Regimen Monograph

A - Regimen Name

DOCE+PERT+TRAS Regimen

DOCEtaxel-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)

back to top

B - Drug Regimen

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

Cycle 1 - Pertuzumab and Trastuzumab Loading Dose:

PERTuzumab^, 1, 2	840 mg	IV over 60 min	Day 1
trastuzumab^, 1, 2	8 mg /kg	IV over 90 min	Day 1

Then,

DOCEtaxel1, 2	75 mg /m²	IV	Day 1

Cycle 2 and Onwards - Pertuzumab and Trastuzumab Maintenance Dose:

PERTuzumab1, 2, 3, 4	420 mg	IV over 30* to 60 min	Day 1

(* if previous 60-minute infusion well-tolerated)

trastuzumab1, 2, 3, 4	6 mg /kg	IV over 30** min	Day 1

(**if previous 90-minute infusion well-tolerated)

Then,

DOCEtaxel†, 1, 2	75 to 100 mg /m²	IV	Day 1

^LVEF must be ≥ 50% before starting treatment.

[1] In the CLEOPATRA trial, pertuzumab was given on day 1, followed by trastuzumab and DOCEtaxel on day 2 . From cycle 2 and onwards, all drugs were given on day 1 if tolerated.

[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 DOCEtaxel discontinued, in the absence of disease progression.

† May consider dose escalation to 100mg/m^2 if the patient tolerated at least one cycle of 75 mg/m^2 without the following events: febrile neutropenia, grade 4 neutropenia for > 5 days, any ANC of < 0.1 x 10^9/L for >1 day , or other ≥grade 3 non-hematologic toxicities.

back to top

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

back to top

D - Premedication and Supportive Measures

Antiemetic Regimen: Low

Other Supportive Care:

Pre-medications for DOCEtaxel (prophylaxis for infusion reaction):

- Dexamethasone* 8 mg PO BID for 3 days, starting 1-day pre-infusion†

*Do not discontinue dexamethasone, even in the absence of an IR, due to the benefits on other adverse effects (e.g. pain and edema).

† Dexamethasone 10-20 mg IV can be given if patient forgot to take oral doses.

Also refer to CCO Antiemetic Recommendations.

back to top

E - Dose Modifications

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

Dosage with toxicity

Trastuzumab and Pertuzumab Dose Levels:

- Dose reductions are not recommended for trastuzumab and pertuzumab. Doses are held or discontinued due to toxicity.
- If trastuzumab is withheld, pertuzumab should also be withheld. Discontinue pertuzumab if trastuzumab is discontinued.

DOCEtaxel Dose Levels:

Dose Level	DOCEtaxel Dose
1	100mg/m2
0	75 mg/m2
-1	55 mg/m2

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	Discontinue trastuzumab and pertuzumab

		baseline	
Symptomatic	Consider discontinuing trastuzumab and pertuzumab	Not applicable	

Other Toxicity:

Toxicity	Recommendation
Hematologic toxicities	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.

DOCEtaxel:

Toxicity (worst in previous cycle)	DOCEtaxel Dose Modification*
Febrile neutropenia / Grade 4 ANC ≥ 7 days	↓ 1 dose level (or G-CSF)
Grade 3 skin/ neuro/ major organ/ non-hematologic toxicity	↓ 1 dose level
Any occurrence of cystoid macular edema	Hold and investigate; refer patient promptly an ophthalmic examination. Discontinue if confirmed
Grade 4 skin/ neuro/ major organ/ non-hematologic toxicity OR Recurrence of Grade 3 toxicity after prior dose reduction	Discontinue
* Do not retreat until ANC ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L, and non-hematologic/organ toxicity ≤ 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).

DOCEtaxel:

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, replace 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

Bilirubin		AST and/or ALT		Alkaline Phosphatase	DOCEtaxel dose	Trastuzumab dose	Pertuzumab dose
> ULN	AND	Any	AND	Any	Do not treat. Discontinue if treatment already started.	No adjustment required	No data
Any	AND	> 1.5 X ULN	AND	> 2.5 x ULN			

Renal Impairment

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

Dosage in the Elderly

For pertuzumab and trastuzumab, no dose adjustment required; the risk of cardiac dysfunction, diarrhea and myelosuppression may be increased in elderly patients. The reported trials did not determine differences in efficacy between patients > 65 years versus younger patients.

For DOCEtaxel, no adjustment required, but caution should be exercised in elderly patients with poor performance status.

back to top

F - Adverse Effects

Refer to pertuzumab, trastuzumab, DOCEtaxel 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 • Myelosuppression ± infection, bleeding (may be severe) • Diarrhea (may be severe; especially	• Nausea, vomiting • Neuropathy (may be severe) • Rash, pruritus(may be	• Anorexia, weight loss • Musculoskeletal pain • Hypersensitivity (may be severe) • Infusion-related	• Cardiotoxicity • Arrhythmia • Arterial/venous thromboembolism • GI obstruction/ perforation • Radiation/injection

with neutropenia) • Fatigue	severe) • Fluid retention (may be severe) • Mucositis • Nail disorder (may be severe) • Dysgeusia	reactions • Cough, dyspnea • Dry skin • Nasopharyngitis • Abdominal pain • Hypertension	site recall reaction • ↑ LFTs • Pancreatitis • Renal failure • Cystoid macular edema • Tear duct obstruction • Secondary malignancy • Tumour lysis syndrome • Seizure • Pneumonitis/Adult Respiratory Distress Syndrome (ARDS) • Disseminated intravascular coagulation (DIC)

back to top

G - Interactions

Refer to pertuzumab, trastuzumab, DOCEtaxel 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.
- Avoid use of DOCEtaxel with CYP3A4 inhibitors. If must use together, consider reducing DOCEtaxel dose (50% for strong inhibitors).
- Avoid use of dronedarone with DOCEtaxel given increased risk of toxicity.

back to top

H - Drug Administration and Special Precautions

Refer to pertuzumab, trastuzumab, DOCEtaxel 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.

DOCEtaxel

- Refer to the respective product monographs for preparation and storage instructions. Mix in 250mL D5W or NS to a maximum concentration of 0.3-0.74 mg/mL. For doses over 200 mg, use a larger volume of the infusion vehicle so the maximum concentration is not exceeded.
- Infuse through main IV line over 1 hour.
- To minimize patients' exposure to DEHP leaching from PVC bags or sets, use polyolefin or polypropylene infusion bags and polyethylene-lined administration sets.
- To minimize hypersensitivity reactions, DOCEtaxel infusion should be started at a slow rate, then increased incrementally to planned rate.
- Monitor patient for signs of alcohol intoxication (due to alcohol content in formulation) during and after the infusion.
- Injection site recall reactions (recurrence of skin reaction at a previous extravasation site after DOCEtaxel is administered at a different site) have been observed.

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 drugs.
- Patients who have a history of severe hypersensitivity reactions to DOCEtaxel or to other drugs formulated with polysorbate 80 or polyethylene glycol 300.
- Patients with neutrophil counts of <1.5 x 10^9/L or with severe liver impairment, with DOCEtaxel

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 trastuzumab treatment, 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 or pertuzumab may occur.
- Use DOCEtaxel with caution in patients with pre-existing effusions or ascites.
- Use DOCEtaxel with caution in patients who have hypersensitivity to paclitaxel.
- Use DOCEtaxel with caution in patients with bilirubin < ULN, or AST and/or ALT < 1.5 x ULN and ALP > 2.5 x ULN, or ANC < 1.5 x 10^9/L
- DOCEtaxel contains ethanol and may cause drowsiness. Patients should be cautioned regarding driving and the use of machinery immediately after receiving the infusion. Ethanol may be harmful to patients at risk of adverse effects such as those with alcoholism, liver disease, epilepsy and children. Cases of alcohol intoxication have been reported.
- Benzyl alcohol (a preservative in BWFI for trastuzumab) has been associated with toxicity in neonates and children up to 3 years old.

Pregnancy & lactation:

- DOCE+PERT+TRAS is **contraindicated** 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 or trastuzumab therapy. Perform appropriate fetal testing if oligohydramnios occurs.
- Breastfeeding is **contraindicated**.
- Fertility Effects:
  - Pertuzumab and trastuzumab: Unknown
  - DOCEtaxel: Probable

back to top

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, including nadir counts; 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)
- Liver function tests; baseline and before each cycle
- Clinical toxicity assessment of infection, bleeding, neurotoxicity, fluid retention, hypersensitivity, fatigue, cutaneous reactions, thromboembolism, cardiovascular, musculoskeletal pain, ophthalmic, GI or respiratory effects; at each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

back to top

J - Administrative Information

Approximate Patient Visit	First cycle: 1.5 hours (day 1), 3 hours (day 2); Subsequent cycles: 2.5 - 4 hours

Pharmacy Workload (average time per visit)	38.687 minutes
Nursing Workload (average time per visit)	94.167 minutes

back to top

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.

Bachelot T, Ciruelos E, Peretz-Yablonski T, et al. A single-arm phase IIIb study of pertuzumab and trastuzumab with a taxane as first-line therapy for patients with HER2-positive advanced breast cancer (PERUSE). Cancer Research 2012; 72(24 Suppl 3):OT1-1-02.

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.

Docetaxel, pertuzumab, trastuzumab drug monographs, Cancer Care Ontario.

Miles D, Ciruelos E, Schneeweiss A, et al. Final results from the PERUSE study of first-line pertuzumab plus trastuzumab plus a taxane for HER2-positive locally recurrent or metastatic breast cancer, with a multivariable approach to guide prognostication. Ann Oncol. 2021 Oct;32(10):1245-55.

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.

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.

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

back to top

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.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

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.

While care has been taken in the preparation of the information contained in the Formulary, 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.

CCO and the Formulary's content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person's use of the information in the Formulary.

back to top