Regimen Monograph

A - Regimen Name

PERT+TRAS Regimen

Pertuzumab-Trastuzumab

Disease Site

Breast

Intent

Palliative

Regimen Category

Evidence-Informed :

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Rationale and Uses

For the treatment of patients with HER2 positive unresectable locally recurrent or metastatic breast cancer, following taxane chemotherapy/pertuzumab/trastuzumab treatment.

Refer to NDFP eligibility forms for detailed funding information.

Supplementary Public Funding

PERTuzumab
New Drug Funding Program (Pertuzumab with Trastuzumab (Biosimilar) - Unresectable Locally Recurrent or Metastatic Breast Cancer) (NDFP Website) (PDRP (NDFP) funding is contingent on the patient previously receiving chemotherapy.)

trastuzumab
New Drug Funding Program (Pertuzumab with Trastuzumab (Biosimilar) - Unresectable Locally Recurrent or Metastatic Breast Cancer) (NDFP Website)

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B - Drug Regimen

Note: Different trastuzumab products are **NOT INTERCHANGEABLE.**

PERTuzumab	420* mg	IV	Day 1
trastuzumab	6* mg /kg	IV	Day 1

*For treatment delays ≥ to 3 weeks (i.e. ≥ 6 weeks from last dose), re-load with loading dose.

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

Until disease progression or unacceptable toxicity.

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D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal

Other Supportive Care:

Also refer to CCO Antiemetic Recommendations.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Dosage with toxicity

Dose reductions are not recommended for pertuzumab and trastuzumab. Doses are held or discontinued due to toxicity.

If trastuzumab is withheld, pertuzumab should also be withheld. Discontinue pertuzumab if trastuzumab is discontinued.

Toxicity	Recommendation
Hematologic Toxicity	Continue pertuzumab and trastuzumab; Monitor for complications of neutropenia (i.e. infections) and treat appropriately
Severe diarrhea	Start anti-diarrheal treatment. Hold pertuzumab if no improvement; restart pertuzumab when diarrhea is under control.
Pulmonary Toxicity	Discontinue permanently and manage symptoms aggressively with beta-agonists, antihistamines and/or corticosteroids. Do not re-challenge.

Cardiotoxicity:

Dose Recommendations for Left Ventricular Dysfunction:

<table>
<tr><th>LVEF during Treatment</th><th>Action</th><th>LVEF at Re-Assessment</th><th>Action</th></tr>
<tr><td rowspan="2">• Asymptomatic AND
• <40% OR
• 40%–45% with a fall of ≥10% points below pre-treatment value</td><td rowspan="2">Hold trastuzumab and pertuzumab x 3 weeks</td><td>• >45% OR
• 40%–45% with a fall of <10% points below baseline</td><td>Restart trastuzumab and pertuzumab</td></tr>
<tr><td>• <40% OR
• LVEF 40-45% with a fall of ≥10% points below baseline</td><td>Discontinue trastuzumab and pertuzumab</td></tr>
<tr><td>Symptomatic</td><td>Consider discontinuing trastuzumab and pertuzumab</td><td colspan="2">Not applicable</td></tr>
</table>

Management of Infusion-related reactions:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Pertuzumab:

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion. • Manage the symptoms. **Restart:** • No specific recommendations can be made at this time.	• No specific recommendations can be made at this time.
3 or 4	• Stop the infusion. • Aggressively manage symptoms.	• Discontinue permanently (do not re-challenge).

Trastuzumab:

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion rate. • Manage the symptoms. Restart: • Once symptoms have resolved, if IR was not severe, consider resuming the infusion at a slower rate.	• Restart and re-challenge with pre-medications (e.g. H1-receptor antagonist and corticosteroid).
3 or 4	• Stop treatment. • Aggressively manage symptoms.	• Discontinue permanently (do not re-challenge).

Hepatic Impairment

No dosage adjustment is required for trastuzumab. Pertuzumab has not been studied in hepatic impairment.

Renal Impairment

Creatinine Clearance (mL/min)	Pertuzumab	Trastuzumab
≥30	No adjustment required	No adjustment required
<30	No data	

Dosage in the Elderly

No dosage adjustment required. The risk of cardiac dysfunction, diarrhea and myelosuppression may be increased in elderly patients.

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F - Adverse Effects

Refer to PERTuzumab, trastuzumab drug monograph(s) for additional details of adverse effects

The following side effects are a summary of those reported in the drug monographs. Certain side effects may be more common when pertuzumab and trastuzumab are combined with chemotherapy (e.g. myelosuppression, anorexia).

Very common (≥ 50%)	**Common (25-49%)**	**Less common (10-24%)**	**Uncommon (< 10%), but may be severe or life-threatening**
• Diarrhea (may be severe) • Nausea, vomiting	• Fatigue • Mucositis • Myelosuppression +/- infection, bleeding (may be severe) • Rash and pruritus • Dysgeusia	• Anorexia, weight loss • Infusion-related reactions • Cough, dyspnea • Dry skin • Nasopharyngitis • Abdominal pain • Hypertension • Paresthesia	• Cardiotoxicity • Arrhythmia • Arterial/venous thromboembolism • Pancreatitis • Renal failure • Secondary malignancy • Pneumonitis • Tumor lysis syndrome • Hypersensitivity

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G - Interactions

Refer to PERTuzumab, trastuzumab drug monograph(s) for additional details

- Avoid concomitant use of trastuzumab with anthracyclines and other cardiotoxic drugs. Exercise extreme caution with anthracycline-based therapy for up to 28 weeks after stopping trastuzumab.

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H - Drug Administration and Special Precautions

Refer to pertuzumab, trastuzumab drug monograph(s) for additional details.

Administration

Pertuzumab

- Do not administer as an intravenous push or bolus.
- Give loading dose IV over 60 minutes; maintenance dose should be given IV over 30-60 minutes.
- Monitor for infusion reactions for 60 minutes following the initial pertuzumab infusion and for 30 minutes following subsequent infusions.
- Dilute required dose in 250 mL Normal Saline.
- Do not use D5W for dilution since pertuzumab is chemically and physically unstable in this solution. Do not admix with other drugs.
- Avoid shaking the solution in order to avoid foaming.
- Compatible with PVC, polyethylene or non-PVC polyolefin bags.
- Refrigerate unopened vials at 2-8°C; protect from light.

Trastuzumab

NOTE: Different trastuzumab products (Herceptin®, and trastuzumab biosimilars), and trastuzumab antibody-drug conjugates (e.g., Enhertu™ trastuzumab deruxtecan, Kadcyla® trastuzumab emtansine), are **not interchangeable**.

- Do not administer as an intravenous push or bolus.
- Mix in 250 mL bag NS. Do not use D5W as it causes protein aggregation. Do not shake.
- Administer loading dose over 90 minutes. Observe during the infusion and for at least 90 minutes after the infusion.
- If no previous IR, subsequent infusions may be administered over 30 minutes. Observe patients during the infusions and for at least 30 minutes after the infusions.
- Should not be mixed or diluted with other drugs.
- Compatible with polyvinylchloride, polyethylene or polypropylene bags
- Diluent supplied - Bacteriostatic Water for Injection (BWFI) - contains benzyl alcohol 1.1%; if patient is hypersensitive to benzyl alcohol, may reconstitute with Sterile Water for Injection, but must be used immediately and discard unused portion.

- Solution reconstituted with the supplied BWFI is stable up to 28 days refrigerated.
- Do not freeze the reconstituted solution.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Contraindications

- Patients with known hypersensitivity to trastuzumab, pertuzumab, Chinese Hamster Ovary (CHO) cell proteins, or any components of these products.

Other Warnings/Precautions

- Trastuzumab and pertuzumab should only be used in patients whose tumours overexpress HER2.
- Exercise extreme caution with pertuzumab in the following patient groups as they have not been studied in clinical trials: Pre-treatment LVEF value of ≤ 50%; a prior history of CHF; decreases in LVEF to <50% during prior trastuzumab adjuvant therapy; conditions that could impair left ventricular function such as uncontrolled hypertension, recent myocardial infarction, serious cardiac arrhythmia requiring treatment or a cumulative prior anthracycline exposure to > 360mg/m^2 of doxorubicin or its equivalent.
- The risk of cardiotoxicity must be weighed against the potential benefits of treatment with trastuzumab, especially in older patients and patients who have had prior cardiotoxic therapy. Use extreme caution in patients with pre-existing cardiac dysfunction (including LVEF < 55% in early breast cancer). Note: in the adjuvant trials, patients with cardiac risk factors were excluded from the trials.
- Exercise caution with trastuzumab in patients with pre-existing pulmonary disease, patients with extensive pulmonary tumour involvement or patients with previous chemo or radiation therapies known to be associated with pulmonary toxicities, as they may experience more severe lung toxicities.
- Patients with dyspnea at rest due to advanced malignancy complications and comorbidities should not treated with trastuzumab, as they may be at increased risk of a fatal infusion reaction or pulmonary events.
- Consider appropriate management of patients with uncontrolled hypertension or history of hypertension before starting trastuzumab.
- Life-threatening infusion-related reactions associated with the administration of trastuzumab or pertuzumab may occur.

Pregnancy/Lactation

- Pertuzumab and trastuzumab are not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **7 months** after the last dose.
- Monitor for oligohydramnios in patients who become pregnant during pertuzumab and trastuzumab therapy. Perform appropriate fetal testing if oligohydramnios occurs.
- Breastfeeding is not recommended.
- Fertility Effects:
    - Pertuzumab and trastuzumab: Unknown

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

- Cardiac assessment, including evaluation of left ventricular function (Echocardiogram or MUGA scan); baseline, q3 months during treatment, then q6 months after trastuzumab and pertuzumab discontinuation x2 years, or longer if continued LVEF decrease, also as clinically indicated (more frequent with asymptomatic reductions in LVEF)
- CBC; as clinically indicated
- Clinical toxicity assessment for infection, bleeding, neurotoxicity, hypersensitivity, fatigue, cutaneous reactions, cardiovascular, GI or respiratory effects; at each visit or as clinically indicated
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- Liver function tests; baseline and as clinically indicated

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J - Administrative Information

Approximate Patient Visit	1.5 hours
Pharmacy Workload (average time per visit)	25.251 minutes
Nursing Workload (average time per visit)	72.500 minutes

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K - References

Bachelot T, Ciruelos E, Schneeweiss A, et al. Preliminary safety and efficacy of first-line pertuzumab combined with trastuzumab and taxane therapy for HER2-positive locally recurrent or metastatic breast cancer (PERUSE). Ann Oncol 2019;30(5):766-773.

Baselga J, Cortés J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012;366(2):109-19.

Swain SM, Kim SB, Cortés J, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol 2013;14(6):461-71.

Pertuzumab and trastuzumab drug monographs, Cancer Care Ontario.

September 2022 Modified statement on non-interchangeability of trastuzumab products; updated NDFP form

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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