Regimen Monograph

A - Regimen Name

PACL+PERT+TRAS Regimen

Paclitaxel-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

- Treatment of patients with HER2 positive (IHC3+ or FISH/SISH ≥ 2) unresectable locally recurrent or metastatic breast cancer with an ECOG status of 0 or 1, LVEF 50% or more at baseline and who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.
- Prior anti-HER2 adjuvant therapy permissible providing relapse free interval ≥ 6 months.

Supplementary Public Funding

PERTuzumab
New Drug Funding Program (Pertuzumab with Trastuzumab (Biosimilar) - Unresectable Locally Recurrent or Metastatic Breast Cancer) (NDFP Website) (Also Refer to this form for trastuzumab NDFP funding criteria.)

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.**

Cycle 1 - Trastuzumab and Pertuzumab Loading Dose:

PERTuzumab†, 1, 2	840 mg	IV over 60 minutes	Day 1
trastuzumab†, 1, 2	8 mg /kg	IV over 90 minutes	Day 1
then,			
PACLitaxel1, 2	175 mg /m²	IV over 3 hours	Day 1

Cycle 2 and Onwards - Trastuzumab and Pertuzumab Maintenance Dose (Q3W):

PERTuzumab1, 2, 3, 4	420 mg	IV over 30* to 60 minutes	Day 1
(* if previous 60-minute infusion well-tolerated)			
trastuzumab1, 2, 3, 4	6 mg /kg	IV over 30** minutes	Day 1
**(if previous 90-minute infusion well-tolerated)			
then,			
PACLitaxel1, 2	175 mg /m²	IV over 3 hours	Day 1

† LVEF must be ≥ 50% before starting treatment

(1) In the CLEOPATRA trial, pertuzumab was given on day 1, followed by trastuzumab and the taxane [docetaxel] on day 2 . From cycle 2 and onwards, pertuzumab, trastuzumab and the taxane were

given on day 1, if all 3 medications were tolerated in cycle 1

(2)Based on the product monograph, pertuzumab and trastuzumab may be administered in any order; however, the taxane should be given after pertuzumab and trastuzumab.

(3) If delayed by ≥ 3 weeks (i.e. ≥ 6 weeks from last dose), re-load with loading dose.

(4) Discontinue pertuzumab if trastuzumab is discontinued. May continue trastuzumab and pertuzumab after PACLitaxel discontinued, in the absence of disease progression.

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

Until disease progression or unacceptable toxicity. If the taxane is discontinued (e.g., after 6-8 cycles or due to unmanageable toxicity), may continue treatment with PERT+TRAS if there is no evidence of disease progression

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D - Premedication and Supportive Measures

Antiemetic Regimen: Low

Other Supportive Care:

Also refer to CCO Antiemetic Recommendations.

Pre-medications for PACLitaxel (prophylaxis for infusion reaction):*:

- Dexamethasone 20 mg PO 12-and 6-hours OR Dexamethasone 20 mg IV 30 minutes pre-infusion†
- Diphenhydramine 25-50 mg IV/PO 30-60 minutes pre-infusion
- Ranitidine 50 mg IV OR Famotidine 20 mg IV 30-60 minutes pre-infusion

*Consider discontinuing pre-medications for PACLitaxel if there was no IR in the first 2 doses.

†Oral and IV dexamethasone are both effective at reducing overall IR rates. Some evidence suggests that oral dexamethasone may be more effective for reducing severe reactions; however, adverse effects and compliance remain a concern.

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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

Pertuzumab and Trastuzumab Dose Levels:

- 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.

PACLitaxel Dose Levels:

Dose Level	Paclitaxel Dose
0	175 mg/m²
-1	135 mg/m²
-2	110 mg/m²

Do not re-escalate the dose after a dose reduction.

Pertuzumab and Trastuzumab:

Cardiotoxicity:

Dose Recommendations for Left Ventricular Dysfunction:

LVEF during Treatment	Action	LVEF at Re-Assessment	Action
• Asymptomatic AND • <40% OR • 40%–45% with a fall of ≥10% points below pre-treatment value	Hold trastuzumab and pertuzumab x 3 weeks	• >45% OR • 40%–45% with a fall of <10% points below baseline	Restart trastuzumab and pertuzumab
		• <40% OR • LVEF 40-45% with a fall of ≥10% points below baseline	Discontinue trastuzumab and pertuzumab

Symptomatic	Consider discontinuing trastuzumab and pertuzumab	Not applicable

Other Toxicity:

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.

PACLitaxel:

Worst toxicity in previous cycle	Dose of paclitaxel
Febrile neutropenia Grade 4 ANC ≥ 5-7 days Grade 4 thrombocytopenia	↓ 1 dose level*
Grade 3 neurotoxicity or other toxicity	↓ 1 dose level*
Grade 4 neurotoxicity or other toxicity, any grade cystoid macular edema	Discontinue
*Patients should not be retreated with paclitaxel until neutrophils ≥ 1.5 x 10^9/L (≥ 1.0 x 10^9/L in AIDS-related Kaposi's sarcoma) and platelet counts ≥ 100 x 10^9/L and other toxicity has recovered to ≤ grade 2	

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).

PACLitaxel:

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion rate. • Manage the symptoms. Restart: • After symptom resolution, restart with pre-medications ± reduced infusion rate.	• Consider re-challenge with pre-medications and at a reduced infusion rate. • After 2 subsequent IRs, consider replacing with a different taxane. Give intensified pre-medications and reduce the infusion rate. • May consider adding oral montelukast ± oral acetylsalicylic acid.
3 or 4	• Stop treatment. • Aggressively manage symptoms.	• Re-challenge is discouraged, especially if vital signs have been affected. • Consider desensitization if therapy is necessary. • There is insufficient evidence to recommend substitution with another taxane at re-challenge. • High cross-reactivity rates have been reported.

Hepatic Impairment

Patients with hepatic impairment may be at risk of PACLitaxel toxicity, especially severe myelosuppression.
Suggested dose modifications:

Bilirubin		AST/ALT	PACLitaxel (% usual dose)	Pertuzumab	Trastuzumab
≤1.25 x ULN	And	2-10 x ULN	75%	No data	No adjustment required
1.26 to 2.5 x ULN	And	<10x ULN	40%		
2.6 to 4 x ULN	And	<10x ULN	25%		
>4 x ULN	And/Or	≥10 x ULN	Consider risk-benefit or Omit		

Renal Impairment

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

Dosage in the Elderly

No dose adjustment required. Patients ≥65 years of age have a higher risk of diarrhea with pertuzumab and severe toxicity with paclitaxel. The risk of cardiac dysfunction and myelosuppression may be increased in elderly patients on trastuzumab.

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F - Adverse Effects

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

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Alopecia • Diarrhea (may be severe) • Neuropathy (may be severe)	• Fatigue • Nausea, vomiting • Hypersensitivity (may be severe) • Mucositis • Myelosuppression ± infection, bleeding (may be severe) • Rash, pruritus (may be severe) • Mucositis	• Anorexia, weight loss • Musculoskeletal pain • Infusion related reaction • Cough, dyspnea (may be severe) • ↑ LFTs (may be severe) • ECG changes	• Cardiotoxicity • Arrhythmia • Arterial thromboembolism • Venous thromboembolism • GI obstruction, perforation • Pancreatitis • Secondary malignancy • Renal failure

	• Dysgeusia	• Dry skin • Nasopharyngitis • Abdominal pain • Hypertension • Hypotension	• Cystoid macular edema • Pneumonitis • Radiation recall • Injection site reactions • Typhlitis • Encephalopathy • Seizure • Tumour lysis syndrome

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G - Interactions

Refer to pertuzumab, trastuzumab, PACLitaxel 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, PACLitaxel 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.

PACLitaxel

- To minimize patients' exposure to DEHP leaching from PVC bags or sets, use polyolefin or polypropylene infusion bags and polyethylene-lined administration sets (with a 0.22 micron in-line filter).
- Dilute in 500-1000 mL Normal Saline or 5% Dextrose, in a final concentration of 0.3-1.2 mg/mL and infuse over 3 hours.

- Extended infusion of paclitaxel is not recommended as primary prophylaxis to reduce paclitaxel IRs.
- Excessive shaking, agitation, or vibration may induce precipitation and should be avoided
- Precipitation may rarely occur with infusions longer than 3 hours.

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

Contraindications

- Patients with known hypersensitivity reactions to trastuzumab, pertuzumab, Chinese Hamster Ovary (CHO) cell proteins, or any components of these drugs.
- Patients with a history of severe hypersensitivity reactions to PACLitaxel or other drugs formulated in Cremophor EL (polyethoxylated castor oil).
- Patients with severe baseline neutropenia (<1.5 x 10^9/L), with PACLitaxel

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 with 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, pertuzumab or paclitaxel may occur.
- PACLitaxel contains ethanol, and is administered with agents such as antihistamines which cause drowsiness. Patients should be cautioned regarding driving and the use of machinery.
- Benzyl alcohol (a preservative in BWFI for trastuzumab) has been associated with toxicity in neonates and children up to 3 years old.

Pregnancy/Lactation

- PACL+PERT+TRAS is 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
  - PACLitaxel: Yes

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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

- CBC, baseline and before each cycle
- Liver and renal function tests; baseline and before each cycle
- 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)
- Blood pressure and pulse; per usual institutional protocol; also during infusion (more

frequently during the first hour of PACLitaxel)

- Ophthalmology if visual impairment; as clinically indicated
- Continuous cardiac rhythm monitoring in patients who developed serious conduction abnormalities; during subsequent infusions of PACLitaxel
- Clinical toxicity assessment of infection, bleeding, neurotoxicity, fluid retention, hypersensitivity, fatigue, cutaneous reactions, thromboembolism, cardiovascular, musculoskeletal pain, GI or respiratory effects; at each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Administrative Information

Approximate Patient Visit	First cycle: 1.5 hours (day 1), 5.5 hours (day 2); Subsequent cycles: 5 hours
Pharmacy Workload (average time per visit)	33.414 minutes
Nursing Workload (average time per visit)	94.167 minutes

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K - References

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Datko F, D'Andrea G, Dickler M, et al. HER2-Targeted Therapy Phase II study of pertuzumab, trastuzumab, and weekly paclitaxel in patients with metastatic HER2-overexpressing metastatic breast cancer. Cancer Res 2012;72(24 Suppl):Abstract P5-18-20.

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Swain SM, Ewer MS, Cortés J, et al. Cardiac tolerability of pertuzumab plus trastuzumab plus docetaxel in patients with HER2-positive metastatic breast cancer in CLEOPATRA: a randomized, double-blind, placebo-controlled phase III study. Oncologist 2013;18(3):257-64.

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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.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

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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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