Regimen Monograph

A - Regimen Name

KADC Regimen

Kadcyla® trastuzumab emtansine

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 adjuvant treatment of patients with human epidermal growth factor receptor 2 (HER2)-positive early breast cancer, who have residual disease after preoperative systemic treatment including trastuzumab.
Supplementary Public Funding	**Kadcyla trastuzumab emtansine** New Drug Funding Program (Trastuzumab Emtansine - Adjuvant Treatment for Early Breast Cancer) (NDFP Website)

back to top

B - Drug Regimen

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

Kadcyla trastuzumab emtansine	3.6 mg /kg	IV	Day 1

back to top

C - Cycle Frequency

REPEAT EVERY 21 DAYS

For a maximum of 14 cycles, until disease progression or unacceptable toxicity, whichever comes first

back to top

D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal

- 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.

Dose levels: Do not re-escalate a previously reduced dose.

Dose level	Intravenous Dose
0 (Starting dose)	3.6 mg/kg every 3 weeks
-1	3 mg/kg every 3 weeks
-2	2.4 mg/kg every 3 weeks
-3	Discontinue permanently

Dosage with toxicity

Toxicity / Counts (x 10^9/L)		**Action / Kadcyla® trastuzumab emtansine dose**
Platelets 25 to <75 on treatment day		Hold*, then restart at the same dose level. If 2 delays are required, restart with ↓ 1 dose level
Platelets < 25 at any time		Hold*, then restart with ↓ 1 dose level
ANC < 1		Hold*, then Consider adding G-CSF and continue current dose, if appropriate, OR consider dose reduction
Grade 3 or 4 neuropathy		Hold* until ≤ grade 2, then consider restarting with ↓ 1 dose level
Pneumonitis	Signs and symptoms suggesting non-radiotherapy-related pneumonitis/ILD	Hold and investigate; discontinue if confirmed.
	Grade 2 radiotherapy-related	Discontinue if not resolving with standard treatment
	Grade 3 or 4 radiotherapy-related	Discontinue
Nodular regenerative hyperplasia		Discontinue
Other grade 3 non-hematologic/organ		Hold* until ≤ grade 1/baseline, then consider restarting with ↓ 1 dose level

Other grade 4 non-hematologic/organ	Discontinue
*Do not resume treatment until platelets are ≥ 75 x 10^9/L, ANC ≥ 1.5 x 10^9/L and other organ toxicities recover to ≤ grade 1 (unless otherwise stated in table). Consider discontinuing if cannot resume treatment after >6 weeks delay.	

Hepatotoxicity

AST		**ALT**		**Bilirubin**	**Action**
> 3 to 5 x ULN on treatment day (Grade 2)					Hold*, then restart at same dose level
> 3 x ULN	or	> 3 x ULN	and	> 2 x ULN	Discontinue^
> 5 to 20 x ULN on treatment day (Grade 3)	or	> 3 to 20 x ULN on treatment day (Grade 2 to 3)	or	> 1 to 2 x ULN on treatment day	Hold*, then restart with ↓ 1 dose level
> 20 x ULN at any time (grade 4)	or	> 20 x ULN at any time (grade 4)	or	> 2 x ULN at any time	Discontinue
*Do not resume treatment until AST and ALT recover to ≤ 3 x ULN and bilirubin ≤ 1 x ULN. ^Permanently discontinue if due to drug-induced liver injury (absence of another likely cause, such as liver metastases)					

Cardiotoxicity

Criteria	**Left Ventricular Ejection Fraction / Cardiotoxicity**	**Action**
1	≥ 50%	Continue and follow routine monitoring guidelines
2	45 to 49 % AND <10% below baseline, and asymptomatic	Continue and repeat LVEF within 3 weeks
3	45 to 49% AND ≥10% below baseline, and asymptomatic	**Hold** and repeat LVEF within 3 weeks. Discontinue permanently if no recovery. If improves to criteria # 1 or # 2 , may restart; monitor closely.

4	< 45% and asymptomatic	**Hold** and repeat LVEF within 3 weeks. Discontinue permanently if LVEF < 45% is confirmed.
5	Symptomatic CHF, Grade 3-4 LVSD[1] or Grade 3-4 heart failure, or Grade 2 heart failure accompanied by LVEF <45%	Discontinue

[1]LVSD = left ventricular systolic dysfunction

Management of Infusion-Related Reactions (IRRs):

Kadcyla® trastuzumab emtansine treatment has not been studied in patients who had trastuzumab permanently discontinued due to IRRs; treatment with Kadcyla® is not recommended for these patients.

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).

Hepatic Impairment

No adjustment to the starting dose is required for mild-moderate hepatic impairment; however, such patients should be treated with caution and closely followed due to the risk of hepatotoxicity. There are no data available for severe hepatic impairment.

Refer to table above for dosing with hepatic toxicity.

Renal Impairment

Creatinine clearance (mL/min)	Starting dose
≥ 30	No dose adjustments needed
< 30	Limited data; no specific recommendations available

Dosage in the Elderly

- No dose adjustment needed for patients > 65 to < 75 years old.
- Safety and efficacy have not been established in patients ≥ 75 years old.

Dosage Based on Ethnicity

No specific dose adjustments are recommended. A higher incidence of grade ≥ 3 thrombocytopenia was observed in 12 of 64 (18.8%) Asian patients vs 30 of 676 (4.4%) non-Asian patients in the pivotal early breast cancer study. Hemorrhage events occurred at a higher incidence in Asian patients; however, severe hemorrhage was very low irrespective of race (only reported in 1 Asian patient).

back to top

F - Adverse Effects

Refer to Kadcyla trastuzumab emtansine 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
• Fatigue	• Nausea, vomiting • ↑ LFTs (may be severe) • Musculoskeletal pain • Myelosuppression ± infection, bleeding (may be non-thrombocytopenic or severe) • Peripheral neuropathy (may be severe) • Headache	• Constipation • Mucositis • Cough, dyspnea • Dry mouth • Insomnia • Diarrhea • Abdominal pain • Dizziness • Injection site reaction	• Cardiotoxicity • Hypersensitivity • Optic neuritis • Nodular regenerative hyperplasia and portal hypertension • Drug-induced liver injury (with hepatic encephalopathy) • Pneumonitis • Extravasation

back to top

G - Interactions

Refer to Kadcyla trastuzumab emtansine drug monograph(s) for additional details

- Avoid concomitant use with strong CYP3A4 inhibitors (e.g. azole antifungals, macrolide antibiotics). Consider delay of Kadcyla® trastuzumab emtansine treatment until CYP3A4 inhibitors have been cleared (about 3 elimination half-lives of the inhibitors). Monitor patient carefully if must co-administer.
- Avoid concomitant use with anthracyclines and other cardiotoxic drugs; exercise extreme caution with anthracycline-based therapy for up to 28 weeks after stopping trastuzumab.
- Exercise caution when used with anticoagulants (including antiplatelet agents); consider additional monitoring for bleeding if concurrent use is necessary

back to top

H - Drug Administration and Special Precautions

Refer to Kadcyla trastuzumab emtansine drug monograph(s) for additional details

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

Kadcyla Administration:

- Reconstitute with sterile water for injection as directed and swirl gently. Do not shake the solution. Must be administered as an IV infusion. Do not administer as an IV push or bolus.
- Further dilute in 250 mL of 0.9% sodium chloride or 0.45% sodium chloride solutions only.
- Do not use dextrose 5% solution as this causes protein aggregation.
- If diluted in 0.9% sodium chloride, must use an in-line 0.2-micron in-line (non-protein absorptive) or 0.22-micron polyethersulfone (PES) filter for infusion.
- Dilutions in 0.45% sodium chloride solution may be used without an in-line filter.
- Administer the first infusion over 90 minutes, observe patient during the infusion and for at least 90 minutes after completion.
- If the first infusion is tolerated, may give subsequent infusions IV over 30 minutes; observe patient during the infusion and for at least 30 minutes after completion.
- If the planned dose is missed, administer this as soon as possible. Adjust the schedule to maintain a 3-week interval between doses.
- Kadcyla® trastuzumab emtansine should not be admixed with other drugs.
- Store unopened vials in a refrigerator at 2-8^{o}C. Do not freeze.

Also refer to Cancer Care Ontario's safety reminder for Kadcyla® Trastuzumab Emtansine.

Contraindications:

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

Warnings/Precautions:

- Caution in patients with dyspnea at rest due to complications of advanced cancer and co-morbidities may be at increased risk of pulmonary events.
- Caution in patients with previous history or at risk of neuropathy (e.g. previous neurotoxic drugs).
- Use caution in patients who have decreased platelets or who are on coagulation or antiplatelet therapies, due to the risk of hemorrhage.
- Use caution in patients with pre-existing hepatic impairment, due to the risk of hepatotoxicity.
- The risk of cardiotoxicity must be weighed against the potential benefits of treatment, especially in older patients, patients with pre-existing cardiac disease (including LVEF 50-55%) and patients who have had prior cardiotoxic therapy.
- Kadcyla® trastuzumab emtansine is not recommended in patients who had discontinued

trastuzumab due to infusion reactions or other toxicity that may be related to trastuzumab (e.g. cardiotoxicity, pneumonitis).
- Kadcyla has not been studied in these patient populations: Patients with baseline AST/ALT > 1.5 x ULN, bilirubin > 1 x ULN (in early breast cancer), grade 3 or 4 peripheral neuropathy, baseline platelets < 100 x 10^9/L, LVEF < 50%, or recent myocardial infarction/unstable angina within 6 months
- Patients should avoid driving, operating machinery or performing tasks that require alertness if they experience fatigue, dizziness or blurred vision.

Pregnancy/lactation:

- Kadcyla® trastuzumab emtansine 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: Yes

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 dose and as clinically indicated
- Liver function tests; baseline and before each dose, more frequent in patients who have severe LFT increases
- LVEF (echocardiogram or MUGA scan); baseline and q3 months during treatment, more frequent with asymptomatic reductions in LVEF; also suggest monitoring after treatment discontinuation especially for patients with pre-existing cardiac dysfunction or ↓LVEF, and as clinically indicated
- Clinical toxicity assessment for infection, bleeding, musculoskeletal pain, fatigue, hypersensitivity or infusion reactions, neurotoxicity, insomnia, GI and pulmonary effects; at each visit

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

back to top

J - Administrative Information

Approximate Patient Visit	First cycle: 1.5-2 hours; Subsequent cycles: 0.5-1 hour
Pharmacy Workload (average time per visit)	19.589 minutes
Nursing Workload (average time per visit)	49.722 minutes

back to top

K - References

von Minckwitz G et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. N Engl J Med 2019;380:617-28.

Kadcyla trastuzumab emtansine drug monograph, Ontario Health (Cancer Care Ontario).

October 2023 Updated cycle frequency 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.

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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