Drug Monograph

A - Drug Name

Kadcyla trastuzumab emtansine

SYNONYM(S): T-DM1

COMMON TRADE NAME(S): Kadcyla®

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B - Mechanism of Action and Pharmacokinetics

Kadcyla® trastuzumab emtansine contains trastuzumab (anti-HER2 IgG1) which is conjugated by a thioether link (MCC) to DM1 (a derivative of maytansine), a microtubule inhibitory drug. The MCC-DM1 complex is the emtansine component of Kadcyla® trastuzumab emtansine. Trastuzumab conjugation helps with targeting cytotoxic DM1 to HER2-overexpressing cells. Trastuzumab inhibits the proliferation of tumour cells that overexpress HER2 and mediates antibody dependent cell mediated cytotoxicity (ADCC) on these cells. DM1 causes apoptosis due to cell cycle arrest at G2/M phase.

Distribution	Pharmacokinetics are linear at the approved treatment dose. Maximum concentrations are reached close to the end of the infusion. There was no accumulation of trastuzumab emtansine or its metabolites after repeated dosing.	
	PPB	93% (DM-1)
	Cross blood brain barrier?	Not expected
Metabolism	DM1 and trastuzumab are separated within the cell via lysosomal degradation. The charged lysine-MCC-DM1 metabolite cannot penetrate non-target cells effectively.	

	Main enzymes involved	DM1 is mainly metabolized by CYP3A4 and a lesser extent by CYP3A5
	Active metabolites	Mainly lysine-MCC-DM1 (low levels)
	Inactive metabolites	Unknown
Elimination	Half-life	3.1-4.5 days
	Feces	80% (DM1 containing catabolites)
	Urine	<10% (DM1 containing catabolites)

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C - Indications and Status

Health Canada Approvals:

- Breast cancer

Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Minimal

Extravasation Potential: Mild irritant

The following adverse effects have been reported mainly in the phase III study (KATHERINE) in adjuvant breast cancer, comparing trastuzumab emtansine to trastuzumab. Adverse effects marked with "^" have been reported in metastatic breast cancer. This table also includes severe, life-threatening and post-marketing adverse effects from other sources.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Cardiotoxicity (3%)	E D
	Hypertension (6%)	E
Dermatological	Alopecia (2%)	E D
	Hand-foot syndrome (1%)	E
	Rash (7%)	E
Gastrointestinal	Abdominal pain (11%)	E
	Constipation (17%)	E
	Diarrhea (12%)	E
	Dry mouth (14%)	E
	Dyspepsia (4%)	E
	Mucositis (15%)	E
	Nausea, vomiting (42%)	I
General	Edema (4%)	E
	Fatigue (50%) (1% severe)	E
Hematological	Myelosuppression ± infection, bleeding (29%) (severe 6%, may be non-thrombocytopenic, including CNS, GI, respiratory bleeding)	E
Hepatobiliary	Drug-induced liver injury (with hepatic encephalopathy)	E
	↑ LFTs (32%) (2% severe)	E
	Other (<1%) (nodular regenerative hyperplasia)	E D
	Portal hypertension (<1%)	E
Hypersensitivity	Hypersensitivity (3%)	E
Injection site	Injection site reaction (≤10%) (extravasation - rare)	I
Metabolic / Endocrine	Abnormal electrolyte(s) (7%) (↓K)	E
Musculoskeletal	Musculoskeletal pain (30%)	E

Nervous System	Dizziness (10%)	E
	Dysgeusia (8%)	I
	Headache (28%)	E
	Insomnia (14%)	E
	Optic neuritis (<1%) ^	E D
	Peripheral neuropathy (28%)	E
Ophthalmic	Blurred vision (4%)	E
	Conjunctivitis (5%) (or dry eye)	E
	Watering eyes (6%)	E
Respiratory	Cough, dyspnea (14%)	E
	Pneumonitis (1%) (2% with radiotherapy)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for Kadcyla® trastuzumab emtansine include fatigue, nausea, vomiting, ↑ LFTs, musculoskeletal pain, myelosuppression ± infection, bleeding, headache, peripheral neuropathy, cough, dyspnea, constipation and mucositis.

There is a risk of cardiotoxicity as **decreases in LVEF** (<40%) have been observed in patients treated with Kadcyla® trastuzumab emtansine. The long-term effect of Kadcyla® trastuzumab emtansine on cardiotoxicity has not been studied.

Thrombocytopenias are generally transient and may be cumulative, with nadir occurring by day 8 and recovery to ≤ grade 2 by the time of the next scheduled dose. Severe or fatal bleeding events (including CNS, GI, respiratory) have been reported (irrespective of ethnicity) and may occur in the absence of thrombocytopenia or other risk factors such as anticoagulant use.

Hepatotoxicity, which can be cumulative, mainly consists of transient asymptomatic increases in serum transaminases. In metastatic breast cancer, transaminases generally peak at day 8 after treatment and recover to < Grade 1 before the next cycle. Fatal cases of hepatotoxicity (including hepatic encephalopathy) have been observed rarely. **Nodular regenerative hyperplasia** (NRH) has been reported. Diagnosis of NRH can be confirmed only by histopathology. It is a rare condition involving widespread benign transformation of hepatic parenchyma into small regenerative nodules, and may lead to non-cirrhotic portal hypertension. NRH should be considered in patients who present with clinical symptoms of portal hypertension and/or cirrhosis-like pattern seen on hepatic CT scan but with normal transaminases and no signs/symptoms of cirrhosis. This condition may be reversible with drug discontinuation.

Infusion-associated symptoms include symptoms such as flushing, chills, pyrexia, dyspnea, hypotension, wheezing, bronchospasm, and tachycardia. These mostly occur during the first dose or after the infusion. Most reactions were ≤ grade 2 and resolved within 24 hours after the infusion ended. Severe hypersensitivity reactions have also occurred.

Extravasation reactions have been observed more frequently within 24 hours of infusion and are usually mild. Specific treatment for extravasation is unknown at this time.

Pneumonitis may or may not be related to Kadcyla® trastuzumab emtansine infusion reactions and can be fatal. Treatment included administration of corticosteroids, oxygen, and permanently discontinuing the drug. Kadcyla® trastuzumab emtansine may also increase the risk of radiation pneumonitis in early breast cancer patients receiving adjuvant radiotherapy.

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E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Before treatment, must confirm tumour overexpression of HER2 by validated assays with either a score of 3+ by immunohistochemistry (IHC) or a ratio of ≥ 2 by in situ hybridization (ISH) or fluorescence in situ hybridization (FISH).

Premedications for nausea and hypersensitivity are generally not needed, but may be given as necessary.

Note: Kadcyla® trastuzumab emtansine is **not interchangeable** with other trastuzumab products (e.g. Herceptin®, trastuzumab biosimilars, or Enhertu™ trastuzumab deruxtecan). There have been fatal reports where the incorrect trastuzumab product was administered to patients with breast cancer in the clinical trials setting.

Fatal overdose with Kadcyla® trastuzumab emtansine has been reported; do not exceed the maximum Kadcyla® trastuzumab emtansine dose of 3.6 mg/kg. For management of a suspected drug overdose, contact the Ontario Poison Centre at 1-800-268-9017.

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

Adults:

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:

Early Breast Cancer:

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.

Metastatic Breast Cancer:

Toxicity / Counts (x 10^9/L)	**Action / Kadcyla® trastuzumab emtansine dose**
Platelets 25 to < 50	Hold*, then restart at the same dose level
Platelets < 25 or ANC < 0.5	Hold*, then restart with ↓ 1 dose level
Grade 3 or 4 neuropathy	Hold* until ≤ grade 2, then consider restarting with ↓ 1 dose level
Signs and symptoms suggesting pneumonitis/ILD	Hold and investigate; discontinue if confirmed.
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). Discontinue if cannot resume treatment after >6 weeks delay.	

Hepatotoxicity

Early Breast Cancer:

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)					

Metastatic Breast Cancer:

AST and ALT		**Bilirubin**	**Action**
>2.5 to 5 x ULN (grade 2)			Continue treatment at same dose level
		> 1.5 to 3 x ULN (grade 2)	Hold*, then restart at same dose level
> 3 x ULN	and	> 2 x ULN	Discontinue^
> 5 to 20 x ULN (grade 3)	or	> 3 to 10 x ULN (grade 3)	Hold*, then restart with ↓ 1 dose level
> 20 x ULN (grade 4)	or	> 10 x ULN (grade 4)	Discontinue
*Do not resume treatment until AST/ALT recover to ≤ 5 x ULN and bilirubin ≤ 1.5 x ULN. ^Permanently discontinue if due to drug-induced liver injury (absence of another likely cause, such as liver metastases)			

<u>Cardiotoxicity</u>

Early Breast Cancer:

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

Metastatic Breast Cancer:

Criteria	Left Ventricular Ejection Fraction / Cardiotoxicity	Action
1	> 45%	Continue and follow routine monitoring guidelines
2	40-45% AND < 10% below baseline and asymptomatic	Continue and repeat LVEF within 3 weeks
3	40-45% 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	<40% and asymptomatic	**Hold** and repeat LVEF within 3 weeks. Discontinue permanently if LVEF < 40% is confirmed.
5	Symptomatic or confirmed CHF	Discontinue

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).

Dosage with 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.

Dosage with 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).

In metastatic breast cancer, the incidences of hemorrhages was similar in Asian and non-Asian patients

Children:

Safety and efficacy have not been established in children <18 years old.

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F - Administration Guidelines

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

- 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 Ontario Health (Cancer Care Ontario)'s safety reminder for Kadcyla® Trastuzumab Emtansine.

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G - Special Precautions

Contraindications:

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

Other 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 > 2.5 x ULN, bilirubin > 1.5 x ULN (in metastatic breast cancer), 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.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Clastogenicity: Yes
- Embryotoxicity: Yes

- Fetotoxicity: Yes
- Teratogenicity: Yes
  Kadcyla® trastuzumab emtansine should not be used in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **7 months** after the last dose.
- Lactation: Not recommended
  Trastuzumab is secreted in milk in animals. IgG is excreted in human milk. Kadcyla® trastuzumab emtansine should not be used during lactation and for **7 weeks** after the last dose.
- Fertility effects: Yes

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H - Interactions

DM1 does not induce or inhibit P450-mediated metabolism *in vitro*, but is a substrate for CYP3A4.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP3A4 inhibitors (i.e. ketoconazole, clarithromycin, ritonavir)	↑ DM1 concentration and/or toxicity	↓ metabolism of DM1	Avoid concomitant use with strong CYP3A4 inhibitors. 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.
Anthracyclines and other cardiotoxic drugs	↑ cardiotoxicity	Additive	Caution; avoid concomitant use; exercise extreme caution with anthracycline-based therapy for up to 28 weeks after stopping trastuzumab
Anticoagulants, antiplatelet agents	↑ risk of bleeding; severe bleeding has been reported	Additive	Caution; consider additional monitoring for bleeding if concurrent use is necessary

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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

Monitor Type	Monitor Frequency
CBC	baseline, 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

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J - Supplementary Public Funding

New Drug Funding Program (NDFP Website)

- Trastuzumab Emtansine - Unresectable Locally Advanced or Metastatic Breast Cancer
- Trastuzumab Emtansine - Adjuvant Treatment for Early Breast Cancer

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K - References

Ballantyne A, Dhillon S. Trastuzumab emtansine: first global approval. Drugs 2013;73:755–65.

Erickson HK, Park PU, Widdison WC, et al.. Antibody-maytansinoid conjugates are activated in targeted cancer cells by lysosomal degradation and linker-dependent intracellular processing. Cancer Res 2006;66(8)4426-33.

Girish S, Gupta M, Wang B, et al. Clinical pharmacology of trastuzumab emtansine (T-DM1): an antibody–drug conjugate in development for the treatment of HER2-positive cancer. Cancer Chemother Pharmacol 2012;69:1229–40.

LoRusso PM, Weiss D, Guardino E, et al. Trastuzumab emtansine: a unique antibody-drug conjugate in development for human epidermal growth factor receptor 2-positive cancer. Clin Cancer Res 2011;17(20):6437-47.

Prescribing Information: Kadcyla® (trastuzumab emtansine). Genentech Inc. (US), September 2020.

Product Monograph: Kadcyla® (trastuzumab emtansine). Hoffmann-La Roche Ltd., July 3, 2020.

Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 2012;367(19):1783-91.

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

August 2023 Modified non-interchangeability statement and Indications section

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L - Disclaimer

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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