CADTH

CADTH Reimbursement Review

Provisional Funding Algorithm

Indication: HER2-positive metastatic breast cancer

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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.

Key Messages

- For patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (MBC) whose disease relapses during or early (within 6 months) of adjuvant or neoadjuvant trastuzumab, subsequent therapy may include trastuzumab emtansine (T-DM1).
- For patients whose disease relapses during or early after (within 6 months) receiving treatment with T-DM1, subsequent therapy may include pertuzumab in combination with trastuzumab and chemotherapy, followed by tucatinib combination therapy.
- Less than 5% of patients may relapse during or early after (within 6 months) receiving treatment with trastuzumab or T-DM1.

Background

CADTH has reviewed and issued recommendations for drugs that can be used in adults with HER2-positive breast cancer.

pERC Recommendations for Tucatinib (Tukysa)

Based on the 2021 review of tucatinib for HER2-positive MBC through the CADTH pan-Canadian Oncology Drug Review (pCODR), the pan-Canadian Oncology Drug Review Expert Review Committee (pERC) issued the following reimbursement recommendation:

- CADTH recommends that tucatinib should be reimbursed by public drug plans 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 T-DM1, separately or in combination, if certain conditions are met:
  - Tukysa should only be reimbursed if prescribed in combination with trastuzumab-capecitabine and the cost of Tukysa is reduced.[1]

pERC Recommendations for Trastuzumab Emtansine (Kadcyla)

Based on the 2019 review of trastuzumab emtansine (T-DM1) for HER2-positive early breast cancer and the 2013 review of trastuzumab emtansine (T-DM1) for HER2-positive MBC, respectively, through the CADTH pan-Canadian Oncology Drug Review (pCODR), the pan-Canadian Oncology Drug Review Expert Review Committee (pERC) issued the following reimbursement recommendation:

- pERC recommends the reimbursement of T-DM1 for the adjuvant treatment of patients with HER2-positive early breast cancer who have residual disease after preoperative systemic treatment.[2]
- pERC recommends funding T-DM1 for patients with HER2-positive, unresectable locally advanced or metastatic breast cancer conditional on:
  - cost-effectiveness being improved to an acceptable level.[3]

pERC Recommendations for Pertuzumab (Perjeta)

Based on the 2021 and 2018 reviews of pertuzumab for HER2-positive early breast cancer and the 2013 review of pertuzumab for HER2-positive MBC, respectively, through the CADTH pan-Canadian Oncology Drug Review (pCODR), the pan-Canadian Oncology Drug Review Expert Review Committee (pERC) issued the following reimbursement recommendations:

- pERC recommends that pertuzumab in combination with trastuzumab and chemotherapy should not be reimbursed for the neoadjuvant treatment of patients with human epidermal growth factor receptor 2 (HER2)-positive, locally advanced, inflammatory, or early-stage breast cancer (either > 2 cm in diameter or node positive).[4]
- 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.[5]
- pERC recommends funding of pertuzumab in combination with trastuzumab and a taxane conditional on 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 6-month interval in which patients had not relapsed to be a clinically reasonable time frame.[6]

pERC Recommendations for Lapatinib (Tykerb)

Based on the 2013 review of lapatinib for HER2-positive MBC, through the CADTH pan-Canadian Oncology Drug Review (pCODR), the pan-Canadian Oncology Drug Review Expert Review Committee (pERC) issued the following reimbursement recommendation:

- pERC does not recommend funding lapatinib in combination with letrozole in postmenopausal patients with hormone receptor positive, HER2-positive MBC.[7]

Implementation Issues

At the request of the participating drug programs, CADTH convened a panel of Canadian clinical experts to provide advice for addressing the outstanding implementation issues as follows:

- the use of pertuzumab-trastuzumab-taxane in patients who relapse during or early after (within 6 months) treatment with trastuzumab or T-DM1 in curative setting
- relative frequency of patients with early-relapsing HER2-positive MBC.

Consultation Process and Objectives

The implementation advice panel comprised 6 Canadian specialists with expertise in the diagnosis and management of patients with HER2-positive MBC, 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 is not necessarily evidence-based but has been developed based on the experience and expertise of the implementation advice panel members; as such, it represents both evidence-based recommendation and experience-informed opinion.

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
Use of pertuzumab-trastuzumab-taxane in patients whose disease relapses during or early after (within 6 months) treatment with trastuzumab or T-DM1 in curative setting.	The panel advises that for patients whose disease relapses during or early after (within 6 months) treatment with trastuzumab, pertuzumab-trastuzumab-taxane chemotherapy should not be administered and T-DM1 should be the subsequent therapy. This suggestion was made based on the availability of T-DM1 as a funded option supported by results of the EMILIA trial which assessed treatment with T-DM1 and allowed for enrolment of patients with prior treatment with trastuzumab, including patients with early disease relapse. Additional information was provided by the Ontario Ministry of Health and the Ontario Health Breast Cancer Drug Advisory Committee in the form of unpublished data. This supplementary information included real-world data on the use of pertuzumab-trastuzumab-taxane in Ontario for the treatment of patients whose disease relapsed early (< 6 months; 125 patients) versus those whose disease relapsed late (≥ 6 months; 608 patients) after completing adjuvant therapy with trastuzumab. The provided data, collected between September 2013 and January 2022, suggested that mean duration of treatment was not statistically different between the patients who relapsed early after adjuvant trastuzumab versus those who relapsed late. The submitted data also included a Kaplan-Meier plot illustrating overall survival curves of patients who relapsed early versus late. The panel reviewed the submitted data and noted that there was considerable uncertainty around the methodological rigour of the data and the provided analysis results. The panel advises that patients whose disease relapses during or early (within 6 months) after prior treatment with T-DM1 can receive treatment with pertuzumab in combination with trastuzumab and chemotherapy. However, the panel was not aware of any relevant evidence to support this guidance, and made this recommendation based on the different mechanisms of action for each therapy.
Relative frequency of patients with early-relapsing HER2-positive MBC.	The panel advises that jurisdictions should anticipate less than 5% of patients with HER2-positive MBC to relapse during or early after (within 6 months) treatment with trastuzumab or T-DM1.

HER2 = human epidermal growth factor receptor 2; MBC = metastatic breast cancer; T-DM1 = trastuzumab emtansine.

In addition to the preceding advice, the panel indicated that all reimbursement recommendations were contingent upon ensuring improved cost-effectiveness so that the relevant treatments will be affordable to public payers.

Panel Discussion

Use of Pertuzumab-Trastuzumab-Taxane in Patients Whose Disease Relapses During or Early After (Within 6 Months) Treatment With Trastuzumab or Trastuzumab Emtansine

The panel was unaware of evidence to inform the use of pertuzumab in combination with trastuzumab and chemotherapy for patients whose disease relapsed during or early after (within 6 months) treatment with adjuvant trastuzumab. The panel stated that the CLEOPATRA trial assessed use of the pertuzumab combination therapy in the first-line metastatic setting. Eligibility criteria of the CLEOPATRA trial allowed for enrolment of patients previously treated with trastuzumab in the adjuvant or neoadjuvant setting; however, eligibility criteria also specified that patients must have been disease-free for a minimum of 12 months after the completion of adjuvant therapy. Therefore, patients whose disease relapsed early were not eligible for enrolment in the CLEOPATRA trial, and use of pertuzumab in combination with trastuzumab and chemotherapy among patients who relapsed early is unclear.

The panel felt uncertain that patients with relapsed disease during treatment with trastuzumab or early following treatment would benefit from the addition of pertuzumab and chemotherapy. Pertuzumab and trastuzumab both target the HER2 protein, and patients who progress on or soon after trastuzumab therapy would be unlikely to respond to another treatment with a similar mechanism. As trastuzumab emtansine (T-DM1) is also available to patients in the metastatic setting, the panel agreed that using this drug for these patients would be preferred over the pertuzumab combination. The panel referenced the EMILIA trial which compared T-DM1 to capecitabine plus lapatinib for HER2-positive MBC;[8] this trial included patients with prior treatment with trastuzumab within 6 months after treatment for early-stage disease. Therefore, the panel suggested that for patients whose disease relapses while or early after receiving trastuzumab, subsequent therapy should be T-DM1. However, the panel acknowledged that this group of patients would not have received treatment with pertuzumab, which makes them ineligible for subsequent treatment with the tucatinib-trastuzumab-capecitabine combination upon disease progression on T-DM1. The panel indicated that they would 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 T-DM1 because of contraindications or toxicity issues, patients who relapse early on T-DM1 (as a first-line or second-line therapy), or patients who relapse early on trastuzumab.[1] The panel discussed that there would be an unmet need for these patients, but that they were unaware of any evidence to inform the use of tucatinib without prior exposure to pertuzumab. The panel acknowledged this limitation in the current treatment algorithm for patients in this scenario but were unable to expand the tucatinib target population beyond that recommended by pERC and approved by Health Canada. The panel noted that 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, the panel suggested that treatment with tucatinib for such patients who have not received prior treatment with pertuzumab be considered on a case-by-case basis.

With a more recent approval of T-DM1 in the adjuvant setting, based on results of the KATHERINE trial,[9] the panel were supportive of using the pertuzumab combination as a subsequent therapy in the first-line metastatic setting for patients who received adjuvant T-DM1. The panel highlighted that, as an antibody drug conjugate, T-DM1 has a different mechanism of action compared with pertuzumab and trastuzumab, which are both monoclonal antibodies. Therefore, patients who relapse on or after T-DM1 are likely to benefit from the pertuzumab combination in the first-line metastatic setting because they will not have had previous exposure to this combination based on previous CADTH-issued funding recommendations in the adjuvant or neoadjuvant settings. Although the panel was unaware of evidence to support this treatment sequence, based on the differences in mechanisms of action, the panel was supportive of using the pertuzumab combination following relapse on T-DM1.

The panel were presented with additional real-world evidence submitted as part of stakeholder feedback to the initial draft algorithm from the province of Ontario regarding the use of pertuzumab in combination with trastuzumab and taxane for patients whose disease relapsed during or early after (within 6 months) treatment with trastuzumab. The information provided demonstrated that patients whose disease relapsed during or early after (within 6 months) treatment with trastuzumab had a similar mean duration of treatment with first-line pertuzumab in combination with trastuzumab and taxane compared with patients whose disease progressed after 6 months of adjuvant trastuzumab; the mean treatment durations were 455 days versus 505 days, respectively. The CADTH team noted limitations of the data provided, including a lack of information regarding the methodology conducted for this analysis, unclear information regarding patient characteristics, and the exploratory nature of the analysis because it was not clear whether a hypothesis was generated before data collection or analysis. In addition, it was noted that the analysis conducted did not have an appropriate comparator group because outcomes of patients whose disease relapsed early and received pertuzumab-trastuzumab-taxane were not compared with the outcomes of those whose disease relapsed early but did not receive pertuzumab-trastuzumab-taxane. The panel agreed with the critique of the evidence provided and also highlighted that the duration of treatment is not an appropriate end point for the assessment of the clinical efficacy of a treatment. Therefore, the panel maintained their position that patients whose disease relapses during or early after (within 6 months) treatment with trastuzumab may better benefit from treatment with T-DM1 than with the pertuzumab combination regimen in the first-line metastatic setting.

The panel discussed the issue of drug funding sustainability. Overall, there were comments about inequity of treatments across Canadian jurisdictions because treatment options and treatment algorithms are not uniform across Canada. Through initiating this algorithm panel, Canadian public drug programs aimed to standardize funding of this drug sequence for patients across all Canadian jurisdictions. The panel acknowledged the limited evidence available to inform the optimal treatment sequence for patients with early disease relapse on either trastuzumab or T-DM1.

Relative Frequency of Patients With Early-Relapsing HER2-Positive MBC

The panel members agreed that the expected frequency of cases of patients with HER2-positive MBC whose disease relapsed within 6 months of completing therapy with trastuzumab or T-DM1 would likely be very low. Although the panel did not know of an exact number of patients this subgroup may represent, it was acknowledged that cancer registries will likely have these data. The supplementary data provided by Ontario Ministry of Health and the Ontario Health Breast Cancer Drug Advisory Committee, as part of stakeholder

feedback, showed that a small proportion of patients who received first-line metastatic treatment with pertuzumab-trastuzumab-taxane experienced disease progression within 6 months of adjuvant therapy. The panel estimated that this subgroup of patients could represent less than 5% of patients with HER2-positive MBC.

Furthermore, the panel discussed that prevalent cases of patients may exist who were diagnosed and treated before the funding of pertuzumab combination therapy for the first-line metastatic setting; these patients would not have received pertuzumab and would be ineligible for tucatinib. Although unmet need was acknowledged for these patients, this was considered out of scope for this panel. The panel advised that jurisdictions consider funding for these patients on a time-limited basis.

Provisional Funding Algorithm

Figure 1 depicts the provisional funding algorithm proposed by the panel. Note that this diagram is a summary representation of the drug funding options for the condition of interest. It is not a treatment algorithm; it is 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.

De Novo Metastatic Disease or No Adjuvant Therapy

For patients who do not receive any adjuvant therapy or are diagnosed de novo with metastatic disease, first-line therapy is recommended to be pertuzumab in combination with trastuzumab and taxane. Upon progression, subsequent therapy is recommended to be T-DM1 in the second line and tucatinib-trastuzumab-capecitabine in the third line.

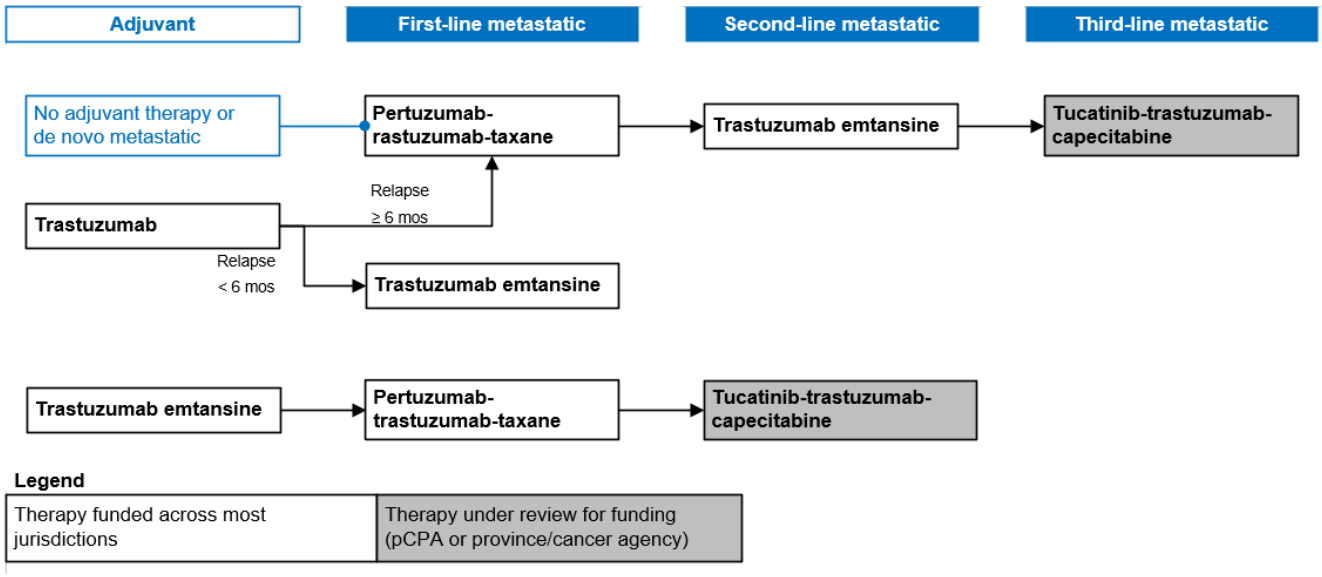
Prior Adjuvant Trastuzumab

For patients who received treatment with trastuzumab in the adjuvant setting, first-line metastatic treatment options can include pertuzumab in combination with trastuzumab and taxane if the patient's disease relapses 6 months or later after completion of adjuvant therapy or T-DM1 if the patient's disease relapses within 6 months following the completion of adjuvant therapy. Patients who experience progression after receiving pertuzumab plus trastuzumab and taxane in the first-line metastatic setting can then be offered T-DM1 in the second-line setting, followed by tucatinib-trastuzumab-capecitabine in the third line setting. No HER2-directed treatments were recommended upon progression for patients who received T-DM1 in the first-line metastatic setting.

Prior Adjuvant T-DM1

Patients who receive treatment with T-DM1 in the adjuvant setting are recommended to receive pertuzumab in combination with trastuzumab and taxane in the first-line metastatic setting upon progression. Subsequent therapy after the pertuzumab combination is recommended to be tucatinib-trastuzumab-capecitabine.

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



pCPA = pan-Canadian Pharmaceutical Alliance.

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