Canada's Drug and
Health Technology Agency

Provisional Funding Algorithm: Proposed Scope

Indication: Hormone receptor–positive, human epidermal growth factor receptor 2–negative breast cancer

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.

1. Background

At the request of the drug programs that participate in the CADTH drug reimbursement review processes, CADTH is convening an implementation advice panel to advise the drug programs on a provisional funding algorithm for drugs used in the treatment of hormone receptor (HR)–positive, human epidermal growth factor receptor 2 (HER2)–negative breast cancer. This advice will be used by the drug programs and the Canadian Association of Provincial Cancer Agencies in the development of their funding criteria. Appendix 1 lists all past CADTH recommendations for drugs in the same therapeutic space. This document outlines a draft scope for the panel discussions, including which drugs are under consideration and questions to be addressed by the panel.

2. Consultation Process and Objectives

The implementation advice panel will be comprised of Canadian clinical specialists with expertise in the diagnosis and management of patients with HR-positive, HER2-negative breast cancer. The objective of the panel will be to provide advice to the participating drug programs regarding the funding algorithm and any related implementation questions. In addition to the clinical panellists and CADTH staff, representatives from public drug programs, the pan-Canadian Pharmaceutical Alliance, and the Canadian Association of Provincial Cancer Agencies may participate in the discussion and provide input in advance of the meeting on the topics for discussion. For more information on the implementation advice process, please refer to *Procedures for CADTH Drug Reimbursement Reviews*.

The CADTH Provincial Advisory Group raised the following issues pertaining to the development of a provisional funding algorithm. These are to be addressed by the implementation advice panel.

Implementation Issues

1. Sequencing of CDK 4/6 inhibitors (abemaciclib, palbociclib, ribociclib) and other targeted therapy and endocrine therapy is based on progression timelines:
   a. if progression occurs within or after 6 months since the completion of 2-year adjuvant therapy with CDK 4/6 inhibitor (abemaciclib)
   b. if progression occurs within or after 12 months since the completion of 5-year endocrine therapy
2. Guidance on how to handle treatment interruption of CDK 4/6 inhibitors in the adjuvant setting (for a maximum duration of 2 years) and/or the subsequent use of CDK 4/6 inhibitors with progression to the advanced or metastatic stage
3. Sequencing of the mammalian target of rapamycin inhibitor (i.e., everolimus with exemestane) with generic everolimus now available in Canada

3. Feedback Opportunities

CADTH welcomes stakeholder feedback from patient and clinician groups as well as manufacturers whose product(s) may be impacted by changes in the funding algorithm. Stakeholders are invited to provide comments and/or complementary information, including published evidence on treatment sequencing, if available, in support of algorithm development. The feedback will be considered in the finalization of the implementation advice scope.

When ready, a draft provisional funding algorithm report will be posted for stakeholder feedback. The final provisional funding algorithm report will be posted on the CADTH website.

4. Drugs

Table 1: List of Drugs Under Consideration

Generic name (brand name)	Manufacturer	Indication(s)
Targeted therapy		
mTOR inhibitor		
Everolimus	Novartis Pharmaceuticals Canada Inc.	**Advanced Breast Cancer** For treatment of postmenopausal women with hormone receptor-positive advanced breast cancer (HR+ advanced BC) in combination with exemestane, after progression or recurrence (failure) on NSAI therapy
CDK4/6 Inhibitor		
Abemaciclib (Verzenio)	Eli Lilly Canada Inc.	**Early Breast Cancer:** In combination with endocrine therapy for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive, early breast cancer at high risk of disease recurrence based on clinicopathological features and a Ki-67 score of at least 20% **Advanced or Metastatic Breast Cancer:** For the treatment of hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer: • In combination with an aromatase inhibitor in postmenopausal women as initial endocrine-based therapy. (First-line systemic therapy/Endocrine Sensitive) • In combination with fulvestrant in women with disease progress following endocrine therapy (Endocrine-Resistant). Pre- or perimenopausal women must also be treated with a gonadotropin-releasing hormone agonist.
Palbociclib (Ibrance)	Pfizer Canada Inc.	**Advanced or Metastatic Breast Cancer:** In combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer whose disease

Generic name (brand name)	Manufacturer	Indication(s)
		progressed after prior endocrine therapy, pre- or perimenopausal women must also be treated with a luteinizing hormone releasing hormone (LHRH) agonist.
Ribociclib (Kisqali)	Novartis Pharmaceuticals Canada Inc.	**Advanced or Metastatic Breast Cancer:** In combination with fulvestrant for the treatment of post-menopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer 9ABC), as initial therapy or following disease progression.
Endocrine therapy		
Aromatase inhibitor		
Anastrozole (Arimdex)	AstraZeneca and generics	The adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer. Hormonal treatment of advanced breast cancer in postmenopausal women.
Exemestane (Aromasin)	Pfizer Canada Inc. and generics	The sequential adjuvant treatment of postmenopausal women with estrogen receptor-positive early breast cancer who have received 2-3 years of initial adjuvant tamoxifen therapy. Hormonal treatment of advanced breast cancer in women with natural or artificially induced postmenopausal status whose disease has progressed following antiestrogen therapy.
Letrozole (Femara)	Novartis Pharmaceuticals Canada and generics	The adjuvant treatment of postmenopausal women with hormone receptor-positive invasive early breast cancer The extended adjuvant treatment of hormone receptor positive invasive early breast cancer in postmenopausal women who have received approximately 5 years of prior standard adjuvant tamoxifen therapy. First-line therapy in postmenopausal women with advanced breast cancer. The hormonal treatment of advanced/metastatic breast cancer after relapse or disease progression, in women with natural or artificially-induced postmenopausal endocrine status, who have previously been treated with anti-estrogens.
Selective Estrogen Receptor Modulators		
Tamoxifen	Generics	The adjuvant treatment of early breast cancer in women with estrogen receptor positive tumours. The treatment of women with hormone responsive locally advanced/ metastatic breast cancer.
Estrogen Receptor Antagonists		
Fulvestrant (Faslodex)	AstraZeneca and generics	Treatment of estrogen receptor-positive, human epidermal growth receptor 2 (HER2)- negative locally advanced or metastatic breast cancer in postmenopausal women not previously treated with endocrine therapy, or Hormonal treatment of locally advanced or metastatic breast cancer in postmenopausal women, regardless of age, who have disease progression following prior anti-estrogen therapy

Appendix 1: CADTH Recommendations on Drugs for HR-Positive, HER2-Negative Breast Cancer

Table 2: Related CADTH Recommendations

Generic name (brand name)	Date of recommendation	Recommendation

Abemaciclib (Verzenio)	Oct 18, 2022	The CADTH pCODR Expert Review Committee (pERC) recommends that abemaciclib (ABE) in combination with endocrine therapy (ET) be reimbursed for the adjuvant treatment of adult patients with hormone receptor (HR)–positive, human epidermal growth factor receptor 2 (HER2)–negative, node-positive early breast cancer at high risk of disease recurrence based on clinicopathological features and a Ki-67 score of at least 20% only if the following conditions are met:
		• Treatment with ABE-ET should be initiated in patients who have:
		  ○ Confirmed HR-positive, HER2-negative, resected invasive early breast cancer without metastases
		  ○ Ki-67 index score of ≥20%
		  ○ Fulfill 1 of the following:
		  ▪ Pathological tumour involvement in ≥4 ipsilateral axillary lymph nodes
		  ▪ Or pathological tumour involvement in 1 to 3 ipsilateral axillary lymph node(s) AND at least 1 of the following criteria:
		• Grade 3 disease
		• Primary tumour size ≥ 5 cm
		  ○ Undergone definitive surgery of primary breast tumour within 16 months of initiating treatment
		• Patients must not have any of the following:
		  ○ Metastatic disease
		  ○ Inflammatory breast cancer
		  ○ Prior treatment with a CDK4/6 inhibitor
		• Abemaciclib in combination with endocrine therapy should be discontinued upon the occurrence of any of the following:
		  ○ Disease recurrence
		  ○ Unacceptable toxicity
		• Patients should be assessed for disease recurrence as per standard clinical practice.
		• Abemaciclib should be reimbursed for a maximum of 2 years (150mg orally twice daily)
		  ○ Endocrine therapy can be continued beyond this time
		• Treatment should be prescribed by clinicians with expertise and experience in treating early breast cancer. Treatment

Generic name (brand name)	Date of recommendation	Recommendation
		should be given in outpatient clinics by qualified practitioners with expertise in systemic therapy delivery. • Ongoing monitoring to assess patients for toxicity is required. • Abemaciclib with endocrine therapy should only be reimbursed when administered in combination. • A reduction in price • The feasibility of adoption of abemaciclib must be addressed.
Abemaciclib (Verzenio)	July 5, 2019	pERC issued separate recommendations for first line systemic therapy/endocrine sensitive patients and for endocrine-resistant patients in the advanced or metastatic setting. **First-Line Systemic Therapy/Endocrine Sensitive (First-line systemic therapy or endocrine sensitive in the advanced or metastatic setting and at least 12 months since completing adjuvant hormone therapy)** pERC conditionally recommends the reimbursement of abemaciclib in combination with non-steroidal aromatase inhibitor (NSAI) for the treatment of HR+, HER2- advanced or metastatic breast cancer in patients as initial endocrine-based therapy (i.e., who have not received any prior treatment for advanced or metastatic disease) if the following condition is met: • Cost-effectiveness being improved to an acceptable level. • The public drug plan cost of abemaciclib should not exceed the public drug plan cost of other available cyclic-dependent kinase (CDK) 4/6 inhibitors **Endocrine-Resistant (progressive disease after prior endocrine therapy in the metastatic setting)** pERC conditionally recommends the reimbursement of abemaciclib for the treatment of HR+, HER2- advanced or metastatic breast cancer, in combination with fulvestrant in patients with disease progression following endocrine therapy if the following condition is met: • Cost-effectiveness being improved to an acceptable level.
Alpelisib (Piqray)	Feb 11, 2022	pERC recommends that alpelisib, in combination with fulvestrant, not be reimbursed for the treatment of postmenopausal women, and men, with hormone receptor-positive, human epidermal growth factor 2 (HER2)negative, PIK3CA-mutated advanced or metastatic breast cancer after disease progression following an endocrine-based regimen with a cyclin-dependent kinase 4 and 6 (CDK4/5) inhibitor.
Ribociclib (Kisqali)	April 22, 2020	pERC conditionally recommends the reimbursement of ribociclib (Kisqali) in combination with fulvestrant as initial therapy or following disease progression in aptients with HR-positive, HER2-negative ABC if the following conditions are met: • Cost-effectiveness improved to an acceptable level

Generic name (brand name)	Date of recommendation	Recommendation
		• Feasibility of adoption addressed (budget impact) Eligible patients include men and post-menopausal women who have not received any prior treatment for ABC or have received up to one line of treatment for ABC. Pre-/peri-menopausal women rended post-menopausal, either chemically or surgically, are eligible and should be treated with a luteinizing hormone-release hormone (LHRH) agonist or bilateral salpingo-oophorectomy.
Palbociclib (Ibrance)	May 3, 2019	pERC recommends reimbursement of Palbociclib (Ibrance) in combination with fulvestrant only if the following conditions are met: • Cost-effectiveness is improved to an acceptable level • Feasibility of adoption (budget impact) is addressed Reimbursement should be in combination with fulvestrant for the treatment of patients with HR-positive, HER2-negative locally advanced (aBC) or metastatic breast cancer (mBC) whose disease has progressed after prior endocrine therapy. Patients should have good performance status and can be of any menopausal status (Perimenopausal and premenopausal women must be treated with an LHRH agonist). Treatment should continue until unacceptable toxicity or disease progression.
Everolimus (Afinitor)	March 25, 2013	pERC recommends funding everolimus (Afinitor) in combination with exemestane, conditional on the cost-effectiveness of everolimus being improved to an acceptable level. Everolimus should be funded for the treatment of hormone-receptor positive, HER2 negative advanced breast cancer, in postmenopausal women with ECOG performance status ≤2 after recurrence or progression following a non-steroidal aromatase inhibitor (NSAI), if the treating oncologist would consider using exemestane, pERC made this recommendation because it was satisfied that there is an overall clinical benefit of everolimus. However, the Committee noted that everolimus could not be considered cost-effective at the submitted price and the Economic Guidance Panel's estimates of the range of incremental cost-effectiveness ratios.