CADTH Reimbursement Review

Provisional Funding Algorithm

Indication: Breast Cancer with Hormone Receptor (HR) Positive, Human Epidermal Growth Factor Receptor 2 (HER2) Negative, with Inclusion of HER2 Low

This report supersedes the CADTH Provisional funding algorithm report for Breast Cancer with Hormone Receptor (HR) Positive, Human Epidermal Growth Factor Receptor 2 (HER2) Negative, or Low dated December 2023.

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

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CADTH

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.

Background

Following a request from jurisdictions, CADTH 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:

- CADTH pCODR 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 CADTH 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 CADTH 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 CADTH following changes to drug funding status. Revisions and updates will occur only upon request by jurisdictions.

Jurisdictional cancer drug programs requested a CADTH 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+ HER2– breast cancer
- re-treatment with a CDK4/6 inhibitor
- sequencing with everolimus and exemestane
- treatment interruption of CDK4/6 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+ HER2- Breast Cancer
- Sequencing guidance on the use of trastuzumab deruxtecan in the HER2 low population for individuals previously classified as HR+ HER2- as well as individuals previously classified as triple-negative breast cancer (TNBC).

These are outlined in Table 1. For this rapid algorithm, the purpose is to incorporate the latest pERC recommendation on Sacituzumab govitecan in 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 two additional systemic therapies in the metastatic setting
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Table 1: Relevant CADTH Recommendations

Generic name (brand name)	Date of recommendation	Recommendation and Guidance on Treatment Sequencing
Sacituzumab govitecan (Trodelvy)	February 20 2024	The CADTH pCODR Expert Review Committee (pERC) recommends that sacituzumab govitecan be reimbursed 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 two additional systemic chemotherapies in the metastatic setting only 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

		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% - 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+ HER2– 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. • pERC agreed with the clinical experts indicated that if taxanes were not used due to a medical contraindication, then the patient should still be 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 one 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 Topoisomerase 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 one prior line of chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Patients have hormone receptive positive (HR-positive) breast cancer should have received at least one 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 one 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 one prior line of endocrine therapy and no longer be considered candidates for endocrine therapy 1.3. good performance status 2. Patients must have had 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 prior to 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 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 in order 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 one 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.

		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 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.
Ribociclib (Kisqali)	June 4, 2020	pERC conditionally recommends reimbursement of ribociclib (Kisqali) in combination with a nonsteroidal AI (NSAI) and an 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 one 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 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.

Table 2: CADTH Implementation Advice Panels on Breast Cancer

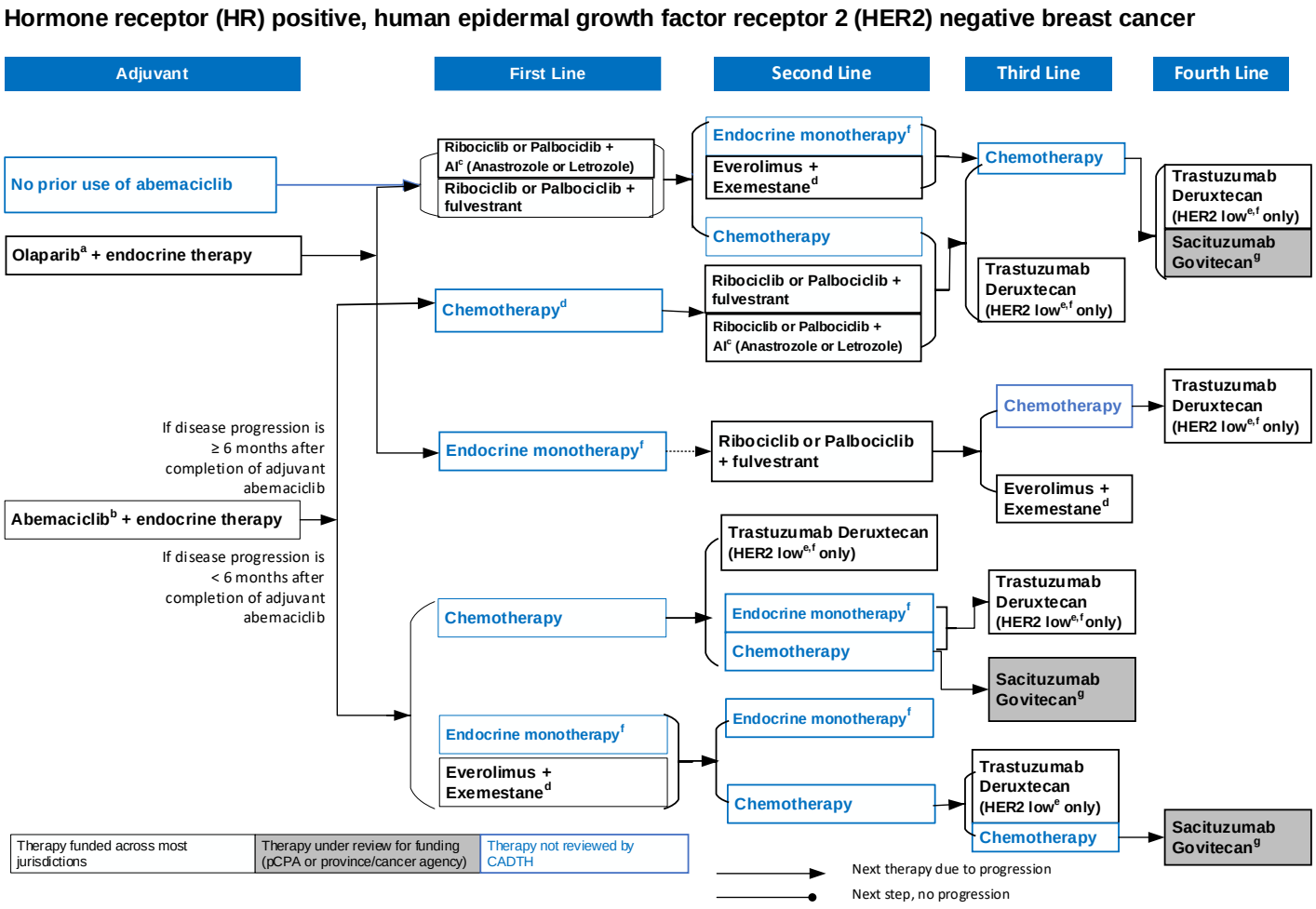
Date of publication	Implementation Advice
December 7, 2023	**Adjuvant treatment options in HR+ HER2- Breast Cancer** Treatment considerations in the Adjuvant Setting of HR+ HER2- Breast Cancer • The panel recommends funding of the following adjuvant treatment options: olaparib + endocrine therapy or abemaciclib + 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 + endocrine therapy, followed by abemaciclb + endocrine therapy if they are deemed very high risk for relapse and have demonstrated high commitment for intensive treatment. *(Note that the Provincial Advisory Group [PAG] Committee was unable to endorse this advice unless more evidence is available to inform the sequential use in this setting.)* **HR+ HER2 Low Patients in advances disease** Treatment considerations in HER2 Low Patients • The panel advises that trastuzumab deruxtecan can be used as per pERC recommendations for patients who meet criteria for HER2-low disease.

March 8, 2023	**HR+ HER2- Breast Cancer**
	
	Selection guidance for treatment options in HR+ HER2- 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
	  ○ chemotherapy
	
	Treatment guidance for individuals who relapse 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 and endocrine therapy is reasonable including ribociclib or palbociclib
	• If the relapse occurs while 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+ HER2- 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.

Provisional Funding Algorithm

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



AI = aromatase inhibitor; HR = hormone receptor; HER2 = human epidermal growth factor 2; pCPA = pan-Canadian Pharmaceutical Alliance;

Notes:

- Single chemotherapy options could include: capecitabine, docetaxel, paclitaxel, nab-paclitaxel, doxorubicin, epirubicin, vinorebine, gemcitabine, eribulin or combinations therapies.
- Endocrine monotherapy options: anastrozole or letrozole, exemestane, tamoxifen, fulvestrant (re-treatment not funded if disease progression occurred during any prior fulvestrant therapy).
- For premenopausal individuals, treatments might include luteinizing hormone-release hormone agonists: goserelin, leuprolide, 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-mutated (gBRCAm) 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 (150mg orally twice daily)

[c] In some jurisdictions, aromatase inhibitors may also include exemestane. Everolimus plus exemestane are under review for funding by province or cancer agency.
[d] Chemotherapy might be the first choice if visceral crisis is suspected; after adequate response, consider other choices.
[e] HER2 Low patients must have the following pathology results: IHC 1+ or IHC2+ with ISH-.
[f] Patients with hormone receptor positive (HR-positive) breast cancer should have received at least one endocrine therapy and be no longer considered for endocrine therapy.
g Patient needs to have received prior endocrine therapy and a CDK4/6 inhibitor in any setting, and at least two 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 in patients who previously progressed on endocrine therapy and were unable to access CKD4/6 inhibitors (due to tolerability issues or funding not available at the time) and are currently on chemotherapy.

HR positive low patients can either be treated following this algorithm (Figure 1) or the TNBC algorithms (Figure 2 and Figure 3) at the physician's discretion. Note that these individuals who follow treatments in HR+ HER2- algorithm would become ineligible for funding options for TNBC setting. Unless new information (e.g., new biopsy results) become available to guide different treatment options, individuals should consistently pursue treatments based on the same funding algorithm (e.g. HR+ HER2- or TNBC but not switch between the two algorithms).

Description of the Provisional Funding Algorithm

Adjuvant Setting

In the adjuvant settings, there are two treatment options available: abemaciclib with endocrine therapy or olaparib with endocrine therapy. Abemaciclib in combination with endocrine therapy is the only CDK4/6 inhibitor approved for use in the adjuvant setting. The adjuvant use of olaparib is for adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm), human epidermal growth factor receptor 2 (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 for patients 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 CDK4/6 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 when not endocrine responsive, additional maintenance options include ribociclib or palbociclib combined with an aromatase inhibitor or with fulvestrant.

- Third or fourth line options may include chemotherapy, everolimus with exemestane, trastuzumab deruxtecan for patients who meet the eligibility criteria for HER2 low including having pathology results for IHC 1+ or IHC 2+ with ISH-. Note that to qualify for trastuzumab deruxtecan, patients with hormone receptor positive breast cancer should have received at least one 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 CDK4/6 inhibitor in any setting, and at least two 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. Sactizumab govitecan is under review for funding.

For patients with disease progression within 6 months of completing adjuvant abemaciclib, available first line options include chemotherapy, endocrine monotherapy, and non-CDK4/6 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 having pathology results for IHC 1+ or IHC 2+ with ISH-. Note that to qualify for trastuzumab deruxtecan, patients with hormone receptor positive breast cancer should have received at least one endocrine therapy or be no longer considered for endocrine therapy. For patients who have not received trastuzumab deruxtecan in the second-line setting, they 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 setting. To be eligible for sacituzumab govitecan, the patient needs to have received prior endocrine therapy and a CDK4/6 inhibitor in any setting, and at least two 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 in patients who previously progressed on endocrine therapy and were unable to access CKD4/6 inhibitors (due to tolerability issues or funding not available at the time) and are currently on chemotherapy. Sactizumab govitecan is under review for funding.

- For patients whose first-line metastatic options included endocrine monotherapy or everolimus-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-. Note that to qualify for trastuzumab deruxtecan, patients with hormone receptor breast cancer should have received at least one endocrine therapy or be no longer considered for endocrine therapy. In this setting following third-line chemotherapy, sacituzumab govitecan may be considered in the fourth-line setting. To be eligible for sacituzumab govitecan, the patient needs to have received prior endocrine therapy and a CDK4/6 inhibitor in any setting, and at least two 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 in patients who previously progressed on endocrine therapy and were unable to access CKD4/6 inhibitors (due to tolerability issues or funding not available at the time) and are currently on chemotherapy. Sactizumab govitecan is under review for funding.

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 patients by consistently following the same funding algorithm (e.g., HR+ HER2- or TNBC but not switch between the two algorithms).