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## Reimbursement Recommendation

# Abemaciclib (Verzenio)

**Indication:** In combination with endocrine therapy for the adjuvant treatment of adult patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative, node-positive, early breast cancer at high risk of disease recurrence based on clinicopathological features

**Sponsor:** Eli Lilly Canada Inc.

**Final recommendation:** Reimburse with conditions

# Summary

## What Is the Canada's Drug Agency Reimbursement Recommendation for Verzenio?

Canada's Drug Agency recommends that public drug plans reimburse Verzenio in combination with endocrine therapy for the adjuvant treatment of adults with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive, early-stage breast cancer at high risk of recurrence based on clinicopathological features 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 estrogen and progesterone hormones, tests negative for the HER2 protein, has been removed by surgery, and is at high risk of coming back based on clinicopathological features, including 4 or more positive axillary lymph nodes (ALNs), or 1 to 3 positive ALNs plus histologic grade 3 disease, or 1 to 3 positive ALNs plus a tumour size of 5 cm or more, or 1 to 3 positive ALNs plus a Ki-67 score of 20% or more (if tumour size is < 5cm and disease is not grade 3).

### What Are the Conditions for Reimbursement?

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

### Why Did We Make This Recommendation?

- Evidence from a clinical trial demonstrated that patients treated with Verzenio in combination with endocrine therapy experienced a delayed return of cancer. 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, and have manageable side effects. Verzenio may also be more accessible because of its oral route of administration.
- Verzenio, combined with endocrine therapy, is not considered cost-effective compared to endocrine therapy alone. Economic evidence suggests that a 51% price reduction is needed for Verzenio to ensure that it, in combination with endocrine therapy, is cost-effective at a $50,000 per quality-adjusted life-year (QALY) gained threshold.
- Based on public list prices, Verzenio is expected to cost the public drug plans $228,000,000 over the next 3 years.

# Summary

## Additional Information

### What Is Breast Cancer?

Breast cancer begins in the cells of the breasts. Invasive early-stage breast cancer without metastases has spread into the surrounding breast tissue but has not spread to different body parts. More than 90% of patients with HR-positive, HER2-negative early-stage breast cancer survive at least 5 years.

### Unmet Needs in Breast Cancer

Patients with early-stage breast cancer removed by surgery but at a high risk of coming back need treatment options that prevent or delay the return of the cancer, 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 $6,264 per patient per 28 days. The cost per patient of 28-day Verzenio, combined with endocrine therapy, ranges between $6,274 and $6,302.

## Recommendation

The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that abemaciclib in combination with endocrine therapy (abemaciclib + ET) be reimbursed for the adjuvant treatment of adults with HR-positive, HER2-negative, node-positive, early-stage breast cancer at high risk of 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 = 5,637 patients) demonstrated that adjuvant treatment with abemaciclib + ET resulted in added clinical benefit when compared with adjuvant ET alone in adults with HR-positive, HER2-negative, node-positive, early-stage breast cancer at high risk of recurrence based on clinicopathological features (including ≥ 4 positive ALNs, or 1 to 3 positive ALNs plus histologic grade 3 disease, or 1 to 3 positive ALNs plus a tumour size of ≥ 5 cm, or 1 to 3 positive ALNs plus a Ki-67 score ≥ 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 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 (TEAEs) 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 (AEs), consistent with previously reported events associated with abemaciclib + 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 ETs provides alternate treatment options to eligible patients who do not tolerate treatments such as aromatase inhibitors (AIs) plus ovarian function suppression (OFS). pERC agreed with the clinical experts that abemaciclib plus tamoxifen could be an alternative in patients who are premenopausal, in which case, OFS can also be used but is not required.

Using the sponsor-submitted price for abemaciclib + ET and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio for abemaciclib + ET was $133,903 per QALY gained compared with ET alone. At this incremental cost-effectiveness ratio, abemaciclib + ET is not cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained for the adjuvant treatment of adults with HR-positive, HER2-negative, node-positive, early-stage breast cancer at high risk of 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 abemaciclib + ET should be initiated in patients who have:<br>1.1. confirmed HR-positive, HER2-negative resected invasive early-stage breast cancer without metastases **and**<br>1.2. fulfill 1 of the following:<br>1.2.1. pathological tumour involvement in ≥ 4 ipsilateral ALNs **or**<br>1.2.2. pathological tumour involvement in 1 to 3 ALNs **and** at least 1 of the following criteria:<br>1.2.2.1. grade 3 disease<br>1.2.2.2. primary tumour size ≥ 5 cm<br>1.2.2.3. Ki-67 index score of ≥ 20%<br>1.3. have undergone definitive surgery of primary breast tumour within 16 months of initiating treatment. | Evidence from the MonarchE trial demonstrated that abemaciclib + ET resulted in a statistically and clinically significant improvement in IDFS in patients with the characteristics listed in the condition. | pERC recognized that the drug plans need to address the availability of Ki-67 testing to implement reimbursement of abemaciclib + ET for patients with 1 to 3 positive ALNs plus a Ki-67score ≥ 20%. Patients with 1 to 3 positive ALNs with grade 3 disease or with a primary tumour size ≥ 5 cm do not require Ki-67 testing. |
| 1.4. Patients must not have metastatic disease. | — | pERC discussed that for patients who do not have metastatic disease, eligibility to receive abemaciclib therapy should be based on the previously outlined initiation criteria and the patient's ability to undergo definitive surgery as determined by the attending clinician. |
| **Discontinuation** | | |
| 2. Abemaciclib, in combination with endocrine therapy, should be discontinued upon the occurrence of any of the following:<br>• disease recurrence<br>• 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 per standard clinical practice. | This condition is based on the opinion of the clinical experts. | — |
| 4. Abemaciclib should be reimbursed for a maximum of 2 years (150 mg orally twice daily). ET can be continued beyond this time. | Patients in the MonarchE trial were treated with abemaciclib 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 abemaciclib is interrupted or delayed in the absence of disease progression, it would be reasonable to resume therapy and administer the remaining doses of abemaciclib to complete 2 years of treatment. The decision to resume |

| Reimbursement condition | Reason | Implementation guidance |
|---|---|---|
| | | therapy should be at the treating clinician's discretion. |
| **Prescribing** | | |
| 5. Treatment should be prescribed by clinicians with expertise and experience treating early-stage breast cancer. Treatment should be given in outpatient clinics by qualified practitioners with expertise in systemic therapy delivery. | This condition is 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. Abemaciclib + ET should only be reimbursed when administered together. | No data were identified supporting the efficacy and safety of abemaciclib + ET when combined with additional anticancer drugs or when abemaciclib is used as monotherapy. | ET can continue as monotherapy after the 2 years of abemaciclib treatment. |
| **Pricing** | | |
| 8. A reduction in price | The ICER for abemaciclib + ET is $133,903 per QALY gained compared to ET alone.<br>A price reduction of 51% for abemaciclib would be required for abemaciclib + ET to achieve an ICER of $50,000 per QALY gained compared to ET alone. Because of 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 abemaciclib + ET must be addressed. | At the submitted price, the incremental budget impact of abemaciclib + ET is expected to be greater than $40,000,000 in years 2 and 3. | — |
| 10. The feasibility of the adoption of abemaciclib + 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. | — |

ALN = axillary lymph node; CDA-AMC = Canada's Drug Agency; 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.

## Discussion Points

- pERC discussed improvement in health-related quality of life (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 Grading of Recommendations, Assessment, Development and Evaluation (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 HRQoL.
- 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 end point 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-positive, HER2-negative 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 to 3 positive ALN plus a Ki-67 score of 20% or higher (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 clinical practice in Canada is currently limited because of 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, which was to reimburse abemaciclib + ET for the adjuvant treatment of adults with HR-positive, HER2-negative, node-positive, early-stage breast cancer at high risk of recurrence based on clinicopathological features and a Ki-67 score of 20% or higher. The current recommendation does not require Ki-67 testing in patients with 4 or more positive ALNs, or 1 to 3 positive ALNs plus histologic grade 3 disease, or 1 to 3 positive ALNs plus a tumour size of 5 cm or more.
- pERC discussed that using olaparib versus abemaciclib in patients with deleterious or suspected deleterious germline *BRCA1*- or *BRCA2*-mutated disease. The committee noted that such patients will qualify for abemaciclib if they meet the eligibility 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*- or *BRCA2*-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 women in Canada. 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 females). In patients with HR-positive, HER2-negative early-stage breast cancer, the 5-year survival rate is greater than 90%. Although patients with early-stage breast cancer have a promising 5-year survival prognosis, a subset of up to 20% to 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). HR-positive breast cancers that express ER or PR, or both, are the most prevalent type of breast cancer. Overexpression of the HER2 oncogene, which belongs to the epidermal growth factor receptor family and enables constitutive activation of growth factor signalling and triggering of breast cancer cell survival, proliferation, and invasion, is associated with poor prognosis. 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 patients with distant metastatic disease, early-stage breast cancer is potentially curable.

Risk factors for recurrence include large tumour size, higher degree of involvement of ALNs, high histologic grade, 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 clinical practice in Canada is currently limited because of variability in routine testing and lack of standardized laboratory assays.

## Sources of Information Used by the Committee

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

- a review of 1 randomized, open-label trial clinical study in patients with HR-positive, HER2-negative, node-positive, early-stage 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 the public drug plans and cancer agencies that participate in the Canada's Drug Agency 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 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 that responded to our call for input and from clinical experts we consulted for the purpose of this review.

## Patient Input

Two patient groups, CBCN and Rethink, submitted patient input for this review. According to CBCN, a diagnosis of early-stage HR-positive, HER2-negative 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 that current treatment for HR-positive, HER2-negative early-stage 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 are of the greatest concern for patients with early-stage breast cancer, and patients have an expectation of treatment to offer a good quality of life. Patients who had experience with abemaciclib indicated that they were willing to try it because it 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 of 20% or greater will remove a barrier to care for patients because of inequitable access to Ki-67 testing across Canada.

## Clinician Input

### Input From Clinical Experts We Consulted

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 OFS plus AI unless contra-indicated or not tolerated. The clinical experts also indicated that despite the previously discussed current treatments, 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 we consulted noted that, for adjuvant therapies, the goal is to improve survival (preferably OS, but IDFS and distant relapse-free survival [DRFS] are also used) and to decrease the risk of recurrence.

### Clinician Group Input

Clinician group input was received from the Ontario Health – Cancer Care Ontario Breast Cancer Drug Advisory Committee, with 5 clinicians contributing to the input. The clinician group noted that despite the advances of treatment in HR-positive, HER2-negative breast cancer, 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 patients who are considered high risk following surgery and chemotherapy (if applicable). The clinician group input indicated that patients best suited for treatment with abemaciclib would be those with HR-positive, HER2-negative early-stage breast cancer at high risk of recurrence who have node-positive disease; this 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 indicated that no extra imaging is needed to assess treatment response, but patients would need extra monitoring for hematologic toxicity and diarrhea; as well as additional support from oncology pharmacists and nursing. 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 reimbursement review process.

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

| Drug program implementation questions | Clinical experts response and comments |
|---|---|
| **Relevant comparators** | |
| Abemaciclib is currently funded in jurisdictions for use in combination with ET for the adjuvant treatment of adults with HR-positive, HER2-negative, node-positive, early-stage breast cancer at high risk of disease recurrence based on clinicopathological features and a Ki-67 score of 20% or greater. This submission represents a criteria modification and/or 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]).<br>Removing the Ki-67 requirement will not likely impact current funding and/or implementation processes for abemaciclib but would allow for more patients to be eligible. PAG noted that approximately 1 out of 3 patients in the MonarchE trial had a Ki-67 score < 20%.<br>The current indication for abemaciclib for HR-positive, HER2-negative early-stage breast cancer requires initiation within 16 months of definitive surgery, per the MonarchE trial. | Both clinical experts agree with this statement. They noted that current processes would omit accessing Ki-67 testing in patients with ≥ 4 positive ALNs or 1 to 3 positive ALNs plus histologic grade 3 disease, or 1 to 3 positive ALN plus a tumour size of ≥ 5 cm. However, for patients with 1 to 3 positive ALNs, histologic grade 1 or 2 disease, a tumour size < 5 cm, and a Ki-67 score ≥ 20% (described as cohort 2 in the MonarchE trial and representing approximately 10% of the included participants) who require access to abemaciclib, ongoing access to Ki-67 testing is still required.<br>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 those with a *BRCA* mutation who are also eligible for adjuvant olaparib.<br><br>pERC agreed with the clinical experts' responses, noting that the committee was unaware of evidence supporting drug sequencing of abemaciclib and olaparib. |

| Drug program implementation questions | Clinical experts response and comments |
|---|---|
| **Considerations for initiation of therapy** | |
| **Disease diagnosis, scoring, or staging for eligibility**<br>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.<br>pERC agreed with the clinical experts' responses. |
| **Eligibility for re-treatment**<br>Those with CDK 4 and 6 inhibitors are eligible for re-treatment in the advanced and/or metastatic disease setting provided there was at least a 6-month interval between any prior abemaciclib for HR-positive, HER2-negative early-stage breast cancer and the development of disease recurrence. | One clinical expert indicated that this is a reasonable approach that many clinicians would use in practice, analogous with other adjuvant situations.<br>pERC agreed with the clinical experts' responses. |
| **Funding algorithm** | |
| Removal of the Ki-67 requirement would be required. | Both clinical experts indicated that it would not be removed entirely, as patients with 1 to 3 ALNs would still need a Ki-67 score ≥ 20% to be eligible if they did not have histologic grade 3 disease or a tumour size of ≥ 5 cm. 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 to 3 positive ALNs if they also had histologic grade 3 disease or a tumour size of ≥ 5cm.<br>pERC agreed with the clinical experts' responses. |
| **System and economic issues** | |
| **Concerns regarding the anticipated budget impact and sustainability**<br>This expands the potentially eligible population for adjuvant abemaciclib, which represents an uncertain magnitude of impact to the budget. PAG notes that approximately 81% of patients in the MonarchE trial completed 2 years of abemaciclib and approximately 1 out of 3 of patients in the MonarchE trial had a Ki-67 score of < 20%. PAG is interested in knowing both the economic (i.e., cost-effectiveness) and budget impact to public drug plans by removing the Ki-67 requirement. | 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 [the trade name for trastuzumab deruxtecan]). Given that these patients, on average, live 5 years with metastatic disease and require treatment during that time, including CDK 4 or 6 inhibitors, then later lines of therapy and supportive care, the total time on treatment is less in this adjuvant setting. The NATALEE study[48] included 1 to 3 ALNs regardless of Ki-67 score. The clinical experts' concern is that we do not exclude patients who would derive a benefit.<br>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 score in cohort 1). However, given that cohort 2 also benefited, we would want a way to access the drug for those with 1 to 3 positive ALNs, if disease is not grade 3 or tumour size is < 5 cm, and a Ki-67 score ≥ 20%.<br>The other clinical expert indicated that all patients who meet the MonarchE trial criteria must have access to abemaciclib irrespective of the budget.<br>pERC agreed with the clinical experts' responses. |

ADC = antibody drug conjugates; ALN = axillary lymph node; CDK = cyclin dependent kinase; ET = endocrine therapy; HER2 = human epidermal receptor 2; HR = hormone receptor; PAG = Provincial Advisory Group; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; SG = sacituzumab govitecan.

# 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 III randomized controlled trial that compared the efficacy and safety of abemaciclib + ET to ET alone in the adjuvant treatment of patients with HR-positive, HER2-negative, node-positive, early-stage breast cancer who completed definitive locoregional therapy and were at high risk of disease recurrence based on clinicopathological features or who had 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 2 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 ALNs and a high Ki-67 score (≥ 20%). The primary efficacy end point was IDFS and the secondary end points included DRFS, OS, HRQoL (e.g., FACT-B), and harms outcomes. The results of IDFS, DRFS, and OS presented in this report are based on the OS interim analysis 3 (IA3) data cut-off after a median follow-up of 54 months. HRQoL measurements (e.g., FACT-B) and health care resource utilization (e.g., hospitalizations, transfusions) are based on the OS interim analysis 2 (IA2) data cut-off after a median follow-up of 42 months. Harms data reported in this review were based on either the OS IA2 or IA3 data cut-off.

### Efficacy Results

**IDFS:** In the intention-to-treat (ITT) population (cohort 1 + cohort 2 of the 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 + ET arm and 585 (20.7%) in the ET alone arm (hazard ratio = 0.680; 95% CI, 0.599, 0.772; P < 0.00001). The between-group differences in IDFS for abemaciclib + ET versus ET alone were 2.8% (95% CI, 1.3% to 4.3%) at 24 months; 4.8% (95% CI, 3.0% to 6.6%) at 36 months; and 7.6% (95% CI, 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 we consulted. Subgroup analyses of OS were largely consistent with the primary analysis.

**DRFS:** 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 were a total of 345 events (12.3%) in the abemaciclib + ET arm and 501 (17.7%) in the ET alone arm (hazard ratio = 0.675; 95% CI, 0.588, 0.774; P < 0.00001). The between-group differences in DRFS for abemaciclib + ET versus ET alone were 2.5% (95% CI, 1.1% to 3.9%) at 24 months; 4.1% (95% CI, 2.4% to 5.8%) at 36 months; and 6.7% (95% CI, 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 we consulted. Subgroup analyses of DRFS were largely consistent with the primary analysis.

**OS:** At a median follow-up of 54 months (OS IA3 cut-off), the 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 ET alone. The between-group difference in OS probability for abemaciclib + ET versus ET alone was 1.1% (95% CI, −0.8% to 3.0%) at 60 months. This 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.

**HRQoL:** At OS IA2 (median follow-up: 42 months), in the safety population for abemaciclib + ET versus ET alone, the least square mean 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.

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

### Harms Results

At OS IA3, most patients in both treatment arms experienced AEs (98.4% in the abemaciclib + ET arm and 88.9% in the ET alone arm). 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 alone arm. The most common AEs (> 20%) that occurred more often in the ET alone arm than in the abemaciclib + ET arm were arthralgia and hot flush. Grade 5 TEAEs were reported rarely (abemaciclib + ET versus ET alone: 0.6% versus 0.4%). At OS IA3, numerically more patients experienced serious AEs in the 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 than in the ET alone arm (18.5% versus 1.1%). Diarrhea was the most common AE to cause treatment discontinuation.

The clinical experts we consulted for this review indicated that, of the reported AEs of special interest, venous thromboembolic events (VTEs) and interstitial lung disease (ILD) and/or 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 alone arm. Any grade of ILD and/or pneumonitis occurred in 3.3% of patients in the abemaciclib + ET arm and 1.3% in the ET alone arm. It indicated that the evidence of combination of

abemaciclib + ET likely results in little-to-no clinically important difference on VTE or ILD and/or pneumonitis when compared with ET monotherapy.

In summary, according to the clinical experts we consulted for this review, the harms results for abemaciclib + ET in the MonarchE trial were generally consistent with those previously reported for abemaciclib + 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, clinically manageable with comedications and/or dose modifications in most patients, and acceptable in the early-stage breast cancer 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 end point. Objective outcomes and validated health-related outcomes were assessed. The statistical approach of gatekeeping to sequentially test the primary and secondary end points was acceptable to account for multiple testing across these analyses. The potential limitations are discussed in the following.

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 end points, patient-reported outcomes, and HRQoL. However, there was minimal evidence of bias for the objective end points.

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

IDFS and DRFS are considered early indicators of a patient's survival, especially for less advanced conditions in which longer survival is expected. OS data in the MonarchE trial 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 are 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 alone arm suggested that a survival signal favouring abemaciclib may be emerging.

Regarding 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 after treatment discontinuation. As a result, there is a risk of bias because of missing outcomes data, as the missing at random assumption underlying the analysis may not be plausible.

The clinical experts we consulted noted that patients in the trial are about a decade younger than patients with early-stage breast cancer encountered in clinical practice who are generally diagnosed and treated in their early to mid-sixties; however, this may be explained by high-risk features potentially being more

prevalent in younger patients. The clinical experts we consulted also noted that the inclusion of patients who were younger and healthier than those seen in clinical practice may have led to fewer harms, where more AEs were manageable and reversible. 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 to 3 positive ALNs. Nevertheless, the clinical experts stated that inclusion of patients who are younger than those seen in clinical practice and the high proportion of patients with prior chemotherapy are unlikely to have a significant impact on the generalizability of the findings to clinical practice in Canada.

Overall, the clinical experts we consulted for this review indicated that the patients included in the MonarchE trial are well representative of patients in clinical practice in Canada so a generalizability concern is unlikely.

### Conclusions

Evidence from the MonarchE trial showed that abemaciclib + ET demonstrated a clinically meaningful benefit compared to ET alone in improving IDFS and DRFS for the adjuvant treatment of adults with HR-positive, HER2-negative, node-positive, early-stage breast cancer at high risk of 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 + ET may not result in a clinical meaningful difference on 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 early-stage breast cancer setting. The safety profile of abemaciclib + ET in the MonarchE trial was generally consistent with known safety profile previously reported for abemaciclib monotherapy and ET alone. 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<br>Markov model |
| **Target population** | Patients with HR-positive, HER2-negative, node-positive, early-stage breast cancer at high risk of recurrence |
| **Treatment** | Abemaciclib + ET<br>ET comprises a combination of physician's choice therapies, including anastrozole (22%), exemestane (8%), letrozole (38%), or tamoxifen (33%). |

| Component | Description |
|---|---|
| **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, disease recurrence, or unacceptable toxicity. |
| **Submitted price** | Abemaciclib<br>50 mg: $112.58 per tablet<br>100 mg: $111.54 per tablet<br>150 mg: $111.86 per tablet |
| **Submitted treatment cost** | The 28-day cost of abemaciclib is $6,264 per patient.<br>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-off of July 3, 2023) |
| **Key limitations** | • The sponsor used a “fixed payoff” approach to apply costs and effects to patients in the model, which we could not fully validate. 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 us as part of the current review — these results could not be validated.<br>• The sponsor's base case predicts a survival benefit with abemaciclib + ET compared to ET (incremental LYs: 2.19) over a 49-year horizon; however, no difference in survival was observed in the MonarchE trial (median follow-up: 54 months). The clinical experts we consulted indicated that it is uncertain whether and to what extent delayed disease progression will translate to gains in OS.<br>• 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 the clinical experts because of 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.<br>• 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. The clinical experts indicated that differences between the ATAC and MonarchE trials (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.<br>• The sponsor assumed that patients with metastatic recurrence after adjuvant abemaciclib + ET would not receive subsequent treatment with a CDK 4 or 6 inhibitor, which underestimates the cost of treating metastatic recurrence and biases the ICER in favour of abemaciclib + ET. The clinical experts indicated that patients with ET-sensitive disease (i.e., recurrence at least 6 months after completing adjuvant treatment) would receive a CDK 4 or 6 inhibitor as part of standard of care in the metastatic setting.<br>• Adjuvant olaparib, a treatment prescribed in Canada for a subset of patients with deleterious or suspected deleterious germline *BRCA1*- or *BRCA2*-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. |

| Component | Description |
|---|---|
| | • We also corrected the sponsor's submitted base case by revising the price of the abemaciclib 150 mg tablet, which was incorrectly programmed into the submitted model. |
| **CDA-AMC reanalysis results** | • Our base case was derived by making changes to the following model parameters: using independent models that assume nonproportional hazards to extrapolate IDFS; adopting alternative parametric distributions to extrapolate IDFS; assuming treatment effectiveness waning starts at year 7 and ends by year 10 after treatment initiation; and revising the proportion of patients with metastatic ET-sensitive disease who receive CDK 4 or 6 inhibitors in the abemaciclib + ET model arm.<br>• In our 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.<br>• 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. |

CDK = cyclin dependent kinase; ET = endocrine therapy; HER2 = human epidermal receptor 2; HR = hormone receptor; ICER = incremental cost-effectiveness ratio; PAG = Provincial Advisory Group; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; SG = sacituzumab govitecan.

## Budget Impact

We identified the following key limitations with the sponsor's analysis: the sponsor may have underestimated the proportion of patients at high risk of disease recurrence based on clinicopathological features, the proportion of patients estimated to receive CDK 4 or 6 inhibitors 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.

We conducted reanalyses of the budget impact analysis 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 CDK 4 or 6 inhibitors in the eligible population, and the peak market shares.

Based on our base case, the estimated budget impact associated with the reimbursement of abemaciclib + ET for the expanded Health Canada indication (i.e., for patients meeting the 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 3-year budget impact of $227,985,601.

We 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 patients from cohort 2 from the indicated population, maintaining the sponsor's original assumption for CDK 4 or 6 inhibitor penetrance, and exploring different estimates for the proportion of patients in cohort 1 who are at a high risk for disease recurrence based on clinicopathological features. Our reanalysis indicated that the budget impact

may range between a 3- to 6-fold increase from what the sponsor originally estimated. These estimates remain uncertain as testing costs were not included in the analysis.

# 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**: Three of the expert committee members did not attend.

**Conflicts of interest**: None

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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.