CADTH Provisional Funding Algorithm

Provisional Funding Algorithm

Indications: Breast cancer with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative, or low; triple negative breast cancer, including HR negative, HER2 negative and HR negative, HER2 low

This report supersedes the CADTH Provisional funding algorithm reports for HR+ HER2- breast cancer dated March 8, 2023, and triple negative breast cancer dated June 14, 2023.

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

December 2023

Key Panel Recommendations

- In patients with hormone receptor (HR)–positive and human epidermal growth factor receptor 2 (HER2)–negative breast cancer, 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 the CADTH pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommendations for these treatment options. For a small population, the panel recommended consideration to be given to sequencing of both drugs.
- The panel advises that patients may switch between sacituzumab govitecan and trastuzumab deruxtecan because of intolerance or toxicities, provided they meet the eligibility criteria for both sacituzumab govitecan and trastuzumab deruxtecan.
- Patients with functionally triple-negative breast cancer (TNBC) (e.g., estrogen receptor [ER] or progesterone receptor low) may follow the treatments in the TNBC algorithm. For ER-low positive results, the current American Society of Clinical Oncology and College of American Pathologists (ASCO/CAP) guidelines refer to the cancer in the sample as having a low level (1% to 10%) of ER expression by immunohistochemistry (IHC).[1]

Please also refer to the Final Advice and Rationale on the Funding Algorithm section.

Background

The provisional funding algorithm process is used to provide advice when the drug programs have indicated that there is need to establish an appropriate place in therapy for the drug under review relative to alternative treatments that are currently reimbursed by the drug programs, including the impact on the appropriate sequencing of treatments for the purposes of reimbursement. The creation of a new provisional funding algorithm or update of an existing provisional funding algorithm is typically initiated following the issuance of a new pERC recommendation when there are potential implications regarding the funding sequence of drugs within a therapeutic area. CADTH will only initiate work on a provisional funding algorithm at the request of its Provincial Advisory Group (PAG).

The following item are considered by the expert panels when advising the jurisdictions on the provisional algorithm for the relevant indication:

- unmet therapeutic need for patients (particularly those in understudied populations)
- evidence supporting a particular sequence of therapies (if available)
- clinical experience and opinion that support a particular sequence of therapies
- clinical practice guidelines
- variability across jurisdictions regarding the reimbursement status of existing treatment options
- affordability and sustainability of the health care system
- implementation considerations at the jurisdictional level.

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. Most 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. Also note that as per process, implementation advice from panellists and the resulting algorithms cannot contradict prior pERC recommendations or expand target populations beyond what was recommended.

Provisional funding algorithms delineate the 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 a drug's funding status. Revisions and updates will occur only upon request by jurisdictions.

Cancer drug programs from federal and provincial jurisdictions requested supplemental implementation advice along with a CADTH provisional funding algorithm for HR-positive HER2-negative breast cancer and TNBC, with the inclusion of HER2-low disease. Refer to Appendix 1 for a list all past CADTH advice and recommendations relevant to this therapeutic area.

Implementation Issues

At the request of the participating drug programs, CADTH convened a panel of clinical experts in Canada to provide advice for addressing the following outstanding 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 HER2-low population for individuals with HR-positive HER2-negative breast cancer, as well as individuals with TNBC.

Consultation Process and Objectives

The implementation advice panel comprised 6 specialists in Canada with expertise in the diagnosis and management of patients with breast cancer, a representative from a public drug program, and a panel chair. The objective of the panel was to provide advice to the participating drug programs regarding the implementation issues noted in the Background section. A consensus-based approach was used, and input from stakeholders was solicited using questionnaires. Stakeholders, including patient and clinician groups, pharmaceutical manufacturers, and public drug programs, were invited to provide input in advance of the meeting.

The advice presented in this report has been developed based on the experience and expertise of the implementation advice panel members and, as such, represents experience-informed opinion; it is not necessarily based on evidence.

Clinician Panellists' Advice on Funding Algorithm

Summary of Implementation Advice

Implementation advice regarding the optimal sequencing of treatments is summarized in Table 1. For each implementation issue, a summary of the relevant panel discussion is provided for additional context.

Table 1: Summary of Advice for Addressing Implementation Issues

Issue	Advice	Rationale
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 abemaciclib + endocrine therapy if they are deemed very high risk for relapse and have demonstrated high commitment for intensive treatment.	Patients who are deemed "high risk" based on factors such as age, nodal status, response to neoadjuvant therapy, Ki-67 score, *BRCA* status, tumour size and grade, and degree of expression for ER and PR weak or strong positive) are considered for adjuvant therapy to reduce risk of relapse. Treatment selection will be guided by clinical trial eligibility criteria. If a patient meets the criteria for both abemaciclib and olaparib in the adjuvant setting, there is no direct comparison data of the 2 regimens to guide treatment choice. The panel noted that they would favour a PARP inhibitor (olaparib) over abemaciclib as the first adjuvant treatment for eligible patients because it has a shorter treatment duration, better tolerability, and data demonstrating OS benefit. For patients considered high risk, the panel advocated that sequential use of adjuvant olaparib followed by abemaciclib may be considered but this is not supported by clinical trial data. However, the panel noted that sequential use of olaparib and abemaciclib, which are 2 non–cross resistant drugs, is expected to help prevent recurrence, which is the goal of treatment in this curative setting for these patients. The panel also noted that sequential use of olaparib and abemaciclib will concern a very small group of patients who are medically fit and eligible, as per the MonarchE[2] and OlympiA[3] clinical trials, *BRCA* mutated, ER positive, and at high risk of recurrence (e.g., 4+ nodes and Ki-67 > 20%).

Issue	Advice	Rationale
Treatment options in HR+ HER2-low advanced disease		
Treatment considerations in patients with HER2-low disease	The panel advises that trastuzumab deruxtecan can be used as per pERC recommendations for patients who meet the criteria for HER2-low disease.	The existing data for an antibody-drug conjugate would favour the use of a CDK4/6 inhibitor in an earlier line of therapy. The majority of patients will receive a CDK4/6 inhibitor in the first-line setting even with visceral crisis. If patients receive first-line chemotherapy, they would likely get a CDK4/6 inhibitor in the second line and would still be eligible for trastuzumab deruxtecan. The panel indicated that there is no evidence to support the use of a CDK4/6 inhibitor after 2 lines of chemotherapy or following antibody-drug conjugate treatment.
Treatment options in TNBC in advanced disease		
Treatment considerations in patients with HER2-low disease	The panel advises that trastuzumab deruxtecan can be used as per pERC recommendations for patients who meet the criteria for HER2-low disease, with prior use of at least 1 line of chemotherapy in the metastatic setting or who developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. The panel advises that patients may switch between sacituzumab govitecan and trastuzumab deruxtecan due to intolerance or toxicities The panel advises allowing patients with functional TNBC (e.g., ER or PR low) to follow treatments in the TNBC algorithm. For ER-low positive results, current ASCO/CAP guidelines refer to the cancer in the sample as having a low level (1% to 10%) of ER expression by IHC.[1]	The panel deliberated on the evidence for sacituzumab govitecan vs. trastuzumab deruxtecan and whether there is any supporting evidence for sequential use. The panel members were aware of emerging evidence to support sequential use, but acknowledged an absence of high-quality evidence. Choosing between sacituzumab govitecan and trastuzumab deruxtecan for patients with HER2-low breast cancer is challenging in the second-line setting. In the absence of head-to-head data, the choice would be individualized and would involve patient and treatment-related considerations, as well as logistical considerations (trastuzumab deruxtecan administered every 3 weeks vs. sacituzumab govitecan administered on day 1 and day 8 as a 3-week cycle, which necessitates travel and distance to an IV infusion clinic) and tolerability.

ASCO/CAP = American Society of Clinical Oncology and College of American Pathologists; ER = estrogen receptor; HER2– = human epidermal growth factor receptor 2 negative; HR+ = hormone receptor–positive; IHC = immunohistochemistry; OS = overall survival; PARP = poly-(ADP-ribose) polymerase; pERC = CADTH pan-Canadian Oncology Drug Review Expert Review Committee; PR = progesterone receptor; TNBC = triple-negative breast cancer; vs. = versus.

In addition to the previously outlined advice, the panel indicated that because an improvement in cost-effectiveness was a condition for reimbursement in each of the recommendations related to the drugs in scope, implementation of any advice herein should be contingent upon ensuring that the relevant treatments are affordable to public payers.

Panel Discussion

Treatment Considerations for the Use of Olaparib and Abemaciclib in the Adjuvant Setting of HR-Positive HER2-Negative Breast Cancer

For patients with HR-positive HER2-negative breast cancer, 2 treatment options are available in the adjuvant setting: olaparib plus endocrine therapy and abemaciclib plus endocrine therapy. It is important to note that olaparib is only indicated in patients with germline *BRCA1* or *BRCA2* mutations, which is a very small subset of patients. Patients who are deemed "high risk" are considered for adjuvant therapy to reduce risk of relapse. Treatment selection is guided by the clinical trial eligibility criteria (monarchE[2] for adjuvant abemaciclib and OlympiA[3] for adjuvant olaparib). Factors that contribute to classifying a patient as high risk include patient-related (e.g., age, menopausal status) and pathologic features (e.g., nodal status, response to neoadjuvant therapy, Ki-67 score, genomic profile such as Oncotype DX score, *BRCA* status, tumour grade, tumour size, degree of expression for ER and PR weak versus strong positive).

If a patient meets the criteria for both abemaciclib and olaparib in the adjuvant setting, there is no direct comparative data of the 2 regimens to guide treatment choice. The panel noted that it would favour a poly-(ADP-ribose) polymerase (PARP) inhibitor (olaparib) over abemaciclib as the first adjuvant treatment for eligible patients because it has a shorter treatment duration, better tolerability, and data demonstrating an overall survival (OS) benefit in germline *BRCA1* and *BRCA2* mutation carriers.

For patients considered to be very high risk, the panel advocated that the sequential use of adjuvant olaparib followed by abemaciclib may be warranted as this is potentially curative therapy. The panel was not aware of any clinical trial data supporting sequential use. It was noted that in the OlympiA trial,[3] the invasive disease-free survival benefit observed with olaparib was higher than the invasive disease-free survival benefit observed with abemaciclib in the MonarchE trial[2] (8.8% at 3 years versus 5.4%), so in patients with germline *BRCA* mutations (gBRCAm) it would be reasonable to prioritize olaparib and then sequence with abemaciclib after 52 weeks, or prioritize olaparib alone rather than sequence (given the lack of data). The panellists explained that since olaparib and abemaciclib have vastly different mechanisms of action, both drugs would work if given sequentially. As curative therapies, sequential use of 2 non–cross resistant drugs can help prevent recurrence, which is an important treatment goal in this setting. The panel reiterated that HR-positive disease has a long risk of recurrence and that patients should be offered as many options (including sequential options) as possible to reduce the risk that will have an impact on the risk of recurrence in the first 5 years, as well as late recurrences.

The panel also noted that sequential use of olaparib and abemaciclib would apply to a very small group of patients who are medically fit and eligible (as per the MonarchE[2] and OlympiA[3] clinical trials), *BRCA* mutated, ER positive, and at high risk of recurrence (e.g., 4 or more nodes and Ki67 > 20%). In practice, sequencing a year of olaparib and then 2 years of abemaciclib after a year of intensive treatment will not be realistic for a significant portion of patients. These patients will have received chemotherapy, surgery, and radiation and may have treatment-induced fatigue and functional impairment at the time of initiating adjuvant abemaciclib and/or olaparib.

Other Comments

The panel indicated that there is no evidence for the use of a CDK4/6 inhibitor after 2 lines of chemotherapy or following an antibody-drug conjugate. The existing data for antibody-drug conjugates would favour a CDK4/6 inhibitor being used in an earlier line setting. The majority of patients will receive a CDK4/6 inhibitor in the first-line setting even when in visceral crisis. If patients receive first-line chemotherapy, they would likely get a CDK4/6 inhibitor in the second line and would still be eligible for trastuzumab deruxtecan. It was noted that although it would be exceedingly rare to use a CDK4/6 inhibitor after 2 lines of chemotherapy, there is no reason that a patient cannot receive a CDK 4/6 inhibitor after 2 lines of chemotherapy (including an antibody-drug conjugate). Translational studies suggest mechanisms of resistance to CDK 4/6 inhibitors (e.g., *Rb* mutation, *FAT1* mutation, *PTEN* loss, *FGFR* amplification, Cyclin E amplification) are likely different than mechanisms of resistance to chemotherapy. Data from the SONIA trial[4] suggests that the sequence of a CDK 4/6 inhibitor (first line versus second line) may be less impactful than any exposure to a CDK 4/6 inhibitor.

The funding algorithm has listed everolimus-exemestane as a second-line therapy after first-line use of a CDK4/6 inhibitor. Based on current provisional funding algorithm for HR-positive HER2-negative breast cancer, everolimus plus appropriate endocrine therapy can be considered following a CDK4/6 inhibitor in the metastatic setting of HR-positive HER2-negative breast cancer. This is based on some limited real-world evidence that indicates prior exposure to a CDK4/6 inhibitor therapy did not impact on reasonable clinical outcomes for patients receiving everolimus plus exemestane. However, the panel indicated that access to everolimus and exemestane is variable across provinces. Currently there is no access to everolimus-exemestane in the provinces of Saskatchewan and British Columbia. In New Brunswick, current provincial funding criteria prohibit the use of everolimus and exemestane if the patient has experienced progression on a CDK 4/6 inhibitor.

Treatment Considerations in the HR-Positive HER2-Low (Advanced Disease) Setting

pERC has issued a positive recommendation for trastuzumab deruxtecan for patients with HER2-low breast cancer as second-line therapy after treatment with at least 1 prior line of chemotherapy in the metastatic setting or who developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. It is expected that many patients will preferentially receive CDK4/6 inhibitors after first-line chemotherapy (if required for visceral crisis).

Treatment Considerations in the HR-Negative, HER2-Low (Advanced Disease) Setting

There are 2 metastatic treatment options under discussion: sacituzumab govitecan and trastuzumab deruxtecan, which are available to patients with HER2-low disease. Given the lack of evidence for sequencing at the time of the pERC review, provincial jurisdictions aren't planning on funding these drugs in sequence. The panel discussed how they would choose between these 2 options and if there is evidence that informs this sequencing.

The panel acknowledged the challenge in choosing between treatment options for this patient population, and panel noted that considerations when choosing between sacituzumab govitecan and trastuzumab deruxtecan for patients with HER2-low and HR-negative disease include the number of chemotherapy

regimens received (the sacituzumab govitecan trial, ASCENT,[5] allowed for 2 or more lines of chemotherapy; the trastuzumab deruxtecan trial, DESTINY-Breast04,[6] allowed for minimum 1 line of chemotherapy), patient logistics (trastuzumab deruxtecan administered every 3 weeks versus sacituzumab govitecan administered on day 1 and day 8 as a 3 week cycle, which means travel and distance to an IV infusion clinic is a consideration), and ensuring no contraindication to the antibody-drug conjugate (e.g., interstitial lung disease for trastuzumab deruxtecan or suggestion of Gilbert's for sacituzumab govitecan). The ASCENT trial[5] was designed for patients with TNBC; the post hoc analysis demonstrated efficacy of sacituzumab for patents with HER2-low disease, with a hazard ratio for median progression free survival (PFS) of 0.44 (95% confidence interval [CI], 0.27 to 0.72) when compared to chemotherapy of physician's choice in the ASCENT trial[5,7] (HER2 low, HR negative). In the DESTINY-Breast04 trial, the median PFS in the hormone receptor–negative cohort was 8.5 months (95% CI, 4.3 to 11.7) in the trastuzumab deruxtecan group and 2.9 months (95% CI, 1.4 to 5.1) in the physician's choice group (hazard ratio = 0.46; 95% CI, 0.24 to 0.89).[6] In the DESTINY-Breast04 trial,[6] the majority of patients were HR positive with only a small (n = 42) cohort being HR negative (TNBC). Therefore, in this population, sacituzumab govitecan could be considered as the preferred antibody-drug conjugate due to the breadth of the data and confidence in the hazard ratios for PFS and OS. The panel noted that further studies and data are required in this area, and unless a head-to-head trial is conducted, there is a need to remain flexible and open as the landscape is rapidly evolving. In the absence of data, the choice would be individualized and may be also guided by the treatment regimen the treating clinician may deem more tolerable to a patient based on their clinical profile.

Treatment Considerations in the ER-Low Setting

The panel acknowledged the report from the pathology panel that ER-low category requires some judgment from the medical oncologist. Individuals with weakly HR-positive disease(1% to 10% staining by IHC) may be funded without prior endocrine therapy if antiestrogen therapy is not advised by the treating oncologist. Individuals who are interpreted to be weakly HR positive (1% to 10% staining by IHC) and are deemed functionally negative by medical oncologists may pursue therapies based on the funding algorithm for TNBC with support from the most recent pathology biopsy results.

Treatment is guided by tumour biology and if there is change in tumour biology status on a repeat biopsy results, then an reassessment may be warranted, with subsequent change in treatment regimen. However, the panel indicated that a TNBC designation is unlikely to change on repeat biopsy.

Other Information

As additional information pertinent to the panel discussion, the panellists suggested reopening the discussion regarding allowing combination pembrolizumab with either capecitabine or olaparib in patients with residual disease following neoadjuvant chemotherapy as per KEYNOTE-522. The panellists believe that there is no rationale to exclude this regimen, particularly in patients with a residual cancer burden score of 2 to 3 with high risk of future relapse despite adjuvant pembrolizumab. They noted that the population of patients with *BRCA*-mutated triple TNBC with residual disease post the KEYNOTE-522 regimen will be low and that clinicians should be able to offer the combination of olaparib with pembrolizumab in this population

(at least with a residual cancer burden of 2 to 3). The panellists feel that not allowing combination use of pembrolizumab with capecitabine presents a national equity issue.

Final Advice and Rationale on the Funding Algorithm

PAG has reviewed the implementation advice as recommended by the clinician panellists. Efforts are made to incorporate the advice while balancing the need for system affordability and sustainability. In the spirit of consistency with treatment implementations across jurisdictions, advice without or based on insufficient or evolving evidence may not be endorsed, or may be recommended to be revisited at a later time when more high-quality evidence is available.

PAG will endorse all with the following exception:

- PAG acknowledges 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.
- PAG acknowledges the panel's wish to reopen the discussion regarding the combination use of pembrolizumab with either capecitabine or olaparib in patients with residual disease following neoadjuvant chemotherapy in TNBC. There is a lack of efficacy data to support this combination use, although safety data are available. As such, the decision remains that this combination use should not be funded until additional evidence is available. PAG also acknowledges that there are differences in dispensing and/or reimbursement adjudication systems across the jurisdictions. This results in some jurisdictions having close oversight of prescribing leading to careful reinforcing of evidence-informed funding algorithms, whereas other jurisdictions may not have visibility of outpatient prescribing of certain medications that fall within evidence-informed funding algorithms.

Additional remarks:

- There are 2 metastatic treatment options under discussion: sacituzumab govitecan and trastuzumab deruxtecan, which are available to patients with HR-negative HER2-low disease. The panel was advised at the meeting that in the absence of evidence for a benefit to the sequencing of sacituzumab govitecan and trastuzumab deruxtecan, provincial jurisdictions aren't planning on funding these drugs in sequence. PAG supports the panel's advice to allow patients to switch between sacituzumab govitecan and trastuzumab deruxtecan due to intolerance or toxicities, provided that the patients meet the eligibility criteria for both sacituzumab govitecan and trastuzumab deruxtecan and that there has been no disease progression on either therapy.
- PAG advises that, for patients who are classified as ER low based on the biopsy results, the clinicians may have an option to follow funded treatment options for HR-positive HER2-negative disease or TNBC, at their clinicians discretion. PAG advises that individuals who follow the treatments in the

HR-positive HER2 algorithm would render them ineligible for funding options in TNBC setting. Unless new information (e.g., new biopsy results) becomes available to guide different treatment options, individuals should consistently pursue treatments based on the same funding algorithm (e.g., HR-positive HER2-negative disease or TNBC but not switch between the 2 algorithms).

- Finally, PAG has a mandate to support recommendations issued by pERC for implementation across the various jurisdictions. However, the final decisions for how these therapies are to be implemented reside with the individual jurisdictions, where they may adapt the advice locally based on regional differences and needs.

Provisional Funding Algorithm

Patients with HR-positive low disease 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 individuals who follow the treatments in the HR-positive HER2-negative algorithm would become ineligible for funding options for the 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-positive HER2-netigative or TNBC but not switch between the 2 algorithms).

Figure 1, Figure 2, and Figure 3 depict the provisional funding algorithm proposed by the panel and approved by PAG. Note that these diagrams are a summary representation of the drug funding options for the condition of interest. They 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 diagram may not contain a comprehensive list of all available treatments, and some drugs may not be funded in certain provinces. All drugs are subject to explicit funding criteria, which may also vary between provinces. Readers are invited to refer to the individual drug entries on the CADTH website for more details.

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

Adjuvant Setting

In the adjuvant settings, there are now 2 new 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 adults with deleterious or suspected deleterious gBRCAm, HER2-negative high-risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy. Olaparib is under review for funding.

Metastatic Setting

For patients who have no prior use of abemaciclib and 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.

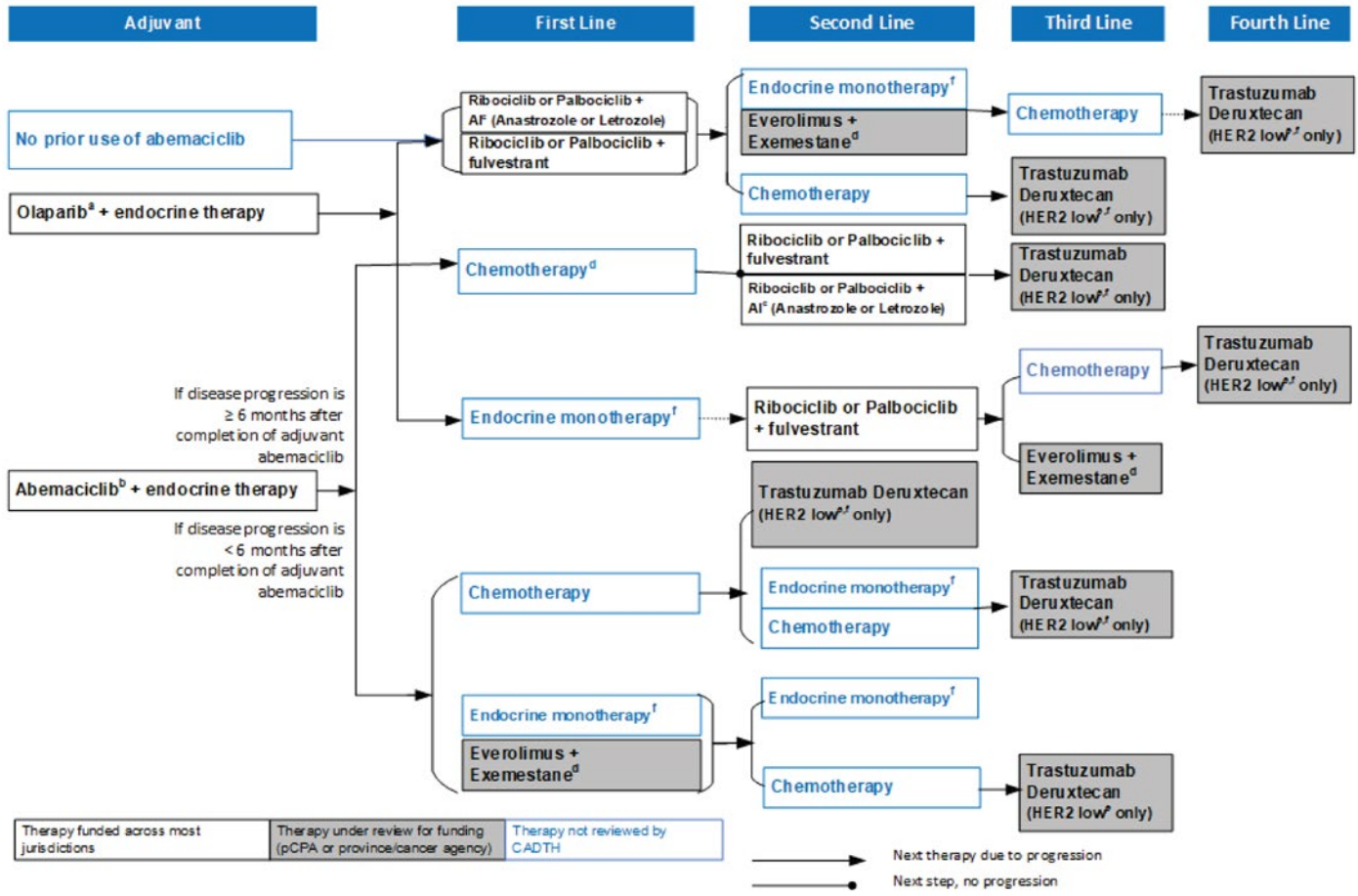
- If chemotherapy is selected as first-line treatment to achieve initial adequate response due to suspected visceral crisis, or when not endocrine responsive, additional maintenance options include ribociclib or palbociclib combined with an aromatase inhibitor or with fulvestrant.
- Third-line options may include chemotherapy or trastuzumab deruxtecan for patients who meet the eligibility criteria for HER2 low, including having pathology results for IHC 1+ or IHC 2+ with in situ hybridization (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. Trastuzumab deruxtecan is currently 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 negative. In addition, patients with HR-positive breast cancer should have received at least 1 endocrine therapy or be no longer considered for endocrine therapy. Trastuzumab deruxtecan is currently under review for funding. 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.
- The second-line options for patients whose first-line metastatic options included endocrine monotherapy or everolimus-exemestane, are endocrine monotherapy or chemotherapy. Upon completion of chemotherapy, their subsequent option may include trastuzumab deruxtecan. 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 for endocrine therapy. Trastuzumab deruxtecan is currently 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-positive HER2-negative disease or TNBC but not switch between the 2 algorithms).

Figure 1: Provisional Funding Algorithm Diagram For HR-Positive HER2-Negative 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, vinorelbine, gemcitabine, eribulin, or combinations therapies.

Endocrine monotherapy options include anastrozole or letrozole, exemestane, tamoxifen, 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, or 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).

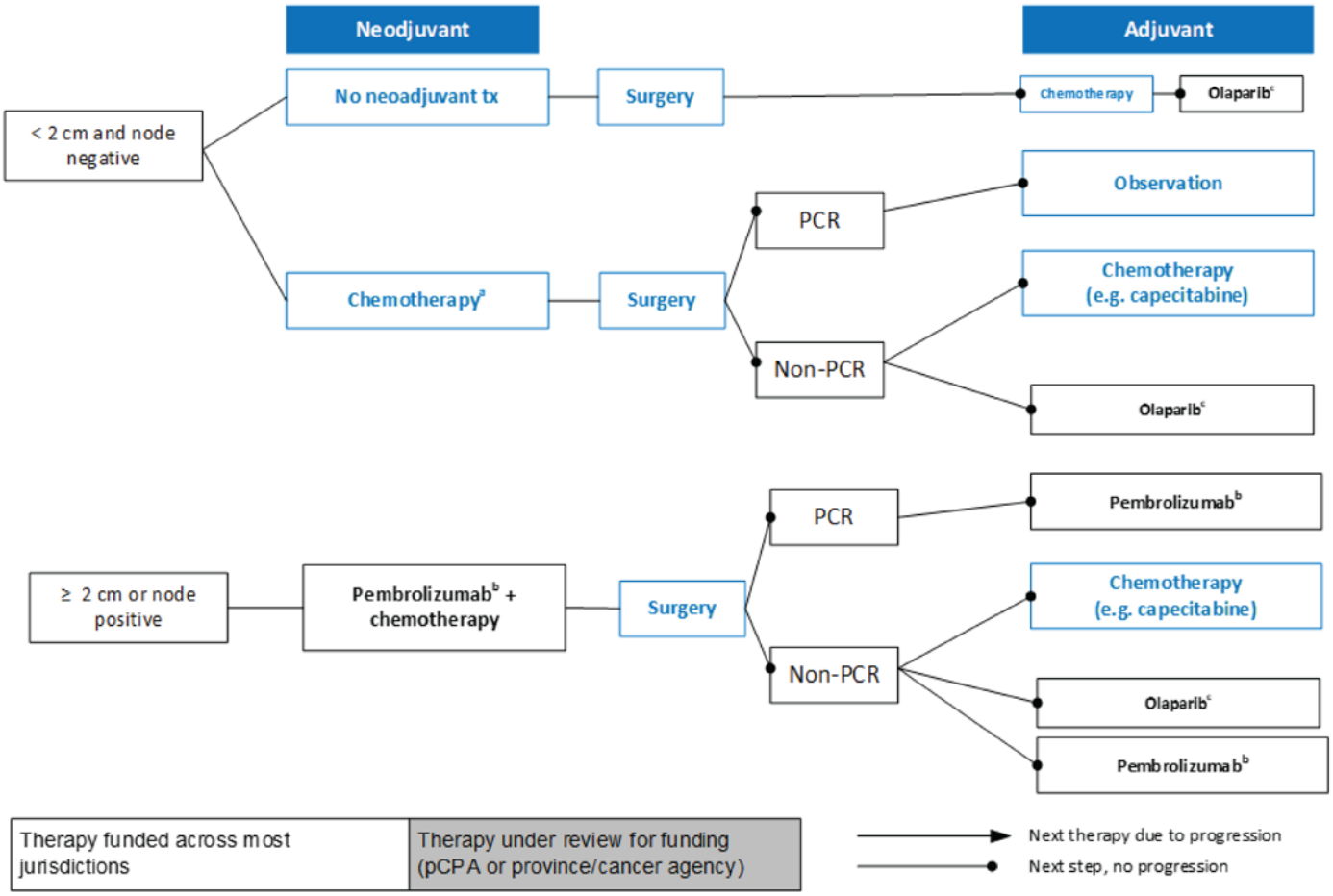
[c] In some jurisdictions, aromatase inhibitors may also include exemestane. Everolimus plus exemestane is under review for funding by the provinces or cancer agencies.

[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 in situ hybridization negative.

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

Figure 2: Provisional Funding Algorithm Diagram for the Neoadjuvant and Adjuvant Setting for Triple-Negative Breast Cancer, With Inclusion of HER2 Low



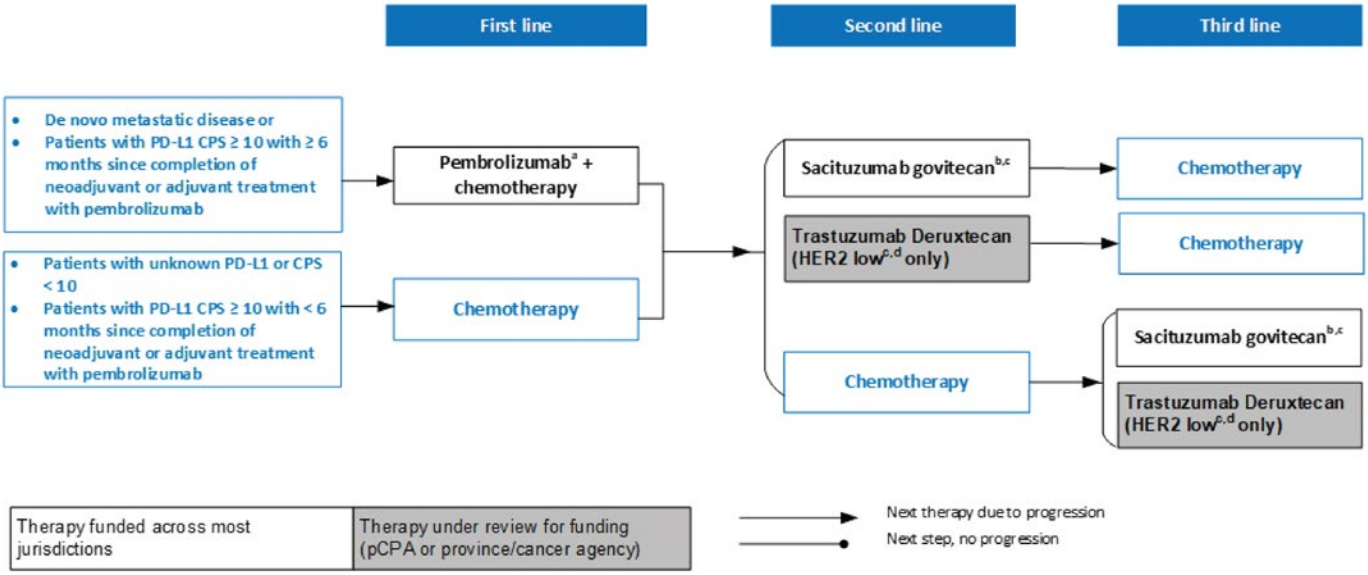
pCPA = pan-Canadian Pharmaceutical Alliance; pCR = pathological complete response.

[a] Patients who have received neoadjuvant chemotherapy must be assessed after surgery. If pCR is not achieved, they may go on to receive further adjuvant treatments (e.g., chemotherapy).

[b] Pembrolizumab should be funded for a maximum of 1 year of 17 cycles in patients without disease progression in this neoadjuvant and adjuvant setting.

[c] Patients with deleterious or suspected germline *BRCA* mutation must have completed neoadjuvant or adjuvant chemotherapy containing anthracyclines, taxanes, or a combination of both.

Figure 3: Provisional Funding Algorithm Diagram for Metastatic Setting for Triple-Negative Breast Cancer, With Inclusion of HER2 Low



CPS = combined positive score; HER2 = human epidermal growth factor 2; HR = hormone receptor; IHC = immunohistochemistry; pCPA = pan-Canadian Pharmaceutical Alliance; PD-L1 = programmed cell death 1 ligand 1; TNBC = triple-negative breast cancer.

Note: Individuals who are weakly HR positive (1 to 10% staining by IHC) and are deemed functionally negative by medical oncologists may pursue therapies based on this funding algorithm for TNBC as per the most recent pathology biopsy results. Note that this would render these individuals ineligible for funding options in the HR-positive HER2-negative 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-positive HER2-negative disease or TNBC but not switch between the 2 algorithms).

[a] Patients must be PD-L1 positive with a CPS of ≥ 10. Pembrolizumab should be funded for a maximum of 35 cycles (200 mg every 3 weeks) or 18 cycles (400 mg every 6 weeks), or 2 years, whichever is longer in this metastatic TNBC setting.

[b] Patients must have received 2 or more prior therapies, at least 1 of them for metastatic disease (including a taxane, regardless of disease stage).

[c] Patients who develop intolerance or toxicities may be considered for switching between sacituzumab govitecan and trastuzumab deruxtecan, provided they meet the eligibility criteria for both sacituzumab govitecan and trastuzumab deruxtecan and that there has been no disease progression on either therapy.

[d] Patients with HER2-low disease must have the following pathology results: IHC 1+ pr IHC2+ with ISH negative.

Neoadjuvant and Adjuvant Options for TNBC, With Inclusion of HER2 Low (Figure 2)

For patients who are node negative with less than 2 cm involvement, neoadjuvant options include no neoadjuvant treatment or neoadjuvant chemotherapy.

- For patients who have not received any neoadjuvant treatment before surgery, the adjuvant options include chemotherapy followed by olaparib (for *BRCA1* or *BRCA2* germline mutation carriers). For patients to receive adjuvant olaparib therapy, they must have completed neoadjuvant or adjuvant chemotherapy containing anthracyclines, taxanes, or a combination of both.
- For patients who have received neoadjuvant chemotherapy, the adjuvant treatment options depend on whether a pathological complete response (pCR) is achieved or not. If pCR is achieved, observation is recommended. For those who have not achieved pCR, options include chemotherapy (e.g., capecitabine) or adjuvant olaparib therapy for germline *BRCA1* or *BRCA2* carriers. For patients to receive adjuvant olaparib therapy, they must have completed neoadjuvant or adjuvant chemotherapy containing anthracyclines, taxanes, or a combination of both.

For patients who are node positive with tumour size of 2 cm or greater, the neoadjuvant option is pembrolizumab in combination with chemotherapy. Note that pembrolizumab should be funded for a maximum of 1 year or 17 cycles in patients without disease progression in the neoadjuvant and adjuvant setting.

- After receiving neoadjuvant treatment, patients should be assessed for pCR. If pCR is achieved, they can continue with adjuvant pembrolizumab therapy. If pCR is not achieved, they have the following adjuvant options: chemotherapy (e.g., capecitabine), olaparib (for germline *BRCA1* and *BRCA2* carriers), or pembrolizumab. Currently these therapies are not funded in combination. For patients to receive adjuvant olaparib therapy, they must have completed neoadjuvant or adjuvant chemotherapy containing anthracyclines, taxanes, or a combination of both (and have germline *BRCA1* or *BRCA2* mutation).

Metastatic Options for TNBC, With Inclusion of HER2 Low (Figure 3)

In the metastatic setting for TNBC, the first-line options include pembrolizumab in combination with chemotherapy or chemotherapy alone.

Patients with a programmed cell death 1 ligand 1 (PD-L1) of 10 or greater (de novo metastatic disease, no prior PD-L1 therapy, or ≥ 6 months from prior PD-L1 therapy) may receive pembrolizumab in combination of chemotherapy in the first-line setting.

For patients with an unknown PD-L1 or a combined positive score of less than 10, or those with a PD-L1 combined positive score of 10 or greater with less than 6 months since completion of neoadjuvant or adjuvant treatment with pembrolizumab, the first-line metastatic option is chemotherapy.

The second-line options include sacituzumab govitecan, trastuzumab deruxtecan, and chemotherapy. To be eligible for sacituzuamb govitecan, patients must have received 2 or more prior therapies, at least 1 of them for metastatic disease (including a taxane, regardless of disease stage). Patients receiving trastuzumab deruxtecan must meet the eligibility criteria for HER2 low. Patients who develop intolerance or toxicities may be considered for switching between sacituzumab govitecan and trastuzumab deruxtecan, provided they meet the eligibility criteria for both sacituzumab govitecan and trastuzumab deruxtecan and that there has been no disease progression on either therapy.

If the patient has received second-line chemotherapy, the third-line option may include sacituzumab govitecan or trastuzumab deruxtecan. To be eligible for sacituzuamb govitecan, patients must have received 2 or more prior therapies, at least 1 of them for metastatic disease (including a taxane, regardless of disease stage). To be eligible for trastuzumab deruxtecan, the patient must meet the eligibility criteria for HER2 low.

If the patient has received sacitizumab govitecan or trastuzumab deruxtecan as a second-line option, the third-line option may include further chemotherapy.

Individuals who are interpreted to be weakly HR positive (1% to 10% staining by IHC) and are deemed functionally negative by medical oncologists may pursue therapies based on this funding algorithm for TNBC with support from the most recent pathology biopsy results. Note that this would render these individuals

ineligible for funding options for HR-positive HER2-negative setting. Unless new information (e.g., new biopsy results) become available to guide different treatment options, individuals should consistently pursue treatments from the same funding algorithm (e.g., HR-positive HER2-negative disease or TNBC but not switch between the 2 algorithms).

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Appendix 1: Past CADTH Advice and Recommendations

Note that this appendix has not been copy-edited.

Table 2: Relevant CADTH Recommendations for HR+ HER2– Breast Cancer

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
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

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		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 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 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

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		1.1.2. Those with THR-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,

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		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.

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
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

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		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

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		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 3: Relevant CADTH Recommendations for TNBC

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
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. 1.1.2.1. 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.

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		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.
Pembrolizumab (Keytruda)	January 24, 2023	pERC recommends that pembrolizumab be reimbursed in combination with chemotherapy, for the treatment of adult patients with locally recurrent unresectable or metastatic TNBC who have not received prior chemotherapy for metastatic disease and whose tumours express PD-L1 (CPS ≥ 10) as determined by a validated test, only if the following conditions are met: 1. Treatment with pembrolizumab in combination with chemotherapy should be reimbursed when initiated in patients who have all of the following: 1.1. metastatic breast cancer or locally recurrent inoperable breast cancer that cannot be treated with curative intent 1.2. not previously treated with chemotherapy in the metastatic or incurable locally advanced setting 1.3. centrally confirmed TNBC, as defined by the most recent ASCO/CAP guidelines[a] 1.4. PD-L1 positive tumours (CPS ≥ 10) 1.5. at least 6 months' time interval between the completion of treatment with curative intent and first documented local or distant disease recurrence.

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		2. Patients must not have: 2.1. unstable CNS metastases 2.2. a clinical contraindication to immunotherapy. 3. Patients should have good performance status. 4. Treatment should be discontinued upon the occurrence of any of the following: 4.1. clinical disease progression 4.2. unacceptable toxicity. 5. Pembrolizumab should be reimbursed for a maximum of 35 cycles (200 mg every 3 weeks) or 18 cycles (400 mg every 6 weeks), or 2 years, whichever is longer. Chemotherapy can be continued beyond this time. 6. Patients are allowed to discontinue 1 or more components of the study treatment at the discretion of the treating clinician in case of serious adverse events. 7. Pembrolizumab in combination with chemotherapy should be prescribed by clinicians with expertise and experience in treating breast cancer; treatment should be delivered in institutions with expertise in immunotherapy drug delivery. 8. Pembrolizumab in combination with chemotherapy (i.e., paclitaxel, nab-paclitaxel, or gemcitabine plus carboplatin) should only be reimbursed when administered in combination. 9. A reduction in price. **Guidance on sequencing:** pERC agreed that treatment with pembrolizumab in combination with chemotherapy may be reasonable if disease recurred at least 6 months post completion of neoadjuvant or adjuvant treatment with pembrolizumab.
Pembrolizumab (Keytruda)	September 19, 2022	pERC recommends that pembrolizumab be reimbursed for the treatment of adult patients with high-risk, early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, only if the following conditions are met: 1. Treatment with pembrolizumab should be initiated only in nonmetastatic ER-negative, PR-negative, HER2–negative breast cancer patients who are: 1.1. suitable for neoadjuvant chemotherapy 1.2. clinically node-positive or cT1c, N1 to 2 or T2 to 3, N0 to 2 (per American Joint Committee on Cancer). 2. Patients must have all of the following: 2.1. good performance status 2.2. no prior systemic therapy for nonmetastatic TNBC 2.3. no clinical contraindication to immunotherapy. 3. To continue in the adjuvant setting, pembrolizumab should be renewed for patients whose treatment is tolerable and whose disease has not progressed before surgery.

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		4. Patients should be assessed for evidence of disease progression as per standard practice. 5. Treatment with pembrolizumab should be discontinued upon the occurrence of any of the following: 5.1. clinical disease progression 5.2. unacceptable toxicity. 6. The maximum duration of reimbursement in the neoadjuvant and adjuvant setting is up to 1 year or 17 cycles in patients without disease progression. 7. Pembrolizumab should only be prescribed by clinicians with expertise and experience in treatment breast cancer. 8. Pembrolizumab should be prescribed in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery. 9. A reduction in price. 10. The feasibility of adoption of pembrolizumab must be addressed. **Guidance on sequencing:** • pERC acknowledged that standard of care now incorporates adjuvant capecitabine; however, there are no available data to inform the relative efficacy and safety of adjuvant capecitabine vs. adjuvant pembrolizumab after neoadjuvant chemotherapy, nor for the combination of capecitabine with pembrolizumab in the adjuvant setting for this patient population. • The clinical experts noted that, unfortunately, the major gap is data availability. The clinical experts noted that it is unclear what should be done (e.g., no capecitabine at all, even if there is no pCR; or attempt pembrolizumab; or stop pembrolizumab and switch to capecitabine). The clinical experts highlighted that similar issues exist with adjuvant olaparib.
Sacituzumab govitecan (Trodelvy)	February 11, 2022	pERC recommends that sacituzumab govitecan be reimbursed for the treatment of adult patients with unresectable locally advanced TNBC or mTNBC who have received 2 or more prior therapies, at least 1 of them for metastatic disease, only if the following conditions are met: 1. Treatment with sacituzumab govitecan should be initiated only in adult patients with unresectable locally advanced TNBC or mTNBC who have received 2 or more prior therapies, at least 1 of them for metastatic disease (including a taxane, regardless of disease stage). 2. Patient must have good performance status. 3. Patient must have all of the following: 3.1. adequate blood counts and organ function 3.2. stable brain metastases or no brain metastases 3.3. no Gilbert disease.

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		4. Assessment for renewal of sacituzumab govitecan should be based on clinical and radiographic evaluation performed every 6 to 9 weeks for the first 9 months after treatment initiation. 5. Treatment with sacituzumab govitecan should be discontinued upon the occurrence of any of the following: 5.1. documented radiographic disease progression 5.2. unacceptable toxicity attributed to sacituzumab govitecan 5.3. clinical deterioration. 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 felt that if a patient was intolerant to a taxane, they were exposed to a taxane and therefore would meet the inclusion criteria (as there was no stipulation for duration of taxane treatment); and that if a patient had a contraindication (e.g., peripheral neuropathy), pERC agreed it would be reasonable to offer sacituzumab govitecan. • pERC agreed with the clinical experts that if sacituzumab govitecan is available, most patients will use it in the second- or third-line setting; and if eligible, patients will likely use it as early as possible, according to the indication. pERC also agreed with the clinical experts that the impact on the treatment paradigm is not clear yet.
Atezolizumab (Tecentriq)	Withdrawn	NA

Table 4: CADTH Implementation Advice Panels on HR+ HER2– Breast Cancer

Date	Main revisions
March 23, 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.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.