Regimen Monograph

A - Regimen Name

TRAS Regimen

Trastuzumab

Disease Site	Gynecologic Endometrial
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	Monotherapy as maintenance (after CRBPPACL+TRAS) for advanced / recurrent HER2-positive serous endometrial cancer
Supplementary Public Funding	**trastuzumab** New Drug Funding Program (Trastuzumab (Biosimilar) - Advanced or Recurrent Endometrial Cancer) (NDFP Website)

back to top

B - Drug Regimen

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

After 6 cycles of CRBPPACL+TRAS, start TRAS monotherapy as maintenance:

trastuzumab	6 mg /kg	IV	Day 1

back to top

C - Cycle Frequency

REPEAT EVERY 21 DAYS

Until disease progression or unacceptable toxicity

back to top

D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal

Febrile Neutropenia Risk: Low

Other Supportive Care:

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

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	• Stop or slow the infusion rate. • Manage the symptoms.	• Restart and re-challenge with pre-medications (e.g. H1-receptor antagonist and corticosteroid).

	Restart: • Once symptoms have resolved, if IR was not severe, consider resuming the infusion at a slower rate.	
3 or 4	• Stop treatment. • Aggressively manage symptoms.	• 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.

back to top

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
• Musculoskeletal pain • Fatigue • Headache • Infusion related flu-like symptoms (most likely with first infusion)	• Cardiotoxicity • Arrhythmia • Hypersensitivity • Infusion-related reaction • Pancreatitis • Interstitial lung disease • Myelosuppression ± infection, bleeding (with chemotherapy) • Arterial / venous thromboembolism (with chemotherapy) • Secondary malignancies (with chemotherapy) • Renal failure (with chemotherapy)

back to top

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.

back to top

H - Drug Administration and Special Precautions

Refer to trastuzumab drug monograph(s) for additional details

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

Administration

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

- 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 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.

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

- 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

back to top

J - Administrative Information

Approximate Patient Visit	0.5 hour
Pharmacy Workload (average time per visit)	19.589 minutes
Nursing Workload (average time per visit)	48.611 minutes

back to top

K - References

Fader AN, Roque DM, Siegel E, et al. Randomized phase II trial of carboplatin-paclitaxel compared with carboplatin-paclitaxel-trastuzumab in advanced (stage III-IV) or recurrent uterine serous

carcinomas that overexpress Her2/Neu (NCT01367002): updated overall survival analysis. Clin Cancer Res 2020 Aug 1;26(15):3928-3935. doi: 10.1158/1078-0432.CCR-20-0953.

Trastuzumab combination and monotherapy for HER2 advanced or recurrent uterine or endometrial cancer: a review of clinical effectiveness and cost-effectiveness. Ottawa: CADTH; 2020 Nov.

April 2023 Modified rationale/uses, Administrative information; added trastuzumab 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.

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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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back to top