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CADTH Reimbursement Recommendation

Capivasertib (Truqap)

Indication: Capivasertib is indicated in combination with fulvestrant for the treatment of adult females with hormone receptor-positive, human epidermal growth factor receptor 2-negative locally advanced or metastatic breast cancer with one or more *PIK3CA/AKT1/PTEN* alterations following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.

Sponsor: AstraZeneca Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the CADTH Reimbursement Recommendation for Truqap?

CADTH recommends that Truqap in combination with fulvestrant should be reimbursed by public drug plans for the treatment of adults with hormone receptor (HR)–positive, human epidermal growth factor receptor 2 (HER2)–negative locally advanced or metastatic breast cancer with 1 or more *PIK3CA, AKT1,* or *PTEN* alterations following progression on at least 1 endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy, if certain conditions are met.

Which Patients Are Eligible for Coverage?

Truqap plus fulvestrant should only be covered to treat adults who have HR-positive, HER2-negative locally advanced or metastatic breast cancer with 1 or more *PIK3CA*, *AKT1,* or *PTEN* alterations and are in relatively good health. Truqap plus fulvestrant should not be covered in patients who have progressed on prior therapy with fulvestrant, received more than 2 lines of hormone therapy, or received more than 1 line of chemotherapy in the metastatic setting.

What Are the Conditions for Reimbursement?

Truqap plus fulvestrant should only be reimbursed if prescribed and administered by health professionals experienced in the management of breast cancer at treatment centres with adequate resources to manage side effects, and if the price of Truqap is reduced. Lastly, it must be feasible to test patients for *PIK3CA, AKT1,* or *PTEN* alterations.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that treatment with Truqap plus fulvestrant was better than treatment with placebo plus fulvestrant in delaying the spread of cancer and may result in patients living longer; therefore, Truqap plus fulvestrant meets some important patient needs. Although Truqap plus fulvestrant likely results in more serious side effects than placebo plus fulvestrant, the side effects are considered manageable.
- Based on CADTH's assessment of the health economic evidence, Truqap does not represent good value to the health care system at the public list price. A price reduction is therefore required. Based on the public list price, Truqap is estimated to cost the public drug plans approximately

Summary

$81 million over the next 3 years. The testing uptake is 1 of the main factors that impacts the size of the budget impact analysis (BIA).

- Prior to initiating treatment with Truqap plus fulvestrant, next-generation sequencing (NGS) is required to confirm the *PIK3CA, AKT1,* or *PTEN* alteration status. This is currently not part of routine practice in many places across Canada. Implementation of testing for *PIK3CA, AKT1,* or *PTEN* alterations will have a substantial health system impact.

Additional Information

What Is HR-Positive, HER2-Negative Locally Advanced or Metastatic Breast Cancer?

Breast cancer can be classified by proteins (receptors) expressed by the cancer cell. The HR-positive and HER2-negative subtype is the most common breast cancer in Canada. Breast cancer is considered locally advanced or metastatic when it spreads to other parts of the body or cannot be removed by surgery.

Unmet Needs in HR-Positive, HER2-Negative Locally Advanced or Metastatic Breast Cancer

Patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer need other treatments that prevent or delay cancer from returning, prolong survival with an acceptable toxicity profile, and maintain quality of life.

How Much Does Truqap Cost?

Treatment with Truqap is expected to cost approximately $9,446 per patient, per 28-day cycle. When used in combination with fulvestrant, the per-patient 28-day cost for Truqap plus fulvestrant in the first 28 days is $10,612, and in subsequent 28-day intervals is $10,029.

Recommendation

The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that capivasertib in combination with fulvestrant be reimbursed for the treatment of adults with HR-positive, HER2-negative locally advanced or metastatic breast cancer with 1 or more *PIK3CA, AKT1,* or *PTEN* alterations following progression on at least 1 endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, double-blind, randomized controlled trial (the CAPItello-291 trial) demonstrated that treatment with capivasertib plus fulvestrant resulted in benefit in progression-free survival (PFS) at 6 months and 12 months compared to placebo plus fulvestrant for adults with locally advanced or metastatic HR-positive, HER2-negative breast cancer with 1 or more *PIK3CA, AKT1,* or *PTEN* alterations (i.e., the altered population) following progression on at least 1 endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy. When compared to placebo plus fulvestrant, the Kaplan-Meier (KM)–estimated between-group difference in probabilities of PFS at 6 months and 12 months were [redacted] (95% confidence interval [CI], [redacted] to [redacted]) and [redacted] (95% CI, [redacted] to [redacted]) in favour of capivasertib plus fulvestrant, respectively, which were considered clinically meaningful by clinical experts. Although the overall survival (OS) data were immature, the results in the altered population were considered promising by pERC. After a median duration of follow-up of approximately 14 months in all patients, the median OS had not been reached in either treatment group, and the KM-estimated between-group difference in probabilities of being alive at 18 months and 24 months were [redacted] (95% CI, [redacted] to [redacted]) and [redacted] (95% CI, [redacted] to [redacted]) in favour of capivasertib plus fulvestrant, respectively. Although the trial showed that treatment with capivasertib plus fulvestrant likely results in an increase in the proportion of patients who experience serious AEs when compared with placebo plus fulvestrant, pERC considered the side effects of capivasertib to be significant but manageable, given that treatment is expected to be prescribed and overseen by clinicians who are experienced in treating breast cancer.

Patients identified a need for accessible and effective treatment options that control disease, prolong life, improve quality of life, and delay chemotherapy. pERC concluded that capivasertib plus fulvestrant meets some important needs identified by patients, as it provides improvements in PFS, may improve OS, and would delay the need for chemotherapy if received as second-line therapy.

Using the sponsor-submitted price for capivasertib and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for capivasertib plus fulvestrant was $221,165 per quality-adjusted life-year (QALY) gained, compared with endocrine monotherapy in adult patients with locally advanced or metastatic HR-positive, HER2-negative breast cancer with 1 or more *PIK3CA, AKT1,* or *PTEN* alterations. At this ICER, capivasertib plus fulvestrant is not cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained. A reduction in the price of capivasertib is therefore required. The

cost-effectiveness of capivasertib plus fulvestrant versus chemotherapy and everolimus plus exemestane is unknown.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Capivasertib plus fulvestrant should be reimbursed in adults aged 18 years or older who meet all of the following criteria: 1.1. documented diagnosis of HR-positive, HER2-negative locally advanced or metastatic breast cancer 1.2. documented evidence of *PIK3CA*, *AKT1,* or *PTEN* gene alteration 1.3. received a least 1 line of hormone therapy in the metastatic setting or progressed on adjuvant hormone therapy on or within 12 months of adjuvant hormone therapy 1.4. good performance status.	In the CAPItello-291 trial, treatment with capivasertib plus fulvestrant demonstrated a clinical benefit in adult patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer with 1 or more *PIK3CA, AKT1,* or *PTEN* alterations following progression on at least 1 endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy. Patients were required to have an ECOG or WHO performance status 0 or 1. Males were eligible, and 7 of 708 patients enrolled in the trial were male.	*PIK3CA, AKT1,* or *PTEN* alterations can be detected by genomic testing of the tumour cells. Multiple techniques for testing are available, such as polymerase chain reaction, NGS, and Sanger sequencing. NGS is the preferred technology due to its higher sensitivity and ability to test for multiple genes simultaneously. Tissue samples collected as part of routine diagnostic care (e.g., tissue biopsy, liquid biopsy) can be used for testing. Testing for *PIK3CA, AKT1,* or *PTEN* alterations could be carried out at the time of metastatic diagnosis.
2. Capivasertib plus fulvestrant should not be initiated in patients who have progressed on prior therapy with fulvestrant, received more than 2 lines of hormone therapy, or received more than 1 line of chemotherapy in the metastatic setting.	The CAPItello-291 trial excluded patients who had received prior therapy with fulvestrant, more than 2 lines of hormone therapy, or more than 1 line of chemotherapy in the metastatic setting.	—
Discontinuation		
3. Treatment with capivasertib plus fulvestrant should be discontinued upon the occurrence of any of the following, whichever occurs first: 3.1. disease progression 3.2. unacceptable toxicity.	Treatment with capivasertib plus fulvestrant in the CAPItello-291 trial was given until disease progression or unacceptable toxicity, whichever occurred first.	—
Prescribing		
4. Capivasertib plus fulvestrant should be administered by health professionals experienced in the management of HR-positive, HER2-negative breast cancer at treatment centres with adequate medical	To ensure that capivasertib plus fulvestrant is prescribed only for appropriate patients and adverse events are managed in an optimal and timely manner.	—

Reimbursement condition	Reason	Implementation guidance
resources and personnel to manage toxicities.		
5. Capivasertib should only be reimbursed when administered in combination with fulvestrant.	There are no data supporting the efficacy and safety of capivasertib plus fulvestrant when used in combination with additional anticancer drugs, or when capivasertib is used as monotherapy for the second-line treatment of HR-positive, HER2-negative locally advanced or metastatic breast cancer with 1 or more *PIK3CA, AKT1,* or *PTEN* alterations.	—
Pricing		
6. A reduction in price of capivasertib.	The ICER for capivasertib plus fulvestrant is $221,165 per QALY gained when compared to endocrine monotherapy. A price reduction of 85% would be required for capivasertib to achieve an ICER of $50,000 per QALY gained when compared to endocrine monotherapy. Cost-effectiveness vs. chemotherapy and everolimus plus exemestane could not be established due to uncertainties with the indirect evidence. As such, larger price reductions may be required to ensure cost-effectiveness vs. these relevant comparators.	—
Feasibility of adoption		
7. The feasibility of adoption of capivasertib plus fulvestrant must be addressed.	At the submitted price, the incremental budget impact of capivasertib plus fulvestrant may be greater than $40 million in years 2 and 3 depending on the number of patients who receive testing.	—
8. The organizational feasibility of conducting testing for *PIK3CA, AKT1,* or *PTEN* alterations must be addressed.	Testing for *PIK3CA, AKT1,* or *PTEN* alterations is required to determine eligibility for capivasertib plus fulvestrant. Clinical experts indicated that implementation of testing for *PIK3CA, AKT1,* or *PTEN* alterations will have a substantial health system impact.	—

ECOG = Eastern Cooperative Oncology Group; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; ICER = incremental cost-effectiveness ratio; NGS = next-generation sequencing; QALY = quality-adjusted life-year; vs. = versus.

Discussion Points

- pERC noted that there is an unmet need for efficacious treatments in the second line and later lines of therapy for patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer. In addition, patients expressed a need to delay using chemotherapy by having alternative treatment options for earlier lines of therapy.

- pERC noted that although the Health Canada indication is for female patients, the reimbursement request to include male patients is appropriate and ensures equitable access to capivasertib plus fulvestrant for all patients with breast cancer regardless of sex or gender, based on clinical expert feedback. pERC and the clinical experts noted that the proportion of male patients (7 out of 708) included in the trial reflected the low population prevalence of breast cancer in males, and that management of breast cancer in males is similar to premenopausal females.
- pERC reviewed input for this review from 2 patient groups, the Canadian Breast Cancer Network (CBCN) and Rethink Breast Cancer. pERC acknowledged that information for the patient group input was sourced from interviews conducted in 2024 and surveys conducted in 2022, 2018 to 2019, 2017, and 2012, and noted that treatment paradigms and patient needs may change over time. pERC also noted that the surveys included a mixed population of patients with breast cancer (i.e., participants were not limited to HR-positive, HER2-negative locally advanced or metastatic breast cancer) and that unmet needs may differ among patients with different subtypes of breast cancer. In addition, some of the patients who contributed to the patient group input (including those who had experience with the drug under review) did not live in Canada, and there are differences between the health care systems, cultures, and patient values in different countries.
- pERC noted that patients and clinicians highlighted improvement in health-related quality of life (HRQoL) as an important outcome and treatment goal for patients with locally advanced or metastatic breast cancer. However, pERC was unable to draw definitive conclusions regarding the effects of capivasertib plus fulvestrant on HRQoL due to concerns about imprecision and missing outcome data in the CAPItello-291 trial.
- pERC acknowledged that patients expressed a need for treatments that have fewer side effects. Although a higher proportion of notable harms were reported in patients taking capivasertib plus fulvestrant than in those taking placebo plus fulvestrant — with noninfectious diarrhea, rash, and stomatitis being the most common — pERC considered the side effects of capivasertib plus fulvestrant to be manageable, albeit more burdensome than fulvestrant monotherapy. No safety outcomes were included in the sponsor-submitted network meta-analysis (NMA); therefore, pERC could not draw definitive conclusions about the safety of capivasertib plus fulvestrant compared to other combination therapies.
- pERC discussed the indirect evidence from the sponsor-submitted NMA. In the NMA, there was heterogeneity in the populations and studies that could not be accounted for in the analyses, which limits the certainty of the results. Due to this limitation, pERC was unable to draw definitive conclusions regarding the comparative efficacy of capivasertib plus fulvestrant relative to exemestane, everolimus plus exemestane, and capecitabine in adult patients with HR-positive, HER2-negative advanced breast cancer with AKT pathway–altered tumours, after progression during or after treatment with endocrine-based regimens.
- pERC considered evidence from an additional randomized phase II study (the FAKTION study) submitted by the sponsor. The FAKTION study reported a longer duration of follow-up for OS than the pivotal CAPItello-291 trial; however, the study had important methodological limitations — such

as imbalances in important baseline characteristics and limited generalizability (e.g., only enrolled female patients who were postmenopausal, and excluded patients with prior CDK4/6 inhibitor treatment) — which precluded pERC from drawing firm conclusions from this evidence.

- pERC noted that NGS testing for patients with advanced (unresectable or metastatic) breast cancer is subject to variability in availability and access to testing platforms and funding arrangements within Canada. While most provincial laboratories in Canada include *PIK3CA*, *AKT1*, and *PTEN* on their NGS panels, funded testing options that target all 3 alterations are currently limited or not available. Furthermore, there are no publicly funded or private genetic testing facilities in the Northwest Territories, Nunavut, and Yukon. Patients also identified a need for equitable access and reimbursement to companion testing to ensure equitable access to this treatment. pERC noted that the clinical experts indicated that implementation of NGS testing for *PIK3CA, AKT1,* or *PTEN* alterations will have a substantial health system impact (e.g., impact on personnel and currently available testing infrastructure). pERC also noted that testing implementation will affect the budget impact of capivasertib plus fulvestrant.

Background

Breast cancer was the second most diagnosed cancer in Canada in 2023 and the most prevalent among females, with projected estimates of about 29,700 new cases in the overall population (29,400 in females and 260 in males) in 2023. HR-positive, HER2-negative breast cancer subtypes are the most prevalent in North America, accounting for at least 60% to 70% of all breast cancer cases. Tumour biopsy with pathology review and biomarker assessment (e.g., including HR and HER2 status) are completed for confirmatory diagnosis and to determine disease subtype and guide treatment decision-making. Beyond 5% to 10% genetic alterations inherited from a parent, genetic alterations can also be acquired within tumour development, often known as somatic alterations. Somatic alterations of interest to this review are in the *PI3K/AKT/mTOR* pathway, which is a cell-signalling pathway regulating cell proliferation and survival. Alterations in the *PI3K/AKT/mTOR* signalling axis are observed in up to 48% of all patients with HR-positive, HER2-negative breast cancer, with activation most frequently arising from *PIK3CA* alterations, occurring in approximately 30% of patients. According to Canadian guidelines, there is currently no specific standard of care (SOC) for patients with HR-positive, HER2-negative breast cancer who have 1 or more *PIK3CA, AKT1,* or *PTEN* alterations; therefore, these patients are currently treated the same as any patient with HR-positive, HER2-negative breast cancer. According to the clinical experts consulted by CADTH, the current treatment paradigm for locally advanced or metastatic HR-positive, HER2-negative breast cancer in Canada does not differ between females and males, and the established first-line treatment is endocrine therapy (ET) with a CDK4/6 inhibitor. Additional therapies available to these patients are based on ET, targeted therapies combined with ET, chemotherapy, and antibody-drug conjugates.

Capivasertib, in combination with fulvestrant, has been approved by Health Canada for the treatment of adult females with HR-positive, HER2-negative locally advanced or metastatic breast cancer with 1 or more *PIK3CA, AKT1,* or *PTEN* alterations following progression on at least 1 endocrine-based regimen in the

metastatic setting or recurrence on or within 12 months of completing adjuvant therapy. This reimbursement request is aligned with the approved Health Canada indication except that it is not limited to females with breast cancer. The recommended dose of capivasertib is 400 mg (two 200 mg oral tablets) taken twice daily for 4 consecutive days, followed by 3 days off treatment. The recommended dose of fulvestrant is 500 mg administered intramuscularly on days 1, 15, and 29, and then once monthly thereafter.

Sources of Information Used by the Committee

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

- a review of 1 phase III, double-blind, randomized controlled trial in patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer
- patient perspectives gathered by 2 patient groups, CBCN and Rethink Breast Cancer
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 3 clinical specialists with expertise diagnosing and treating patients with locally advanced or metastatic breast cancer
- input from 2 clinician groups, including the Research Excellence Active Leadership (REAL) Canadian Breast Cancer Alliance and Ontario Health Cancer Care Ontario (OH-CCO)'s Breast Cancer Drug Advisory Committee
- a review of the indirect evidence from 1 indirect treatment comparison submitted by the sponsor
- a review of 1 phase II trial addressing gaps in the pivotal evidence
- a review of testing procedure considerations for detecting *PIK3CA, AKT1,* or *PTEN* alterations related to capivasertib
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups who responded to CADTH's call for input and from clinical expert(s) consulted by CADTH for the purpose of this review.

Patient Input

Two patient groups, the CBCN and Rethink Breast Cancer, provided input for this review. Information from the CBCN group was sourced from 3 online surveys: the CBCN 2022 Triple Negative Breast Cancer Patient Survey (981 participants, of whom 31 had metastatic HR-positive breast cancer), the CBCN's 2017 Metastatic Breast Cancer Patient Survey (180 metastatic patients, of whom 38 had metastatic HR-positive breast cancer), and the CBCN's 2012 Metastatic Breast Cancer Patient and Caregiver Survey Report (71

patients and 16 caregivers). No patients taking the current drug under review participated in these surveys conducted by CBCN.

Information from Rethink Breast Cancer was gathered through programming and meetings with breast cancer patients, as well as an online survey with 78 patients living with metastatic breast cancer (which ran from September 2018 and April 2019). Rethink Breast Cancer also conducted interviews with 5 patients (4 in the US and 1 in Canada) living with HR-positive, HER2-negative metastatic breast cancer. Among them, the 4 US patients had experience taking capivasertib for HR-positive, HER2-negative metastatic breast cancer. The patient in Canada reported taking a CDK4/6 inhibitor and having a *PIK3CA* mutation.

The 2 groups highlighted that metastatic disease poses a significant or debilitating impact on patients' quality of life. Rethink Breast Cancer stated that breast cancer may affect younger patients more aggressively, especially those diagnosed in their 20s, 30s and early 40s, as they face age-specific issues such as fertility or family-planning challenges, diagnosis during pregnancy, childcare, impact on relationships, body image, dating and sexuality, feeling isolated from peers who do not have cancer, career hiatuses, and financial insecurity. The CBCN also noted similar concerns.

The CBCN highlighted that current treatment goals for patients with metastatic breast cancer include controlling the progression of the disease (extending life) and reducing cancer-related symptoms (extending or stabilizing quality of life). They further noted that patients diagnosed with HR-positive, HER2-negative metastatic breast cancer have limited targeted treatment options, poor prognosis, and poor survival outcomes.

Rethink Breast Cancer described that patients go to great lengths to avoid standard chemotherapy and they suffer both emotionally and physically due to this reason. The group added that patients on standard chemotherapy have a lot of difficulty managing their illnesses. Rethink Breast Cancer indicated that the primary improvement that metastatic breast cancer patients seek is to extend their life beyond what is expected with the current publicly funded therapies available and with a better quality of life.

Rethink Breast Cancer noted that all 4 patients who had been taking the drug under review highlighted the importance of having access to new therapies that have the possibility of extending their life. Three of these patients shared that they are experiencing good quality of life while taking capivasertib, allowing them to continue to work, enjoy time with loved ones, and live their lives.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical experts indicated that since the treatment goal for patients is palliative, the unmet needs of patients would be new treatments that would delay progression, prolong OS, and improve quality of life, while exposing patients to minimal toxicity. The experts noted that patients become refractory to current treatment options and subsequent therapy is limited to chemotherapy, which has significant impact on quality of life and resource utilization. The clinical experts agreed that capivasertib plus fulvestrant would be used in the second-line setting, and would alter the current treatment paradigm because there are no

targeted treatments in the second-line setting for most patients. The clinical experts indicated that the patients best suited for treatment with capivasertib plus fulvestrant would be those eligible for second-line therapy following treatment with an aromatase inhibitor and CDK4/6 inhibitor. The experts highlighted that, in their local practice, they rarely test for *PIK3CA, AKT1,* or *PTEN* alterations (outside of clinical trials) because testing is not funded, given that there are no publicly funded treatments requiring this companion diagnostic. The clinical experts indicated that, in clinical practice, a combination of radiographic (approximately every 3 months), biochemical, and clinical parameters are used to determine whether a patient is responding or progressing on treatment. The experts agreed that a clinically meaningful response includes radiological response or stabilization, improvement in patient symptoms, and maintenance of HRQoL. The clinical experts indicated that treatment with capivasertib plus fulvestrant should be discontinued if the patient experiences disease progression (as defined radiologically or clinically) or treatment is intolerable, or based on patient preference. The clinical experts noted that patients receiving capivasertib plus fulvestrant should be under the care of a medical oncologist who can manage toxicity associated with the therapy, within the community. They noted that it would be reasonable for patients to receive the therapy at a distributed oncology centre where day-to-day follow-up is with a general practitioner in oncology.

Clinician Group Input

Input on the review of capivasertib was received from 2 clinician groups: the REAL Canadian Breast Cancer Alliance and OH-CCO Breast Cancer Drug Advisory Committee. A total of 13 clinicians (8 from the REAL Canadian Breast Cancer Alliance and 5 from the OH-CCO Breast Cancer Drug Advisory Committee) provided input for this submission.

Both clinician groups emphasized that the primary goals of systemic treatment for advanced breast cancer are to improve or prolong survival, maintain or improve quality of life, and manage or minimize toxicities associated with treatment, as well as alleviate symptoms and delay the initiation of chemotherapy. The REAL Canadian Breast Cancer Alliance group emphasized that treatment options with survival benefit and good tolerability are limited for patients in the second-line setting (i.e., those who have relapsed on first-line therapy in the metastatic setting) and patients who relapse on or within 12 months of completing adjuvant ET. Similar to the clinical experts consulted by CADTH, the group further indicated that treatment goals that are not being met by currently available treatments in this population are improving OS, maintaining quality of life, minimizing toxicities, and delaying the onset of chemotherapy. They also noted that not all patients experience a response to available treatments and patients may become refractory to current treatment options; thus, additional treatment options might be needed for these patients.

While the OH-CCO's Breast Cancer Drug Advisory Committee indicated that the current drug under review would add an additional line of endocrine-based therapy, the REAL Canadian Breast Cancer Alliance group recommended it as a treatment option for all patients (males and premenopausal, perimenopausal, and postmenopausal females) who have HR-positive, HER2-negative metastatic breast cancer and have progressed on first-line SOC treatment in the metastatic setting or have progressed on or within 12 months after completing adjuvant ET and have 1 or more *PIK3CA, AKT1,* or *PTEN* alterations.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH Reimbursement Review process. The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs (refer to Table 2).

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
The CAPItello-291 phase III study evaluated capivasertib plus fulvestrant vs. placebo plus fulvestrant in patients with HR-positive, HER2-negative advanced breast cancer experiencing recurrence or progression on or after an ET-containing regimen. There is no funded standard of care for HR-positive, HER2-negative advanced breast cancer targeting *PIK3CA, AKT1,* or *PTEN* alterations in patients who have progressed following at least 1 endocrine-based regimen in the metastatic setting. In the first-line setting, most patients receive a CDK4/6 inhibitor plus aromatase inhibitor. As per the CADTH provisional funding algorithm, patients receiving second-line or later-line treatment are treated with available funded therapies, including endocrine monotherapy (e.g., fulvestrant), a CDK4/6 inhibitor plus fulvestrant (only if no CDK4/6 inhibitor was administered in the first line) or everolimus plus exemestane (not yet funded in the majority of provinces if the patient has previous exposure to CDK4/6 inhibitors), various chemotherapy agents (capecitabine, docetaxel, paclitaxel, nab-paclitaxel, doxorubicin, epirubicin, vinorelbine, gemcitabine, 5 fluorouracil-epirubicin-cyclophosphamide), and (if HER2-low) trastuzumab deruxtecan (for patients who have received a prior line of chemotherapy and are no longer eligible for endocrine therapy).	Comment from the drug plans to inform pERC deliberations.
Considerations for initiation of therapy	
Are patients with stable brain metastases eligible for capivasertib plus fulvestrant?	The clinical experts indicated that patients with stable brain metastases should be eligible for capivasertib plus fulvestrant. The concurrent use of steroid therapy may increase the risk of hyperglycemia but would be clinically appropriate with monitoring. pERC agreed with the clinical experts.
Considerations for discontinuation of therapy	
In the CAPItello-291 study, treatment was discontinued for objective radiologic disease progression or clinical disease progression or worsening of disease. What are the criteria to discontinue capivasertib plus fulvestrant in real-world clinical practice? If there is radiologic disease progression, but no clinical deterioration or worsening of disease, can treatment be continued beyond radiologic progression?	The clinical experts noted that treatment with capivasertib plus fulvestrant should continue if patients are clinically responding, and should not continue beyond disease progression or unacceptable toxicities. pERC agreed with the clinical experts.

Implementation issues	Response
Can capivasertib be continued as a single drug if fulvestrant is discontinued due to toxicity, and vice versa?	The clinical experts noted that if fulvestrant is discontinued, treatment with capivasertib as a single drug should not be continued, but if capivasertib is discontinued due to toxicity that cannot be managed with dose reduction or delays, fulvestrant monotherapy can be continued. pERC agreed with the clinical experts.
Generalizability	
Eligibility in the CAPItello-291 study included having an ECOG performance status of 0 or 1. Should patients with an ECOG performance status > 1 be eligible?	The clinical experts indicated that it would be reasonable to extend eligibility to patients with an ECOG performance status of 2 or less. pERC agreed with the clinical experts.
Adult females (premenopausal and/or postmenopausal) and adult males with metastatic breast cancer were eligible for the CAPItello-291 study. Premenopausal or perimenopausal females were required to be rendered postmenopausal through surgical or chemical means. Should male breast cancer patients use a GnRH agonist in combination with fulvestrant and capivasertib?	The clinical experts indicated that male patients should receive a GnRH agonist in combination with fulvestrant and capivasertib. The clinical experts also noted that because management of breast cancer in both males and females is similar, the reimbursement request for the inclusion of male patients is appropriate and ensures equitable access to capivasertib plus fulvestrant for all patients with breast cancer, regardless of sex or gender. pERC agreed with the clinical experts.
Should patients currently receiving alternate second-line or later-line therapy be switched to capivasertib plus fulvestrant at the time of implementation, if the therapy is recommended and considered superior?	The clinical experts indicated that patients receiving alternate second-line or later-line therapy who are clinically stable or responding to treatment should not be switched to capivasertib plus fulvestrant, but should be eligible to receive capivasertib plus fulvestrant if they experience disease progression or intolerance, with no prior exposure to fulvestrant. pERC agreed with the clinical experts, but noted that patients who have not progressed on prior therapy with fulvestrant should be eligible. pERC noted that patients with more than 1 line of prior chemotherapy in the metastatic setting should not be eligible.
Should patients who have received more than 2 lines of hormone therapy who otherwise meet the reimbursement criteria be eligible for capivasertib plus fulvestrant on a time-limited basis?	pERC indicated that patients who did not have capivasertib plus fulvestrant available to them in the second or third line, did not have prior fulvestrant, and had only 1 prior chemotherapy regimen should be eligible on a time-limited basis for this therapy.
Care provision issues	
Fulvestrant is a monthly injection (500 mg IM on days 1, 15, and 29, then monthly thereafter). Capivasertib is an oral therapy dosed as 400 mg twice a day (2 tablets of 200 mg taken twice a day, for a total daily dose of 800 mg) on an empty stomach, given on an intermittent weekly dosing schedule. Patients are dosed on days 1 to 4 in each week (4 days on, 3 days off) of a 28-day treatment cycle. The dosing schedule may be confusing for some patients. Capivasertib is a substrate of CYP3A4, although data suggest that glucuronidation may be the major metabolic route. Coadministration of some CYP3A4 inhibitors may increase exposure to capivasertib and hence potentially affect toxicity, while CYP3A4 inducers may decrease the exposure to capivasertib and may potentially affect efficacy.	Comment from the drug plans to inform pERC deliberations.

Implementation issues	Response
Drug-drug interaction checking should be performed before initiating therapy and whenever any other therapies are being considered.	
The drug plans noted there is a relatively high frequency of adverse effects associated with capivasertib, including diarrhea, rash, nausea, hyperglycemia, and potential hypersensitivity that requires careful monitoring, assessment, and intervention as needed, including capivasertib dose reduction.	Comment from the drug plans to inform pERC deliberations.
PIK3CA, AKT1, or *PTEN* testing is not a currently funded standard of care. What are the methods or assays with which *PIK3CA, AKT1,* or *PTEN* alterations can be tested? What is the optimal timing for biomarker testing? (e.g., at the time of diagnosis, or as part of eligibility assessment before initiation?) Is the *PIK3CA, AKT1,* or *PTEN* alteration or mutation stable, or does it need to be repeated periodically?	The clinical experts indicated that NGS is the preferred assay to test for *PIK3CA, AKT1,* or *PTEN* alterations. They also noted that there are other technologies available, such as polymerase chain reaction and Sanger sequencing, but NGS is superior because it can test for multiple alterations at the same time. The clinical experts indicated that the optimal time for biomarker testing could be at the time of metastatic diagnosis, and because *PIK3CA, AKT1,* or *PTEN* alterations are considered stable, repeat testing is likely not required. Additional information regarding testing for *PIK3CA, AKT1,* or *PTEN* alterations is available in the Testing Procedure Assessment Report.
What percentage of HR-positive, HER2-negative metastatic breast cancer cases harbour *PIK3CA, AKT1,* or *PTEN* alterations?	In HR-positive, HER2-negative breast cancers, *PI3K/AKT/mTOR* pathway activation most frequently arises from *PIK3CA* alterations, occurring in approximately 30% of patients. A further approximately 4% of advanced breast cancers harbour *AKT1*-activating alterations or amplifications, and approximately 5% have inactivating alterations in *PTEN*.
A previous phase II study (the FAKTION study) suggested that benefit was limited to tumours with *PIK3CA, AKT1,* or *PTEN* mutations. Is there a difference between *PIK3CA, AKT1,* or *PTEN* pathway alterations and mutations, and are any different outcomes expected in these groups?	The clinical experts noted that *PIK3CA, AKT1,* or *PTEN* alterations and mutations are terms that are used interchangeably in the literature and generally have the same meaning. pERC agreed with the clinical experts.
System and economic issues	
The sponsor estimates that 214 patients in year 1, 308 patients in year 2, and 393 patients in year 3 would receive treatment with capivasertib plus fulvestrant. These patient numbers yielded direct drug costs for capivasertib plus fulvestrant of $16.1 million, $23.2 million, and $29.6 million in years 1 to 3, respectively. This resulted in an incremental budget impact of $8.9 million in year 1, $12.8 million in year 2, and $16.4 million in year 3, amounting to a 3-year incremental budget impact of $38.1 million. What are the CADTH-estimated patient numbers and BIA?	This is addressed in the Pharmacoeconomic Review.
The sponsor estimates the total pan-Canadian 3-year incremental budget impact of *PIK3CA, AKT1,* or *PTEN* alteration testing would be $3.9 million. What are the CADTH estimated testing costs?	This is addressed in the Pharmacoeconomic Review.

Implementation issues	Response
Generic fulvestrant is commercially available. Confidential prices are available for all CDK4/6 inhibitors and trastuzumab deruxtecan. There are generics commercially available for aromatase inhibitors, everolimus, and all chemotherapy comparators.	Comment from the drug plans to inform pERC deliberations.

GnRH = gonadotropin hormone-releasing hormone; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2; ECOG = Eastern Cooperative Oncology Group; IM = intramuscular; NGS = next-generation sequencing; pERC = pan-Canadian Oncology Drug Review Expert Review Committee.

Clinical Evidence

Systematic Review

Description of Studies

One ongoing, phase III, randomized controlled trial (RCT) (the CAPItello-291 trial; N = 708) met the inclusion criteria for the systematic review conducted by the sponsor. The objective of the CAPItello-291 trial was to assess the efficacy and safety of capivasertib plus fulvestrant compared with matched placebo plus fulvestrant in adults with locally advanced (inoperable) or metastatic HR-positive, HER2-negative breast cancer. The trial enrolled patients who had disease recurrence or progression during or after aromatase inhibitor therapy, with or without a CDK4/6 inhibitor. The trial included 2 populations that were analyzed separately: the overall population (all enrolled patients; N = 708) and the altered population (N = 289), which included patients who tested positive for tumours with 1 or more *PIK3CA, AKT1,* or *PTEN* alterations and is the focus of the reimbursement request. Enrolled patients were randomly assigned in a 1:1 ratio to receive capivasertib 400 mg, taken orally twice daily, in combination with fulvestrant 500 mg, administered intramuscularly every 14 days for the first 3 injections and every 28 days thereafter, or matching placebo plus fulvestrant. Randomization was stratified by liver metastases (yes or no), prior use of CDK4/6 inhibitors (yes or no), and geographic location (region 1, 2, or 3). The outcomes relevant to the CADTH review included the primary outcome of PFS per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as assessed by the investigators, and secondary outcomes of OS and safety. HRQoL as measured via the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire – 30 items (EORTC QLQ-C30) and the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer Module – 23 items (EORTC QLQ-BR23), a secondary outcome in the trial, was also considered relevant. At the request of the sponsor, PFS2 (defined as the time from randomization until second progression on next-line treatment or death due to any cause) and time to first subsequent chemotherapy were included for the altered population. These outcomes are included in Appendix 1. The trial population was predominately white (58%) and female (99%), with a mean age of 58 years (range, 26 to 90 years). Overall, key baseline characteristics were generally balanced between treatment groups in both populations. Most patients were postmenopausal females (77.0%), had previously received a CDK4/6 inhibitor (70%), and had an ECOG performance status of 0 (66.0%), indicating good overall performance. A similar proportion of patients in both groups had an altered tumour status (approximately 41%). In the altered population, the placebo plus fulvestrant group had a higher proportion of patients with an ECOG performance

status of 0 (72.4% versus 60.0%) and a lower proportion of patients with an ECOG performance status of 1 (26.9% versus 40.0%) than the capivasertib plus fulvestrant group. Further, the placebo plus fulvestrant group had a higher proportion of patients who had received no prior lines of therapy for advanced or metastatic cancer (14.9% versus 7.7%) and a lower proportion of patients who had received 1 prior line of therapy for advanced or metastatic cancer (59.0% versus 69.0%) compared with the capivasertib plus fulvestrant group.

Efficacy Results

Only those efficacy outcomes and analyses of subgroups identified as important to this review are reported. Efficacy and safety data were evaluated at the planned primary analysis for PFS with a data cut-off date of August 15, 2022. This data cut-off date was an interim analysis for OS. This section includes data from both the overall population and the altered population. The focus of the Health Canada indication and reimbursement request is the altered population; however, because the overall population also included a proportion of patients with known AKT-altered status, the results for the overall population were also included. It should be noted that 59% of patients in the overall population did not meet the reimbursement request (i.e., were of known nonaltered or unknown alteration status).

Progression-Free Survival

In the overall population, at the data cut-off, PFS events were reported for 258 patients (72.7%) in the capivasertib plus fulvestrant group and 293 patients (83.0%) in the placebo plus fulvestrant group. In the altered population, PFS events occurred in 121 patients (78.1%) in the capivasertib plus fulvestrant group and 115 patients (85.8%) in the placebo plus fulvestrant group. The median duration of follow-up in all patients in the capivasertib plus fulvestrant and placebo plus fulvestrant groups was [redacted] and [redacted] months (range not reported), respectively. In the overall population, the median PFS was 7.2 months (95% CI, 5.5 to 7.4) in the capivasertib plus fulvestrant group, versus 3.6 months (95% CI, 2.8 to 3.7) in the placebo plus fulvestrant group (log-rank test P < 0.001), with a between-group hazard ratio of 0.60 (96.5% CI, 0.50 to 0.72). In the altered population, the median PFS was 7.3 months (95% CI, 5.5 to 9.0) in the capivasertib plus fulvestrant group, versus 3.1 months (95% CI, 2.0 to 3.7) in the placebo plus fulvestrant group (log-rank test P < 0.001), with a between-group hazard ratio of 0.50 (95% CI, 0.38 to 0.65). The results of sensitivity analyses were consistent with the primary analysis, and the results were consistent across the exploratory subgroup analysis by previous use of a CDK4/6 inhibitor in favour of capivasertib plus fulvestrant. For the exploratory subgroup analysis by AKT pathway nonaltered status in the overall population, the hazard ratio was 0.70 (95% CI, 0.56 to 0.88) in favour of capivasertib plus fulvestrant. This subgroup included patients with both known nonaltered status and unknown alteration status. Among patients with known nonaltered status, the hazard ratio was 0.79 (95% CI, 0.61 to 1.02), and among patients with unknown alteration status, the hazard ratio was 0.52 (95% CI, 0.32 to 0.83). The point estimate for the hazard ratio for the known nonaltered subgroup (0.79) falls outside the 95% CI for the hazard ratio for both the overall population and the altered population. As noted by Health Canada, the effect observed in the overall population was likely driven by patients in the altered population, and the effect observed in the nonaltered population was likely driven by the population with unknown or no results.[25]

In the overall population, the KM-estimated probability of PFS at 6 and 12 months was [redacted] (95% CI, [redacted] to [redacted]) versus [redacted] (95% CI, [redacted] to [redacted]), and [redacted] (95% CI, [redacted] to [redacted]) versus [redacted] (95% CI, [redacted] to [redacted]) in the capivasertib plus fulvestrant and placebo plus fulvestrant groups, respectively. In the altered population, the KM-estimated probability of PFS at 6 and 12 months was [redacted] (95% CI, [redacted] to [redacted]) versus [redacted] (95% CI, [redacted] to [redacted]) (between-group difference, [redacted] [95% CI, [redacted] to [redacted]), and [redacted] (95% CI, [redacted] to [redacted]) versus [redacted] (95% CI, [redacted] to [redacted]) (between-group difference, [redacted] [95% CI, [redacted] to [redacted]), respectively.

Overall Survival

By the August 15, 2022, data cut-off date, the median OS had not been reached in either group, with [redacted] and [redacted] of patients experiencing an event in the capivasertib plus fulvestrant group and placebo plus fulvestrant group, respectively. In the overall population, the hazard ratio was 0.74 (95% CI, 0.56 to 0.98) and 0.69 (95% CI, 0.45 to 1.05) in the altered population. In the overall population, the KM-estimated probability of being alive at 18 months and 24 months was 73.9% (95% CI, 68.3 to 78.7) versus 65.0% (95% CI, 58.7 to 70.6), and [redacted] (95% CI, [redacted] to [redacted]) versus [redacted] (95% CI, [redacted] to [redacted]) in the capivasertib plus fulvestrant group and placebo plus fulvestrant group, respectively. In the altered population subgroup, the KM-estimated probability of being alive at 18 months and 24 months was 73.2% (95% CI, 64.8 to 80.0) versus 62.9% (95% CI, 53.1 to 71.2) (between-group difference, [redacted] [95% CI, [redacted] to [redacted]), and [redacted] (95% CI, [redacted] to [redacted]) versus [redacted] (95% CI, [redacted] to [redacted]) (between-group difference, [redacted] [95% CI, [redacted] to [redacted]) in the capivasertib plus fulvestrant group and placebo plus fulvestrant group, respectively.

Health-Related Quality of Life

In the altered population, baseline global health status scores were similar in both treatment groups, and at cycle 10, the between-group least squares (LS) mean difference from baseline was [redacted] (95% CI, [redacted] to [redacted]; total sample = [redacted]). For EORTC QLQ-BR23, baseline scale scores were similar in both treatment groups and suggested intermediate-to-high functioning (median scores ≥ 55) and low symptomatology (median scores < 20), except for scores for future perspective and upset by hair loss. At cycle 17, the between-group mean difference in change from baseline was [redacted] (95% CI, [redacted] to [redacted]; total sample = [redacted]) for body image, [redacted] (95% CI, −[redacted] to [redacted]; total sample = [redacted]) for sexual functioning, not estimable for sexual enjoyment (total sample = [redacted]), [redacted] (95% CI, [redacted] to [redacted]; total sample = [redacted]) for future perspective, [redacted] (95% CI, [redacted] to [redacted]; total sample = [redacted]) for systemic therapy side effect symptoms, [redacted] (95% CI, [redacted] to [redacted]; total sample = [redacted]) for breast symptoms, [redacted] (95% CI, [redacted] to [redacted]; total sample = [redacted]) for arm symptoms, and [redacted] ([redacted] to [redacted]; total sample = [redacted]) for upset by hair loss. The HRQoL results were generally consistent across cycles and reflected those of the overall population (data not shown).

Harms Results

Harms data reported in this section are from the data cut-off date of August 15, 2022. Because the sample size of the overall population was larger than that of the altered population, the harms data summarized in this section are for the overall population; this approach was considered appropriate by the CADTH review team. The safety profile of capivasertib plus fulvestrant in the altered population reflected the overall population. Most patients in the trial reported at least 1 adverse event (AE) (96.6% with capivasertib plus fulvestrant and 82.3% with placebo plus fulvestrant). The most frequently reported AEs of any grade in the

capivasertib plus fulvestrant group were diarrhea (72.4%, versus 20.0% with placebo plus fulvestrant), rash (38.0%, versus 7.1% with placebo plus fulvestrant), and nausea (34.6%, versus 15.4% with placebo plus fulvestrant). The most frequently reported AEs in the placebo plus fulvestrant group were also diarrhea and nausea. A numerically higher proportion of serious AEs was reported in patients taking capivasertib plus fulvestrant (16.1%) than in patients taking placebo plus fulvestrant (8.0%). The most common serious AE with capivasertib plus fulvestrant was diarrhea (1.7%, versus 0.3% with placebo plus fulvestrant). Study treatment discontinuation due to AEs was numerically higher in the capivasertib plus fulvestrant group (9.3%) than the placebo plus fulvestrant group (0.6%). The most common AE leading to discontinuation of capivasertib or placebo was rash ([redacted] versus [redacted] with placebo). Deaths were reported in 24.5% of patients in the capivasertib plus fulvestrant group, and 30.6% of patients in the placebo plus fulvestrant group. The majority of deaths in both groups were attributed to disease progression ([redacted] in the capivasertib plus fulvestrant group and [redacted] in the placebo plus fulvestrant group). A higher proportion of notable AEs was reported in patients taking capivasertib plus fulvestrant ([redacted]) than in patients taking placebo plus fulvestrant ([redacted]). The most common notable harms with capivasertib plus fulvestrant were noninfectious diarrhea (72.4%, versus 20.3% with placebo plus fulvestrant), rash (38.0%, versus 7.1% with placebo plus fulvestrant), and stomatitis ([redacted] versus [redacted] with placebo plus fulvestrant).

Critical Appraisal

The CAPItello-291 trial randomization procedures, including the stratification factors, were appropriate and conducted by interactive response technology. In the altered population, the placebo plus fulvestrant group had a higher proportion of patients with an ECOG performance status of 0 (72.4% versus 60.0%) and a lower proportion of patients with an ECOG performance status of 1 (26.6% versus 40.0%) than the capivasertib plus fulvestrant group. Further, the placebo plus fulvestrant group had a higher proportion of patients who had received no prior lines of therapy for advanced or metastatic cancer (14.9% versus 7.7%) and a lower proportion of patients who had received 1 prior line of therapy for advanced or metastatic cancer (59.0% versus 69.0%) compared with the capivasertib plus fulvestrant group. These imbalances were likely due to chance, as all other baseline characteristics of patients appeared balanced between groups, and therefore were unlikely to have resulted in bias. To minimize the risk of bias in the measurement of the outcome, the trial performed tumour assessments using RECIST version 1.1 criteria and radiographic scans were assessed by blinded independent central review (BICR) as a sensitivity analysis. The PFS results for BICR were similar to primary investigator-assessed results. Sample size and power calculations were based on PFS and OS in the overall population and PFS in the altered population, and the trial was powered to detect significant differences for both outcomes. Prespecified analyses of OS and PFS in the overall and altered populations were appropriately controlled for multiple comparisons. All other analyses were descriptive. This included HRQoL outcomes as measured by the EORTC QLQ-C30 and EORTC QLQ-BR23, which were deemed clinically important outcomes for the disease. The sample sizes for the subgroup analyses of PFS were small. The trial may not have been powered to detect subgroup differences. While the trial met its primary objective of assessing PFS, the median OS was not reached in either treatment group, and there was imprecision in the estimates for between-group differences in survival probability at 18 months and 24 months (i.e., the 95% CIs were wide and included the potential for no difference between the 2 treatment

groups). In addition, there is uncertainty whether the PFS benefits (as a surrogate outcome for OS) will translate into survival benefits. Because the results at the data cut-off represent an interim analysis for OS and the results were based on few events, longer follow-up is needed to inform the true effect of capivasertib plus fulvestrant compared with placebo plus fulvestrant on survival. The certainty of evidence for many HRQoL outcomes was limited because of risk of bias due to missing outcomes data — both at baseline and at the selected follow-up times — and imprecision. Based on visual inspection of the KM plots for PFS and OS, it does not appear there was any major violation of the proportional hazards (PH) assumption. However, the results of the PH assessment in the sponsor-submitted NMA showed evidence of nonproportional hazards across most studies, including the CAPItello-291 trial. As such, the hazard ratios for PFS and OS may not be fully reflective of the true effects.

In general, the population requested for reimbursement aligns with the Health Canada indication, except that the reimbursement request is not limited to female patients. Enrolment in the CAPItello-291 trial was open to both male and female patients, and 7 males were enrolled. The clinical experts consulted by CADTH agreed that including males in the reimbursement request is appropriate since the proportion of included patients reflected the low prevalence of breast cancer in males, and that management of breast cancer in both males and females is similar. Given the small proportion of males in the trial, it was not possible to ascertain from the data whether males would experience different treatment outcomes compared with females. However, the clinical experts agreed that they would expect similar efficacy and harms among males and females. The dosing and administration of capivasertib plus fulvestrant was consistent with the Health Canada–approved product monograph. Patients with *PIK3CA, AKT1,* or *PTEN*-altered tumours (the altered population, which is the focus of the Health Canada–approved indication) were identified by postrandomization central testing of tumour tissue collected before randomization based on a prespecified list of molecular alterations, using a validated assay. The CADTH team considered this diagnostic approach appropriate, although the clinical experts noted that testing for *PIK3CA, AKT1,* or *PTEN* tumour alterations is not part of routine clinical practice and access to testing varies across Canada. According to the clinical experts consulted by CADTH, the eligibility criteria and baseline characteristics of the CAPItello-291 trial were generalizable to adults with HR-positive, HER2-negative advanced or metastatic breast cancer with 1 or more *PIK3CA, AKT1,* or *PTEN* alterations in the Canadian setting. The trial included outcomes that were important to patients and clinicians. The patient group indicated that stopping disease progression, prolonging life, improving HRQoL, and reducing treatment side effects are important to them.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was used to assess the certainty of the evidence for outcomes considered most relevant to inform CADTH's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null.

The reference points for the certainty of evidence assessment for PFS and OS were set according to the presence or absence of an important effect based on thresholds informed by the clinical experts consulted for this review. The reference point for the certainty of the evidence assessment for EORTC QLQ-C30 global health status score and EORTC QLQ-BR23 functional and symptom scales scores were set according to the presence or absence of an important effect based on a threshold suggested by the sponsor that was informed by the literature. Due to the lack of a formal minimal important difference (MID) estimate for serious adverse events (SAEs), the target of the certainty of evidence assessment was set according to the presence or absence of any (non-null) effect. The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- survival outcomes (PFS and OS)
- HRQoL outcomes (EORTC QLQ-C30 global health status and EORTC QLQ-BR23 functional and symptom scales scores)
- harms outcomes (SAEs).

Results of GRADE Assessments

Table 3 presents the GRADE summary of findings for capivasertib plus fulvestrant versus placebo plus fulvestrant.

Table 3: Summary of Findings for Capivasertib Plus Fulvestrant Versus Placebo Plus Fulvestrant for Patients With HR-Positive, HER2-Negative Locally Advanced or Metastatic Breast Cancer — Altered Population

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Capivasertib plus fulvestrant	Placebo plus fulvestrant	Difference		
PFS – FAS, August 15, 2022, data cut-off							
Probability of PFS at 6 months[a] Median follow-ups: • [redacted] months for capivasertib plus fulvestrant • [redacted] months for placebo plus fulvestrant	289 (1 RCT)	NA	[redacted] per 1,000 [redacted]	[redacted] per 1,000	[redacted] more per 1,000 [redacted] more to [redacted] more)	High[b]	Capivasertib plus fulvestrant results in a clinically important increase in the probability of PFS at 6 months when compared with placebo plus fulvestrant.
Probability of PFS at 12 months[a] Median follow-ups: • [redacted] months for capivasertib plus fulvestrant • [redacted] months for placebo plus fulvestrant	289 (1 RCT)	NA	[redacted] per 1,000 [redacted]	[redacted] per 1,000	[redacted] more per 1,000 ([redacted] more to [redacted] more)	Moderate[c]	Capivasertib plus fulvestrant likely results in a clinically important increase in the probability of PFS at 12 months when compared with placebo plus fulvestrant.
OS – FAS, August 15, 2022, data cut-off							
Probability of survival at 18 months[a] Median follow-ups: • [redacted] months for capivasertib plus fulvestrant • [redacted] months for placebo plus fulvestrant	289 (1 RCT)	NA	[redacted] per 1,000 [redacted])	[redacted] per 1,000	[redacted] more per 1,000 ([redacted] fewer to [redacted] more)	Low[d]	Capivasertib plus fulvestrant may result in a clinically important increase in the probability of survival at 18 months when compared with placebo plus fulvestrant.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Capivasertib plus fulvestrant	Placebo plus fulvestrant	Difference		
Probability of survival at 24 months[a] Median follow-ups: • [redacted] months for capivasertib plus fulvestrant • [redacted] months for placebo plus fulvestrant	289 (1 RCT)	NA	[redacted] per 1,000 ([redacted] to [redacted])	[redacted] per 1,000	[redacted] more per 1,000 ([redacted] fewer to [redacted] more)	Low[e]	Capivasertib plus fulvestrant may result in a clinically important increase in the probability of survival at 24 months when compared with placebo plus fulvestrant.
EORTC QLQ-C30 global health status – FAS, August 15, 2022, data cut-off							
LS mean change from baseline in global health status; scores range from 0 to 100, with higher scores indicating better health status Time point: cycle 10	[redacted] (1 RCT)	NA	[redacted])	[redacted]	[redacted])	Low[f]	Capivasertib plus fulvestrant may result in little to no clinically important difference in global health status at cycle 10 when compared with placebo plus fulvestrant.
EORTC QLQ-BR23 scales – FAS, August 15, 2022, data cut-off							
Mean change from baseline in body image score;[a] scores range from 0 to 100, with higher scores indicating better body image Time point: cycle 17	[redacted] (1 RCT)	NA	[redacted] (SD = [redacted])	NR	[redacted])	Very low[g]	The evidence is very uncertain about the effect of capivasertib plus fulvestrant on body image at cycle 17 when compared with placebo plus fulvestrant.
Mean change from baseline in sexual functioning score;[a] scores range from 0 to 100, with higher scores indicating better sexual	[redacted] (1 RCT)	NA	[redacted] |(SD = [redacted])	NR	[redacted])	Very low[h]	The evidence is very uncertain about the effect of capivasertib plus fulvestrant on sexual functioning at cycle 17 when compared with placebo plus fulvestrant.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Capivasertib plus fulvestrant	Placebo plus fulvestrant	Difference		
functioning Time point: cycle 17							
Mean change from baseline in sexual enjoyment score;[a] scores range from 0 to 100, with higher scores indicating better sexual enjoyment Time point: cycle 17	| (1 RCT)	NA	NE	NE	NE	NA[i]	There is no evidence for the effect of capivasertib plus fulvestrant on sexual enjoyment at cycle 17 when compared with placebo plus fulvestrant.
Mean change from baseline in future perspective score;[a] scores range from 0 to 100, with higher scores indicating better future perspective Time point: cycle 17	[redacted] (1 RCT)	NA	[redacted] (SD = [redacted])	NR	[redacted])	Very low[g]	The evidence is very uncertain about the effect of capivasertib plus fulvestrant on future perspective at cycle 17 when compared with placebo plus fulvestrant.
Mean change from baseline in systemic therapy side effects score;[a] scores range from 0 to 100, with higher scores indicating greater level of side effects Time point: cycle 17	[redacted] (1 RCT)	NA	[redacted] (SD = [redacted])	NR	[redacted])	Very low[j]	The evidence is very uncertain about the effect of capivasertib plus fulvestrant on systemic therapy side effects at cycle 17 when compared with placebo plus fulvestrant.
Mean change from baseline in breast symptoms score;[a] scores range from 0 to 100, with higher scores indicating greater level of symptoms Time point: cycle 17	[redacted] (1 RCT)	NA	[redacted] (SD = [redacted])	NR	[redacted])	Very low[j]	The evidence is very uncertain about the effect of capivasertib plus fulvestrant on breast symptoms at cycle 17 when compared with placebo plus fulvestrant.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Capivasertib plus fulvestrant	Placebo plus fulvestrant	Difference		
Mean change from baseline in arm symptoms score;[a] scores range from 0 to 100, with higher scores indicating greater level of symptoms Time point: cycle 17	[redacted] (1 RCT)	NA	[redacted] (SD = [redacted])	NR	[redacted])	Very low[j]	The evidence is very uncertain about the effect of capivasertib plus fulvestrant on arm symptoms at cycle 17 when compared with placebo plus fulvestrant.
Mean change from baseline in upset by hair loss score;[a] scores range from 0 to 100, with higher scores indicating greater level of being upset Time point: cycle 17	[redacted] (1 RCT)	NA	NR	NR	[redacted])	Very low[g]	The evidence is very uncertain about the effect of capivasertib plus fulvestrant on upset by hair loss at cycle 17 when compared with placebo plus fulvestrant.
Harms – safety population, August 15, 2022, data cut-off							
SAEs[a] Median follow-ups: • [redacted] months for capivasertib plus fulvestrant • [redacted] months for placebo plus fulvestrant	289 (1 RCT)	NR	[redacted] per 1,000 (NR)	[redacted] per 1,000	[redacted] more per 1,000 ([redacted] fewer to [redacted] more)	Moderate[k]	Capivasertib plus fulvestrant likely results in an increase in the proportion of patients who experience SAEs when compared with placebo plus fulvestrant. The clinical importance of the increase is uncertain.

CI = confidence interval; EORTC QLQ-BR23 = European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer Module – 23 items; EORTC QLQ-C30 = European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire – 30 items; FAS = full analysis set; LS = least squares; MID = minimal important difference; NA = not applicable; NE = not estimable; NR = not reported; RCT = randomized controlled trial; SD = standard deviation.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a]The between-group absolute effects at the time point was requested by CADTH from the sponsor to facilitate the GRADE assessment (i.e., PFS, OS, EORTC QLQ-BR23 scales, and SAEs).

[b]A between-group absolute risk difference of 5% (50 fewer or more events per 1,000 patients) at 6 months was clinically important according to the clinical experts. The point estimate and entire confidence exceeded the threshold.

[c]Rated down 1 level for serious imprecision due to the 95% CI for the between-group difference including the possibility of an important benefit and a trivial effect when compared with placebo plus fulvestrant; a between-group absolute risk difference of 5% (50 fewer or more events per 1,000 patients) was clinically significant at 12 months according to the clinical experts.

[d]Rated down 2 levels for very serious imprecision due to the 95% CI for the between-group difference including the possibility of an important benefit, little to no difference, and possible harm when compared to placebo plus fulvestrant; a between-group absolute risk difference of 5% (50 fewer or more events per 1,000 patients) was clinically significant at 18 months according to the clinical experts.

[e]Rated down 2 levels for very serious imprecision due to the 95% CI for the between-group difference including the possibility of an important benefit and important harm when compared to placebo plus fulvestrant; a between-group absolute risk difference of 5% (50 fewer or more events per 1,000 patients) was clinically significant at 24 months according to the clinical experts.

[f]Rated down 2 level for risk of bias due to missing outcome data. There is no imprecision in the estimate (the point estimate and entire 95% CI for the between-group difference shows little to no difference). Based on the sponsor's suggestion and informed by ranges identified in the literature, a 10-point change from baseline in EORTC QLQ-C30 global health status score was considered clinically important.

[g]Rated down 2 levels for very serious imprecision due to the 95% CI for the between-group difference including the possibility of both benefit and harm when compared with placebo plus fulvestrant; based on the sponsor's suggestion that was informed by ranges identified in the literature, a 10-point change from baseline in EORTC QLQ-BR23 scale score was considered clinically important. Rated down 2 levels for risk of bias due missing outcome data.

[h]Rated down 1 level for serious imprecision due to the 95% CI for the between-group difference including the possibility of both benefit and little to no difference when compared with placebo plus fulvestrant; based on the sponsor's suggestion that was informed by ranges identified in the literature, a 10-point change from baseline in in EORTC QLQ-BR23 scale score was considered clinically important. Rated down 2 levels for risk of bias due to missing outcome data.

[i]Not estimable due to missing outcome data.

[j]Rated down 1 level for serious imprecision due to the 95% CI for the between-group difference including the possibility of both harm and little to no difference when compared with placebo plus fulvestrant; based on the sponsor's suggestion that was informed by ranges identified in the literature, a 10-point change from baseline in in EORTC QLQ-BR23 scale score was considered clinically important. Rated down 2 levels for risk of bias due to missing outcome data.

[k]Rated down 1 level for serious imprecision due to the 95% CI for the between-group absolute risk difference including the possibility of both benefit and harm. No known MID so target of certainty appraisal was any effect.

Source: CAPItello-291 Clinical Study Report[26] (details included in the table are from the sponsor's Summary of Clinical Evidence) and the sponsor's response to requested additional information.

Long-Term Extension Studies

No long-term extension studies were submitted by the sponsor.

Indirect Comparisons

One sponsor-submitted NMA was included in the submission to inform the pharmacoeconomic model and to identify indirect comparisons that fill gaps in the comparative evidence for other treatments of interest for HR-positive, HER2-negative advanced or metastatic breast cancer. The objective of the NMA was to indirectly compare the treatment effects of capivasertib versus other relevant comparators for the treatment of adult patients with HR-positive, HER2-negative advanced breast cancer with AKT pathway-altered tumours, after progression during or after treatment with endocrine-based regimens. The protocol of the systematic review and NMA was a priori registered in the International Prospective Register of Systematic Reviews.

Description of Studies

The systematic literature review identified 33 studies that informed the feasibility assessment, of which 10 were included in the NMA. The base-case network was plotted to compare capivasertib 400 mg plus fulvestrant 500 mg to fulvestrant 250 mg or 500 mg, exemestane 25 mg, everolimus 10 mg plus exemestane 25 mg, and capecitabine monotherapy 1,250 mg/m^2. The comparison across studies suggested differences for menopausal status, prior CDK4/6 inhibitor use, HER2 status, AKT pathway alteration status, and line of therapy. Fixed and random effects NMAs were conducted for PFS and OS using a Bayesian framework and results were summarized as hazard ratios and 95% credible intervals (CrIs). The NMA used the altered population data from the CAPItello-291 and FAKTION trials, whereas the other included studies did not report on AKT pathway-altered tumours. An assessment of the PH assumption was performed for PFS and OS that included visual inspection of the log-cumulative hazards and the scaled Schoenfeld residual plots, and by evaluation of the Grambsch-Therneau nonproportionality test.

Efficacy Results

The results for both PFS and OS favoured capivasertib plus fulvestrant versus exemestane 25 mg, fulvestrant 500 mg and fulvestrant 250 mg. For both PFS and OS, the results comparing capivasertib plus fulvestrant to everolimus 10 mg plus exemestane 25 mg and capecitabine 2,500 mg/m^2 favoured capivasertib plus fulvestrant; however, the 95% CrIs included the possibility of no difference or that the comparator was favoured (i.e., crossed the null). The results of the PH assessment showed evidence of nonproportional hazards across most studies.

Harms Results

Harms were not assessed in the NMA.

Critical Appraisal

The methods used to conduct the systematic literature review and NMA were prespecified with an a priori protocol, and used appropriate criteria to search databases, select studies, extract data, and assess risk of bias of the included studies. Selection bias is expected to be low given the comprehensiveness of the searches and methods for study selection. The NMA included relevant outcomes identified by the

CADTH team (PFS and OS); however, important outcomes such HRQoL and harms were not included in the comparisons. Overall, the network was sparse (i.e., many comparisons but few studies). The results of the inconsistency analysis indicated that the consistency assumption was met for PFS, although the only closed loop in the network did not include capivasertib plus fulvestrant. It was not possible to assess for inconsistency across direct and indirect evidence in the NMA for OS, due to the absence of loops in the network (i.e., no direct evidence). The PH assumption was violated in almost all comparisons for PFS and OS; as such, the hazard ratios may not be fully reflective of the true effects. The exchangeability assumption was violated as there were several notable sources of heterogeneity for potential effect modifiers across the included studies. Identified variables of concern included AKT pathway alterations, prior CDK4/6 inhibitor treatment, HER2 status, region of enrolment, line of therapy, and menopausal status. Specifically, of the 10 included studies, only 2 reported results on patients with AKT pathway alterations (the CAPItello-291 and FAKTION studies), both involving capivasertib. For other treatments, there was no evidence in the population with AKT pathway alterations. Only 1 of the 10 included studies (the CAPItello-291 study) reported subgroup data based on prior CDK4/6 inhibitor treatment, which is recognized as a prognostic factor. Although the authors provided evidence for treatment effect modifiers, it was not clear how they were identified (i.e., whether a literature review or expert consensus was performed). As such, it is not clear whether all treatment effect modifiers were accounted for in the feasibility assessment. In addition, the median follow-up times across the included trials were not reported. In general, the magnitude and direction of potential bias due to heterogeneity and lack of proportionality on outcome estimates cannot be predicted. Due to these limitations in the NMA, no definitive conclusions could be drawn on the relative treatment effects of capivasertib plus fulvestrant versus other relevant comparators.

Studies Addressing Gaps in the Evidence From the Systematic Review

Description of Studies

The FAKTION trial (N = 140) was an investigator-initiated, multicentre, randomized, double-blind, placebo-controlled, biomarker-adaptive, phase II trial in which patients were enrolled from 19 hospitals in the UK. The sponsor submitted this study because it contained longer follow-up for OS compared to the pivotal trial. Eligible patients were postmenopausal females with locally advanced or metastatic HR-positive, HER2-negative breast cancer not suitable for surgical resection. Patients were considered suitable for endocrine treatment but had received no more than 3 previous lines of endocrine treatment and up to 1 line of chemotherapy for advanced breast cancer. They also had progressive disease during treatment with a third-generation aromatase inhibitor or had relapsed on an aromatase inhibitor in the adjuvant setting. Patients were randomized 1:1 to receive fulvestrant 500 mg with either capivasertib 400 mg twice daily or placebo until disease progression, unacceptable toxicity, withdrawal of consent, or loss to follow-up. Allocation was balanced by minimization according to *PIK3CA* mutation status (mutated vs wild-type), *PTEN* expression status (null versus detected in ≥ 1% of tumour cells at moderate or strong intensity or ≥ 10% of cells at weak intensity), measurable versus nonmeasurable disease, and primary versus secondary resistance to a third-generation aromatase inhibitor. The outcomes relevant to the CADTH review included the primary outcome of investigator-assessed PFS and secondary outcomes of OS and safety.

The FAKTION trial included an overall population, which included both expanded pathway–altered and pathway-nonaltered subgroups. The expanded pathway–altered subpopulation included patients who tested positive for tumours with 1 or more *PIK3CA, AKT1,* or *PTEN* alterations and is the focus of the indication and reimbursement request under review. Test results were considered positive if either assay (Foundation One CDx [F1CDx] Clinical Trial NGS assay testing of tumour biopsy samples and/or GuardantOMNI RUO assay testing of plasma) detected 1 or more *PIK3CA, AKT1,* or *PTEN* alterations. Because the clinical experts consulted by CADTH indicated that NGS is the preferred assay to test for *PIK3CA, AKT1,* or *PTEN* alterations, this section included efficacy outcomes for the NGS-identified pathway-altered analysis set as well. In the expanded pathway–altered subpopulation, the median age was 60 years (interquartile range [IQR], 55 years to 69 years) in the capivasertib plus fulvestrant arm and 62 years (range, 56 years to 68 years) in the placebo plus fulvestrant arm. Some notable imbalances were observed between the treatment groups in the patient characteristics for the expanded pathway–altered subpopulation. The capivasertib plus fulvestrant group had a higher proportion of patients with an ECOG performance status of 1 (36% versus 24%) than the placebo plus fulvestrant group. Most patients had metastatic disease (96%) and the sites of metastases were largely imbalanced between the treatment groups. Visceral disease was present in 30 patients (77%) in the capivasertib plus fulvestrant group and 24 patients (65%) in the placebo plus fulvestrant group. The capivasertib plus fulvestrant group had a higher proportion of patients with primary aromatase inhibitor resistance (38% versus 27%), but a lower proportion of patients with secondary aromatase inhibitor resistance (62% versus 73%). By the data cut-off date of November 25, 2021, the median follow-up for the expanded pathway–altered subpopulation was 58.5 months (IQR, 45.9 months to 64.1 months) for patients treated with fulvestrant plus capivasertib and 62.3 months (IQR, 62.1 months to 70.3 months) with fulvestrant plus placebo. For the expanded pathway–altered subgroup, the median follow-up was 54.3 months (IQR, 45.5 months to 61.2 months) for the fulvestrant and capivasertib group and 62.3 months (IQR, 62.1 months to not reached) for the fulvestrant and placebo group.

Efficacy Results

Progression-Free Survival

A PFS event was recorded for 66 (87%) of 76 patients in the expanded pathway–altered subgroup: 30 (77%) of 39 patients receiving capivasertib plus fulvestrant and 36 (97%) of 37 patients receiving placebo plus fulvestrant. Median PFS was 12.8 months (95% CI, 6.6 to 18.8) in the capivasertib plus fulvestrant group versus 4.6 months (95% CI, 2.8 to 7.9) in the placebo plus fulvestrant group (adjusted hazard ratio = 0.44; 95% CI, 0.26 to 0.72).

Similar results were observed in the NGS-identified pathway-altered analysis set, in which a PFS event was recorded for 25 (74%) of 34 patients who received capivasertib and all 29 patients (100%) who received placebo. Median PFS was 13.4 months (95% CI, 6.6 to 20.7) in the capivasertib plus fulvestrant group versus 3.1 months (95% CI, 2.8 to 7.1) in the placebo plus fulvestrant group (adjusted hazard ratio = 0.36, 95% CI, 0.20 to 0.65).

Overall Survival

At the time of analysis, 57 (75%) of 76 patients in the expanded pathway–altered subgroup had died. Of these, 25 (64%) of the 39 patients received capivasertib plus fulvestrant and 32 (86%) of the 37 patients received placebo plus fulvestrant. Median OS in the expanded pathway-altered subgroup receiving capivasertib plus fulvestrant was 38·9 months (95% CI, 23.3 to 50.7) compared with 20.0 months (95% CI, 14.8 to 31.4) for those receiving placebo plus fulvestrant (adjusted hazard ratio = 0.46; 95% CI, 0.27 to 0.79).

Similar results were observed in the post hoc analysis involving the NGS-identified pathway-altered subgroup, where an OS event was recorded for 21 (61%) of 34 patients who received capivasertib plus fulvestrant and 25 (86%) of 29 patients who received placebo plus fulvestrant. Median OS was 39.0 months (95% CI, 22.3 to 50.7) in the capivasertib plus fulvestrant group versus 20.9 months (95% CI, 14.1 to 35.4) in the placebo plus fulvestrant group (adjusted hazard ratio = 0.44; 95% CI, 0.24 to 0.81).

Harms Results

Safety analyses included all patients who had received at least 1 dose of assigned study drug. All randomly assigned patients were included in the safety analyses. The most commonly reported AEs were diarrhea, nausea, hyperglycemia, fatigue, vomiting, decreased appetite, and rash (maculopapular). The proportion of participants experiencing grade 3 to 5 AEs (irrespective of causality) was 45 (65%) of 69 in the capivasertib plus fulvestrant group and 35 (50%) of 70 in the placebo plus fulvestrant group. The most common grade 3 to 4 AEs experienced by patients were hypertension (22 [32%] of 69 in the capivasertib plus fulvestrant group versus 18 [25%] of 71 in the placebo plus fulvestrant group), diarrhea (10 [14%] versus 3 [4%]), rash (14 [20%] versus 0), infection (4 [6%] versus 2 [3%]), and fatigue (1 [1%] versus 3 [4%]). Although serious adverse reactions (reported only in the capivasertib plus fulvestrant group) were reported, the total number of SAEs irrespective of causality were not reported in the publication. The most commonly reported SAEs experienced by patients were dyspnea, back pain, lower respiratory tract infection, pain, abdominal pain, and noncardiac chest pain. As of the data cut-off date, 21 patients (30%) in the capivasertib group and 31 patients (44%) in the placebo group had died. A total of 2 deaths occurred among patients with AEs.

Critical Appraisal

The FAKTION trial was a randomized, double-blind, placebo-controlled, phase II trial. The randomization and masking procedures were appropriate. Because it was a phase II trial including fewer patients and aiming to provide preliminary evidence about the efficacy and harms of the study drug, the results cannot be considered confirmatory. Despite randomization, imbalances were observed at baseline in patients' disease characteristics (e.g., ECOG performance status, histopathological subtype, visceral disease, aromatase inhibitor given as last treatment before registration, previous endocrine treatment, and *PIK3CA or PTEN* results). Due to the small sample size, there is an increased risk that prognostic balance was not achieved, as evidenced by imbalances in patients' baseline disease and demographic characteristics. As such, it is possible that the observed effects were either overestimated or underestimated and may have been driven by prognostic differences between the 2 groups (i.e., may not be reflective of the true treatment effect). Results of the Schoenfeld's tests for the PH assumption were not statistically significant, although these may have not been powered to detect a violation. No major violations of the PH assumption were noted via

visual inspection of the KM plots. The differences in PFS and OS between the treatment groups observed in the FAKTION trial for the altered patient group were considered clinically meaningful by the clinical experts consulted for this review. Both patients and investigators were blinded to the capivasertib plus fulvestrant or placebo plus fulvestrant assignment. PFS was assessed by the investigator, without adjudication, via blinded independent committee review. It is possible that patients and investigators may have become unblinded due to imbalances in notable harms across the 2 treatment groups (e.g., more patients experienced diarrhea and rash in the capivasertib plus fulvestrant group). As such, there may be an increased risk of bias in the measurement of PFS and subjective harms; however, the presence and direction of bias is uncertain. Censoring reasons seemed balanced between the treatment groups.

The population enrolled in the FAKTION trial was postmenopausal females with histological confirmation of HR-positive, HER2-negative locally advanced or metastatic inoperable breast cancer that was not amenable to curative surgical resection, which was a subset of the Health Canada–indicated population (premenopausal and postmenopausal adult females). The narrower patient population may affect the generalizability of the trial results in the Canadian setting. In addition, male patients and patients with prior CDK4/6 inhibitor treatment were not enrolled. Male patients would be included in the patient population of the sponsor's reimbursement request, although they are not included in the Health Canada indication. The clinical experts consulted by CADTH noted that all patients in Canada who are candidates for treatment with capivasertib plus fulvestrant will have been treated with CDK4/6 inhibitors because they are now part of usual first-line treatment in combination with ET, and males would also be considered candidates for treatment. HRQoL was not measured, which is considered important by both patients and clinicians. No data on race or ethnicity of patients was available, which made it difficult to contextualize the results in the Canadian setting. The dosing and administration of capivasertib plus fulvestrant was consistent with the Health Canada–approved product monograph.

Testing Procedure Considerations

In HR-positive, HER2-negative breast cancers, *PI3K/AKT/mTOR* pathway activation most frequently arises from *PIK3CA* alterations, occurring in approximately 30% of patients. A further approximately 4% of advanced breast cancers harbour *AKT1*-activating alterations or amplifications, and approximately 5% have inactivating alterations in *PTEN*. Alterations in certain higher risk genes can also influence breast cancer survival. In HR-positive breast cancer, patients harbouring 1 or more *PIK3CA, AKT1,* or *PTEN* alterations have been associated with accelerated disease progression and worse clinical outcomes.

To receive capivasertib plus fulvestrant, confirmation of *PIK3CA, AKT1,* or *PTEN* alterations through NGS testing of biopsy tissue could be carried out at the time of metastatic diagnosis. Clinical experts agreed the optimal time for testing could be at the time of metastatic diagnosis, and that NGS is the method of choice.

Key considerations and relevant information available from materials submitted by the sponsor, input from the clinical experts, and sources from the literature were validated by the review team and are summarized in Table 4.

Table 4: Considerations for NGS Testing for *PIK3CA, AKT1,* or *PTEN* Alterations for Establishing Treatment Eligibility for Capivasertib in Patients With HR-Positive, HER2-Negative Locally Advanced or Metastatic Breast Cancer

Consideration	Criterion	Available Information
Health system	Availability of the testing procedure in jurisdictions across Canada	The clinical experts indicated that the majority of large clinical centres across the provinces have in-house capability for NGS testing. Ontario is the only jurisdiction that offers provincial-level funding for testing of any of the 3 genes of interest. There are no publicly funded or private genetic testing facilities in the Northwest Territories, Nunavut, or Yukon. [redacted]
	Number of individuals in Canada expected to require the test (e.g., per year)	The population eligible for testing was estimated to be 2,757 (2,722 females and 35 males) per year. The sponsor noted that testing uptake would reach 70% within the next 3 years, meaning not all those eligible for testing would receive it.
	Testing procedure as part of routine care	The testing procedure is not currently performed as part of routine care for HR-positive, HER2-negative breast cancer.
	Repeat testing requirements	The clinical experts indicated the optimal time for biomarker testing could be at the time of metastatic diagnosis, and because *PIK3CA, AKT1,* or *PTEN* alterations are considered stable, repeat testing is likely not required.
	Impact on health care human resources by provision of the testing procedure	Implementation of NGS testing for *PIK3CA, AKT1,* or *PTEN* alterations could have significant health system impacts, such as increased workload for pathologists, lab technicians, bioinformaticians, and oncologists. There could also be an impact on currently available testing infrastructure.
Patient-oriented	Accessibility of the testing procedure in jurisdictions across Canada	There is inconsistent access to testing for *PIK3CA, AKT1,* or *PTEN* alterations across jurisdictions. Most patients currently access testing through clinical trials, special programs, or private payment options.
	Expected wait times for the testing procedure	NGS testing for *PIK3CA, AKT1,* or *PTEN* alterations can be done using previously collected tissue samples in most cases. The turnaround time is up to 6 weeks for FFPE specimens.
	Burden associated with the testing procedure for patients, families, and/or caregivers	Based on the experiences of the clinical experts, financial burden is the main barrier to testing for *PIK3CA, AKT1,* or *PTEN* alterations, since the current model involves patients paying out-of-pocket for NGS testing. [redacted]
Clinical	Clinical utility of the testing procedure	Studies have confirmed the utility of NGS in guiding targeted next-line therapy for metastatic breast cancer.
	Risks of harm associated with the testing procedure	Because testing for *PIK3CA, AKT1,* or *PTEN* alterations can be done using previously collected tissue samples in most cases, there is no additional risk of harm associated with the testing as part of establishing treatment eligibility.
Cost	Projected cost of the testing procedure	The cost of NGS was $750 per test. The cost to identify an eligible patient was estimated to be [redacted] (on average a positive test occurs for every [redacted] patients tested). [redacted]

FFPE = formalin fixed, paraffin embedded; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; NGS = next-generation sequencing.

Economic Evidence

Cost and Cost-Effectiveness

Table 5: Summary of Economic Evidence

Component	Description
Type of economic evaluation	Cost-utility analysis PSM
Target populations	Adult female patients with HR-positive, HER2-negative, locally advanced or metastatic breast cancer with 1 or more *PIK3CA, AKT1,* or *PTEN* alterations following progression on at least 1 endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy in Canada
Treatment	Capivasertib used in combination with fulvestrant
Dose regimen	The recommended dose of capivasertib in combination with fulvestrant is 400 mg (two 200 mg tablets) taken orally twice daily, approximately 12 hours apart (total daily dose of 800 mg) for 4 days, followed by 3 days off treatment, until disease progression or unacceptable toxicity occurs.
Submitted price	Capivasertib, 160 mg: $147.60 per tablet Capivasertib, 200 mg: $147.60 per tablet
Submitted treatment cost	The per-patient 28-day cost of capivasertib is $9,446. When used in combination with fulvestrant, the per-patient 28-day cost for capivasertib plus fulvestrant in the first 28 days is $10,612, and in subsequent 28-day intervals is $10,029.
Comparators	• Chemotherapy (capecitabine, paclitaxel) • Endocrine monotherapy (basket of anastrozole, exemestane, fulvestrant, letrozole, tamoxifen) • Everolimus plus exemestane
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (20 years)
Key data source	CAPItello-291 trial
Key limitations	• The long-term impact of capivasertib plus fulvestrant vs. endocrine monotherapy on overall survival is uncertain. By applying the proportional hazards assumption, the sponsor assumed the impact of capivasertib plus fulvestrant on mortality risk would be sustained indefinitely, even after progression and treatment discontinuation. Clinical experts consulted by CADTH noted the impact on overall survival would likely wane over time with the greatest benefit occurring while on therapy. • Due to methodological limitations with the network meta-analysis, the relative efficacy of capivasertib plus fulvestrant vs. chemotherapy and everolimus plus exemestane is unknown. Therefore, cost-effectiveness of capivasertib plus fulvestrant vs. these comparators is unknown. The CADTH base-case analysis focused on the comparison of capivasertib plus fulvestrant to endocrine monotherapy. • The sponsor only modelled one additional line of therapy after treatment discontinuation. This underestimated the costs of subsequent therapies making any assessment of subsequent

Component	Description
	therapy costs unreliable. • An error was identified that underestimated the cost of testing.
CADTH reanalysis results	• CADTH incorporated the following changes to address the identified limitations for the base case: correcting the cost of testing,; using different assumptions when extrapolating PFS and OS for capivasertib plus fulvestrant, and removing the subsequent therapy cost. • Given the limitations with the NMA, the CADTH base case focused on the comparison of capivasertib plus fulvestrant and endocrine monotherapy only. • In the CADTH base case, capivasertib plus fulvestrant was associated with an ICER of $221,165 per QALY gained (incremental QALYS: 0.54; incremental costs: $118,477) when compared to endocrine monotherapy. • A price reduction of at least 85% is required for capivasertib plus fulvestrant to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained.

ICER = incremental cost-effectiveness ratio; LY = life-year; PSM = partitioned survival model; QALY = quality-adjusted life-year; vs. = versus.

Budget Impact

The following key limitations were identified with the sponsor's analysis: the market uptake for capivasertib in a population with known *PIK3CA, AKT1,* or *PTEN* alterations was underestimated; the estimation of subsequent therapy only looked at 1 additional line and was highly uncertain; the use of Ki-67 testing for early breast cancer patients with a high risk of recurrence to receive abemaciclib was uncertain; prevalence was used to estimate the size of the abemaciclib population rather than incidence; the prevalent population of patients with breast cancer for the late relapse to the metastatic subgroup was miscalculated; the proportion of patients with early breast cancer that is HR-positive and HER2-negative who relapse to metastatic breast cancer was overestimated; and the costs of drug acquisition were underestimated.

Correcting for these limitations suggests that the reimbursement of capivasertib for the Health Canada–indicated population (adult females with HR-positive, HER2-negative locally advanced or metastatic breast cancer with 1 or more alterations in *PIK3CA, AKT1,* or *PTEN* following progression on at least 1 endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy) would be associated with a 3-year budget impact of $81,103,794 (year 1: $16,102,743; year 2: $26,971,824; year 3: $38,029,227). Scenario analyses show inclusion of male patients only slightly increases the BIA from $81,103,794 over 3 years to $82,030,101. If testing uptake reached 100%, then the budget impact would increase to $135,910,918. This shows that testing uptake is 1 of the main factors that impacts the size of the BIA.

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Philip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung; Dr. Michael Crump, Dr. Jennifer Fishman, Mr. Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Christian Kollmannsberger,

Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: July 10, 2024

Regrets: One expert committee member did not attend.

Conflicts of interest: None

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