

## CADTH Reimbursement Recommendation

# Pertuzumab (Perjeta)

**Indication:** In combination with trastuzumab and chemotherapy 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)

**Sponsor:** Hoffmann-La Roche Limited

**Final recommendation:** Do not reimburse

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

## What Is the CADTH Reimbursement Recommendation for Perjeta?

CADTH recommends that Perjeta should not be reimbursed by public drug plans in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of human epidermal growth factor receptor 2 (HER2)-positive, locally advanced, inflammatory, or early-stage breast cancer (either > 2 cm in diameter or node positive).

## Why Did CADTH Make This Recommendation?

- Evidence from 2 clinical trials demonstrated that adding Perjeta to trastuzumab and chemotherapy for treatment before surgery to remove cancer increases the chance of having no residual cancer, but there was no evidence demonstrating improvements in long-term survival outcomes.
- It is unclear whether Perjeta meets the needs identified by patients, which included preventing recurrence and development of metastases, stabilizing disease, and maintaining quality of life.

## Additional Information

### What Is Breast Cancer?

HER2-positive breast cancers are those that start in the breast and have cells with high levels of HER2 protein. In 2020, there were approximately 27,200 new cases of breast cancer and 5,100 deaths from breast cancer in Canada.

### Unmet Needs in Breast Cancer

Although systemic treatment before surgery to remove cancer is meant to be curative, there is still a risk of the cancer returning.

### How Much Does Perjeta Cost?

Treatment with Perjeta is expected to cost approximately \$6,764 and \$3,382 for loading and maintenance doses, respectively, per 21-day cycle. When used in combination with trastuzumab and taxane chemotherapy, the sponsor estimated the cost of the loading dose to be \$11,563 and the 21-day cycle cost of the maintenance dose to be \$7,248.

## Recommendation

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (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).

## Rationale for the Recommendation

Patients identified a need for access to new effective treatments that prevent recurrence and development of metastases and stabilize disease, but the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) concluded there was uncertainty whether neoadjuvant pertuzumab meets this need given the limitations of the evidence on long-term outcomes. Two of the trials reviewed by pERC, NeoSphere and PEONY, included a comparison to a relevant treatment (trastuzumab plus docetaxel chemotherapy) and were the focus of pERC's deliberation. The NeoSphere and PEONY trials demonstrated that neoadjuvant (preoperative) treatment with pertuzumab in combination with trastuzumab and chemotherapy significantly improved pathologic complete response (pCR) rates, the primary outcome of both trials, compared with trastuzumab and chemotherapy. However, there is no evidence demonstrating that adding pertuzumab to trastuzumab and chemotherapy improves long-term outcomes. The longer-term outcomes assessed in each trial (NeoSphere: disease-free survival [DFS] and progression-free survival [PFS]; PEONY: overall survival [OS], DFS, event-free survival [EFS], and PFS), either did not show a statistically significant difference in outcome between the treatment groups (NeoSphere trial) or the data were considered immature by the sponsor and therefore were not available for review (PEONY trial). Neither trial was powered to assess survival end points. Therefore, there is no definitive evidence of improved survival when pertuzumab is added to trastuzumab and chemotherapy neoadjuvant treatment regimens. Although pERC acknowledged pCR is used as a decision point in the treatment pathway for early breast cancer, it remains unclear at the trial or population level whether the improvements in pCR observed with the addition of pertuzumab translate to clinically meaningful improvements in event-free or OS outcomes. Patients also desire access to new effective treatments for early breast cancer that have manageable side effects and maintain quality of life. pERC considered that the addition of pertuzumab to trastuzumab results in a manageable safety profile; however, no conclusions could be drawn on its impact on patient quality of life because none of the pivotal trials measured this outcome.

## Discussion Points

- pERC discussed that approximately 15% to 20% of patients diagnosed with early breast cancer are HER2-positive. HER2-positive breast cancer is not considered a rare condition, but it is associated with poorer prognosis without anti-HER2-positive treatment compared with prognosis for patients without HER2 overexpression. The introduction of HER2-directed therapy has significantly improved the outcomes of patients with HER2-positive breast cancer and neoadjuvant systemic treatment with trastuzumab and chemotherapy is the current standard of care in Canada for locally advanced, inflammatory, or early-

stage breast cancer (stages II and III). pERC agreed with the clinician input to CADTH that the intent of neoadjuvant treatment in early breast cancer is curative, and the goals of treatment are to downstage the tumour to avoid mastectomy in favour of less invasive breast-conserving surgery, assess the response to systemic therapy (pathologic response), reduce the risk of recurrence, maintain quality of life, and reduce the need for adjuvant (post-operative) trastuzumab emtansine (T-DM1), which is an effective treatment associated with a higher risk of toxicity than trastuzumab.

- pERC noted that since the 2015 recommendation issued by pERC for the same indication, there is additional evidence in the current submission from 1 phase III, double-blind, placebo-controlled trial, PEONY (N = 329), that compared pertuzumab-trastuzumab plus docetaxel to placebo-trastuzumab plus docetaxel in an Asian patient population with early-stage or locally advanced HER2-positive breast cancer. Data from the PEONY trial confirmed the results for the pCR end point from the NeoSphere trial, showing a statistically significant higher total pCR (tpCR) rate in the breast and axillary nodes with pertuzumab-trastuzumab and docetaxel compared with placebo-trastuzumab plus docetaxel (39.3% versus 21.8%) for a between-group difference in tpCR of 17.45% (95% CI, 6.89% to 28.01%; P = 0.0014). The pathologic complete response in the breast (bpCR) rate observed in the trial was consistent with the tpCR rate (42.0% versus 23.6%), for a between-group difference of 18.37% (95% CI, 7.60% to 29.15%). However, data on the long-term outcomes assessed in the PEONY trial, including OS, DFS, EFS, and PFS, were considered immature by the sponsor and were not available for review. The median time on study was █ weeks in the pertuzumab-trastuzumab plus docetaxel arm and █ weeks in the trastuzumab plus docetaxel arm. pERC noted that, similar to the NeoSphere trial, the PEONY trial was not powered to assess survival end points and quality of life outcomes were not measured.
- pERC considered evidence from meta-analyses that examined pCR as a surrogate end point for long-term outcomes in patients who have received neoadjuvant treatment for early breast cancer. Multiple meta-analyses have demonstrated an association between pCR and EFS or OS at the individual patient level based on responder analyses (i.e., comparisons of outcomes of patients with and without pCR irrespective of the neoadjuvant treatment received); however, at the trial or population level, there is insufficient evidence of an association and the magnitude of pCR improvement that is needed to predict long-term prognosis. pERC agreed that an association at both the individual and trial or population level is required to validate pCR as a surrogate end point for survival outcomes in the neoadjuvant treatment setting. pERC discussed that although pCR is a decision point in the treatment pathway for early breast cancer, its impact on long-term outcomes remains unclear.
- pERC discussed the evidence on breast-conserving surgery outcomes from the included trials (NeoSphere and TRYPHAENA) and noted that despite the higher rates of pCR achieved in the pertuzumab-containing treatment arms, no differences in rates of breast-conserving surgery were observed. In the NEOSPHERE trial, breast-conserving surgery occurred in 23.2% of patients in the pertuzumab-trastuzumab plus docetaxel arm and in 22.6% of patients in the trastuzumab plus docetaxel arm; similar results were reported in the TRYPHAENA trial. pERC acknowledged that the interpretation of these data is complicated by patients' and physicians' preferences for mastectomy versus breast-conserving surgery.

- In the NeoSphere and PEONY trials, the percentage of patients experiencing adverse events (AEs) and discontinuing treatment due to AEs was similar between pertuzumab-trastuzumab plus docetaxel and trastuzumab plus docetaxel trial arms. The most common AEs in both arms were alopecia, neutropenia, and diarrhea; the most common grade 3 or higher AE was neutropenia. pERC noted that the new evidence in the current submission did not signal any new safety concerns with pertuzumab and therefore considered that with the addition of pertuzumab to trastuzumab the safety profile remains manageable.
- Input from patient groups indicated that patients with early breast cancer desire new treatments that delay recurrence and the development of metastases while also maintaining quality of life. Based on the available evidence, pERC concluded there was uncertainty whether neoadjuvant pertuzumab meets these patient needs given the limitations of the available evidence on long-term outcomes and the absence of data assessing its impact on patient quality of life. pERC noted that EFS and OS data from the PEONY trial were expected in 2022 and discussed that the long-term data from this trial or other evidence could form the basis of a resubmission to CADTH.
- pERC discussed the economic evaluation results and agreed that the cost-effectiveness of adding pertuzumab to current standard of care of trastuzumab and chemotherapy was unknown given the limitations identified with the clinical evidence. The committee also noted that avoiding T-DM1 toxicity in the adjuvant setting is an important consideration for patients and acknowledged its inclusion in the submitted economic evaluation and budget impact analysis.

## Background

Pertuzumab is a monoclonal antibody that targets the extracellular dimerization domain of the HER2 receptor protein, blocking ligand-dependent heterodimerization of HER2 with other members of the HER family. Pertuzumab therefore inhibits ligand-initiated intracellular signalling through 2 pathways, the mitogen-activated protein kinase and phosphoinositide-3-kinase pathways, causing cell growth arrest and apoptosis. Pertuzumab has a Health Canada indication for use, in combination with trastuzumab and chemotherapy, 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).

## Submission History

The original CADTH review of neoadjuvant pertuzumab (July 16, 2015) was for off-label use for the same indication. It included 2 open-label randomized trials: NeoSphere and TRYPHAENA. NeoSphere (N = 417) was a 4-arm phase II trial that randomized patients with HER2-positive locally advanced, inflammatory, or primary operable breast cancer to trastuzumab plus docetaxel, pertuzumab-trastuzumab plus docetaxel, pertuzumab-trastuzumab, or pertuzumab plus docetaxel. TRYPHAENA (N = 225) was also a phase II trial in the same patient population that randomized patients to 1 of 3 arms: pertuzumab-trastuzumab in cycle 1 to cycle 6 plus FEC (fluorouracil, epirubicin, cyclophosphamide) in cycle 1 to cycle 3 and docetaxel in cycle 4 to cycle 6, FEC in cycle 1 to cycle 3 followed by pertuzumab-trastuzumab plus docetaxel in cycle 4 to cycle 6, or pertuzumab-trastuzumab

plus docetaxel and carboplatin in cycle 1 to cycle 6. pERC focused its deliberation on the NeoSphere trial because the TRYPHAENA trial included pertuzumab in all treatment groups. Based on evidence from the NeoSphere trial, pERC issued a “do not reimburse” recommendation and cited they could not conclude that neoadjuvant treatment with pertuzumab-trastuzumab plus docetaxel resulted in a net clinical benefit compared with trastuzumab and docetaxel because pCR had not been validated as a surrogate end point for either EFS or OS.

This new submission for neoadjuvant pertuzumab includes evidence from 4 pivotal trials: the NeoSphere and TRYPHAENA trials and 2 additional trials, PEONY and BERENICE, which are described in the Clinical Evidence section.

## Sources of Information Used by the Committee

To make their recommendation, pERC considered the following information:

- a review of 4 clinical studies (3 randomized controlled trials [RCTs] and 1 non-RCT) of neoadjuvant treatment in patients with early-stage HER2-positive breast cancer
- patient perspectives gathered by 2 patient groups: the Canadian Breast Cancer Network (CBCN) and Rethink Breast Cancer
- input from public drug plans and cancer agencies that participate in the CADTH review process
- two clinical specialists with expertise diagnosing and treating patients with early-stage HER2-positive breast cancer
- input from 2 clinician groups, including the BC Cancer Breast Tumour Group (BCC-BTG) and the Ontario Health (Cancer Care Ontario) Breast Cancer Drug Advisory Committee (OH-CCO's BCDAC)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

## Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient input and from clinical experts consulted by CADTH for the purpose of this review.

### Patient Input

- Two patient groups provided input: CBCN and Rethink Breast Cancer. Information was gathered by use of 2 online surveys (1 with 52 respondents [all Canadian] and 1 with 62 respondents [60% Canadian]) and a phone interview (11 interviewees).
- Patients described the emotional distress associated with a type of breast cancer with a poorer prognosis before the advent of HER2-directed therapy. Patients also noted the adverse effects associated with the disease and treatments (i.e., cardiotoxicity, fever, cough, muscle pain, fatigue, diarrhea, and nausea) and noted that the fatigue, pain,

and nausea most negatively impacted their daily lives. Patients also noted the financial burden associated with lost income and treatment costs, with 17% of respondents in 1 survey reporting a very large financial impact and 38% reporting some financial impact. Patients also indicated there is inequity of access to neoadjuvant treatments from private insurance coverage.

- The most important outcomes to patients were the elimination of cancer cells, prevention of recurrence and development of metastases, and stabilizing disease. Maintaining quality of life was also rated by the majority of patients as very important or important, as was managing adverse effects. In some cases, this meant avoiding chemotherapy and other intensive therapies, whereas some patients were clear that they were very willing to tolerate new adverse effects from drugs to extend life expectancy. Patients also desired equitable access to new effective treatments.

## Clinician Input

The input from the clinical experts consulted by CADTH included the following:

- Per indication, pertuzumab in the neoadjuvant setting would be used in combination with trastuzumab and chemotherapy. The shift in the treatment paradigm would simply be the addition of pertuzumab to the standard therapies already being used.
- The patients most likely to respond to the addition of pertuzumab would be those who have HER2-positive breast cancer. According to the clinical experts, all patients who are HER2-positive and are candidates for neoadjuvant therapy would be eligible for the addition of pertuzumab to their regimen, and those who are not candidates for either chemotherapy (due to being too ill) or for neoadjuvant therapy (small stage I cancer) would not be eligible for pertuzumab. It was noted that it is very rare for a patient to be too ill to receive chemotherapy in the neoadjuvant setting.
- The clinical experts noted that response in the neoadjuvant setting is determined at the time of surgery when pCR is assessed. Before surgery, patients would most likely be assessed every 2 weeks to 3 weeks when they receive their chemotherapy, typically by a physical examination, although sometimes it may be supplemented by imaging of the breast (ultrasound or MRI). If the tumour grows or does not respond during therapy, the chemotherapy protocol may be modified or the patient may be sent for surgery earlier than planned. A clinically meaningful response is shrinking of the tumour to facilitate surgical removal.
- One of the clinical experts consulted by CADTH believed that increasing pCR rates would result in a reduced risk of relapse in this population.
- With respect to deciding when to discontinue treatment, the clinical experts noted that this may occur if the tumour is growing, in which case surgery may be performed earlier than planned or, in some cases, other chemotherapy protocols may be instituted. Patients with clear disease progression after receiving 1 cycle or 2 cycles of optimized taxane-based chemotherapy should be considered for discontinuation.
- One clinical expert noted that the addition of pertuzumab to the current treatment paradigm is important because this is a curable disease that often occurs in younger patients. The other clinical expert noted the importance of increased rates of tumour downstaging and pCR in reducing longer-term treatment-related morbidity.

## Clinician Group Input

Two clinician groups provided input: BCC-BTG and OH-CCO's BCDAC.

- The clinician groups noted that the greatest need for pertuzumab is in patients with inflammatory breast cancer and inoperable stage IIIC breast cancers to downstage for primary surgery.
- The clinician groups did not specifically refer to their experiences with pertuzumab, however 1 clinician group noted that combining pertuzumab with trastuzumab is the international standard of care in stage II and stage III HER2-positive breast cancer.

## Drug Program Input

The drug programs provided input on each drug being reviewed through CADTH's reimbursement review process by identifying issues that may impact their ability to implement a recommendation. The drug plans noted that the current standard of care in most provinces for the neoadjuvant treatment of HER2-positive breast cancer is trastuzumab plus chemotherapy. Pertuzumab is an IV drug and would be administered in an outpatient chemotherapy centre for appropriate administration and monitoring of infusion-related reactions. The drug plans highlighted several enablers to the implementation of pertuzumab in the neoadjuvant setting that include the dose and frequency of pertuzumab in the neoadjuvant setting is the same as in the metastatic setting, it is an add-on drug to existing treatment, and drug wastage is not a concern since pertuzumab vials contain the amount of the fixed dose. Barriers to implementation were also identified that include the high cost of pertuzumab and the additional preparation time and chair time needed for the infusion. Pertuzumab is administered for 4 cycles to 6 cycles before surgery; the drug plans noted that given the high cost of pertuzumab, there is a significant difference in cost between 4 cycles and 6 cycles.

The clinical experts consulted by CADTH were asked about implementing pertuzumab into current provincial drug plans. Most implementation questions related to the dosing schedule and administration, the eligible patient population, pCR as a surrogate end point, and re-treatment with pertuzumab in subsequent lines of treatment.

## Clinical Evidence

### Pivotal Studies and Protocol-Selected Studies

#### Description of Studies

Four trials, all identified as pivotal by the sponsor, were included in the CADTH review. NeoSphere (N = 417, randomized 1:1:1:1 across 4 treatment arms) was an open-label RCT that had a pertuzumab-trastuzumab plus docetaxel arm and a trastuzumab plus docetaxel arm. PEONY (N = 329, randomized 2:1 across 2 treatment arms) was a double-blind RCT that randomized patients to either pertuzumab-trastuzumab plus docetaxel or trastuzumab plus docetaxel. The TRYPHAENA trial (N = 225, randomized 1:1:1 across 3 treatment arms) and BERENICE trial (N = 400 distributed 1:1 across 2 cohorts, non-RCT) were designed to compare different background regimens of chemotherapy combined with pertuzumab-trastuzumab. This CADTH review focused on the NeoSphere and PEONY trials; the TRYPHAENA and BERENICE trials provided supportive evidence, where available. All trials included patients with HER2-positive early breast cancer.

- The 4 trials featured a neoadjuvant treatment phase followed by surgery and then an adjuvant treatment phase.
  - In the NeoSphere and PEONY trials, the neoadjuvant phase lasted 4 cycles and consisted of the treatments described previously. In the adjuvant phase of the NeoSphere trial, patients in each treatment arm received 3 cycles of FEC and trastuzumab for up to 1 year. The adjuvant phase of the PEONY trial included 3 cycles of FEC followed by pertuzumab and trastuzumab from cycle 8 to cycle 17 in the arm that received pertuzumab and trastuzumab plus docetaxel in the neoadjuvant phase and placebo and trastuzumab from cycle 8 to cycle 17 in the arm that received trastuzumab plus docetaxel in the neoadjuvant phase.
  - In the neoadjuvant phase of the TRYPHAENA trial, arm A received pertuzumab and trastuzumab plus FEC for 3 cycles followed by pertuzumab and trastuzumab plus docetaxel for 3 cycles, arm B received FEC for 3 cycles then pertuzumab and trastuzumab plus docetaxel for 3 cycles, and arm C received pertuzumab plus docetaxel-carboplatin-trastuzumab (TCH) for 6 cycles. In the adjuvant phase, all patients in each treatment arm received trastuzumab from cycle 7 onward, up to 1 year.
  - In the BERENICE trial, cohort A received doxorubicin plus cyclophosphamide from cycle 1 to cycle 4, pertuzumab and trastuzumab plus paclitaxel from cycle 5 to cycle 8; cohort B received FEC from cycle 1 to cycle 4, followed by pertuzumab and trastuzumab plus docetaxel from cycle 5 to cycle 8. For the adjuvant phase, both treatment arms received pertuzumab and trastuzumab.
- The primary outcome of the NeoSphere trial was bpCR rate at the conclusion of the neoadjuvant treatment phase; the primary outcome of the PEONY trial was tpCR rate, also at the conclusion of the neoadjuvant treatment phase. The PEONY trial also included bpCR rate at the conclusion of the neoadjuvant phase. Both trials were designed to report on various longer-term outcomes such as OS, PFS, EFS, and DFS; however, these outcomes were assessed during or after the adjuvant treatment phase. The primary objectives of the TRYPHAENA and BERENICE trials were to assess safety and tolerability. The primary safety outcomes in the TRYPHAENA trial were the incidence of symptomatic cardiac events and clinically significant left ventricular ejection fraction decline, and the primary safety outcomes in the BERENICE trial were incidence of New York Heart Association (NYHA) class III and class IV heart failure and left ventricular ejection fraction decline.
- Patients in the 4 trials were approximately 50 years old at baseline and the majority (70% to 80%) were White, except for the PEONY trial, in which all patients were Asian. Most patients (nearly 90%) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 and the rest were ECOG performance status of 1. Approximately half (47% in NeoSphere, 51% in PEONY) of patients had either estrogen receptor– or progesterone receptor–positive breast cancer, except for the BERENICE trial, in which approximately two-thirds of patients had estrogen receptor– or progesterone receptor–positive breast cancer. In terms of baseline disease category, the majority of patients in the NeoSphere and TRYPHAENA trials were stage T2N0M0 (NeoSphere: █, TRYPHAENA: 31%) or stage T2N1M0 (NeoSphere: █, TRYPHAENA: 33%). In the PEONY trial, most patients were stage T2 (67%), followed by T3 (22%), and had lymph node positivity (76%). In the BERENICE trial, most patients were stage T2 (67%) followed by T3 (20%), and N1 (47%) and M0 (100%).

## Efficacy Results

The median time on study in the NeoSphere trial was █ weeks (range = █ weeks) in the pertuzumab-trastuzumab plus docetaxel arm and █ weeks (range = █ weeks) in the

trastuzumab plus docetaxel arm. In the PEONY trial, the median time on study was █ weeks (range = █ weeks) in the pertuzumab-trastuzumab plus chemotherapy arm and █ weeks (range = █ weeks) in the trastuzumab plus chemotherapy arm. In the TRYPHAENA trial, median time on study ranged from █ weeks (range = █) to █ weeks in the 3 treatment arms. In the BERENICE trial, median time on study was █ weeks (range = █ weeks) in cohort A and █ weeks (range = █ weeks) in cohort B.

Assessment of longer-term outcomes, such as OS, DFS, EFS, and PFS, included treatment regimens received in both the neoadjuvant and adjuvant phases of treatment. OS was not assessed in the NeoSphere trial, OS data were not yet mature from the PEONY trial according to the sponsor, and there was no comparative OS data available from the TRYPHAENA or BERENICE trials. Data for invasive DFS or EFS were not available from the included trials because it was either not assessed or it was reported as not yet mature by the sponsor. In the NeoSphere trial, DFS events occurred in 14.9% of patients in the pertuzumab-trastuzumab plus docetaxel arm and 17.5% of patients in the trastuzumab plus docetaxel arm; these results were consistent with those reported in the TRYPHAENA trial, in which the DFS events were 14.5% in arm A, 11.9% in arm B, and 15.3% in arm C. The DFS data were not yet mature in the PEONY trial according to the sponsor, and DFS was not assessed in the BERENICE trial. With respect to PFS, in the NeoSphere trial, progression events occurred in 15.9% of patients in the pertuzumab-trastuzumab plus docetaxel arm and in 17.8% of patients in the trastuzumab plus docetaxel arm (hazard ratio [HR] = 0.69; 95% CI, 0.34 to 1.40). These results were consistent with the PFS data reported in the TRYPHAENA trial, in which the PFS event rates were 13.7% in arm A, 14.7% in arm B, and 18.2% in arm C. Data on PFS were not yet mature in the PEONY trial according to the sponsor, and PFS was not assessed in the BERENICE trial. None of the trials were powered to assess between-group differences in these longer-term outcomes.

In the NeoSphere trial, a pCR was achieved by 45.8% of patients in the pertuzumab-trastuzumab plus docetaxel arm and 29.0% of patients in the trastuzumab plus docetaxel arm, for a difference in pCR rates between groups of 16.8% (95% CI, 3.5% to 30.1%; P = 0.0094). In the PEONY trial, the independent review committee (IRC)-assessed tpCR rate was 39.3% in the pertuzumab-trastuzumab plus docetaxel arm and 21.8% in the trastuzumab plus docetaxel arm, for a difference in tpCR rates of 17.45% (95% CI, 6.89% to 28.01%; P = 0.0014). The difference in pCR rates between the 2 trials may reflect the different definitions of pCR used; in the NeoSphere trial, only breast tissue was used to assess pCR, whereas tissue from the breast and nodes were used in the PEONY trial. Additionally, the PEONY trial reported the bpCR rate as a secondary outcome, and the IRC-assessed bpCR rate was consistent with that of the tpCR rate (42.0% versus 23.6%), for a between-group difference of 18.37% (95% CI, 7.60% to 29.15%). The pCR rates ranged from 57.3% to 66.2% across the 3 arms in the TRYPHAENA trial and were 60.7% and 61.8% in the 2 cohorts in the BERENICE trial.

In the NeoSphere trial, a complete response (CR) was observed in 18.9% of patients in the pertuzumab-trastuzumab plus docetaxel arm and 18.3% of patients in the trastuzumab plus docetaxel arm; a partial response (PR) was observed in 49.1% of patients and 49.3% of patients in the 2 arms, respectively, when assessed by X-ray or mammography. When assessed by clinical examination, CR was observed in 25.0% versus 21.6% of patients in the 2 arms, respectively, and PR was observed in 63.0% versus 59.8% of patients, respectively. In the PEONY trial, clinical response was assessed as a secondary outcome, and an objective response (defined as obtaining either CR or PR) during cycle 1 to cycle 4 occurred in 88.6% of patients in the pertuzumab-trastuzumab plus docetaxel arm and 78.2% of patients in the

trastuzumab plus docetaxel arm, for a difference in objective response rates between groups of 10.40% (95% CI, 1.12% to 19.69%). A CR was observed in 11.0% versus 10.0% of patients in the 2 arms, respectively; PR was observed in 77.6% versus 68.2% of patients in the 2 arms, respectively.

Duration of response, health-related quality of life (HRQoL), and symptoms were not assessed in the included studies. Breast-conserving surgery occurred in 23.2% of patients in the pertuzumab-trastuzumab plus docetaxel arm and in 22.6% of patients in the trastuzumab plus docetaxel arm in the NeoSphere trial. This outcome was not assessed in the PEONY trial. In the TRYPHAENA trial, the percentage of patients who underwent breast-conserving surgery was consistent with that of the NeoSphere trial, ranging between 16.7% and 27.0% of patients across treatment arms; in the BERENICE trial, it was 44.4% and 42.9% in the 2 cohorts.

## Harms Results

The percentage of patients experiencing AEs was similar in the pertuzumab-trastuzumab plus docetaxel arm and the trastuzumab plus docetaxel arm, occurring in 96% to 98% of patients across treatment arms in the NeoSphere and PEONY trials. The most common AEs in the trials (pertuzumab-trastuzumab plus docetaxel versus trastuzumab plus docetaxel) were alopecia (NeoSphere: 63.6% versus 65.4%; PEONY: 49.1% in both arms), neutropenia (NeoSphere: 50.5% versus 62.6%; PEONY: 48.2% versus 44.5%), and diarrhea (NeoSphere: 45.8% versus 33.6%; PEONY: 38.5% versus 16.4%). The most common grade 3 or higher AE was neutropenia (NeoSphere 44.9% versus 57.0%; PEONY: 38.1% versus 32.7%). Similar results were seen in the TRYPHAENA and BERENICE trials, in which approximately 99% of patients experienced an AE at some time during the study; neutropenia was the most common grade 3 or higher AE.

A serious adverse event (SAE) occurred in 10.3% of patients in the pertuzumab-trastuzumab plus docetaxel group and 16.8% of patients in the trastuzumab plus docetaxel group in the NeoSphere trial, and in 10.1% versus 8.2% of patients, respectively, in the PEONY trial. Febrile neutropenia was the most common SAE in NeoSphere, occurring in 5.6% of patients in the pertuzumab-trastuzumab plus docetaxel arm and 6.5% of patients in the trastuzumab plus docetaxel arm; in the PEONY trial, it occurred in 1.8% of patients in the pertuzumab-trastuzumab plus docetaxel arm and no patients in the trastuzumab plus docetaxel arm. In the TRYPHAENA trial, 28% of patients experienced a SAE across the treatment arms; in the BERENICE trial, 24% of patients experienced a SAE. Febrile neutropenia was the most common SAE in both studies, occurring in approximately 10% of patients.

Few patients across the trials stopped treatment due to an AE: 0.9% of patients in the pertuzumab-trastuzumab plus docetaxel arm versus no patients in the trastuzumab plus docetaxel arm in the NeoSphere trial and 0.5% of patients in the pertuzumab-trastuzumab plus docetaxel arm and no patients in the trastuzumab plus docetaxel arm in the PEONY trial. The number of patients withdrawing due to an AE was 7% across arms in the TRYPHAENA trial and 3.5% across cohorts in the BERENICE trial.

One patient died in each of the pertuzumab-trastuzumab plus docetaxel and trastuzumab plus docetaxel arms in the NeoSphere trial; both deaths were considered to be due to complications of breast cancer. One patient died in the pertuzumab-trastuzumab plus docetaxel arm in the PEONY trial due to a suicide. There were no deaths in the trastuzumab plus docetaxel arm.

Among notable harms, in the NeoSphere trial, cardiac dysfunction occurred in 2.8% of patients in the pertuzumab-trastuzumab plus docetaxel arm and 0.9% of patients in the trastuzumab plus docetaxel arm. No patients in the PEONY trial had a left ventricular ejection fraction decline to less than 40% or a primary or secondary cardiac event. Events of drug hypersensitivity and/or anaphylaxis occurred in 5.6% of patients in the pertuzumab-trastuzumab plus docetaxel arm and in 1.9% of patients in the trastuzumab plus docetaxel arm in the NeoSphere trial and in 3.2% versus 1.8% of patients in both arms in the PEONY trial, respectively.

## Critical Appraisal

- NeoSphere was an open-label study, and no centralized blinded review of pathology was conducted when assessing pCR rates. Although pathology findings are unlikely to be biased by knowledge of treatment assignment, a blinded review of pathology is recommended by regulatory bodies. With respect to the primary outcome, pCR was defined differently in the NeoSphere and PEONY trials. In the NeoSphere trial, the primary outcome of pCR included only breast tissue (commonly described as bpCR), whereas in the PEONY trial, assessment of pCR for the primary outcome included tissue from the breast and nodes, referred to as tpCR, the latter being the recommended method by the FDA. The TRYPHAENA and BERENICE trials only provide limited supportive information regarding efficacy because neither trial had a comparator nor were designed to test hypotheses with respect to efficacy outcomes and the BERENICE trial was not a randomized trial. The alpha level in the NeoSphere trial was set at 0.2 instead of the traditional 0.05, which may have increased the risk of finding a statistically significant difference in pCR rates between arms when none existed.
- OS was not assessed as an efficacy outcome in the NeoSphere trial, and the OS data from the PEONY trial were not yet mature according to the sponsor. Therefore, there is no information to determine whether the addition of pertuzumab to neoadjuvant treatment with trastuzumab and docetaxel improves this important outcome. HRQoL and symptoms were also not assessed in any of the trials. Although these outcomes may not be as important in early breast cancer and in the neoadjuvant setting, assessment of HRQoL would help in assessing the impact of AEs from the addition of pertuzumab.

## Indirect Comparisons

No indirect comparisons were submitted by the sponsor, and none were found in the literature that would inform this review.

## Other Relevant Evidence

There were no other studies that were found that would be relevant to this review.

## Economic Evidence

### Cost and Cost-Effectiveness

**Table 1: Summary of Economic Evaluation**

Component	Description
<b>Type of economic evaluation</b>	Cost-utility analysis Markov model
<b>Target population</b>	Patients with HER2-positive, locally advanced, inflammatory, or early breast cancer (either > 2 cm in diameter or node positive). Aligns with the reimbursement request.
<b>Treatment</b>	IV infusion pertuzumab (Perjeta) in combination with trastuzumab and taxane chemotherapy (PHT)
<b>Submitted price</b>	Pertuzumab, 840 mg loading dose and 420 mg maintenance dose, IV infusion: \$8.05 per mg or \$3,381.81 per pack (420 mg)
<b>Treatment cost</b>	The cost per 21-day cycle of pertuzumab for loading and maintenance doses were \$6,763.62 (840 mg) and \$3,381.81 (420 mg), respectively. When used in combination with trastuzumab and taxane chemotherapy, the loading dose cost is \$11,563.05 and the maintenance cost is \$7,248.22.
<b>Comparator</b>	Neoadjuvant IV trastuzumab (100% biosimilar) plus chemotherapy (HT)
<b>Perspective</b>	Canadian publicly funded health care payer
<b>Outcome</b>	QALYs, LYs
<b>Time horizon</b>	Lifetime (51 years)
<b>Key data source</b>	PEONY trial: pCR rate and EFS in the neoadjuvant setting KATHERINE trial: risk of disease recurrence for non-pCR patients Pooled analysis by Swain et al. 2019: risk of disease recurrence for pCR patients
<b>Submitted results</b>	ICER for PHT compared with HT was \$27,986 per QALY (0.29 incremental QALYs, \$8,000 incremental costs)
<b>Key limitations</b>	<ul style="list-style-type: none"> <li>• The sponsor’s model is predicated on an association between pCR and long-term survival outcomes (i.e., EFS and OS). Although patient-level evidence suggests an association between pCR and improved survival outcomes, evidence at the trial or population level does not establish that a difference in pCR rates between treatment arms will predict a difference in long-term survival end points (DFS, EFS, or OS) between 2 treatments.</li> <li>• Although pCR may be considered a prognostic marker on an individual patient basis, the evidence is not sufficient to identify a magnitude of pCR improvement that predicts long-term survival. This uncertainty limits any assessment of cost-effectiveness given the limitations identified with the sponsor’s key assumption.</li> <li>• The sponsor’s model did not account for the direct impact of neoadjuvant PHT on survival outcomes (disease recurrence or death) and health utility because these were based on information from patients in the adjuvant setting.</li> </ul>

Component	Description
CADTH reanalysis results	<ul style="list-style-type: none"> <li>• CADTH undertook several corrections to the sponsor's analysis to align with Canadian practice and best practices for economic modelling. These corrections had only minor impacts on the sponsor's base case.</li> <li>• The sponsor's base case and CADTH-corrected analysis results are associated with substantial methodological and structural uncertainty and must be viewed with caution due to the identified limitations regarding the clinical evidence and modelling that could not be addressed by CADTH.</li> <li>• CADTH undertook several exploratory scenario analyses assessing the key drivers of the model, which indicated that the cost-effectiveness of PHT is highly sensitive to the association between pCR and EFS. PHT is not cost-effective at a WTP threshold of \$50,000 per QALY if the HR for patients with a pCR relative to non-pCR patients to achieve EFS was greater than 0.41 (sponsor's HR = 0.33). If the HR is equal to 1, PHT was more costly and less effective than HT.</li> <li>• Other key drivers included the time at which non-pCR patients are considered cured and the continuation of pertuzumab as an adjuvant therapy.</li> </ul>

DFS = disease-free survival; EFS = event-free survival; HR = hazard ratio; HT = trastuzumab in combination with taxane chemotherapy; ICER = incremental cost-effectiveness ratio; iDFS = invasive disease-free survival; LY = life-year; mBC = metastatic breast cancer; OS = overall survival; pCR = pathological complete response; PHT = pertuzumab in combination with trastuzumab and taxane chemotherapy; QALY = quality-adjusted life-year; WTP = willingness to pay; vs. = versus.

## Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the population of eligible patients was slightly underestimated, the proportion of patients receiving neoadjuvant treatment was underestimated, the use of branded trastuzumab with pertuzumab was inappropriate, the uptake of pertuzumab was underestimated, subsequent therapies for recurrent or metastatic disease were not considered, and the actual prices paid by plans for comparators are unknown.

The CADTH reanalyses included correcting the number of eligible patients, increasing the proportion of patients receiving neoadjuvant therapy, assuming biosimilar trastuzumab would be used regardless of pertuzumab usage, and increasing the predicted uptake of pertuzumab.

Based on the CADTH reanalyses, the budget impact of introducing neoadjuvant pertuzumab in combination with trastuzumab and chemotherapy in the indicated population is expected to be \$7,318,741 in year 1, \$10,162,230 in year 2, and \$13,709,519 in year 3, for a 3-year total budget impact of \$31,190,490.

## pCODR Expert Review Committee Information

### Initial Meeting Date: September 8, 2021

#### Members of the Committee

Dr. Maureen Trudeau (Chair), Dr. Catherine Moltzan (Vice-Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Kelvin Chan, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christine Kennedy, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Ms. Valerie McDonald, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

**Regrets:** One expert committee member did not attend

**Conflicts of interest:** None

## Reconsideration Meeting Date: January 12, 2022

### Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

**Regrets:** None

**Conflicts of interest:** None