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

Reimbursement Review

Pertuzumab (N/A)

Draft Supplemental Material

Requester: Public drug programs

Therapeutic area: Early-stage breast cancer

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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.

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Appendix 1: Treatment Characteristics

Table 1: Key Characteristics of Pertuzumab and Trastuzumab

Treatment	Mechanism of action	Indication[a]	Recommended dosage and route of administration	Serious adverse effects or safety issues
Pertuzumab	Monoclonal antibody that targets the extracellular dimerization domain of HER2, and blocks ligand-dependent heterodimerization of HER2 with other HER family members. This inhibits intracellular signaling, resulting in cell growth arrest and apoptosis.	In combination with trastuzumab and chemotherapy, for: • neoadjuvant treatment of patients with HER2+ locally advanced, inflammatory or early stage breast cancer (either >2 cm in diameter or node positive)	IV infusion • 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, the recommended dose of trastuzumab is either an IV infusion with an initial dose of 8 mg/kg followed every 3 weeks by a dose of 6 mg/kg, or a fixed dose of 600 mg SC initially and every 3 weeks thereafter.	Left ventricular dysfunction Embryo-fetal toxicity Hypersensitivity reactions/anaphylaxis and infusion-related reactions
Trastuzumab	Monoclonal antibody that binds to the extracellular domain of the HER2 receptor, inhibiting HER2-mediated signaling and inducing antibody-dependent cellular cytotoxicity, leading to cancer cell death.	Patients with ECOG status of 0-1 who overexpress HER2: • following surgery and after chemotherapy • following adjuvant chemotherapy consisting of doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel • in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin	IV or Sc *IV 3-weekly schedule:* • initial: 8 mg/kg as a 90-minute infusion • maintenance: 6 mg/kg 3 weeks later and then 6 mg/kg repeated at 3 weekly intervals administered as infusions over approximately 90 minutes *IV Weekly schedule:* • initial: 4mg/kg	Cardiotoxicity Infusion Reactions (intravenous formulation); Pulmonary Toxicity Embryo-fetal toxicity

Treatment	Mechanism of action	Indication[a]	Recommended dosage and route of administration	Serious adverse effects or safety issues
			• maintenance: 2mg/kg every week *SC schedule:* 600 mg SC every three weeks	

cm = centimetres; ECOG = Eastern Cooperative Oncology Group; HER2 = human epidermal growth factor receptor-2; IV = intravenous; kg = kilograms; MAP = mitogen activated protein; mg = milligrams; PI3K = phosphoinositide-3 kinase; SC = subcutaneous.

[a] Health Canada–approved indication.

Source: Product Monographs for pertuzumab,[1] trastuzumab[2]

Clinical Review Appendices

Appendix 2: Methods of the Clinical Review

For the systematic review, we included studies that adhered to the a priori eligibility criteria detailed in Table 2 in the main review report. We also included long-term extension studies of included randomized controlled trials, regardless of whether there was a comparison group. Studies addressing gaps were those identified by the review team and/or clinical experts that did not meet the eligibility criteria but were considered to address important gaps in the Systematic Review evidence.

Search Strategy

Strategy for Primary Studies (Systematic Review)

An information specialist performed the literature search for clinical studies, using a peer-reviewed search strategy according to the PRESS Peer Review of Electronic Search Strategies checklist. PRESS Peer Review of Electronic Search Strategies checklist.

Published literature was identified by searching the following bibliographic databases: MEDLINE via Ovid and Embase via Ovid. All Ovid searches were run simultaneously as a multi-file search. Duplicates were removed using Ovid deduplication for multi-file searches, followed by manual deduplication in EndNote. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the PICOS framework and research questions. The main search concepts were pertuzumab in combination with trastuzumab and breast cancer. The following clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, World Health Organization's International Clinical Trials Registry Platform search portal, Health Canada's Clinical Trials Database, the European Union Clinical Trials Register, and the European Union Clinical Trials Information System.

CDA-AMC search filters were applied to limit retrieval to randomized controlled trials, controlled clinical trials, or any other type of clinical trials. Retrieval was limited to publications since January 1, 2020, and was not limited by publication language. The date limit was applied as a recent CDA-

AMC review[3] on the same topic included studies published up to 2020. Conference abstracts were excluded from the search results. Detailed search strategies are outlined below.

The initial search was completed on February 28, 2025. Regular alerts updated the search until the meeting of the Formulary Management Expert Committee on July 17, 2025.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from Grey Matters: A Practical Tool For Searching Health-Related Grey Literature. Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency). Google was used to search for additional internet-based materials. See Appendix 1 for more information on the grey literature search strategy.

Clinical Literature Search

Overview

Interface: Ovid

Databases

- MEDLINE All (1946-present)
- Embase (1974-present)

Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: February 28, 2025

Alerts: Monthly search updates until project completion

Search filters applied: randomized controlled trials, controlled clinical trials, or any other type of clinical trial

Limits

- Publication date limit: 2020-present
- Humans

- Conference abstracts: excluded

Table 2: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Truncation symbol for one or no characters only
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Keyword heading word
.dq	Candidate term word (Embase)
.pt	Publication type
.rn	Registry number
.nm	Name of substance word (MEDLINE)
.yr	Publication year
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

Warning

To conduct a comprehensive search, we may have included antiquated, non-inclusive, or potentially stigmatizing terms that may have appeared in past and present literature. We recognize and acknowledge the inappropriate and harmful nature of terms that may appear in search strategies and include this warning so the reader can determine how they would like to proceed.

The warning is modified from the University of Michigan Library's guidance, Addressing antiquated, non-standard, exclusionary, and potentially offensive terms in evidence syntheses and systematic searches.

Multi-Database Strategy

1	PHESGO.ti,ab,kf,ot,hw,rn,nm.
2	(pertuzumab* or Perjeta* or Omnitarg or rhuMAb?2C4 or rhuMAb2C4 or 2C4 antibod* or RO4368451 or RO 4368451 or MOAB 2C4 or MOAB2C4 or BCD?178 or BDC 178 or EG1206A or HLX11 or HS627 or HS 627 or R1273 or R 1273 or gl 1209 or gl1209 or rg1273 or rg 1273 or TQB2440 or monoclonal antibody 2C4 or K16AIQ8CTM).ti,ab,kf,ot,hw,rn,nm.
3	exp Trastuzumab/
4	(trastuzumab* or Herceptin* or trazimera or anti?c?erB?2 or anticerB2 or anti?ERB?2 or antiERB2 or MOAB HER2 or MOAB HER 2 or MOABHER2 or MOABHER 2 or rhuMab HER21 or rhuMABHER21 or rhuMABHER 21 or rhuMAB HER 21 or P188ANX8CK).ti,ab,kf,ot,rn,nm.
5	3 or 4
6	2 and 5
7	1 or 6
8	exp Breast Neoplasms/
9	((breast* or mamma or mammar* or lobular*) adj5 (cancer* or carcinoid* or carcinoma* or carcinogen* or adenocarcinoma* or adeno-carcinoma* or malignan* or neoplas* or sarcoma* or tumo?r* or mass* or HER2 or HER 2 or HER2+ or HER 2+ or BrCa)).ti,ab,kf.
10	8 or 9
11	7 and 10
12	11 use medall
13	hyaluronidase plus pertuzumab plus trastuzumab/
14	PHESGO.ti,ab,kf,dq.
15	13 or 14
16	exp *pertuzumab/
17	(pertuzumab* or Perjeta* or Omnitarg or rhuMAb?2C4 or rhuMAb2C4 or 2C4 antibod* or RO4368451 or RO 4368451 or MOAB 2C4 or MOAB2C4 or BCD?178 or BDC 178 or EG1206A or HLX11 or HS627 or HS 627 or R1273 or R 1273 or gl 1209 or gl1209 or rg1273 or rg 1273 or TQB2440 or monoclonal antibody 2C4).ti,ab,kf,dq.
18	16 or 17
19	exp *trastuzumab/

20	(trastuzumab* or Herceptin* or trazimera or anti?c?erB?2 or anticerB2 or anti?ERB?2 or antiERB2 or MOAB HER2 or MOAB HER 2 or MOABHER2 or MOABHER 2 or rhuMab HER21 or rhuMABHER21 or rhuMABHER 21 or rhuMAB HER 21).ti,ab,kf,dq.
21	19 or 20
22	18 and 21
23	15 or 22
24	exp *breast cancer/
25	((breast* or mamma or mammar* or lobular*) adj5 (cancer* or carcinoid* or carcinoma* or carcinogen* or adenocarcinoma* or adeno-carcinoma* or malignan* or neoplas* or sarcoma* or tumo?r* or mass* or HER2 or HER 2 or HER2+ or HER 2+ or BrCa)).ti,ab,kf.
26	24 or 25
27	23 and 26
28	27 use oemezd
29	28 not conference abstract.pt.
30	12 or 29
31	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Clinical Study or Adaptive Clinical Trial or Equivalence Trial).pt.
32	(Clinical Trial or Clinical Trial, Phase I or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV or Clinical Trial Protocol).pt.
33	Multicenter Study.pt.
34	Clinical Studies as Topic/
35	exp Clinical Trial/ or exp Clinical Trials as Topic/ or Clinical Trial Protocol/ or Clinical Trial Protocols as Topic/ or exp "Clinical Trial (topic)"/
36	Multicenter Study/ or Multicenter Studies as Topic/ or "Multicenter Study (topic)"/
37	Randomization/
38	Random Allocation/
39	Double-Blind Method/
40	Double Blind Procedure/
41	Double-Blind Studies/
42	Single-Blind Method/

43 Single Blind Procedure/
44 Single-Blind Studies/
45 Placebos/
46 Placebo/
47 Control Groups/
48 Control Group/
49 Cross-Over Studies/ or Crossover Procedure/
50 (random* or sham or placebo*).ti,ab,hw,kf.
51 ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
52 ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
53 (control* adj3 (study or studies or trial* or group*)).ti,ab,hw,kf.
54 (clinical adj3 (study or studies or trial*)).ti,ab,hw,kf.
55 (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.
56 (phase adj6 (study or studies or trial*)).ti,ab,hw,kf.
57 ((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw,kf.
58 ((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw,kf.
59 allocated.ti,ab,hw.
60 ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.
61 ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.
62 (pragmatic study or pragmatic studies).ti,ab,hw,kf.
63 ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.
64 ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.
65 trial.ti,kf.
66 or/31-65
67 exp animals/
68 exp animal experimentation/
69 exp models animal/
70 exp animal experiment/
71 nonhuman/

72	exp vertebrate/
73	or/67-72
74	exp humans/
75	exp human experiment/
76	or/74-75
77	73 not 76
78	66 not 77
79	30 and 78
80	limit 79 to yr="2020 -Current"
81	remove duplicates from 80

Clinical Trials Registries

ClinicalTrials.gov

Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials.

[Search terms: (PHESGO or pertuzumab* or Perjeta* or Omnitarg or rhuMAb 2C4 or rhuMAb2C4 or 2C4 antibod*)]

WHO ICTRP

International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials.

[Search terms: (PHESGO or pertuzumab* or Perjeta* or Omnitarg or rhuMAb 2C4 or rhuMAb2C4 or 2C4 antibod*)]

Health Canada's Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials.

[Search terms: PHESGO, pertuzumab*, Perjeta*, Omnitarg, rhuMAb 2C4, rhuMAb2C4, 2C4 antibod*]

EU Clinical Trials Register

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms: (PHESGO or pertuzumab* or Perjeta* or Omnitarg or rhuMAb 2C4 or rhuMAb2C4 or 2C4 antibod*)]

EU Clinical Trials Information System

European Union Clinical Trials Information System, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms: PHESGO, pertuzumab*, Perjeta*, Omnitarg, rhuMAb 2C4, rhuMAb2C4, 2C4 antibod*]

Grey Literature

Search dates: February 19-21, 2025
Keywords: PHESGO, pertuzumab, Perjeta, Omnitarg, rhuMAb 2C4, rhuMAb2C4, 2C4 antibody, 2C4 antibodies
Limits: none
Updated: Search updated prior to the completion of stakeholder feedback period
Relevant websites from the following sections of the grey literature checklist *Grey Matters: A Practical Tool for Searching Health-Related Grey Literature* were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trials Registries
- Databases (free)
- Internet Search

Strategy for Indirect Treatment Comparisons

A focused literature search for indirect treatment comparisons dealing with pertuzumab in combination with trastuzumab and breast cancer was run in MEDLINE on February 25, 2025. No search limits were applied.

Other Searches

- An additional search was conducted on March 19, 2025 to identify additional studies using the CDA-AMC observational studies and Real-world data filters. The search concepts were pertuzumab in combination with trastuzumab and breast cancer. No search limits were applied.

Study Selection

Two reviewers independently selected relevant studies for inclusion in 2 stages, first by titles and abstracts and then by full texts. Any record considered relevant by either reviewer at the title and abstract stage was reviewed by full text. The 2 reviewers agreed on the studies included in the report.

Data Extraction and Critical Appraisal

One reviewer extracted relevant data from the included studies with verification by a second reviewer. One reviewer appraised the internal and external validity of the available evidence in consideration of inputs by the clinical experts and input from a methodologist.

Appendix 3: Results of the Studies Included in the Systematic Review

Patient Disposition in the Included Studies

Table 3: Patient Disposition in the PEONY Trial

Characteristic	Pertuzumab + Trastuzumab + Docetaxel N = 218	Placebo + Trastuzumab + Docetaxel N = 110
Screened	383	
Randomized	219	110
Randomized and treated	218	110
Started neoadjuvant therapy	218	110
Discontinued neoadjuvant treatment	4	2
Adverse event	1	0
Withdrawal by patient	2	1
Progression of disease	0	1
Death	1	0
Underwent surgery	210	105
Did not undergo surgery	4	3
Progression of disease	2	1
Withdrawal by patient	1	1
Physician decision	1	1
Started adjuvant FEC treatment, n (%)	208	103
Discontinued adjuvant FEC treatment, n (%)	4	4
Withdrawal by patient	4	3
Recurrence of disease	0	1
Started adjuvant anti-HER2 treatment, n (%)	204	99
Completed adjuvant anti-HER2 treatment, n (%)	198	94
Discontinued adjuvant anti-HER2 treatment, n (%)	6	5
Withdrawal by patient	1	0
Recurrence of disease	4	4
Pregnancy	1	0
Physician decision	0	1

Characteristic	Pertuzumab + Trastuzumab + Docetaxel N = 218	Placebo + Trastuzumab + Docetaxel N = 110
Started treatment-free follow-up, n (%)	208	104
Alive in follow-up, n (%)	175	82
Discontinued study	33	22
Death	11	11
Lost to follow-up	9	4
Withdrawal by patient	13	3
Non-compliance	0	1
Other	0	3
ITT population	219	110
Safety population	218	110

FEC = 5-fluorouracil, epirubicin, cyclophosphamide; HER2 = human epidermal growth factor receptor 2; ITT = intention-to-treat.

Source: Huang et al., (2024)[4]

Table 4: Patient Disposition in the NEOSPHERE Trial

Characteristic	Pertuzumab + Trastuzumab, + Docetaxel N = 107	Trastuzumab + Docetaxel N = 107
Randomized	107	107
Discontinued neoadjuvant treatment	5	4
Death	1	0
Disease progression	1	0
Protocol violation	2	1
Refused treatment	1	1
Failed to return	0	1
Other	0	1
Surgery and valid pCR assessment	102	104
Entered adjuvant treatment	102	103
Withdrew from adjuvant treatment	8	5
Entered post-treatment follow-up phase	102	98
Withdrew from follow-up phase	19	21

Characteristic	Pertuzumab + Trastuzumab, + Docetaxel N = 107	Trastuzumab + Docetaxel N = 107
ITT population	107	107
Safety population	107[a]	107[b]

ITT = intention to treat; pCR = pathological complete response.

a. One patient randomized to pertuzumab + docetaxel arm received treatment with the pertuzumab + trastuzumab + docetaxel; and was therefore included in the pertuzumab + trastuzumab + docetaxel safety population.
b. One patient randomized to pertuzumab + docetaxel arm received trastuzumab + docetaxel treatment, and was therefore included in the trastuzumab + docetaxel safety population.

Source: Ginanni et al., (2016)[5]
Reprinted from Lancet Oncology, 17/6, Gianni L, Pienkowski T, Im YH, Tseng LM, Liu MC, Lluch A, Starosławska E, de la Haba-Rodriguez J, Im SA, Pedrini JL, Poirier B, Morandi P, Semiglazov V, Srimuninnimit V, Bianchi GV, Magazzù D, McNally V, Douthwaite H, Ross G, Valagussa P., 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial, 791-800, Copyright (2016), with permission from Elsevier.

Treatment Exposure and Concomitant Medications

Table 5: Exposure to Study Treatments during the Neoadjuvant Treatment Period in PEONY (Safety Population)

Exposure	Pertuzumab + Trastuzumab + Docetaxel N = 218	Placebo + Trastuzumab + Docetaxel N = 110
Pertuzumab/placebo		
Treatment duration, weeks		
Mean (SD)	12.0 (1.2)	12.0 (0.7)
Median (range)	12.0 (3 to 16)	12.0 (6 to 14)
Number of cycles		
Mean (SD)	3.9 (0.4)	4.0 (0.2)
Media (range)	4.0 (1 to 4)	4.0 (2 to 4)
Number of cycles, no. of patients (%)		
1	3 (1.4)	0
2	1 (0.5)	1 (0.9)
3	0	1 (0.9)
4	214 (98.2)	108 (98.2)
Cumulative Dose, mg		
Mean (SD)	2082.7 (162.9)	2084.9 (96.6)
Median (range)	2100.0 (840 to 2520)	2100.0 (1260 to 2100)
Number of infusion modifications, n (%)		
0	211 (96.8)	110 (100.0)

1	7 (3.2)	0
Number of infusion modifications due to an AE:		
0	212 (97.2)	110 (100.0)
1	6 (2.8)	0

AE = adverse event, SD = standard deviation.

Source: Shao et al., (2020)[6]

Table 6: Exposure to Study Treatments during the Overall Treatment Period in NEOSPHERE (Safety Population)

Characterisitcs	Pertuzumab + Trastuzumab + Docetaxel N = 107	Trastuzumab + Docetaxel N = 107
Pertuzumab – Number of cycles, median (range)	4 (1 to 4)	NA
Number of patients completing 4 cycles, n (%)	102 (95.3)	NA
Number of cycles delayed, slowed down, interrupted, or discontinued, n (%)	31 (7·4)	NA
Total dose received, mg, median (range)	2100 (300 to 2940)*	NA

NA = not applicable.

Source: Ginanni et al., (2016)[5]

Detailed Harms Results

Table 7: Summary of Harms during the Overall Treatment Period from PEONY and NEOSPHERE (Safety Populations)

Characteristic	PEONY		NEOSPHERE	
	Pertuzumab +, Trastuzumab + Docetaxel N = 218	Placebo + Trastuzumab + Docetaxel N = 110	Pertuzumab + Trastuzumab + Docetaxel N = 107	Trastuzumab + Docetaxel N = 107
Patients with any AE, n (%)				
Any Grade	218 (100)	109 (99.1)	105 (98.1)	107 (100)
Alopecia	115 (52.8)	56 (50.9)	73 (68.2)	75 (70.1)
Neutropenia	154 (70.6)	73 (66.4)	68 (63.6)	80 (74.7)
Leukopenia	135 (61.9)	67 (60.9)	NR	NR

Characteristic	PEONY		NEOSPHERE	
	Pertuzumab +, Trastuzumab + Docetaxel N = 218	Placebo + Trastuzumab + Docetaxel N = 110	Pertuzumab + Trastuzumab + Docetaxel N = 107	Trastuzumab + Docetaxel N = 107
Nausea	84 (38.5)	40 (36.4)	71 (66.4)	70 (65.4)
Vomiting	NR	NR	39 (36.4)	31 (29.0)
Anemia	75 (34.4)	37 (33.6)	NR	NR
Fatigue	NR	NR	35 (32.7)	35 (32.7)
Rash	NR	NR	30 (28.0)	26 (24.3)
Mucosal inflammation	NR	NR	33 (30.8)	28 (26.2)
Myalgia	NR	NR	25 (23.4)	24 (22.4)
Asthenia	NR	NR	29 (27.1)	22 (20.6)
Headache	NR	NR	35 (32.7)	35 (32.7)
Alanine aminotransferase increased	64 (29.4)	41 (37.3)	NR	NR
Aspartate aminotransferase increased	54 (24.8)	34 (30.9)	NR	NR
Upper respiratory tract infection	58 (26.6)	14 (12.7)	NR	NR
Decreased appetite	40 (18.3)	13 (11.8)	NR	NR
Patients with Grade 3 or worse AEs				
Grade 3 or worse AE, n (%)	154 (70.6)	75 (68.2)	78 (72.9)	87 (81.3)
Neutropenia	129 (59.2)	61 (55.5)	59 (55.1)	71 (66.4)
Febrile neutropenia	11 (5.0)	4 (3.6)	12 (11.2)	10 (9.3)
Anemia	9 (4.1)	5 (4.5)	NR	NR
Thrombocytopenia	7 (3.2)	1 (0.9)	NR	NR
Granulocytopenia	NR	NR	1 (0.9)	1 (0.9)
Leucopenia	75 (34.4)	38 (34.5)	6 (5.6)	13 (12.1)
Menstruation irregular	8 (3.7)	0	4 (3.7)	6 (5.6)
Alopecia	NR	NR	5 (4.7)	1 (0.9)
Rash	NR	NR	2 (1.9)	2 (1.9)
Drug hypersensitivity	NR	NR	1 (0.9)	0
Alanine aminotransferase increased	NR	NR	0	3 (2.8)
Mucosal inflammation	NR	NR	2 (1.9)	0
Asthenia	NR	NR	2 (1.9)	0

Characteristic	PEONY		NEOSPHERE	
	Pertuzumab +, Trastuzumab + Docetaxel N = 218	Placebo + Trastuzumab + Docetaxel N = 110	Pertuzumab + Trastuzumab + Docetaxel N = 107	Trastuzumab + Docetaxel N = 107
Urinary tract infection	NR	NR	2 (1.9)	2 (1.9)
Radiation skin injury	NR	NR	2 (1.9)	2 (1.9)
SAEs				
Patients with ≥ 1 SAE, n (%)	37 (17.0)	15 (13.6)	22 (20.6)	21 (19.6)
Neutropenia	NR	NR	6 (5.6)	1 (0.9)
Febrile neutropenia	9 (4.1)	3 (2.7)	8 (7.5)	10 (9.3)
Myelosuppression	3 (1.4)	0	NR	NR
Pneumonia	4 (1.8)	1 (0.9)	NR	NR
Pyrexia	NR	NR	1 (0.9)	1 (0.9)
Diarrhea	NR	NR	0	2 (1.9)
Left ventricular dysfunction	NR	NR	3 (2.8)	0
Appendicitis	NR	NR	0	1 (0.9)
Neutropenic infection	NR	NR	1 (0.9)	1 (0.9)
Metrorrhagia	NR	NR	0	1 (0.9)
Acute pyelonephritis	NR	NR	2 (1.9)	0
Wound infection	NR	NR	0	2 (1.9)
AEs leading to treatment withdrawal				
Patients who stopped treatment due to AEs, n (%)	2 (0.9)	0	5 (4.7)	0
Death due to AEs				
Patients who died	2 (0.9)	2 (1.8)	1 (0.9)	0
Cause of death	Suicide in the neoadjuvant period and pneumonia in the treatment-free follow-up period	Sudden death in the treatment-free follow-up period	Fulminant hepatitis in the neoadjuvant phase	2 (1.9)
AEs of Special Interest				
LVEF decline to < 50% and by ≥ 10% from baseline	2 (0.9)	2 (1.8)	9 (8.4)	1 (0.9)
Diarrhea, any Grade	89 (40.8)	19 (17.3)	55 (51.4)	41 (38.3)
Diarrhea, Grade 3 or worse	NR	NR	7 (6.5)	4 (3.7)

Characteristic	PEONY		NEOSPHERE	
	Pertuzumab +, Trastuzumab + Docetaxel N = 218	Placebo + Trastuzumab + Docetaxel N = 110	Pertuzumab + Trastuzumab + Docetaxel N = 107	Trastuzumab + Docetaxel N = 107
Drug hypersensitivity	NR	NR	1 (0.9)	0
Infusion reactions	48 (22.0)	10 (9.1)	NR	NR
Adjuvant T-DM1 utilization	NR	NR	NR	NR

AE = adverse event; LVEF = left ventricular ejection fraction; NA = not applicable; NR = not reported; SAE = serious adverse event; T-DM1 = trastuzumab emtansine.

Sources: Huang et al., (2024)[4], Gianni et al., (2016)[5]
Table adapted from Huang, et al Neoadjuvant–adjuvant pertuzumab in HER2-positive early breast cancer: final analysis of the randomized phase III PEONY trial. Nat Commun. 2024 Mar 9;15:2153. doi: 10.1038/s41467-024-45591-7 https://www.nature.com/articles/s41467-024-45591-7. Copyright 2020 to the authors. Used under Creative Commons Attribution 4.0 International License https://creativecommons.org/licenses/by/4.0/

Reprinted from Lancet Oncology, 17/6, Gianni L, Pienkowski T, Im YH, Tseng LM, Liu MC, Lluch A, Starosławska E, de la Haba-Rodriguez J, Im SA, Pedrini JL, Poirier B, Morandi P, Semiglazov V, Srimuninnimit V, Bianchi GV, Magazzù D, McNally V, Douthwaite H, Ross G, Valagussa P., 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial, 791-800, Copyright (2016), with permission from Elsevier.

Appendix 4: Results of the Studies Addressing Gaps in the Systematic Review Evidence

Treatment Exposure and Concomitant Medications

Table 8: Neoadjuvant Treatment Exposure and Subsequent Treatments for NeoPowER and van der Voort et al.

Characteristic	NeoPowER 2024		van der Voort et al. 2022	
	P + H + CT (N = 125)	H + CT (N = 134)	P + H + CT (N = 453)	H + CT (N = 671)
NAT				
NAT duration (days), median (range)	116 (11 to 226)	153 (14 to 210)	NR	NR
Anthracyclines administration, n (%)	56 (44.4)	111 (82.8%)	238 (52.5)	530 (79.0)
NAT duration cutoffs, n (%)				
≤ 4 cycles	49 (38.9)	21 (15.7)	30 (6.6%)	671 (100)
5 to 8 cycles	77 (61.1)	113 (84.3)		
≥ 9 cycles	0	0	423 (93.4)	0
Type of taxane, n (%)				
Paclitaxel	37 (29.4)	125 (93.3)	NR	NR
Docetaxel	79 (62.7)	5 (3.7)	NR	NR
Switch	9 (7.1)	4 (3.0)	NR	NR
Post-NAT				
Adjuvant CT, n (%)	36 (28.8)	9 (6.7)	7 (1.5)	13 (1.9)
Radiotherapy	94 (75.2)	103 (76.9)	366 (80.8)	549 (81.8)
Type of BC surgery, n (%)				
Breast conserving	68 (54.4)	67 (50.0)	253 (55.8)	353 (52.6)
Mastectomy	56 (44.8)	67 (50.0)	192 (42.4)	318 (47.4)
None	3 (2.4)	0	8 (1.8)	0

BC = breast cancer; CT = chemotherapy; H = trastuzumab; NAT = neoadjuvant treatment; NR = not reported; P = pertuzumab.

Sources: Canino et al. (2024);[7] Van der Voort et al. (2022).[8]

Table 9: Neoadjuvant treatment exposure and subsequent treatments 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)
NAT						
Anthracyclines administration, n (%)	479 (83.0)	747 (78.5)	NR	NR	164 (15.9)	161 (15.6)
NAT duration cutoffs, n (%)						
4 to 5 cycles	0	0	0	0	≥ 4: 560 (100)	≥ 4: 472 (100)
6 to 8 cycles	577 (100)	951 (100)	298 (100)	201 (100)		
Type of taxane, n (%)						
Paclitaxel	144 (25.0)	565 (59.4)	NR	NR	NR	NR
Docetaxel	433 (75.0)	386 (40.6)	NR	NR	NR	NR
Switch	0	0	NR	NR	NR	NR
Post-NAT						
Type of BC surgery, n (%)						
Breast conserving	407 (70.5)	691 (72.7)	NR	NR	NR	NR
Mastectomy	170 (29.5)	260 (27.3)	NR	NR	NR	NR
None	0	0	NR	NR	NR	NR

BC = breast cancer; CT = chemotherapy; H = trastuzumab; NAT = neoadjuvant treatment; NR = not reported; P = pertuzumab.

Sources: Bilici et al. (2023);[9] Ren et al. (2023);[10] Cheng et al. (2022).[11]

Additional Efficacy Results

Table 10: Additional Efficacy Results from NeoPowER

Characteristic	P + H + CT	H + CT
Distant relapse events, n of N (%)	9 of 124 (7.3)	12 of 133 (9.0)
3-year DFRS rate, % (95% CI)	89.7 (82.6 to 96.8)	93.8 (89.7 to 97.9)
Deaths, n of N (%)	3 of 124 (2.4)	14 of 134 (10.4)
3-year OS rate, % (95% CI)	100	96.1 (92.7 to 99.5)

CT = chemotherapy; DRFS = distant relapse free survival; H = trastuzumab; OS = overall survival; P = pertuzumab.

Sources: Canino et al. (2024).[7]

Table 11: Additional Efficacy Results from HER2PATH

HER2PATH	P + H + CT (N = 577)	H + CT (N = 951)
Relapse rate, n (%)	26 (4.5)	116 (12.2)

HER2PATH	P + H + CT (N = 577)	H + CT (N = 951)
EFS time (mo), median (95% CI)	98.0 (43.7 to 152.3)	NR
EFS time (mo), mean (95% CI)	95.8 (82.3 to 109.3)	103.9 (100.2 to 107.6)
2-year EFS rate, %	95	NR
2-year EFS rate, %	90.4	

CI = confidence interval; CT = chemotherapy; EFS = event free survival; H = trastuzumab; mo = month; NR = not reported; P = pertuzumab.

Sources: Bilici et al. (2023).[9]

Table 12: Additional Efficacy Results from van der Voort et al.

	P + H + CT (N = 453)	H + CT (N = 671)
5-year BCSS rate, %	95[a]	92[b]
5-year OS rate, % (95% CI)	95 (92.5 to 96.6)	90 (88.2 to 92.7)

BCSS = breast cancer specific survival; CI = confidence interval; CT = chemotherapy; H = trastuzumab; OS = overall survival; P = pertuzumab.

Source: Van der Voort et al. (2022).[8]

a. 452 patients were included in the BCSS analysis.
b. 670 patients were included in the BCSS analysis.

Detailed Harms Results

Table 13: Key Harms Results from RWE Studies

Outcome	Study	Event rate, n of N (%)	
		P + H + CT	H + CT
TEAEs, any Grade			
Anemia	NeoPowER 2024	NR (13.1)	NR (16.7)
	CSBrS-015 2022	11 of 321 (3.4)	NR
Asthenia	NeoPowER 2024	NR (11.9)	NR (8.2)
	HER2PATH 2023	70 of 577 (12.1)	77 of 951 (8.1)
Hair loss	CSBrS-015 2022	83 of 321 (25.9)	NR
Headache	HER2PATH 2023	81 of 577 (14.0)	111 of 951 (11.7)
Myelosuppression	CSBrS-015 2022	18 of 321 (5.4)	NR
Neutropenia	NeoPowER 2024	NR (11.9)	NR (14.7)
	HER2PATH 2023	13 of 577 (2.3)	22 of 951 (2.3)
Nausea	NeoPowER 2024	NR (9.8)	NR (11.9)
	HER2PATH 2023	61 of 577 (10.6)	97 of 951 (10.2)
Nausea and vomiting	CSBrS-015 2022	71 of 321 (22.1)	NR

Outcome	Study	Event rate, n of N (%)	
		P + H + CT	H + CT
Liver damage	CSBrS-015 2022	19 of 321 (5.9)	NR
Rash	NeoPowER 2024	NR (6.1)	NR (4.5)
	HER2PATH 2023	102 of 577 (17.7)	83 of 951 (8.7)
Reduced granulocyte count	CSBrS-015 2022	100 of 321 (31.2)	NR
UTI	HER2PATH 2023	86 of 577 (14.9)	111 of 951 (11.7)
Grade 3 to 4 AEs			
Patients with ≥1 Grade 3 AE	CSBrS-015 2022	24 of 321 (7.5)	NR
Hair loss	CSBrS-015 2022	73 of 321 (22.7)	NR
Liver damage	CSBrS-015 2022	2 of 321 (0.1)	NR
Nausea and vomiting	CSBrS-015 2022	12 of 321 (3.7)	NR
Neutropenia	NeoPowER 2024	NR (8.5)	NR (10.0)
	HER2PATH 2023	4 of 577 (0.7)	16 of 951 (1.7)
Peripheral edema	HER2PATH 2023	3 of 577 (0.5)	11 of 951 (1.2)
Reduced granulocyte count	CSBrS-015 2022	39 of 321 (12.1)	NR
UTI	HER2PATH 2023	9 of 577 (1.6)	15 of 951 (1.6)
SAEs			
Patients with 1 SAE	NeoPowER 2024	1 of 125 (0.08) UTI	2 of 134 (1.5) typhlitis; sepsis
Discontinuations due to AEs			
Patients who stopped early	NeoPowER 2024	NR (2.0)	NR (9.0)
AEs of special interest			
Significant or serious LVEF reduction event	NeoPowER 2024[a,b]	1 of 111 (0.9)	2 of 94 (2.1)
	HER2PATH 2023[c]	0 of 577	0 of 951
	CSBrS-015 2022[d]	0 of 321	NR
Mild LVEF reduction event	HER2PATH 2023	1 of 577 (0.02)	2 of 951 (0.02)
Diarrhea, any Grade	NeoPowER 2024	NR (19.8)	NR (9.2)
	HER2PATH 2023	156 of 577 (27.0)	152 of 951 (16.0)
	CSBrS-015 2022	65 of 321 (20.2)	NR
Diarrhea, Grade 3 or 4	NeoPowER 2024	NR (0.9)	NR (0.2)
	HER2PATH 2023	7 of 577 (1.2)	8 of 951 (0.8)
	CSBrS-015 2022	11 of 321 (3.4)	NR
Drug hypersensitivity, any Grade	NeoPowER 2024	NR (2.4)	NR (3.5)
Drug hypersensitivity, Grade 3 or 4	NeoPowER 2024	0	0

Outcome	Study	Event rate, n of N (%)	
		P + H + CT	H + CT
Neurotoxicity, any Grade	NeoPowER 2024	NR (4.3)	NR (6.5)
Neurotoxicity, Grade 3 or 4	NeoPowER 2024	NR (0.3)	0
Toxicity leading to death	HER2PATH 2023	0 of 577	0 of 951
Adjuvant T-DM1 utilization	NeoPowER 2024	35 of 125 (28.0)	7 of 134 (5.2)

AE = adverse event; NR = not reported; CT = chemotherapy; H = trastuzumab; LVEF = left ventricular ejection fraction; P = pertuzumab; SAE = severe adverse event; T-DMI = trastuzumab emtansine; UTI = urinary tract infection.

a. Significant event: decrease in LVEF of 10 to 15% from baseline and < 50% or ≥ 16% from baseline.
b. Two timepoints were required to evaluated cardiac safety.
c. Significant event: >10% decrease in LVEF to <50% from baseline; serious event: symptomatic left ventricular systolic dysfunction.
d. Significant event: >10% decrease in LVEF from baseline; serious event: other serious cardiovascular AE.

Sources: Canino et al. (2024);[7] Bilici et al. (2023);[9] Cheng et al. (2022).[11]

Economic Review Appendices

Appendix 5: Cost Comparison Table

The comparators presented in Table 14 have been deemed to be appropriate based on feedback from clinical experts and drug plans. Recommended doses were based on regimen monographs from Cancer Care Ontario[12] and validated by clinical experts. If discrepancies in dosing between the monograph and Canadian clinical practice exist, the dose specified by clinical experts was used. Pricing for comparator products was based on IQVIA Delta PA database.[13]

The recommended dose of pertuzumab in combination with trastuzumab and chemotherapy is 840 mg for the first cycle, followed by 420 mg for subsequent cycles (Table 1). At $3,636 per 420 mg vial, the treatment acquisition cost of pertuzumab in combination with trastuzumab and chemotherapy is $346.30 daily for the first cycle and $173.15 for the subsequent cycles, with incremental costs of $9,696 and $4,848 per patient per 28-day cycle for the first and subsequent cycles, respectively. Results may differ by jurisdiction depending on individual list prices for the drug under review compared to those presented in Table 14.

Table 14: CDA-AMC Cost Comparison Table for treatment for HER2-positive locally advanced, inflammatory, or early-stage breast cancer

Treatment	Strength / concentration	Form	Price	Recommended dosage	Daily cost ($)	Cost per 28-day cycle[a] ($)
Pertuzumab	30 mg/ml	420 mg vial	3,636.1206	840 mg IV on Day 1 for the first cycle, followed by 420 mg on Day 1 for subsequent cycles. Administer 3 to 6 21-day cycles as part of one of the regimens outlined	First cycle: 346.30 Subsequent cycles: 173.15	First cycle: 9,696 Subsequent cycles: 4,848

Treatment	Strength / concentration	Form	Price	Recommended dosage	Daily cost ($)	Cost per 28-day cycle[a] ($)
				below, when trastuzumab is administered[b]		
Pertuzumab (4 cycles) + AC-PACL (DD) + TRAS						First cycle: 20,439 Subsequent cycles: 15,557
Pertuzumab (4 cycles) + AC-PACL (W) + TRAS						First cycle: 19,992 Subsequent cycles: 15,110
Pertuzumab (3 cycles) + FEC-D + TRAS						First cycle: 13,933 Subsequent cycles: 9,051
Pertuzumab (6 cycles) + CRBP-D + TRAS						First cycle: 14,277 Subsequent cycles: 9,395
AC-PACL (DD) + TRAS						
Doxorubicin	2 mg/mL	10 mg vial 50 mg vial 200 mg vial	50 252.25 973	60 mg/m2 IV on Day 1 every 2 weeks for 4 cycles	39.61	1,109
Cyclophosphamide	20 mg/mL	500 mg vial 1,000 mg vial 2,000 mg vial	107.81 115 150	600 mg/m2 IV on Day 1 every 2 weeks for 4 cycles	8.21	230
Paclitaxel	6 mg/mL	30 mg vial 96 mg vial 150 mg vial 300 mg vial	300 1,196.8 1,870 3,740	After AC is complete: 175 mg/m2 on Day 1 every 2 weeks for 4 cycles	267.14	7,480
Trastuzumab IV	21 mg/mL	150 mg vial 440 mg vial	506.145 1,417.196	After AC is complete: First cycle: 8 mg/kg IV on day 1; Thereafter: 6 mg/kg IV on day 1 every 3 weeks for another 3 cycles	First cycle: 68.69 Subsequent cycles: 67.48	First cycle: 1,923 Subsequent cycles: 1,890
AC-PACL (DD) + TRAS regimen						First cycle: 10,742 Subsequent cycles: 10,709
AC-PACL (W) + TRAS						

Treatment	Strength / concentration	Form	Price	Recommended dosage	Daily cost ($)	Cost per 28-day cycle[a] ($)
Doxorubicin	2 mg/mL	10 mg vial 50 mg vial 200 mg vial	50 252.25 973	60 mg/m2 IV on Day 1 every 3 weeks for 4 cycles	26.4	739
Cyclophosphamide	20 mg/mL	500 mg vial 1,000 mg vial 2,000 mg vial	107.81 115 150	600 mg/m2 IV on Day 1 every 3 weeks for 4 cycles	5.48	153
Paclitaxel	6 mg/mL	30 mg vial 96 mg vial 150 mg vial 300 mg vial	300 1,196.8 1,870 3,740	After AC is complete: 80 mg/m2 every week for 12 weeks	267.14	7,480
Trastuzumab IV	21 mg/mL	150 mg vial 440 mg vial	506.145 1,417.196	After AC is complete: First cycle: 8 mg/kg IV on day 1; Thereafter: 6 mg/kg IV on day 1 every 3 weeks for another 3 cycles	First cycle: 68.69 Subsequent cycles: 67.48	First cycle: 1,923 Subsequent cycles: 1,890
AC-PACL (W) + TRAS regimen						First cycle: 10,296 Subsequent cycles: 10,262
FEC-D + TRAS						
Fluorouracil	50 mg/mL	5,000 mg vial	160.9	500 mg/m2 IV on Day 1 every 3 weeks for 3 cycles	1.32	37
Epirubicin	2 mg/mL	10 mg vial 50 mg vial 100 mg vial	40.12 200.91 779.54	100 mg/m2 IV on Day 1 every 3 weeks for 3 cycles	25.15	704
Cyclophosphamide	20 mg/mL	500 mg vial 1,000 mg vial 2,000 mg vial	107.81 115 150	500 mg/m2 IV on Day 1 every 3 weeks for 3 cycles	5.48	153
Docetaxel	10 mg/mL 10 mg/mL 20 mg/mL 20 mg/mL	80 mg vial 160 mg vial 200 mg vial 800 mg vial	970.2 1,940.4 2,490 4,950	After FEC is complete: 100 mg/m2 IV on Day 1 every 3 weeks for 4 cycles	50.68	1,419
Trastuzumab IV	21 mg/mL	150 mg vial 440 mg vial	506.145 1,417.196	After AC is complete: First cycle: 8 mg/kg IV on day 1; Thereafter: 6 mg/kg IV on day 1	First cycle: 68.69 Subsequent cycles: 67.48	First cycle: 1,923 Subsequent cycles: 1,890

Treatment	Strength / concentration	Form	Price	Recommended dosage	Daily cost ($)	Cost per 28-day cycle[a] ($)
				every 3 weeks for another 3 cycles		
FEC-D + TRAS regimen						First cycle: 4,237 Subsequent cycles: 4,203
CRBP-D + TRAS						
Carboplatin	10 mg/mL	50 mg 150 mg 450 mg 600 mg	70 210 599.9985 775.002	Target AUC 6 on Day 1 every 3 weeks for 6 cycles[c]	56.9	1,593
Docetaxel	10 mg/mL 10 mg/mL 20 mg/mL 20 mg/mL	80 mg vial 160 mg vial 200 mg vial 800 mg vial	970.2 1,940.4 2,490 4,950	75 mg/m2 IV on Day 1 every 3 weeks for 6 cycles	38.01	1,064
Trastuzumab IV	21 mg/mL	150 mg vial 440 mg vial	506.145 1,417.196	First cycle: 8 mg/kg IV on day 1; Thereafter: 6 mg/kg IV on day 1 every 3 weeks for another 5 cycles	First cycle: 68.69 Subsequent cycles: 67.48	First cycle: 1,923 Subsequent cycles: 1,890
CRBP-D + TRAS regimen						First cycle: 4,581 Subsequent cycles: 4,547
Neoadjuvant Trastuzumab Emtansine (TDM-1)						
Trastuzumab Emtansine	20 mg/mL	100 mg vial 160 mg vial	2,128.93[d] 3,406.288 [d]	3.6 mg/kg IV every 3 weeks	263.58	7,380

Note: All prices are from the IQVIA Delta PA database[13] (accessed May 2025), unless otherwise indicated, and do not include dispensing fees but do assume wastage of excess medication in vials. Doses are from the Cancer Care Ontario Drug Formulary regimen database.[12] Mean patient body weight was assumed to be 69 kg, while mean body surface area was 1.72 m^2 and glomerular filtration rate was assumed to be 125 mL/min.

[a] Cost standardized to 28-day cycles to allow for comparison among regimens of different cycle lengths

[b] The number of cycles of pertuzumab is dependent upon the number of cycles of trastuzumab given in the neoadjuvant setting with each chemotherapy regimen

[c] Dose calculated using Calvert method[14] where dose is Target AUC * (GFR + 25).

[d] CADTH Review Perjeta[3]

References

1. Hoffmann-La Roche Limited. *Pertuzumab (Perjeta): 420mg/14 mL vial for injection Sterile Concentrate for Solution for Infusion [product monograph]*. Hoffmann-La Roche Limited; 2021. Accessed 2025 May 2. https://assets.roche.com/f/173850/x/db5cf0854e/perjeta_pm_e.pdf
2. Hoffmann-La Roche Limited. *Tastuzumab (Herceptin): 600mg/5 mL vial for injection. Sterile solution for subcutaneous use only [product monograph]*. Hoffmann-La Roche Limited; 2020. Accessed 2025 May 2. https://assets.roche.com/f/173850/x/48ab743c65/herceptinsc_pm_e.pdf
3. CADTH Reimbursement Recommendation: Pertuzumab (Perjeta). *Can J Health Technol*. 2022;2(2)
4. Huang L, Pang D, Yang H, et al. Neoadjuvant-adjuvant pertuzumab in HER2-positive early breast cancer: final analysis of the randomized phase III PEONY trial. *Nat Commun*. 2024;15(1):2153. doi:10.1038/s41467-024-45591-7
5. Gianni L, Pienkowski T, Im YH, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. *Lancet Oncol*. 2016;17(6):791-800. doi:10.1016/S1470-2045(16)00163-7
6. Shao Z, Pang D, Yang H, et al. Efficacy, Safety, and Tolerability of Pertuzumab, Trastuzumab, and Docetaxel for Patients With Early or Locally Advanced ERBB2-Positive Breast Cancer in Asia: The PEONY Phase 3 Randomized Clinical Trial. *JAMA Oncol*. 2020;6(3):e193692. doi:10.1001/jamaoncol.2019.3692
7. Canino F, Barbolini M, De Giorgi U, et al. Safety and efficacy analysis of neoadjuvant pertuzumab, trastuzumab and standard chemotherapy for HER2-positive early breast cancer: real-world data from NeoPowER study. *BMC Cancer*. 2024;24(1):735. doi:10.1186/s12885-024-12506-0
8. van der Voort A, Liefaard MC, van Ramshorst MS, et al. 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. *Breast*. 2022;65:110-115. doi:10.1016/j.breast.2022.07.005
9. Bilici A, Olmez OF, Kaplan MA, et al. Impact of adding pertuzumab to trastuzumab plus chemotherapy in neoadjuvant treatment of HER2 positive breast cancer patients: a multicenter real-life HER2PATH study. *Acta Oncol*. 2023;62(4):381-390. doi:10.1080/0284186X.2023.2202330
10. Ren X, Zhang X, Ma X, et al. Changes in HER2 status and survival outcomes in patients with non-pathological complete response after neoadjuvant targeted treatment. *Medicine (Baltimore)*. 2023;102(39):e34903. doi:10.1097/MD.0000000000034903
11. Cheng Y, Xiang H, Xin L, Duan X, Liu Y, Chinese Society of Breast Surgery CSoSoCMA. Neoadjuvant therapy for early human epidermal growth factor receptor 2 positive breast cancer in China: A multicenter real-world study (CSBrS-015). *Chin Med J (Engl)*. 2022;135(19):2311-2318. doi:10.1097/CM9.0000000000002197
12. Cancer Care Ontario. Funded evidence-informed regimens. Accessed April 14, 2025, https://www.cancercareontario.ca/en/drugformulary/regimens
13. IQVIA. *DeltaPA*. 2023. Accessed May 28, 2025. https://www.iqvia.com/
14. Calvert AH, Newell DR, Gumbrell LA, et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol*. 1989;7(11):1748-56. doi:10.1200/jco.1989.7.11.1748