Canada's Drug Agency
L'Agence des médicaments du Canada
Drugs. Health Technologies and Systems. Médicaments, technologies de la santé et systèmes.

Feedback on Draft Recommendation

Interested party information	
Project number	PX0379-000
Brand name (generic)	Perjeta (Pertuzumab)
Indication(s)	In combination with trastuzumab and chemotherapy for early stage HER2-positive breast cancer in the neoadjuvant setting
Organization	REAL Canadian Breast Cancer Alliance
Contact information[a]	Name: Dr. Mita Manna

Interested party agreement with the draft recommendation		
1. Does the interested party agree with the committee's recommendation.	Yes	☐
	No	☒

On behalf of the REAL Alliance, we would like to thank the committee for its thorough review and positive direction regarding pertuzumab in the neoadjuvant setting for early stage HER2-positive breast cancer as standard of care in published guidelines, clinical expert input and aligns with patient values.

REAL Alliance clinicians agree with CDA Reimbursement Draft Recommendations:
Table 1 for:

- **Initiation (Items 1.1, 1.2, 1.3)**
- **Discontinuation and Renewal (Items 2.1, 2.2)**
- **Prescribing (Item 3)**

These criteria are aligned with current clinical best practices and reflect patient-centered priorities.

Items to reconsider:
For pricing and its rationale (Table 1, Item 4), we offer an alternative perspective to the conclusion that adding pertuzumab will result in a net increase in overall drug acquisition costs without sufficient Canadian evidence to offset this.

1) The draft recommendation states: *"The reimbursement of pertuzumab is expected to increase overall drug acquisition costs. No recent evidence was identified regarding the cost-effectiveness of pertuzumab relative to relevant comparators. A cost-effective analysis would be needed to determine whether pertuzumab is cost-effective."* In addition, the Clinical and Pharmacoeconomics Combined Report notes: *"No Canadian cost-effectiveness studies published since 2020 were identified based on a literature search conducted on May 12, 2025."*
    - However, in our clinician input letter, the **REAL Alliance provided Canadian real-world evidence from the Montreal Jewish General Hospital (Panet et al. 2023)**. In this study (n=83), neoadjuvant pertuzumab more than doubled pCR rates (67% vs. 27%, p = 0.0016) and achieved cost neutrality ($65,150 CAD for HP vs. $66,116 CAD for trastuzumab alone), primarily due to reduced adjuvant T-DM1 use. This is a clear Canadian example of cost neutrality in practice and directly contrasts with the +$15,125 incremental cost noted in the pharmacoeconomic report. The Jewish General experience directly addresses what

HTA bodies consistently request: Canadian outcomes, Canadian costs, and Canadian delivery settings.

- **International evidence also supports pertuzumab's cost-effectiveness**. An Italian analysis (Zambelli A et al. 2023) demonstrated that higher pCR rates yield downstream savings by reducing adjuvant T-DM1 use and its associated toxicities. These findings align with Canadian real-world data and reinforce that the economic case for pertuzumab is consistent across health systems; not only in Canada.

2) We recognize that FMEC reviewed both pCR- and EFS-based models from the 2022 CADTH analysis, but in both scenarios pertuzumab was ultimately projected as costlier.
   - **We believe this conclusion undervalues the treatment-deescalation impact of pCR,** which FMEC itself acknowledges as clinically meaningful. Achieving pCR spares patients adjuvant T-DM1—a regimen that is more expensive, resource-intensive, and associated with higher toxicity—in favour of less costly trastuzumab (including biosimilars). This is an immediate, patient-relevant, and resource-saving benefit, even before considering mature OS data. Future modeling should explicitly reflect this pathway logic, consistent with how clinicians make treatment decisions in practice.
   - Beyond pCR, **new survival evidence further strengthens the case for pertuzumab**. Five-year outcomes from PEONY now show event-free survival of 84.8% with pertuzumab versus 73.7% with placebo (HR 0.53; 95% CI 0.32–0.89) and disease-free survival of 86.0% versus 75.0% (HR 0.52; 95% CI 0.30–0.88) (Huang L et al. 2024). Given these results, continuing to assume equivalent impact on EFS in economic modeling would be inaccurate and requires updating.

3) We also encourage consideration of the minimal incremental impact on health system resources.
   - **Pharmacy preparation time is negligible**, as pertuzumab is administered in a fixed dose, requires no pre- or post-medications, and can be prepared concurrently with other chemotherapy agents.
   - **Infusion time impact is similarly minimal**, since pertuzumab is delivered alongside standard regimens without the need for additional patient visits. By contrast, adjuvant T-DM1 is weight-based, requires pre-treatment bloodwork before each cycle, and has longer infusion times, creating a more significant operational burden.

In summary, we support the majority of the proposed reimbursement conditions and appreciate the positive stance on pertuzumab funding. We respectfully request that the final recommendation reflect (i) Canadian real-world evidence demonstrating cost neutrality, (ii) the updated survival data now available, and (iii) the minimal incremental operational impact of neoadjuvant pertuzumab. Including these elements will strengthen the final recommendation and provide a more complete, practical picture for provincial decision-makers.

Expert committee consideration of the input

2. Does the recommendation demonstrate that the committee has considered the input that your organization provided?	Yes	☐
	No	☒

While we are generally aligned with the majority of the draft recommendations, our input is only partially reflected in the pricing rationale (Table 1, Item 4).

- **Canadian RWE (Panet et al. 2023):** Montreal Jewish General Hospital data (n=83) showed pertuzumab more than doubled pCR rates (67% vs. 27%) and achieved cost neutrality

($65,150 vs. $66,116) by reducing adjuvant T-DM1 use. This directly contrasts the +$15,125 incremental cost cited in the report.

- **Updated PEONY outcomes (Huang L et al. 2024):** 5-year results confirm improved EFS (84.8% vs. 73.7%, HR 0.53) and DFS (86.0% vs. 75.0%, HR 0.52). Modeling pertuzumab as having no EFS benefit (HR=1) should be adjusted accordingly.
- **International evidence (new, not in our initial submission):** An Italian cost-effectiveness study (Zambelli A et al. 2023) also showed higher pCR rates translate into savings by reducing adjuvant T-DM1. This reinforces that the economic case is consistent across health systems.

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Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐

If not, please provide details regarding the information that requires clarification.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐

If not, please provide details regarding the information that requires clarification.

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒

Yes, the reimbursement conditions are clearly stated, and the rationale for a potential price reduction is transparent. However, the rationale does not fully incorporate evidence that could materially affect provincial budget impact models.

In particular, Canadian real-world data (**Panet et al. 2023**) demonstrate cost neutrality through reduced adjuvant T-DM1 use — a finding not reflected in the draft rationale. A more practical approach for modeling would mirror how treatment is adopted in practice according to the consensus SOC recommendation of the REAL Alliance which reflects Canadian practice patterns (Manna M. et al, 2024). This structure better reflects current Canadian clinical pathways and avoids inflated cost projections:

- 3–6 cycles of PHT in the neoadjuvant setting
- Adjuvant trastuzumab alone for patients achieving pCR
- 12–14 cycles of T-DM1 only for those with residual disease (as in KATHERINE)

In addition, we cannot emphasize enough the treatment-deescalation value of pCR. Achieving pCR spares patients adjuvant T-DM1 — a regimen that is more costly, resource-intensive, and associated with higher toxicity — in favour of less expensive and widely available trastuzumab (including biosimilars). This is an immediate, patient-relevant, and resource-saving benefit that should be explicitly reflected in future modeling.

Finally, we note that other G7 countries have already issued positive HTA opinions and reached successful pricing agreements for neoadjuvant pertuzumab. This shows it is feasible to secure a budget impact model that balances payer requirements with manufacturer negotiations.

[a] CDA-AMC may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- To maintain the objectivity and credibility of the CDA-AMC drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CDA-AMC may contact your group with further questions, as needed.
- Please see the *Procedures for Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please list any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.
  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
3. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☒
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Dr. Jean-Francois Boileau • Dr. Nathaniel Bouganim • Dr. Christine Brezden-Masley • Dr. Jeffrey Cao • Dr. Stephen Chia • Dr. Scott Edwards • Dr. Karen Gelmon • Dr. Nayyer Iqbal • Dr. Anil Abraham Joy • Dr. Kara Laing • Dr. Nathalie Levasseur • Dr. Mita Manna • Dr. Callista Phillips • Dr. Daniel Rayson • Dr. Maged Salem		

- Dr. Sandeep Sehdev
- Dr. Christine Simmons

C. New or Updated Conflict of Interest Declarations

NONE