Canada's Drug Agency
L'Agence des médicaments du Canada

Reimbursement Review

Pertuzumab (N/A)

Draft Review Report

Requester: Public drug programs

Therapeutic area: Early-stage breast cancer

Version: Draft - Confidential
Publication Date: TBC
Report Length: 38 Pages

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Key Messages

What is HER2-positive Breast Cancer?

- Human epidermal growth factor receptor 2 (HER2)-positive breast cancer is a subtype of breast cancer characterized by overexpression of the HER2 protein, which is associated with more aggressive disease and a higher risk of recurrence.
- In Canada, breast cancer is the second most common cancer, with an estimated 30,800 new cases in 2024, of which approximately 15% to 20% are HER2-positive.

What are the Treatment Goals and Current Treatment Options for HER2-positive Breast Cancer?

- The goals of therapy for patients with early HER2-positive breast cancer are to improve the chance of cure and overall survival, reduce the risk of recurrence, minimize toxicity, and improve patients' health-related quality of life.
- Current standard treatment for early-stage HER2-positive breast cancer includes neoadjuvant chemotherapy with HER2-targeted therapy (trastuzumab). After surgery, patients with a pathological complete response (pCR) continue trastuzumab to complete one year of therapy, while those with residual disease may receive trastuzumab emtansine.

What is Pertuzumab and Why Did We Conduct This Review?

- Pertuzumab is a HER2 inhibitor targeted therapy that is administered by intravenous infusion (840 mg loading dose, followed by 420 mg every 3 weeks for 3 to 6 cycles in the neoadjuvant setting). Health Canada has approved pertuzumab, in combination with trastuzumab and chemotherapy, for the neoadjuvant treatment of patients with HER2-positive locally advanced, inflammatory, or early-stage breast cancer (greater than 2 cm in diameter or node-positive).
- At the request of the participating public drug programs, we reviewed pertuzumab to inform a recommendation on whether it should be reimbursed for the neoadjuvant treatment of patients with HER2-positive locally advanced, inflammatory, or early-stage breast cancer (greater than 2 cm in diameter or node-positive).
    - CDA-AMC previously reviewed pertuzumab for this indication in 2015 and 2022. In both reviews, the pan-Canadian Oncology Drug Review Expert Review Committee issued negative reimbursement recommendations due to the lack of evidence linking improvements in pCR to meaningful long-term outcomes, as well as the absence of robust evidence demonstrating improvements in long-term survival outcomes.

How Did We Evaluate Pertuzumab?

- We reviewed the clinical evidence on the beneficial and harmful effects and compared costs of pertuzumab versus other treatments used in Canada for the neoadjuvant treatment of patients with HER2-positive locally advanced, inflammatory, or early-stage breast cancer (greater than 2 cm in diameter or node-positive). Trastuzumab plus chemotherapy was considered a relevant treatment to compare with pertuzumab.
    - The clinical evidence was identified through systematic searches for available studies.
    - The review was also informed by 4 patient group submissions, 4 clinician group submissions, and 1 industry submission in response to our call for input and by input from the participating public drug programs around issues that may impact their ability to implement a recommendation. We consulted three specialists with expertise in the diagnosis and management of breast cancer as part of the review process.

What Did We Find?

Clinical Evidence from Randomized Controlled Trials

- We reviewed the following evidence on the efficacy and safety of pertuzumab and trastuzumab plus docetaxel compared with trastuzumab plus docetaxel in adult patients with HER2-positive early-stage breast cancer:
    - One double-blind, multicenter, phase 3 randomized controlled trial (PEONY)
    - One open-label, multicenter, phase 2 randomized controlled trial (NEOSPHERE)
- The evidence suggests:
    - Pertuzumab with trastuzumab plus chemotherapy resulted in a clinically important improvement in pCR compared to placebo with trastuzumab plus chemotherapy
    - Compared to trastuzumab plus chemotherapy, pertuzumab with trastuzumab plus chemotherapy improved event-free survival at 5 years
    - While there were clinical meaningful improvements in progression-free survival and overall survival at 5 years, these results are uncertain due to imprecision
    - The PEONY trial found a favourable effect of pertuzumab on 5-year disease-free survival, but the results of NEOSPHERE on disease-free survival were uncertain due to imprecision
    - Adding pertuzumab to trastuzumab plus chemotherapy did not appear to introduce significant safety or tolerability issues.

Clinical Evidence from Real-World Evidence Studies

- We reviewed the following evidence on the efficacy and safety of pertuzumab and trastuzumab plus docetaxel versus trastuzumab plus docetaxel in adult patients with HER2-positive early-stage breast cancer:
    - One prospective multicenter cohort study using data from national breast cancer registry database (van der Voort et al.)
    - One retrospective multicenter cohort study using data from a national breast cancer registry database (HER2PATH)
    - Two retrospective multicenter cohort studies using data from electronic medical records (NeoPowER and CSBrS-015)
    - One retrospective single-center cohort study using data from electronic medical records (Ren et al.).
- The evidence suggests:
    - Pertuzumab with trastuzumab plus chemotherapy resulted in a clinically important improvement in pCR compared to placebo with trastuzumab plus chemotherapy in 4 of 5 real world evidence studies
    - The effect on distant relapse-free survival and overall survival at 3 years were very uncertain due to risk of bias and imprecision
    - Pertuzumab with trastuzumab plus chemotherapy resulted in clinically important improvements in breast cancer free-survival and overall survival at 5 years compared to placebo with trastuzumab plus chemotherapy.
    - Adding pertuzumab to trastuzumab plus chemotherapy did not appear to introduce significant safety or tolerability issues.
- Key evidence gaps include evidence on the effect of neoadjuvant pertuzumab regimens currently used in Canada on long-term survival outcomes (more that 5 years) health-related quality of life, and (direct evidence on) trastuzumab emtansine utilization in the adjuvant setting.

Economic Evidence

- Reimbursing pertuzumab for the neoadjuvant treatment of patients with HER2-positive locally advanced, inflammatory, or early-stage breast cancer is expected to increase costs to the public drug programs.

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Abbreviations

AE	adverse event
BCSS	breast cancer-free survival
bpCR	pathologic complete response in the breast
DFS	disease-free survival
DRFS	distant relapse-free survival
EFS	event-free survival
HER2	human Epidermal Growth Factor Receptor-2
HRQoL	health-related quality of life
ITC	indirect treatment comparison
ITT	intention-to-treat population
LVEF	left ventricular ejection fraction
OS	overall survival
pCR	pathologic complete response
PFS	progression-free survival
SAE	serious adverse event
tpCR	total pathologic complete response
T-DM1	trastuzumab emtansine

Background

Introduction

The objective of the Clinical Review is to review and critically appraise the evidence on the beneficial and harmful effects of pertuzumab 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 (greater than 2 cm in diameter or node-positive). The focus will be placed on comparing pertuzumab to relevant comparators and identifying gaps in the current evidence. The economic review consists of a cost comparison for pertuzumab compared with relevant comparators for the same population. The comparator considered relevant to the review was trastuzumab.

Pertuzumab, in combination with trastuzumab and chemotherapy, has previously been reviewed twice by CDA-AMC for the neoadjuvant treatment of patients with HER2-positive locally advanced, inflammatory, or early-stage breast cancer (greater than 2 cm in diameter or node-positive), in 2015[1] and 2022[2]. In 2015, the pan-Canadian Oncology Drug Review Expert Review Committee issued a negative recommendation, as there was no demonstrated progression-free survival (PFS) benefit, and it was unclear whether pCR correlated with survival outcomes. In 2022, the pan-Canadian Oncology Drug Review Expert Review Committee issued again a recommendation against reimbursement, as available evidence did not show significant differences in PFS and disease-free survival (DFS), and other survival outcomes were either immature or not reported.

A review of the evidence for pertuzumab in the neoadjuvant setting was requested by the Oncology Working Group. The request was prompted by emerging evidence suggesting potential efficacy and safety benefits and opportunities for cost minimization, particularly by reducing reliance on adjuvant T-DM1, which has notable toxicity concerns. The Oncology Working Group highlighted new data supporting the efficacy of anthracycline-free regimens and requested that the review focus specifically on the neoadjuvant phase of treatment. Emerging evidence included an updated analysis of the PEONY trial, which assessed the neoadjuvant use of pertuzumab and trastuzumab in patients with HER2-positive early breast cancer, providing longer-term outcome data and additional safety information, and real-world evidence (RWE) studies evaluating the effectiveness and safety of neoadjuvant pertuzumab-trastuzumab combined with chemotherapy in clinical practice.

Table 1: Information on the Drug Under Review and on the CDA-AMC Review

Item	Description
Information on the drug under review	
Drug (product)	Pertuzumab, 840 mg loading dose and 420 mg maintenance dose, IV infusion
Relevant Health Canada indication	Pertuzumab is indicated, in combination with trastuzumab and chemotherapy, for the neoadjuvant treatment of patients with HER2-positive locally advanced, inflammatory, or early-stage breast cancer (greater than 2 cm in diameter or node-positive).
Mechanism of action	Monoclonal antibody that targets HER2 dimerization, blocking HER2-HER family interactions and inhibiting MAPK and PI3K signaling pathways
Recommended dosage	Early breast cancer: • Initial: 840 mg as a 60-minute infusion • Maintenance: 420 mg every 3 weeks as a 30- to 60-minute infusion When administered with pertuzumab: • Trastuzumab IV: Initial 8 mg per kg, followed by 6 mg per kg every 3 weeks • Trastuzumab SC: Fixed 600 mg every 3 weeks
Data protection status	Expired in April 2021
Status of generic drugs / biosimilars	None approved or under review in Canada
Information on the CDA-AMC review	

Item	Description
Requester	Oncology Working Group
Indication under consideration for reimbursement	Pertuzumab in combination with trastuzumab and chemotherapy for early stage HER2+ breast cancer in the neoadjuvant setting

HER2 = human epidermal growth factor receptor 2; IV = intravenous; MAPK = mitogen-activated protein kinase; PI3K = phosphoinositide 3-kinase; SC = subcutaneous.

Sources of Information

The contents of the Clinical Review report are informed by studies identified through systematic literature searches and input received from interested parties.

Calls for patient group, clinician group, and industry input are issued for each Non-Sponsored Reimbursement Review. We received 4 patient group submissions from Breast Cancer Canada, the Inflammatory Breast Cancer Network Foundation Canada, the Canadian Breast Cancer Network, and Rethink Breast Cancer. In addition, 4 clinician group submissions were received from Ontario Health (Cancer Care Ontario) Breast Cancer Drug Advisory Committee, the Breast Medical Oncology Group, the Juravinski Cancer Centre in Hamilton, Ontario, and the Research Excellence, Active Leadership Canadian Breast Cancer Alliance. A letter of support was also provided by the Sunnybrook Odette Cancer Centre. Hoffmann-La Roche Limited provided input for this review as well.

Patient and clinician input was gathered through various methods. Breast Cancer Canada conducted an electronic survey from February 15 to 23, 2025, targeting individuals diagnosed with stage 2 or 3 HER2-positive breast cancer who received neoadjuvant, adjuvant, or both types of treatment. A total of 228 survivors responded, providing insights on treatment experiences and financial impacts using the validated COST: A FACIT Measure of Financial Toxicity tool, and demographic factors, with 85 (37%) reporting receipt of HER2-targeted therapy in the neoadjuvant setting.

The IBC Network Foundation Canada gathered input through its online support forum of 68 members, inviting participation via discussion boards, email surveys, and freeform responses. Twelve HER2-positive respondents provided detailed feedback in early 2025, most of whom had been diagnosed with stage 3 or 4 inflammatory breast cancer between 2016 and 2025, and nine had received pertuzumab during their treatment.

The Canadian Breast Cancer Network contributed input through written testimony from a patient with experience taking pertuzumab for HER2-positive breast cancer, along with findings from its 2022 Triple Negative Breast Cancer Survey. One detailed testimony was submitted in February 2025 and included in full.

Rethink Breast Cancer gathered information through ongoing engagement with the breast cancer community, including insights from key patient advisors, support groups, peer networks, and social media interactions. For this submission, they also drew on findings from a 2021 online survey completed by 62 women (35 with experience taking pertuzumab), follow-up interviews with seven respondents, and two in-depth interviews conducted in February 2025 with Canadian patients who recently accessed or attempted to access pertuzumab.

The Ontario Health (Cancer Care Ontario) Breast Cancer Drug Advisory Committee provided input through a combination of teleconference meetings and emails. The Breast Medical Oncology Group at the Juravinski Cancer Centre in Hamilton, Ontario, offered input, with views reflecting a consensus opinion from the group of authors. The REAL Canadian Alliance provided expert guidance on treating early-stage HER2-positive breast cancer with pertuzumab, trastuzumab, and chemotherapy, based on a recent publication (October 2024), supported by clinical expertise, literature reviews, clinical trials, and international congress data.

The full submissions received are available on the project landing page in the consolidated input document: Pertuzumab (PX0379-000)

Input from patient and clinician groups is considered throughout the review, including in the selection of outcomes to include in the Clinical Review and in the interpretation of the clinical evidence. Relevant patient and clinician group input and industry input is summarized in the Disease Background, Current Management, and Unmet Needs and Existing Challenges sections.

The drug programs provide input on each drug being reviewed through the Reimbursement Review process by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted for this review are summarized and provided to the expert committee in a separate document.

Each review team includes at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process. Three specialists with expertise in the diagnosis and management of breast cancer participated as part of the review team, with representation from Alberta, British Columbia, and Ontario.

Disease Background

Breast cancer is the most common cancer reported worldwide.[3] In Canada, breast cancer is estimated to be the second most common cancer, with an estimated 30,800 new cases diagnosed in 2024. In 2024, a total of 88,100 people are expected to die from cancer in Canada. Among these, 5500 deaths are expected due to breast cancer.[4]

There is considerable heterogeneity in breast cancer. Treatment strategies also depend on molecular features, such as if there is activation of HER2, hormonal receptors (estrogen receptor and progesterone receptor), gene mutations and markers of the immune microenvironment (e.g., programmed death-ligand 1).[3] For this review, the focus is on patients with early HER2-positive breast cancer.

Current Management

Early stage breast cancer is considered curable. In patients with HER2-positive breast tumors, the availability of HER2 targeted therapy has changed the natural history of the disease.[3] Most patients with a tumor greater than 2 cm or at least 1 positive lymph node should receive neoadjuvant HER2 targeted therapy in addition to taxane-based chemotherapy with or without anthracyclines.

The clinical experts have expressed that the standard of care in other international jurisdictions is to offer dual HER2 targeted therapies (e.g., pertuzumab in combination with trastuzumab) in the neoadjuvant setting. This rationale for this treatment strategy is to offer synergy as trastuzumab and pertuzumab have been reported to target different extracellular regions of the HER-2 tyrosine kinase receptor[5]to enhance apoptosis.

However, in Canada, most jurisdictions only fund single-HER2 targeted therapy with trastuzumab in the neoadjuvant setting. In a recent publication (Guidance for Canadian Breast Cancer practice: National Consensus Recommendations for the Systemic Treatment of Patients with HER2_ Breast Cancer in Both the Early and Metastatic Setting),[6] the authors have issued the following recommendation:

For patients with HER2+ early breast cancer with tumors larger than 2 centimeters or those with nodal disease, the standard of care is neoadjuvant therapy with trastuzumab plus pertuzumab plus chemotherapy.

European Society for Medical Oncology[7] and National Comprehensive Cancer Network[8] have issued similar recommendations, endorsing the use of combination trastuzumab and pertuzumab together for patients with HER2+ early breast cancer.

Treatment Goals

The clinical experts consulted for this review indicated that the goals of therapy for patients with early breast cancer were to improve the chance of cure and OS, decreasing the risk of breast cancer recurrence and improving pathological complete response rates. Additional treatment goals were to minimize toxicity and to minimize invasive surgeries. In addition, maintaining patients' quality of life was highlighted as an important treatment goal in the input submitted by both patient and clinician groups.

Current Treatment Options

The clinical experts consulted for this review indicated that for patients with early stage (e.g., stage II-III) HER2 positive breast cancer, the current standard treatment options in the neoadjuvant setting include chemotherapy with HER2 targeted therapy with trastuzumab.

Following surgery, the adjuvant treatment option(s) would depend on pathological findings. If pathological complete response is achieved, the patient is to continue with trastuzumab for a total of 1 year. If there is evidence of residual disease, the patient is to receive trastuzumab emtansine (T-DM1) in the adjuvant setting. Some patients with residual disease may also receive targeted therapies such as neratinib, following T-DM1.

Other adjuvant treatment options include additional chemotherapy, radiation and endocrine therapy.

Unmet Needs and Existing Challenges

The clinical experts expressed that the greatest treatment gap in the early stage of HER2 positive breast cancer setting is the lack of access to neoadjuvant pertuzumab for stage II-III patients. They advocate that this combination treatment strategy allows more patients to achieve pCR.

In addition, clinical experts indicated that using pertuzumab in the neoadjuvant setting may allow patients to receive less toxic downstream treatments. Echoing the perspectives of both patient and clinician groups, the clinical experts explained that if a patient achieves pCR, the adjuvant treatment would typically be trastuzumab, which is generally well tolerated. However, for patients with residual disease, the recommended adjuvant treatment is T-DM1, which is more costly, requires more frequent monitoring, and associated with higher toxicity.[9]

Consistent with input from clinician groups, one expert also noted that, based on clinical experience, many patients who achieve pCR can omit anthracycline from the chemotherapy backbone in the adjuvant setting, thereby avoiding the cardiotoxicity risks associated with it.

Clinical experts also highlighted that, because pertuzumab is not publicly funded for neoadjuvant use, patients with private insurance may access it through private infusion clinics. This creates a two-tier system and inequitable access to treatment. Furthermore, it complicates care coordination, as monitoring of pertuzumab infusions cannot be integrated with other neoadjuvant therapies.

Clinician groups emphasized that these gaps in effectiveness, safety, and access disproportionately affect patients without private insurance or financial means, exacerbating disparities along socioeconomic and geographic lines, particularly for equity-deserving or historically marginalized populations.

Similarly, patient groups noted that, although dual HER2-directed neoadjuvant therapy has been the standard of care in other G7 countries for nearly a decade, access in Canada through public funding is very limited. As a result, patients face significant financial burdens, psychological distress, and poorer survival outcomes, with some relying on personal savings, loans, or fundraising to afford pertuzumab.

Considerations for Using the Drug Under Review

Contents within this section have been informed by input from the clinical expert(s) consulted for the purpose of this review and from clinician groups. The following has been summarized by the review team.

Place in Therapy

According to the clinical experts, neoadjuvant pertuzumab would be added to the current standard of neoadjuvant chemotherapy and trastuzumab, administered concurrently with other neoadjuvant treatments containing trastuzumab. This treatment would not continue into the adjuvant phase. Clinician groups similarly emphasized that pertuzumab would be incorporated into the neoadjuvant setting to enhance, rather than replace, current first-line regimens with the goal of increasing pCR rates. Ontario Health and the Breast Medical Oncology Centre also agree that pertuzumab targets the underlying disease process, not just symptoms, and would enhance the current treatment paradigm, rather than dramatically altering it.

Patient Population

Clinical experts and clinician groups agreed that patients with Stage II–III HER2-positive early breast cancer who are eligible for neoadjuvant therapy are also appropriate candidates for the addition of pertuzumab. According to the clinician groups, all patients suitable for trastuzumab-based treatment are expected to be suitable for pertuzumab addition as well

Assessing the Response to Treatment

The clinical experts indicated that treatment response would be assessed clinically throughout the neoadjuvant treatment course, as per standard practice. After surgery, pathological staging would be performed to evaluate the neoadjuvant treatment response and determine if a pathological complete response (pCR) is achieved. Additionally, response to therapy is monitored both clinically and radiologically during clinic visits. Toxicity and cardiac function are also closely monitored through clinical assessments.

Clinician groups aligned with this perspective and further emphasized the importance of regular cycle-by-cycle clinical and radiologic assessments to guide ongoing management. They also highlighted that treatment is generally delivered in outpatient cancer clinics or chemotherapy suites under the supervision of trained oncologists, given the complexity of neoadjuvant regimens.

Discontinuing Treatment

The clinical experts indicated that the decision to discontinue treatment with pertuzumab should be based on factors such as disease progression or unacceptable toxicity. However, they noted that neoadjuvant pertuzumab is generally well tolerated, with low rates of treatment discontinuation.

Prescribing Considerations

Patients receiving pertuzumab should be under the care of a medical oncologist with experience with the treatment of breast malignancies. Pertuzumab should be administered in a cancer facility, and the monitoring of treatment response should be conducted by medical oncologists and surgeons.

Clinical Review

Methods

We conducted a systematic review to identify current evidence for pertuzumab in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of early-stage HER2-positive breast cancer in adults. Studies were selected according to the eligibility criteria in Table 2. We also included long-term extension studies of included randomized controlled trials (RCTs), indirect treatment comparisons (ITCs) that adhered to the eligibility criteria except for the study design criteria, and studies addressing gaps that did not meet the eligibility criteria but were considered to address important gaps in the Systematic Review evidence.

Relevant comparators included treatments used in clinical practice in Canada in the patient population under review. We selected outcomes for review considering clinical expert input, and patient and clinician group inputs. Selected outcomes are those considered relevant to expert committee deliberations. Detailed methods for literature searches, study selection, data extraction, and risk of bias appraisal are in the Supplemental Material in Appendix 2.

Table 2: Systematic Review Eligibility Criteria

Criteria	Description
Population	Adult patients aged 18 years or older with HER2-positive locally advanced, inflammatory, or early-stage breast cancer (greater than 2 cm in diameter or node-positive)
Intervention	**Neoadjuvant regimen:**

	Dual HER2 blockade (pertuzumab-trastuzumab) plus taxane-based* chemotherapy with or without anthracycline-based** chemotherapy (with variable dosing and treatment frequencies) *a taxane may include docetaxel or paclitaxel **an anthracycline may include doxorubicin, idarubicin, epirubicin
Comparator	**Neoadjuvant regimen:** Single HER2 blockade (trastuzumab) plus taxane-based* chemotherapy with or without anthracycline-based** chemotherapy (with variable dosing and treatment frequencies) *a taxane may include docetaxel or paclitaxel **an anthracycline may include doxorubicin, idarubicin, epirubicin

Outcomes	**Efficacy outcomes:**
	• Pathological complete response
	• Progression free survival
	• Event free survival
	• Disease free survival
	• Overall survival
	
	HRQoL:
	• EORTC QLQ-C30
	• EQ-5D
	
	Harms outcomes:
	• TEAE, AE grade ≥3, SAE, withdrawal due to AE, death due to AE
	• AEs of special interest:
	  ○ Left ventricular dysfunction
	  ○ Diarrhea
	  ○ Hypersensitivity
	  ○ Infusion reactions
	  ○ T-DM1 utilization in the adjuvant setting

Study design	Published Phase III and IV RCTs

AE = adverse events; HER2 = human Epidermal Growth Factor Receptor-2; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D = European Quality of Life-5 Dimensions; HRQoL = health-related quality of life; RCT = randomized controlled trial; SAE = serious adverse events; T-DM1 = trastuzumab emtansine.

Clinical Evidence

An information specialist conducted a literature search of key bibliographic databases, trial registries, and grey literature sources, using a peer-reviewed search strategy. The initial search was completed on February 28, 2025, with alerts maintained until the committee meeting on July 17, 2025. See Appendix 2 in the Supplemental Materials document for detailed search strategies.

From the 2022 CADTH clinical review,[2] we included 3 reports of 2 trials. These included the PEONY trial[10] and the NEOSPHERE trial.[11,12] Although NeoSphere was a phase 2 trial, it contributes to the body of evidence supporting pertuzumab's use in the neoadjuvant setting. The study enrolled a demographically and geographically diverse population, with sites across North America (including Canada and Mexico), Europe, South America, and Asia, enhancing the generalizability and relevance of its findings to Canadian clinical practice. Furthermore, NeoSphere played a pivotal role in establishing the international standard of care for neoadjuvant treatment in HER2-positive breast cancer. As such, it serves as a valuable complement to the PEONY trial and strengthens the overall evidence base supporting pertuzumab in this setting.

From the current search for primary studies, we identified 648 unique records via the searches of databases and registers, of which we excluded 633 by title and abstract. We screened 15 records by full text and included 1 updated report of the PEONY trial[13] in the systematic review. We did not identify any new RCTs or long-term extension studies.

From the search for ITCs, we identified 61 unique records via the searches of databases and trial registers. No ITCs relevant to the report were identified.

We also identified 5 reports of 5 comparative RWE studies, which are presented in the section on Studies Addressing Gaps in the Systematic Review Evidence.

Systematic Review

Description of Studies

Study Characteristics

Characteristics of the studies are summarized in Table 3: Characteristics of the Included Studies.

PEONY

The PEONY trial[10,13] was a multinational, multicenter, randomized, double-blind, phase 3 trial conducted across 72 hospitals in the Asia-Pacific region. The trial aimed to evaluate the efficacy and safety of adding pertuzumab to trastuzumab and chemotherapy in both the neoadjuvant and adjuvant settings for patients with early HER2-positive breast cancer in Asia.

A total of 329 patients were enrolled between March 14, 2016, and March 13, 2017. Participants were randomized in a 2:1 ratio using an interactive voice/web response system to receive 4 cycles of intravenous pertuzumab (840 mg loading dose followed by 420 mg maintenance doses), trastuzumab (8 mg/kg loading dose followed by 6 mg/kg maintenance doses), and docetaxel (75 mg/m²) (n = 219), or intravenous placebo plus trastuzumab and docetaxel (n = 110), administered every 3 weeks before surgery. Following neoadjuvant therapy and surgery, all patients received adjuvant treatment with 5-fluorouracil, epirubicin, and cyclophosphamide for 3 cycles. Subsequently, patients continued with pertuzumab or placebo in combination with trastuzumab every three weeks for up to 1 year, or until disease recurrence or unacceptable toxicity. Randomization was stratified by hormone receptor status (positive for estrogen and/or progesterone receptors vs. negative) and disease stage (early vs. locally advanced).

The primary outcome was total pCR (tpCR), defined as the absence of invasive cancer in the breast and axillary lymph nodes following neoadjuvant therapy and surgery. Outcomes were evaluated by both blinded central and local pathology review. Additional secondary endpoints included EFS, DFS, OS, and safety. EFS was defined as the time from randomization to the first documented event, including disease progression before surgery (according to Response Evaluation Criteria in Solid Tumours v1.1), disease recurrence after surgery (local, regional, distant, or contralateral), or death from any cause. In this context, in situ contralateral disease was not considered progression, whereas invasive contralateral disease was. DFS was measured from the date of surgery (when no evidence of disease was first recorded) to the earliest occurrence of recurrence (at any site) or death from any cause. OS was defined as the time from randomization to death from any cause.

Following completion or discontinuation of treatment, patients were monitored every 3 months during the first year and every 3 months thereafter, for up to 5 years after the last patient was randomized or until disease progression or recurrence. Patients without an event at the time of analysis were censored at the last date known to be alive and event-free.

Safety outcomes included the incidence, type, and severity of adverse events, including serious and cardiac-related events. Left ventricular ejection fraction (LVEF) was monitored throughout the study, with significant declines defined as a reduction of 10% or more from baseline to below 50%.

NEOSPHERE

The NEOSPHERE trial[11,12] was an international, multicenter, randomized, open-label, phase 2 study designed to evaluate the efficacy and safety of pertuzumab in combination with trastuzumab and docetaxel as neoadjuvant treatment for patients with HER2-

positive breast cancer. A total of 417 patients were enrolled between December 17, 2007, and December 22, 2009, across 59 centers in 16 countries.

Eligible participants were adults aged 18 years or older with centrally confirmed HER2-positive, operable, locally advanced, or inflammatory breast cancer, with tumor size greater than 2 cm. HER2 positivity was defined as immunohistochemistry 3+, or 2+ and positive for fluorescence or chromogenic in-situ hybridization. Patients were randomized in a 1:1:1:1 ratio to 1 of 4 neoadjuvant treatment arms: trastuzumab plus docetaxel, pertuzumab plus trastuzumab plus docetaxel, pertuzumab plus trastuzumab, or pertuzumab plus docetaxel. For this review, we present data from the relevant treatment groups, i.e., pertuzumab plus trastuzumab plus docetaxel versus trastuzumab plus docetaxel.

All treatments were administered every 3 weeks for 4 cycles: trastuzumab (8 mg/kg loading, then 6 mg/kg), pertuzumab (840 mg loading, then 420 mg), and docetaxel (75 mg/m², with potential escalation to 100 mg/m²). Following surgery, most patients received 3 cycles of adjuvant fluorouracil, epirubicin, and cyclophosphamide. All patients continued trastuzumab to complete 1 year of HER2-targeted therapy. Radiotherapy and endocrine therapy were administered according to local guidelines. Chemotherapy dose reductions were permitted, while HER2-targeted therapy doses remained fixed.

The primary endpoint of the NEOSPHERE trial was pCR in the breast (bpCR), defined as the absence of invasive cancer in the resected tumor tissue, with the presence of in situ disease permitted. Pathological assessments were conducted according to standardized guidelines and periodically reviewed by a blinded consultant pathologist to ensure consistency. Secondary endpoints included PFS, defined as the time from randomization to disease progression or death; DFS, defined as the time from surgery to recurrence or death; and safety.

Table 3: Characteristics of the Included Studies

First author, year, study name, design, locations, study period, study population	Inclusion criteria	Exclusion critera	Relevant intervention and comparator	Relevant outcomes and follow-up
Shao et al., 2020; Huang et al., 2024 PEONY study DB RCT (Phase 3) 23 sites (China, Korea, Thailand, Taiwan) First patient randomized: March 14, 2016 Final analysis data cut-off: March 14, 2022 N = 329.	• Adults aged ≥18 years diagnosed with early stage or locally advanced BC with histologically confirmed HER2-positive BC • HER2+ (defined as 3+ score by IHC in >10% of immunoreactive cells or HER2 gene amplification (ratio of HER2 gene signals to centromere 17 signals ≥2.0) by ISH • HR status known (ER or PgR) • ECOG PS ≤1 • Baseline LVEF ≥ 55% measured by ECHO or MUGA scan.	• Stage 4 metastatic BC • Inflammatory BC • Previous anti-cancer therapy or radiotherapy for any malignancy • History of other malignancy within 5 years of screening, except for appropriately treated carcinoma in situ of the cervix, NMSC, or Stage 1 uterine cancer • Serious cardiac illness or medical condition.	***Intervention*** *Neoadjuvant phase:* • P: 840 mg loading dose, then 420 mg maintenance dose • H: 8mg per kg loading dose, 6 mg per kg maintenance dose • Docetaxel Followed by surgery *Adjuvant phase*: 3 cycles of FEC, then P + H at above doses for cycles 8 to 17, or until disease recurrence or unacceptable toxicity ***Comparator*** *Neoadjuvant phase:* • Placebo + H + CT *Adjuvant phase*: 3 cycles of FEC, then P + H at above doses for cycles 8 to 17, or until disease recurrence or unacceptable toxicity.	*Efficacy* • tpCR • DFS • EFS • OS *Harms* • AEs • SAEs • WAEs • Death • AESI Follow-up: median 62.9 months

First author, year, study name, design, locations, study period, study population	Inclusion criteria	Exclusion critera	Relevant intervention and comparator	Relevant outcomes and follow-up
Gianni et al., 2012; Gianni et al., 2016 NEOSPHERE study OL RCT (Phase 2) 59 sites; 16 countries in North America (Canada, Mexico), Europe, South America, and Asia First patient enrolled: December 17, 2007 Final analysis data cut-off: October 20, 2014 N = 417	• Adults aged ≥18 years with HER2-positive BC. • Primary tumor size >2 cm in diameter. • Disease stage: operable (T2 to T3, N0 to N1, M0), locally advanced (T2to T3, N2 to N3, M0 or T4a to c, any N, M0), or inflammatory (T4d, any N, M0). • No prior cancer therapy. • HER2 status confirmed as IHC 3+ or IHC 2+ with HER2 gene amplification by fluorescence or chromogenic in-situ hybridisation. • ECOG PS = 0 or 1. • Baseline LVEF ≥ 55% measured by echocardiography or MUGA scan.	• Stage 4 (metastatic) disease • Bilateral BC • Other malignancy • Inadequate bone marrow function • Inadequate renal function • Impaired liver function • Impaired cardiac function • Uncontrolled hypertension • Pregnancy • Refusal to use contraception.	***Intervention*** *Neoadjuvant phase:* • P: 840mg loading dose followed by 420 mg every 3 weeks • H: 8 mg per kg loading dose on day 1 cycle 1, 6 mg/kg maintenance dose every 3 weeks • Docetaxel: 75 mg per m^2 then escalated up to 100mg per m^2 *Adjuvant phase:* FEC × 3 cycles + H for up to 1 year ***Comparator*** *Neoadjuvant phase:* • H + taxane-based CT *Adjuvant phase:* FEC × 3 cycles plus H for up to 1 year.	*Efficacy* • bpCR • DFS • PFS *Harms* • AEs • AEs • SAEs • WAEs • Death • AESI Follow-up: median 60 months

AE = adverse event; BC = breast cancer; DB = Double-Blind; bpCR = breast pathological complete response; CT = chemotherapy; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ECHO = echocardiography; EFS = event-free survival; ER = estrogen receptor; FEC = fluorouracil, epirubicin, and cyclophosphamide; FISH = fluorescence in situ hybridization; H = trastuzumab; HR = hormone receptor; IHC = immunohistochemistry; LVEF = left ventricular ejection fraction; MUGA = multiple gated acquisition; NMSC = non-small cell carcinoma; OL = open label; OS = overall survival; PgR = progesterone receptor; RCT = randomized controlled trial; SAE = serious adverse event; tpCR = total pathological complete response; WAE = withdrawals due to adverse events.

Sources: Shao et al. (2020),[10] Huang et al. (2024),[13] Gianni et al. (2012),[11] Gianni et al.(2016)[12]

Statistical Testing and Analysis Populations

PEONY

The study was powered at 85% to detect a 15% absolute improvement in tpCR (expected 20% in the placebo group) at a two-sided alpha of 0.05, with a sample size of 328 and a 2:1 randomization ratio. The tpCR rate was estimated using the Clopper-Pearson method. Treatment arms were compared using a stratified Cochran-Mantel-Haenszel test (stratified by disease category and hormone receptor status), and an unadjusted Fisher exact test was also conducted. Absolute between-group differences in tpCR were calculated using the Hauck-Anderson method. Patients with missing or unevaluable tpCR assessments were classified as non-responders. No formal sensitivity analyses were pre-specified.

EFS and OS were assessed in the ITT population, and DFS was assessed among patients who underwent surgery. Kaplan-Meier methods were used to estimate 5-year survival rates, and stratified Cox proportional hazards models were used to calculate hazard ratios and 95% confidence intervals. The safety population included all patients who received at least 1 dose of study treatment and had a baseline safety assessment.

NEOSPHERE

The NEOSPHERE trial was powered at 80% to detect a 15% absolute difference in pCR between the relevant treatment groups, assuming an expected pCR of 40% in pertuzumab with trastuzumab plus docetaxel group and 25% in trastuzumab plus docetaxel group, with a sample size of 100 patients in each group and randomization at a 1:1 ratio. pCR was calculated for each group by dividing the number of patients achieving pCR by the total number in the ITT population. Statistical comparisons between in the intervention and comparator group were performed using a 2-sided Cochran-Mantel-Haenszel test at an α level of 0.2, stratified by disease stage and hormone receptor status. The trial was not powered to detect statistically significant differences in secondary efficacy endpoints, which were analyzed descriptively.

Efficacy analyses were assessed in the ITT population. Safety analyses included all patients who received at least 1 dose of study treatment and had a baseline safety assessment.

Patient Disposition

Details of the patient disposition for PEONY and NEOSPHERE are presented in Appendix 4 of the Supplemental Material document.

PEONY

In the PEONY trial, 383 patients were screened for eligibility. After excluding 54 for not meeting eligibility criteria, 329 patients were randomized to receive either pertuzumab (n = 219) or placebo (n = 110) and a total of 218 patients in the pertuzumab arm and 110 in the placebo arm began neoadjuvant treatment. Among those who were treated in the neoadjuvant period, 4 patients in the pertuzumab group and 2 patients in the placebo group discontinued neoadjuvant treatment. Four patients in the pertuzumab group and 2 patients in the placebo group did not undergo surgery.

A total of 208 patients in the pertuzumab arm and 103 patients in the placebo arm started adjuvant treatment. Of these, 204 patients in the pertuzumab arm and 99 patients in the placebo arm began adjuvant anit-HER2 treatment. By the end of adjuvant treatment, 198 patients in the pertuzumab arm and 94 in the placebo arm had completed their anti-HER2 treatment.

Subsequently, 208 patients in the pertuzumab arm and 104 patients in the placebo arm had entered the treatment-free follow up period. At the clinical cutoff data, 175 patients (79.9%) in the pertuzumab arm and 82 patients (74.5%) in the placebo arm had completed the study with 5 years of follow-up (median follow-up: 62.9 months).

NEOPSHERE

In the NEOSPHERE trial, 107 patients were randomly assigned to the pertuzumab and trastuzumab plus docetaxel group and 107 patients to the trastuzumab plus docetaxel group. Among those who were treated, 5 patients in the pertuzumab group and 4 patients in the group not receiving pertuzumab discontinued neoadjuvant treatment. The reasons for discontinuation included protocol violation, disease progression (n = 1 in the pertuzumab group) and death (n = 1 in the pertuzumab group).

A total of 102 patients in the pertuzumab and trastuzumab plus docetaxel arm and 103 patients in the trastuzumab plus docetaxel arm started adjuvant treatment. Of these, 94 patients in the pertuzumab and trastuzumab plus docetaxel arm and 98 patients in the trastuzumab plus docetaxel arm completed adjuvant treatment.

One hundred and two patients in the pertuzumab and trastuzumab plus docetaxel arm and 98 patients in the trastuzumab plus docetaxel arm entered the treatment-free follow-up period. At the clinical cutoff date, 83 patients in the pertuzumab and trastuzumab plus docetaxel arm and 77 patients in the trastuzumab plus docetaxel arm had completed the study with 5 years of follow-up (median follow-up: 60 months).

Baseline Characteristics

Patients' baseline characteristics for the study population in PEONY are presented in Table 4. Patients' baseline characteristics for the study population in the NEOSPHERE trial are presented in Table 5.

Table 4: Summary of Baseline Characteristics in PEONY - ITT Population

Characteristic	Pertuzumab, Trastuzumab, + Docetaxel N = 219	Placebo, Trastuzumab, + Docetaxel N = 110
Median age, years (range)	49 (24 to 72)	49 (27 to 70)
Age, n (%)		
< 40 years	40 (18.3)	18 (16.4)
40 to 49 years	75 (34.2)	40 (36.4)
50 to 64 years	96 (43.8)	44 (40.0)
65 years and more	8 (3.7)	8 (7.3)
ECOG performance status, n (%)		
0	198 (90.4)	97 (88.2)
1	21 (9.6)	13 (11.8)
Hormone receptor status, n (%)		
ER and PgR negative	105 (47.9)	54 (49.1)
ER and/or PgR positive	114 (52.1)	56 (50.9)
Menopausal status, n (%)		
Pre-menopausal	132 (60.3)	65 (59.1)
Post-menopausal	87 (39.7)	45 (40.9)
Disease status, n (%)		
Early stage	152 (69.4)	77 (70.0)
Locally advanced	67 (30.6)	33 (30.0)
Primary tumor stage, n (%)		
T2	155 (70.8)	71 (64.5)
T3	45 (20.5)	29 (26.4)
T4	19 (8.7)	10 (9.1)
Lymph node status, n (%)		
Positive	160 (73.1)	89 (80.9)
Negative	59 (26.9)	21 (19.1)
Histologic subtype, n (%)		
Ductal	203 (92.7)	103 (93.6)
Lobular	4 (1.8)	1 (0.9)
Comedo	0	1 (0.9)
Other/comedo	15 (6.8)	8 (7.3)
HER2 status IHC score, n (%)		
1+	2 (0.9)	0
2+	65 (29.7)	22 (20.0)
3+	152 (69.4)	88 (80.0)

ECOG = Eastern Cooperative Oncology Group performance status; ER = estrogen receptor; FEC = fluorouracil, epirubicin, and cyclophosphamide; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; PgR = progesterone receptor.

Source: Shao et al., (2020)[10]

Table 5: Summary of Baseline Characteristics in NEOSPHERE in the ITT Population

Characteristic[a]	Pertuzumab, Trastuzumab, + Docetaxel N = 107	Trastuzumab + Docetaxel N = 107
Median age (years, range)	50 (28 to 77)	50 (32 to 74)
Ethnic origin		
Black	2 (2)	0
White	77 (72)	80 (75)
Asian	23 (21)	25 (23)
Other	5 (5)	2 (2)
ECOG performance status		
0	96 (90)	100 (94)[b]
1	11 (10)	6 (6)[b]
ER-positive or PR-positive, or both	50 (47)	50 (47)
ER-negative and PR-negative	57 (53)	57 (53)
Operable	65 (61)	64 (60)
Locally advanced	32 (30)	36 (34)
Inflammatory	10 (9)	7 (7)
Lymph node status		
N0	31 (29)[b]	32 (30)
N1	53 (50)[b]	48 (45)
N2	22 (21)[b]	22 (21)
N3	0	5 (5)
Median tumor size (mm) at clinical breast examination (range)	55 (20 to 150)	50 (20 to 200)

ECOG = Eastern Cooperative Oncology Group; ER = estrogen receptor; ITT = intention-to-treatment; PR = progesterone receptor.

a. Data are number (%) unless otherwise specified.
b. Data missing for one patient.

Source: Gianni et al. (2012),[11]
Reprinted from Lancet Oncology, 13/1, Gianni L, Pienkowski T, Im YH, Roman L, Tseng LM, Liu MC, Lluch A, Staroslawska E, de la Haba-Rodriguez J, Im SA, Pedrini JL, Poirier B, Morandi P, Semiglazov V, Srimuninnimit V, Bianchi G, Szado T, Ratnayake J, Ross G, Valagussa P., Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial, 25-32, Copyright (2012), with permission from Elsevier.

Treatment Exposure and Concomitant Medications

Details of study drug exposure in PEONY and NEOSPHERE are summarized in Appendix 4 of the Supplemental Material document.

PEONY

On average, patients received 3.9 of the 4 planned cycles of neoadjuvant treatment. The mean cumulative dose of pertuzumab was 2082.7 mg and Infusion modification with pertuzumab occurred in 3.2% of patients. Concomitant medications were not reported in the trial.

NEOSPHERE

In the neoadjuvant phase, the median number of pertuzumab cycles in both groups was 4, with 98% of patients completing all 4 planned cycles. Of the total pertuzumab cycles administered, 57% were delayed, slowed, or interrupted in the pertuzumab and

trastuzumab plus docetaxel group. Radiotherapy to the breast or axilla and adjuvant hormonal treatment were evenly distributed across groups. Data on concomitant medications were not reported in the trial.

Critical Appraisal

Internal Validity

The risk of bias in the randomization process was likely low. PEONY used an interactive web and voice response system for randomization with stratification by disease stage and hormone receptor status. In NEOSPHERE, randomization was carried out via an interactive voice-response system using dynamic allocation, stratified by disease stage and hormone receptor status. Although there were slight imbalances in race, Eastern Cooperative Oncology Group status, lymph node status, and breast cancer type between treatment groups, the clinical experts did not expect such imbalances would introduce bias to the study results.

Investigators and study personnel were blinded from treatment assignment, and a placebo matched to pertuzumab was used to maintain blinding throughout the study. In contrast, the NEOSPHERE trial was open-label, and patients, caregivers, and trial personnel were aware of treatment assignments. While this open-label design increases the risk of bias in the measurement of subjective outcomes, such as adverse events, the impact on objective efficacy outcomes (e.g., survival outcome or pCR) was likely limited. The clinical experts stated that non-blinding wouldn't have affected the primary efficacy outcome. pCR is assessed using strict, standardized pathology protocols, making it an objective outcome. Therefore, the lack of blinding would not have introduced bias into the pCR results.

Both trials conducted efficacy analyses using an ITT approach, preserving the benefits of randomization. In NEOSPHERE, patients who were enrolled but not randomized were excluded, and all randomized patients were included in efficacy analyses, minimizing bias.

Regarding multiplicity, NEOSPHERE used the Simes method to handle multiple comparisons across treatment arms but employed a liberal alpha of 0.2 given its phase II, proof-of-concept design, which may have increased the risk of type I error on the primary endpoint of bpCR (p=0.014) and moreover, no consistent difference in favor of combination therapy was found on PFS and DFS. In PEONY, multiplicity adjustment beyond the primary endpoint of tpCR was not formally described, and p-values (ranged from 0.043 to 0.26) for secondary analyses (EFS, DFS and OS) should be considered exploratory in nature and no statistical inference could be drawn on those outcomes. Therefore, this limits the ability to draw definitive conclusions about the overall efficacy on clinically important outcomes such as OS, DFS and PFS of pertuzumab in combination with trastuzumab and chemotherapy in this setting.

Treatment exposure during the neoadjuvant period was generally consistent with the planned regimen across both PEONY and NEOSPHERE, with patients receiving close to the planned number of treatment cycles. Withdrawal rates were low and generally balanced between treatment groups. Treatment modifications or delays due to adverse events were low and similar across treatment arms. For the primary dichotomous outcome of pCR, missing data were handled conservatively by treating missing responses as non-responders, minimizing the risk of bias. For survival outcomes, missing data were addressed through censoring at the time of the last follow-up without disease progression, following standard survival analysis methods in both studies. Therefore, missing data and withdrawals are unlikely to have introduced substantial bias into the efficacy results. It is unknown what would be the impact from concomitant treatment as no data provided.

In the PEONY and NEOSPHERE studies, the interpretation of survival outcomes (DFS, EFS, PFS and OS) may be complicated as patients who received pertuzumab during the neoadjuvant phase also continued to receive pertuzumab in the adjuvant setting. This introduces potential confounding, making it difficult to determine whether any observed survival benefits are due to neoadjuvant pertuzumab alone. However, the clinical experts consulted by CDA-AMC indicated that it would be reasonable to attribute the benefit to the neoadjuvant pertuzumab. Evidence from the APHINITY trial,[14] which evaluated adjuvant pertuzumab, found a 5% improvement in 3-year invasive DFS but no benefit in OS at 6 years. Therefore, the experts considered it appropriate to conclude that the observed effects in PEONY and NEOSPHERE are likely due to neoadjuvant pertuzumab rather than adjuvant administration.

External Validity

While PEONY was conducted in Asia, the clinical expert consulted during the previous review indicated that the findings from the study could still be applicable to the Canadian population. Both PEONY and NEOSPHERE included only female participants, despite being open to all adult patients in the PEONY study. While there was no direct evidence in men with HER2-positive breast cancer, they were generally treated the same as females according to the clinical experts.

The clinical experts consulted by CDA-AMC noted that the regimens used in both the PEONY and NEOSPHERE trials did not fully reflect current standard practices in Canada. Specifically, the trials utilized regimens that did not include anthracycline-based chemotherapy, which is often used as part of the initial treatment approach in Canada, followed by pertuzumab-trastuzumab combined with taxane-based chemotherapy. In addition, both trials included pertuzumab in the adjuvant phase of the intervention phases. The clinical experts confirmed that this is not how pertuzumab is applied in Canadian clinical practice. Moreover, neither trial included the use of T-DM1 as adjuvant treatment, which is the current treatment strategy for patients with residual disease in Canada. However, the clinical experts believed that these limitations did not significantly impact on the generalizability of the results. They acknowledged that the trials were conducted during an earlier treatment era and emphasized the importance of reassessing clinical strategies in light of newer treatment strategies.

The primary and secondary outcomes, including pCR in both trials and OS in PEONY, are clinically relevant and important in Canadian practice. These outcomes are aligned with the treatment goals for HER2-positive breast cancer, and their inclusion in the trials ensures their relevance. Also, both trials had adequate follow-up to assess the relevant outcomes of interest.

Neither study assessed health-related quality of life (HRQoL), which is an important factor highlighted in the patient input, especially considering that many patients with early-stage breast cancer may be asymptomatic.

Results

Efficacy

Results for outcomes important to this review from PEONY and NEOSPHERE are presented in Table 6.

Key results include the following:

- In the PEONY trial, the between-group difference and odds ratio for tpCR favoured pertuzumab plus trastuzumab and docetaxel compared to placebo plus trastuzumab and docetaxel.
- In the NEOSPHERE trials, the between-group difference in bpCR favoured pertuzumab plus trastuzumab and docetaxel over trastuzumab and docetaxel.
- In NEOSPHERE, DFS and PFS at 5 years did not improve with the addition of pertuzumab to trastuzumab and docetaxel.
- In PEONY, the hazard ratios for EFS and DFS at 5 years favoured pertuzumab over placebo.
- In PEONY, the evidence was insufficient to suggest a difference in 5-year OS between pertuzumab and placebo.

Table 6: Summary of Key Efficacy Results - PEONY and NEOSPHERE (ITT Population)

Characteristic	PEONY		NEOSPHERE	
	Pertuzumab + Trastuzumab + Docetaxel N = 219	Placebo + Trastuzumab + Docetaxel N = 110	Pertuzumab + Trastuzumab + Docetaxel N = 107	Trastuzumab + Docetaxel N = 107
tpCR				
Responders, n (%)	86 (39.3)	24 (21.8)	NR	NR
Absolute between-group difference (95% CI)	17.5 (6.9 to 28.0)[a]	Reference	NR	NR
P value	0.001		NR	NR
OR (95% CI)	Reference	0.43 (0.25 to 0.73)	NR	NR
P value	NR		NR	NR

Characteristic	PEONY		NEOSPHERE	
	Pertuzumab + Trastuzumab + Docetaxel N = 219	Placebo + Trastuzumab + Docetaxel N = 110	Pertuzumab + Trastuzumab + Docetaxel N = 107	Trastuzumab + Docetaxel N = 107
bpCR				
Responders, n (%)	NR	NR	49 (45.8)	31 (29.0)
95% CI	NR	NR	36.1 to 55.7	20.6 to 38.5
Absolute between-group difference (95% CI)	NR	NR	16.82 (3.5 to 30.1)	Reference
P value	NR	NR	0.0141[b]	
PFS				
Patients with event, n (%)	NR	NR	17 (15.9)	19 (17.8)
5-year PFS rate, %, (95% CI)	NR	NR	86 (77 to 91)	81 (71 to 87)
HR (95% CI)	NR	NR	0.69 (0.34 to 1.40)[c]	Reference
P value	NR	NR	NR	NR
EFS				
Patients with event, n (%)	32 (14.6)	27 (24.5)	NR	NR
3-year EFS rate, %[d]	88.9	79.7	NR	NR
Absolute between-group difference (95% CI)[e]	9.2 (0.29 to 18.1)		NR	NR
P value	0.043		NR	NR
5-year EFS rate, %[d]	84.8	73.7	NR	NR
Absolute between-group difference (95% CI)[e]	11.1 (1.2 to 21.0)		NR	NR
P value	0.027		NR	NR
5-year HR (95% CI)	0.53 (0.32 to 0.89)[f]		NR	NR
DFS				
Patients with event, n (%)	29 (13.8)	25 (23.8)	15 (4.9)	18 (17.5)
3-Year DFS rate, n (%)[d]	90.1	81.1	NR	NR
Absolute between-group difference (95% CI)[e]	9.0 (0.30 to 17.7)		NR	NR
P value	0.043		NR	NR
5-Year DFS rate, % (95% CI)[d]	86.0 (NR)	75.0 (NR)	84 (72 to 91)	81 (72 to 88)
Absolute between-group difference (95% CI)[e]	11.0 (1.2 to 20.7)		NR	NR
P value	0.028		NR	NR
5-year HR (95% CI)	0.52 (0.30 to 0.88)[f]		0.60 (0.28 to 1.27)[c]	Reference
OS				
Patients with event, n (%)	12 (5.5)	11 (10.0)	NR	NR
3-year OS rates[d]	97.0	91.0	NR	NR
Absolute between-group difference (95% CI)[e]	6.0 (0.08 to 12.1)		NR	NR
P value	0.053		NR	NR
5-year OS rates[d]	93.9	90.0	NR	NR
Absolute between-group difference (95% CI)[e]	3.9 (2.9 to 10.7)		NR	NR
P value	0.262		NR	NR
5-year HR (95% CI)	0.53 (0.23 to 1.19)[f]		NR	NR

bpCR = breast pathological complete response; CI = confidence interval; DFS = disease-free survival; EFS = event-free survival; HR = hazard ratio; NR = not reported; OS = overall survival; PFS = progression-free survival; tpCR = total pathological complete response.

a. Approximate 95% CI for difference of two rates using Hauck-Anderson method.
b. P value from Cochran-Mantel-Haenszel test, with Simes multiplicity adjustment.
c. HR is based on Cox proportional hazard regression stratified by breast cancer type and hormone positivity.
d. The Kaplan–Meier approach was used to estimate survival rates at the time point (i.e., 3 years or 5 years) for each treatment arm.
e. The 2-sided log-rank test was used to make an exploratory comparison of survival distribution between the 2 treatment arms.
f. The stratified Cox proportional-hazards model was used to estimate the HR between the 2 treatment arms and its 95% CI.

Sources: Shao et al. (2020),[10] Huang et al. (2024),[13] Gianni et al. (2012),[11] Gianni et al.(2016)[12]

Harms

Details of harm results for PEONY and NEOSPHERE are presented in Appendix 4 of the Supplemental Material document.

Key results include the following:

- In PEONY, 100% of patients in the pertuzumab with trastuzumab plus docetaxel arm and 99.1% in the placebo with trastuzumab plus docetaxel arm experienced at least 1 treatment-emergent AE. Common AEs in both arms were neutropenia (70.6% and 66.4%), leukopenia (61.9% and 60.9%), and alopecia (52.8% and 50.9%). In NEOSPHERE, 98.1% in the pertuzumab with trastuzumab plus docetaxel arm and 100% in the trastuzumab plus docetaxel arm had at least 1 treatment-emergent AE, with common events in both arms including alopecia (68.2% and 70.1%), neutropenia (63.6% and 74.7%), and nausea (66.4% and 65.4%).
- In PEONY, 70.6% of patients in the pertuzumab with trastuzumab plus docetaxel arm and 68.2% in the placebo with trastuzumab plus docetaxel arm had 1 or more grade 3 or higher AEs, with neutropenia being most common in both arms (59.2% and 55.5%). In NEOSPHERE, 72.9% in the pertuzumab with trastuzumab plus docetaxel group and 81.3% in the trastuzumab plus docetaxel group had 1 or more grade 3 or higher AEs, with neutropenia being the most common in both arms (55.1% and 66.4%).
- In PEONY, 17% of patients in the pertuzumab group and 13.6% in the placebo group had SAEs, with febrile neutropenia being the most common SAE in both groups (4.1% and 2.7%). In NEOSPHERE, 21% in the pertuzumab arm and 20% in the comparator arm had SAEs, with febrile neutropenia being the most common in both arms (7.5% and 9.3%).
- In PEONY, 2 patients (0.9%) in the pertuzumab group and no patients in the placebo group discontinued treatment due to AEs. In NEOSPHERE, 5 patients (4.7%) in the pertuzumab group and 0 in the comparator group discontinued treatment due to AEs.
- In PEONY, 2 patients (0.9%) died in the pertuzumab group (suicide and pneumonia) and 2 patients (1.8%) in the placebo group (sudden death in both patients). In NEOSPHERE, 1 patient (0.9%) in the pertuzumab group died from fulminant hepatitis (and no deaths in the comparator group).
- In PEONY, AEs of special interest were diarrhea (any grade, 40.8% in the pertuzumab with trastuzumab plus docetaxel arm and 17.3% in the placebo with trastuzumab plus docetaxel arm), infusion reactions (22.0% and 9.1%), and LVEF decline (0.9% and 1.8%). In NEOSPHERE, AEs of special interest included diarrhea (any grade, 51.4% in the pertuzumab with trastuzumab plus docetaxel arm and 38.3% in the trastuzumab plus docetaxel arm) and LVEF decline (8.4% and 0.9%, respectively). Drug hypersensitivity occurred in 1 (0.9%) patient in the pertuzumab group and no patients in the comparator group. T-DM1 utilization in the adjuvant setting was not reported.

Studies Addressing Gaps in the Systematic Review Evidence

Five comparative non-randomized RWE studies have been summarized to provide additional evidence of the efficacy and harms of pertuzumab in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of early-stage HER2-positive breast cancer in adults.

Table 7: Summary of Gaps in the Systematic Review Evidence

Evidence gap	First author, year	Study name
Effect on survival outcomes (OS, EFS, DFS, PFS) following NAT with pertuzumab	Canino et al., 2024[15]	Safety and efficacy analysis of neoadjuvant pertuzumab, trastuzumab and standard chemotherapy for HER2–positive early breast cancer: real–world data from NeoPowER study
	van der Voort et al., 2022)[16]	Efficacy of neoadjuvant treatment with or without pertuzumab in patients with stage II and III HER2-positive breast cancer: a nationwide cohort analysis of pathologic response and 5-year survival
Effect of NAT with pertuzumab in real world setting	Bilici et al., 2023[17]	Impact of adding pertuzumab to trastuzumab plus chemotherapy in neoadjuvant treatment of HER2 positive breast cancer patients: a multicenter real-life HER2PATH study
	Ren et al., 2023[18]	Changes in HER2 status and survival outcomes in patients with non-pathological complete response after neoadjuvant targeted treatment
	Cheng et al., 2022[19]	Neoadjuvant therapy for early human epidermal growth factor receptor 2 positive breast cancer in China: A multicenter real-world study (CSBrS-015)

EFS = event-free survival; DFS = disease free survival; event free survival; NAT = neoadjuvant therapy; OS = overall survival; progression free survival.

Description of Studies

Characteristics of the included RWE studies are summarized in Table 8.

The outcome definitions and statistical testing methods for each outcome in each study are detailed in the footnotes of Table 11.

Table 8: Characteristics of Studies Addressing Gaps in Systematic Review Evidence

First author, year, study name, design, sample size, country, funding source(s)	Inclusion criteria	Exclusion criteria	Relevant intervention(s) and comparator(s)	Relevant outcomes, data source, follow-up
Canino et al., 2024 NeoPowER study Retrospective multicenter cohort study N = 260 Italy No funding.	• Adults (≥18 years) with BC • ECOG performance status of 0 or 1 • Operable, locally advanced, or inflammatory BC: T2-3, N0-1, M0 • Locally advanced or inflammatory: T2-3, N2-3, M0 or T4a-d, any N, M0 • HER2 overexpression confirmed by IHC 3+ or IHC 2+ with ISH amplification • >1 and ≤8 courses of NAT • Underwent adequate surgical treatment on tumor and nodes • Not enrolled in any clinical trials.	• Metastatic disease (Stage IV) at diagnosis • HER2-negative BC (HER2 score 0, 1+, or 2+ with ISH negative) • Failure to undergo surgery after NAT due to patient refusal, evidence of metastatic disease, or other reasons.	*Intervention, neoadjuvant phase:* • P: 840 mg loading dose, then 420 mg every 21 days • H: 8 mg per kg loading dose, then 6 mg per kg every 21 days (or an alternative weekly regimen: 4 mg/kg loading dose, then 2 mg per kg weekly) • Taxane-based CT (docetaxel or paclitaxel) *Comparator, neoadjuvant phase:* H + CT	• pCR • DRFS • OS • Harms Data source: Electronic medical records Follow-up: median 6 years.
Bilici et al. 2023 HER2PATH study Retrospective nationwide cohort study N = 1,528 Turkey Funding: Roche Pharmaceuticals Turkey.	• Female patients aged ≥18 years who had been diagnosed with histologically confirmed HER2-positive BC • HER2 overexpression confirmed by IHC 3+ or IHC 2+ with ISH amplification • Treated with H + taxane with or without P as NAT • Underwent breast surgery at participating centers.	NR	*Intervention, neoadjuvant phase:* • P: 840 mg loading dose, then 420 mg every 3 weeks • H: 8 mg per kg loading dose, then 6 mg per kg • Taxane-based CT (docetaxel or paclitaxel) *Comparator, neoadjuvant phase:* H + taxane-based CT	• pCR • Harms Data source: National database on HER2+ BC (21 participating centers) Follow-up: median 39 months (for patients with no events), range 1 to 124 months.
Ren et al. 2023 Retrospective single center cohort study N = 499 China Funding: 100 Foreign Expert Plan of Hebei Province; Hebei Province Key Research & Development Program; Natural Science Foundation of Hebei Province.	• Pathological examination confirmed BC before NAT • HER2-positivity detected by IHC before adjuvant treatment • No distant metastasis • Completion of scheduled 6 to 8 cycles of neoadjuvant CT.	• Previous history of other malignant tumors • Previous history of endocrine treatment • Targeted treatment and radiotherapy • Other immunohistochemical subtypes.	*Intervention, neoadjuvant phase:* P + H + CT* *Comparator, neoadjuvant phase:* H + CT* *Drug usage and dosage were determined according to the 2017 Chinese Society of Clinical Oncology BC diagnosis and treatment guidelines.	• pCR Data source: Electronic medical records Follow-up: median 22 months, range 7 to 55 months.

First author, year, study name, design, sample size, country, funding source(s)	Inclusion criteria	Exclusion criteria	Relevant intervention(s) and comparator(s)	Relevant outcomes, data source, follow-up
Cheng et al., 2022 CSBrS-015 study Retrospective multicenter cohort study with PSM N: Overall = 1,032 PSM = 798 China Funding: Beijing Medical Award Foundation; Beijing Science and Technology Innovation Medical Development Foundation; Youth Cultivation Fund of the Beijing Medical Award Foundation; Interdisciplinary Clinical Research Project of Peking University First Hospital.	• Adults (≥18 years) with HER2-positive female BC diagnosis by core needle biopsy. • HER2-positivity detected by IHC before adjuvant treatment • ≥4 cycles of NAT with H + P + CT or H + CT. • Scheduled surgical treatment. • Complete clinicopathological data.	• Distant metastasis • Incomplete clinicopathological data • <4 cycles of NAT • Incomplete surgical treatment.	*Intervention, neoadjuvant phase:* • Taxane-based CT + Carboplatin + H + P; or • Taxane-based CT + H + P; or • Anthracyclines + Cyclophosphamide, then Taxane-based CT + H + P *Comparator, neoadjuvant phase:* • Taxane-based CT + Carboplatin + H; or • Taxane-based CT + H; or • Anthracyclines + Cyclophosphamide, then Taxane-based CT + H; or • Taxane-based CT + Cyclophosphamide + H	• pCR • Harms (intervention arm only) Data source: Electronic medical records Follow-up: NR.
van der Voort et al., 2022 Prospective nationwide cohort study N = 1,124 The Netherlands Funding: Team Westland Foundation.	• Clinical stage II or III HER2-positive BC • Received neoadjuvant CT + H with or without P.	No NAT or H	*Intervention, neoadjuvant phase:* • P: 840 mg loading dose, then 420 mg • H: 8 mg per kg loading dose, then 6 mg per kg • Carboplatin-taxane-based CT *Comparator, neoadjuvant phase:* H + Taxane-based CT	• pCR • BCSS • OS Data source: Netherlands Cancer Registry Follow-up: 6 years.

BCSS = breast cancer-specific survival; DRFS = distant relapse-free survival; ECOG = Eastern Cooperative Oncology Group; H = trastuzumab; HER2 = Human Epidermal Growth Factor Receptor 2; IHC = immunohistochemistry; M0 = no distant metastases; N0, N1, N2, N3 = nodal staging; NAT = neoadjuvant therapy; NBRST = Neoadjuvant Breast Registry Symphony Trial; NeoPowER = Neoadjuvant Pertuzumab and Trastuzumab for Breast Cancer Study; NR = not reported; OS = overall survival; P = pertuzumab; pCR = pathological complete response; PSM = propensity score matching; RWE = real world evidence; T0, T2, T3, T4 = tumor staging.

Sources: Canino et al. (2024);[15] Bilici et al. (2023);[17] Ren et al. (2023);[18] Cheng et al. (2022);[19] Van der Voort et al. (2022).[16]

Treatment Exposure and Subsequent Treatments

Details of patients' neoadjuvant treatment exposure and post-neoadjuvant treatments (i.e., adjuvant and surgical) in each included study are in Appendix 4 of the Supplemental Material document.

Baseline Characteristics

Patients' baseline characteristics for each study are presented in Table 9 and Table 10.

Table 9: Baseline Characteristics for NeoPowER and van der Voort et al.

Characteristic	NeoPowER 2024		van der Voort et al. 2022	
	P + H + CT (N = 126)	H + CT (N = 134)	P + H + CT (N = 453)	H + CT (N = 671)
Age (years), median (range) or n (%)	52 (28 to 76)	51.5 (28 to 84)	> 50: 189 (41.7)	> 50: 308 (45.9)
Menopausal, n (%)	62 (49.2)	68 (50.7)	NR	NR
ECOG status, n (%)				
0	64 (50.8)	111 (82.8)	272 (60)	313 (46.6)
1	2 (1.6%)	23 (17.2)	33 (7.3)	46 (3.9)
2	NR	NR	1 (0.2)	1 (0.1)
4	NR	NR	0 (0)	1 (0.1)
Unknown	60 (47.6)	0	147 (32.5)	310 (46.2)
HR status, n (%)				
HR positive	77 (61.1)	83 (61.9)	273 (60.3)	421 (62.7)
HR negative	49 (38.9)	51 (38.1)	180 (39.7)	249 (37.1)
Tumor stage, n (%)				
T1	NR	NR	T0 to T2: 317 70)	T0 to T2: 469 (69.9)
T2	92 (73.0)	99 (73.9)		
T3	34 (27.0)	35 (26.1)	T3 to T4: 136 (30)	T3 to T4: 202 (30.1)
T4	NR	NR		
Lymph node stage, n (%)				
N0	50 (39.7)	48 (35.8)	157 (34.7)	217 (32.3)
N1	N1 to N3: 76 (27.0)	N1 to N3: 86 (64.2)	293 (64.7)	450 (67.1)
N2			0	0
N3			0	0
Unknown	0	0	3 (0.7)	4 (0.6)
Histological grade, n (%)				
Grade 1	NR		1 to 2: 217 (47.9)	1 to 2: 216 (32.2)
Grade 2	29 (23.0)	22 (16.4)		
Grade 3	85 (67.5)	102 (76.1)	225 (49.7)	376 (56.0)
Unknown	12 (9.5)	10 (7.5)	11 (2.4)	79 (11.8)
Histological subtype, n (%)				
Ductal or NST	116 (92.1)	127 (94.8)	433 (95.6)	640 (95.4)
Lobular	3 (2.4)	6 (4.5)	19 (4.2)	27 (4.0)
Others	8 (9.3)	1 (0.7)	1 (0.2)	4 (0.6)

CT = standard neoadjuvant chemotherapy; ECOG = Eastern Cooperative Oncology Group; H = trastuzumab; HR = hormone receptor; N0, N1, N2, N3 = nodal staging; NR = not reported; NST = invasive carcinoma of no special type; P = pertuzumab; T1, T2, T3, T4 = tumor staging.

Sources: Canino et al. (2024);[15] Van der Voort et al. (2022).[16]

Table 10: Baseline Characteristics for HER2PATH, Ren et al., and CSBrS-015

Characteristic	HER2PATH 2023		Ren et al. 2023		CSBrS-015 2023	
	P + H + CT (N = 577)	H + CT (N = 951)	P + H + CT (N = 298)	H + CT (N = 201)	P + H + CT (N = 560)	H + CT (N = 472)
Age (years), median (range) or n (%)	47 (22 to 88)	47 (20 to 81)	≥ 50: 168 (56.4)	≥ 50: 110 (54.7)	50 (43 to 56)	
Menopausal	231 (40.0)	440 (46.3)	154 (51.7)	89 (44.3)	NR	NR
HR or ER status, n (%)						
HR positive	NR	NR	171 (57.4)	118 (58.7)	315 (30.5)	284 (27.5)
HR negative	NR	NR	127 (42.6)	83 (41.3)	245 (23.7)	188 (18.2)
Tumor stage, n (%)						
T1	T0 to 1T: 261 (45.2)	T0 to T1: 378 (39.7)	23 (7.7)	21 (10.5)	49 (4.7)	61 (5.9)
T2	T2 to T4: 316 (54.8)	T2 to T4: 573 (60.3)	185 (62.1)	120 (59.7)	330 (32.0)	393 (38.1)
T3			37 (12.4)	24 (11.9)	79 (7.7)	64 (6.2)
T4			53 (17.8)	36 (17.9)	39 (3.8)	17 (1.6)
Lymph node stage, n (%)						
N0	NX and N0: 165 (29.6)	NX and N0: 229 (24.9)	19 (6.4)	17 (8.5)	132 (12.8)	189 (18.3)
N1	N1 to N3: 392 (70.4)	N1 to N3: 689 (75.1)	154 (51.7)	95 (46.8)	269 (26.1)	222 (21.5)
N2			59 (19.8)	36 (17.9)	85 (8.2)	43 (4.2)
N3			66 (22.2)	53 (26.4)	74 (7.2)	18 (1.7)

CT = standard neoadjuvant chemotherapy; ER = estrogen receptor; H = trastuzumab; HR = hormone receptor; N0, N1, N2, N3 = nodal staging; NR = not reported; P = pertuzumab; T1, T2, T3, T4 = tumor staging.

Sources: Bilici et al. (2023);[17] Ren et al. (2023);[18] Cheng et al. (2022).[19]

Critical Appraisal

NeoPowER

Confounding was expected in the NeoPowER study and important confounding domains were identified by their clinical importance and multiple regression was used to account for potential confounders (e.g., menopausal status, body mass index, clinical lymph node, stage at diagnosis, grading, estrogen receptors, progesterone receptors, hormone receptor status, Ki67, neoadjuvant treatment duration cycles, neoadjuvant anthracycline, and time to surgery). However, there may still be residual confounding.

Selection of patients into the study differed between the treatment groups. The intervention group was made up of patients from 5 centers over 6 years (from 2016 to 2022) who met the inclusion criteria, while the patients in the comparison group (historical controls) were from a single cancer center over 14 years (from 2007 to 2021). Also, the median follow-up duration was 36.5 (range 5 to 77) and 71 (range 10 to 176) months in the intervention and control groups respectively. The difference in follow-up durations between the 2 study groups may also introduce bias in the reporting of safety, which was the primary endpoint.

The open-label design of the study should not have affected the secondary endpoints of pCR, distant relapse-free survival (DRFS), and OS, as confirmed by the clinical experts. However, the lack of blinding may have resulted in risk of bias in subjective reporting of harms.

One person in the intervention group who stopped treatment due to an adverse event was not included in the pCR analysis. Three patients were excluded from the DRFS analysis because of incomplete data and 2 patients were excluded from the OS analysis (reasons not reported). This missing data was unlikely to affect results.

During the study period, there was a change in clinical practice. T-DM1 for HER2-positive early breast cancer patients with residual invasive disease after neoadjuvant treatment became available in Italy following the publication of the KATHERINE trial,[20] which found that T-DM1 decreased the risk of invasive disease or death compared to trastuzumab alone. Eighty-five percent of patients in the study received adjuvant treatment before 2019, when T-DM1 became available for patients with residual invasive disease after neoadjuvant treatment. Therefore, the impact of neoadjuvant pertuzumab on downstream treatment with T-DMI cannot be accurately assessed. The study occurred in multiple centers in Italy, but according to clinical experts was likely generalizable to Canada.

HER2PATH

The first 25 patients (at minimum) who used pertuzumab after March 2019 (when it started to be used in Turkey) from each participating centers in the national database on HER2-positive breast cancer were included in the intervention group. The 50 most recent patients at each center who did not use pertuzumab and completed neoadjuvant chemotherapy were included in the comparator group. It was unclear if the start of treatment and the start of follow-up coincided for each participant.

Interpretation of results for pCR (primary endpoint) was limited by improper causal inference analyses. Specifically, the study applied logistic regression to predict the achievement of pCR, but did not adjust for confounding. Menopausal status, ECOG performance status, histology subtype, T status, histological grade, and type of anthracycline treatment were significantly different between patients receiving pertuzumab and patients not receiving pertuzumab. Therefore, it is uncertain whether the difference in pCR could be completely attributable to the use of pertuzumab. In addition, the pCR rate was reported for each treatment group; however, the estimated between-group difference with CIs was not reported, precluding judgments about the precision of the differences.

The open-label design of the studies should not have affected pCR, as confirmed by the clinical experts. However, the lack of blinding may have resulted in risk of bias in subjective reporting of harms.

Interpretation of EFS was limited by incomplete and potentially selective reporting and short follow-up time. The 2-year EFS rate was reported for the overall study population (90.4%) and the intervention group (95%) but not reported for the comparator group. The mean EFS time for each treatment arm (95.8 months with pertuzumab and 103.9 months without pertuzumab) and the Kaplan-Meier curves for EFS time were presented. However, the study authors and our clinical experts acknowledged that 2 years was insufficient follow-up time to draw meaningful conclusions about EFS.

The study was limited to the therapeutic options available for use in within the study period. For example, T-DM-1 was not available for adjuvant treatment during the study period in Turkey and participants in both treatment groups with non-pCR continued to receive trastuzumab as adjuvant treatment. Therefore, the of the pertuzumab on adjuvant T-DM-1 utilization could not be assessed. The study used data collected from 21 centers participating in the national database in Turkey, and according to clinical experts was likely generalizable to Canada.

Ren et al. 2023

The effect estimate for pCR was not adjusted for potential confounding by prognostic factors. Details of neoadjuvant therapy for each group were not reported, and there may unmeasured and residual confounding due to imbalanced co-interventions between treatment groups. Therefore, it is uncertain whether the difference in pCR could be completely attributable to the use of pertuzumab. Patients who met the selection criteria from 2018 and 2021 were enrolled in the study. The end date of follow-up was October 14, 2022. Therefore, we assume that the start of follow-up and the start of treatment coincided for each participant.

The open-label design of the studies should not have affected pCR (secondary endpoint), as confirmed by the clinical experts.

The primary objective of the study was to assess the changes in HER2 expression in patients with HER2-positive breast cancer before and after neoadjuvant treatment. This outcome was not relevant to our review. DFS and OS were reported for patients who achieved pCR compared to patients who did not achieve pCR and in patients with HER2 negative compared to those who were HER2 non-negative. Survival outcomes were not reported for patients who received pertuzumab with neoadjuvant therapy versus

those who did not receive pertuzumab with neoadjuvant therapy. Therefore, the effect of pertuzumab on DFS and OS could not be assessed.

The study was conducted in 1 university hospital breast center in China, which may limit the generalizability to other treatment centers.

CSBrS-015

Propensity score 1:1 matching was used to account for confounding by age, tumor stage, lymph node stage, clinical stage, and hormone receptor status. After matching, the baseline patient and disease characteristics were comparable between the 2 groups. However, there was a risk of bias due to residual confounding.

Patients who met the eligibility criteria between March 1, 2019 and December 31, 2020 at participating centers were selected to be in the study. It was unclear if the start of treatment and the start of follow-up coincided for each participant. Patients were required to have complete clinicopathological data to be included, which may have biased selection into the study.

The open-label design of CSBrS-015 study should not have affected pCR, as confirmed by the clinical experts. However, the lack of blinding may have resulted in risk of bias in subjective reporting of harms. Harms outcomes were reported in a subset (321 of 560, 57.3%) of patients who completed the neoadjuvant therapy of pertuzumab plus trastuzumab plus chemotherapy and who had complete records of AEs. There was no comparison of incidence of AEs between treatment groups. Therefore, no causal inference can be made about the increased risk of AEs with the addition of neoadjuvant pertuzumab.

The study used data collected from 30 breast surgery wards at tertiary hospitals in China, and according to clinical experts was likely generalizable to Canada.

Van der Voort et al.

Confounding was accounted for using multivariable analyses to adjust for baselined characteristics associated with pCR, BCSS, and OS, as identified by the study authors in the clinical literature (age, hormone receptor status, histological grade, clinical tumor stage, and clinical lymph node status). However, there may still be residual confounding.

Patients who met the eligibility criteria from November 2013 to January 2016 from the Netherlands Cancer Registry were selected into the study. Participants were diagnosed in the same period, and the start of follow-up and start of treatment coincided for each participant. The Netherlands Cancer Registry had nationwide coverage in all hospitals and data was routinely collected prospectively by trained and expert data managers. It is not clear whether those collecting data were aware of the intervention. We can assume they were not blinded.

Since pertuzumab was not reimbursed until January 2016, most patients in the pertuzumab group (93.4%) had participated in the TRAIN-2 RCT, which assessed neoadjuvant chemotherapy with anthracyclines compared to chemotherapy without anthracyclines. Participants in the comparator group received trastuzumab plus chemotherapy at hospitals not participating in the TRAIN-2 trial. It is unknown if these differences could have resulted in selection bias.

Eleven patients in the intervention group (no axillary staging post chemotherapy) and 19 patients from the comparator group (6 had no breast surgery and 11 had no axillary staging post chemotherapy) were not included in the pCR analysis. Imputation was not used for missing pCR values. The authors claimed that the availability of the pCR outcome could perhaps be related to the outcome itself. Also, since data was extracted from the Netherlands Cancer Registry and not the TRAIN-2 trial, the reasons for the missing outcomes (and other missing data) were not known. One patient in each treatment group was excluded from the BCC analysis due to unknown cause of death, and all patients were included in the OS analysis. Censoring was used for patients who were alive at the last follow-up visit.

Multiple imputation was used to handle missing data on hormone receptor status, multiple imputations, and tumor grade, with 10 imputations based on the maximum percentage missing data (10%). There were no meaningful differences in results from the imputed data set compared to the complete case analysis. Imputation was not used for clinical nodal status.The study took place in multiple sites in the Netherlands, and according to clinical experts was likely generalizable to Canada.

Efficacy

Results for outcomes important to this review are presented in Table 11. Key results include the following:

- In the HER2PATH, Ren et al, CSBrS-015, and van der Voort et al. studies, pertuzumab plus trastuzumab and chemotherapy had a favourable effect on tpCR compared to trastuzumab and chemotherapy.
- In the NeoPowER study, there was insufficient evidence to suggest a difference between pertuzumab plus trastuzumab and chemotherapy versus trastuzumab and chemotherapy on tpCR.
- In NeoPowER, DRFS and OS did not improve with the addition of pertuzumab to trastuzumab and chemotherapy at 3 years.
- In van der Voort et al., the hazard ratios for BCSS and OS at 5 years favoured pertuzumab plus trastuzumab and chemotherapy compared to trastuzumab and chemotherapy.

Additional efficacy results are presented in Appendix 4 of the Supplemental Material document

Table 11: Key Efficacy Results from RWE Studies

Study	Event rate, n of N (%)		Effect estimate (95% CI)	P value
	P + H + CT	H + CT		
pCR				
NeoPowER 2024[a,b]	57 of 125 (45.6)	54 of 134 (40.3)	aOR 1.63 (0.92 to 3.00)[c,d]	0.120
HER2PATH 2023[a]	383 of 577 (66.4)	540 of 951 (56.8)	NR	< 0.001
Ren et al. 2023[e]	179 of 298 (60.1)	76 of 201 (37.8)	Chi-square 23.795 (NR)	< 0.001
CSBrS-015 2022, all[a]	324 of 560 (57.9)	163 of 472 (34.5)	NR	NR
CSBrS-015 2022, PSM[a,f]	227 of 399 (56.9)	140 of 399 (35.1)	Chi-square 20.6 (NR)	< 0.001
van der Voort et al. 2022[g]	282 of 434 (65.0)	269 of 660 (40.7)	aOR 2.91 (2.20 to 3.84)[h,i,j]	< 0.001
3-year DRFS[k]				
NeoPowER 2024	9 of 124 (7.3)	12 of 133 (9.0)	aHR 1.44 (0.52 to 3.99)[d,l]	0.488
5-year BCSS[m]				
van der Voort et al. 2022	24 of 452 (5.3)	66 of 670 (9.8)	aHR 0.58 (0.36 to 0.95)[j,n,o]	0.029
3-year OS[p]				
NeoPowER 2024	3 of 124 (2.4)	14 of 133 (10.4)	aHR 0.41 (0.09 to 1.83)[d,l]	0.242
5-year OS[p]				
van der Voort et al. 2022	26 of 453 (5.7)	77 of 671 (11.5)	aHR 0.51 (0.32 to 0.82)[j,n]	NR

aHR = adjusted hazards ratio; aOR = adjusted odds ratio; BCSS = breast cancer specific survival; CI = confidence interval; CT = chemotherapy; DRFS = distant relapse free survival; H = trastuzumab; NR = not reported; DRFS = distant relapse free survival; OS = overall survival; P = pertuzumab; pCR = pathologic complete response; PSM = propensity score matching; RWE = real-word evidence.

Sources: Canino et al. (2024);[15] Bilici et al. (2023);[17] Ren et al. (2023);[18] Cheng et al. (2022);[19] Van der Voort et al. (2022).[16]

a. pCR was defined as absence of residual invasive neoplastic cells at microscopic examination of the breast and axillary lymph nodes (ypT0/is, ypN0) after neoadjuvant treatment.
b. The presence of isolated tumor cells was not considered pCR.
c. Univariable and multivariable logistic regression models were applied to assess the impact of study arms and covariates on pCR.

d. The effect estimates were adjusted for imbalanced parameters between groups (e.g., menopausal status, body mass index, clinical lymph node, stage at diagnosis, grading, estrogen receptors, progesterone receptors, hormone receptor status, Ki67, neoadjuvant treatment duration cycles, neoadjuvant anthracycline, and time to surgery).
e. pCR was defined as non-invasive carcinoma in the primary breast lesion (possibly ductal carcinoma in situ) and lymph nodes in the negative area (ypT0 or Tis N0Mo), or residual cancer burden grade 0.
f. Confounding factors (age, T stage, N stage, clinical stage, and hormone receptor status) were eliminated and propensity score matching was conducted.
g. pCR was defined as complete disappearance of all invasive tumor cells of the breast and axilla, with either presence or absence of ductal or lobular carcinoma in situ (ypT0/is, ypN0).
h. Results are based on the imputed data set. Missing data (up to 10%) was addressed using multiple imputation with 10 iterations. Complete case results were aOR 2.90 (95% CI 2.17 to 3.88), P < 0.001, N = 999.
i. Univariable logistic regression was used to identify potential associations between patient and tumor characteristics and pCR. Factors that were identified to be associated with pCR or survival in previous studies were included in the multivariate model, as were factors with P < 0.05 in univariable analysis.
j. Adjusted for differences in baseline characteristics. The covariates inclusion in all multivariable regression models was driven by both their clinical relevance and the imbalances that emerged from the univariable analysis.
k. DRFS was time from first date of no disease (i.e., date of surgery) to first documentation of distant relapsed disease or last follow-up.
l. Calculated using Kaplan-Meier estimators and comparisons between curves were performed with the Mantel-Cox log-rank test. Cox proportional hazard regression models were used.
m. BCSS was defined as time from diagnosis of primary breast cancer until death from breast cancer or censoring other causes of death.
n. Estimated with the Kaplan Meier method. Cause-specific Cox proportional hazard regression models were used for survival analyses.
o. Results are based on the imputed data set. Missing data (up to 10%) was addressed using multiple imputation with 10 iterations. Complete case results were aOR 0.54 (95% CI 0.33 to 0.91), P = 0.021, N = 1025.
p. Overall survival was defined as the time from date of primary breast cancer diagnosis to date of death of any cause or last follow-up date.

Harms

Details of harm results for the NeoPowER, HER2PATH, and CSBrS-015 studies are presented in Appendix 5 of the Supplemental Material document. Key results include the following:

- The overall number of patients with at least 1 AE was not reported in any study. In the NeoPowER study, common AEs were anemia (13%.1% with pertuzumab and 16.7% without pertuzumab), neutropenia (11.9% in the pertuzumab group and 14.7% in the no pertuzumab group), and nausea (9.8% in pertuzumab group and 14.7% in no pertuzumab group). In HER2PATH the most common AEs were upper respiratory tract infection (12.7% with pertuzumab and 14.9% with no pertuzumab) and headache (11.7% with pertuzumab and 14.0% without pertuzumab). In CSBrS-015, the most common AEs in the pertuzumab group were reduced granulocyte count (31.2%), hair loss, (25.9%), and nausea and vomiting (22.1%); AEs were not reported for the comparator group.

- In CSBrS-015, 7.5% of patients in the pertuzumab group reported Grade 3 to 4 AEs; the most common were hair loss (22.7%) and reduced granulocyte count (12.1%). In NeoPowER, the most common Grade 3 to 4 AE was neutropenia (8.5% in pertuzumab group and 10.0% in trastuzumab plus chemotherapy group). In HER2PATH, the most frequent Grade 3 to 4 AEs were neutropenia (1.7% with pertuzumab and 0.7% with comparator) and peripheral edema (1.2% with pertuzumab and 0.5% with trastuzumab plus chemotherapy).

- In NeoPowER, SAEs occurred in 1 patient (0.08%) in the pertuzumab with trastuzumab plus chemotherapy group, with urinary tract infection, and 2 patients in the trastuzumab plus chemotherapy group, with typhlitis and sepsis. The number of patients with SAEs was not reported in HER2PATH and CSBrS-015.

- In the NeoPowER study, treatment discontinuations due to an AE occurred in 2% patients in the pertuzumab group and 9% patients in the comparator group; details of the AEs were not reported. The number of patients who stopped treatment was not reported in HER2PATH and CSBrS-015

- Deaths due to an AE were not reported in any RWE study.

- In NeoPowER, AEs of special interest were diarrhea (any grade, 19.8% in the pertuzumab with trastuzumab plus chemotherapy arm and 9.2% in the trastuzumab plus chemotherapy arm), significant LVEF decline (0.9% and 1.8%, respectively) and mild drug hypersensitivity (2.4% in pertuzumab group 3.5% in comparator group). In HER2PATH, AEs of special interest included diarrhea (any grade, 27.0% in the pertuzumab with trastuzumab plus docetaxel arm and 16.0% in the trastuzumab plus docetaxel arm) and mild LVEF decline (1 patient in the pertuzumab with trastuzumab plus

chemotherapy arm and 2 patients in the trastuzumab plus chemotherapy arm); In CSBrS-015, AEs of special interest included diarrhea (any grade, 20.2%) in the pertuzumab group. In the 3 studies, grade 3 to 4 diarrhea was reported in less than 4% of patients in each treatment group. No significant decreases in LVEF occurred in HER2PATH and CSBrS-015.

Discussion

Efficacy

The primary goal of neoadjuvant therapy in HER2-positive breast cancer is to improve pCR. At the last reimbursement review in 2022, pERC acknowledged the use of pCR as a decision point in the treatment pathway for early breast cancer. However, the committee expressed that it remained unclear whether the improvement in pCR observed with the additional pertuzumab translated to clinically meaningful improvement in event-free or OS outcomes. Since then, the results on PFS, DFS, EFS and OS are available and have been reported in this review for NeoSphere, PEONY, and 2 RWE studies. These results on long term survival outcomes are mixed and as previously reported, there are limitations of these findings and definitive conclusions cannot be drawn.

Based on feedback from clinical experts consulted, this review did not focus on whether pCR is a valid surrogate endpoint for OS outcomes. Rather, the review focused on additional advantages to achieving pCR. Specifically, patients without residual disease would receive more conservative adjunctive therapy rather than T-DM1, which is associated with several toxicities and treatment discontinuation due to severe or intolerable side effects. Therefore, it was appropriate according to the clinical experts consulted by CDA-AMC that the PEONY and NEOSPHERE trials both assessed pCR as the primary outcome, although each defined pCR differently. In NEOSPHERE, the addition of pertuzumab to trastuzumab and docetaxel resulted in a statistically significant increase of 16.82% in bpCR compared to trastuzumab and docetaxel alone. NEOSPHERE was an older study and does not reflect the current guidance on the assessment of pCR, namely that no evidence of invasive cancer from breast tissue and all sampled regional lymph node (i.e., tpCR).[21-23] The definitions of pCR used for the primary outcome in PEONY trial and the 5 RWE studies more closely reflect this guidance. The clinical experts confirmed that clinicians will look at tpCR, rather than bPCR, to determine if patients should receive T-DMI. In the PEONY trial pertuzumab with trastuzumab and docetaxel led to a statistically significant increase of 17.5% in tpCR compared to placebo with trastuzumab plus docetaxel. According to clinical experts, any increase in pCR rates is clinically meaningful, as patients achieving pCR would not be subsequently treated with T-DM1.

The clinical experts noted that the relatively lower pCR rates with pertuzumab in the 2 RCTs (39.3% in PEONY and 45.8% in NEOSPHERE) likely reflect the chemotherapy backbone not aligning with current clinical practice, as the anthracycline component of the third-generation neoadjuvant regimen was administered post-surgery rather than as part of the neoadjuvant phase. Higher pCR rates would be expected if the full regimen were delivered upfront, as is now the standard of care in Canada. Indeed, apart from NeoPowER, 4 RWE studies (HER2PATH, Ren et al., CSBrS-015, and van der Voort et al.) reported pCR rates of 56.9% to 66.4% following neoadjuvant pertuzumab.

Overall findings from the RWE studies also indicated that pertuzumab plus trastuzumab and chemotherapy results in clinical improvement in tpCR compared to trastuzumab and chemotherapy. There was inconsistency finding stemming from 1 study (NeoPowER); specifically, 4 RWE studies (HER2PATH, Ren et al., CSBrS-015, and van der Voort et al.) found statistically significant improvements in tpCR with pertuzumab plus trastuzumab and chemotherapy compared to trastuzumab and chemotherapy, but the NeoPowER study reported no statistically significant difference between treatment groups on tpCR. While all the RWE studies had study limitations, the finding of NeoPowER was very uncertain due to risk of bias and imprecision (low event rates, small population, and wide confidence intervals around the odds ratio).

Although there was no statistically significant improvement in PFS in NEOSPHERE, the clinical experts acknowledged that the hazard ratio of 0.68 for 5-year PFS was clinically meaningful. However, the certainty of evidence was lowered due to imprecision as the confidence intervals were wide and the lower bound of the 95% CI for the difference in PFS included the possibility of little to no clinically significant benefit.

PEONY showed higher 3- and 5-year EFS rates in the pertuzumab group versus the placebo group, with a 5-year hazard ratio of 0.53 that was both statistically significant and clinically meaningful according to the clinical experts.

In PEONY, the 3- and 5-year DFS rates were higher with pertuzumab compared to the placebo arm, with a 5-year hazard ratio of 0.52 that was both statistically significant and clinically meaningful according to the clinical experts. In NEOSPHERE, the 5-year HR for DFS of 0.60 meaningful according to the clinical experts, but not statistically significant. The certainty of evidence was lowered due to imprecision as the confidence intervals were wide and the lower bound of the 95% CI for the difference in PFS included the possibility of little to no clinically significant benefit.

In the NeoPowER study, the addition of pertuzumab to trastuzumab and chemotherapy did not impact DRFS at 3 years statistically or clinically. The clinical experts suggested that 3 years was insufficient follow-up time to assess survival outcomes in adults with early-stage HER2-positive breast cancer. Also, this result was very uncertain due to risk of bias and imprecision. In the RWE study by van der Voort et al, the adjusted hazard ratio of 0.58 for 5-year BCSS was both statistically significant and clinically meaningful. This finding has some uncertainty due to the possibility of residual confounding and imprecision.

While the 3-year and 5-year between-group difference in OS (6.0% and 3.9%) and the 5-year hazard ratio of 0.53 were not statistically significant in the PEONY trial, the clinical experts noted that a 4% absolute between-group difference in OS and the estimated hazard ratio were clinically meaningful. However, the certainty of evidence was very uncertain due to imprecision as the number of events was low, the confidence intervals were wide, and the lower bound of the 95% CI for the difference in OS included the possibility of little to no clinically significant benefit. In contrast, the RWE study by van der Voort et al reported an adjusted hazard ratio of 0.51 for 5-year overall survival, which was both statistically significant and clinically meaningful. This finding also has some uncertainty due to residual confounding and imprecision.

In the NeoPowER study, the hazard ratio for 3-year overall survival of 0.41 for pertuzumab to trastuzumab and chemotherapy versus pertuzumab to trastuzumab and chemotherapy was clinically meaningful according to the clinical experts. However, this result was very uncertain due to risk of bias and imprecision as the number of events was low and the lower bound of the 95% CI for the difference in OS included the possibility of little to no clinically significant benefit. As suggested but the clinical experts, 3 years may be insufficient follow-up time to assess OS.

HRQoL was not assessed in the included studies. The clinical experts noted that formal HRQoL assessments, such as the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 and the European Quality of Life-5 Dimensions, are not typically conducted in routine clinical practice. In practice, toxicity profiles and treatment completion rates are often used as indirect surrogates for assessing patient experience.

Harms

The 2 included RCTs and 3 RWE studies reported harms in patients with early-stage HER2-positive breast cancer taking pertuzumab. In the RCTs, the number of patients with treatment-emergent AEs was similar in patients receiving pertuzumab in addition to trastuzumab and chemotherapy compared to those who did not receive pertuzumab. The PEONY trial found that patients in the pertuzumab group reported more upper respiratory tract infections and decreased appetite compared to the placebo group. Otherwise, all other AEs, AEs of grade 3 or higher, and SAEs were balanced between treatment groups across studies. Also, the low rate of treatment discontinuation due to AEs and death and the completion of all cycles of neoadjuvant therapy suggest that the addition of pertuzumab to trastuzumab and chemotherapy was generally well tolerated.

The addition of pertuzumab was associated with a higher incidence of certain AEs of special interest, such as diarrhea (any grade) and infusion reactions. However, the clinical experts highlighted that these side effects were manageable and aligned with clinicians' experiences from treating patients with pertuzumab in the neoadjuvant setting. The number of LVEF events, Grade 3 to 5 diarrhea, drug hypersensitivity, and neurotoxicity with pertuzumab were low. The clinical experts had no concerns regarding the overall safety profile of pertuzumab.

Reducing the need for T-DM1 in the adjuvant setting was considered an important potential benefit of pertuzumab. Although direct evidence on the effect of neoadjuvant pertuzumab on adjuvant T-DM1 was lacking, we can indirectly conclude that the decrease in residual disease (i.e., increased pCR rates with pertuzumab) will result in less utilization of adjuvant T-DMI.

Conclusion

Current treatment options for early-stage HER2-positive breast cancer are limited by the lack of publicly funded access to neoadjuvant pertuzumab, an unmet need that creates treatment inequities, as access often depends on private insurance coverage. This treatment gap impacts clinical outcomes and restricts treatment de-escalation, such as avoiding anthracycline-based chemotherapy and T-DM1 and their associated toxicities, in patients achieving pCR. When considered as a whole, the body of evidence suggests that adding pertuzumab to standard neoadjuvant regimens with trastuzumab plus chemotherapy improves pCR rates, a key outcome for assessing treatment response. Additional clinically meaningful benefits were observed across survival outcomes such as DFS, EFS, and BCSS. However, there were mixed findings for 5-year OS and the definitive effect of pertuzumab on OS remains a gap in the clinical evidence. In terms of harms, adding pertuzumab to neoadjuvant therapy did not appear to significantly increase safety or tolerability concerns.

Economic Review

The economic review consisted of a cost comparison for pertuzumab 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 (greater than 2 cm in diameter or node-positive). Relevant chemotherapy regimens were included as a reference, as pertuzumab would be incorporated into—and not replace—current first-line regimens in the neoadjuvant setting. The cost per patient per 28-day cycle of the current first-line regimens varies between $1,890 and $10,709 excluding first cycles, which have higher costs due to higher dosages of certain drugs.

Based on public list prices, pertuzumab in combination with trastuzumab and chemotherapy is expected to have an incremental cost per patient of $4,848 per 28-day cycle (Supplemental Material, Table 14). As such, the reimbursement of pertuzumab 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 is expected to increase overall drug acquisition costs.

When considering the cost consequences of reimbursing pertuzumab in the neoadjuvant setting, a costing exercise was conducted to estimate how this impacts subsequent therapy costs in the adjuvant setting, particularly by reducing reliance on adjuvant T-DM1, which is the standard treatment if a patient does not achieve pCR after neoadjuvant treatment and surgery. If a patient achieves pCR, the standard adjuvant treatment is trastuzumab, a drug less costly than TDM-1. Therefore, if neoadjuvant pertuzumab increases the proportion of patients achieving pCR, there are potential savings in the group of patients that receives adjuvant trastuzumab instead of TDM-1. To estimate potential savings due to the reduced use of adjuvant TDM-1, CDA-AMC estimated the total drug costs in the neoadjuvant and adjuvant settings, considering the different possible treatments and potential increases in pCR rates with the reimbursement of neoadjuvant pertuzumab (Table 12). Neoadjuvant pertuzumab + trastuzumab was assumed to be used for 4 3-week cycles as this is the duration of most chemotherapy regimens. It was also assumed that adjuvant TDM-1 would be administered for 18 3-week cycles and that adjuvant trastuzumab would be administered for 14 3-week cycles as its maximum treatment duration is 18 3-week cycles or one year, including the neoadjuvant phase. Clinical experts validated the assumptions and input parameters.

Table 12 Incremental cost of Neoadjuvant Pertuzumab accounting for potential savings in adjuvant phase of treatment

Study	pCR (%)		Total drug costs ($)		Incremental cost
	Standard care	Pertuzumab	Standard care[a]	Pertuzumab[b]	($)
NeoPower 2024[15]	40.3	45.6	54,259.17	69,384.2	15,125
HER2PATH 2023[17]	56.8	66.4	44,746.54	57,392.52	12,646
Ren 2023[18]	37.8	60.1	55,700.48	61,024.62	5,324
CSBrS-015 2022[19] all	34.5	57.9	57,603.01	62,292.97	4,690
CSBrS-015 2022[19] PSM	35.1	56.9	57,257.09	62,869.49	5,612
van der Voort 2022[16]	40.7	65	54,028.56	58,199.65	4,171

pCR = pathological complete response

[a] Includes the following drugs: adjuvant TDM-1 (no pCR) or adjuvant trastuzumab (pCR)

[b] Includes the following drugs: neoadjuvant pertuzumab, in addition to adjuvant TDM-1 (no pCR) or adjuvant trastuzumab (pCR)

The total drug cost of neoadjuvant pertuzumab is $18,180. pCR rates in the RWE studies included in this review varied from 34.5% to 56.8% in the standard care groups (trastuzumab and chemotherapy) and from 45.6% to 66.4% in the pertuzumab groups (pertuzumab in addition to trastuzumab and chemotherapy). All the studies found greater pCR rates in the groups where pertuzumab was added in the neoadjuvant phase. Assuming that the chemotherapy costs are equal between the two groups and accounting for the costs savings due to improved pCR rates and reduced use of TDM-1, pertuzumab could have incremental costs of up to $15,125.

Overall, the costing exercise demonstrates that the reimbursement of pertuzumab can offset 16.8% or more of the total incremental drug costs due to improved pCR rates with its addition to trastuzumab and chemotherapy in the neoadjuvant setting. This exercise has several limitations, most notably that it does not account for additional factors that will also impact the costs and effectiveness of the entire treatment, such as differences in effectiveness between neoadjuvant pertuzumab and trastuzumab, adverse events and drug toxicities. Additionally, it does not account for those patients that cannot tolerate TDM-1 for the full recommended duration of treatment of 14 cycles. A cost-utility analysis would be more appropriate as it would have captured all the possible clinical benefits and the additional factors that impact the cost-effectiveness of pertuzumab.

As part of the submission to CDA-AMC in 2022 the sponsor submitted an economic evaluation which was appraised by the CDA-AMC review team. The CDA-AMC appraisal concluded that results from the economic analysis are contingent on the acceptability of the assumption that improved pCR translates into better survival outcomes. Several exploratory scenario analyses were undertaken to assess key drivers of the model, which indicated that the cost-effectiveness of pertuzumab in combination with trastuzumab and chemotherapy was highly sensitive to the association between pCR and EFS. For example, pertuzumab was not cost-effective at a threshold of $50,000 per QALY if the EFS hazard ratio for patients with a pCR relative to those with no pCR was greater than 0.41 (sponsor's HR = 0.33). If the HR is equal to 1, pertuzumab was more costly and less effective than trastuzumab plus chemotherapy.

Additional items for consideration are provided in the following bullets:

- Evidence from clinical trials[12,13] suggests that, compared to placebo with trastuzumab plus chemotherapy, pertuzumab with trastuzumab plus chemotherapy resulted in a clinically important improvement in pCR and event-free survival at 5 years, whereas its impact on progression-free survival and overall survival at 5 years is uncertain due to imprecision. Real-world evidence studies[15-19] also suggest that the addition of pertuzumab results in a clinically important improvement in pCR, as well as breast cancer free-survival and overall survival at 5 years, although its effects on distant relapse-free survival and overall survival at 3 years are uncertain due to risk of bias and imprecision.
- As of May 12, 2025, pertuzumab is only available as a brand name product in Canada. There are no biosimilars currently under review at Health Canada.
- No healthcare resource use outcomes were reported in the clinical trials and RWE studies included in the clinical review.
- Pertuzumab was reviewed by CDA-AMC in 2015 and 2022[2,24], and received a "do not reimburse" recommendation in both occasions. pERC concluded that at that time there was no evidence demonstrating improvements in long-term outcomes with the addition of pertuzumab to trastuzumab and chemotherapy. Economic evidence from this review found that pertuzumab in combination with trastuzumab and chemotherapy relative to neoadjuvant IV trastuzumab plus taxane chemotherapy may be cost effective at a $50,000 per QALY threshold. However, this is uncertain and contingent on improvements in OS.
- No Canadian cost-effectiveness studies published since 2020 were identified based on a literature search conducted on May 12, 2025.

Conclusion

The reimbursement of pertuzumab 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 is expected to increase overall drug acquisition costs. Based on the clinical review conclusions, pertuzumab in combination with trastuzumab and chemotherapy is expected to improve pCR and event-free survival, however improvements in long-term progression-free survival and overall survival are uncertain due to imprecision or high risk of bias in RWE studies. The addition of pertuzumab did not appear to introduce significant safety or tolerability issues.

Given that pertuzumab in combination with trastuzumab and chemotherapy is associated with increased drug acquisition costs and incremental benefits in terms of pCR and progression-free survival, a cost-effectiveness analysis would be required to determine the cost-effectiveness of pertuzumab in combination with trastuzumab and chemotherapy relative to trastuzumab and chemotherapy in the neoadjuvant setting. Given uncertainty in the clinical evidence, results from any economic evaluation would also be highly uncertain. This was the conclusion that was reached in CDA-AMC's 2022 appraisal of the sponsor submitted economic evaluation. Crucially, cost effectiveness is contingent on improvements in OS.

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