Canadian Journal of Health Technologies

CADTH

October 2022 Volume 2 Issue 10

CADTH Reimbursement Recommendation

Abemaciclib (Verzenio)

Indication: In combination with endocrine therapy for the adjuvant treatment of adult patients with hormone receptor (HR)–positive, human epidermal growth factor receptor 2 (HER2)–negative, node-positive, early breast cancer at high risk of disease recurrence based on clinicopathological features and a Ki-67 score of at least 20%

Sponsor: Eli Lilly Canada Inc.

Final recommendation: Reimburse with conditions

CADTH

ISSN: 2563-6596

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Verzenio?

CADTH recommends that Verzenio in combination with endocrine therapy should be reimbursed by public drug plans for the adjuvant treatment of adult patients with hormone receptor (HR)–positive, human epidermal growth factor receptor 2 (HER2)–negative, node-positive, early breast cancer at high risk of disease recurrence based on clinicopathological features and a Ki-67 score of at least 20% if certain conditions are met.

Which Patients Are Eligible for Coverage?

Verzenio in combination with endocrine therapy should only be covered in patients whose breast cancer has receptors for the hormones estrogen and progesterone, tests negative for the HER2 protein, has been removed by surgery, and is at high risk of coming back based on certain risk features and the results of a biomarker test (i.e., Ki-67 test score ≥ 20%).

What Are the Conditions for Reimbursement?

Verzenio in combination with endocrine therapy should only be reimbursed if prescribed by clinicians with expertise in delivering systemic therapy and if the cost is reduced.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that patients treated with Verzenio in combination with endocrine therapy experienced longer times until their cancer returned. Verzenio in combination with endocrine therapy meets patient needs for effective treatments that reduce the risk of their breast cancer coming back, maintain quality of life, have manageable side effects, and may be more accessible due to Verzenio's oral route of administration.
- Verzenio in combination with endocrine therapy is not considered cost-effective compared to endocrine therapy alone. Economic evidence suggests that a 24% price reduction is needed to ensure Verzenio is cost-effective at a $50,000 per quality-adjusted life-year threshold.
- Based on public list prices, Verzenio is expected to cost the public drug plans $30,066,951 over 3 years.

Additional Information

What Is Breast Cancer?

Breast cancer begins in the cells of the breasts. Invasive early breast cancer without metastases has spread into the surrounding breast tissue but has not spread to different body parts. Approximately 94% of patients with HR-positive, HER2-negative early breast cancer survive at least 5 years.

Unmet Needs in Breast Cancer

Patients with early breast cancer that has been removed by surgery but has a high risk to come back are in need of treatment options that prevent or delay the cancer from returning, prolong survival with an acceptable toxicity profile, and maintain quality of life.

How Much Does Verzenio Cost?

Treatment with Verzenio is expected to cost approximately $5,514 per 28 days.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that abemaciclib (ABE) in combination with endocrine therapy (ET) be reimbursed for the adjuvant treatment of adult patients with hormone receptor (HR)–positive, human epidermal growth factor receptor 2 (HER2)–negative, node-positive early breast cancer at high risk of disease recurrence based on clinicopathological features and a Ki-67 score of at least 20% only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III multi-centre, randomized, open-label trial (monarchE; N = 2,003 for patients in cohort 1 with a Ki-67 score ≥ 20%) demonstrated that adjuvant treatment with ABE-ET resulted in added clinical benefit compared with adjuvant ET alone in adult patients with HR-positive, HER2-negative, node-positive early breast cancer at high risk of disease recurrence based on clinicopathological features and a Ki-67 score of at least 20%. Results from the monarchE trial showed a statistically significant and clinically meaningful improvement in invasive disease-free survival (IDFS) with ABE-ET compared with ET alone with a hazard ratio (HR) of 0.64 (95% confidence interval [CI], 0.48 to 0.87). Although those patients treated with ABE-ET appeared to have more adverse events (AEs) overall than those treated with ET alone, pERC noted that no new safety signals were observed and agreed that most AEs could be managed with dose modifications and best supportive care. Patients identified a need for effective treatments that reduce the risk of recurrence, maintain quality of life, have manageable side effects, and are affordable and accessible. pERC concluded that ABE-ET met some patient needs because it reduces the risk of recurrence, has manageable side effects, and may be more accessible due to the oral route of administration of ABE. Although patients expressed an unmet need for treatments that maintain quality of life, no definitive conclusion could be reached regarding the effects of ABE-ET on health-related quality of life (HRQoL) due to a significant decline in the number of patients available to provide HRQoL assessments over time and the open-label design of the monarchE trial.

Using the sponsor-submitted price for ABE and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for ABE-ET was $78,438 per quality-adjusted life-year (QALY) gained compared with ET. At this ICER, ABE-ET is not cost-effective at a $50,000 per QALY willingness-to-pay (WTP) threshold for patients with HR-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence and Ki-67 score of at least 20%. A reduction in price is required for ABE-ET to be considered cost-effective at this threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with ABE-ET should be initiated in patients who have: 1.1. confirmed HR-positive, HER2-negative,	Evidence from the monarchE trial demonstrated that ABE-ET resulted in a statistically and clinically significant	pERC recognized that the drug plans will need to address the availability of Ki-67 testing to

Reimbursement condition	Reason	Implementation guidance
resected invasive early breast cancer without metastases 1.2. Ki-67 index score of ≥ 20% 1.3. fulfill 1 of the following: 1.3.1. pathological tumour involvement in ≥ 4 ipsilateral axillary lymph nodes 1.3.2. or pathological tumour involvement in 1 to 3 ipsilateral axillary lymph node(s) AND at least 1 of the following criteria: 1.3.2.1. grade 3 disease 1.3.2.2. primary tumour size ≥ 5 cm 1.4. undergone definitive surgery of primary breast tumour within 16 months of initiating treatment.	improvement in IDFS in patients with characteristics listed in the condition.	implement reimbursement of ABE-ET and noted that a national approach to developing standardized Ki-67 testing protocols would be of value.
2. Patients must not have any of the following: 2.1. metastatic disease 2.2. inflammatory breast cancer 2.3. prior treatment with a CDK4/6 inhibitor.	The monarchE trial excluded patients with metastatic disease, inflammatory breast cancer, and prior treatment with a CDK4/6 inhibitor. There is no evidence to suggest these patients will benefit from treatment with ABE-ET.	—
Discontinuation		
3. Abemaciclib in combination with endocrine therapy should be discontinued upon the occurrence of any of the following: 3.1. disease recurrence 3.2. unacceptable toxicity.	Consistent with clinical practice, patients in the monarchE trial discontinued treatment upon progression or unacceptable toxicity.	—
4. Patients should be assessed for disease recurrence as per standard clinical practice.	As per clinical expert opinion.	—
5. ABE should be reimbursed for a maximum of 2 years (150 mg orally twice daily). 5.1. Endocrine therapy can be continued beyond this time.	Patients in the monarchE trial were treated with ABE for a maximum of 2 years. Treatment with ET was continued to complete at least 5 years (and up to 10 years) of treatment if medically appropriate.	If treatment with ABE is interrupted or delayed in the absence of disease progression, it would be reasonable to resume therapy and administer the remaining doses of ABE to complete 2 years of treatment. Determination to resume therapy should be at the discretion of the treating clinician.

Reimbursement condition	Reason	Implementation guidance
Prescribing		
6. Treatment should be prescribed by clinicians with expertise and experience in treating early breast cancer. Treatment should be given in outpatient clinics by qualified practitioners with expertise in systemic therapy delivery.	This will ensure that treatment is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
7. Ongoing monitoring to assess patients for toxicity is required.	According to clinical expert opinion, patients would require ongoing monitoring for hematologic toxicity, diarrhea, and other toxicities.	—
8. ABE-ET should only be reimbursed when administered in combination.	There are no data supporting the efficacy and safety of ABE-ET when used in combination with additional anticancer drugs or when ABE is initially used as monotherapy.	ET can continue as monotherapy after the 2 years of ABE.
Pricing		
9. A reduction in price.	The ICER for ABE-ET is $78,438 compared with ET. A price reduction for ABE of 24% would be required for ABE-ET to be able to achieve an ICER of $50,000 per QALY compared with ET. Due to the high degree of uncertainty in cost-effectiveness, a higher price reduction may be warranted.	—
Feasibility of adoption		
10. The feasibility of adoption of ABE must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption given the difference between the sponsor's estimate and CADTH's estimates.	—

ABE = abemaciclib; CDK4/6 = cyclin-dependent kinases 4 and 6; ET = endocrine therapy; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; ICER = incremental cost-effectiveness ratio; IDFS = invasive disease-free survival; pERC = CADTH pCODR Expert Review Committee.

Discussion Points

- Patients with HR-positive, HER2-negative, node-positive early breast cancer who have clinicopathological features as per the cohort 1 patient population in the monarchE trial with a Ki-67 score of at least 20% have a higher risk of developing metastatic disease. There is a need for adjuvant treatments that prevent disease recurrence and potentially cure patients at high risk of disease recurrence.
- pERC noted that the population for reimbursement was limited to the subset of patients in cohort 1 of the monarchE trial who had a Ki-67 score of at least 20%, in accordance with the Health Canada–approved indication. pERC acknowledged that although the

monarchE trial included subsets of patients with other clinicopathological features than those specified in the Health Canada indication, these subgroups were out of scope for this review.

- pERC noted that the subset of patients in cohort 1 of the monarchE trial with a Ki-67 score of at least 20% was included in the hierarchical statistical testing procedure of the monarchE trial for the primary end point of IDFS. pERC deliberated on the value of IDFS in the adjuvant setting of early breast cancer. Although IDFS has not shown to reliably predict treatment effects in overall survival (OS) in the present target population, pERC noted that IDFS was defined according to standardized criteria for adjuvant breast cancer trials and agreed with the clinical experts that the improvement in IDFS with ABE-ET compared with ET alone as observed in the monarchE trial was clinically meaningful to patients at high risk of developing metastatic disease.
- Results for OS were formally tested in the overall population of the monarchE trial (N = 5,637) and were immature after a median follow-up of 27 months, leading to uncertainty regarding long-term survival benefits of ABE-ET in the population for reimbursement. pERC noted that even with sufficient follow-up time, OS results may be confounded because patients were permitted to receive subsequent anticancer therapies.
- pERC considered that determination of the Ki-67 score by a validated test is required before initiation of treatment with ABE-ET. pERC acknowledged that the use of Ki-67 testing in Canadian clinical practice is currently limited due to variability in routine testing and lack of standardized laboratory assays. However, pERC recognized that drug plans will need to address this issue upon implementation of reimbursement of ABE-ET and noted that a national approach to developing standardized Ki-67 testing protocols would be of value.
- pERC discussed the toxicity profile of ABE-ET and noted that there were more frequent toxicities with ABE-ET compared with ET alone. The most common AEs in the ABE-ET group were diarrhea, neutropenia, fatigue, leukopenia, abdominal pain, nausea, and anemia; however, treatment discontinuation as a consequence was relatively rare. pERC felt that these AEs were expected and manageable in most patients.

Background

Breast cancer is the most commonly diagnosed cancer among women in Canada, and the second most common cancer in men and women combined. In 2020, 27,700 women were diagnosed with breast cancer, representing approximately 25% of new cancer cases in Canada. Breast cancer is the second leading cause of cancer deaths among women, accounting for 14% of all cancer deaths. The 5-year net survival for breast cancer is greater than 85% among women diagnosed before 85 years of age, after which it drops to approximately 73%.

Patients with breast cancer are stratified and treated based on the expression status of certain tumour receptors that serve as important prognostic and predictive biomarkers, including estrogen receptor (ER) and progesterone receptor (PR). HR-positive breast cancers with hormone receptor expression (i.e., ER, PR, or both) are the most prevalent type of breast cancer, accounting for 70% to 80% of all breast cancers. Overexpression of the *HER2* oncogene, which belongs to the epidermal growth factor receptor (*EGFR/HER*) family, enables constitutive activation of growth factor signalling and triggering breast cancer cell survival,

proliferation, and invasion is associated with poor prognosis. Approximately 85% of patients with breast cancer do not have tumours that overexpress HER2 and are HER2-negative. HR-positive, HER2-negative tumours are the most common subtype of breast cancer, accounting for approximately 70% of breast cancers. More than 90% of patients with breast cancer are diagnosed with early-stage disease, which is defined as not having spread beyond the breast tissue or nearby lymph nodes. Unlike a diagnosis of distant metastatic disease, early-stage breast cancer is potentially curable. In patients with HR-positive, HER2-negative early breast cancer, the 5-year survival rate is 94.3%.

Although many patients with HR-positive, HER2-negative disease will not experience recurrence or have distant recurrence with standard therapies alone, primarily ET, approximately 7% to 11% of patients with early breast cancer experience a local recurrence during the first 5 years after treatment, and nearly 30% eventually experience disease relapse with metastases following treatment with curative intent, often with distant metastases, at which time their prognosis is poor. Risk factors for recurrence include large tumour size, higher degree of involvement of axillary lymph nodes (ALNs), high histologic grade, positive or close margins, age, HR and HER2 status (positive), and high tumour proliferation rate (Ki-67). Ki-67 immunohistochemistry testing is a prognostic factor for the risk of recurrence. However, the use of immunohistochemistry Ki-67 testing in Canadian clinical practice is currently limited due to variability in routine testing and lack of standardized laboratory assays.

Sources of Information Used by the Committee

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

- a review of 1 randomized, open-label clinical study in patients with HR-positive, HER2-negative, node-positive early breast cancer who completed definitive locoregional therapy and are at high risk of recurrence
- patient perspectives gathered by 2 patient groups: Rethink Breast Cancer (Rethink) and the Canadian Breast Cancer Network (CBCN)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with breast cancer
- input from 1 clinician group: the Ontario Health-Cancer Care Ontario (OH-CCO) Breast Cancer Drug Advisory Committee
- 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 experts consulted by CADTH for the purpose of this review.

Patient Input

Two patient groups, Rethink and the CBCN, submitted patient input for this review. Respondents from Rethink stated that a breast cancer diagnosis and treatment had a devasting and traumatic impact on a young person's life, and many patients express a willingness to take on whatever treatments are needed to lower the chance of recurrence. Patients who had experience with ABE indicated that they were willing to endure the additional side effects of a stronger therapy to ensure they were doing everything they could to treat what they know is an aggressive form of breast cancer. The CBCN respondents reported that the following factors were the most important when considering treatment options: effectiveness of treatment, reducing the risk of recurrence, maintaining quality of life, manageable side effects, and affordable and accessible treatments. Maintaining mobility, productivity, and an ability to continue childcare duties were also highlighted by survey respondents as important when deciding on treatment options. CBCN respondents noted that patients have an expectation that ABE will provide a possibility for improving their rate of IDFS and reduce their risk of recurrence, allowing them to live a better quality of life.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical experts consulted by CADTH noted that very few treatments developed in recent years have improved survival or quality of life in the adjuvant breast cancer setting and therefore there is a need for treatments to reduce recurrence risk and improve survival outcomes. Tolerability issues such arthralgias and mood disturbances are common with ET, particularly in young and premenopausal women. Drugs that can prolong time to recurrence without compromise in quality of life are highly desired. The clinical experts noted that ABE is a new indication in this setting. For eligible patients, ABE would be added to standard adjuvant ET with or without ovarian suppression.

Clinician Group Input

Clinician group input was received from the OH-CCO Breast Cancer Drug Advisory Committee, with 3 clinicians contributing to the submission. The clinician group noted that up to 30% of patients with high-risk clinical and/or pathologic features may experience distant recurrence and stated that there is a need for superior treatment options to prevent early recurrence and improve survival. Patients most likely to benefit from ABE would be those with HR-positive, HER2-negative early breast cancer at high risk of recurrence who are node-positive as per inclusion criteria of the monarchE trial. Patients who are least suitable for ABE would be those excluded from enrolment as per monarchE trial eligibility criteria. Abemaciclib would be used in addition to ET in high-risk patients following surgery and chemotherapy (if applicable). The clinician group input strongly recommended against the inclusion of a high Ki-67 score as the sole criteria for drug eligibility, noting that the Ki-67 score is prognostic and not predictive and that it is not a standard pathology test for breast cancer in Ontario.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Considerations for initiation of therapy	
In the trial, patients must have been assigned within 16 months of definitive breast cancer surgery. What is the maximum allowable time frame since surgery to be eligible for ABE?	According to the inclusion criteria of the monarchE trial, patients had to be randomized within 16 months from the time of definitive breast cancer surgery. pERC agreed with the clinical experts that the trial inclusion criteria were reasonable.
Can patients be retreated again with CDK4/6 inhibitors in the metastatic setting? If yes, what is the minimum disease-free interval requirement?	In the monarchE trial, [redacted] patients in the ABE-ET group, received a CDK4/6 inhibitor (i.e., palbociclib) as subsequent treatment. pERC agreed with the clinical experts that CDK4/6 inhibitors are currently approved and funded in the metastatic breast cancer setting. pERC agreed that re-treatment with a CDK4/6 inhibitor may be reasonable if disease recurrence is ≥ 6 months after completion of adjuvant ABE.
Considerations for discontinuation of therapy	
If a patient has an interruption within 2 years from starting treatment, do you give a total of 2 years of ABE or complete 2 years of ABE from the start of treatment?	In the monarchE trial, patients received ABE 150 mg orally twice daily for up to 2 years. pERC agreed with the clinical experts that if treatment with ABE would be interrupted or delayed in the absence of disease progression, it would be reasonable to resume therapy and administer the remaining doses of ABE to complete 2 years of treatment. Determination to resume therapy should be at the discretion of the treating clinician.
Care provision issues	
Ki-67 testing may not be routinely performed on breast cancer samples. Is Ki-67 testing required to be completed on patients who may be eligible for ABE?	A Ki-67 score of at least 20% is 1 of the criteria specified in the Health Canada indication. Evidence from the monarchE trial demonstrated a clinical benefit in patients in cohort 1 with a Ki-67 score of at least 20%. pERC considered that determination of the Ki-67 score by a validated test is required before initiation of treatment with ABE-ET.
System and economic issues	
The addition of ABE-ET could have a substantial impact on budget.	For pERC consideration.

ABE = abemaciclib; CDK4/6 = cyclin-dependent kinases 4 and 6; ET = endocrine therapy; pERC = CADTH pCODR Expert Review Committee.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Study

A single sponsor-submitted pivotal study was included in the systematic review; the monarchE trial is an ongoing phase III open-label randomized controlled trial comparing the efficacy and safety of ABE-ET to ET alone in the adjuvant treatment of patients with HR-positive, HER2-negative, node-positive early breast cancer who completed definitive

locoregional therapy and who were at high risk of recurrence based on clinicopathological features or a high (20% or higher) Ki-67 index. The primary efficacy end point was IDFS, and the secondary end points included distant relapse-free survival (DRFS) and OS. A total of 5,637 patients in 38 countries, including 44 patients from Canada, were randomized to treatment with either ABE-ET or ET alone. Patients with at least 1 positive lymph node were recruited into 2 cohorts; patients in cohort 1 (n = 5,120) were eligible based on high-risk clinicopathological features (i.e., ≥ 4 positive ALNs or 1 to 3 positive ALNs and at least 1 of the following: tumour size ≥ 5 cm or histologic grade 3) and cohort 2 (n = 517) included patients based on 1 to 3 positive ALNs and high Ki-67 index (≥ 20%). There were 3,917 (76%) patients in cohort 1 who had Ki-67 testing results available and, of these, 2,003 patients (51%) had a high Ki-67 index; this patient population is aligned with the Health Canada–approved indication and the current reimbursement request. Patients in cohort 1 with a Ki-67 index of at least 20% were predominantly female (99.2%) with a mean age of 51.6 years (standard deviation [SD] = 11.1) and an Eastern Cooperative Oncology Group Performance Score (ECOG PS) of 0 (86.3%); 54.4% of patients were postmenopausal.

Efficacy Results

Overall Survival

At interim analysis 1 for OS (April 1, 2021), OS data were immature. There were 95 deaths (42 in the ABE-ET arm and 53 in the ET arm) in the cohort 1 Ki-67 High population. The hazard ratio (HR) between treatment arms was 0.767 (95% confidence interval [CI], 0.511 to 1.152).

Invasive Disease-Free Survival

At the interim analysis (March 16, 2020), [redacted] IDFS events were observed ([redacted] in the ABE-ET arm and [redacted] in the ET arm). The HR between treatment arms was [redacted] (95% CI, [redacted] to [redacted]; P = [redacted]).

At the final IDFS analysis (July 8, 2020), with a median follow-up of 19.1 months, [redacted] IDFS events were observed ([redacted] in the ABE-ET arm and [redacted] in the ET arm). The HR between treatment arms was 0.643 (95% CI, 0.475 to 0.872, P = 0.0042). The 2-year IDFS rates in the ABE-ET versus ET arm were 91.3% versus 86.1%.

At the additional follow-up analysis (April 1, 2021) with a median follow-up of 27 months, 262 IDFS events were observed (104 in the ABE-ET arm, and 158 in the ET arm). The HR between treatment arms was 0.63 (95% CI, 0.49 to 0.80). The 3-year IDFS rates in the ABE-ET versus ET arms were 86.1% versus 79.0%.

Distant Relapse-Free Survival

At the interim analysis (March 16, 2020), a total of [redacted] events were observed, ([redacted] in the ABE-ET arm, and [redacted] in the ET arm). The HR between treatment arms was [redacted] (95% CI, [redacted] to [redacted]). The 2-year DRFS rates in the ABE-ET versus ET arms were [redacted] versus [redacted].

At the final primary outcome (IDFS) analysis (July 8, 2020), a total of [redacted] events were observed ([redacted] in the ABE-ET arm, and [redacted] in the ET arm). The HR between treatment arms was [redacted] (95% CI, [redacted] to [redacted]). The 2-year DRFS rates in the ABE-ET versus ET arms were [redacted] versus [redacted].

At the additional follow-up analysis (April 1, 2021), a total of 220 events were observed (85 in the ABE-ET arm, and 135 in the ET arm). The HR between treatment arms was 0.599 (95% CI, 0.456 to 0.787). The 3-year DRFS rate in the ABE-ET versus ET arms was 87.8% versus 82.6%.

Health-Related Quality of Life

The mean scores for the Functional Assessment of Cancer Therapy – Breast (FACT-B) and EQ-5D-5L scales were similar in the 2 treatment arms, and changes from baseline scores in both arms were less than the minimally important difference of the baseline SD.

Health Care Resource Utilization

As of the final primary outcome (IDFS) analysis (July 8, 2020), [redacted] of patients in the ABE-ET arm and [redacted] of patients in the ET arm reported at least 1 hospitalization. The majority of patients were hospitalized due to [redacted]. Transfusions were reported for [redacted] of patients in the ABE-ET arm and [redacted] of patients in the ET arm. [redacted] was the most commonly reported AE requiring a transfusion ([redacted] of patients in the ABE-ET arm and [redacted] of patients in the ET arm).

Harms Results

As of the final primary outcome (IDFS) analysis (July 8, 2020), 97.9% of patients in the ABE-ET arm, and 87.2% of patients in the ET arm experienced at least 1 treatment-emergent adverse event (TEAE). The most frequent TEAEs were diarrhea (82.6%), neutropenia (45.2%), and fatigue (39.2%) in the ABE-ET arm, and arthralgia (33.1%), hot flush (21.8%), and fatigue (16.6%) in the ET arm. Serious AEs occurred in 13.3% of patients in the ABE-ET arm, and 7.8% of patients in the ET arm. The most frequently reported serious AEs in both arms were pneumonia (0.9% and 0.5%, respectively). Grade 3 or higher TEAEs occurred in 47.4% of patients in the ABE-ET arm, and 14.2% of patients in the ET arm. The most frequently reported grade 3 or higher TEAEs in the ABE-ET arm were neutropenia (19.1%), leukopenia (10.9%), and diarrhea (7.7%). The most common grade 3 or higher TEAEs in the ET arm were neutropenia (0.7%), arthralgia (0.7%), and lymphopenia (0.5%). A total of 481 patients (17.2%) discontinued ABE due to AEs. The 3 most common reasons for discontinuations of ABE were: diarrhea (5.1%), fatigue (1.9%), and neutropenia (0.9%).

[redacted]

Diarrhea was reported for 82.6% of patients in the ABE-ET arm and 7.8% of patients in the ET arm.

Neutropenia was reported for 45.2% of patients in the ABE-ET arm and 5.2% of patients in the ET arm. Venous thromboembolic events were reported in 2.4% of patients in the ABE-ET arm and 0.6% of patients in the ET arm.

Interstitial lung disease or pneumonitis was reported for 1.5% of patients in the ABE-ET arm and 0.4% of patients in the ET arm.

Critical Appraisal

The monarchE trial was a randomized, open-label trial. Because Ki-67 index was not a stratification factor, the population of interest (cohort 1 Ki-67 High) cannot be considered to be truly randomized, and analyses of this population are therefore at risk of confounding due potential prognostic imbalances across treatment groups. However, this risk is likely to be low since available baseline characteristics appeared well balanced. Although patient

blinding would have been impractical and challenging given the differences in the 2 study treatment regimens and different known toxicity profiles, performance and detection bias that may result from lack of blinding of patients and investigators to assigned study treatments cannot be ruled out. The primary outcome (IDFS) was investigator assessed but based on objective criteria and thus unlikely to be greatly affected by the lack of investigator blinding. The subjective patient-reported outcomes may have been biased due to the open-label design of the trial, a high rate of attrition at later follow-up times, and HRQoL results being analyzed in the overall safety population of the monarchE trial, rather than the population for reimbursement (i.e., patients in cohort 1 with Ki-67 index score of ≥ 20%). OS data remain immature. Given the correlation of disease-free survival surrogates with OS is debatable, it is unclear if improvements in IDFS observed in patients in the ABE-ET arm of the trial would translate into OS benefits.

The trial included a heterogenous population of patients with early breast cancer and a wide range of clinical presentations of high recurrence risk were well-represented. The clinical experts consulted noted that the trial population was approximately a decade younger than patients with early breast cancer encountered in clinical practice, potentially explained by high-risk features being more prevalent in younger patients. The inclusion of younger and healthier patients may have led to a more favourable toxicity profile in which more AEs were manageable and/or reversible. Unlike the monarchE trial that implemented standardized Ki-67 central testing, Ki-67 testing is not routinely performed in clinical practice and its reproducibility is affected by several factors, including time and method of biopsy, specimen preparation, and assay used.

Conclusions

Based on data from the monarchE trial, ABE-ET demonstrated a statistically significant benefit compared with ET alone in improving IDFS in women and men with HR-positive, HER2-negative, node-positive early breast cancer at high risk of disease recurrence based on clinicopathological features and a Ki-67 score of at least 20%. DRFS was tested outside of the statistical hierarchy but appeared to be supportive of the primary efficacy results. It is not yet clear whether IDFS benefits will translate to improved OS because the data remain immature and follow-up is ongoing. The safety profile of ABE was consistent with the known adverse effects profile of ABE. Effects on HRQoL and health resource utilization remain uncertain due to high attrition and a lack of between-group statistical testing for these outcomes. Although a much longer follow-up time will likely be needed to determine the efficacy of ABE-ET in terms of OS, given the slow event rate in this setting, the addition of ABE to ET in this new indication could help optimize adjuvant treatment to improve outcomes in terms of disease recurrence. Uncertainties remain regarding the validity and generalizability of Ki-67 testing and practical considerations for its implementation in clinical practice in determining patient eligibility for treatment with ABE.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Patients with HR-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence and a Ki-67 score of at least 20%
Treatment	Abemaciclib + endocrine therapy (ABE-ET; ET comprised of anastrozole, exemestane, letrozole, or tamoxifen)
Submitted price	Abemaciclib, 50 mg: $98.4714 per tablet Abemaciclib, 100 mg: $99.9704 per tablet Abemaciclib, 150 mg: $98.4714 per tablet Abemaciclib, 200 mg: $99.9704 per tablet
Treatment cost	ABE + anastrozole: $5,541 ABE + exemestane: $5,552 ABE + letrozole: $5,553 ABE + tamoxifen: $5,524 to $5,534
Comparator	ET (letrozole, anastrozole, tamoxifen, exemestane)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (49 years)
Key data source	monarchE trial (Ki-67 score of at least 20% subgroup of cohort 1)
Key limitations	• The sponsor used a "fixed payoff" approach that could not be fully validated by CADTH. Patients with metastatic recurrence after ABE-ET or ET were assigned a fixed number of LYs calculated using the results of pharmacoeconomic models that were not provided to CADTH as part of the current review • The sponsor's base case predicts a survival advantage with ABE-ET compared with ET (incremental gain: 3.60 LYs) over a 49-year horizon; however, no difference in survival was observed in the monarchE trial. Clinical experts consulted by CADTH indicated that it is highly uncertain whether delayed disease progression will translate to gains in OS. Given the sponsor's "fixed payoff" approach, CADTH was unable to validate the survival benefit predicted for patients in the metastatic health state, introducing additional uncertainty into the sponsor's base case. • The long-term impact of ABE-ET on IDFS is highly uncertain. In the sponsor's analysis, 97% of the total incremental QALYs predicted are accrued in the invasive disease-free health state, and all incremental QALYs were accrued through extrapolation. The extrapolation curve chosen by the sponsor for IDFS resulted in the incremental effectiveness of ABE-ET vs. ET increasing after patients discontinued ABE, which clinical experts considered highly uncertain. • The sponsor assumed that the effectiveness of ABE-ET would begin to wane after 8 years (i.e., 6 years after the ABE stopping rule was imposed) and that waning would continue for a period of 19 years. The sponsor supported the assumptions using evidence from a separate class of drug with a different mechanism of action. Clinical experts consulted by CADTH considered this assumption to be implausible. • The sponsor assumed that patients with metastatic recurrence after adjuvant ABE-ET would not receive

Component	Description
	subsequent treatment with a CDK4/6 inhibitor. Clinical experts consulted by CADTH indicated that a proportion of patients with ET-sensitive disease (recurrence at least 6 months after adjuvant ABE-ET treatment) would receive a CDK4/6 inhibitor as part of standard of care for metastatic recurrence. The assumption that no patients receive CDK4/6 inhibitors after ABE-ET likely underestimates the cost of treating metastatic recurrence and biases the ICER in favour of ABE-ET.
CADTH reanalysis results	• Given the modelling approach adopted by the sponsor, the cost-effectiveness of ABE-ET is highly uncertain. CADTH undertook reanalyses that adopted an alternative extrapolation assumption for IDFS, which used alternative assumptions about treatment effectiveness waning. CADTH was unable to fully validate the submitted model owing to the use of a "fixed payoff" approach that relied on external models not provided to CADTH. CADTH's base case estimate of cost-effectiveness therefore remains highly uncertain. • Based on CADTH reanalyses, ABE-ET remained more costly and more effective than ET alone: ICER = $78,438 per QALY (incremental costs = $81,924; incremental QALYs = 1.04). • A price reduction of at least 24% for ABE would be required for ABE-ET to be considered optimal at a WTP threshold of $50,000 per QALY compared to ET alone. • This estimate is subject to the high degree of uncertainty due to the limitations described — most notably the "fixed payoff" approach — and further price reduction may be warranted. CADTH notes that all the predicted benefit with ABE-ET is accrued in the extrapolation period; it is uncertain whether this benefit will be realized in practice.

ABE = abemaciclib; CDK4/6 = cyclin-dependent kinases 4 and 6; ET = endocrine therapy; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; ICER = incremental cost-effectiveness ratio; IDFS = invasive disease-free survival; LY = life-year; QALY = quality-adjusted life-year.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis, including the number of patients eligible for ABE-ET is uncertain, including the proportion of patients at high risk of recurrence based on clinicopathologic features and Ki-67 score; the market share of comparators is uncertain; and the costs associated with ABE in year 3 are likely underestimated.

In the CADTH reanalysis, it was assumed that all patients who are potentially eligible for ABE-ET based on clinicopathological features will undergo Ki-67 testing. In the CADTH base case, the budget impact of reimbursing ABE for use as adjuvant treatment in combination with ET is expected to be $7,066,272 in year 1, $10,953,457 in year 2, and $12,046,862 in year 3, with a 3-year total of $30,066,591. The budget impact is sensitive to uncertainty in the number of patients deemed to be at high risk based on clinicopathologic features, Ki-67 test positivity rates, and assumptions about the market uptake.

pERC Information

Members of the Committee

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

Meeting date: August 10, 2022

Regrets: 3 of the expert committee members did not attend

Conflicts of interest: None