Regimen Monograph

Regimen Name | Drug Regimen | Cycle Frequency | Premedication and Supportive Measures | Dose Modifications | Adverse Effects | Interactions | Drug Administration and Special Precautions | Recommended Clinical Monitoring | Administrative Information | References | Other Notes | Disclaimer

A - Regimen Name

TRAS Regimen

Trastuzumab

Disease Site

Gastrointestinal
Esophagus
Gastric / Stomach

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 advanced (non-resectable; locally advanced, recurrent or metastatic) adenocarcinoma of the esophagus, stomach, or gastroesophageal junction (Refer to NDFP form)
- Trastuzumab may be started with 5-FU (or capecitabine) AND cisplatin or oxaliplatin chemotherapy, or it can be added to chemotherapy later provided that there has been no disease progression

Supplementary Public Funding

trastuzumab
New Drug Funding Program (Trastuzumab (Biosimilar) - Advanced Gastric, Gastroesophageal, or Esophageal Cancer) (NDFP Website)

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B - Drug Regimen

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

Maintenance dose:

trastuzumab*	6 mg /kg	IV	Day 1; q21 days

*Refer to NDFP form for alternative trastuzumab dosing schedule (4 mg/kg IV maintenance dose q14 days)

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

As a single agent until disease progression or unacceptable toxicity, following completion of chemotherapy plus trastuzumab

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D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal

Febrile Neutropenia Risk: Low

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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	• 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).

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
• 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)

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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: Different trastuzumab products are **NOT-INTERCHANAGEABLE**.

- 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.

Missed Dose

- If a dose is missed by ≤ 1 week, the product monograph recommends the usual maintenance dose (6 mg/kg) should be administered as soon as possible (do not wait until the next planned cycle) and subsequent maintenance doses should be administered 21 days later (based on patient's maintenance dose/schedule).

- If a dose is missed by > 1 week, the product monograph recommends a re-loading dose (8 mg/kg) should be administered (over 90 minutes) as soon as possible, followed by the usual maintenance dose administered 21 days later (based on patient's maintenance dose/schedule).

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.

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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.

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

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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

Bang YJ, Van Cutsem E, Feyereislova A; ToGA Trial Investigators. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010 Aug 28;376(9742):687-97.

Trastuzumab drug monograph, Ontario Health (Cancer Care Ontario).

PEBC Advice Documents or Guidelines

- Systemic Therapy for Advanced Gastric and Gastro-Esophageal Carcinoma

February 2023 Updated rationale and uses section

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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.

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.

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