Provisional Funding Algorithm

Indication: Breast cancer that is hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative, with inclusion of HER2 low.

This report supersedes the CDA-AMC provisional funding algorithm report for breast cancer with HR positive, HER2 negative, or HER2 low dated April 2024.

For triple-negative breast cancer, including HR negative HER2 negative and HR negative HER2 low, please refer to the CDA-AMC Provisional Funding Algorithm report dated December 2023.

Please always check Provisional Funding Algorithms to ensure you are reading the most recent algorithm report.

Background

Following a request from jurisdictions, Canada's Drug Agency (CDA-AMC) may design or update an algorithm depicting the sequence of funded treatments for a particular tumour type. These algorithms are proposals for the jurisdictions to implement and adapt to the local context. As such, they are termed "provisional." Publishing of provisional algorithms is meant to improve transparency of the oncology drug funding process and promote consistency across jurisdictions.

Provisional funding algorithms are based on 3 principal sources of information:

- pan-Canadian Oncology Drug Expert Review Committee (pERC) reimbursement recommendations and/or implementation guidance regarding drug place in therapy and sequencing
- implementation advice from panels of clinicians convened by CDA-AMC concerning sequencing of drugs in the therapeutic space of interest
- existing oncology drug reimbursement criteria and legacy funding algorithms adopted by jurisdictional drug plans and cancer agencies.

Note that provisional funding algorithms are not treatment algorithms; they are neither meant to detail the full clinical management of each patient nor the provision of each drug regimen. The diagrams may not contain a comprehensive list of all available treatments, and some drugs may not be funded in certain jurisdictions. All drugs are subject to explicit funding criteria, which may also vary between jurisdictions. Readers are invited to refer to the cited sources of information on the CDA-AMC website for more details.

Provisional funding algorithms also delineate treatment sequences available to patients who were never treated for the condition of interest (i.e., incident population). Time-limited funding of new options for previously or currently treated patients (i.e., prevalent population) is not detailed in the algorithm.

Provisional funding algorithms may contain drugs that are under consideration for funding. Algorithms will not be dynamically updated by CDA-AMC following changes to drug funding status. Revisions and updates will occur only upon request by jurisdictions.

Jurisdictional cancer drug programs requested a provisional funding algorithm on breast cancer with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative or low. However, no outstanding implementation issues were identified, and no additional implementation advice is provided in this report. The algorithm depicted herein is meant to reflect the current and anticipated funding landscape based on the previously mentioned sources of information.

History and Development of the Provisional Funding Algorithm

In the first panel algorithm in March 2023, CADTH developed the first provisional funding algorithm incorporating recommendations the following implementation issues:

- selection guidance for treatment options in HR-positive, HER2-negative breast cancer
- re-treatment with a cyclin-dependent kinase (CDK) 4 or 6 inhibitor
- sequencing with everolimus and exemestane

- treatment interruption of CDK 4 or 6 inhibitors within 2 years of adjuvant setting.

A second panel algorithm was convened in December 2023 and CADTH updated the provisional funding algorithm to incorporate recommendations on the following implementation issues:

- sequencing guidance on the use of olaparib and abemaciclib in the adjuvant setting of HR-positive, HER2-negative breast cancer
- sequencing guidance on the use of trastuzumab deruxtecan in the population of individuals with breast cancer classified as HR positive, HER2 negative, and HER2 low, as well as individuals with breast cancer classified as triple negative (TNBC).

These recommendations are outlined in Table 1.

A rapid algorithm completed in April 2024 incorporated the pERC recommendation on sacituzumab govitecan in the treatment of adults with unresectable locally advanced or metastatic HR-positive, HER2-negative (immunohistochemistry [IHC] 0, IHC 1+, or IHC 2+ with in situ hybridization (ISH) negative) breast cancer who have received endocrine-based therapy and at least 2 additional systemic therapies in the metastatic setting.

For this rapid algorithm, the purpose is to incorporate the latest pERC recommendation on capivasertib in combination with fulvestrant for the treatment of adults with HR-positive, HER2-negative, locally advanced or metastatic breast cancer with 1 or more *PIK3CA, AKT1,* or *PTEN* alterations following progression on at least 1 endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.

Patients who have HR-positive low breast cancer can either be treated following this algorithm (Figure 1 and Figure 2) or the TNBC algorithms (refer to Figure 2 and Figure 3 in the funding algorithm published on December 2023) at their physician's discretion. Note that the individuals treated following the HR-positive, HER2-negative algorithm would become ineligible for funding options in the TNBC setting. Unless new information (e.g., new biopsy results) becomes available to guide different treatment options, individuals should consistently be treated based on the same funding algorithm (e.g., HR-positive, HER2-negative or TNBC, but not switch between the 2 algorithms).

Table 1: Relevant CADTH Recommendations

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
Abemaciclib (Verzenio)	October 22, 2024	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 following conditions are met. 1. Treatment with abemaciclib + ET should be initiated in patients who have: 1.1. Confirmed HR-positive, HER2-negative resected invasive early breast cancer without metastases and

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		1.2. Fulfill 1 of the following: 1.2.1. pathological tumour involvement in ≥ 4 ipsilateral ALNs or 1.2.2. pathological tumour involvement in 1 to 3 ALNs and at least 1 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. 1.4. Patients must not have metastatic disease. 2. Abemaciclib, in combination with endocrine therapy, should be discontinued upon the occurrence of any of the following: 2.1. Disease recurrence 2.2. Unacceptable toxicity 3. Patients should be assessed for disease recurrence as per standard clinical practice. 4. ABE should be reimbursed for a maximum of 2 years (150 mg orally twice daily). ET can be continued beyond this time. 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. 6. Ongoing monitoring to assess patients for toxicity is required. 7. Abemaciclib + ET should only be reimbursed when administered together. 8. A reduction in price 9. The economic feasibility of adoption of abemaciclib + ET must be addressed 10. The feasibility of the adoption of abemaciclib + ET must be addressed **Guidance on sequencing:** • The clinical experts 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, histologic grade 1 or 2 disease, and tumour size < 5cm, and Ki-67 ≥ 20% (described as Cohort 2 in the MonarchE trial and representing ~10% of the included participants), requiring access to abemaciclib ongoing access to Ki-67 testing is still required. • 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. • 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. • 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.

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		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.
Capivasertib (Truqap)	September 18, 2024	pERC recommends that capivasertib in combination with fulvestrant be reimbursed for the treatment of adults with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer with 1 or more *PIK3CA/AKT1/PTEN* alterations following progression on at least 1 endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy only if the following conditions are met. 1. Capivasertib plus fulvestrant should be reimbursed in adults aged 18 years or older who meet all the following criteria: 1.1. documented diagnosis of HR-positive, HER2-negative locally advanced or metastatic breast cancer 1.2. documented evidence of *PIK3CA*, *AKT1* or *PTEN* gene alteration 1.3. received at least 1 line of hormone therapy in the metastatic setting or progressed on adjuvant hormone therapy or within 12 months of adjuvant hormone therapy 1.4. good performance status. 2. Capivasertib plus fulvestrant should not be initiated in patients who have progressed on prior therapy with fulvestrant, received more than 2 lines of hormone therapy, or received more than 1 line of chemotherapy in the metastatic setting. 3. Treatment with capivasertib plus fulvestrant should be discontinued upon the occurrence of any of the following, whichever occurs first: 3.1. disease progression 3.2. unacceptable toxicity 4. Capivasertib plus fulvestrant should be administered by health professionals experienced in management of HR-positive, HER2-negative breast cancer at treatment centres with adequate medical resources and personnel to manage toxicities. 5. Capivasertib should only be reimbursed when administered in combination with fulvestrant. 6. A reduction in price of capivasertib 7. The feasibility of adoption of capivasertib plus fulvestrant must be addressed 8. The organizational feasibility of conducting testing for *PIK3CA/AKT1/PTEN* alterations must be addressed. **Guidance on sequencing:** • The clinical experts noted that treatment with capivasertib plus fulvestrant should continue if patients are clinically responding, and should not continue beyond disease progression or unacceptable toxicities. pERC agreed with the clinical experts. • The clinical experts noted that if fulvestrant is discontinued, treatment with capivasertib as a single agent should not be continued, but if capivasertib is discontinued due to toxicity that cannot be managed with dose reduction or delays, fulvestrant monotherapy can be continued. pERC agreed with the

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		clinical experts. • The clinical experts indicated that patients receiving alternate second- or later-line of therapy who are clinically stable or responding to treatment should not be switched to capivasertib plus fulvestrant, but should be eligible to receive capivasertib plus fulvestrant if they experience disease progression or intolerance, with no prior exposure to fulvestrant. pERC agreed with the clinical experts, but noted that patients who have not progressed on prior therapy with fulvestrant should be eligible. pERC noted that patients with more than 1 line of prior chemotherapy in the metastatic setting should not be eligible. • pERC indicated that patients that did not have capivasertib + fulvestrant available to them second- or third-line, have not had prior fulvestrant, and have had only 1 prior chemotherapy regimen should be eligible on a time limited basis for this therapy. • The clinical experts indicated that NGS is the preferred assay to test for *PIK3CA/AKT1/PTEN* alterations. They also noted that there are other technologies available such as polymerase chain reaction and Sanger sequencing, but NGS is superior because it can test for multiple mutations at the same time. ◦ The clinical experts indicated the optimal time for biomarker testing could be at the time of metastatic diagnosis, and since *PIK3CA/AKT1/PTEN* alterations are considered stable, repeat testing is likely not required. ◦ Additional information regarding testing for *PIK3CA/AKT1/PTEN* alterations is available in the Testing Procedure Assessment Report.
Sacituzumab govitecan (Trodelvy)	February 20, 2024	CADTH recommends that Trodelvy should be reimbursed by public drug plans for the treatment of adult patients with unresectable locally advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (IHC 0, IHC 1+, or IHC 2+/ISH–) breast cancer who have received endocrine-based therapy and at least 2 additional systemic therapies in the metastatic setting, if the following conditions are met: 1. Treatment with sacituzumab govitecan should be initiated in adult patients with unresectable locally advanced or metastatic breast cancer who meet all of the following criteria: 1.1. documented evidence of HR-positive HER2-negative breast cancer 1.2. previously treated with at least 1 taxane, at least 1 prior anticancer hormonal treatment, and at least 1 CDK4/6 inhibitor in any setting. 1.3. refractory to or relapsed after 2 to 4 prior systemic chemotherapy regimens for metastatic disease. 2. Patients must have good performance status. 3. Patients must not have: 3.1. active CNS metastases and/or carcinomatous meningitis 3.2. received prior treatment with a topoisomerase 1 inhibitor as a free form or as part of other formulations 4. Treatment with sacituzumab govitecan should be discontinued upon the occurrence of any of the following: 4.1. disease progression 4.2. unacceptable toxicity attributed to sacituzumab govitecan

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		5. Assessment of disease progression should be based on clinical and radiographic evaluations as per clinical standard of care. 6. Sacituzumab govitecan should only be prescribed by clinicians with expertise and experience in treating breast cancer in approved centres for sacituzumab govitecan. 7. A reduction in price. 8. The feasibility of adoption of sacituzumab govitecan must be addressed. **Guidance on sequencing:** • pERC discussed the place of sacituzumab govitecan in therapy and agreed that to be eligible to receive sacituzumab govitecan patients should be previously treated with endocrine-based therapy and a CDK4/6 inhibitor, and have experienced treatment failure on at least 2 systemic chemotherapy regimens in the metastatic setting, as the TROPiCS-02 trial demonstrated survival benefit with sacituzumab govitecan in these patients. pERC further discussed that patients with low hormone receptor expression (1% to 10% expression by IHC) for whom endocrine therapy is not advised should be eligible to receive sacituzumab govitecan. However, the committee estimated this subgroup of patients to be relatively small in size. pERC acknowledged that, based on the recently published CADTH Provisional Funding Algorithm (PH0033-000; December 7, 2023), clinicians may have an option to treat patients with a low hormone receptor expression using treatment options for HR-positive HER2-negative disease, or those for triple-negative breast cancer, but not both. pERC agreed that neoadjuvant or adjuvant therapy for early-stage disease would qualify as 1 of the required prior chemotherapy regimens if the development of unresectable, locally advanced, or metastatic disease occurred within a 12-month period of the initiation of the therapy. • pERC agreed with the clinical experts that patients who have not received taxanes due to a medical contraindication, should still be considered eligible for sacituzumab govitecan. • The experts pointed out that, although this population is likely small, there may be patients who previously progressed on endocrine therapy and were not able to access CKD4/6 inhibitors before they became covered and are currently on chemotherapy. Ideally, if these patients are well enough, they can be considered for sacituzumab govitecan. • pERC agreed with the experts that consideration should also be given to patients who could not tolerate a CDK4/6 inhibitor or were not able to take it due to medical contraindications. These individuals should not be excluded from consideration for sacituzumab govitecan if they are otherwise fit to receive it. pERC also agreed with the clinical experts that patients who may not have received a prior CDK4/6 inhibitor and no longer eligible for 1 should be considered for a time-limited opportunity to receive sacituzumab govitecan. Acknowledging that the TROPiCS-02 trial excluded patients who received prior treatment with a topoisomerase 1 inhibitor, pERC agreed that considerations should be given to patients who experienced intolerance or severe toxicity to a prior poisomerase inhibitor.
Trastuzumab deruxtecan (Enhertu)	July 18, 2023	The CADTH pCODR Expert Review Committee (pERC) recommends that trastuzumab deruxtecan be reimbursed for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received at least 1 prior line of chemotherapy in the metastatic

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		setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Patients with hormone receptive positive (HR-positive) breast cancer should have received at least 1 and be no longer considered for endocrine therapy. This recommendation is dependent upon the following conditions: 1. Adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have all the following: 1.1. treated with at least 1 prior line of chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy 1.2. patients who are hormone receptive positive must have been treated with at least 1 prior line of endocrine therapy and no longer be considered candidates for endocrine therapy 1.3. good performance status 2. Patients must not have any of the following: 2.1. symptomatic spinal cord compression 2.2. uncontrolled CNS metastases 2.3. current ILD/pneumonitis 3. Trastuzumab deruxtecan must be discontinued upon the occurrence of any of the following: 3.1. progressive disease per mRECIST v 1.1 3.1.1. Assessment for disease progression must be based on clinical and radiographic evaluation every 2 to 3 months, or as per physician's discretion 3.1.2. unacceptable toxicity 4. Trastuzumab deruxtecan must only be prescribed by clinicians with experience and expertise in treating advanced breast cancer in centres with expertise in the administration of IV drugs. 5. Trastuzumab deruxtecan must not be used in combination with other cancer drugs 6. A reduction in price 7. The feasibility of adoption of trastuzumab deruxtecan must be addressed. **Guidance on sequencing:** • The clinical experts and breast pathologist consulted by CADTH noted that there is existing HER2 testing infrastructure in Canada. Given HER2-low is a novel classification, the clinical experts suggested there may be interobserver discordance and lack of reproducibility when differentiating 0 and 1+ to determine HER2 IHC status, since historically, the interpretation of these 2 categories was less rigorous. pERC agreed with the clinical experts that with increased awareness and adequate training, Canadian pathologists and oncologists will be able to correctly identify HER2-low patients. The pathologist indicated that it may be necessary to re-read archival samples from before 2022 to differentiate between IHC 0 and IHC 1+. It was also noted that the pathologist that the VENTANA testing kit may lead to different results than the Dako testing kit. • Providing that the patient is able to tolerate the treatment, the clinical experts suggested that access to trastuzumab deruxtecan should not be limited by a

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		maximum number of previous lines of chemotherapy. pERC acknowledged the time-limited need at the initial onset of reimbursement of trastuzumab deruxtecan and agreed with the clinical experts. Additionally, the experts noted that once trastuzumab deruxtecan becomes readily available it is unlikely that patients would receive extended lines of chemotherapy before receiving trastuzumab deruxtecan. • The experts agreed that patients should not switch from a treatment that is working to receive trastuzumab deruxtecan. • pERC agreed with the clinical experts consulted who noted that patients classified as TNBC, but are truly HER2-low, who have received first-line pembrolizumab in combination with chemotherapy, should be eligible for second-line treatment with trastuzumab deruxtecan.
Olaparib (Lynparza)	March 20, 2023	pERC recommends that olaparib be reimbursed for the adjuvant treatment of adult patients with deleterious or suspected gBRCAm, HER2-negative, high-risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy, only if the following conditions are met: 1. Treatment with olaparib should be initiated in patients with deleterious or suspected deleterious gBRCAm, HER2-negative, high-risk early breast cancer if 1 of the following criteria is met: 1.1. For patients who underwent initial surgery and received adjuvant chemotherapy: 1.1.1. Those with TNBC must be axillary node–positive or axillary node–negative with pT ≥ 2 cm, or 1.1.2. Those with HR-positive, HER2-negative disease must have ≥ 4 involved pathologically confirmed positive lymph nodes. OR 1.2. For patients who underwent neoadjuvant chemotherapy followed by surgery: 1.2.1. Those with TNBC must have residual invasive breast cancer in the breast and/or resected lymph nodes (non-pCR), or 1.2.2. Those with HR-positive, HER2-negative patients must have residual invasive cancer in the breast and/or the resected lymph nodes (non-pCR) and a CPS + EG[a] score ≥ 3. 2. Patients must have confirmation of a gBRCAm before olaparib treatment is initiated. 3. Patients are not eligible if they have HER2-positive or metastatic breast cancer. 4. Patients must have completed neoadjuvant or adjuvant chemotherapy containing anthracyclines, taxanes, or the combination of both. 5. Olaparib should be initiated within up to 12 weeks of completion of the last treatment, including surgery, chemotherapy, or radiation therapy. 6. Treatment with olaparib should be discontinued upon the occurrence of any of the following, whichever occurs first: 6.1. disease recurrence 6.2. unacceptable toxicity 6.3. completion of a total of 1 year of treatment.

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		7. Olaparib should be prescribed by clinicians with expertise and experience in treating breast cancer. 8. A reduction in price. **Guidance on sequencing:** • pERC acknowledged that while at least 6 cycles of chemotherapy had to be used in the trial, in real practice there might be situations where chemotherapy is stopped early (e.g., due to toxicity), and these patients may still be offered olaparib. • Olaparib could be restarted if the prolonged break was not due to olaparib-induced toxicity or not related to disease recurrence. • The clinical experts stated that there are safety data on olaparib in combination with pembrolizumab, and in combination with capecitabine in other disease sites. These safety data were not reviewed in this submission. As well, there are no efficacy data to support the use of these combinations in early breast cancer. • According to the clinical experts, there may be situations where high-risk patients will start treatment beyond the 12-week window used in the trial, such as up to 4 months after the last therapy. As a result, olaparib should be initiated within up to 12 weeks of completion of the last treatment, including surgery, chemotherapy, or radiation therapy. pERC agreed with the clinical experts that there may be situations where some high-risk patients will start treatment beyond the 12-week window used in the trial.

Abemaciclib (Verzenio)	October 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 negative (HER2)–, 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 ET

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		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). • ET can be continued beyond this time. • 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. • Ongoing monitoring to assess patients for toxicity is required. • Abemaciclib with ET 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 nonsteroidal 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 ET 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 ET if the following condition is met: • Cost-effectiveness being improved to an acceptable level.
Alpelisib (Piqray)	February 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.

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Ribociclib (Kisqali)	June 4, 2020	pERC conditionally recommends reimbursement of ribociclib (Kisqali) in combination with a nonsteroidal AI (NSAI) and a luteinizing hormone-release hormone (LHRH) agonist as initial endocrine-based therapy in patients with pre- or perimenopausal HR-positive, HER2-negative advanced or metastatic breast cancer if the following conditions are met: • cost-effectiveness improved to an acceptable level • feasibility of adoption addressed (budget impact).
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 patients with HR-positive, HER2-negative advanced breast cancers if the following conditions are met: • cost-effectiveness improved to an acceptable level • feasibility of adoption addressed (budget impact) Eligible patients include men and postmenopausal women who have not received any prior treatment for ABC or have received up to 1 line of treatment for ABC. Premenopausal or perimenopausal women rendered postmenopausal, either chemically or surgically, are eligible, and should be treated with a 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 (ABC) or metastatic breast cancer (mBC) whose disease has progressed after prior ET. 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.
Ribociclib (Kisqali)	April 18, 2018	pERC conditionally recommends reimbursement of ribociclib (Kisqali) in combination with letrozole for the treatment of postmenopausal women with hormone receptor (HR)–positive, human epidermal growth factor receptor 2 (HER2)–negative advanced or metastatic breast cancer who have not received any prior treatment for advanced or metastatic disease, only if the following conditions are met: • cost-effectiveness being improved to an acceptable level • feasibility of adoption (budget impact) being addressed.
Palbociclib (Ibrance)	November 21, 2016	pERC recommends reimbursement of palbociclib (Ibrance) conditional on the cost-effectiveness being improved to an acceptable level. Reimbursement should be in combination with letrozole, for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer who have not received any prior treatment for metastatic disease. Treatment should continue until unacceptable toxicity or disease progression. Patients should have good performance status and neither be resistant to prior (neo)adjuvant aromatase

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		inhibitor therapy, nor have active or uncontrolled metastases to the central nervous system.
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 Eastern Cooperative Oncology Group Performance Status (ECOG) performance status ≤ 2 after recurrence or progression following a nonsteroidal 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.

HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; IHC = immunohistochemistry; ISH = in situ hybridization; pERC = pan-Canadian Oncology Drug Review Expert Review Committee.

Table 2: CADTH Implementation Advice Panels on HR-Positive, HER2-Negative, With Inclusion of HER2-Low, Breast Cancer

Indication	Date of publication	Implementation advice
HR-positive HER2-negative or HER2-low breast cancer and triple-negative breast cancer, including HR negative HER2 negative and HR negative HER2 low	December 7, 2023	**Adjuvant treatment options in HR-positive HER2-negative breast cancer** Treatment considerations in the adjuvant setting of HR-positive HER2-negative breast cancer[a] • The panel recommends funding of the following adjuvant treatment options: olaparib plus endocrine therapy or abemaciclib plus endocrine therapy based on patients' individual characteristics and whether they meet the eligibility criteria as per pERC recommendations for these treatments. • A patient may be considered for sequential use of olaparib plus endocrine therapy followed by abemaciclib plus endocrine therapy if they are deemed very high risk for relapse and have demonstrated high commitment for intensive treatment. **Patients with HR-positive HER2-low breast cancer in advanced stage of disease** Treatment considerations in patients with HER2-low breast cancer • The panel advises that trastuzumab deruxtecan can be used as per pERC recommendations for patients whose breast cancer meets the criteria of HER2-low disease.

HR-positive HER2-negative breast cancer	March 8, 2023	**Selection guidance for treatment options in HR-positive HER2-negative breast cancer**
		Treatment options for individuals who relapse within 6 months of completing adjuvant therapy.
		• The panel advises that for individuals who relapse within 6 months of completing adjuvant therapy with a CDK4/6 inhibitor, appropriate treatment options to consider include:
		  ◦ endocrine therapy
		  ◦ other targeted therapies combined with hormone therapy

Indication	Date of publication	Implementation advice
		◦ chemotherapy. Treatment guidance for individuals whose cancer relapses at or after 6 months when adjuvant therapy has been completed. ● The panel advises that for individuals who relapse at or after 6 months when adjuvant therapy with a CDK4/6 inhibitor has been completed: ◦ Treatment with a CDK4/6 inhibitor and endocrine therapy is reasonable including ribociclib or palbociclib. ◦ If the relapse occurs while the patient is on an aromatase inhibitor as an endocrine therapy, switching to fulvestrant may also be an option. **Re-treatment with CDK4/6 inhibitor** The panel agreed that the 6-month time limit for allowing re-treatment with a CDK4/6 inhibitor was reasonable (as advised by pERC) given the lack of evidence in this setting. Currently, CDK4/6 inhibitor options that are available in the metastatic setting only include ribociclib and palbociclib. **Sequencing with everolimus with exemestane** The panel advises that everolimus plus appropriate endocrine therapy is reasonable to consider a post CDK4/6 inhibitor in metastatic setting of HR-positive HER2-negative breast cancer. **Treatment interruption of CDK4/6 inhibitors during the 2 years of adjuvant setting** Treatment with a CDK4/6 inhibitor in the adjuvant setting should be completed for a total of 24 months within a 3-year period from beginning to completion as long as there is no disease progression.

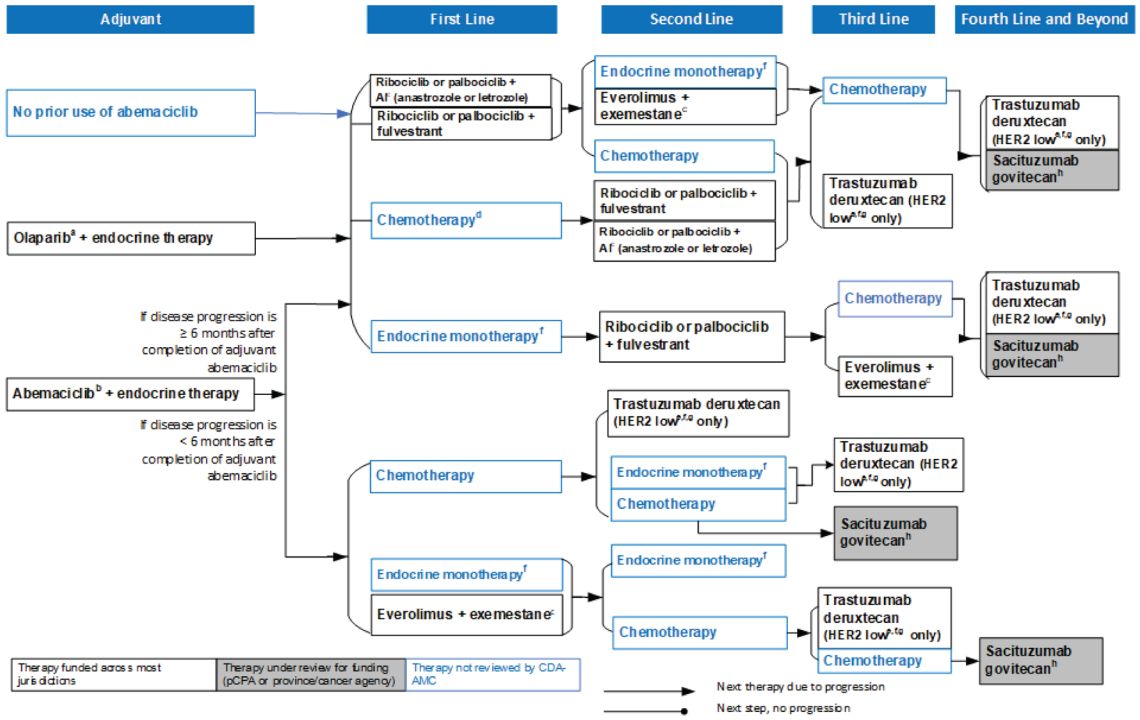
CDK = cyclin-dependent kinase; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor.

[a]In the panel algorithm published in December 2023, the Provincial Advisory Group (PAG) acknowledged the panel's advice for the sequential use of olaparib, followed by abemaciclib in the adjuvant setting of HR-positive, HER2-negative breast cancer, if and when patients meet the eligibility for both olaparib and abemaciclib. However, there is an absence of sufficient clinical evidence at this time to support this advice as noted by the panellists. Even though this sequential use only impacts a very small population, PAG suggests revisiting this advice once there is evidence available to inform the sequential use in this setting.

Provisional Funding Algorithm

In the adjuvant setting, there are 2 targeted treatment options available for HR-positive, HER2-negative breast cancer: abemaciclib with endocrine therapy or olaparib with endocrine therapy. In the metastatic setting, patients who have no prior use of abemaciclib, who have received adjuvant olaparib with endocrine therapy, or for patients with disease progression 6 months after completing adjuvant abemaciclib, the first-line options include ribociclib or palbociclib with an aromatase inhibitor or with fulvestrant, chemotherapy, and endocrine monotherapy. Second-line options include endocrine monotherapy, everolimus with exemestane, chemotherapy, or trastuzumab deruxtecan. Third-line or fourth-line options may include chemotherapy, everolimus with exemestane, trastuzumab deruxtecan, or sacituzumab govitecan. Patients with HR-positive low breast cancer can either be treated following this algorithm (Figure 1) or the previously published TNBC algorithms (refer to Figure 2 and Figure 3 in the funding algorithm published in December 2023) at their physician's discretion.

Figure 1: Provisional Funding Algorithm Diagram for HR-Positive, HER2-Negative Breast Cancer, With Inclusion of HER2-Low



AI = aromatase inhibitor; CDA-AMC = Canada's Drug Agency; CDK = cyclin-dependent kinase; HER2 = human epidermal growth factor 2; HR = hormone receptor; IHC = immunohistochemistry; ISH = in situ hybridization; pCPA = pan-Canadian Pharmaceutical Alliance.

Notes: Single chemotherapy options could include capecitabine, docetaxel, paclitaxel, nab-paclitaxel, doxorubicin, epirubicin, vinorelbine, gemcitabine, eribulin, or combinations therapies.

Endocrine monotherapy options include anastrozole or letrozole, exemestane, tamoxifen, and fulvestrant (re-treatment not funded if disease progression occurred during any prior fulvestrant therapy).

For individuals who are premenopausal, treatments might include luteinizing hormone-release hormone agonists, such as goserelin, leuprolide, and buserelin.

Breast cancer therapies are available for patients of all genders.

[a]Olaparib adjuvant therapy is for patients with deleterious or suspected deleterious germline *BRCA* mutation who have been treated with neoadjuvant or adjuvant chemotherapy. Patients must have confirmation of germline *BRCA* mutation before olaparib treatment is initiated.

[b]Abemaciclib should be reimbursed for a maximum of 2 years (150 mg orally twice daily).

[c]In some jurisdictions, aromatase inhibitors may also include exemestane. Funding for everolimus plus exemestane may vary by province or cancer agency.

[d]Chemotherapy might be the first choice if visceral crisis is suspected; after adequate response, consider other choices.

[e]Patients with HER2-low breast cancer must have the following pathology results: IHC 1+ or IHC2+ with ISH negative.

[f]Patients with HR-positive breast cancer should have received at least 1 endocrine therapy and no longer be considered for endocrine therapy.

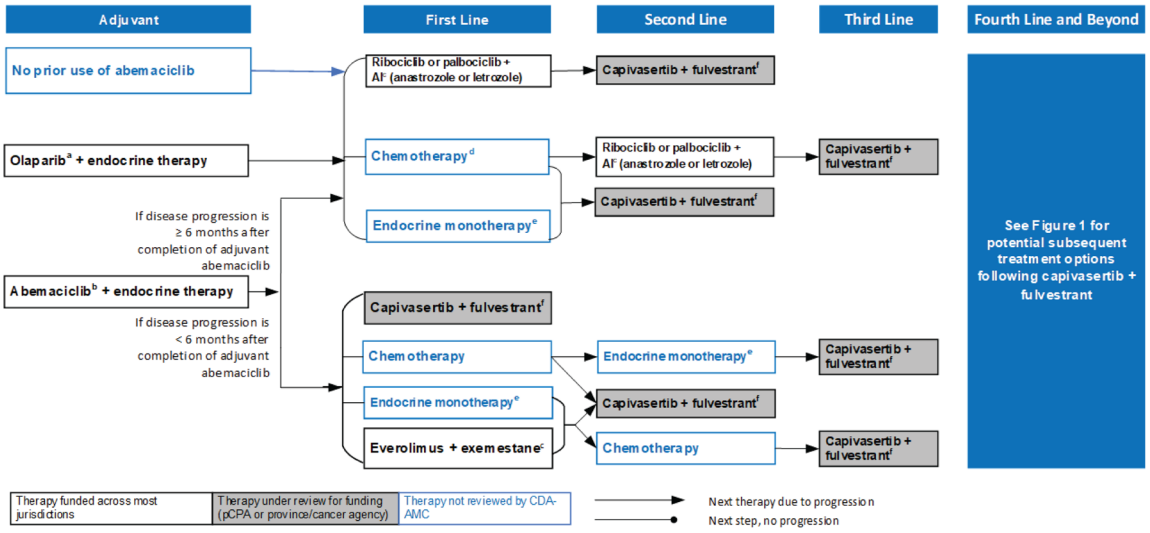
[g]Patients whose disease progresses on trastuzumab deruxtecan do not have the option for subsequent administration of sacituzumab govitecan.

[h]Patients need to have received prior endocrine therapy, a CDK 4 or 6 inhibitor in any setting, and at least 2 additional systemic chemotherapies in the metastatic setting. Neoadjuvant or adjuvant therapy for early-stage disease would qualify as 1 of the required prior chemotherapy regimens if the development of unresectable, locally advanced, or metastatic disease occurred within a 12-month period of the initiation of the therapy. Sacituzumab govitecan can be considered for patients whose disease previously progressed on endocrine therapy and who were not able to tolerate or access CKD 4 or 6 inhibitors before they became covered and are currently receiving chemotherapy. Patients whose disease progresses on sacituzumab govitecan do not have the option of subsequent administration of trastuzumab deruxtecan.

Patients with HR-positive low breast cancer can either be treated following this algorithm (Figure 1) or the previously published TNBC algorithms (refer to Figure 2 and Figure 3 in the funding algorithm published in December 2023) at their physician's discretion. Note that individuals who follow treatments in the HR-positive, HER2-negative algorithm would become ineligible for funding options in the TNBC setting. Unless new information (e.g., new biopsy results) becomes available to guide different treatment options, individuals

should consistently be treated based on the same funding algorithm (e.g., HR-positive, HER2-negative or TNBC, but not switch between the 2 algorithms).

Figure 2: Provisional Funding Algorithm Diagram for Additional Treatment Options for HR-Positive, HER2-Negative Breast Cancer, With Inclusion of HER2-Low, With *PIK3CA, AKT1,* or *PTEN* Alterations



AI = aromatase inhibitor; CDA-AMC = Canada's Drug Agency; HER2 = human epidermal growth factor 2; HR = hormone receptor; pCPA = pan-Canadian Pharmaceutical Alliance.

[a]Olaparib adjuvant therapy is for patients with a deleterious or suspected deleterious germline *BRCA* mutation whose disease has been treated with neoadjuvant or adjuvant chemotherapy. Patients must have confirmation of germline *BRCA* mutation before olaparib treatment is initiated.

[b]Abemaciclib should be reimbursed for a maximum of 2 years (150 mg orally twice daily).

[c]In some jurisdictions, aromatase inhibitors may also include exemestane. Funding for everolimus plus exemestane may vary by province or cancer agency.

[d]Chemotherapy might be the first choice if visceral crisis is suspected; after adequate response, consider other choices.

[e]Patients with HR-positive breast cancer should have received at least 1 endocrine therapy and no longer be considered for endocrine therapy.

[f]Capivasertib plus fulvestrant is indicated for patients with 1 or more *PIK3CA*, *AKT1*, or *PTEN* alterations. Patients must have received at least 1 line of hormone therapy in the metastatic setting or have disease that progressed on adjuvant hormone therapy or within 12 months of adjuvant hormone therapy. Capivasertib plus fulvestrant should not be initiated in patients who have disease that progressed on prior therapy with fulvestrant, received more than 2 lines of hormone therapy, or received more than 1 line of chemotherapy in the metastatic setting.

Description of the Provisional Funding Algorithm

HR-Positive, HER2-Negative Breast Cancer, With Inclusion of HER2-Low (Figure 1)

Adjuvant Setting

In the adjuvant settings, there are 2 targeted treatment options available: abemaciclib with endocrine therapy or olaparib with endocrine therapy. Abemaciclib in combination with endocrine therapy is the only CDK 4 or 6 inhibitor approved for use in the adjuvant setting. The adjuvant use of olaparib is for adults with deleterious or suspected deleterious germline *BRCA*-mutated, HER2-negative, high-risk early breast cancer that has been treated with neoadjuvant or adjuvant chemotherapy.

Metastatic Setting

For patients who have no prior use of abemaciclib, who have received adjuvant olaparib with endocrine therapy, or those with disease progression 6 months after completing adjuvant abemaciclib, the first-line options include ribociclib or palbociclib with an aromatase inhibitor (e.g., anastrozole or letrozole) or with fulvestrant. Other options include chemotherapy and endocrine monotherapy.

- For patients who have received a CDK 4 or 6 inhibitor plus an aromatase inhibitor or fulvestrant in the first-line setting, the second-line options include endocrine monotherapy, everolimus with exemestane, or chemotherapy.
- If chemotherapy is selected as first-line treatment to achieve initial adequate response due to suspected visceral crisis, or if there is not a response to endocrine therapy, the additional maintenance options are ribociclib or palbociclib combined with an aromatase inhibitor or with fulvestrant.
- Third-line or fourth-line options may include chemotherapy, everolimus with exemestane, and trastuzumab deruxtecan for patients who meet the eligibility criteria for HER2 low, including having pathology results for IHC 1+ or IHC 2+ with ISH negative. Note that to qualify for trastuzumab deruxtecan, patients with HR-positive breast cancer should have received at least 1 endocrine therapy or be no longer considered eligible for endocrine therapy. Another option in this setting is sacituzumab govitecan. To be eligible for sacituzumab govitecan, the patient needs to have received prior endocrine therapy and a CDK 4 or 6 inhibitor in any setting, and at least 2 additional systemic chemotherapies in the metastatic setting. Neoadjuvant or adjuvant therapy for early-stage disease would qualify as 1 of the required prior chemotherapy regimens if the development of unresectable, locally advanced, or metastatic disease occurred within 12 months from the initiation of the therapy. Sacituzumab govitecan can be considered in patients whose disease previously progressed on endocrine therapy and who were not able to tolerate or access CDK 4 or 6 inhibitors before they were covered and are currently receiving chemotherapy. Sacituzumab govitecan can also be considered in patients who experienced intolerance or severe toxicity to a prior topoisomerase inhibitor. Sacituzumab govitecan is under review for funding.

For patients with disease progression within 6 months of completing adjuvant abemaciclib, the available first-line options include chemotherapy, endocrine monotherapy, and non-CDK 4 or 6–targeted therapies in combination with endocrine therapy, which would be everolimus with exemestane.

- The second-line options for those who have received metastatic first-line chemotherapy include trastuzumab deruxtecan, endocrine monotherapy, and further chemotherapy. Patients receiving trastuzumab deruxtecan must meet the eligibility criteria for HER2 low, including pathology results for IHC 1+ or IHC 2+ with ISH negative. Note that to qualify for trastuzumab deruxtecan, patients with HR-positive breast cancer should have received at least 1 endocrine therapy or be no longer considered for endocrine therapy. Patients who have not received trastuzumab deruxtecan in the second-line setting may be eligible for third-line treatment following second-line endocrine monotherapy or chemotherapy. Sacituzumab govitecan is another third-line option for those who have received metastatic first-line chemotherapy and further chemotherapy in the second line. To

be eligible for sacituzumab govitecan, the patient needs to have received prior endocrine therapy and a CDK 4 or 6 inhibitor in any setting, and at least 2 additional systemic chemotherapies in the metastatic setting. Neoadjuvant or adjuvant therapy for early-stage disease would qualify as 1 of the required prior chemotherapy regimens if the development of unresectable, locally advanced, or metastatic disease occurred within a 12-month period of therapy initiation. Sacituzumab govitecan can be considered in patients whose disease previously progressed on endocrine therapy and who were not able to tolerate or access CDK 4 or 6 inhibitors before they became covered and are currently receiving chemotherapy. Sacituzumab govitecan can also be considered in patients who experienced intolerance or severe toxicity to a prior topoisomerase inhibitor. Sacituzumab govitecan is under review for funding.

- For patients whose first-line metastatic options included endocrine monotherapy or everolimus plus exemestane, their second-line options include endocrine monotherapy or chemotherapy. Upon completion of chemotherapy, their subsequent option may include trastuzumab deruxtecan or further chemotherapy. Patients receiving trastuzumab deruxtecan must meet the eligibility criteria for HER2 low, including having pathology results for IHC 1+ or IHC 2+ with ISH negative. In addition, patients with HR-positive breast cancer should have received at least 1 endocrine therapy or be no longer considered eligible for endocrine therapy. In this setting, following third-line chemotherapy, sacituzumab govitecan may be considered in the fourth line. To be eligible for sacituzumab govitecan, the patient needs to have received prior endocrine therapy and a CDK 4 or 6 inhibitor in any setting, and at least 2 additional systemic chemotherapies in the metastatic setting. Neoadjuvant or adjuvant therapy for early-stage disease would qualify as 1 of the required prior chemotherapy regimens if the development of unresectable, locally advanced, or metastatic disease occurred within 12 months of therapy initiation. Sacituzumab govitecan can be considered in patients whose disease previously progressed on endocrine therapy and who were not able to tolerate or access CDK 4 or 6 inhibitors before they became covered and are currently receiving chemotherapy. Sacituzumab govitecan can also be considered in patients who experienced intolerance or severe toxicity to a prior topoisomerase inhibitor. Sacituzumab govitecan is under review for funding.

HR-Positive, HER2-Negative Breast Cancer, With Inclusion of HER2-Low and *PIK3CA*, *AKT1*, and *PTEN* Alterations (Figure 2)

Patients with *PIK3CA*, *AKT1*, or *PTEN* alterations may be eligible for the treatment options discussed in Figure 1. In addition, they may be eligible to receive capivasertib plus fulvestrant, per the funding algorithm outlined in Figure 2. Capivasertib plus fulvestrant is indicated for patients with 1 or more *PIK3CA*, *AKT1*, or *PTEN* alterations and is under review for funding. Patients must have received at least 1 line of hormone therapy in the metastatic setting or have disease that progressed on adjuvant hormone therapy or within 12 months of adjuvant hormone therapy. Capivasertib plus fulvestrant should not be initiated in patients whose disease progressed on prior therapy with fulvestrant, who received more than 2 lines of hormone therapy, or who received more than 1 line of chemotherapy in the metastatic setting.

Adjuvant Setting

In the adjuvant settings, there are 2 targeted treatment options available: abemaciclib with endocrine therapy or olaparib with endocrine therapy. Abemaciclib in combination with endocrine therapy is the only CDK 4 or 6 inhibitor approved for use in the adjuvant setting. The adjuvant use of olaparib is for adults with deleterious or suspected deleterious germline *BRCA*-mutated, HER2-negative, high-risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy.

Metastatic Setting

For patients who have no prior use of abemaciclib, who have received adjuvant olaparib with endocrine therapy, or those with disease progression 6 months after completing adjuvant abemaciclib, the first-line options include ribociclib or palbociclib with an aromatase inhibitor (e.g., anastrozole or letrozole). Other options include chemotherapy and endocrine monotherapy.

- For patients who have received a CDK 4 or 6 inhibitor plus an aromatase inhibitor in the first-line setting, the second-line option is capivasertib plus fulvestrant.
- If chemotherapy is selected as first-line treatment to achieve initial adequate response due to suspected visceral crisis, or if there is not a response to endocrine therapy, additional maintenance options ribociclib or palbociclib combined with an aromatase inhibitor or capivasertib plus fulvestrant. To be eligible for capivasertib plus fulvestrant, patients must have disease progression on adjuvant hormone therapy or be within 12 months of adjuvant hormone therapy. For those who receive ribociclib or palbociclib combined with an aromatase inhibitor in the second line, the third-line option is capivasertib plus fulvestrant.
- If endocrine monotherapy is selected as first-line treatment, capivasertib plus fulvestrant is the second-line option.

For patients with disease progression within 6 months of completing adjuvant abemaciclib, the available first-line options include chemotherapy, capivasertib plus fulvestrant, endocrine monotherapy, and non-CDK 4 or 6–targeted therapies in combination with endocrine therapy, which would be everolimus with exemestane. Capivasertib plus fulvestrant is also a first-line treatment option for patients with disease progression on or within 12 months of completing adjuvant hormone therapy.

- The second-line options for those who have received metastatic first-line chemotherapy are endocrine monotherapy or capivasertib plus fulvestrant. For those who receive endocrine monotherapy in the second-line, the third-line option is capivasertib plus fulvestrant.
- For patients whose first-line metastatic option is endocrine monotherapy or everolimus plus exemestane, their second-line options include capivasertib plus fulvestrant or chemotherapy. Upon completion of chemotherapy, their subsequent option may include capivasertib plus fulvestrant.

Note that unless new information becomes available (e.g., new biopsy results) to guide different treatment options, medical oncologists with support from pathology results (and any additional pathologists' guidance, as appropriate) should identify the appropriate treatment options for the patient by consistently following the same funding algorithm (e.g., HR-positive, HER2-negative or TNBC, but not switch between the 2 algorithms).

Patients who have HR-positive low breast cancer can either be treated following this algorithm (Figure 1 or Figure 2) or the previously published TNBC algorithms (refer to Figure 2 and Figure 3 in the funding algorithm published on December 2023) at their physician's discretion. Note that individuals treated following the HR-positive, HER2-negative algorithm would become ineligible for funding options in the TNBC setting. Unless new information (e.g., new biopsy results) becomes available to guide different treatment options, individuals should consistently be treated based on the same funding algorithm (e.g., HR-positive, HER2-negative or TNBC, but not switch between the 2 algorithms).

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