

Regimen Monograph

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A - Regimen Name

TRAS Regimen

Trastuzumab

Disease Site Breast

Intent Adjuvant

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 breast cancer patients who are node-positive or high-risk node-negative and HER2 positive, who have received adjuvant or neoadjuvant chemotherapy.

Supplementary Public Funding [trastuzumab](#)
 New Drug Funding Program (Trastuzumab (Biosimilar) - Adjuvant Treatment for Breast Cancer) ([NDFP Website](#)) (PDRP (NDFP) funding is contingent on the patient previously receiving chemotherapy.)

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B - Drug Regimen

Note: Different trastuzumab products are **not interchangeable**.

LOADING DOSE (cycle 1):

[trastuzumab](#)^{1, 2} 8 mg /kg IV over 90 min Day 1

MAINTENANCE DOSE (starting cycle 2):

[trastuzumab](#)^{1, 2} 6 mg /kg IV over 30 min* Day 1

*If loading dose was well-tolerated

¹May be administered sequentially (all chemotherapy regimens) or concurrently (non-anthracycline containing regimens only; for regimens such as FEC-D or AC-paclitaxel, may be given concurrently only with the non-anthracycline cycles)

²In general, the dose of trastuzumab should be delayed if the chemotherapy cycle is delayed for scheduling convenience.

If the delay is ≤ 1 week, the usual maintenance dose should be administered.

If the delay is > 1 week, the product monograph recommends that the loading dose should be repeated.

For q3w dosing, consider repeating the loading dose for treatment delays ≥ 3 weeks (i.e. ≥ 6 weeks from last dose). [Breast Disease Site Group consensus]

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

For a usual treatment duration of one year unless limited by cardiotoxicity risk (may be funded for up to 18 treatments over a maximum period of 14 months)

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D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal

Febrile Neutropenia Risk: Low

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

Dosage with Myelosuppression: No adjustment required

Dosage with Cardiotoxicity:

Product Monograph recommendations

- Trastuzumab should be held with a fall in LVEF (product monograph suggests if LVEF falls ≥ 10 points from baseline and/or if LVEF falls to $< 50\%$). Repeat LVEF in 3 weeks and consider discontinuing. Discontinue if clinically significant cardiac dysfunction or cardiac failure develops.

Canadian Consensus Guidelines

- Discontinue if symptomatic.

Management of trastuzumab therapy in adjuvant breast cancer patients with asymptomatic decreases in LVEF (Mackey et al 2008):

Relationship of LVEF to Lower Limit of Normal (LLN)	Trastuzumab dose modification based on asymptomatic LVEF decrease from baseline		
	≤ 10 percentage points	10-15 percentage points	≥ 15 percentage points
Within facility's normal limits	Continue	Continue	Hold and repeat MUGA/ECHO after 4

			weeks
1-5% below LLN	Continue ¹	Hold and repeat MUGA/ECHO after 4 weeks ^{1, 2}	Hold and repeat MUGA/ECHO after 4 weeks ^{2, 3}
≥ 6% below LLN	Continue and repeat MUGA/ECHO after 4 weeks ³	Hold and repeat MUGA/ECHO after 4 weeks ^{2, 3}	Hold and repeat MUGA/ECHO after 4 weeks ^{2,3}

¹ Consider cardiac assessment and starting ACEI therapy

² After 2 holds, consider permanent trastuzumab discontinuation

³ Start ACEI therapy and refer to cardiologist

Management of Infusion-related reactions:

Also refer to the CCO guideline for detailed description of [Management of Cancer Medication-Related Infusion Reactions](#).

Grade	Management	Re-challenge
1 or 2	<ul style="list-style-type: none"> Stop or slow the infusion rate. Manage the symptoms. <p>Restart:</p> <ul style="list-style-type: none"> Once symptoms have resolved, if IR was not severe, consider resuming the infusion at a slower rate. 	<ul style="list-style-type: none"> Restart and re-challenge with pre-medications (e.g. H1-receptor antagonist and corticosteroid).
3 or 4	<ul style="list-style-type: none"> Stop treatment. Aggressively manage symptoms. 	<ul style="list-style-type: none"> Discontinue permanently (do not re-challenge).

Dosage with other toxicity:

Toxicity	Action
Pulmonary Toxicity	Discontinue permanently and manage symptoms aggressively with beta-agonists, antihistamines and/or corticosteroids. Do not re-challenge.

Hepatic Impairment

No adjustment required.

Renal Impairment

No adjustment required. The disposition of trastuzumab is not altered based on serum creatinine.

Dosage in the Elderly

No adjustment required; the risk of cardiac dysfunction and myelosuppression may be increased in elderly patients. The reported trials did not determine differences in efficacy between patients ≥ 65 years versus younger patients.

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F - Adverse Effects

Refer to [trastuzumab](#) drug monograph(s) for additional details of adverse effects

Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
<ul style="list-style-type: none"> • Musculoskeletal pain • Fatigue • Headache • Infusion related flu-like symptoms (most likely with first infusion) 	<ul style="list-style-type: none"> • Cardiotoxicity • Arrhythmia • Hypersensitivity • Infusion-related reaction • Pancreatitis • Interstitial lung disease • Myelosuppression \pm infection, bleeding (with chemotherapy) • Arterial / venous thromboembolism (with chemotherapy) • Secondary malignancies (with

- | | |
|--|-----------------------------------------------------|
| | chemotherapy
• Renal failure (with chemotherapy) |
|--|-----------------------------------------------------|

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G - Interactions

Refer to [trastuzumab](#) drug monograph(s) for additional details

- Avoid concomitant use with anthracyclines and other cardiotoxic drugs. Use with extreme caution with anthracyclines for up to 28 weeks after stopping trastuzumab.

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H - Drug Administration and Special Precautions

Refer to [trastuzumab](#) drug monograph(s) for additional details

Administration

NOTE: Herceptin® (trastuzumab) and Kadcyła® (trastuzumab emtansine) are **NON-INTERCHANGEABLE**. There have been fatal reports where the incorrect trastuzumab product was administered to patients with breast cancer in the clinical trials setting.

Different trastuzumab products are **not interchangeable**.

- DO NOT ADMINISTER AS AN IV 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, Chinese Hamster Ovary (CHO) cell proteins, or any components of this product.

Other Warnings/Precautions

- Trastuzumab should only be used in patients whose tumours overexpress HER2. Refer to product monograph for details on testing.
- The risk of cardiotoxicity must be weighed against the potential benefits of 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 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 be 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.
- Use with caution before or after anthracyclines (for up to 28 weeks after trastuzumab discontinuation due to long half-life).
- Life-threatening infusion-related reactions associated with the administration of trastuzumab may occur.
- Benzyl alcohol (a preservative in BWFI) has been associated with toxicity in neonates and children up to 3 years old.

Pregnancy/Lactation

- Trastuzumab is not recommended for use in pregnancy. Impairment of fetal renal growth and/or function impairment resulting in oligohydramnios (including neonatal fatal cases) have been reported. 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 trastuzumab therapy. Perform appropriate fetal testing if oligohydramnios occurs.
- Breastfeeding is not recommended.
- Fertility effects: Unknown.
 - No data in humans; animal studies showed no evidence of impaired fertility.

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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

- Infusion-associated symptoms; During the infusion and observe for at least 90 minutes afterwards (for loading dose), and at least 30 minutes afterwards (maintenance dose)
- Cardiac assessment, including evaluation of left ventricular function (Echocardiogram or MUGA scan); Baseline, q3 months during treatment, then q6 months after trastuzumab discontinuation x2 years (and annually up to 5 years after last trastuzumab dose in adjuvant breast cancer patients who received anthracyclines), or longer if continued LVEF decrease, also as clinically indicated (more frequent monitoring in asymptomatic LVEF reductions)
- Clinical exam for symptoms of cardiac failure, pulmonary toxicity and diarrhea; At each visit
- Grade toxicity using the current [NCI-CTCAE \(Common Terminology Criteria for Adverse Events\) version](#)

Suggested Clinical Monitoring

- CBC; As clinically indicated

- Liver function tests; As clinically indicated

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J - Administrative Information

Approximate Patient Visit	First cycle: 1.5 hours; Subsequent cycles: 0.5 hour
Pharmacy Workload (average time per visit)	19.589 minutes
Nursing Workload (average time per visit)	48.611 minutes

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K - References

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.

de Lemos ML, Mason K, Badry N, et al. Trastuzumab therapy in breast cancer: To reload or not to reload? *J Oncol Pharm Pract* 2014 Aug;20(4):319-20.

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Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med*. 2005;353(16):1659-71.

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human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol 2012;30(31):3792-9.

Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 2011;365(14):1273-83.

Swain SM, Jeong JH, Geyer CE Jr, et al. Longer therapy, iatrogenic amenorrhea, and survival in early breast cancer. N Engl J Med 2010;362(22):2053-65.

Trastuzumab drug monograph, Cancer Care Ontario.

PEBC Advice Documents or Guidelines

- [Optimal Systemic Therapy for Early Female Breast Cancer](#)

February 2022 Removed EBP forms

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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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