Canadian Journal of Health Technologies

CADTH

February 2022 Volume 2 Issue 2

CADTH Reimbursement Recommendation

Alpelisib (Piqray)

Indication: In combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)-negative, *PIK3CA*-mutated advanced or metastatic breast cancer after disease progression following an endocrine-based regimen with a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor

Sponsor: Novartis Pharmaceuticals Inc.

Recommendation: Do not reimburse

CADTH

ISSN: 2563-6596

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Piqray?

CADTH recommends that Piqray should not be reimbursed by public drug plans in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor–positive, human epidermal growth factor 2 (HER2)-negative, *PIK3CA*-mutated advanced or metastatic breast cancer after disease progression following an endocrine-based regimen with a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor.

Why Did CADTH Make This Recommendation?

- There is not enough robust clinical evidence to demonstrate a benefit in adding Piqray to fulvestrant therapy in the relevant patient population.
- It is unclear whether Piqray meets the needs identified by patients, including delaying disease progression, extending overall survival, and maintaining or improving quality of life. Patients also identified a need for a treatment with minimal side effects, but many patients in the studies discontinued treatment with Piqray due to side effects.

Additional Information

What Is Breast Cancer?

HER2-negative, *PIK3CA*-mutated breast cancers are those that start in the breast and have cells without high levels of HER2 protein and have mutations in the *PIK3CA* gene. In 2020, there were approximately 27,200 new cases of breast cancer and 5,100 deaths from breast cancer in Canada.

Unmet Needs in Breast Cancer

In patients with advanced or metastatic HER2-negative breast cancer, currently available treatments after disease progression are not effective and chemotherapy has many side effects.

How Much Does Piqray Cost?

Treatment with Piqray in combination with fulvestrant is expected to cost approximately $7,082 per patient per 28-day cycle for the first cycle and $5,916 per patient per 28-day cycle for subsequent cycles.

Recommendation

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) recommends that alpelisib, in combination with fulvestrant, not be reimbursed for the treatment of postmenopausal women, and men, with hormone receptor–positive, human epidermal growth factor 2 (HER2)-negative, *PIK3CA*-mutated advanced or metastatic breast cancer after disease progression following an endocrine-based regimen with a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor.

Rationale for the Recommendation

There is insufficient evidence that alpelisib meets an unmet therapeutic need in the patient population requested for reimbursement by the sponsor. Patients expressed a desire for treatments that delay progression of their disease, prolong life without sacrificing quality of life, and have fewer adverse effects than current therapies. One randomized controlled trial (RCT), the SOLAR-1 study, did not demonstrate that treatment with alpelisib plus fulvestrant resulted in added clinical benefit in a small subpopulation (N = 20) of postmenopausal women, and men, with hormone receptor–positive, HER2-negative, *PIK3CA*-mutated advanced or metastatic breast cancer after disease progression following an endocrine-based regimen with a CDK4/6 inhibitor relative to placebo plus fulvestrant. The RCT was not designed to test hypotheses in this subgroup, and the results of post hoc statistical comparisons between the treatments for progression-free survival (PFS) and overall survival (OS) within this subgroup were not statistically significant. Results from 1 cohort within the BYLieve study, which included patients that matched the relevant patient population, did not demonstrate added clinical benefit of treatment with alpelisib plus fulvestrant versus any relevant comparators due to the noncomparative design of the study. An additional analysis comparing the BYLieve cohort with patients in the Flatiron database was limited by several sources of bias that precluded pERC from concluding that treatment with alpelisib plus fulvestrant resulted in added clinical benefit for the population targeted by the reimbursement request relative to standard of care (SOC) therapies. Additionally, treatment was stopped prematurely due to increased adverse events (AEs) in the alpelisib group versus the placebo group in the SOLAR-1 study. pERC concluded there is a high degree of uncertainty regarding the magnitude of the treatment benefit with alpelisib plus fulvestrant in patients with hormone receptor–positive, HER2-negative, *PIK3CA*-mutated advanced or metastatic breast cancer after disease progression following an endocrine-based regimen with a CDK4/6 inhibitor.

Discussion Points

- pERC deliberations focused on the data for alpelisib in combination with fulvestrant in the population requested for reimbursement by the sponsor: postmenopausal women, and men, with hormone receptor–positive, HER2-negative, *PIK3CA*-mutated advanced or metastatic breast cancer after disease progression following an endocrine-based regimen with a CDK4/6 inhibitor. This population differs from the broader population of the Health Canada–approved indication for alpelisib in that it specifies that patients must have received a CDK4/6 inhibitor along with a previous endocrine-based regimen.

- The committee noted that the results from the entire *PIK3CA* mutant cohort, which consisted mostly of patients without prior CDK4/6 inhibitor treatment, could not be generalized to patients with prior CDK4/6 inhibitor treatment. This was in accordance with input from the clinical experts consulted by CADTH for the review, the design of the SOLAR-1 study, and regulatory reviews from other jurisdictions.
- The evidence submitted to support the clinical and economic evaluations of alpelisib (with fulvestrant) primarily came from the observational study that compared the cohort from the BYLieve study that contained the requested reimbursement population with a real-world cohort derived from the Flatiron database. Although the study used accepted methods to match patients from both cohorts, the committee noted differences between the cohorts on certain characteristics and that some clinically relevant prognostic variables were not used in the matching. Therefore, bias in the efficacy estimate due to selection bias, measurement error, unmeasured confounding, and residual confounding was possible, and the validity of the results of the study was highly uncertain.
- pERC discussed patient input that metastatic breast cancer can have a significant impact on patients' quality of life, employment, daily activities, and relationships. Patients reported having to undergo multiple lines of treatment and experienced a wide range of outcomes and side effects. pERC recognized the need for an effective alternative treatment option for patients with metastatic breast cancer who have disease progression. Given the limitations of the available evidence on the comparative effectiveness, including the lack of data on health-related quality of life, pERC concluded that the evidence did not clearly demonstrate that alpelisib meets these important patient needs.
- pERC discussed patients' desire for new treatments with fewer or more manageable adverse effects. Approximately half of patients who had experience with alpelisib reported that the drug's adverse effects were the same or worse than other treatments they had received. Hyperglycemia, gastrointestinal effects, fatigue, rash, and stomatitis were the most commonly reported AEs in the SOLAR-1 and BYLieve studies with alpelisib treatment. Of note, treatment was stopped prematurely due to increased AEs in the alpelisib group (27.2%) versus the placebo group (5.8%) in the safety population of the SOLAR-1 study. Therefore, it is unclear whether alpelisib would meet the need for a treatment that is easier to tolerate.
- The sponsor indicated that a new phase III trial will be conducted for alpelisib plus fulvestrant in patients with prior CDK4/6 inhibitor treatment. The trial will be a double-blind, placebo-controlled RCT in men and postmenopausal women with hormone receptor–positive, HER2-negative, *PIK3CA*-mutated advanced breast cancer who have progressed on or after treatment with an aromatase inhibitor (AI) and a CDK4/6 inhibitor. As stated by the sponsor, the planned study population aligns with the population targeted by the reimbursement request. The first patient visit is expected to occur in October 2021, with the first interpretable results for the trial planned for the third quarter of 2024.
- *PIK3CA* testing is not currently publicly funded in any jurisdictions in Canada.
- Although updated OS results for the BYLieve study are available, the results do not provide evidence for the efficacy of alpelisib plus fulvestrant versus relevant comparators due to the lack of a comparator arm in the study.

Background

Alpelisib has a Health Canada 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 an endocrine-based regimen. Alpelisib is a phosphatidylinositol 3-kinase (PI3K) inhibitor with inhibitory activity predominantly against PI3K catalytic subunit alpha. It is available as 50 mg, 150 mg, and 200 mg oral tablets, and the Health Canada–approved dose is 300 mg taken orally, once daily, on a continuous basis. The sponsor's reimbursement request is for alpelisib in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor–positive, HER2-negative, *PIK3CA*-mutated advanced or metastatic breast cancer after disease progression following an endocrine-based regimen with a CDK4/6 inhibitor. The reimbursement request differs from the Health Canada indication in that it specifies that patients must have received CDK4/6 inhibitor with a previous endocrine-based regimen.

Sources of Information Used by the Committee

To make their recommendation, the committee considered the following information:

- a review of 1 RCT in patients with hormone receptor–positive, HER2-negative, *PIK3CA*-mutated advanced or metastatic breast cancer after disease progression on or after AI therapy
- a review of 1 noncomparative cohort study and 1 observational study in patients with hormone receptor–positive, HER2-negative, *PIK3CA*-mutated advanced or metastatic breast cancer after disease progression on or after an endocrine-based regimen with a CDK4/6 inhibitor
- patient perspectives gathered by 3 patient groups: the Canadian Breast Cancer Network (CBCN), Rethink Breast Cancer, and CanCertainty
- input from public drug plans and cancer agencies that participate in the CADTH review process
- two clinical specialists with expertise diagnosing and treating patients with breast cancer
- input from 1 clinician group: the Breast Medical Oncology group at the Ottawa Hospital Cancer Centre
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Information was gathered from the following:

- patient and caregiver responses from 2 online surveys (with 90 patient respondents and 71 patient and 16 caregiver respondents, respectively) and a telephone interview with 1 patient that were conducted by the CBCN
- patient responses from an online survey (24 patient respondents) and telephone interviews with 6 of the survey respondents that were conducted by Rethink Breast Cancer (including responses from 18 patients who fulfilled the requested reimbursement criteria)
- published reports relating to breast cancer and oral cancer drugs, summarized by CanCertainty.

The physical impact of metastatic breast cancer is variable across individuals with most patients reporting some or moderate to significant or debilitating impact on their quality of life due to the symptoms of fatigue, insomnia, and pain. Many negative impacts on patients and their families' daily lives were identified, including restrictions in patients' ability to remain employed, care for children and dependents, be social, exercise, pursue hobbies and interests, and spend time with loved ones. The patient groups identified the following measures of effectiveness as the most important: PFS, OS, quality of life, and adverse effects. Survey results indicated that patients are willing to tolerate side effects for drugs that can improve long-term health outcomes.

Clinician Input

Input From Clinical Experts Consulted by CADTH

Current therapies for advanced or metastatic breast cancer beyond the first-line setting have low response rates and have rarely been shown to improve OS. Chemotherapy options are more poorly tolerated than endocrine therapy and many available chemotherapy options are administered intravenously, requiring more hospital visits and reliance on institutions. Alpelisib would be the first treatment available specifically for patients with *PIK3CA*-mutated cancer.

For tumours harbouring a *PIK3CA* mutation, alpelisib would be added to an already established SOC option for the second-line treatment of advanced or metastatic hormone receptor–positive HER2-negative breast cancer (i.e., fulvestrant). Alpelisib would not be used as a first-line treatment given the strong evidence for the use of CDK4/6 inhibitors with endocrine therapy in that setting. Patients with advanced or metastatic hormone receptor–positive HER2-negative breast cancer, activating mutations in the *PIK3CA* gene (identified using liquid biopsy or tissue testing on archival or newly obtained tumour tissue), good performance status, expected survival of longer than 3 months, and no type 1 diabetes mellitus or uncontrolled type 2 diabetes mellitus would be best suited for treatment with alpelisib plus fulvestrant. Alpelisib with fulvestrant would not be recommended for patients who are intolerant of other treatments or for whom other treatments are contraindicated. In patients with life-threatening visceral organ metastases, chemotherapy would be recommended before considering treatment with alpelisib and fulvestrant. Patients would not be suited for treatment with alpelisib plus fulvestrant if they have poor performance status, have type 1 or uncontrolled type 2 diabetes mellitus, are unable to understand and manage potential toxicities and dosing and monitoring requirements, or are noncompliant with follow-up.

Treatment response is monitored using a combination of clinical examination, laboratory evaluation (markers of organ function with or without tumour markers), and radiographic evaluation. Treatment continues as long as the disease is stable or responding on radiographic scans according to the RECIST criteria. Treatment with alpelisib and fulvestrant

should be discontinued if there is disease progression, intolerable or dangerous toxicity (especially uncontrolled hyperglycemia), or an event or development of a comorbidity that adversely impacts performance status or survival (e.g., stroke).

Treatment with alpelisib and fulvestrant would be prescribed by medical oncologists or associated team physicians with expertise in cancer therapies and toxicity management. Patients would be treated on an outpatient basis under medical oncology supervision and fulvestrant injections would be administered in a hospital outpatient clinic.

Clinician Group Input

One clinician group submission was received from 6 clinicians with the Breast Medical Oncology group at the Ottawa Hospital Cancer Centre. Input from the clinician group was largely aligned with input from the clinical experts consulted by CADTH. Due to the small percentage of patients in the pivotal trial who had previously received the current first-line SOC with CDK4/6 inhibitors, opinions within the clinical group were divided on whether it would be appropriate to offer alpelisib to this patient population.

Drug Program Input

There were several questions from the drug plans regarding patient populations that would be suitable for treatment with alpelisib plus fulvestrant, discontinuation of alpelisib or fulvestrant, and *PIK3CA* mutation testing. Patients were excluded from the pivotal trial for alpelisib if they had an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or higher, were receiving luteinizing hormone-releasing hormone (LHRH) agonist for induction of ovarian suppression, had inflammatory breast cancer, had symptomatic visceral disease, had received prior chemotherapy in the metastatic setting, had received prior fulvestrant, had uncontrolled central nervous system metastases, or had type 1 diabetes or uncontrolled type 2 diabetes. According to the clinical experts consulted by CADTH, patients receiving LHRH agonist for induction of ovarian suppression would be eligible, while patients in the other groups (aside from those with diabetes) could be considered for eligibility on a case-by-case basis or if they met certain other criteria.

The drug plans also wanted to know if alpelisib could be continued as monotherapy if fulvestrant was discontinued or interrupted. The clinical experts indicated that alpelisib could be continued during an interruption but not after discontinuation. Conversely, the drug plans also wanted to know if patients who had to discontinue alpelisib due to intolerance could continue with single-agent fulvestrant. The clinical experts considered it appropriate to continue these patients on single-agent fulvestrant. In response to a related question, the experts also considered it appropriate to permanently discontinue alpelisib after it had been discontinued for more than 4 weeks due to unresolved toxicity. Another drug plan question was whether it would be appropriate to offer it to patients on chemotherapy with no evidence of progressive disease or intolerance alpelisib plus fulvestrant. The clinical experts did not consider this appropriate because patients doing well on chemotherapy would not be switched to a different therapy.

With regards to *PIK3CA* mutation testing, the drug plans asked which patients should be tested for the *PIK3CA* mutation and when in the course of treatment this testing should occur. According to the clinical experts consulted by CADTH, patients identified as best suited for alpelisib plus fulvestrant treatment should be tested. These patients would have advanced or metastatic hormone receptor–positive, HER2-negative breast cancer; good ECOG performance status; expected survival of longer than 3 months; and no type 1 diabetes

mellitus or uncontrolled type 2 diabetes mellitus. Testing should be performed at diagnosis of de novo metastatic breast cancer, at relapse following treatment for early breast cancer, or at progression on first-line therapy for advanced or metastatic breast cancer.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

The CADTH systematic review identified 1 relevant study, the SOLAR-1 study. SOLAR-1 (N = 572) was a placebo-controlled, double-blind, parallel-group RCT that randomized patients 1:1 to alpelisib 300 mg orally daily or matching-administration placebo in combination with fulvestrant 500 mg intramuscularly on day 1, day 15, day 29, and every 28 days afterward. Men and postmenopausal women with hormone receptor–positive, HER2-negative advanced or metastatic breast cancer and previous endocrine therapy were randomized within each of 2 cohorts based on *PIK3CA* mutation status: *PIK3CA* mutant and *PIK3CA* nonmutant. The primary and key secondary outcomes were PFS and OS in the *PIK3CA* mutant cohort (N = 341). Endocrine therapy with a CDK4/6 inhibitor was not a part of the SOC at the time the study was conducted (enrolment was from 2015 to 2017) and only 20 patients in the *PIK3CA* mutant cohort had received prior CDK4/6 inhibitor treatment. Therefore, only 20 met the reimbursement criteria requested by the sponsor.

Within the *PIK3CA* mutant cohort, there were 20 patients identified as having prior CDK4/6 inhibitor treatment according to the randomization stratum. Female patients were included only if they were postmenopausal and were not receiving an LHRH agonist for induction of ovarian suppression. In the subgroup with prior CDK4/6 inhibitor treatment, all patients had an ECOG performance status of 0 or 1, most patients were White, and most had secondary endocrine resistance. In the entire cohort, most patients were White, had an ECOG performance status of 0 (the remaining having a performance status of 1), had 1 or 2 metastatic sites, had 1 line of prior medication therapy, and had no prior hormonal therapy in the metastatic setting.

Efficacy Results

At the final PFS analysis within the subgroup with prior CDK4/6 inhibitor treatment (N = 20) at the June 12, 2018 data cut-off, median PFS was 5.5 (95% confidence interval [CI], 1.58 to 16.76) months in the alpelisib group and 1.8 (95% CI, 1.68 to 3.58) months in the placebo group. The hazard ratio for the alpelisib group versus the placebo group was 0.48 (95% CI, 0.17 to 1.36).

At the final OS analysis at the April 23, 2020 data cut-off, median OS was 29.8 (95% CI, 6.67 to 38.21) months in the alpelisib group and 12.9 (95% CI, 2.46 to 34.60) months in the placebo group. The hazard ratio for the alpelisib group versus the placebo group was 0.67 (95% CI, 0.21 to 2.18).

Harms Results

Almost all patients in the *PIK3CA* mutant cohort (n = 341) reported at least 1 AE (99.4% in the alpelisib group and 90.6% in the placebo group). Most of the AEs that occurred in at

least 10% of at least 1 treatment group were more common in the alpelisib group compared with the placebo group. All of the AEs reported by more than 20% of patients in the alpelisib group were also more common in the alpelisib group: hyperglycemia, diarrhea, nausea, rash, decreased appetite, decreased weight, stomatitis, vomiting, fatigue, and alopecia.

Serious adverse events (SAEs) were reported in 39.6% of the alpelisib group and 19.9% of the placebo group. The most common SAEs were hyperglycemia (10.1% in the alpelisib group and zero in the placebo group); osteonecrosis of the jaw (3.6% in the alpelisib group and zero in the placebo group); and stomatitis, acute kidney injury, and rash (2.4% in the alpelisib group and zero in the placebo group for each).

Withdrawals from treatment due to AE were more common in the alpelisib group (27.2%) versus the placebo group (5.8%). The most common AEs leading to discontinuation were reported in the alpelisib group alone: hyperglycemia (6.5%), rash (4.7%), and diarrhea (3.6%).

On-treatment deaths up to 30 days after the last dose of study treatment occurred in 4.1% of the alpelisib group and 5.8% of the placebo group. The most common cause of on-treatment death was breast cancer (3.6% in the alpelisib group and 4.1% in the placebo group); other causes of on-treatment death were reported for 1 patient each.

The following notable harms identified in the systematic review protocol occurred in more than 10% of at least 1 treatment group and were more common in the alpelisib group: hyperglycemia, diarrhea, nausea, rash, vomiting, and maculopapular rash.

Critical Appraisal

No relevant conclusions could be drawn regarding PFS and OS in patients treated with alpelisib and fulvestrant versus placebo and fulvestrant because the SOLAR-1 study was not designed to test hypotheses in the subgroup of patients with prior CDK4/6 inhibitor treatment and did not include outcomes in this subgroup in the statistical testing hierarchy. Only the results in this small subgroup can inform comparative efficacy in the patient population targeted by the sponsor's reimbursement request since the efficacy results in the entire *PIK3CA* mutant cohort cannot be generalized to the relevant patient population.

Other Relevant Evidence

Description of Studies

There were 2 additional relevant studies included in the sponsor's submission to CADTH that were considered to address important gaps in the evidence included in the systematic review. The BYLieve study, a noncomparative cohort study, included 1 cohort of patients treated with alpelisib and fulvestrant that matched the patient population relevant to the sponsor's reimbursement request. In a separate observational study, the relevant cohort of the BYLieve study was compared, following propensity score weighting, with a database-derived cohort treated with non-alpelisib SOC.

Noncomparative Cohort Study

The BYLieve study assigned patients to 1 of 3 cohorts based on their most recent previous anticancer therapy. Of the 3 cohorts, cohort A (n = 127) was relevant and included patients with hormone receptor–positive, HER2-negative advanced or metastatic breast cancer and a confirmed *PIK3CA* mutation who had received any CDK4/6 inhibitor plus any AI as their immediate prior treatment. These patients were assigned to receive alpelisib plus fulvestrant

at the same dosages as in the SOLAR-1 study. The primary end point in the BYLieve study was the proportion of patients who were alive without disease progression at 6 months by local investigator assessment using Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST v1.1) criteria. The outcomes of PFS, OS, as well as safety data were also evaluated in the BYLieve study.

Progression and Survival Results

As of the data cut-off date, 61 of 121 (50.4%) patients in the cohort A modified full analysis set (N = 121) were alive without progressive disease per investigator assessment at 6 months (95% CI, 41.2% to 59.6%). The study met the primary objective for cohort A because the lower bound of the 95% CI was greater than 30%. The median PFS by investigator assessment was 7.3 (95% CI, 5.6 to 8.3) months. The PFS rates by investigator assessment at 6 months and 12 months were 54.1% (95% CI, 44.3% to 62.9%) and 27.3% (95% CI, 17.6% to 37.8%), respectively.

The median OS was 17.3 (95% CI, 17.2 to 20.7) months. The OS rates at 6 months and 12 months were 91.9% (95% CI, 84.9% to 95.7%) and 75.2% (95% CI, 62.5% to 84.2%), respectively. The sponsor indicated in the clinical study report that OS data should be interpreted with caution due to the proportion of patients alive and continuing follow-up at the time of the data cut-off date.

Harms Results

Almost all patients in cohort A (99.2%) experienced at least 1 treatment-emergent AE. The most common AEs (≥ 20%) were diarrhea (59.8%), hyperglycemia (58.3%), nausea (45.7%), fatigue (29.1%), decreased appetite (28.3%), rash (28.3%), stomatitis (26.8%) and vomiting (23.6%). Overall, 26.0% of patients experienced an SAE. The most common SAEs were hyperglycemia (5.5%), maculopapular rash (3.1%), dyspnea (2.4%), pleural effusion (2.4%), abdominal pain (1.6%), and haematemesis (1.6%). The most common AEs leading to discontinuation of study treatment were rash (3.9%) and colitis, hyperglycemia, urticaria, and vomiting (1.6% each). As of the data cut-off date, 7 (5.5%) patients had died during study treatment or within 30 days of the last dose of study drug; 4 of these on-treatment deaths were attributed to breast cancer.

The following notable harms were reported: hyperglycemia (58.3%), hypersensitivity and anaphylactic reactions (10.2%), diarrhea (59.8%), nausea (45.7%), rash (28.3%), vomiting (23.6%), maculopapular rash (14.2%), pneumonitis (0.8%), and severe cutaneous skin reactions (0.8%).

Critical Appraisal

The BYLieve study is unable to inform the efficacy of alpelisib plus fulvestrant versus a relevant comparator due to its noncomparative study design. There was also no statistical hypothesis testing in the relevant outcomes of interest, PFS and OS.

Observational Study

The observational study compared cohort A from the BYLieve study with a real-world cohort derived from the Flatiron database. Cohort A from the BYLieve study (n = 120), which received alpelisib plus fulvestrant following treatment with a CDK4/6 inhibitor plus AI, was compared with the Flatiron cohort (n = 95), which received non-alpelisib SOC following treatment with a CDK4/6 inhibitor and non-fulvestrant endocrine therapy. PFS was compared between the cohorts following weighting of the Flatiron cohort based on propensity scores.

Efficacy Results

Following propensity score weighting to estimate the average treatment effect on the treated, median PFS was 3.7 (95% CI, 3.1 to 6.1) months in the Flatiron cohort and 7.3 (95% CI, 5.6 to 8.3) months in the BYLieve cohort with a P value of 0.040 for the log-rank test. The weighted hazard ratio for PFS in the BYLieve cohort versus the Flatiron cohort was 0.62 (95% CI, 0.44 to 0.85; P = 0.002). The observational study included sensitivity analyses assessing the sensitivity of the results to the form of confounding adjustment, namely greedy matching and exact matching. The results of those analyses were not meaningfully different from the primary analysis results. No sensitivity analysis to the assumption of no unmeasured confounding was performed.

Harms Results

Harms were not assessed in the observational study.

Critical Appraisal

Overall, there remains a great deal of uncertainty regarding the efficacy of alpelisib compared with SOC due to the inherent limitations of observational data. Although the adjustment approaches in this study may have resulted in adequately balanced observable prognostic factors categorized as they were, bias in the efficacy estimate due to selection bias, measurement error, unmeasured confounding, and residual confounding cannot be ruled out. No attempts were made to assess nor estimate the possible magnitude of such bias.

Economic Evidence

Table 1: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-effectiveness analysis Semi-Markov cohort model
Target population	Postmenopausal women, and men, with hormone receptor–positive, HER2-negative, *PIK3CA*-mutated advanced or metastatic breast cancer after disease progression following an endocrine-based regimen with a CDK 4/6 inhibitor (which aligns with the sponsor's reimbursement request)
Treatment	Alpelisib plus fulvestrant
Submitted price	Alpelisib, 150 mg tablet: $95.23; 200 mg tablet: $95.23; 200 mg + 50 mg tablet: $190.46
Treatment cost	Alpelisib 28-day cycle cost: $5,333 Alpelisib plus fulvestrant first 28-day cycle: $7,082; subsequent 28-day cycles: $5,916
Comparators	SOC (everolimus plus exemestane)
Perspective	Canadian publicly funded health care payer
Outcomes	LYs, QALYs
Time horizon	Lifetime (15 years)
Key data source	BYLieve trial (alpelisib plus fulvestrant) and Flatiron data (SOC)

Component	Description
Key limitations	• There is insufficient direct comparative clinical efficacy and safety data for alpelisib plus fulvestrant compared with relevant comparator agents (e.g., capecitabine and fulvestrant monotherapy) for patients meeting the reimbursement request criteria. In the absence of direct comparative evidence, the sponsor submitted a propensity score–weighted observational study of alpelisib plus fulvestrant compared with SOC that was not sufficiently robust to inform the cost-effectiveness analysis. • SOC, as defined by the sponsor, does not reflect the most common comparator agents used in practice. The sponsor assumed that the historical control group from the Flatiron database would be equivalent to everolimus plus exemestane, which is not covered by public dug plans for this patient population. According to the clinical experts consulted by CADTH for this review, relevant comparators that are more commonly used in Canadian clinical practice include fulvestrant monotherapy and single-agent chemotherapy. The cost-effectiveness of alpelisib plus fulvestrant compared with these agents is unknown. • PFS in patients receiving second-line treatment with alpelisib plus fulvestrant and SOC was overestimated. The sponsor used data from the BYLieve vs. Flatiron analysis to derive parametric survival curves to extrapolate over the 15-year time horizon of the model. The clinical experts consulted by CADTH for this review considered the sponsor's estimates to be overestimates of the percentage of patients that would remain progression-free in practice. This approach led to an overestimate of the incremental QALYs gained for alpelisib plus fulvestrant compared to SOC. • The sponsor did not account for *PIK3CA* retesting costs in the analysis. The clinical experts consulted by CADTH indicated that for patients who test negative for the *PIK3CA* mutation on an initial liquid biopsy, it is recommended to universally retest patients with a tumour tissue test. Omission of these costs underestimated the incremental cost of treatment with alpelisib plus fulvestrant compared with relevant comparator agents. • The sponsor adjusted the cost of alpelisib and the cost of everolimus using an RDI of 0.837 for alpelisib and 0.86 for everolimus, and derived TTD assumptions for SOC using the PFS curve. The derived TTD curve relied on several naive comparisons and assumptions resulting in substantial uncertainty in the estimates. The use of RDIs < 1.0 and uncertainty in the TTD assumptions resulted in an underestimate and uncertainty in the incremental costs of alpelisib plus fulvestrant. • The sponsor used treatment-specific health state utility estimates that were based on a regression analysis from data derived from the full population of SOLAR-1. These data had several limitations, including a lack of face validity for utilities derived for the PFS (off-treatment) and PPS health states, which led to an overestimate of incremental QALYs in favour of alpelisib plus fulvestrant.
CADTH reanalysis results	• CADTH was unable to derive a base case due to the lack of robust comparative clinical efficacy data. CADTH undertook exploratory reanalyses using alternative assumptions in the model. • CADTH's exploratory reanalyses assessed the impact of alternative model assumptions including a revised price for everolimus, an alternate parametric PFS curve, alternate estimates for the percentage of patients progressing due to death, the inclusion of *PIK3CA* retesting costs, an RDI of 1.0 for oral drugs, removal of treatment-specific health state utility estimates, the use of an alternate hazard ratio for the derivation of TTD curves from PFS, and setting AE incidence equal between treatments. • Based on the steps taken in the CADTH's exploratory reanalysis, alpelisib plus fulvestrant is associated with an ICER of $319,592 per QALY gained compared with SOC. A price reduction of 99% is required for alpelisib plus fulvestrant to be cost-effective at a $50,000 per QALY threshold.

AE = adverse event; CDK4/6 = cyclin-dependent kinase 4 and 6; HER2-negative = human epidermal growth factor 2-negative; ICER = incremental cost-effectiveness ratio; LY = life-year; PFS = progression-free survival; PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; QALY = quality-adjusted life-year; RDI = relative dose intensity; SOC = standard of care; TTD = time to treatment discontinuation.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: limited generalizability of the modelled comparators, uncertainty in market share estimates for

comparator agents in the reference and new drug scenario, underestimate of the percentage of patients likely to be tested for a *PIK3CA* mutation, and underestimate of treatment costs using RDI assumptions.

CADTH revised the price of everolimus and removed the RDI assumptions to align with the pharmacoeconomic model, revised the market share estimates for comparator agents in the reference and new drug scenario, and increased the percentage of patients likely to be tested for a *PIK3CA* mutation. In the CADTH reanalysis, the estimated budget impact for alpelisib plus fulvestrant was $10,066,084 in year 1, $11,122,569 in year 2, and $12,751,037 in year 3, for a 3-year expected budget impact of $33,939,690.

The inclusion of *PIK3CA* testing costs and the price and market share assumptions for alpelisib are key drivers of the results. Changes to the assumptions related to the percentage of patients eligible for public coverage could significantly increase the budget impact.

pCODR Expert Review Committee Information

Initial meeting date: September 8, 2021

Members of the Committee

Dr. Maureen Trudeau (Chair), Dr. Catherine Moltzan (Vice-Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Kelvin Chan, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christine Kennedy, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Ms. Valerie McDonald, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Regrets: None

Conflicts of interest: None

Reconsideration meeting date: January 12, 2022

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung, Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Regrets: None

Conflicts of interest: None