice aims to maintain quality of life for as long as possible in patients with advanced cancer before switching to chemotherapy.

In our 2017 Survey, the majority of respondents experienced metastases to their bones, liver and lungs. Twelve percent of metastatic patients reported metastases to their brain while 20% reported metastases to other body parts-including ovaries, pancreas and scalp. Most of the HR-positive, HER2-negative, metastatic breast cancer patients (90) patients had or were receiving hormone therapy, 73 patients had surgery, 66 patients had been or were currently being treated with chemotherapy, and 63 patients had or were receiving radiation therapy.

Key Factors for Decision-Making Around Treatment

Respondents in our 2017 Survey indicated that the following key factors influenced their decision-making around treatments:

1. Effectiveness of the treatment – how well the treatment stabilized their disease and delayed progression of their disease.

2. Prolonging life without sacrificing quality of life – being able to maintain productive, active lives with minimal disruption to daily routines.

3. Side effect management – minimizing risk while stabilizing their disease.

4. Cost and accessibility of treatments – affordability and ease of accessing treatments.

Treatment efficacy:

When asked how important progression-free survival was in considering treatments, the HR-positive metastatic patients in our 2017 Survey revealed that efficacy of the treatment is critical to their decision-making. Fifty-six percent of them indicated that progression-free survival of less than 3 months was important or very important, 68% indicated that progression-free survival of 3-5 months was important or very important and 85% indicated that progression-free survival of 6 months or longer was important or very

important. When asked about overall survival, 95% of the HR-positive metastatic patients indicated that overall survival was important or very important when considering treatment options.

Metastatic patients in our 2017 Study also spoke on the importance of effectiveness in their decision-making anecdotally:

"Effectiveness in patients similar to myself" -Patient respondent

Effectiveness is most important and then all other things being equal - least side effects"-Patient respondent

"The most important factors for me are progression free survival and quality of life." -Patient respondent

"Anything to prolong my survival and maintain quality of life." -Patient respondent

"Survival is of upmost importance to me." -Patient respondent

Quality of life:

Quality of life was routinely cited by patients as a key factor in making treatment decisions. In our 2017 Survey, 87% of the HR-positive metastatic breast cancer patients revealed that quality of life was important or very important to them when considering treatment options.

This concern was reiterated anecdotally:

"Quality of life as well as keeping progression at bay. "-Patient respondent

"Always quality of life. If I am to suffer greatly then no that is not what I want. "-Patient respondent

"How it will affect the quality of life I currently experiencing, truth is I will never be the person I was before Stage IV"-Patient respondent

"Quality of Life is of primary importance"-Patient respondent

"Quality of life is more important to me than quantity. I want what time I have left to be somewhat of a life. I don't want to spend the whole time being so sick that I am incapacitated"-Patient respondent

"Mainly progression free survival and quality of life are the most important factors." -Patient respondent

"I want to live as long as possible with a good quality of life. "-Patient respondent

Patient willingness to tolerate treatment side effects:

In our 2012 Metastatic Patient and Caregiver Survey, the responses to what level of side effects and how much impact on one's quality of life would be worth extending progression-free disease by six months was shown to be determined at the personal level.

When asked to rate how much impact different symptoms of cancer and cancer treatment would be considered tolerable:

• Almost two-thirds of patients indicated that when it comes to fatigue, nausea, depression, problems with concentration, memory loss, diarrhea and insomnia, some or a moderate impact on one's quality of life would be considered acceptable, and approximately one quarter of patients indicated that a strong or debilitating impact would be considered acceptable.

• 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.

Similar responses were also found in our 2017 Survey. The majority of HR-positive metastatic breast cancer respondents indicated that pain, fatigue, nausea, lack of concentration, diarrhea, insomnia, and hair loss were very acceptable or somewhat acceptable symptoms in exchange for 6 months or less of benefits from breast cancer treatment. The majority of HR-positive metastatic respondents indicated that depression as a symptom in exchange of 6 months or less of benefits from breast cancer treatment was somewhat acceptable (53% respondents) Similarly, the majority indicated the memory loss would be somewhat acceptable (61% of respondents) When it came to the symptom of vomiting, only 45 % of HR-positive metastatic respondents indicated that it would be somewhat acceptable.

These responses were also related anecdotally:

"Risks vs benefits. Some adverse side effects are worth the benefits for short term." - Patient respondent

"I can deal with pretty significant side effects if the outcome of treatment is optimistic" Patient respondent

The financial burden of treating and managing breast cancer:

The financial burden associated with living with advanced breast cancer extends far beyond any loss of income during a temporary or permanent absence from employment. In addition to the loss of income during illness, metastatic breast cancer patients can incur substantial costs associated with treatment and disease management.

Research on the financial impact of breast cancer on patients identified the following:

• 80% of breast cancer patients report a financial impact due to their illness.

• 44% of patients have used their savings, and 27% have taken on debt to cover costs.[3]

These findings were consistent with the responses in our 2012 Survey:

• Nearly one-third of patients indicated that the cost of medication, the cost of alternative treatments (i.e. massage, physiotherapy, etc.) to manage symptoms and side effects, and the time required to travel to treatment had a significant or debilitating impact on their quality of life.

• 24% of patients indicated that the costs associated with travel had a significant or debilitating impact on their quality of life, and 41% of patients indicated that it had some or moderate impact on their quality of life.

In our 2017 Survey, 52% of HR-positive, metastatic patients indicated that the cost of prescription medications had a significant or some impact on their treatment decision-making and quality of life.

Other financial barriers that metastatic breast cancer patients mentioned include: not qualifying for insurance at work, inability to change employers due to loss of insurance, and the prohibitive cost of new treatment options.

"Many of the next step treatments are very expensive [and not covered by government programs] and it is a HUGE struggle to get [coverage]. […] When dealing with an incurable disease the last thing you want to have to do is spend time on a letter writing campaign to argue about whether or not you should receive the drugs [recommended by your physician]. At about $1500.00 a week, I don't know many who can afford that." - Patient respondent

"Always a concern as you never know if the next drug will be covered or how long it takes to get approval from private coverage. Many times it delays treatment and this weighs on one's mind" -Patient respondent

"I feel that Canada is slow in getting access to premium drugs" -Patient respondent

"When I turn 65 I will no longer have private insurance. I will not be able to afford the medication I currently take never mind any future medication that I may require." -Patient respondent

[3] Janet Dunbrack, Breast Cancer: Economic Impact and Labour Force Re-entry. Canadian Breast CancerNetwork, 2010

"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

Patient Access to Local Resources and Supports During Treatment

When living with cancer, many patients experience significant barriers and challenges around availability of health care services and quality childcare in their community. In response to the 2012 Survey questions about the availability of supports such as childcare, transportation and alternative treatments in their community:

• Among patients with children or other dependents, 53% indicated that there is minimal or no access to appropriate care for their loved ones when they are experiencing debilitating symptoms related to their cancer, and 40% identified barriers to accessing quality care during cancer treatment.

Patient Willingness to Tolerate Risk

When asked in the 2012 Survey about their willingness to tolerate risk with a new treatment:

• 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

Need for Personal Choice

What was revealed in the responses to the open ended question, and which was confirmed in the key informant interviews, is that it is imperative that women with metastatic breast cancer have access to, and the option of what drugs they take. Most patients are well aware of the adverse effects of treatment up front and they want to make a personal choice that works for them. Metastatic breast cancer patients expressed the need for personal choice and autonomy in our 2012 Survey as well as in the 2017 Survey:

"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." – 2012 Survey

"I believe that I would prefer to tolerate severe restrictions in the quality of my life, if it meant that I would be able to have a longer period without progression." – 2012 Survey

"It would be nice to have more choices and more information about them. I was lucky to get on a clinical trial perhaps because my oncologist was a research oncologist and involved in many. While I knew friend and acquaintances that had Stage IV BC and never informed of clinical trials, and sadly several did not survive the disease." – 2017 Survey

"Accessibility to new drugs- not limiting choices." – 2017 Survey

"Complete access to drug treatment choices and trials." – 2017 Survey

5. Improved Outcomes

For metastatic patients, extension of progression-free survival (PFS) is of critical concern. Like any other treatment for metastatic breast cancer, patients have an expectation that alpelisib (Piqray) plus fulvestrant will extend their progression-free survival with good quality of life. This is based on data from the Phase III SOLAR-1 trial showing that progression-free-survival was nearly twice as long (11 months) in patients with PIK3CA mutations receiving alpelisib compared to the placebo group (5.7 months).

The overall response rate was 35.7% for patients with a PIK3CA mutation receiving alpelisib combined with fulvestrant versus only 16.2% for patients receiving fulvestrant alone, indicating that just over one-third (36%) of patients with measurable PIK3CA mutations responded to alpelisib plus fulvestrant and experienced at least a 30% reduction in overall tumour size.

Adverse Effects

The SOLAR-1 trial showed that alpelisib used in combination with fulvestrant was well tolerated by patients. Commonly reported side effects included: hyperglycaemia, nausea, decreased appetite, and rash.

The patient that was interviewed by CBCN shared that while she had side effects from alpelisib, they were largely manageable with time. Patient 1 shared that while she did experience significant side effects from the treatment, she did not find it to be debilitating.

"Now that it's been two years since I've been on it, I have a much better handle on it now"

Impact of Treatment Options to Patients

By delaying the progression of the disease, this treatment can relieve cancer-related symptoms, and improve a patient's quality of life. When living with no or with minimal cancer-related symptoms, and with minimal side effects from the treatment, patients are able to reduce the impact of cancer on their ability to care for children and dependents, continue with their employment and earn income, spend time with loved ones and

participate in their life in a meaningful way by engaging in social activities, travelling, maintaining friendships, and pursuing personal interests.

The patient we interviewed on alpelisib indicated that alpelisib has been a more preferable treatment compared to other treatments such as chemotherapy.

Value to Patients

The value to patients of extending the time that their cancer is progression-free cannot be overestimated. Patients living with metastatic breast cancer are aware that their advanced disease will progress with worsening symptoms until death, and embrace opportunities to try new treatments, even if benefits may be as little as a six month extension of progression-free disease. It is also very important for patients to have good quality of life when receiving treatment for metastatic disease. Patients that we speak to on a regular basis acknowledge the importance to have the energy to attend their children's activities and to spend time with family and friends.

6. Experience With Drug Under Review

Patient Profile:

CBCN connected with a patient from the United States with experience on the treatment:

Patient 1- is a 42 year old woman, diagnosed at age 38 with de novo metastatic breast cancer, HR+, HER2-, ductal and lobular carcinoma in March 2017. She has both the ATM germline mutation and PIK3CA mutation. She has previously been treated with four cycles of Adriamycin and Cytoxane, followed by two years of Palbociclib (Ibrance) and letrozole. She has been on Alpelisib as of August 2019.

The Impact of the Treatment on the Disease

The patient expressed her gratitude at having access to this treatment. Patient 1 noted her personal satisfaction with the treatment, it's impact on her metastatic disease and noted her oncologists confidence in using the therapy.

"Piqray is actually keeping the cancer under control even better than Ibrance did…. We looked at a couple of other things, my doctor and I, but because I had the mutation, the whole idea of precision medicine and focusing on the weak spots in the cancer specifically, that was why my doctor felt like it would be the best way to go." Patient 1

"It's been more effective than anything else I've been on. So my tumour markers came down precipitously in the very first month. And they fluctuate, but we could see a change after the very first PET scan, significantly. Mets that had remained active for years on Ibrance were gone."

"When I was diagnosed, I had a super high disease load. So I went from so much disease to stability on Ibrance, but there was still a lot of active mets. And now I have one active mets. So it really was effective on the mets."

Assessing Risks Associated with the Treatment

The patient discussed the adjustment period she had with the treatment. She experienced hyperglycemia, nausea and fatigue and how she has been able to manage these side effects. While the overall tolerability of her side effects fluctuated, she ranked her quality of life on Piqray as mid-range once she adjusted to the medication.

"I think there's always a learning curve, and I feel that the Piqray learning curve was longer for me than it was for Ibrance. And now that it's been two years since I've been on it, I have a much better handle on it now. "

"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. "

"*But outside of the hyperglycemia, pretty intense fatigue. For the hyperglycemia, I'm on Jardiance, and that's kept the hyperglycemia under control. I do get a fair bit of nausea as well, and I've got a variety of medications that I take at different times of the day to keep the nausea under control. The fatigue: I drink a lot of coffee, and I've had to adjust my activity levels. The fatigue has been something that has been a side effect of every medication I've been on, so I feel that that's a side effect that I've become a little bit more able to handle. "*

"Going on Piqray, it {quality of life} definitely dipped below a five and was around a four. I would say that I've clawed my way back to that six area after being on it for a few months and getting used to the side effects."

"The change has definitely affected my productivity. Not destroyed it, but it's taken a hit. I've had to step back from some things that I was doing because of the fatigue."

Patient 1 noted that the side effect profile of the treatment was ultimately worth it for her if it could continue to control her cancer as it has.

"I have to say that if the medication is going to be effective in controlling the cancer, there are not many side effects that would be completely unacceptable. At this point in my cancer treatment, the hyperglycemia was not something that I was excited about, but I've been able to manage it. So again, I'm just not sure that any side effects would be categorically unacceptable because my goal is to have the cancer be under control or dead as much as possible. Having the side effects be something that can be managed—like fatigue is something that I can manage—that's acceptable to me."

Alternatives To The Treatment
The patient noted that she was continuing to monitor other options for managing her metastatic disease.

"My doctor and I have been watching the PARP inhibitors Lynparza That was definitely an option. "

"Trying out a different CDK4/6 inhibitor. I was only on Ibrance, and so there's still Kisqali and Verzenio available. Xeloda was one of the other ones that my doctor talked about. Those are all still available in my arsenal for later."

She also elaborated on the value of having access to Piqray, and to a precision oncology therapy beyond the standard therapies available for metastatic hormone-receptor positive breast cancer.

"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."

The Social and Financial Impact of the Treatment
As the patient accessed the medication in the United States she did not discuss the financial impact of the treatment but she did specifically address what having access to Piqray meant to her and her family.

"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."

7. Companion Diagnostic Test

At this time, PIK3CA mutation testing is only available through select clinical testing programs and is not implemented routinely in breast cancer care in Canada.

Accessing testing and treatment is of great importance for hormone-receptor-positive breast cancer patients with a PIK3CA mutation. It is imperative that all HR-positive, HER2-negative metastatic/advanced breast cancer patients who could benefit from this therapy are being identified and offered genomic profiling to assess their eligibility for treatment with Piqray. It is critical that access to adequate oncogenomic testing does not create a barrier for access to effective therapies for metastatic patients.

8. Anything Else?

Is there anything else specifically related to this drug review that CADTH reviewers or the expert committee should know?

We note that Piqray, as a precision oncology therapeutic, treats cancer patients based on the presence of a specific tumour biomarker. We hope that CADTH will consider continuing to engage the manufacturer and other stakeholders to develop novel approaches to support translation into models of assessment for potential value in clinical practice in Canada.

Funding this type of molecularly targeted therapeutic would provide an important therapeutic option for metastatic and advanced breast cancer patients whose tumors test positive for a PIK3CA-mutation and are in need of further treatment options.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

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

   CBCN did connect with the manufacturer, Novartis Canada, to connect us with patients with experience on the treatment.

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

   All other research, interviews and outreach to patients was conducted independently by the Canadian Breast Cancer Network, as was the compilation of information and data for the writing of this submission.

   The Canadian Breast Cancer Network is committed to adhering to the Code of Conduct Governing Corporate Funding

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
Novartis Canada				x

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.

Name: Niya Chari
Position: Director of Health Policy and Public Affairs
Patient Group: Canadian Breast Cancer Network
Date: May 7, 2021

CADTH

CADTH Reimbursement Review
Patient Input Template

Name of the Drug and Indication	**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.**
Name of the Patient Group	**CanCertainty**
Author of the Submission	[redacted]
Name of the Primary Contact for This Submission	[redacted]
Email	[redacted]
Telephone Number	[redacted]

1. About Your Patient Group

The CanCertainty Coalition is the united voice of more than 30 Canadian patient groups, cancer health charities, and caregiver organizations from across the country, joining together with oncologists and cancer care professionals to significantly improve the affordability and accessibility of cancer treatment.

For more information about the CanCertainty Coalition, please visit: https://www.cancertaintyforall.ca/

2. Information Gathering

Alpelisib is indicated for patients with hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative breast cancer with a mutation in the *PIK3CA* gene who have progressed following an endocrine-based regime. As an orally administered oncology drug, alpelisib is not automatically funded by certain provincial governments. In Ontario and the Atlantic provinces, only individuals over the age of 65 are automatically covered for oral oncology drugs.

The goal of our data collection efforts was to estimate the number of patients who are at risk of severe financial burden as a result of their diagnosis. We calculated the number of yearly HR-positive, HER2-negative breast cancer cases with the *PIK3CA* gene among the under 65 population who do not have private or automatic public prescription drug coverage.

More than 70% of breast cancers are HR-positive, HER2-negative. Knowing the hormone receptor status is important in deciding on treatment options. If a cancer is HR-positive, hormone therapy drugs can be used to either lower estrogen levels or stop estrogen from acting on breast cancer cells. This is the current standard treatment for HR-positive breast cancers. However, despite the advance in endocrine therapy for HR-positive breast cancers, about 50% of these tumours acquire resistance to hormonal therapy. One mode of resistance is through mutation of the *PIK3CA* gene which induces

hyperactivation of a cell proliferation pathway. This mutation occurs in about 40% of patients with HR-positive, HER2-negative breast cancer. Treatment of these patients with alpelisib increased progression free survival over those who only received endocrine therapy [1].

Breast cancer incidence rates were sourced from the Canadian Cancer Registry (2017)[2]. They provide a breast cancer incidence rate for each five year age group in each province. We applied the age-specific incidence rates to the 2017 population demographics[3] of each province to arrive at the estimated new breast cancer cases each year by age and province. We chose to measure "potential financial toxicity" using data on lack of private drug coverage. The Canadian Life and Health Insurance Association[4] provides data on "extended health coverage." For each province, we extracted the percentage of individuals under the age of 65 without private drug coverage AND without automatic public drug coverage. These province specific percentages were applied to the HR-positive, HER2-negative rates and *PIK3CA* gene mutations rates to arrive at the final estimation: *the number of yearly HR-positive, HER2-negative breast cancer cases with the PIK3CA gene among the under 65 population without private or automatic public prescription drug coverage.*

Each year, we estimate that 5,745 breast cancer patients will develop the *PIK3CA* mutation and be indicated for alpelisib.

Of these 5,745 cases, 2,992 will be under the age of 65. Depending on where these individuals live, their oral oncology medication may or may not be covered by the provincial government. For the 1,169 patients under 65 living in British Columbia, Alberta, Saskatchewan, and Manitoba oral oncology medication is automatically covered. Residents of Ontario and the Atlantic provinces under the age of 65 are not automatically covered under public plans. Their route to treatment access is not simple. By our estimations, 235 of these Ontario cancer patients will not have private health insurance. Before they can receive their medication these patients will have to navigate a complicated process of funding applications, approval delays, locating a pharmacy, and waiting for their medication in the mail. They will incur out-of-pocket costs and sizeable portion of their income will go towards their medication.

Assuming alpelisib is ultimately funded by the provinces and territories, the following chart details the number of patients in each province/territory that would be face financial barriers in accessing this treatment:

	Yearly breast cancer cases[i]		HR-positive, HER2-negative[ii]		PIK3CA mutation[iii]		Without private drug coverage[iv]	
	Over 65	Under 65	Over 65	Under 65	Over 65	Under 65	Over 65	Under 65
Canada[v]	9,831	10,685	6,882	7,479	2,753	2,992	0	266
BC	1,694	1,768	1185	1238	474	495	0	0
AB	1,329	1,612	930	1129	372	451	0	0
SK	401	356	281	249	112	100	0	0
MB	429	439	300	308	120	123	0	0
ON	4,945	5,592	3,462	3,914	1,385	1,566	0	235
NB	340	306	238	214	95	86	0	17
NS	418	338	293	237	117	95	0	9
PE	51	61	35	43	14	17	0	3

[1] André, F., Ciruelos, E., Rubovszky, G., Campone, M., Loibl, S., Rugo, H. S., ... Juric, D. (2019). *Alpelisib for PIK3CA-Mutated, Hormone Receptor–Positive Advanced Breast Cancer. New England Journal of Medicine, 380(20), 1929–1940.* doi:10.1056/nejmoa1813904

[2] Statistics Canada. Table 13-10-0111-01 Number and rates of new cases of primary cancer, by cancer type, age group and sex. DOI: https://doi.org/10.25318/1310011101-eng

[3] Statistics Canada. (2017) *Annual Demographic Estimates: Canada, Provinces and Territories* [Data Visualisation Tool]. https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1710000501

[4] Sutherland, Greg, and Thy Dinh. *Understanding the Gap: A Pan-Canadian Analysis of Prescription Drug Insurance Coverage.*

NL	225	212	157	149	63	59	0	2

(i) Estimated from province and age-specific incidence rates from Stats Canada for the year 2017.
(ii) Approximately 70% of breast cancer cases are HR-positive, HER2-negative.
(iii) Approximately 40% of HR-positive, HER2-negative breast cancer cases have the PIK3CA mutation.
(iv) Province specific private drug coverage rates provided by The Canadian Life and Health Insurance Association.
(v) Excluding Quebec (who do not report cancer cases in the same manner) and the territories (for whom we do not have health insurance data).

Limitations

We calculated these estimates to highlight an issue, not to be absolutely precise.

- The estimation of 40% of HR-positive, HER2-negative patients developing the *PIK3CA* gene mutation is just that, an estimation. The epidemiology on mutations in this group is not rigorous. This percentage was estimated from a series of observational studies that used different sampling techniques and testing methods. The prevalence of the *PIK3CA* mutation varied between studies, centered around 40%.
- We do not know if *PIK3CA* mutations occur at different rates in the over 65 population versus the under 65 population. Different age-specific rates of mutation could either overestimate or underestimate the prevalence among the under 65 population.
- Just because someone younger than 65 does not have private insurance does not mean that they are without financial support for their oral oncology medication. In each province, multiple programs exist to support individuals with high drug costs. Based on our experience as a patient advocacy group, we made the assumption that individuals with private health insurance incur less cost when prescribed oral oncology drugs.
- The information on the number of Canadians who have progressed on hormone therapies is not available. Not all Canadians who develop the *PIK3CA* mutation will require alpelisib.

3. Disease Experience

Treatment access problems are so difficult that in many hospitals and cancer centres across Canada, such as those in Ontario, a new type of social worker known as a *drug access navigator* has been established (and funded) to assist patients and clinicians navigate the byzantine treatment access structures. In Ontario, the organization that supports these navigators is known as the Oncology Drug Access Navigators of Ontario (ODANO). They describe the problem that their association works to resolve as follows[5]: *Drugs are an important part of cancer treatment, yet patients often have difficulty accessing coverage for the most effective medicines. The complexity of cancer drug coverage in Canada can overwhelm patients and families.*

And

For example, although cancer drugs administered in hospitals and clinics are often offered free of charge to patients, half of all new cancer drugs are taken at home and, therefore, many are not covered by the public health system. Unfortunately, many of our patients do not have any private insurance. If a patient is fortunate enough to have private coverage, many drug plans require a 20% co-payment, which can quickly become a financial burden to patients on expensive medications.

British Columbia, Alberta, Saskatchewan, Manitoba, Quebec, NWT, Yukon, and Nunavut cover the reimbursement of oral cancer drugs for all in need. Ontario and the Atlantic provinces do not.

In Ontario and Atlantic provinces, with respect to access to approved cancer treatments, there is institutional discrimination against those who are young, uninsured and who have cancer requiring take-

[5] https://odano.ca/

home cancer treatment. With 60% of all new cancer drugs being developed with oral formulations, this issue urgently needs to be resolved through policy change. Traditionally, cancer treatments were administered to patients by an IV in the hospital. Over the past 15 or so years, an increasing number of effective cancer treatments can be taken at home by pill or injection. Take-home cancer medications are now a fundamental part of today's cancer treatments and should be recognized equally within our health care systems. Patients requiring an intravenous treatment can start that medication as soon as needed and don't face any financial or administrative burdens provided the drug is included on the provincial formulary.

However, when take-home cancer medications are prescribed, patients in Ontario and the Atlantic provinces, who are under 65, and lack adequate private insurance, have to apply to a variety of funding assistance programs and ultimately pay a significant deductible or co-pay from their personal savings. In some cases, the cost to the patient might be as high as $23,400 annually, based upon Nova Scotia's Family Pharmacare Program. To qualify for assistance programs, patients and their families have to submit significant amounts of personal and financial information and often face weeks of stressful delay in starting their cancer treatment until the paperwork and approvals are resolved.

Even for patients with private drug insurance, the reality is that many face significant co-pays, deductibles or annual/lifetime caps. For example, some private insurance plans have a cap of $2,000 for prescription drugs for the entire year. The majority of take-home cancer drugs cost more than $20,000 per year. Two-tiered pharmacare in Ontario and the Atlantic Provinces discriminates on the basis of age, income, geography, cancer type, and cancer treatment, and is financially ruining many lives.

A survey[6] of over 1,600 Nova Scotians, commissioned by the CanCertainty Coalition, demonstrates that drug coverage for cancer patients is a serious and growing problem.

- More than half (57 percent) of Nova Scotians expect the provincial health care system will pay for take-home cancer medications. In reality, patients will ultimately pay a significant deductible or co-pay from their personal funds.
- Three out of five people in Nova Scotia (60 percent) said they would consider leaving the province if faced with having to pay for their cancer drugs. Only seven percent could afford monthly drug costs of over $200.

4. Experiences With Currently Available Treatments

Take-home cancer drugs (THCD) are medications used for the active treatment of cancer and are usually dispensed for administration in the home (e.g., oral chemotherapy). These drugs have become a standard treatment for many cancers and present opportunities for patients, providers, and the health system. However, flaws in our current drug coverage system result in some patients not being able to access these treatments.

The term "financial toxicity" describes the distress and hardship arising from the financial burden of cancer treatment. Even in counties with government funded universal healthcare, financial toxicity is an issue for cancer patients and their families. Financial toxicity comes in many forms: out-of-pocket costs, lost income, travel expenses etc. Patients may deal with their financial burden by delaying or foregoing care. They may take less medication than prescribed, utilize over-the-counter drugs in place of prescribed medications, decline procedures, and skip appointments in an attempt to defray costs. The combination of high drug prices, particularly of oral targeted anticancer drugs, and increased cost sharing has made patients more vulnerable to medication non-adherence. Patients who are younger, have lower income, and are uninsured appear to be at greater risk of medication non-adherence. Although government funded public healthcare exists in many very high development index countries, financial toxicity is still

[6] Strategic Directions. *Cancertainty & Strategic Directions IVR Report*. 2017. Available at: https://d3n8a8pro7vhmx.cloudfront.net/cancertainty/pages/119/attachments/original/1490212245/CanCertaintySurvey_October2016.pdf

common among cancer patients and caregivers. The evidence suggests that those with a shorter time since diagnosis, not currently working, and with more severe cancers have higher rates of financial toxicity, including stress and strain[7].

An unfunded oral oncology drug is financially toxic compared to a funded IV oncology drug. The disease experience of cancer patients that require oral drugs is a dual track of disease and economic hardships. After receiving their diagnosis, deciding on a medication, and dealing with the side effects, patients in Ontario and the Atlantic provinces have to consider the financial side of their diagnosis. *"Hearing that you have cancer is devastating. Finding out that you can't pay for the medication that will make you well is catastrophic. It doesn't have to be this way"* ([redacted], Ontario).

The financial side of cancer treatment is unnecessarily burdensome. *"When you are going through any kind of sickness, whatever the severity of it, the last thing you should have to worry about is your medication cost"* ([redacted], Ontario). In addition to dealing with cancer, and not being well enough to work, patients in Ontario and the Atlantic provinces spend days on end, sometimes months, wading through paperwork in order to get approval for coverage of the oral chemotherapy that has kept them alive. Because some cancer treatments are not automatically funded, treatment is delayed for many patients. They wait weeks for government approval before dealing with insurance companies and pharmacies to receive their prescription. Patients often pay out-of-pocket for the first few weeks of their treatment, which they may not be reimbursed for. *"My doctor prescribed a new drug that is not covered by the government therefore I had to find insurance to cover it which costs around $5000.00 a month, I came up with insurance to cover it but I had to pay the pharmacy first then the insurance would reimburse me some time later. My problem I do not have the $5000 to pay out let alone wait till they reimburse me"* ([redacted], Ontario).

"Cancer isn't fair, but access to treatment should be!" ([redacted], Ontario).

5. Improved Outcomes

6. Experience With Drug Under Review

CanCertainty's focus for this submission is on issues related the distress and hardship arising from the financial burdens associated with cancer treatment. If alpelisib were to be reimbursed for patients with breast cancer, there would be some patients under 65 in Ontario and Atlantic Canada that would face significant financial and administrative barriers in accessing treatment.

7. Companion Diagnostic Test

N/A

8. Anything Else?

Equitable Access

We recommend that pCODR, when assessing and reporting on implementation issues with respect to alpelisib, examine the issues of equitable access across all Canadian jurisdictions.

Safety

With respect to implementation, we believe pCODR should also examine the issue of safety with respect to take-home cancer drugs. From 2006 to 2001, it is estimated that Ontario's computerized

[7] Longo, C.J., Fitch, M.I., Banfield, L. *et al.* Financial toxicity associated with a cancer diagnosis in publicly funded healthcare countries: a systematic review. *Support Care Cancer* **28,** 4645–4665 (2020). https://doi.org/10.1007/s00520-020-05620-9

provider entry system, the *Oncology Patient Information System* (OPIS) prevented 8,500 adverse drug events, 5,000 physician office visits, 750 hospitalizations, 57 deaths, and saved millions in annual healthcare costs. But, this system is only used for only IV Drugs[8]. As a result, patients requiring take-home cancer drugs (THCD) in Ontario are (currently) subject to significant safety challenges, and health systems are subject to significant annual costs (physician office visits, hospitalizations etc).

In Ontario, dispensing and delivery models for THCD have been documented to be inconsistent and pose serious safety concerns for patients and their families. Some patients receive their medication from hospital pharmacies, some from specialty pharmacies, and some from community pharmacies that lack specialization and training in the handling of toxic cancer medications. This contrasts with the robust guidelines and clear processes that have been developed for intravenous cancer drugs (IVCD) where delivery is more comprehensive, organized, safer and patient-centred than THCD. There are numerous known safety and quality deficits related to the current method of community dispensing of THCD including incorrect dosing and handling, limited monitoring and non-adherence (which can lead to under or overdosing), serious toxicity, morbidity, and mortality. Patient lives and well-being are at stake. Ontario urgently needs to reform its systems for THCD dispensing that embed high-quality, safe practices that recognize the unique aspects of these drugs.

In April 2017, Cancer Care Ontario organized the Oncology Pharmacy Task Force with the mandate to advise Cancer Care Ontario (CCO) on how to enhance the current system for THCD delivery to optimize quality and safety; and subsequently, to deliver a report to the Ministry of Health and Long-Term Care (MOHLTC) based on the findings of the Task Force. The Task Force included representatives from patient advocacy groups, pharmacy and pharmacist associations, regulatory and standard setting organizations, and subject matter experts. On March 25th, 2019 the report was completed and published on the CCO website, **but there has been no follow up or action taken to the many important recommendations.** The report Enhancing the Delivery of Take-Home Cancer Drugs in Ontario (March 2019) can be found at:

https://www.cancercareontario.ca/sites/ccocancercare/files/guidelines/full/1_CCO_THCD_Report_25Apr2019.pdf

CanCertainty suggests that pCODR examine the issues of safety and dispensing when examining and reporting on issues concerning pan-Canadian implementation of alpelisib.

[8] eHealth Ontario. *Cancer Care Ontario and eHealth Ontario Partner to Deliver Safer Chemotherapy Treatment.* Toronto, ON: 2011. Available at: https://ehealthontario.on.ca/en/news/view/cancer-care-ontario-ehealth-ontario-partner-to-deliver-safer-chemotherapy

COST OF SAME TAKE-HOME CANCER TREATMENT BY PROVINCE

CANCERTAINTY
EQUAL AND FAIR CANCER TREATMENT FOR ALL

CANCER PATIENTS IN ONTARIO AND ATLANTIC FACE SIGNIFICANT OUT OF POCKET COSTS

[1] Ontario
$3,400 Trillium Deductible
(4% of household net income)

[2] Québec
$1,046 Maximum Individual Deductible

[3] New Brunswick
$2,000+ Annual Insurance Premium per adult, $0 annual deductible, $30 copayment per prescription

[4] Nova Scotia
$23,400 Deductible, $17,550 Copayment, NS Family Pharmacare pays 100% after $29,250

[5] Prince Edward Island
$14,400 Family Deductible under Catastrophic Drug Program = 12% on household income > $100,000

[6] Newfoundland & Labrador
$8,500 (10% Net family income)
Out-of-pocket limit set at 5%, 7.5%, or 10% of net family income

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CANCER IS CANCER.
TREATMENT IS TREATMENT.
WHEREVER IN CANADA YOU LIVE.
WWW.CANCERTAINTYFORALL.CA

ASSUMPTIONS

1. Based on total household income of $120,000 ($85,000 net).
2. Oral cancer medication costing $6,000 per month for 12 months.
3. No private insurance.

SOURCES
http://www.health.gov.on.ca/en/public/programs/drugs/programs/odb/opdp_trillium.aspx
http://www.ramq.gouv.qc.ca/en/citizens/prescription-drug-insurance/Pages/amount-to-pay-prescription-drugs.aspx
NS Family Pharmacare Calculator: http://novascotia.ca/dhw/pharmacare/family-calculator.asp
NS Family Pharmacare Deductibe must be paid in FULL before patients start to pay "only" the copay amount of 20% per prescription.
NLPD Assurance Plan via http://www.parl.gc.ca/Content/LOP/ResearchPublications/prb0906-e.htm
New Brunswick Drug Plan Premium: http://www2.gnb.ca/content/gnb/en/departments/health/MedicarePrescriptionDrugPlan/NBDrugPlan/Premiums.html
http://healthpei.ca/catastrophic

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

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

   This submission was completed exclusively using CanCertainty resources and personnel and contract personnel.

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

Data was collected and analyzed using CanCertainty personnel/contract personnel.

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
AstraZeneca			x	

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.

Name: Robert Bick
Position: Co-Lead
Patient Group: CanCertainty
Date: May 14, 2021

CADTH

Patient Input Template for CADTH CDR and pCODR Programs

Name of the Drug and Indication	**Piqray (alpelisib), in combination with fulvestrant, is indicated 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.**
Name of the Patient Group	**Rethink Breast Cancer**
Author of the Submission	[redacted]
Name of the Primary Contact for This Submission	[redacted]
Email	[redacted]
Telephone Number	[redacted]

1. About Your Patient Group

If you have not yet registered with CADTH, describe the purpose of your organization. Include a link to your website.

Rethink Breast Cancer's mission is to empower young people worldwide who are concerned about and affected by breast cancer through education, support and advocacy. Since 2001, we have been building community for young women dealing with breast cancer and providing support and resources to help them live the best quality of life. Because up to 30% of all breast cancers become metastatic, Rethink Breast Cancer has always worked closely with young MBC patients—women who, sadly, leave our community far soon. We represent the voice of young women dealing with breast cancer and strive to ensure their needs and values are heard and considered in all aspects of breast cancer treatment and care at all stages of their breast cancer experience. www.rethinkbreastcancer.com

2. Information Gathering

CADTH is interested in hearing from a wide range of patients and caregivers in this patient input submission. Describe how you gathered the perspectives: for example, by interviews, focus groups, or survey; personal experience; or a combination of these. Where possible, include **when** the data were gathered; if data were gathered **in Canada** or elsewhere; demographics of the respondents; and **how many** patients, caregivers, and individuals with experience with the drug in review contributed insights. We will use this background to better understand the context of the perspectives shared.

Online patient surveys were conducted between March 31 and April 8, 2021. The surveys asked questions about the impact of breast cancer on the lives of patients, the effect of current treatments and their willingness to accept side effects for improved health outcomes. The survey also included questions directed to patients with Piqray treatment experience. Potential respondents were identified through messages to Rethink Breast Cancer's mailing list as well as the Young Women's Network and partner organizations. Messages were also posted on Facebook and Twitter as well as the Cancer Connection and Cancer Survivors Network online discussion forum.

A total of 24 women completed the patient survey. Of these respondents, 4 are from Canada (representing British Columbia and Ontario) and 20 are from the United States. Six of the respondents in this group agreed to participate in telephone interviews with staff members to discuss their treatment experience and elaborate on their feedback.

3. Disease Experience

CADTH involves clinical experts in every review to explain disease progression and treatment goals. Here we are interested in understanding the illness from a patient's perspective. Describe how the disease impacts patients' and caregivers' day-to-day life and quality of life. Are there any aspects of the illness that are more important to control than others?

All 24 respondents are post-menopausal women who have been diagnosed with HR-positive, HER2-negative, advanced or metastatic breast cancer with a PIK3CA mutation. All of the respondents also have treatment experience with Piqray and received Piqray in combination with fulvestrant. 22 respondents reported that they had been treated with an aromatase inhibitor prior to receiving Piqray, while 2 were unsure. 20 respondents were treated with a CDK 4/6 inhibitor prior to receiving Piqray; 4 were not. In total, 18 respondents completely match the indication for this review.

2 respondents were diagnosed in 2018, 4 were diagnosed in 2017, 3 were diagnosed in 2016, 7 were diagnosed between 2011-2015, and 8 were diagnosed in 2010 or earlier.

11 respondents are currently receiving third-line treatment or higher, 6 are receiving treatment after recurrence, 5 are receiving second-line treatment, 1 is receiving first-line treatment and 1 has had no evidence of disease for six months or less.

4. Experiences With Currently Available Treatments

CADTH examines the clinical benefit and cost-effectiveness of new drugs compared with currently available treatments. We can use this information to evaluate how well the drug under review might address gaps if current therapies fall short for patients and caregivers.

Describe how well patients and caregivers are managing their illnesses with currently available treatments (please specify treatments). Consider benefits seen, and side effects experienced and their management. Also consider any difficulties accessing treatment (cost, travel to clinic, time off work) and receiving treatment (swallowing pills, infusion lines).

All 24 respondents provided information about the treatments they had received since their diagnosis. Every respondent received fulvestrant in combination with Piqray. Over half of respondents were also treated with letrozole or palbociclib.

Treatments Received	n	Treatments Received	n
Fulvestrant (Faslodex)	24	Paclitaxel (Taxol)	2
Letrozole (Femara)	19	Ribociclib (Kisqali)	1
Palbociclib (Ibrance)	17	Goserelin (Zoladex)	1
Exemestane (Aromasin)	10	Denosumab (Xgeva)	1
Anastrozole (Arimidex)	9	Pertuzumab (Perjeta)	1
Tamoxifen (Nolvadex)	6	Trastuzumab (Herceptin)	1
Capecitabine (Xeloda)	6	Trastuzumab emtansine (Kadcyla)	1
Abemaciclib (Verzenio)	3	Doxorubicin, cyclophosphamide and paclitaxel (AC-T)	1
Everolimus (Afinitor)	3	Talazoparib (Talzenna)	1

Most respondents have undergone multiple lines of treatment and reported a wide range of outcomes and side effects.

Fatigue was the most commonly reported side effect of these treatments (100%, n=24), followed by diarrhea (83%), loss of appetite (75%), nausea (54%) and headache (46%).

Fatigue, diarrhea and hyperglycemia were identified as the most difficult to tolerate side effects of previous treatments.

Most respondents (86%, n=21) did not report any difficulty accessing treatment.

5. Improved Outcomes

CADTH is interested in patients' views on what outcomes we should consider when evaluating new therapies. What improvements would patients and caregivers like to see in a new treatment that is not achieved in currently available treatments? How might daily life and quality of life for patients, caregivers, and families be different if the new treatment provided those desired improvements? What trade-offs do patients, families, and caregivers consider when choosing therapy?

Rethink Breast Cancer asked patients to evaluate the importance of different outcomes for their breast cancer treatment on a scale of 1 (not important) to 5 (very important). Controlling disease progression is considered the most important patient value with every respondent giving it the highest possible score.

Importance of outcome	1 - not important	2	3	4	5 – very important	Average
Controlling disease progression	0.00% 0	0.00% 0	0.00% 1	0.00% 0	100.00% 24	5.00 24
Reducing symptoms	0.00%	8.33%	29.17%	25.00%	37.50%	3.92

	0	2	7	6	9	24
Maintaining quality of life	0.00% 0	0.00% 0	4.17% 1	37.50% 9	58.33% 14	4.54 24
Managing side effects	0.00% 0	0.00% 0	25.00% 6	0.00% 6	50.00% 12	4.25 24
Preventing recurrence	12.50% 3	4.17% 1	0.00% 0	8.33% 2	75.00% 18	4.29 61

Comments include:

- Anything that gives people months or years is beneficial.
- As long as it's working, it's tolerable.

Respondents were also asked if they would be willing to tolerate new side effects from new drugs to extend life expectancy. On a scale of 1 (will not tolerate side effects) to 10 (will tolerate significant side effects), respondents gave an average score of 7.6 and no respondent gave an answer lower than 5, indicating that patient values are willing to tolerate side effects for drugs that can improve long-term health outcomes.

Comments include:

- I have a seven-year-old and nine-year-old. I'm not ready to leave them.
- I will tolerate pretty much anything within reason in order to find and stay on a drug that keeps the tumour burden low.

6. Experience With Drug Under Review

CADTH will carefully review the relevant scientific literature and clinical studies. We would like to hear from patients about their individual experiences with the new drug. This can help reviewers better understand how the drug under review meets the needs and preferences of patients, caregivers, and families.

How did patients have access to the drug under review (for example, clinical trials, private insurance)? Compared to any previous therapies patients have used, what were the benefits experienced? What were the disadvantages? How did the benefits and disadvantages impact the lives of patients, caregivers, and families? Consider side effects and if they were tolerated or how they were managed. Was the drug easier to use than previous therapies? If so, how? Are there subgroups of patients within this disease state for whom this drug is particularly helpful? In what ways?

18 respondents completely match the indication for this review:

1. They have HR-positive, HER2-negative, advanced or metastatic breast cancer.
2. Their breast cancer includes a PIK3CA mutation.
3. They are post-menopausal.
4. They have been treated with Piqray in combination with fulvestrant.
5. They were treated with an aromatase inhibitor and a CDK 4/6 inhibitor prior to receiving Piqray.

The feedback from these 18 respondents will be described in this section.

Patient Experience

All of the respondents had at least 4 months of experience with Piqray: 7 respondents had received Piqray for 4-6 months, 3 respondents had received it for 7-12 months, 2 respondents had received it for 13-18 months, and 5 respondents had received it for 19-24 months.

12 respondents were still receiving Piqray at the time of the survey, 5 stopped receiving it because it did not control their cancer and 1 person stopped receiving it because she could not tolerate the side effects.

10 respondents required a dose reduction due to side effects, 1 respondent had to discontinue treatment before restarting, and 1 person discontinued treatment after the dose reduction failed to alleviate the side effects.

Quality of Life

Patients were asked to rate the change to their quality of life on Piqray compared to other treatments they had received on a scale of 1 (much worse) to 5 (much better). While respondents felt that Piqray had improved their quality of life, the impact seems to have been weak in most areas with no average score higher than 3.61. Drug side effects were the notable exception – most respondents felt these were the same or worse than other treatments they had received.

Change to quality of life on Perjeta	1 – much worse	2	3	4	5 – much better	Average
Controlling disease	5.56% 1	11.11% 2	38.89% 7	22.22% 4	22.22% 4	3.44 18
Metastatic cancer symptoms	0.00% 0	5.56% 1	50.00% 9	16.67% 3	27.78% 5	3.61 18
Drug side effects	16.67% 3	22.22% 4	33.33% 6	22.22% 4	5.56% 1	2.67 18
Maintaining quality of life	0.00% 0	33.33% 6	27.78% 5	27.78% 5	11.11% 2	3.16 18
Preventing recurrence	5.88% 1	0.00% 0	52.94% 9	23.53% 4	17.65% 3	3.47 17
Ability to work	5.88% 1	17.65% 3	52.94% 9	17.65% 3	5.88% 1	3.00 17
Ability to sleep	5.56% 1	5.56% 1	50.00% 9	33.33% 6	5.56% 1	3.27 18
Ability to drive	0.00% 0	5.56% 1	61.11% 11	22.22% 4	11.11% 2	3.38 18
Ability to perform household chores	5.88% 1	17.65% 3	35.29% 6	29.41% 5	11.76% 2	3.24 17
Ability to care for children	0.00% 0	13.33% 2	46.67% 7	33.33% 5	6.67% 1	3.33 15

Side Effects

Large majorities of patients experienced diarrhea (88.9%, n=18), reduced appetite (77.8%), weight loss (72.2%) and alopecia (66.7%). While not cited as frequently, hyperglycemia was often highlighted during patient interviews as being especially hard to manage.

When asked how much they could tolerate the side effects associated with Piqray on a scale of 1 (completely intolerable) to 10 (completely tolerable), the average score was 6.47. However, it should be noted that only two respondents gave a score lower than 5. Thus, it might be more accurate to say that most respondents did not find the side effects associated with Piqray to be intolerable.

Rating	Responses	Rating	Responses
1	5.88% 1	6	5.88% 1
2	0.00% 0	7	5.88% 1
3	5.88% 0	8	17.65% 3
4	5.88% 1	9	11.76% 2
5	23.53% 4	10	17.65% 3

Comments include:

- I wish I had my hair, I wish I didn't have to follow such a strict diet, and every so often and I feel nauseous, but I have stage four cancer. I know that any drug is going to have side effects and this is so much better than Taxol.
- [Nausea] got so bad at one point that I couldn't even stand looking at a picture of food … but that passed.
- I am tolerating, but it is difficult.
- Important to find effective ways to manage SE right away, especially in the first 4 months when there are so SE that are pretty overwhelming.
- I find Piqray extremely manageable … if you do what you're supposed to do.
- This is not an easy drug [repeated multiple times during interview]
- Piqray worked for almost 18 months and was tough but manageable. I did not have any of the major side effects like blood sugar issues or the rash. I got itchy but that was controlled with antihistamines. I do lose my sense of taste and appetite but that was minor and manageable, although I did lose weight.

Several respondents also said that dose reductions made an important difference in helping them manage the side effects associated with Piqray.

When discussing the side effects they had experienced from Piqray, interviewees would often contrast them with the side effects they had experienced with previous treatments. The side effects were described as unpleasant, but generally manageable.

Comments include:

- The reality is - if you have cancer, none of the drugs are without side effects.
- It gave me another year and a half or so without having to go to chemo.

PIK3CA Treatment Option

Respondent feedback about the mental or emotional value of having a dedicated treatment option for PIK3CA-mutated breast cancer was inconclusive. Respondents were broadly split about whether Piqray helped their mental or emotional well-being.

Comments include:

- Absolutely, without this drug I would be going through lines of treatment more quickly. About 40% of MBC have this mutation that up to now had no good treatment option.
- After reading A LOT about Piqray, I was very nervous to start taking it.
- This specific mutation is being attacked and that really made me feel good. And that was one reason why I was willing to put up with a lot in order to stay on that drug.

7. Companion Diagnostic Test

If the drug in review has a companion diagnostic, please comment. Companion diagnostics are laboratory tests that provide information essential for the safe and effective use of particular therapeutic drugs. They work by detecting specific biomarkers that predict more favourable responses to certain drugs. In practice, companion diagnostics can identify patients who are likely to benefit or experience harms from particular therapies, or monitor clinical responses to optimally guide treatment adjustments.

What are patient and caregiver experiences with the biomarker testing (companion diagnostic) associated with regarding the drug under review?

Consider:

- Access to testing: for example, proximity to testing facility, availability of appointment.
- Testing: for example, how was the test done? Did testing delay the treatment from beginning? Were there any adverse effects associated with testing?
- Cost of testing: Who paid for testing? If the cost was out of pocket, what was the impact of having to pay? Were there travel costs involved?
- How patients and caregivers feel about testing: for example, understanding why the test happened, coping with anxiety while waiting for the test result, uncertainty about making a decision given the test result.

Piqray has a companion diagnostic, which is used to identify PIK3CA mutations. Of our respondents:

79% of respondents (n=24) have received genomic testing of their tumor – 21% received a blood test, 21% had their tumor biopsied, and 37.5% received both a blood test and a biopsy. Most respondents were tested for a PIK3CA mutation after their cancer became metastatic (30%) or when previous lines of treatment failed (52%).

One of the Canadian patients we interviewed by telephone shared her experience with a companion diagnostic for the P1K3CA mutation to determine eligibility in a clinical trial. Her longest wait times were for a biopsy time and then waiting for results, recalling her wait time for a biopsy was about 3 weeks and her wait time for the results was about 4 weeks. The clinical trial nurse phoned her with the results and her treatment started quickly after that. Reflecting back on the experience with companion diagnostic testing, she shared:

"The biopsy itself took several hours and was challenged by getting enough of a sample for analysis. In one case the sample sent to Switzerland; the more recent sample was sent to California. In both cases I asked that, depending on sample availability, enough material be collected for a Foundation One analysis. My thinking was that if I didn't qualify for the clinical trial, ie. have the mutation, then I would submit a sample for analysis to Foundation One. Cost was an issue.

I think access to liquid biopsy would improve the information flow assuming the blood biopsy provides adequate information. I also think it's important to have access to Foundation One testing when tumours become resistant to treatment. Knowledge and information are power and can help with decision making recognizing that there may not be effective treatments available. It would help with finding clinical trials.

I had a reasonable understanding of why the test was happening. At that time it was the only way to get the mutation confirmed. What was more difficult was understanding how the biopsy would be done and what it would feel like. The radiologist was excellent and clear in his explanation however given the location of my tumours, it is quite a rigorous and somewhat painful process.

I was excited, nervous, and anxious while waiting for the results. Excited because we were moving forward with getting what felt like better information. Nervous because of the unknown, uncertain path forward. And anxious because time was passing without a treatment plan. I have a low tumour burden and keeping it low is key to my ongoing survival and health."

8. Biosimilar

If the drug in review is a biosimilar (also known as a subsequent entry biologic), please outline any expectations or concerns held by patients, caregivers, and families about the biosimilar. If the biosimilar was less expensive than the brand name drug, what would the impact be for patients, caregivers, and families?

9. Anything Else?

Is there anything else specifically related to this drug review that CADTH reviewers or the expert committee should know?

When asked if they would recommend Piqray to other patients with breast cancer, 17 of 18 respondents who matched the full indication for this review said that they would. The lone dissenter indicated that she would rather use Piqray as a last resort. Respondents emphasized that they were willing to tolerate side effects for a drug like Piqray that could potentially control disease progression. However, they also acknowledged that managing these side effects could be a significant challenge.

Asked to elaborate, respondents commented:

- Piqray is kicking my cancer's butt and I have a relatively decent quality of life. I do encourage women to keep their oncologist informed of side effects, to get a dose reduction when possible and to drink a lot of water.
- If it's your only option before IV chemo, then it certainly doesn't hurt to give it a try.
- I finally bought a calendar … after I started in Piqray. I had been scared to plan anything.
- I would suggest they try it but they need to be closely monitored for side effects.
- Piqray controlled my cancer for almost a year and a half, which was a pretty long time, and my side effects were manageable. This treatment was easier to handle than most I'd been on.
- It's very manageable; you can manage the side effects and it really works. It really slows down the cancer.
- This is not an "easy" drug to take given the many and sometimes difficult SE that occur. That said it is the only drug out there targeting this mutation which makes it extremely useful and worth pursuing.
- Is it worth it? Well yeah. Here I am. I thought I would be dying now. I'm not.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

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

   We asked Novartis to provide us with information about the general characteristics of the drug and its benefits. We asked our Scientific Advisory Committee (medical oncologists) about this drug and its benefits and whether it addressed an unmet need. Adam Waiser is a freelance health technology assessment writer who we contracted to help us with writing this submission.

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

   We contracted Adam Waiser to help us develop the survey we used to collect the data used in this submission. All interviews were conducted by Rethink Breast Cancer staff. Adam Waiser helped us analyze the findings of our survey and interviews.

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
Novartis				X

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.

Name: MJ DeCoteau
Position: Executive Director
Patient Group: Rethink Breast Cancer
Date: May 14, 2021