Regimen Monograph

A - Regimen Name

ENHE Regimen

Enhertu trastuzumab deruxtecan

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

For the treatment of unresectable locally advanced or metastatic HER2-positive breast cancer in patients* who have good performance status, and have either:

- received at least 1 prior anti-HER2-based regimen for unresectable locally advanced or metastatic disease, OR
- experienced disease recurrence during or within 6 months of completing neoadjuvant or adjuvant treatment with an anti-HER2-based regimen.

*__NOT__ treated with an anti-HER2 antibody-drug conjugate in the unresectable locally advanced or metastatic setting

Refer to the NDFP form for details.

Supplementary Public Funding	**Enhertu trastuzumab deruxtecan** New Drug Funding Program (Trastuzumab Deruxtecan - Unresectable Locally Advanced or Metastatic Breast Cancer) (NDFP Website)

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B - Drug Regimen

Note: Enhertu™ trastuzumab deruxtecan is **not interchangeable** with other trastuzumab products (e.g. Herceptin®, trastuzumab biosimilars, or Kadcyla® trastuzumab emtansine).

Enhertu trastuzumab deruxtecan	5.4 mg /kg	IV	Day 1

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

Until disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: High (*)
(*based on Breast Advisory Committee expert opinion; a 2-3 drug antiemetic regimen is recommended in the product monograph)

- 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.

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E - Dose Modifications

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

Enhertu™ trastuzumab deruxtecan is **not interchangeable** with other trastuzumab products (e.g. Herceptin®, trastuzumab biosimilars, or Kadcyla® trastuzumab emtansine).

Dosage with toxicity

Dose Level	Trastuzumab Deruxtecan Dose* (mg/kg)
0	5.4
-1	4.4
-2	3.2
-3	Discontinue

*Do not re-escalate a previously reduced dose.

Dose Modification for Toxicity:

Toxicity / Grade		Action
Interstitial lung disease (ILD)/ pneumonitis	Grade 1	Hold*. Consider corticosteroid (e.g. >0.5 mg/kg/day prednisolone or equivalent). If resolved in ≤ 28 days, resume at same dose level. If resolved in > 28 days, resume at 1 dose level ↓.
	Grade ≥ 2	Discontinue permanently. Initiate corticosteroids (e.g. ≥1 mg/kg/day prednisolone or equivalent) and continue for at least 14 days followed by gradual taper for at least 4 weeks.
Neutropenia	Grade 3	Hold*. Resume at same dose level.
	Grade 4	Hold*. Resume at 1 dose level ↓.
Febrile neutropenia		Hold*. Resume at 1 dose level ↓.

*Do not restart treatment until ILD/pneumonitis resolved to Grade 0, ANC ≥ 1x 10^9/L, or febrile neutropenia resolved.

Dose Modification for Left Ventricular Ejection Fraction (LVEF) Decreased:

	LVEF		Absolute Decrease from Baseline	Action
Asymptomatic	> 45%	AND	10 - 20%	Continue dose.
	40 - 45%	AND	< 10%	Continue dose. Reassess within 3 weeks.
		AND	10 - 20%	Hold dose. Reassess within 3 weeks. If LVEF recovered to within 10% from baseline, resume at same dose level. If not recovered to within 10% from baseline, discontinue permanently.
	< 40%	OR	> 20%	Hold dose. Reassess within 3 weeks. If LVEF < 40% or absolute decrease > 20% from baseline confirmed, discontinue permanently.
Symptomatic	Any			Discontinue permanently

Management of Infusion-Related Reactions (IRRs):

Enhertu™ trastuzumab deruxtecan has not been studied in patients with a history of severe hypersensitivity reactions to other monoclonal antibodies.

Stop or slow the infusion rate (e.g. by 50%) if infusion reactions occur. Discontinue for severe reactions.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Hepatic Impairment

Bilirubin		AST	Trastuzumab Deruxtecan Dose
≤ ULN	AND	> ULN	No dose adjustment.
>1 to 1.5 x ULN	AND	any	
>1.5 to 3 x ULN	AND	any	Insufficient data. Monitor closely for toxicity.
>3 to 10 x ULN	AND	any	No data available.

Renal Impairment

Patients with moderate or severe renal impairment may be at increased risk of developing ILD/pneumonitis.

Creatinine Clearnace (mL/min)	Trastuzumab Deruxtecan Dose
≥ 60	No dose adjustment.
≥ 30 to < 60	No dose adjustment. Monitor closely for toxicity.
< 30	No data available.

Dosage in the Elderly

No dose adjustment is required in patients ≥ 65 years. No clinically relevant differences in efficacy were observed based on age. Some clinical studies suggested a difference in safety between patients ≥ 65 years compared to younger patients.

Dosage Based on Gender

Gender has no significant effect on pharmacokinetic parameters of trastuzumab deruxtecan, or released topoisomerase I inhibitor, based on population pharmacokinetic analysis.

Dosage Based on Ethnicity

Ethnicity has no significant effect on pharmacokinetic parameters of trastuzumab deruxtecan, or released topoisomerase I inhibitor, based on population pharmacokinetic analysis.

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F - Adverse Effects

Refer to Enhertu trastuzumab deruxtecan 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
• Nausea, vomiting (generally mild)	• Fatigue • Myelosuppression ± infection, bleeding (may be severe) • Alopecia • Constipation • ↑ LFTs • Musculoskeletal pain • Anorexia, weight loss • Diarrhea	• Headache • Abdominal pain • Mucositis • ↓ K • Dizziness • Peripheral neuropathy • Cough, dyspnea • Pneumonitis (may be severe) • Dyspepsia	• Infusion related reaction • Decreased ejection fraction

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G - Interactions

Refer to Enhertu trastuzumab deruxtecan drug monograph(s) for additional details.

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H - Drug Administration and Special Precautions

Refer to Enhertu trastuzumab deruxtecan drug monograph(s) for additional details.

Administration:

Enhertu™ trastuzumab deruxtecan is **not interchangeable** with other trastuzumab products (e.g. Herceptin®, trastuzumab biosimilars, or Kadcyla® trastuzumab emtansine).

- Reconstitute each vial with sterile water for injection to a final concentration of 20 mg/mL and gently swirl. Do not shake the solution.
- Further dilute in 100 mL of D5W. Do NOT use sodium chloride solution.
- A polyvinylchloride (PVC) or polyolefin infusion bag is recommended. Invert infusion bag gently to mix.
- Administer as an IV infusion only with a 0.20 or 0.22 micron in line polyethersulfone (PES) or polysulfone (PS) filter. Do NOT administer as an IV push or bolus.
- Do not admix with other drugs or administer other drugs through the same IV line.
- Administer the first infusion over 90 minutes. If well tolerated, may give subsequent infusions IV over 30 minutes.
- If the diluted solution was stored refrigerated (2°C to 8°C), allow solution to reach room temperature before administration.
- If a planned dose is missed, administer as soon as possible. Adjust the schedule to maintain a 3-week interval between doses.
- Cover reconstituted drug and diluted solution to **protect from light** during storage and administration.
- Store unopened vials in a refrigerator at 2-8^{o}C in the original carton. Do not freeze.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Contraindications:

- Patients with known hypersensitivity to this drug or any components of its components.

Warning/Precautions:

- Enhertu™ trastuzumab deruxtecan is **not interchangeable** with other trastuzumab products (e.g. Herceptin®, trastuzumab biosimilars, or Kadcyla® trastuzumab emtansine).
- Trastuzumab deruxtecan has not been studied in patients with a history of clinically significant cardiac disease, baseline LVEF < 50% or severe hypersensitivity reactions to other monoclonal antibodies.
- Patients with a previous history of ILD/pneumonitis or with moderate or severe renal impairment may be at a higher risk of developing ILD/pneumonitis.

- Patients should use caution when driving, operating machinery or performing tasks that require alertness if they experience fatigue and dizziness.

Pregnancy/Lactation:

- Enhertu™ trastuzumab deruxtecan 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: Probable

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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

- CBC; Baseline, before each dose and as clinically indicated
- LVEF; Baseline and as clinically indicated
- Liver function tests; Baseline and as clinically indicated
- Renal function tests; Baseline and as clinically indicated
- Clinical toxicity assessment for infection, bleeding, fatigue, hypersensitivity or infusion reactions, GI, respiratory and dermatological effects; At each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Administrative Information

Approximate Patient Visit	0.5 to 1.5 hours
Pharmacy Workload (average time per visit)	30.10 minutes
Nursing Workload (average time per visit)	37.417 minutes

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K - References

Enhertu™ trastuzumab deruxtecan drug monograph. Ontario Health (Cancer Care Ontario).

Modi S, Saura C, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. N Engl J Med 2020;382(7):610-621. doi: 10.1056/NEJMoa1914510

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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.

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.

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