CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

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

Sponsor: Eli Lilly Canada Inc.

Recommendation: Reimburse with Conditions

Version: 1.0
Publication Date: September 2024
Report Length: 15 Pages

Single Technology

CADTH

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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.

Recommendation

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

Rationale for the Recommendation

One multicentre, randomized, open-label, phase III trial (MonarchE; N = 5637 patients) demonstrated that adjuvant treatment with abemaciclib + ET resulted in added clinical benefit when compared with adjuvant ET alone, in adult patients with HR+, HER2-, node-positive, early breast cancer at high risk of disease recurrence based on clinicopathological features (including ≥4 positive axillary lymph nodes (ALN), OR 1-3 positive ALN + histologic grade 3 disease, and/or, 1-3 positive ALN + tumour size of ≥ 5cm, OR 1-3 positive ALN + Ki-67 ≥ 20%). The MonarchE trial showed that treatment with abemaciclib + ET resulted in a statistically significant and clinically meaningful improvement in invasive disease-free survival (IDFS) compared with ET alone, with a hazard ratio (HR) of 0.680 (95% confidence interval [CI]: 0.599 to 0.772).

pERC noted that the proportion of patients who experienced treatment-emergent adverse events in the MonarchE trial was higher overall with abemaciclib + ET than with ET alone. However, the committee agreed with the clinical experts' observation that the safety results indicated mostly low-grade adverse events, consistent with previously reported events associated with ABE + ET in the locally advanced or metastatic breast cancer setting, without new or unexpected safety signals reported in the trial. Therefore, pERC concluded that the AEs were predictable, reversible, or clinically manageable, 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 abemaciclib + ET met some of the patients' needs as it reduces the risk of recurrence and has manageable side effects. Furthermore, the ability to combine abemaciclib with various endocrine therapies provides alternate treatment options to eligible patients who do not tolerate treatments such as aromatase inhibitors (AI)+ovarian function suppression (OFS). pERC agreed with the clinical experts that abemaciclib + tamoxifen could be an alternative in premenopausal patients, in which case, OFS can also be used but is not required.

Using the sponsor submitted price for ABE + ET and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for ABE + ET was $133,903 per quality-adjusted life-year (QALY) gained compared with ET alone. At this ICER, ABE + ET is not cost-effective at a willingness to pay (WTP) threshold of $50,000 per QALY gained for the adjuvant treatment of adult patients with HR+, HER2-, node-positive, early breast cancer at high risk of disease recurrence based on clinicopathological features. A price reduction for abemaciclib is required for abemaciclib + ET to be considered cost-effective at a $50,000 per QALY gained 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 resected invasive early breast cancer without metastases 1.2 Fulfill one of the following: 1.2.1 Pathological tumour involvement in ≥ 4 ipsilateral axillary lymph nodes or 1.2.2 pathological tumour involvement in 1 to 3 ipsilateral axillary lymph node(s) AND at least one of the following criteria: 1.2.2.1 Grade 3 disease 1.2.2.2 Primary tumour size ≥5 cm. 1.2.2.3 Ki-67 index score of ≥20% 1.3 Undergone definitive surgery of primary breast tumour within 16 months of initiating treatment.	Evidence from the MonarchE trial demonstrated that ABE+ET resulted in a statistically and clinically significant improvement in IDFS in patients with characteristics listed in the condition.	pERC recognized that the drug plans need to address the availability of Ki-67 testing to implement reimbursement of ABE+ET for patients with 1-3 positive ALN + Ki-67 ≥ 20%.
2.1 Patients must not have metastatic disease.		—
Discontinuation		
2. Abemaciclib, in combination with endocrine therapy, should be discontinued upon the occurrence of any of the following: 9.1 Disease recurrence 9.2 Unacceptable toxicity	Consistent with clinical practice, patients in the MonarchE trial discontinued treatment upon disease recurrence or unacceptable toxicity.	—
3. Patients should be assessed for disease recurrence as per standard clinical practice.	Based on the opinion of clinical experts.	—
4. ABE should be reimbursed for a maximum of 2 years (150 mg orally twice daily). Endocrine therapy can be continued beyond this time.	Patients in the MonarchE trial were treated with ABE for 2 years. Treatment with ET in the trial could be continued for 5 years (and up to 10 years) if medically appropriate.	If treatment with ABE were 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. The decision to resume therapy should be at the treating clinician's discretion.

Reimbursement Condition	Reason	Implementation Guidance
Prescribing		
5. 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.	To ensure that treatment is prescribed only for appropriate patients and that adverse effects are managed optimally and promptly.	—
6. 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.	—
7. ABE+ET should only be reimbursed when administered in combination	No data were identified supporting the efficacy and safety of ABE+ET when combined with additional anticancer drugs or when ABE is used as monotherapy.	ET can continue as monotherapy after the 2 years of ABE.
Pricing		
8. A reduction in price	The ICER for ABE + ET is $133,903 per QALY gained compared to ET alone. A price reduction of 51% for ABE would be required for ABE + ET to achieve an ICER of $50,000 per QALY gained compared to ET alone. Due to the high degree of uncertainty in cost-effectiveness, a price reduction of more than 51% may be warranted.	—
Feasibility of Adoption		
9. The economic feasibility of adoption of ABE+ET must be addressed	At the submitted price, the incremental budget impact of ABE+ET is expected to be greater than $40 million in years 2 and 3.	—
10. The feasibility of the adoption of ABE + ET 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 the CDA-AMC estimate.	

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

Discussion Points

- pERC discussed improvement in HRQoL, which patients identified as an important outcome. The MonarchE pivotal trials evaluated HRQoL using the Functional Assessment of Cancer Therapy – Breast Cancer (FACT-B) instrument. Based on the FACT-B Total Score at 12 months and 24 months, a GRADE assessment indicated that treatment with the abemaciclib + ET combination may result in no clinically meaningful difference in patients' HRQoL compared with ET monotherapy. Therefore, pERC determined that while abemaciclib + ET likely improves IDFS, there was insufficient evidence to conclude that the benefit would translate into improving a patient's health-related quality of life.

- pERC noted that overall survival (OS) was an important outcome in breast cancer treatment and observed that the MonarchE trial's OS data were immature after a median follow-up of 54 months, leading to uncertainty regarding the long-term survival benefits of abemaciclib + ET in the population for reimbursement. However, the committee agreed with the clinical experts that IDFS is a clinically meaningful, well-recognized, and accepted endpoint for adjuvant breast cancer clinical trials, the attainment of which would result in potentially less treatment in the future and an extended cancer-free period. pERC also agreed that the survival duration for patients with early-stage HR+ HER2- breast cancer can be very long, and it may be challenging to demonstrate OS benefit in this patient population in a clinical trial setting.

- pERC considered that for patients with 1-3 positive ALN + Ki-67 ≥ 20% (described as Cohort 2 in the MonarchE trial), a validated Ki-67 test is required before initiating treatment with abemaciclib + ET. The committee acknowledged that Ki-67 testing in Canadian clinical practice is currently limited due to variability in routine testing and lack of standardized laboratory assays. However, pERC discussed that the current recommendation is unlikely to increase the requirement of Ki-67 testing, given that it reduces the category of patients who require the test to initiate treatment compared with the 2022 pERC recommendation. The 2022 recommendation was to reimburse abemaciclib + ET for the adjuvant treatment of adult patients with HR+, HER2-, node-positive, early breast cancer at high risk of disease recurrence based on clinicopathological features and a Ki-67 score ≥20%. The current recommendation does not require Ki-67 testing in patients with ≥4 positive axillary lymph nodes (ALN), or 1-3 positive ALN + histologic grade 3 disease, or 1-3 positive ALN + tumour size of ≥ 5cm.

- pERC discussed using olaparib versus abemaciclib in patients with deleterious or suspected deleterious germline BRCA1/2-mutated disease. The committee noted that such patients will qualify for abemaciclib if they meet eligible criteria. However, there are currently no evidence-based criteria for choosing olaparib or abemaciclib or how to use them sequentially. Adjuvant Olaparib for the subset of patients with deleterious or suspected deleterious germline BRCA1/2-mutated disease was omitted as a comparator from the economic analysis. Therefore, the analysis does not reflect the current treatment landscape, where both olaparib and abemaciclib are recommended options in the adjuvant setting. The cost-effectiveness of abemaciclib + ET compared to olaparib + ET in this subgroup of patients is unknown.

Background

Breast cancer is the most diagnosed cancer and the second leading cause of cancer-related death among Canadian women. In 2022, a total of 28,600 females were diagnosed with breast cancer and 5,500 females died from the disease (14% of all cancer deaths among women). In patients with HR+, HER2- EBC, the 5-year survival rate is greater than 90%. Although patients with EBC have a promising 5-year survival prognosis, a subset of up to 20-30% of patients will nonetheless experience disease recurrence in the first 10 years. When recurrences are distant, patients are defined as having metastatic disease which is incurable. Patients with high-risk clinicopathological features, particularly those with a high burden of nodal involvement, have been shown to be at a higher risk of disease recurrence.

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). Hormone receptor (HR) positive (HR+) breast cancers that express ER or PR or both are the most prevalent type of breast cancer. Overexpression of the human epidermal growth factor 2 (HER2) oncogene, which belongs to the epidermal growth factor receptor (EGFR/HER) family and enables constitutive activation of growth factor signaling and triggering breast cancer cell survival, proliferation, and invasion is associated with poor prognosis. HR+, HER2- tumours are the most common subtype of breast cancer. accounting for approximately 70% of breast cancers. Over 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 patients with distant metastatic disease, early-stage breast cancer is potentially curable.

Although many patients with HR+, HER2- disease will not experience recurrence or have distant recurrence with standard therapies alone, a subset of up to 20-30% of patients will nonetheless experience disease recurrence in the first 10 years. When recurrences are distant, patients are defined as having metastatic disease which is incurable.

Risk factors for recurrence include large tumour size, higher degree of involvement of axillary lymph nodes (ALNs), high histologic grade, age, HR and HER2 status (positive), and high tumour proliferation rate (Ki-67). Ki-67 immunohistochemistry (IHC) testing is a prognostic factor for the risk of recurrence. However, the use of IHC 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 trial clinical study in patients with HR+HR+, HER2-, node positive early breast cancer who completed definitive locoregional therapy and are at high risk of recurrence based on clinicopathological features.
- 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 CDA-AMC (CADTH) review process
- Two clinical specialists with expertise diagnosing and treating patients with breast cancer
- Input from one clinician group, the Ontario Health-Cancer Care Ontario 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 CDA-AMC (CADTH's) call for input and from clinical experts consulted by CDA-AMC (CADTH) for the purpose of this review.

Patient Input

Two patient groups, the Canadian Breast Cancer Network (CBCN) and Rethink Breast Cancer (Rethink) submitted patient input for this review. According to CBCN, a diagnosis of early-stage HR+, HER2- breast cancer has a significant impact on the life of the patient, and treatment of breast cancer has a significant impact on the emotional and physical well-being of patients. Rethink highlighted that those diagnosed in their 20s, 30s and early 40s 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 don't have cancer, career hiatuses, and financial insecurity. Both groups agreed upon that current treatment for HR+, HER2- early breast cancer depends on the details of the persons diagnosis and the characteristics revealed on their pathology report. It is usually treated with a combination of surgery, chemotherapy, radiation therapy, and hormonal therapy, which can reduce the risk of early-stage breast cancer coming back. Both groups indicated that treatment efficacy, minimizing side effects, and reducing the risk of recurrence is of the greatest concern for early-stage breast cancer patients, and patients have an expectation of treatment to offer a good quality of life. Patients who had experience with ABE indicated that they were willing to try because abemaciclib can potentially lower the possibility of recurrence, and it is well-tolerated Rethink emphasized that the removal of the requirement for a Ki-67 score ≥20% will remove a barrier to care for patients due to inequitable access across Canada to Ki-67 testing.

Clinician input

Input from clinical experts consulted by CADTH

The clinical experts indicated that the standard of care of adjuvant therapies and the type of adjuvant ET is guided by menopausal status. The clinical experts indicated that for premenopausal women with high-risk node positive disease, optimal ET should be ovarian function suppression plus AI (OFS + AI) unless contra-indicated or not tolerated. The clinical experts also indicated that despite current treatments discussed above, many people develop metastatic disease, which is incurable once it occurs. Hence, there is an urgent need for new treatment to address this high risk of serious, life-threatening metastatic breast cancer. Furthermore, treatments that target underlying mechanisms that drive breast cancer recurrence are needed. The clinical experts consulted by CADTH noted that, for adjuvant therapies, the goal is to improve survival (preferably OS, but invasive disease-free survival and distant relapse-free survival are also used), and to decrease risk of recurrence.

Clinician group input

Clinician group input was received from the Ontario Health Cancer Care Ontario (OH-CCO) Breast Cancer Drug Advisory Committee, with 5 clinicians contributing to the input. The clinician group noted that despite the advances of treatment in HR+, HER2- BC, up to 50% of patients with high-risk clinical and/or pathologic features may experience distant recurrence. The clinician group stated that, therefore, superior treatment options are needed to prevent early recurrence and development of metastases for this group of patients, so that abemaciclib would be used in addition to ET in high-risk patients following surgery and chemotherapy (if applicable). Clinician group indicated that patients best suited for treatment with abemaciclib would be HR+, HER2- early breast cancer (EBC) at high risk of recurrence who are node positive and would align with the inclusion criteria of the MonarchE clinical trial (i.e. both Cohort 1 and cohort 2 of the trial). The Clinician group believed that no extra imaging is needed to assess treatment response, but patients would need extra monitoring for hematologic toxicity, and diarrhea; and additional support from oncology pharmacists and nursing would be required. The discontinuation factors for abemaciclib would be disease progression and toxicity.

Drug Program Input

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

Table 2: Summary of Drug Plan Input and Clinical Expert Response

Drug Program Implementation Questions	Clinical Experts Response/comments
Relevant comparators	
Abemaciclib is currently funded in jurisdictions in this patient population. This submission represents a criteria modification/expanded eligible population, which would remove the requirement for a Ki-67 score of 20% or greater. Therefore, the majority of PAG input for this submission (PC0345) will provide the current status for abemaciclib (based on the prior pERC recommendation [PC0282]). **Removing the Ki-67 requirement** will not likely impact current funding/implementation processes for abemaciclib but would allow for more patients to be eligible. PAG notes that approximately 1/3 of patients on the MonarchE trial had Ki-67 of less than 20%. The current indication for abemaciclib for HR+/HER2- EBC requires initiation within 16 months of definitive surgery, as per MonarchE.	Both clinical experts agree with this statement. They noted that current processes would omit accessing Ki-67 patients with ≥4 positive ALN or 1-3 positive ALN + histologic grade 3 disease, or 1-3 positive ALN + tumour size of ≥ 5cm. However, for patients with 1-3 positive ALN + Ki-67 ≥ 20% (described as Cohort 2 in the MonarchE trial and representing ~10% of the included participants), access to abemaciclib would require Ki67 ≥20%. The clinical experts stated that most clinicians use abemaciclib, but some use olaparib or try to sequence the drugs. However, they did not have a widely accepted standard for what to do with BRCA mutation carriers who are also eligible for adjuvant olaparib. . *pERC agreed with the clinical experts' responses*
Considerations for initiation of therapy	
a) Disease diagnosis, scoring or staging for eligibility If recommended, implementing this submission would remove the need to identify potential patient eligibility with additional Ki-67 testing of tumours. Ki-67 testing is not a reflexively conducted test in many jurisdictions.	Both clinical experts agreed that Ki-67 testing is not reflexively done. So, removing the criteria will remove additional logistical steps from the clinicians' and pathology perspective. *pERC agreed with the clinical experts' responses*
b) Eligibility to retreatment CDK 4/6 inhibitors are eligible for retreatment in advanced/metastatic disease provided there was at least a 6-month interval between any prior abemaciclib for HR+/HER2- EBC and the development of disease recurrence.	One clinical expert indicated that this is a reasonable approach which many clinicians would use in practice, analogous with other adjuvant situations. *pERC agreed with the clinical experts' responses*
Funding algorithm (oncology only)	
Other aspects: Removal of Ki-67 requirement would be required	Both clinical experts indicated that it would not be removed entirely, as patients with 1-3 ALN would still need a Ki-67 score ≥20% to be eligible if they did not have histologic grade 3 disease or tumour size of ≥ 5cm. However, Ki-67 testing is expected to be less, as there would not be a need to test those with ≥ 4 lymph nodes or those with 1-3 positive ALN if they also had histologic grade 3 disease or tumour size of ≥ 5cm. *pERC agreed with the clinical experts' responses*
System and economic issues	
a) Concerns regarding the anticipated budget impact and sustainability This expands the potentially eligible population for adjuvant abemaciclib, which represents an impact to budget of uncertain magnitude. PAG notes that	One clinical expert indicated that this is hard to quantify. However, given a 6.7% (at least) reduction in the development of metastatic disease at 5 years, we are preventing these individuals from developing metastatic disease and requiring the subsequent palliative lines of therapy later (including ADCs such as SG or Enhertu). Given that these patients, on average, live 5 years with metastatic disease and require treatment

Drug Program Implementation Questions	Clinical Experts Response/comments
approximately 81% of patients on MonarchE completed 2 years of abemaciclib and approximately 1/3 of patients on the MonarchE trial had Ki-67 of less than 20%. PAG is interested in knowing both the economic (i.e. cost effectiveness) and budget impact to public drug plans by removing ki-67 requirement.	during that time, including CDK 4/6 inhibitors, then later lines of therapy and supportive care, the total time on treatment is less in this adjuvant setting. NATALEE study [48] included all LN1-3 regardless of Ki-67. The clinical experts' concern is that we do not exclude patients who would derive a benefit. It may be worthwhile to clarify the economic impact of testing Ki-67. Removing it as a criterion would assist with access through Cohort 1 (particularly given that benefit was seen regardless of Ki-67 in Cohort 1). However, given Cohort 2 also benefited, we would want a way to access the drug for those who are 1-3 lymph nodes positive, if not grade 3 or tumour size <5 cm and Ki-67 ≥ 20%. The other clinical expert indicated that all patients who meet MonarchE criteria must have access to abemaciclib irrespective of the budget. *pERC agreed with the clinical experts' responses*

ADC = antibody drug conjugates; ALN = axillary lymph node; CDK = cyclin dependent kinase; Enhertu = trade name for trastuzumab deruxetecan; ET= endocrine therapy; HER2 = human epidermal receptor 2; HR-positive = hormone receptor-positive; PAG = provincial advisory group; SG = sacituzumab govetican.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of study

One sponsor-submitted pivotal study was included in the systematic review; the MonarchE trial is an ongoing open-label phase 3 randomized controlled trial that compared the efficacy and safety of abemaciclib + ET to ET alone in the adjuvant treatment of patients with HR+, HER2-, node positive early breast cancer who completed definitive locoregional therapy and were at high risk of recurrence based on clinicopathological features or a high (20% or higher) Ki-67 index. A total of 5,637 patients in 38 countries, including 44 patients from Canada, were randomized to treatment with either abemaciclib + ET or ET alone. Patients with at least 1 positive lymph node were recruited into two cohorts; patients in Cohort 1 (n=5,120, 90.8%) 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, 9.2%) included patients based on 1 to 3 positive axillary lymph nodes and high Ki-67 index (≥ 20%). The primary efficacy endpoint was IDFS, and the secondary endpoints included DRFS, OS, HRQOL (e.g., FACT-B) and the harms outcomes. The results of IDFS, DRFS and OS presented in this report are based on the OS IA3 data-cut-off after a median follow-up of 54 months. HRQOL measurements (e.g., FACT-B) and Health care resource utilization (hospitalizations, transfusions) are based on OS IA2 data cut-off after a median follow-up of 42 months. Harms data reported in this review was based on either OS IA2 or OS IA3 data cut-off.

Efficacy Results

Invasive Disease-Free Survival: In the ITT population (Cohort 1 + Cohort 2 of MonarchE trial), a treatment benefit for IDFS was first observed at IA2 in an analysis that was controlled for multiplicity. At OS IA3 (a median follow-up of 54 months), the median IDFS was not reached in either of the treatment arms. There was a total of 407 events (14.5%) in the abemaciclib plus ET and 585 (20.7%) in the ET arm (hazard ratio = 0.680; 95% CI: 0.599, 0.772; p < 0.00001). The between-group differences (95% CI) in IDFS for abemaciclib + ET versus ET alone were 2.8% (1.3 % to 4.3%) at 24 months; 4.8% (3.0% to 6.6%) at 36 months; and 7.6% (5.2% to 10.0%) at 60 months. The IDFS between group difference at 36 month and 60 months was considered clinically meaningful by the clinical experts consulted by CDA-AMC. Subgroup analyses of OS were largely consistent with the primary analysis.

Distant Relapse-Free Survival: The analysis of DRFS was uncontrolled for multiplicity. In the ITT population, at OS IA3 (a median follow-up of 54 months) the median DRFS was not reached in either of the treatment arms. There was a total of 345 (12.3%) events in the abemaciclib plus ET arm and 501 (17.7%) in the ET arm (hazard ratio = 0.675, 95% CI: 0.588, 0.774; p < 0.00001). The between-group differences (95%CI) in DRFS for abemaciclib + ET versus ET alone were 2.5% (1.1% to 3.9%) at 24 months; 4.1% (2.4% to 5.8%) at 36 months; and 6.7% (4.5% to 9.0%) at 60 months. The DRFS between group difference at 36 month and 60 months was considered clinically meaningful by the clinical experts consulted by CDA-AMC. Subgroup analyses of DRFS were largely consistent with the primary analysis.

Overall Survival: At a median follow up of 54 months (OS IA3 cut-off), OS results remained immature with 442 deaths in the ITT population, corresponding to a 68% information fraction of the 650 events required for the final OS analysis. The median OS was not reached in either of the treatment arms. The estimated hazard ratio was 0.903 (95% CI, 0.749 to 1.088; p = 0.284) for abemaciclib + ET compared to the ET alone. The between-group difference (95%CI) in OS probability for abemaciclib + ET versus ET alone was 1.1% (-0.8% to 3.0%) at 60 months. It indicated that the combination of Abemaciclib + ET likely results in little-to-no clinically important difference in OS when compared with ET monotherapy at 60 months.

Health-related quality of life: At OS IA 2 cut-off (median follow-up: 42 months), in the safety population for abemaciclib + ET versus ET alone, the least square mean (LSM) difference in change from baseline in FACT-B total score at 24 months was -2.60, 95% CI, -3.5 to -1.69 points, P<0.001. At 12 months following treatment discontinuation (also known as additional Follow-up 2), the least square mean difference in change from baseline was -0.79, 95% CI, -1.76 to 0.18 points; P=0.110. It indicated that the combination of abemaciclib + ET may result in little-to-no clinically important difference in FACT-B when compared with ET monotherapy at 24 months and at 12 months following treatment discontinuation.

Healthcare resource utilization: At OS IA2 (median follow-up: 42 months), numerically more patients experienced hospitalizations due to AEs than that in ET arms (13.8% vs. 8.8%). Patients were hospitalized mostly due to system organ class infections and infestations (196 [3.5%] patients), specifically pneumonia (23 [0.8%] in the abemaciclib plus ET and 15 [0.5%] in the ET arm). Also, numerically more patients experienced transfusions than that in ET arms (1.6% vs. 0.4%). Anemia was the most commonly reported AE requiring a transfusion, with 32 patients (1.1%) in the abemaciclib plus ET group and 7 (0.3%) patients in the ET group.

Harms Results

At OS IA3 data cut-off, most patients in both treatment arms experienced adverse events (AEs) (98.4% in the abemaciclib + ET arm, and 88.9% in the ET arm). Patients with the most common AEs (>30%) were diarrhea, neutropenia, fatigue, leukopenia and abdominal pain, which occurred more frequently in the abemaciclib + ET arm than that in ET arm. The most common AEs (>20%) which occurred more often in the ET arm than in the abemaciclib + ET arm were arthralgia and hot flush. Grade 5 treatment emergent adverse events (TEAE) were reported rarely (abemaciclib + ET vs.ET: 0.6% vs. 0.4%). At OS IA3, numerically more patients experienced SAEs in abemaciclib + ET arm (15.6% versus 9.2%).

At OS IA2, the proportion of patients who discontinued treatment because of AEs was higher in the abemaciclib + ET arm compared to the ET arm (18.5% versus 1.1%). Diarrhea was the most common AE to cause treatment discontinuation.

The clinical experts CADTH consulted for this review indicated that, of the reported AEs of special interest, venous thromboembolic event (VTEs) and interstitial lung disease (ILD)/pneumonitis are most clinically important. Any grade of VTEs occurred among 2.5% of patients in the abemaciclib + ET arm and 0.7% in the ET arm. Any grade of ILD/pneumonitis occurred in 3.3% of patients in the abemaciclib + ET arm and 1.3% in the ET arm. It indicated that the evidence of combination of abemaciclib + ET likely results in little-to-no clinically important difference on VTE or interstitial lung disease (ILD)/pneumonitis when compared with ET monotherapy.

In summary, according to the clinical experts CDA-AMC consulted for this review, the harms results for abemaciclib +ET in MonarchE were generally consistent with that previously reported for abemaciclib and ET in the locally advanced or metastatic breast cancer setting; with no new or unexpected harms identified in the MonarchE trial. Overall, most AEs were predictable, low-grade, reversible, and clinically manageable with co-medications and/or dose modifications in most patients and acceptable in the EBC curative setting.

Critical Appraisal

An appropriate method of randomization was reported. Sample size was adequate, and the study was powered (based on the ITT population) to test its primary endpoint. Objective outcomes and validated health related outcomes were assessed. The statistical approach of gatekeeping to sequentially test the primary and secondary endpoints was acceptable to account for multiple testing across these analyses. The potential limitations are discussed below:

The trial was an open label design. Performance and detection bias that may result from lack of blinding of patients and investigators to assigned study treatments cannot be ruled out. For example, patient's knowledge of their assigned treatment could result in over- or underestimation of safety endpoints and patient reported outcomes (PROs) and HRQoL. However, there was minimal evidence of bias for the objective endpoints.

DRFS analysis was not controlled for multiple comparisons, the analysis was at increased risk of type I error (i.e., false positive findings).

IDFS and DRFS are considered early indicators of patient's survival, especially for less advanced conditions in which longer survival is expected. OS data in MonarchE remain immature, which is expected in this disease setting with longer survival prognosis. The efficacy of abemaciclib + ET regarding OS will require a larger number of events and a longer follow up. Considering the OS data is not mature yet at OS IA3, it is unclear if improvements in IDFS and DRFS observed in patients in the abemaciclib + ET arm of the MonarchE trial would translate into clinical meaningful OS benefits. OS did not reach statistical significance; however, the lower number of deaths in the abemaciclib + ET arm compared with the ET arm suggested that a survival signal favoring abemaciclib may be emerging.

Regarding to the HRQoL (e.g., FACT-B), the sponsor noted that differences across treatment arms were evaluated based on numerical estimates and the interpretation should be viewed as exploratory. In addition, there was a substantial attrition rate for HRQoL (e.g. FACT-B) assessments over time, with 70.3% of patients contributing to the assessments at visit 27 and 64.3% of patients contributing to the assessments 12 months post treatment discontinuation. As a result, there is a risk of bias due to missing outcome data, because the missing at random assumption underlying the analysis may not be plausible.

The clinical experts consulted by CADTH noted that patients in the trial are about a decade younger than patients with early breast cancer encountered in clinical practice who are generally diagnosed and treated in their early to mid 60s, although this may be explained by high-risk features potentially being more prevalent in younger patients. The clinical experts consulted by CADTH also noted that the inclusion of younger and healthier patients may have led to fewer harms, where more AEs were manageable, and reversable. In addition, a total of 98% patients had prior chemotherapy (i.e., neo- or adjuvant chemotherapy) in both groups. However, the clinical experts indicated that the prior chemotherapy in this setting may not be used as much in current practice with the integration of genomic testing for patients with 1-3 nodes positive. Nevertheless, the clinical experts stated that inclusion of younger patients and the high proportion patients with prior chemotherapy are unlikely to have a significant impact on the generalizability of the findings in the Canadian clinical practice.

Overall, the clinical experts CADTH consulted for this review indicated that the patients included in MonarchE are well representative of patients in Canadian clinical practice. It is unlikely to have a generalizability concern.

Conclusions

Evidence from the MonarchE trial showed that abemaciclib + ET demonstrated a clinically meaningful benefit compared to endocrine (ET) alone in improving IDFS, DRFS 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. It is not yet clear whether IDFS and DRFS benefits will translate to improved OS benefit as the data remain immature at OS IA3. Longer follow-up time is needed to determine the OS benefit compared with ET alone in the health Canada indicated population given that patients with early -stage breast cancer usually have a long survival time. Abemaciclib in combination with endocrine therapy may not result in a clinical meaningful difference on the HRQoL assessed with FACT-B. In terms of harms, most AEs of abemaciclib + ET were predictable, reversible, and clinically manageable in most patients and acceptable in

the EBC setting. The safety profile of abemaciclib + ET in MonarchE was generally consistent with known safety profile previously reported for abemaciclib monotherapy and ET. The MonarchE trial did not identify any new safety signals.

Economic Evidence

Cost and Cost-Effectiveness

Table 3: Summary of Economic Evaluation

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.
Treatment	Adjuvant abemaciclib in combination with ET (abemaciclib + ET). ET is comprised of a combination of physician's choice therapies, including anastrozole (22%), exemestane (8%), letrozole (38%), or tamoxifen (33%).
Dose regimen	The recommended dose of abemaciclib is 150 mg twice daily, when taken in combination with ET, until the completion of either 2 years of therapy or until disease recurrence or unacceptable toxicity.
Submitted price[a]	Abemaciclib 50 mg: $112.58 per tablet 100 mg: $111.54 per tablet 150 mg: $111.86 per tablet
Submitted treatment cost	The 28-day cost of abemaciclib is $6,264 per patient. When used in combination with ET, the 28-day costs per patient are as follows: abemaciclib + anastrozole ($6,291); abemaciclib + exemestane ($6,301); abemaciclib + letrozole ($6,302); and abemaciclib + tamoxifen ($6,274).
Comparator	Adjuvant ET
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (49 years)
Key data source	MonarchE trial (Intention-to-treat, overall survival interim analysis 3 data-cut [ITT OS IA3]; July 3, 2023)
Key limitations	• The sponsor used a "fixed payoff" approach to apply costs and effects to patients in the model, which could not be fully validated by CADTH. That is, patients with metastatic recurrence after abemaciclib + ET or ET alone were assigned a fixed number of LYs, which were calculated using the results of pharmacoeconomic models that were not provided to CADTH as part of the current review – these results could not be validated. • The sponsor's base case predicts a survival benefit with abemaciclib + ET compared to ET (incr. LYs: 2.19) over a 49-year horizon; however, no difference in survival was observed in the MonarchE trial (median follow up: 54 months). Clinical experts consulted by CADTH indicated that it is uncertain whether and to what extent delayed disease progression will translate to gains in OS. • The long-term impact of abemaciclib + ET on IDFS is highly uncertain. The sponsor's modelling choices resulted in sustained increases in the IDFS benefit of abemaciclib + ET during the extrapolated period, a concern noted by clinical experts due to the absence of evidence supporting this assumption. The entirety of incremental QALYs predicted by the sponsor's analysis are accrued in the 'Invasive Disease Free' health state, with 94% of these accrued through extrapolation. • The sponsor adopted treatment waning assumptions based on the ATAC trial, using evidence from a separate class of drug with a different mechanism of action in patients with unknown HER2 status. Clinical experts indicated that differences between ATAC and MonarchE (e.g. study population, mechanism of action of treatments) restrict the degree to which evidence from the ATAC trial can be generalized to predict the prolonged efficacy of abemaciclib + ET.

Component	Description
	• The sponsor assumed that patients with metastatic recurrence after adjuvant abemaciclib + ET would not receive subsequent treatment with a CDK4/6 inhibitor, which underestimates the cost of treating metastatic recurrence and biases the ICER in favour of abemaciclib + ET. Clinical experts indicated that patients with ET-sensitive disease (i.e., recurrence at least 6 months after completing adjuvant treatment) would receive a CDK4/6 inhibitor as part of standard of care in the metastatic setting. • Adjuvant olaparib, a treatment prescribed in Canada for a subset of patients with deleterious or suspected deleterious germline BRCA1/2-mutated disease, was omitted as a comparator from the analysis. This omission fails to reflect the current treatment landscape, where both olaparib and abemaciclib are recommended options in the adjuvant setting. The cost-effectiveness of abemaciclib + ET compared to olaparib + ET in this subgroup of patients is unknown. • CADTH additionally corrected the sponsor's submitted base case by revising the price of abemaciclib 150 mg tablet, which was incorrectly programmed in the submitted model.
CADTH reanalysis results	• The CADTH base case was derived by making changes to the following model parameters: using independent models that assume non-proportional hazards to extrapolate IDFS; adopting alternative parametric distributions to extrapolate IDFS; assuming treatment effectiveness waning starts at year 7 and ends by year 10 post-treatment initiation; and revising the proportion of patients with metastatic ET-sensitive disease who receive CDK4/6 inhibitors in the abemaciclib + ET model arm. • In the CADTH base case, abemaciclib + ET was associated with an ICER of $133,903 per QALY gained compared to ET alone (incremental costs: $103,572; incremental QALYs: 0.77). A price reduction of 51% for abemaciclib would be required for abemaciclib + ET to be cost-effective compared to ET alone at a willingness-to-pay threshold of $50,000 per QALY gained. • The cost-effectiveness of abemaciclib + ET was sensitive to assumptions concerning the persistence of long-term treatment effects. When assuming no waning of treatment effect, the ICER for abemaciclib + ET decreased to $122,027 per QALY gained compared with ET alone. When assuming no further effect beyond the duration of the MonarchE trial (median follow up: 54 months), the ICER for abemaciclib + ET increased to $167,833 per QALY gained compared with ET alone.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the sponsor may have underestimated the proportion of patients at high risk of recurrence based on clinicopathological features, the proportion of patients estimated to receive CDK4/6 inhibitor in the eligible population and the Ki-67 testing rate, the proportion of patients potentially eligible as Cohort 2 (through Ki 67 testing and by scoring ≥ 20%), the market shares and uptake for the reference and new drug scenarios, and the peak market share assumptions. Additionally, costs with Ki 67 testing and adjuvant olaparib as a comparator were omitted from the budget impact analysis.

CADTH conducted re-analyses of the BIA by adjusting the proportion of patients estimated to be at high risk of recurrence based on clinicopathological features, the proportion of patients potentially eligible as Cohort 2 (through Ki 67 testing and by scoring ≥ 20%), the proportion of patients estimated to be treated with CDK4/6 inhibitor in the eligible population and adjusting the peak market shares.

Based on the CADTH base case, the estimated budget impact associated with the reimbursement of abemaciclib + ET for the expanded Health Canada indication (i.e., for patients meeting criteria for Cohort 1 or Cohort 2 of the MonarchE trial) is expected to be $11,905,600 in Year 1, $75,275,792 in Year 2, $140,804,210 in Year 3, for a three-year budgetary impact of $227,985,601.

CADTH conducted scenario analyses to address uncertainty using alternative Ki 67 testing rates, maintaining the sponsor's original assumptions for market shares in the reference scenario, removing Cohort 2 patients from the indicated population, maintaining the sponsor's original assumption for CDK 4/6 inhibitor penetrance, and exploring different estimates for the proportion of Cohort 1 patients that are at a high risk for recurrence based on clinicopathological features. CADTH reanalysis indicated that the budgetary impact may range between a three to a six-fold increase from what the sponsor originally estimated. These estimates remain uncertain as testing costs were not included in the analysis.

pCODR Expert Review Committee (pERC) Information

Members of the Committee:

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Phillip 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: August 14, 2024

Regrets

3 of the expert committee members did not attend.

Conflicts of Interest

None