CADTH Reimbursement Review

Provisional Funding Algorithm

Indication: HER2-positive metastatic breast cancer

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CADTH

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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 three principal sources of information:

1) CADTH pCODR 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 status. Revisions and updates will occur only upon request by jurisdictions.

Jurisdictional cancer drug programs requested a CADTH provisional funding algorithm on 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 (T-DM1) 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 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	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 one 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 conditional upon the cost-effectiveness and feasibility of adoption being improved. 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.
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.
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.

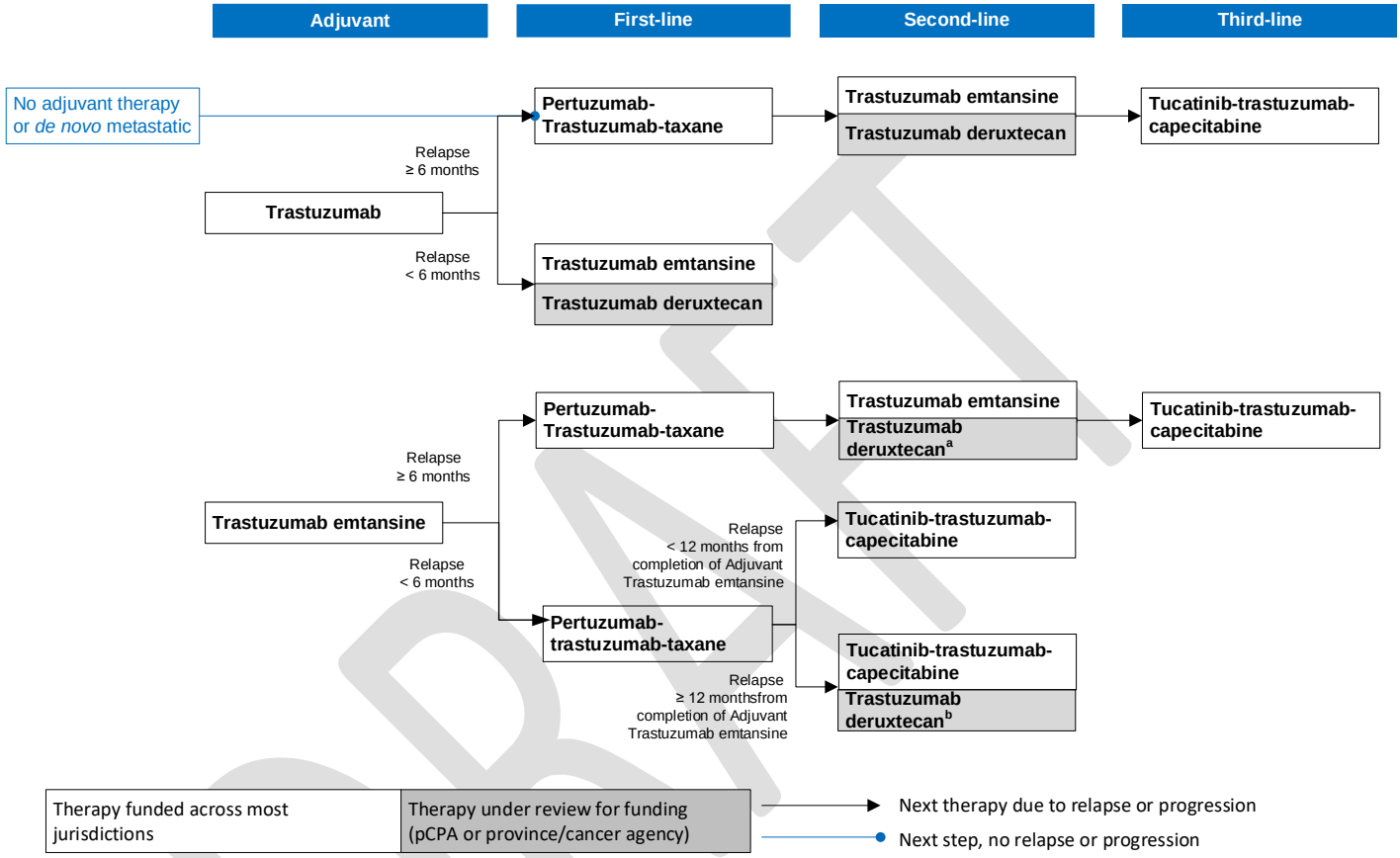
Trastuzumab emtansine (Kadcyla)	January 10, 2014	pERC recommends funding trastuzumab emtansine (T-DM1) for patients with HER2-positive, unresectable locally advanced or metastatic breast cancer conditional on its cost-effectiveness being improved to an acceptable level. Funding should be for patients 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 that a six-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; MBC = metastatic breast cancer; pERC = pan-Canadian Oncology Drug Review Expert Review Committee;

Provisional Funding Algorithm

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

Alt text: A flow diagram depicting the therapies that are funded or under review for funding across most jurisdictions for patients with HER2-positive MBC across adjuvant, first line, second line, and third line. Full description can be found below the figure.



[a] Note that trastuzumab deruxtecan can be used in setting if relapse is ≥ 12 months from completion of adjuvant trastuzumab emtansine

[b] An individual may relapse < 6 months from adjuvant use of Trastuzumab emtansine who have subsequently received pertuzumab-trastuzumab-taxane as a first-line option in the metastatic setting. To qualify for trastuzumab deruxtecan as a second line option, the relapse at that time must be ≥ 12 months from the completion of adjuvant trastuzumab emtansine.

pCPA = pan-Canadian Pharmaceutical Alliance

Description of the Provisional Funding Algorithm

Patients with no adjuvant therapy or *de novo* disease or late relapse with any prior adjuvant trastuzumab-based treatment

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 any prior adjuvant trastuzumab-based 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.

Prior adjuvant trastuzumab with early relapse (< 6 months)

if that patient's disease relapses within 6 months following the completion of adjuvant therapy of trastuzumab. The subsequent first line option would be trastuzumab conjucate including trastuzumab emtansine or trastuzumab deruxtecan. Trastuzumab deruxtecan is currently under review for funding.

Prior adjuvant trastuzumab emtansine

Patients who relapse less than 6 months after receiving treatment with trastuzumab emtansine in the adjuvant setting have the option of receiving pertuzumab in combination with trastuzumab and taxane in the first-line setting. Patients who relapse less than 12 months after completion of adjuvant trastuzumab emtansine, have the option of receiving tucatinib in combination with trastuzumab and capecitabine in the second line. For patients with disease relapse of 12 months or greater from adjuvant trastumab emtansine, the second line option would be a choice of tucatinib in combination with trastuzumab and capecitabine or trastuzumab deruxtecan.