



Provisional Funding Algorithm

Indication: HER2-positive metastatic breast cancer

This report supersedes the CADTH Provisional Funding Algorithm report for HER2-positive metastatic breast cancer dated April 12, 2022.

Please always check [CADTH Provisional Funding Algorithms | CADTH](#) to ensure you are reading the most recent algorithm report.

Publication date: January 2023



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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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

Background

Following a request from jurisdictions, CADTH 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:

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

It should be noted 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.

Additionally, provisional funding algorithms 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 statuses. Revisions and updates will occur only upon request by jurisdictions.

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

History and Development of the Provisional Funding Algorithm

CADTH first published a [provisional funding algorithm report](#) for HER2-positive MBC in April 2022. This was a panel algorithm to address the use of pertuzumab-trastuzumab-taxane in patients with de novo metastatic disease or prior adjuvant use of trastuzumab or trastuzumab emtansine, as well as the appropriate sequencing of tucatinib-trastuzumab-capecitabine.

Jurisdictional cancer drug programs have recently requested to update this rapid algorithm to incorporate the [CADTH recommendation for trastuzumab deruxtecan](#) (Enhertu) for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received a prior treatment with an anti HER2-based regimen in the metastatic setting or developed disease recurrence during or within 6 months of completing neoadjuvant or adjuvant therapy.

Table 1: Relevant CADTH Recommendations

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
Trastuzumab deruxtecan (Enhertu)	October 17, 2022	<p>pERC recommends that trastuzumab deruxtecan be reimbursed for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received at least 1 prior anti-HER2-based regimen either in the metastatic setting, or in the neoadjuvant or adjuvant setting and developed disease recurrence during or within 6 months of completing neoadjuvant or adjuvant treatment conditional upon the cost-effectiveness and feasibility of adoption being improved.</p> <p>PAG noted that the proposed place in therapy for trastuzumab deruxtecan is currently occupied by trastuzumab emtansine (Kadcyla). The clinical experts consulted by CADTH for this review responded that based on the results of the DESTINY-Breast03 study, trastuzumab deruxtecan would likely displace trastuzumab emtansine as the second-line treatment of choice for patients with no contraindications in the metastatic setting. pERC acknowledged that some patients may choose therapy with trastuzumab emtansine based on its toxicity profile. pERC also noted that patients should be able to switch from trastuzumab deruxtecan to trastuzumab emtansine for toxicity reasons if there is no evidence of disease progression.</p>
Pertuzumab (Perjeta)	February 17, 2022	pERC recommends that pertuzumab in combination with trastuzumab and chemotherapy not be reimbursed for the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early-stage breast cancer (either > 2 cm in diameter or node positive).
Tucatinib (Tukysa)	November 17, 2021	pERC recommends that tucatinib in combination with trastuzumab and capecitabine be reimbursed for the treatment of patients with locally advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received prior treatment with trastuzumab, pertuzumab, and trastuzumab emtansine separately or in combination.

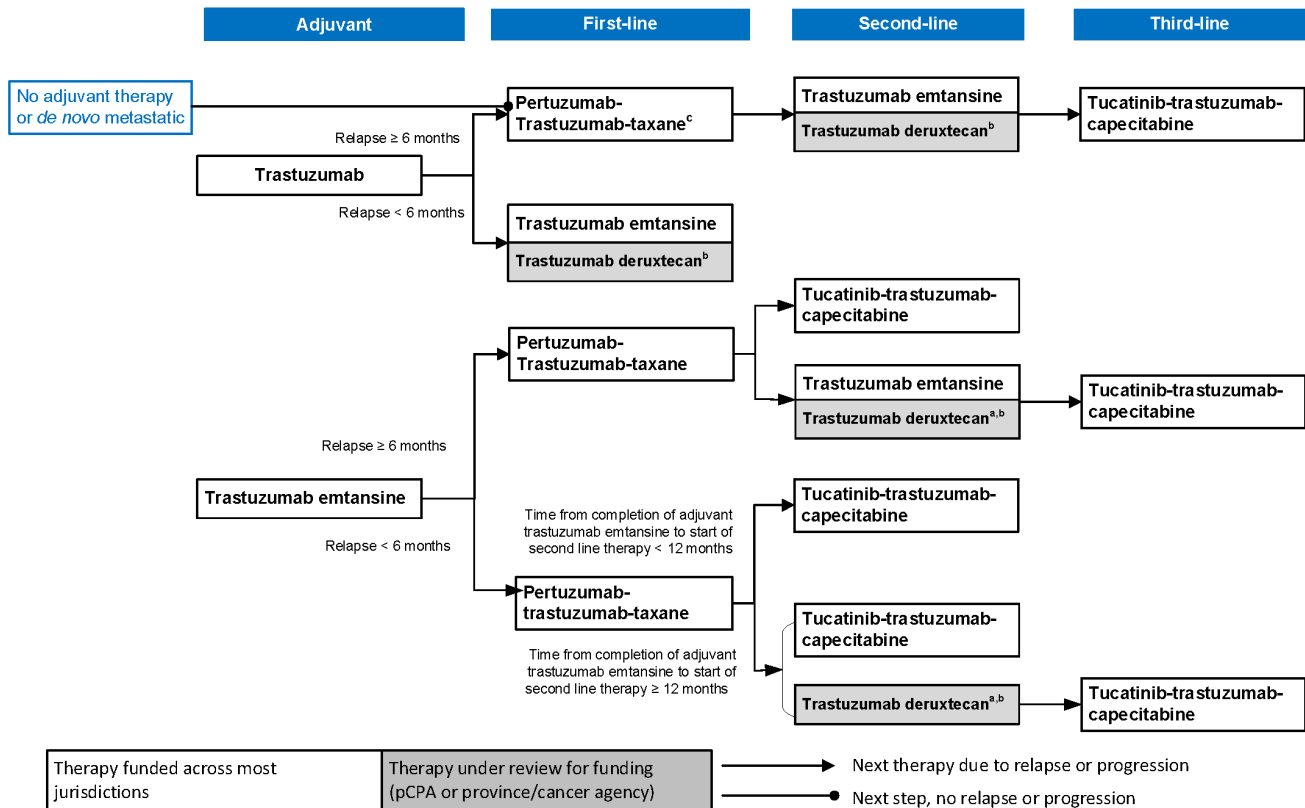


Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
Trastuzumab emtansine (Kadcyla)	January 22, 2020	pERC recommends the reimbursement of trastuzumab emtansine for the adjuvant treatment of patients with HER2-positive early breast cancer who have residual disease after preoperative systemic treatment.
Pertuzumab and trastuzumab (Perjeta- Herceptin Combo Pack)	November 29, 2018	pERC does not recommend reimbursement of pertuzumab in combination with trastuzumab and chemotherapy for the treatment of HER2-positive early breast cancer patients at high risk of recurrence. High risk of recurrence is defined as either node-positive or hormone receptor-negative disease.
Trastuzumab emtansine (Kadcyla)	January 10, 2014	pERC recommends funding trastuzumab emtansine (T-DM1) for patients with HER2-positive, unresectable locally advanced or metastatic breast cancer conditional on its cost-effectiveness being improved to an acceptable level. Funding should be for patients who have an ECOG performance status 0 or 1. Patients must have received prior treatment with trastuzumab plus chemotherapy in the metastatic setting or have disease recurrence during or within 6 months of completing adjuvant therapy with trastuzumab plus chemotherapy.
Pertuzumab and trastuzumab (Perjeta- Herceptin Combo Pack)	August 1, 2013	pERC recommends funding pertuzumab in combination with trastuzumab and a taxane (Perjeta) conditional on the cost-effectiveness being improved to an acceptable level. Funding should be for the palliative treatment of patients with HER2-positive unresectable locally recurrent or metastatic breast cancer with an ECOG status of 0 or 1 who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. In the case of patients who received trastuzumab in the adjuvant setting, pERC considered a 6-month interval in which patients had not relapsed to be a clinically reasonable time frame. However, pERC considered the length of this interval should be flexible and based on the judgment of the treating oncologist. pERC made this recommendation because it was satisfied that there is an overall clinical benefit of pertuzumab. However, the committee noted that pertuzumab could not be considered cost-effective at the submitted confidential price and the Economic Guidance Panel's estimates of the range of incremental cost-effective ratios.
Lapatinib (Tykerb)	July 5, 2013	pERC does not recommend funding lapatinib (Tykerb) in combination with letrozole in postmenopausal patients with hormone receptor positive, HER2-positive MBC. The committee made this recommendation because it was uncertain that there was an overall net clinical benefit of lapatinib plus letrozole when other effective treatment options are available and because lapatinib plus letrozole is not cost-effective compared with letrozole alone or compared with trastuzumab plus anastrozole.

ECOG = Eastern Cooperative Oncology Group Performance Status; HER2 = human epidermal growth factor receptor 2; MBC = metastatic breast cancer; PAG = Provincial Advisory Group; pERC = pan-Canadian Oncology Drug Review Expert Review Committee.

Provisional Funding Algorithm

Figure 1: Provisional Funding Algorithm Diagram for HER2-positive MBC



HER2 = human epidermal growth factor receptor 2; MBC = metastatic breast cancer; pCPA = pan-Canadian Pharmaceutical Alliance; pERC = pan-Canadian Oncology Drug Review Expert Review Committee.

^a Note that trastuzumab deruxtecan can be used in this setting if it has been ≥ 12 months from completion of adjuvant trastuzumab emtansine, independent of disease progression.

^b pERC noted that patients should be able to switch from trastuzumab deruxtecan to trastuzumab emtansine for toxicity reasons if there is no evidence of disease progression.

^c In some provinces, pertuzumab-trastuzumab-taxane may be available for patients who relapse less than 6 months after adjuvant trastuzumab.

Description of the Provisional Funding Algorithm

Patients With No Adjuvant Therapy or Patients Who Have Received Adjuvant Trastuzumab

For patients who do not receive any adjuvant therapy, are diagnosed de novo with metastatic disease or late relapse (with more than 6 months since the completion of prior adjuvant trastuzumab treatment), pertuzumab in combination with trastuzumab and taxane is funded in the first line. Upon progression, trastuzumab emtansine is

funded in the second line. Trastuzumab deruxtecan is currently under review for funding in the second line. In the third line, tucatinib-trastuzumab-capecitabine is funded.

If the patient's disease relapses within 6 months following the completion of adjuvant trastuzumab, the subsequent first-line option would be trastuzumab conjugate, which includes trastuzumab emtansine or trastuzumab deruxtecan. Trastuzumab deruxtecan is currently under review for funding.

Patients Who Have Received Adjuvant Trastuzumab Emtansine

Relapse 6 Months or More After Adjuvant Trastuzumab Emtansine

Patients who relapse 6 months or longer after completing treatment with adjuvant trastuzumab emtansine will have the first-line option of pertuzumab in combination with trastuzumab and taxane. The following are second-line options: tucatinib-trastuzumab-capecitabine, trastuzumab emtansine, and trastuzumab deruxtecan. Trastuzumab deruxtecan must be used for those who are 12 or more months from the completion of adjuvant trastuzumab emtansine, independent of disease progression. Individuals who have received either trastuzumab emtansine or trastuzumab deruxtecan are eligible for a third-line option of tucatinib-trastuzumab-capecitabine.

Relapse Fewer Than 6 Months After Adjuvant Trastuzumab Emtansine

Patients who relapse fewer than 6 months after completing adjuvant trastuzumab emtansine will also have the first-line option of pertuzumab in combination with trastuzumab and taxane. Both tucatinib-trastuzumab-capecitabine and trastuzumab deruxtecan are second-line options. Trastuzumab deruxtecan must be used for those who are 12 or more months from the completion of adjuvant trastuzumab emtansine, independent of disease progression. The third-line option for those who have received trastuzumab deruxtecan as a second-line option, can be tucatinib-trastuzumab-capecitabine.

Additional Remarks

Note that this rapid algorithm has been requested by jurisdictional cancer drug programs to incorporate the [new CADTH recommendation for trastuzumab deruxtecan](#) without changing any other drug implementation advice from previous panel discussions on the use of pertuzumab and chemotherapy following treatment with trastuzumab.

Particularly, this report continues to acknowledge that there are patients who may not have received treatment with pertuzumab, which continues to make them ineligible for subsequent treatment with the tucatinib-trastuzumab-capecitabine combination upon disease progression on antibody drug conjugates (e.g., trastuzumab emtansine or trastuzumab deruxtecan). This report continues to be supportive of more open access to tucatinib if the provinces decide to follow the pERC implementation guidance on tucatinib indicating combination therapy with tucatinib plus trastuzumab and capecitabine fills a treatment gap in patients who cannot receive pertuzumab or



antibody drug conjugates because of contraindications or toxicity issues, patients who relapse early on an antibody drug conjugate (as a first-line or second-line therapy), or patients who relapse early on trastuzumab, as there is an unmet need for these patients. However, there is also a lack of evidence to inform the use of tucatinib without prior exposure to pertuzumab. This is a limitation in the current treatment algorithm for these patients but the algorithm must align with the pERC recommendation for tucatinib and be consistent with Health Canada's approved indications. Some jurisdictions may have more flexible policies regarding the funding of pertuzumab, and clinicians may advise patients to receive pertuzumab triplet to be eligible for subsequent treatment with tucatinib. However, such treatment practices may not be ideal for this small subgroup of patients because of the lack of data informing efficacy and because it would be costly to jurisdictions. Therefore, treatment with tucatinib for patients who have not received prior treatment with pertuzumab should be considered on a case-by-case basis.