CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Pertuzumab (Perjeta)

Indication: 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)

Recommendation: Do Not Reimburse

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PERTUZUMAB (PERJETA — Hoffmann-La Roche Limited)

Therapeutic Area: Early stage breast cancer

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that pertuzumab in combination with trastuzumab and chemotherapy 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).

Rationale for the Recommendation

Patients identified a need for new treatments that prevent recurrence and metastases, but 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 thus were the focus of pERC's deliberation. NeoSphere and PEONY demonstrated that neoadjuvant (pre-operative) treatment with pertuzumab in combination with trastuzumab and chemotherapy significantly improved pathologic complete response (pCR) rates, the primary outcome of both trials, when compared to 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), or the data were considered immature by the sponsor and therefore were not available (PEONY) for review. Neither trial was powered to assess survival endpoints, therefore there is no definitive evidence of improved survival when pertuzumab is added to trastuzumab and chemotherapy neoadjuvant treatment regimens. As such, it is unclear 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 new treatments for early breast cancer that have manageable side effects and maintain quality of life. While pERC considered that the addition of pertuzumab to trastuzumab results in a manageable safety profile, no conclusions could be drawn on its impact on patient quality of life since none of the pivotal trials measured this outcome.

Discussion Points

- pERC discussed that approximately 15% to 20% of patients who are diagnosed with early breast cancer are HER2-positive, and thus HER2-positive breast cancer is not considered a rare condition but is associated with poorer prognosis without anti-HER2-positive treatment when compared to 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 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 a drug 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-postive breast cancer. Data from the PEONY trial confirmed the results for the pCR endpoint from the NeoSphere trial, showing a statistically significant higher total pCR rate in the breast and axillary nodes (tpCR) with pertuzumab-trastuzumab and docetaxel when 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, 28.01; p=0.0014). The 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, 29.15). However, data on the long-term outcomes assessed in PEONY, including OS, DFS, EFS and PFS, were considered immature by the sponsor and were not available for review. The median time on study was [redacted] weeks in the pertuzumab-trastuzumab plus docetaxel arm and [redacted] weeks in the trastuzumab plus docetaxel arm. pERC noted that similar to NeoSphere, the PEONY trial was not powered to assess survival endpoints and quality of life outcomes were not measured.
- pERC considered evidence from meta-analyses that examined pCR as a surrogate measure 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 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 level is required to validate pCR as a surrogate measure for survival outcomes in the neoadjuvant treatment setting.
- 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, and the most common grade ≥3 AE was neutropenia. pERC noted that the new evidence in the current submission did not signal any new safety concerns with the drug and therefore considered that the addition of pertuzumab to trastuzumab results in a manageable safety profile.
- 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 are expected in the year 2022 and discussed that the long-term data from this trial 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 avoidance of 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 and thus blocks ligand-dependent heterodimerization of HER2 with other members of the HER family. Pertuzumab therefore inhibits ligand-initiated intracellular signaling 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 and 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 either pertuzumab-trastuzumab in cycles 1 to 6 plus FEC (fluorouracil, epirubicin, cyclophosphamide) in cycles 1 to 3 and docetaxel in cycles 4 to 6, FEC in cycles 1 to 3 followed by pertuzumab-trastuzumab plus docetaxel in cycles 4 to 6, or pertuzumab-trastuzumab plus docetaxel and carboplatin in cycles 1 to 6. pERC focused its deliberation on the NeoSphere trial since TRYPHAENA included pertuzumab in all treatment groups. Based on evidence from NeoSphere, 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, as pCR had not been validated as a surrogate endpoint for either EFS or OS.

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

Sources of Information Used by the Committee

To make their recommendation, the Committee considered the following information:

- A review of 4 clinical studies (3 randomized controlled trials [RCT] 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, the CBCN and Rethink Breast Cancer. Information was gathered by use of a survey (52 respondents, all Canadian), phone interview (11 interviewees), and an online survey (62 respondents, 60% Canadian).

- Patients described the emotional distress associated with a type of breast cancer that had a poorer prognosis prior to 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 fatigue, pain and nausea most negatively impact their daily lives. Patients also noted the financial burden associated with lost income, and treatment

costs, with 17% of respondents in one 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 preventing metastases. Maintaining quality of life was also rated by the majority of patients as very important or important, as was managing adverse effects. Patients were clear that they were very willing to tolerate new adverse effects from drugs in order to extend life expectancy.

Clinician Input

Input from clinical experts consulted by CADTH

- 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.
- According to the clinical experts consulted by CADTH, 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.
- The clinical experts noted that ultimately, response in the neoadjuvant setting is determined at the time of surgery, when assessment of pCR is performed. Prior to surgery, patients would most likely be assessed every 2 to 3 weeks at the time they come in to receive their chemotherapy, typically by a physical exam, although sometimes it may be supplemented by imaging of the breast (ultrasound or magnetic resonance imaging [MRI]). If during therapy the tumour is growing or not responding, the chemotherapy protocol may be modified, or the patient may be sent for surgery earlier than planned. A clinically meaningful response is a shrinkage of the tumour to facilitate surgical removal.
- One of the clinical experts consulted by CADTH believes 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 to 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, given that 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, the BCC-BTG and the 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 one clinician group noted that combining pertuzumab with trastuzumab is the international standard of care in Stage II and III HER2-positive breast cancer.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's reimbursement review processes by identifying issues that may impact their ability to implement a recommendation. The drug plans noted that in most provinces, the current standard of care for the neoadjuvant treatment of HER2-positive breast cancer is trastuzumab plus chemotherapy. Pertuzumab,

being an IV drug, 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 being 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 to 6 cycles before surgery and 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 questions related to the implementation of pertuzumab into current provincial drug plans. Overall, most implementation questions related to the dosing schedule and administration, the eligible patient population, pCR as an endpoint, and retreatment 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 an arm that contained pertuzumab-trastuzumab plus docetaxel and an arm that contained trastuzumab plus docetaxel. 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. TRYPHAENA (N=225, randomized 1:1:1 across 3 treatment arms) and BERENICE (N=400 distributed 1:1 across 2 cohorts, non-RCT) were designed to compare different background regimens of chemotherapy combined with pertuzumab-trastuzumab. The primary focus of this CADTH review was the NeoSphere and PEONY trials, with TRYPHAENA and BERENICE providing 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 NeoSphere and PEONY, the neoadjuvant phase lasted 4 cycles, and consisted of the treatments described above. In the adjuvant phase of NeoSphere, patients in each treatment arm received 3 cycles of FEC and trastuzumab for up to 1 year. The adjuvant phase of PEONY included 3 cycles of FEC followed by pertuzumab-trastuzumab for cycles 8 to 17 in the arm that received pertuzumab-trastuzumab plus docetaxel in the neoadjuvant phase and placebo-trastuzumab for cycles 8 to 17 in the arm that received trastuzumab plus docetaxel in the neoadjuvant phase.
    - In the neoadjuvant phase of TRYPHAENA, Arm A received pertuzumab-trastuzumab plus FEC for 3 cycles followed by pertuzumab-trastuzumab plus docetaxel for 3 cycles; Arm B received FEC for 3 cycles then pertuzumab-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 onwards, up to 1 year.
    - In BERENICE, Cohort A received doxorubicin plus cyclophosphamide for cycles 1 to 4, pertuzumab-trastuzumab plus paclitaxel for cycles 5 to 8, and Cohort B received FEC for cycles 1 to 4, followed by pertuzumab-trastuzumab plus docetaxel for cycles 5 to 8. For the adjuvant phase, both treatment arms received pertuzumab-trastuzumab.
- The primary outcome of NeoSphere was the bpCR rate at the conclusion of the neoadjuvant treatment phase, and the primary outcome of PEONY was the tpCR rate, also at the conclusion of the neoadjuvant treatment phase. PEONY also reported on the 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 objective of TRYPHAENA and BERENICE was to assess safety and tolerability. The primary safety outcomes in TRYPHAENA were the incidence of symptomatic cardiac events and clinically significant left ventricular ejection fraction (LVEF) decline, and the primary safety outcomes in BERENICE were the incidence of New York Heart Association (NYHA) Class III and IV heart failure and LVEF decline.
- Patients in the 4 trials were approximately 50 years old at baseline and the majority (70% to 80%) were Caucasian, except for PEONY, where all patients were Asian. Most patients (nearly 90%) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 and the rest were ECOG 1. Approximately half (47% in NeoSphere, 51% in PEONY) of

patients were either estrogen or progesterone receptor-positive, except for BERENICE, in which approximately two-thirds of patients were estrogen or progesterone receptor-positive. In terms of baseline disease category, the majority of patients in NeoSphere and TRYPHAENA were Stage T2N0M0 (NeoSphere: [redacted], TRYPHAENA: 31%) or Stage T2N1M0 (NeoSphere: [redacted], TRYPHAENA: 33%). In PEONY, most patients were stage T2 (67%), followed by T3 (22%), and were lymph node positive (76%). In BERENICE, most patients were stage T2 (67%) followed by T3 (20%), and N1 (47%) and M0 (100%).

Efficacy results

The median time on study in NeoSphere was [redacted] weeks (range: [redacted] weeks) in the pertuzumab-trastuzumab plus docetaxel arm and [redacted] weeks (range: [redacted] weeks) in the trastuzumab plus docetaxel arm. In PEONY, the median time on study was [redacted] weeks (range: [redacted] weeks) in the pertuzumab-trastuzumab plus chemotherapy arm and [redacted] weeks (range: [redacted] weeks) in the trastuzumab plus chemotherapy arm. In TRYPHAENA, median time on study ranged from [redacted] weeks (range: [redacted]) to [redacted] weeks in the 3 treatment arms. In BERENICE, median time on study was [redacted] weeks (range: [redacted] weeks) in Cohort A and [redacted] weeks (range: [redacted] 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 NeoSphere, and OS data are not yet mature from PEONY according to the sponsor, and there are no comparative OS data available from TRYPHAENA or BERENICE. Data for invasive DFS or EFS were not available from the included trials, either because it was not assessed or because the data were reported as not yet mature by the sponsor. In NeoSphere, 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 and these results were consistent with those reported in TRYPHAENA, where 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 PEONY according to the sponsor, and DFS was not assessed in BERENICE. With respect to PFS, in NeoSphere, 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, for a hazard ratio of 0.69 (95% CI: 0.34, 1.40). These results were consistent with the PFS data reported in TRYPHAENA, where 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 PEONY according to the sponsor and PFS was not assessed in BERENICE. None of the trials were powered to assess between-group differences in these longer-term outcomes.

In NeoSphere, 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, 30.1), p=0.0094. In PEONY, the 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, 28.01), p=0.0014. The difference in pCR rates between the two trials may reflect the different definitions of pCR used, as NeoSphere used only breast tissue to assess pCR while PEONY used breast and nodes. Additionally, PEONY 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, 29.15). The pCR rates ranged from 57.3% to 66.2% across the 3 arms in TRYPHAENA and were 60.7% and 61.8% in the 2 cohorts in BERENICE.

In NeoSphere, 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, and a partial response (PR) was observed in 49.1% of patients and 49.3% of patients, respectively, when assessed by X-ray/mammography. When assessed by clinical exam, a CR was observed in 25.0% versus 21.6% of patients, respectively and a PR was observed in 63.0% versus 59.8% of patients, respectively. In PEONY, clinical response was assessed as a secondary outcome, and an objective response (defined as obtaining either a CR or PR) during cycles 1 to 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 10.2% (95% CI: 7.89, 28.83). A CR was observed in 11.0% versus 10.0% of patients, and a PR was observed in 77.6% versus 68.2% of patients, 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 NeoSphere. This outcome was not assessed in PEONY. In TRYPHAENA, the percentage of patients undergoing breast-conserving surgery was consistent with that of NeoSphere, ranging between 16.7% and 27.0% of patients across treatment arms, and in BERENICE it was 44.4% and 42.9% in the 2 cohorts.

Harms results

The percentage of patients experiencing AEs was similar between pertuzumab-trastuzumab plus docetaxel and trastuzumab plus docetaxel, occurring in 96% to 98% of patients across treatment arms in NeoSphere and PEONY. 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 each), 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 AE was neutropenia (NeoSphere 44.9% versus 57.0%; PEONY: 38.1% versus 32.7%). Similar results were seen in TRYPHAENA and BERENICE, where approximately 99% of patients experienced an AE at some time during the study, and neutropenia was the most common grade ≥3 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 NeoSphere, and in 10.1% versus 8.2% of patients, respectively, in PEONY. 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, and in PEONY, occurring in 1.8% of patients in the pertuzumab-trastuzumab plus docetaxel arm and no patients in the trastuzumab plus docetaxel arm. In TRYPHAENA, 28% of patients experienced a SAE across the treatment arms, and in BERENICE 24% of patients experienced a SAE. Febrile neutropenia was the most common SAE in both studies, occurring in about 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 NeoSphere, and 0.5% of patients in the pertuzumab-trastuzumab plus docetaxel arm and no patients in the trastuzumab plus docetaxel arm in PEONY. The number of patients withdrawing due to an AE was 7% across arms in TRYPHAENA and 3.5% across cohorts in BERENICE.

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

Among notable harms, in NeoSphere, 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, and no patients in PEONY had a LVEF decline to less than 40%, or a primary or secondary cardiac event. Events of drug hypersensitivity/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 NeoSphere, and in 3.2% versus 1.8% of patients in PEONY, 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 between NeoSphere and PEONY. In NeoSphere, the primary outcome of pCR included only breast tissue (commonly described as bpCR) while in PEONY, assessment of pCR for the primary outcome included breast and nodes, referred to as tpCR, and the latter is the recommended method by the FDA. TRYPHAENA and BERENICE only provide limited, supportive information regarding efficacy, as neither trial had a comparator, neither were deigned to test hypotheses with respect to efficacy outcomes, and BERENICE was not a randomized trial. The alpha level in NeoSphere was set at 0.2 instead of the traditional 0.05, and this might have increased the risk of finding a statistically significant difference in pCR rates between arms where none existed.
- OS was not assessed as an efficacy outcome in NeoSphere and the OS data from PEONY 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, and 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
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Patients with HER2-positive, locally advanced, inflammatory, or early breast cancer (either >2 cm in diameter or node positive). Aligns with the reimbursement request
Treatment	Intravenous infusion pertuzumab (Perjeta) in combination with trastuzumab and taxane chemotherapy (PHT)
Submitted price	Pertuzumab, 840 mg loading dose and 420 mg maintenance dose, intravenous infusion: $8.05 per mg or $3,381.81 per pack (420 mg)
Treatment cost	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 while the maintenance cost is $7,248.22.
Comparator	Neoadjuvant IV trastuzumab (100% biosimilar) plus chemotherapy (HT)
Perspective	Canadian publicly funded health care payer
Outcome	QALYs, LYs
Time horizon	Lifetime (51 years)
Key data source	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: risk of disease recurrence for pCR patients
Submitted results	ICER for PHT compared with HT was $27,986 per QALY (0.29 incremental QALYs, $8,000 incremental costs)
Key limitations	• The sponsor's model is predicated on an association between pCR and long-term survival outcomes, i.e., EFS and OS. While 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 endpoints (DFS, EFS, or OS) between two treatments. • While 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. As such, this uncertainty limits any assessment of cost-effectiveness given the limitations identified with the sponsor's key assumption. • The sponsor's model did not account for the direct impact of neoadjuvant PHT on survival outcomes (disease recurrence or death) and health utility as these were based on information from patients in the adjuvant setting.
CADTH reanalysis results	• 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. • 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. • 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

Component	Description
	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. • Other key drivers included the time at which non-pCR patients are considered cured, and the continuation of pertuzumab as an adjuvant therapy.

EFS = event-free survival; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; iDFS = invasive disease-free survival; mBC = metastatic breast cancer; 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 prices actually paid by plans for comparators are unknown.

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 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 three-year total budget impact of $31,190,490.

pCODR Expert Review Committee (pERC) Information

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.

Meeting Date: September 8, 2021

Regrets

One expert committee member did not attend.

Conflicts of Interest

None.