Reimbursement Review

Provisional Funding Algorithm

Indication: Triple-Negative Breast Cancer

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

Publication date: June 2023

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

Background

Following a request from jurisdictions, CADTH will 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 triple-negative breast cancer. 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

This is the first provisional funding algorithm to be developed by CADTH in triple-negative breast cancer (TNBC). This funding algorithm aims to incorporate the following CADTH recommendations: sacituzumab govitecan for unresectable locally advanced or metastatic triple-negative breast cancer, pembrolizumab for high-risk early-stage triple-negative breast cancer in neoadjuvant and adjuvant setting, pembrolizumab for locally recurrent unresectable or metastatic triple-negative breast cancer, and olaparib for adjuvant treatment in adult patients with deleterious or suspected germline BRCA-mutated (gBRCAm), human epidermal growth factor receptor 2 (HER2)-negative high risk early breast cancer.

Table 1: Relevant CADTH Recommendations

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. 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

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

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		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. 2. Patients must not have: 2.1. unstable CNS metastases

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

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		PR-negative, HER2-negative breast cancer patients who are: 1.1. suitable for neoadjuvant chemotherapy 1.2. clinically node-positive or cT1c, N1-2 or T2-3, N0-2 (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. 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

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

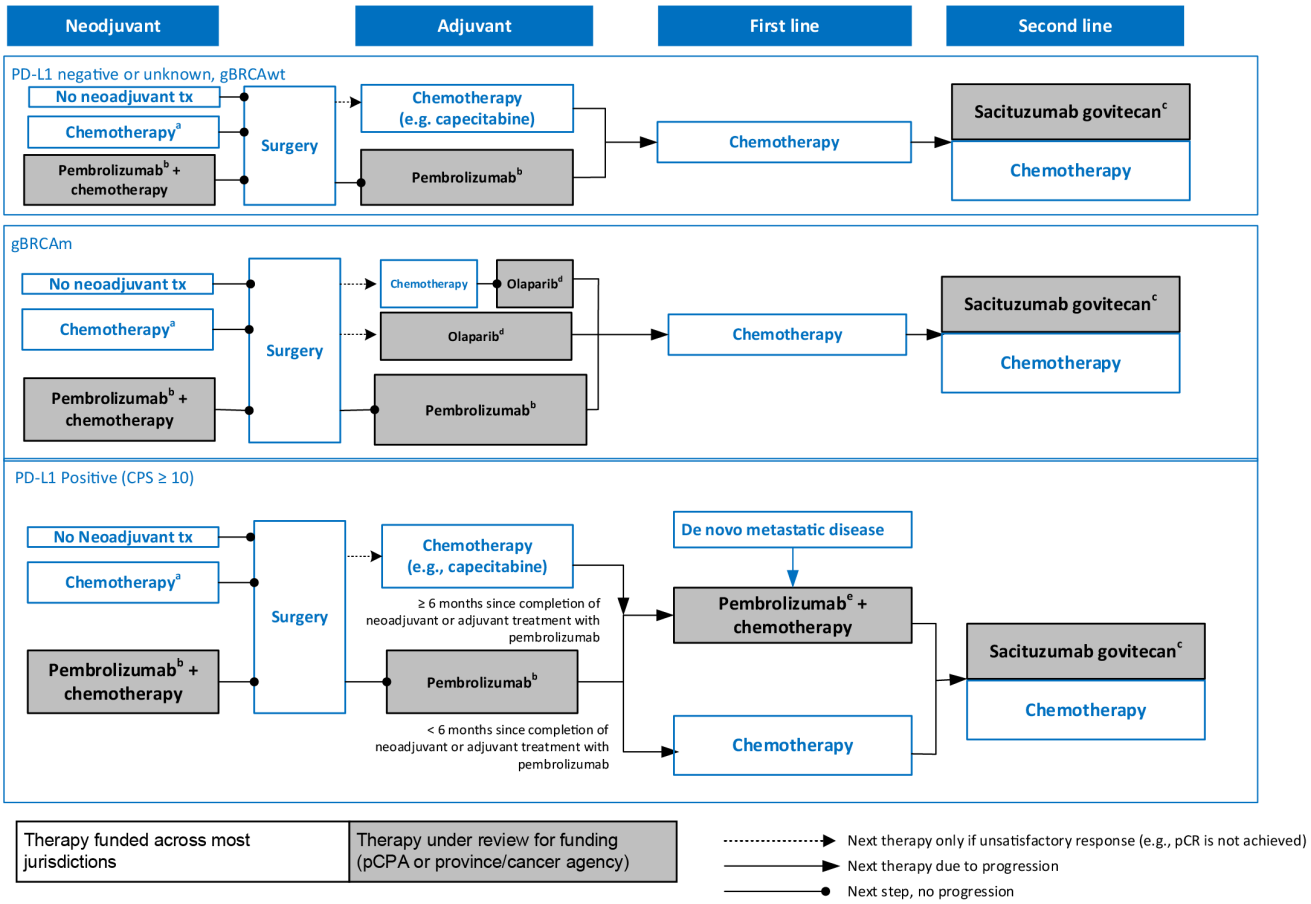
Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		5.2. unacceptable toxicity attributed to sacituzumab govitecan 5.3. clinical deterioration. 6. Sacituzumab govitecan should only be prescribed by clinicians with expertise and experience in treating 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

ASCO = American Society of Clinical Oncology; CAP = College of American Pathologists; CNS = central nervous system; CPS = combined positive score; ER = estrogen receptor; gBRCAm = germline *BRCA* mutation; gBRCAwt = negative for germline *BRCA* mutation; HER2= human epidermal growth factor receptor 2; HR = hormone receptor; mTNBC = metastatic triple-negative breast cancer; NA = not applicable; pCR = pathological complete response; PD-L1=programmed cell death 1 ligand 1; PR = progesterone receptor; TNBC = triple-negative breast cancer.

[a] The CPS + EG is a disease scoring system that includes clinical stage, estrogen receptor status, nuclear grade, and post-treatment pathologic stage

Provisional Funding Algorithm

Figure 1: Provisional Funding Algorithm Diagram for TNBC



CPS = combined positive score; gBRCAm = germline *BRCA* mutation; gBRCAwt = negative for germline *BRCA* mutation; mTNBC = metastatic triple-negative breast cancer; pCPA = pan-Canadian Pharmaceutical Alliance; pCR = pathological complete response; PD-L1=programmed cell death 1 ligand 1; TNBC = triple-negative breast cancer; tx = treatment.

[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 or pembrolizumab).

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

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

[d] Patients must have completed neoadjuvant or adjuvant chemotherapy containing anthracyclines, taxanes, or a combination of both.

[e] 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 mTNBC setting.

Description of the Provisional Funding Algorithm

PD-L1 Negative or Unknown, gBRCAwt Triple-Negative Breast Cancer

In the early stages of TNBC, patients have access to various chemotherapy regimens in the neoadjuvant and adjuvant settings. Also, not all patients will receive neoadjuvant treatment and may proceed directly to surgery.

Another option in the neoadjuvant setting is pembrolizumab, which can be given with chemotherapy and then continue as monotherapy as adjuvant treatment after surgery, as long as there is no disease progression. Currently, pembrolizumab is under review for funding in this setting.

In the metastatic setting, chemotherapy is the first-line option. Upon progression, second-line options include chemotherapy or sacitumab govitecan. For patients to be eligible for sacitumab govitecan, they must have received 2 or more prior therapies, at least 1 of them for metastatic disease (including a taxane, regardless of disease stage).

gBRCAm Triple-Negative Breast Cancer

In the early stages of TNBC, patients have access to various chemotherapy regimens in the neoadjuvant and adjuvant settings. Also, not all patients will receive neoadjuvant treatment and may proceed directly to surgery.

Another option in the neoadjuvant setting is pembrolizumab, which can be given with chemotherapy and then continue as monotherapy as adjuvant treatment after surgery, as long as there is no disease progression. Currently, pembrolizumab is under review for funding in this setting.

Another option in this setting is that following neoadjuvant or adjuvant chemotherapy containing anthracyclines, taxanes, or a combination of both, patients may also receive olaparib. Currently, olaparib is under review for funding.

In the metastatic setting, chemotherapy is the first-line option. Upon progression, second-line options include chemotherapy or sacitumab govitecan. For patients to be eligible for sacitumab govitecan, they must have received 2 or more prior therapies, at least 1 of them for metastatic disease (including a taxane, regardless of disease stage).

PD-L1 Positive (Combined Positive Score ≥ 10%) Triple-Negative Breast Cancer

In the early stages of TNBC, patients have access to various chemotherapy regimens in the neoadjuvant and adjuvant settings. Also, not all patients will receive neoadjuvant treatment and may proceed directly to surgery.

Another option in the neoadjuvant setting is pembrolizumab, which can be given with chemotherapy and then continue as monotherapy as adjuvant treatment after surgery, as long as there is no disease progression. Currently, pembrolizumab is under review for funding in this setting.

In the metastatic setting, chemotherapy is the first-line option. Pembrolizumab is also available in combination with chemotherapy for treatment of locally recurrent unresectable or metastatic TNBC (mTNBC), for patients who have not received prior chemotherapy for metastatic disease and whose tumours express programmed cell death 1 ligand 1 (PD-L1) with a combined positive score (CPS) greater than or equal to 10. To be funded in this setting, individuals must have received pembrolizumab 6 or more months since the completion of neoadjuvant or adjuvant treatment, or individuals must have de novo metastatic disease.

Upon progression, second-line options include chemotherapy or sacitumab govitecan. Both pembrolizumab and sacituzumab govitecan are under review for funding in this setting. For patients to be eligible for sacitumab govitecan, they must have received 2 or more prior therapies, at least 1 of them for metastatic disease (including a taxane, regardless of disease stage).

Additional Remarks

This provisional funding algorithm has been developed to align with pERC recommendations, as well as approved Health Canada indications. Pembrolizumab, for example, is approved for the treatment of adult patients with high-risk, early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, then continued as monotherapy as adjuvant treatment after surgery.

This report acknowledges that, based on stakeholder feedback, some clinicians may prefer to use different adjuvant treatment options after surgery based on disease response to neoadjuvant therapy and BRCA status. Although some international guidelines and references cite the combination use of pembrolizumab with capecitabine or olaparib based on safety data, there is a current absence of efficacy data to support the inclusion of combination use in the adjuvant setting in this funding algorithm.

It is also acknowledged that jurisdictions differ in their provision or delivery of orally administered anticancer agents; therefore, local policies and procedures will guide implementation of this funding algorithm.

Lastly, this report acknowledges the need to develop a pan-Canadian consensus for the definition of TNBC. Currently, there is jurisdictional variation in the pathologic reporting of estrogen receptor and progesterone receptor (ER/PR) status. Similarly, pathologic reporting of HER2 status also requires pan-Canadian discussion for the definition of “HER2 low” breast cancer. With support from the Canadian Association of Provincial Cancer Agencies, planning is underway by CADTH to establish a pan-Canadian

panel of pathologists and medical oncologists to address these pathologic definitions and implementation issues in the near future.