Regimen Monograph

A - Regimen Name

NPAC(W)+PERT+TRAS Regimen

Nab-Paclitaxel (weekly)-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)

nab-PACLitaxel
New Drug Funding Program (Nab-Paclitaxel - Metastatic Breast Cancer) (NDFP Website) (Publicly funded under specific conditions)

back to top

B - Drug Regimen

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

Do not substitute nab-PACLitaxel for or with other paclitaxel formulations.

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,

nab-PACLitaxel1, 2	100-150 mg /m²	IV over 30 minutes	Days 1, 8

(Publicly funded under specific conditions, see PDRP (NDFP) eligibility forms)

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 min infusion well-tolerated)

then,

nab-PACLitaxel1, 2	100-150 mg /m²	IV over 30 minutes	Days 1, 8

(Publicly funded under specific conditions, see PDRP (NDFP) eligibility forms)

† 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, reload with loading doses.

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

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:

Also refer to CCO Antiemetic Recommendations.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

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 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.

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>

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.

Nab-paclitaxel:

Worst Toxicity / Counts (x 10^9/L)	Nab-paclitaxel (% of previous dose)
ANC < 0.5 ≥ 7 days OR febrile neutropenia OR Delay of next cycle due to persistent neutropenia (ANC < 1.5)	Hold*†^, then 80%
Grade 3 or 4 thrombocytopenia or bleeding	Hold*†^, then 80%. Discontinue if recurs.
Grade 2 or 3 cutaneous toxicity	Hold*†^, then 80%
Grade 3 mucositis or diarrhea	Hold*†^, then 80%
Grade 3 or 4 sensory neuropathy	Hold*†^, then 80%
Other grade 3 related organ/non-hematologic toxicity (except nausea/ vomiting /alopecia)	Hold*†^, then 80%

Other grade 4 related organ/non-hematologic toxicity OR Severe hypersensitivity OR Any cystoid macular edema	Discontinue
Pneumonitis	Hold and investigate; discontinue if confirmed

*On day 1 of each cycle do not treat until ANC ≥ 1.5 x 10^9/L and platelets ≥ 100 x 10^9/L. On days 8 and 15, do not treat until ANC ≥ 1 x 10^9/L and platelets ≥ 75 x 10^9/L.

†Do not treat until non-hematologic toxicity ≤ grade 2 (or ≤grade 1 for mucositis, diarrhea, neuropathy or cutaneous toxicity).

^Discontinue treatment if there is a third occurrence of toxicity that would require dose reduction.

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

Patients with hepatic impairment may be at increased risk of myelosuppression from nab-paclitaxel and should be closely monitored.

Suggested dose modifications:

Bilirubin		AST	Nab-paclitaxel* (% previous dose)	Pertuzumab	Trastuzumab
>1 to ≤ 1.5 x ULN	and	≤ 10 x ULN	100%	No data	No adjustment required
>1.5 to ≤ 5 x ULN	and	≤ 10 x ULN	↓ to 80%**		
> 5 x ULN	or	> 10 x ULN	Discontinue		

*Based on clinical judgment – less conservative adjustments can be considered if hepatic changes are secondary to metastases rather than hepatic cirrhosis or hepatitis. Patients with elevated baseline bilirubin were excluded from clinical trials.

**Reduced dose may be escalated to 100% if treatment is tolerated for at least 2 cycles at the reduced dose.

Renal Impairment

Creatinine Clearance (mL/min)	Trastuzumab	Pertuzumab	Nab-paclitaxel* (% previous dose - suggested)
≥ 30 to < 90	No adjustment required	100%	100%
< 30		No data	Discontinue

*Based on clinical judgment. Patients with elevated baseline creatinine were excluded from clinical trials

Dosage in the Elderly

No dose adjustment required for pertuzumab or trastuzumab. The risk of cardiac dysfunction, diarrhea and myelosuppression may be increased in elderly patients.

No dose adjustment is required for nab-paclitaxel. Patients age 65 years or older may have higher incidence of neutropenia in cycle 1. Patients aged 65 and older who received nab-paclitaxel monotherapy for metastatic breast cancer had a higher incidence of epistaxis, diarrhea, dehydration, fatigue and peripheral edema.

back to top

F - Adverse Effects

Refer to pertuzumab, trastuzumab, nab-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) • Sensory neuropathy (may be severe) • Nausea, vomiting	• Fatigue • Musculoskeletal pain • ↑ LFTs (may be severe) • ECG changes • Myelosuppression ± infection, bleeding (may be severe) • Rash, pruritus (may be severe) • Dysgeusia	• Anorexia, weight loss • Constipation • Infusion related reaction • Mucositis • Cough, dyspnea (may be severe) • Nasopharyngitis • Abdominal pain • Creatinine increased (may be severe) • Hypertension • Edema	• Cardiotoxicity • Arrhythmia • Arterial/Venous thromboembolism • Autonomic neuropathy • Hemolytic uremic syndrome, TTP • GI obstruction, perforation • Renal failure • Pancreatitis • Pneumonitis • Secondary malignancy • Tumour lysis syndrome • Hypersensitivity • Injection site reaction • Keratitis, cystoid macular edema

back to top

G - Interactions

Refer to pertuzumab, trastuzumab, nab-PACLitaxel drug monograph(s) for additional details

- Avoid concomitant use with anthracyclines or other cardiotoxic drugs. Exercise extreme caution with anthracyclines up to 28 weeks after stopping trastuzumab.

back to top

H - Drug Administration and Special Precautions

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

Do not substitute nab-PACLitaxel for or with other paclitaxel formulations.

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.

Nab-paclitaxel

- Refer to the product monograph for full instructions on reconstitution.
- The reconstituted suspension should be milky and homogenous without visible particulates.
- Avoid shaking drug suspension in order to minimize foaming.
- No further dilution is required after reconstitution. Transfer reconstituted drug to an empty, sterile IV PVC or non-PVC infusion bag.
- Infuse intravenously over 30 minutes. Slower infusion rates may increase the likelihood of infusion-related reactions.
- DEHP-free containers or administration sets may be used but are not required.
- Do not admix with other drugs.
- Use of syringes and IV bags containing silicone oil as lubricant may cause formation of proteinaceous strands. If strands are observed by visual inspection of IV bag, administer reconstituted suspension through filter of at least 15 µm pore size. If this is not possible, discard the product.
- Store unopened vials at room temperature (20-25°C) in original package to protect from light.

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, nab-paclitaxel, Chinese Hamster Ovary (CHO) cell proteins, or any components of these products.
- Patients with baseline ANC of < 1.5 x 10^9/L on day 1 of each treatment cycle

Other Warning/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.
- Do not administer nab-paclitaxel to patients with platelets < 100 x 10^9/L.
- The use of nab-paclitaxel in patients exhibiting hypersensitivity to paclitaxel or human albumin has not been studied.
- The use of albumin-containing solutions and nab-paclitaxel is associated with a remote risk of viral transmission, including CJD.
- Radiation recall and pneumonitis have been reported in patients treated with nab-paclitaxel and concurrent radiotherapy.
- Nab-paclitaxel is not recommended for use in patients with a history of interstitial lung disease, multiple allergies, progressive dyspnea or unproductive cough.
- Caution is recommended prior to driving or operating machinery if fatigue, weakness or dizziness are present, with nab-paclitaxel

Pregnancy/Lactation

- This regimen is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners while on treatment and after the last treatment dose. Recommended methods and duration of contraception may differ depending on the treatment. Refer to the drug monograph(s) for more information.
- Breastfeeding is not recommended during this treatment and after the last treatment dose. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).
- Fertility Effects:
  - Pertuzumab and trastuzumab: Unknown
  - Nab-paclitaxel: 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.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

- CBC; baseline and before each treatment day
- Liver function tests; baseline and before each cycle
- Renal function tests; baseline and as clinically indicated
- 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)
- Clinical toxicity assessment for infection, bleeding, neurotoxicity, hypersensitivity, fatigue, cutaneous reactions, musculoskeletal pain, cardiovascular, thromboembolism, local reactions, ophthalmic, GI or respiratory effects; at each visit

- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- ECG; As clinically indicated for patients at risk of arrhythmia

back to top

J - Administrative Information

Approximate Patient Visit	1.5 to 2 hours (day 1; cycle 2 and onwards); 1 hour (nab-paclitaxel only days)
Pharmacy Workload (average time per visit)	37.846 minutes
Nursing Workload (average time per visit)	50.833 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 TD, Ciruelos E, Peretz-Yablonski T, et al. First-line pertuzumab (P), trastuzumab (H), and taxane therapy for HER2-positive locally recurrent/metastatic breast cancer: Interim safety results from PERUSE. J Clin Oncol 2014;32:5s:548 (abstract).

Bachelot TD, 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 supp):OT1-1-02 (abstract).

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.

Nab-paclitaxel, pertuzumab and trastuzumab drug monographs, Cancer Care Ontario.

November 2023 Modified Pregnancy/breastfeeding section

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