HTA submission Q/A for addition of pertuzumab to trastuzumab in neoadjuvant treatment of HER2 early breast cancer.

Project Number: PX0379-000
Generic Drug Name (Brand): Pertuzumab (PERJETA)
Indication: In combination with trastuzumab and chemotherapy for early stage HER2+ breast cancer in the neoadjuvant setting.
Name of Clinician Group: REAL Alliance
Author of Submission: Dr. Mita Manna

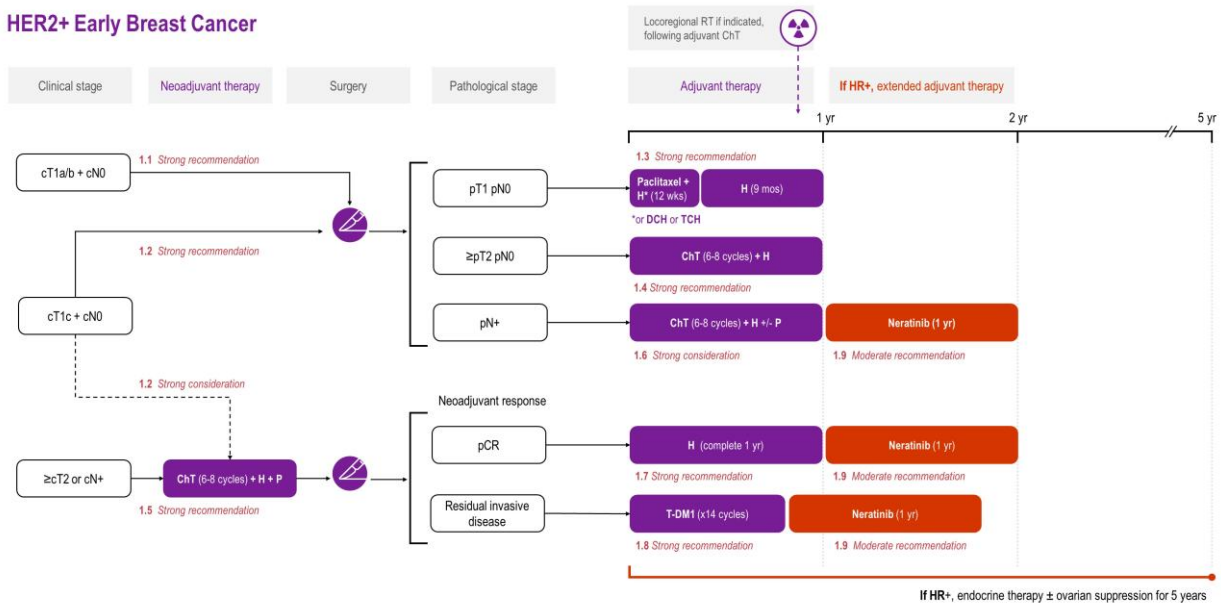
Table IV: Research Questions

1. **What is the effectiveness of pertuzumab in combination with trastuzumab and chemotherapy for neoadjuvant treatment of early stage HER2-positive breast cancer?**

Pertuzumab and trastuzumab complement each other in dual HER2 blockade, with trastuzumab binding to HER2's domain IV (preventing receptor dimerization) and pertuzumab targeting domain II (preventing receptor heterodimerization)[1]. In a recent publication, the REAL Canadian Alliance provided their expert guidance on treating patients with pertuzumab + trastuzumab and chemotherapy for early stage HER2-positive breast cancer [2]. The recommendation reads as follows:

> **Recommendation 3.1.5: For patients with HER2+ early breast cancer with ≥cT2 or those with nodal disease (cN+), the standard of care is neoadjuvant therapy with trastuzumab + pertuzumab + chemotherapy. (I,A)**

This recommendation is based on many clinical trials (summarized in table I) demonstrating that neoadjuvant therapy with pertuzumab + trastuzumab + chemotherapy improves the rates of pathologic complete response (pCR) and can help avoid the morbidity of axillary lymph node dissection, as well as reduce the number of disease recurrence. Studies, including a retrospective analysis from British Columbia, also show that patients who achieve pCR have better survival [3]. This evidence supports using pCR as a reliable marker for improved outcomes and allows for de-escalation of further adjuvant treatments, such as reducing the need for subsequent therapies like T-DM1 or T-DXd (Figure 1)



ChT, chemotherapy; cN0, no nodal disease based on clinical assessment; CR, complete response; cT1a/b, tumour ≤1 cm on clinical assessment; cT1c, tumours >1 cm but ≤ 2 cm on clinical assessment; cT2, tumours >2 cm but ≤5 cm on clinical assessment; DCH, docetaxel + cyclophosphamide + trastuzumab; H, trastuzumab; HR, hormone receptor; p, based on pathologic assessment; P, pertuzumab; RT, radiotherapy; TCH, docetaxel + carboplatin + trastuzumab

Figure 1. Treatment algorithm for HER2+ early breast cancer. Figure taken from Manna et al 2024

Study Name	Population	Arms	Outcomes	Safety	Impact
NeoSphere [4]	Operable, locally advanced, or inflammatory HER2+ breast cancer (N=417)	Docetaxel + HP vs. Docetaxel + H	pCR : 45.8% vs. 29.0% (p = 0.0141). 5-year PFS : 86% vs. 81% (HR 0.69, 95% CI 0.34–1.40)	Similar tolerability, few grade 3 or higher AEs	Demonstrates a significant improvement in pCR rates with the addition of pertuzumab, highlighting its potential benefit in the neoadjuvant treatment of HER2+ breast cancer.
PEONY [5]	Asian patients with early or locally advanced HER2+ breast cancer (N=329)	Docetaxel + HP vs. Docetaxel + H	pCR : 39.3% vs. 21.8% (p = 0.001). 5-year EFS : 84.8% vs. 73.7% (HR 0.53, 95% CI 0.32–0.89). 5-year DFS : 86.0% vs. 75.0% (HR 0.52, 95% CI 0.30–0.88)	Higher diarrhea and grade 3 neutropenia with HP	Reinforces the efficacy of dual HER2 blockade with pertuzumab in increasing pCR and EFS rates, which is particularly relevant for the Asian population.
BERENICE [6]	Early-stage, locally advanced, or inflammatory HER2+ breast cancer (n=400)	ddAC + T + HP vs FEC + D + HP	pCR: 61.8% vs 60.7%. 5-year EFS: 90.8% vs 89.2%. 5-year OS: 96.1% vs 93.8%	Consistent with anticipated profiles, common AEs: neutropenia, febrile neutropenia, diarrhea	Highlights the real-world impact of adding pertuzumab, improving pCR rates and potentially influencing cost-effectiveness considerations.
Jewish General Hospital retrospective study [7]	localized HER2 positive breast cancer (N=83)	HP vs. H	pCR; 67% vs. 27%; p = 0.0016) Need for axillary dissection (28% vs 39%)	NA	Highlights the real-world impact of adding pertuzumab, improving pCR rates and potentially influencing cost-effectiveness considerations.
TRYPHAENA [8]	HER2+ operable, locally advanced, or inflammatory breast cancer (N=225)	Anthracyclon regimens: A. FEC + HP →docetaxel + HP B. FEC→ docetaxel + HP vs Anthracyclin-free regimen: C. docetaxel + carboplatin + HP	3-year DFS; 87% vs 88% vs 90%	No difference in cardiac toxicity across arms, two serious AEs reported in the FEC followed by docetaxel + HP arm	Findings support the use of non-anthracycline regimens, which are associated with lower cardiotoxicity, making them a safer option for patients requiring dual HER2 blockade.
TRAIN-2 [9]	Stage II or III early HER2+ breast cancer (N=438)	HP + Anthracycline vs. HP + Non-anthracycline	pCR in ypT0/is, ypN0 : 67% vs 68% EFS; 93% vs 94%	Reduced grade 4 neutropenia and fewer serious AEs in	Underscores the comparable efficacy of anthracycline and non-anthracycline regimens,

			3-year OS: 97.7% vs 98.2%	non-anthracycline arm	with the latter offering better tolerability, providing a strong case for minimizing toxicity in treatment planning.
NeoHIP **[10]**	Stage II-III early HER2+ (N=138)	THP vs THP-Pembro vs TH-Pembro	pCR in ypT0/TisypN0; 48.3% vs 67.2% vs 25.0% pCR in ypT0ypN0; 43.1% vs 51.7% vs 20.0% pCR in ypT0/Tis; 50.0% vs 68.9% vs 25.0%	Consistent with anticipated profiles, common AEs: neutropenia, febrile neutropenia, diarrhea	TH-Pembro arm was prematurely discontinued due to low pCR rates which underscores the benefit of adding pertuzumab to neoadjuvant treatment

2. **What are the benefits of reduced toxicity as there is published evidence that the addition of neoadjuvant pertuzumab allows omission of anthracycline (and adjuvant TDM-1 for patients who achieved pCR)?**

Anthracycline-taxane combinations with HER2-targeted agents have long been a cornerstone of (neo)adjuvant chemotherapy for HER2-positive breast cancer. However, they carry a low but serious risk of long-term cardiac toxicity, febrile neutropenia and secondary malignant neoplasms [11,12]. To address these concerns, anthracycline-free regimens using carboplatin and taxanes have been explored in HER2+ clinical trials, such as PREDIX HER2, TRAIN2, TRYPHAENA (Phase II), and BCIRG006 (Phase III) [8,9,13,14]. These studies have shown similar efficacy to anthracycline-based regimens but with improved cardiac safety.

Notably, the TRAIN-2 study highlights that replacing anthracycline with non-anthracycline regimens in combination with the dual HER2 blockade does not compromise the effectiveness of the blockade [9]. This change significantly reduces the risk of acute cardiotoxicity and long-term survivorship cardiotoxicity. Additionally, non-anthracycline regimens are generally more tolerable, leading to fewer side effects like nausea, vomiting, and myelosuppression, thus enhancing patients' quality of life. They also reduce the need for supportive care, such as growth factors or antiemetics, alleviating the overall treatment burden on both patients and healthcare systems.

The use of pertuzumab in neoadjuvant therapy for HER2-positive breast cancer significantly boosts the pCR rate (table 1). This higher pCR rate means fewer patients are left with residual disease, which in turn reduces the need for adjuvant T-DM1—a treatment typically reserved for higher-risk patients. While T-DM1 is effective, it carries additional costs and a greater risk of side effects such as thrombocytopenia and neuropathy. By achieving a better response upfront with pertuzumab, the treatment pathway becomes more streamlined, minimizing further toxicity and ultimately enhancing overall curative intent treatment outcomes.

3. **What are the benefits of the reduction of toxicity related to lower use of adjuvant T-DM1?**

The following is based on data generated by the KATHERINE study [15] which compared T-DM1 to trastuzumab in the adjuvant setting of HER2+ treatment:

Better adherence: The discontinuation rate due to adverse events is significantly higher with T-DM1 (18.0%) compared to trastuzumab (2.1%). This highlights the better tolerability of adjuvant trastuzumab as a single agent, allowing more patients to complete their treatment regimen without interruption, maximizing event-free survival with trastuzumab.

Lower risk of serious adverse events (AEs): Serious AEs occurred in 12.7% of patients treated with T-DM1, compared to 8.1% in those treated with trastuzumab. The lower incidence of serious AEs with trastuzumab reduces the risk of hospitalization and other complications that can affect patients' overall treatment outcomes and health resource utilization.

Manageable AEs: T-DM1 is associated with specific AEs such as decreased platelet counts (5.7%), elevated liver enzymes (23.1% for alanine aminotransferase and 28.4% for aspartate aminotransferase), peripheral sensory neuropathy (18.6%), and pneumonitis (2.6%). These side effects can be challenging to manage and may require additional medical interventions, which can increase the treatment burden on patients and health resource utilization.

4. **What is the expected cost comparison of the different neoadjuvant and adjuvant treatment strategies? (e.g., if neoadjuvant pertuzumab-trastuzumab-chemotherapy leads to higher pathologic complete response, fewer patients will receive adjuvant T-DM1).**

Upfront cost savings based on effectiveness

The upfront cost-effectiveness of using neoadjuvant pertuzumab-trastuzumab (HP) + chemotherapy to reduce adjuvant T-DM1 was evaluated in a retrospective analysis from the Jewish General Hospital in Montreal, Quebec [7]. The study found that adding pertuzumab to trastuzumab in the neoadjuvant setting in their center more than doubled the pCR rate (67% vs. 27%, $p = 0.0016$), thereby considerably reducing the number of patients requiring adjuvant T-DM1. Despite the upfront cost of adding pertuzumab, the mean anti-HER2 drug cost per patient remained cost-neutral, with 65,150 CAD in the HP group versus 66,116 CAD in the trastuzumab-alone group.

Beyond direct drug cost

The findings from the Jewish General Hospital in Montreal suggest that shifting drug costs from adjuvant T-DM1 to neoadjuvant pertuzumab maintains overall cost balance while improving clinical outcomes by increasing pCR rates. However, this analysis only accounts for direct drug costs. When considering the additional cost savings from lower rates of serious adverse events (SAEs) and reduced toxicity management associated with T-DM1, as outlined in question 3 (see Table II for more details), the financial advantage of prioritizing neoadjuvant HP becomes even more evident. This approach not only optimizes disease response and treatment sequencing but also reduces the burden of managing T-DM1-related toxicities, further strengthening the health resource economic and clinical rationale for neoadjuvant dual HER2 blockade.

Moreover, achieving pCR in the neoadjuvant setting is associated with a lower rate of disease recurrence. Fewer recurrences mean that patients are less likely to require prolonged, expensive

systemic therapies, such as T-DXd, which would otherwise add to long-term healthcare expenditures.

Table II. Comparison of the onset of adverse events (AEs) in the KATHERINE trial [15] for T-DM1 and pertuzumab, providing context for their impact on the economic model.

	T-DM1		Trastuzumab	
	All grade (%)	Grade 3-4 (%)	All grade (%)	Grade 3-4 (%)
Fatigue	50	1.1	34	0.1
Nausea	42	0.5	13	0.3
Transaminases increased	32	1.5	8	0.4
Musculoskeletal pain	30	0.7	29	0.7
Hemorrhage	29	0.4*	10	0.3
Thrombocytopenia	29	6	2.4	0.3
Headache	28	0	17	0.1
Peripheral neuropathy	28	1.6	14	0.1
Arthralgia	26	0.1	21	0
Epistaxis	22	0	3.5	0
Constipation	17	0.1	8	0
Myalgia	15	4	11	0
Stomatitis	15	0.1	8	0.1
Vomiting	15	0.5		0.3
Insomnia	14	0	12	0.1
Dry mouth	14	0.1	1.3	0
Cough	14	0.1	12	0
Diarrhea	12	0.8	13	0.3
Abdominal pain	11	0.4		0.3
Pyrexia	10	0	4	0
Urinary tract	10	0.3	6	0.1
Infection	10	1.1	9	0.1
Anemia	10	0.1	8	0.3
Dizziness	15	4	11	0

* Included one fatal hemorrhage.

About REAL Alliance:

The Research Excellence, Active Leadership (REAL) Canadian Breast Cancer Alliance is an equitable standing nucleus committee of multi-disciplinary, clinical-academic oncologists across Canada and Breast Cancer Canada, a patient organization. Formed in December 2023 in recognition that a national ecosystem of leadership should address evidence-based guidance and recommendations for equitable breast cancer clinical management. REAL Alliance publishes national clinical consensus recommendations, routinely updated, for timely health policy, funding, and consistent clinical adoption based on research evidence and medical specialty expertise to ensure optimal outcomes for breast cancer patients across all provinces and territories in Canada.

Information Gathering:

As per a recent publication (OCT 2024), the REAL Canadian Alliance provided their expert guidance on treating patients with pertuzumab + trastuzumab and chemotherapy for early stage HER2-positive breast cancer [2]. Our recommendations were compiled to reflect our clinical opinion as medical specialists in breast cancer on what we believe is best for our patients. Our opinion is based on literature review, level 1 data from clinical trials, and recent data releases from international congresses, as well as our collective clinical expertise.

We urge CDA to consider our clinical recommendation as per the evidence in this document along with the submissions put forward by patient advocacy groups to make an informed decision regarding the place in therapy for pertuzumab with trastuzumab and chemotherapy in patients with early stage HER2+ breast cancer in the neoadjuvant setting. The collective expertise from this group equates to decades of clinical experience in the management of patients with breast cancer, and aligns with well-established global standard of care.

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