ADVERSE EVENTS MANAGEMENT HANDBOOK

Your guide to managing adverse events (AEs) that may be associated with patients taking ENHERTU.

ENHERTU (trastuzumab deruxtecan) as monotherapy, indicated for:

- the treatment of adult patients with unresectable, locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen

has been issued marketing authorization ***with conditions***, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for ENHERTU, please refer to Health Canada's Notice of Compliance with conditions - drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html.

HER2=human epidermal growth factor receptor 2.

AstraZeneca Daiichi-Sankyo

ENHERTU® trastuzumab deruxtecan

How to use this handbook

This handbook was created to inform you about adverse events (AEs) that may occur in your patients taking ENHERTU and recommendations on how to help manage these AEs.

It is important to recognize and address the signs and symptoms early. Management information for AEs included in this guide are:

- AE incidence in ENHERTU clinical trials
- AE signs and symptoms to recognize
- AE management and dosage adjustment information

The sections in this handbook include:

Unresectable locally advanced or metastatic HER2-positive (IHC 3+ or IHC 2+/ISH+) **gastric or GEJ adenocarcinoma**

Dose modifications

Respiratory

Hematologic

Cardiovascular

Infusion-related reactions

Advise patients of the risk and the need to immediately report symptoms and consult the ENHERTU Product Monograph for more details on other AEs, dosing, administration, and treatment modifications following AEs.

AE=adverse event; GEJ=gastroesophageal junction; HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; ISH=*in situ* hybridization.

ENHERTU® trastuzumab deruxtecan

Table of contents

The safety of ENHERTU 6.4 mg/kg was evaluated in a pooled analysis of 229 patients with unresectable locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma in DESTINY-Gastric01 (N=125), DESTINY-Gastric02 (N=79) and DS8201-A-J101 (Gastric Cancer cohort, N=25).[1]*

In the pooled studies, the most common adverse reactions in patients treated with ENHERTU 6.4 mg/kg (frequency ≥20%) were:

Adverse Reaction	ENHERTU (N=229) 6.4 mg/kg
	Any Grade (%)
nausea	65.5
decreased appetite	54.1
fatigue	52.8
neutropenia	49.3
anemia	49.3
thrombocytopenia	34.5
vomiting	32.3
diarrhea	32.3
leukopenia	29.3
constipation	25.8
alopecia	22.3
pyrexia	20.5

Adapted from the ENHERTU Product Monograph

The most common serious adverse reactions (frequency >1%) were:

- **decreased appetite (7.0%)**
- **ILD (3.9%)**
- **pneumonia (3.9%)**
- **nausea (2.2%)**
- **vomiting (1.7%)**
- **dehydration (1.7%)**
- **anemia (1.7%)**
- **diarrhea (1.3%)**
- **abdominal pain (1.3%)**
- **pyrexia (1.3%)**

There were 2 (0.9%) patients with adverse reactions leading to death, one each attributed to ILD and pneumonia.

GEJ=gastroesophageal junction; HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; ILD=interstitial lung disease; ISH=*in situ* hybridization.

Adverse reactions leading to ENHERTU dose modifications, dose reduction or treatment discontinuation in the pooled analysis of DESTINY-Gastric01, DESTINY-Gastric02 and DS8201-A-J101 trials.[1]

Dose interruption due to adverse reactions occurred in **39.3% of patients treated with ENHERTU 6.4 mg/kg**	The most frequent adverse reactions (>2%) associated with dose interruption were: • neutropenia (17.9%) • anemia (8.3%) • decreased appetite (7.0%) • leukopenia (5.2%) • fatigue (4.4%) • ILD (3.5%) • pneumonia (3.5%) • thrombocytopenia (2.6%) • upper respiratory tract infection (2.2%)
Dose reductions due to adverse reactions occurred in **27.5% of patients treated with ENHERTU**	The most frequent adverse reactions (>2%) associated with dose reduction were: • neutropenia (9.2%) • decreased appetite (8.3%) • nausea (6.6%) • fatigue (5.7%) • febrile neutropenia (2.2%)
Treatment discontinuation due to adverse reactions occurred in **11.4% of patients treated with ENHERTU**	The most frequent adverse reaction (>2%) associated with permanent discontinuation was: • ILD (6.6%)

Adapted from the ENHERTU Product Monograph

Infusion-related reactions occurred in 2% of patients treated with ENHERTU in the DESTINY-Gastric01 trial.

GEJ=gastroesophageal junction; HER2=human epidermal growth factor receptor 2; ILD=interstitial lung disease.
* The safety profile of ENHERTU was evaluated in a pooled analysis of 229 patients with unresectable locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma in DESTINY-Gastric01 (N=125), DESTINY-Gastric02 (N=79) and DS8201-A-J101 (Gastric Cancer cohort, N=25) who received at least one dose of ENHERTU 6.4 mg/kg. In DESTINY-Gastric01, the median duration of treatment was 4.6 months (range: 0.7 to 29.7) in ENHERTU-treated patients (primary cohort). In DESTINY-Gastric02 the median duration of treatment was 4.3 months (range: 0.7 to 15.9) in the ENHERTU single arm study.

Common adverse events (≥1% all grades) reported in patients treated with ENHERTU in DESTINY-Gastric01 and DESTINY-Gastric02[1]*

MedDRA System Organ Class/Preferred Term or Grouped Term		DESTINY-Gastric01				DESTINY-Gastric02	
		ENHERTU 6.4 mg/kg N=125		Physician's Choice of Chemotherapy N=62		ENHERTU 6.4 mg/kg N=79	
		Any Grade[a] n (%)	Grade 3 or 4[a] n (%)	Any Grade[a] n (%)	Grade 3 or 4[a] n (%)	Any Grade[a] n (%)	Grade 3 or 4[a] n (%)
Blood and Lymphatic System Disorders	Neutropenia[b]	81 (65)	64 (51)	22 (35)	15 (24)	20 (25)	10 (13)
	Anemia[c]	72 (58)	48 (38)	19 (31)	14 (23)	27 (34)	11 (14)
	Leukopenia[d]	48 (38)	26 (21)	22 (35)	7 (11)	8 (10)	4 (5)
	Lymphopenia[e]	29 (23)	15 (12)	2 (3)	1 (2)	4 (5)	3 (4)
	Thrombocytopenia[f]	50 (40)	14 (11)	4 (6.5)	2 (3)	17 (22)	3 (4)
	Febrile neutropenia	6 (5)	6 (5)	2 (3)	2 (3)	2 (3)	2 (3)
Gastrointestinal Disorders	Nausea	79 (63)	7 (6)	29 (47)	1 (2)	52 (66)	6 (8)
	Vomiting	33 (26)	0	5 (8)	0	33 (42)	2 (3)
	Diarrhea	41 (33)	3 (2)	20 (32)	1 (2)	28 (35)	1 (1)
	Abdominal pain[g]	19 (15)	1 (0.8)	9 (15)	2 (3)	16 (20)	2 (3)
	Constipation	31 (25)	0	15 (24)	0	21 (27)	0
	Stomatitis[h]	14 (11)	2 (2)	3 (5)	0	1 (1)	0
General Disorders and Administration Site Conditions	Fatigue[i]	69 (55)	11 (9)	27 (44)	3 (5)	44 (56)	4 (5)
	Pyrexia	31 (25)	0	10 (16)	0	8 (10)	0
	Edema peripheral	14 (11)	0	0	0	4 (5)	0
Hepatobiliary Disorders	Hepatic function abnormal	11 (9)	4 (3)	1 (2)	1 (2)	0	0
Infections and Infestations	Upper respiratory tract infection[j]	21 (17)	1 (0.8)	8 (13)	0	1 (1)	0
	Pneumonia	13 (10)	3 (2)	1 (2)	0	2 (3)	2 (3)
Injury, Poisoning and Procedural Complications	Infusion-related reaction[k]	2 (2)	0	0	0	0	0

* Date of data cut-off: 03 June 2020 (DESTINY-Gastric01), 09 April 2021 (DESTINY-Gastric02).

MedDRA System Organ Class/Preferred Term or Grouped Term		DESTINY-Gastric01				DESTINY-Gastric02	
		ENHERTU 6.4 mg/kg N=125		Physician's Choice of Chemotherapy N=62		ENHERTU 6.4 mg/kg N=79	
		Any Grade[a] n (%)	Grade 3 or 4[a] n (%)	Any Grade[a] n (%)	Grade 3 or 4[a] n (%)	Any Grade[a] n (%)	Grade 3 or 4[a] n (%)
Investigations	Aspartate aminotransferase increased	12 (10)	3 (2)	3 (5)	0	10 (13)	1 (1)
	Alanine aminotransferase increased	9 (7)	2 (2)	3 (5)	0	6 (8)	1 (1)
	Blood bilirubin increased	10 (8)	1 (0.8)	0	0	4 (5)	1 (1)
	Blood alkaline phosphatase increased	11 (9)	4 (3)	2 (3)	0	6 (8)	1 (1)
Metabolism and Nutrition Disorders	Hypokalemia	10 (8)	5 (4)	4 (6)	4 (6)	12 (15)	1 (1)
	Decreased appetite	76 (61)	21 (17)	28 (45)	8 (13)	26 (33)	4 (5)
	Dehydration	8 (6)	3 (2)	2 (3)	1 (2)	2 (3)	0
Respiratory, Thoracic and Mediastinal Disorders	Interstitial lung disease[l]	16 (13)	3 (2)	0	0	6 (8)	0
	Dyspnea	1 (0.8)	0	1 (2)	0	7 (9)	1 (1)
	Cough	6 (5)	0	2 (3)	0	8 (10)	1 (1)
	Epistaxis	4 (3)	0	0	0	6 (8)	0
Skin and Subcutaneous Tissue Disorders	Alopecia	28 (22)	0	9 (15)	0	19 (24)	0
	Pruritus	10 (8)	0	2 (3)	0	2 (3)	0
	Rash[m]	7 (6)	0	3 (5)	0	1 (1)	0

Adapted from the ENHERTU Product Monograph

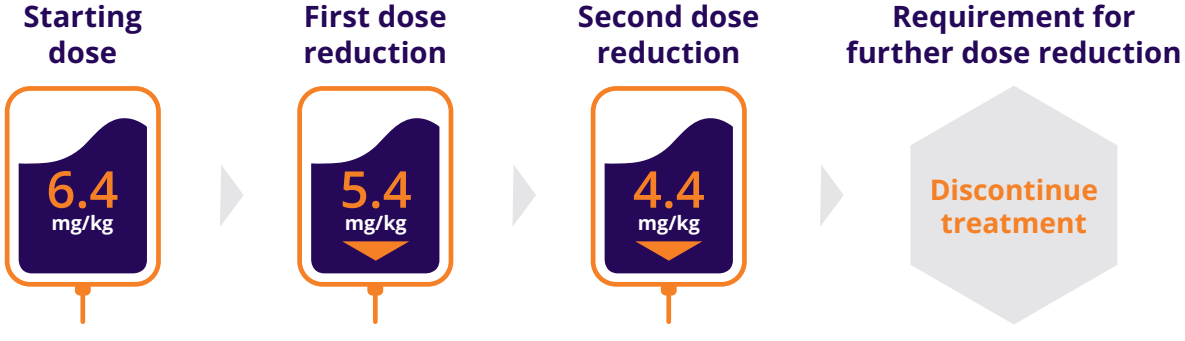
MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term.
a DESTINY-Gastric01 was graded as per National Cancer Institute Common Terminology Criteria for Adverse Events v.4.03 (NCI CTCAE v.4.03). DESTINY-Gastric02 was graded as per NCI CTCAE v.5.0.
b Grouped term of neutropenia includes PTs of neutropenia and neutrophil count decreased.
c Grouped term of anemia includes PTs of anemia, hemoglobin decreased, hematocrit decreased, and red blood cell count decreased.
d Grouped term of leukopenia includes PTs of leukopenia and white blood cell count decreased.
e Grouped term of lymphopenia includes PTs of lymphopenia and lymphocyte count decreased.
f Grouped term of thrombocytopenia includes PTs of thrombocytopenia and platelet count decreased.
g Grouped term of abdominal pain includes PTs of abdominal pain, abdominal discomfort, gastrointestinal pain, abdominal pain lower, and abdominal pain upper.
h Grouped term of stomatitis includes PTs of stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosal blistering.
i Grouped term of fatigue includes PTs of fatigue, asthenia, and malaise.
j Grouped term of upper respiratory tract infection includes PTs of upper respiratory tract infection, influenza, influenza-like illness, nasopharyngitis, pharyngitis, sinusitis, and rhinitis.
k Cases include PT of infusion-related reaction.
l Interstitial lung disease includes events that were adjudicated as ILD: pneumonitis, interstitial lung disease, and pneumonia.
m Grouped term of rash includes PTs of rash, rash pustular, and rash maculo-papular.

Dose modifications[1]

Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of ENHERTU (see table below as well as pages 13, 15, 17, 19 and 22-23).

ENHERTU dose should not be re-escalated after a dose reduction is made.

Dose reduction schedule



Adapted from the ENHERTU Product Monograph

Premedication

ENHERTU is emetogenic, which includes delayed nausea and/or vomiting. Prior to each dose of ENHERTU, patients should be premedicated with a combination regimen of two or three medicinal products (e.g., dexamethasone with either a 5-HT3 receptor antagonist and/or an NK1 receptor antagonist, as well as other medicinal products as indicated) for prevention of chemotherapy-induced nausea and vomiting per institutional guidelines.

Please consult the ENHERTU Product Monograph at enhertu-en.azpm.ca for more details on dosing, administration and dose modification following adverse reactions.

5-HT3=5-hydroxytryptamine 3; NK1=neurokinin 1.

Management of adverse events

Respiratory

Interstitial lung disease (ILD)/pneumonitis[1]

In clinical studies, of the 229 patients with unresectable locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, ILD occurred in 25 (10.9%) of patients as determined by independent review. Median time to first onset was 2.8 months (range: 1.2 to 21.0).

Most ILD cases were Grades 1 or 2 (pooled data):

- Grade 1: 2.6%
- Grade 2: 6.6%
- Grade 3: 0.9%
- Grade 4: 0.4%
- Grade 5: 0.4%

Signs and symptoms of ILD/pneumonitis[1]

- Cough
- Dyspnea
- Fever
- New or worsening respiratory symptoms

Patients should be advised to immediately report any of the signs and symptoms listed on the left.

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

Monitor and promptly investigate signs and symptoms of ILD/pneumonitis.

Patients with suspected ILD/pneumonitis should be evaluated by radiographic imaging, and consultation with a pulmonologist should be considered.

GEJ=gastroesophageal junction; HER2=human epidermal growth factor receptor 2; ILD=interstitial lung disease.

Recommended dose modifications for ENHERTU following interstitial lung disease (ILD)/pneumonitis[1]

<table>
<tr><th>Adverse event</th><th>Severity†</th><th colspan="2">Treatment modification</th></tr>
<tr><td rowspan="5">ILD/pneumonitis</td><td rowspan="3">Asymptomatic ILD/pneumonitis (Grade 1)</td><td colspan="2">Interrupt ENHERTU until resolved to Grade 0, then:</td></tr>
<tr><td>• if resolved in 28 days or less from date of onset.</td><td>Maintain dose.</td></tr>
<tr><td>• if resolved in greater than 28 days from date of onset.</td><td>Reduce dose one level (see page 10).</td></tr>
<tr><td colspan="3">Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., >0.5 mg/kg/day prednisolone or equivalent).</td></tr>
<tr><td rowspan="2">Symptomatic ILD/pneumonitis (Grade 2 or greater)</td><td colspan="2">Permanently discontinue ENHERTU.</td></tr>
<tr><td colspan="2">Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥1 mg/kg/day prednisolone or equivalent).
Continue corticosteroid treatment for at least 14 days followed by gradual taper for at least 4 weeks.</td></tr>
</table>

Adapted from the ENHERTU Product Monograph

For important information on ILD/pneumonitis risk minimization, please consult Health Care Professional Guide: Important Risk Minimization Information on ILD/Pneumonitis with Treatment of ENHERTU® (Trastuzumab deruxtecan).

You can also refer to the ENHERTU Product Monograph for more information on treatment management strategies for ILD/pneumonitis.

ILD=interstitial lung disease.
† Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v.5.0).

ENHERTU® trastuzumab deruxtecan

Hematologic

Neutropenia[1]

Of the 229 patients with unresectable locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, a decrease in neutrophil count was reported in 103 (45.0%) patients. Grade 3 or 4 events were reported in 77 (33.6%) patients. Febrile neutropenia was reported in 3.9% of patients.

Signs and symptoms of an infection which may be caused by neutropenia[2]

- Chills, sweating
- Shortness of breath
- Cough or sore throat
- Fatigue or feeling unwell
- Constipation or diarrhea
- Mouth sores
- Areas of swelling, redness or pain
- Changes in urination (burning, urgency, frequency)
- Vaginal discharge or itching
- Faintness, shuffling gait, excessive sleepiness
- Fever along with decrease in the number of neutrophils (febrile neutropenia)

Monitor complete blood counts prior to ENHERTU initiation and prior to each dose, and as clinically indicated. Based on the severity of neutropenia, ENHERTU may require dose interruption or reduction.

GEJ=gastroesophageal junction; HER2=human epidermal growth factor receptor 2.

Recommended dose modifications for ENHERTU following neutropenia[1]

Adverse event	Severity†	Treatment modification	
Neutropenia	Grade 3 (less than 1.0-0.5 x 10^9/L)	**Interrupt ENHERTU until resolved to Grade 2 or less.**	**Maintain dose.**
	Grade 4 (less than 0.5 x 10^9/L)	**Interrupt ENHERTU until resolved to Grade 2 or less.**	**Reduce dose one level (see page 10).**
Febrile neutropenia	Absolute neutrophil count of less than 1 x 10^9/L and temperature greater than 38.3°C or a sustained temperature of 38°C or greater for more than one hour	**Interrupt ENHERTU until resolved.**	**Reduce dose one level (see page 10).**

Adapted from the ENHERTU Product Monograph

† Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v.5.0).

Hematologic

Anemia/Thrombocytopenia[1]

In patients with gastric cancer treated with ENHERTU 6.4 mg/kg (N=229), 25.3% (58/229) received a transfusion within 28 days after onset of anemia or thrombocytopenia. Transfusions were primarily for anemia.

Signs and symptoms of thrombocytopenia[5]

- Petechiae
- Ecchymoses
- Epistaxis
- Bleeding (oral, gastrointestinal, genitourinary)

Recommended dose modifications for ENHERTU following thrombocytopenia[1]

Adverse event	Severity†	Treatment modification	
Thrombocytopenia	Grade 3 (platelets less than 50 to 25 x 10^9/L)	**Interrupt ENHERTU until resolved to Grade 1 or less.**	**Maintain dose.**
	Grade 4 (platelets less than 25 x 10^9/L)	**Interrupt ENHERTU until resolved to Grade 1 or less.**	**Reduce dose one level (see page 10).**

Adapted from the ENHERTU Product Monograph

† Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v.5.0).

Cardiovascular

Left ventricular ejection fraction (LVEF) decrease[1]

Of the 229 patients with unresectable locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, LVEF decrease was reported in 15 patients (6.5%), of which 14 (6.1%) were Grade 2 and 1 (0.4%) was Grade 3.

Signs and symptoms of LVEF decrease[3]

- Dyspnea
- Orthopnea
- Paroxysmal nocturnal dyspnea
- Fatigue
- Weakness
- Exercise intolerance
- Dependent edema
- Cough
- Weight gain
- Abdominal distension
- Nocturia
- Cool extremities

LVEF should be assessed prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. LVEF decrease should be managed through treatment interruption.

GEJ=gastroesophageal junction; HER2=human epidermal growth factor receptor 2; LVEF=left ventricular ejection fraction.

Recommended dose modifications for ENHERTU following left ventricular ejection fraction (LVEF) decrease[1]

Adverse event	Severity†		Treatment modification	
Decreased left ventricular ejection fraction (LVEF)	LVEF greater than 45% and absolute decrease from baseline is 10% to 20%		**Continue treatment with ENHERTU.**	
	LVEF 40% to 45%	And absolute decrease from baseline is less than 10%	**Continue treatment with ENHERTU**. * Repeat LVEF assessment within 3 weeks.	*
		And absolute decrease from baseline is 10% to 20%	**Interrupt ENHERTU**. * Repeat LVEF assessment within 3 weeks.	*
			If LVEF **recovers to within 10% from baseline.**	**Resume** treatment with ENHERTU at the **same dose**.
			If LVEF **has not recovered to within 10% from baseline.**	**Permanently discontinue ENHERTU.**
	LVEF less than 40% or absolute decrease from baseline is greater than 20%		**Interrupt ENHERTU**. * Repeat LVEF assessment within 3 weeks.	*
			If LVEF of **less than 40% or absolute decrease from baseline of greater than 20%** is confirmed.	**Permanently discontinue ENHERTU.**
	Symptomatic congestive heart failure (CHF)		**Permanently discontinue ENHERTU.**	

LVEF=left ventricular ejection fraction.
† Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v.5.0).

Adapted from the ENHERTU Product Monograph

ENHERTU® trastuzumab deruxtecan

Infusion-related reactions (IRRs)

Cases of infusion-related reactions (IRRs), including a serious case of hypersensitivity, were reported in clinical studies of ENHERTU.

ENHERTU has not been studied in patients with a history of severe hypersensitivity reactions to other monoclonal antibodies.

Signs and symptoms of IRRs[4]

- Dyspnea, bronchospasm
- Rash, flushing, urticaria, pruritus
- Hypotension, light-headedness, dizziness, weakness
- Abdominal pain, nausea, vomiting, cramps, diarrhea
- Back pain

Patients should be monitored for IRRs. The infusion rate should be slowed or interrupted if the patient develops infusion-related symptoms.

ENHERTU may require dose interruption or discontinuation, depending on the severity of the IRR. ENHERTU should be permanently discontinued in case of severe infusion-related reactions.

Important safety information for ENHERTU

Clinical use:

- No clinically relevant differences in efficacy were observed between patients ≥65 years and those younger than 65 years. Evidence from clinical studies suggests the use in the geriatric population is associated with differences in safety.
- For pediatrics (<18 years of age), no data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

Contraindications:

- Hypersensitivity to ENHERTU or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container.

Most serious warnings and precautions:

Interstitial lung disease (ILD) and pneumonitis: Fatal cases have been reported with ENHERTU. ILD was more frequently reported in patients with moderate renal impairment in clinical trials. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue ENHERTU in all patients with Grade 2 or higher ILD/pneumonitis. Advise patients of the risk and the need to immediately report symptoms.

Embryo-fetal toxicity: Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception.

Risk of medication errors: There is a risk of medication errors between ENHERTU (trastuzumab deruxtecan) and trastuzumab or trastuzumab emtansine.

Other relevant warnings and precautions:

- Left ventricular ejection fraction (LVEF) decrease
- Symptomatic congestive heart failure (CHF)
- Driving and operating machinery
- Anemia/thrombocytopenia
- Neutropenia
- Infusion-related reactions (IRR)
- Race
- Fertility
- Teratogenic risk
- Pregnant women or women of child-bearing potential
- Breast-feeding women

For more information:

Please consult the ENHERTU Product Monograph at enhertu-en.azpm.ca for important information relating to adverse reactions, drug interactions, and dosing information which have not been discussed in this piece.

The Product Monograph is also available by calling 1-800-668-6000.

Summary

Recommended treatment modifications for ENHERTU following adverse events[1]

Adverse event	Severity†	Treatment modification	
Interstitial lung disease (ILD)/ pneumonitis	Asymptomatic ILD/pneumonitis (Grade 1)	**Interrupt ENHERTU until resolved to Grade 0, then:**	
		• **if resolved in 28 days or less** from date of onset.	**Maintain dose.**
		• **if resolved in greater than 28 days** from date of onset.	**Reduce dose one level (see page 10).**
		Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., >0.5 mg/kg/day prednisolone or equivalent).	
	Symptomatic ILD/pneumonitis (Grade 2 or greater)	**Permanently discontinue ENHERTU.**	
		Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥1 mg/kg/day prednisolone or equivalent). Continue corticosteroid treatment for at least 14 days followed by gradual taper for at least 4 weeks.	
Neutropenia	Grade 3 (less than 1.0-0.5 x 10^9/L)	**Interrupt ENHERTU until resolved to Grade 2 or less.**	**Maintain dose.**
	Grade 4 (less than 0.5 x 10^9/L)	**Interrupt ENHERTU until resolved to Grade 2 or less.**	**Reduce dose one level (see page 10).**
Febrile neutropenia	Absolute neutrophil count of less than 1 x 10^9/L and temperature greater than 38.3°C or a sustained temperature of 38°C or greater for more than one hour	**Interrupt ENHERTU until resolved.**	**Reduce dose one level (see page 10).**
Thrombocytopenia	Grade 3 (platelets less than 50 to 25 x 10^9/L)	**Interrupt ENHERTU until resolved to Grade 1 or less.**	**Maintain dose.**
	Grade 4 (platelets less than 25 x 10^9/L)	**Interrupt ENHERTU until resolved to Grade 1 or less.**	**Reduce dose one level (see page 10).**

Adverse event	Severity†		Treatment modification	
Decreased left ventricular ejection fraction (LVEF)	LVEF greater than 45% and absolute decrease from baseline is 10% to 20%		**Continue treatment with ENHERTU.**	
	LVEF 40% to 45%	And absolute decrease from baseline is less than 10%	**Continue treatment with ENHERTU**. * Repeat LVEF assessment within 3 weeks.	*
		And absolute decrease from baseline is 10% to 20%	**Interrupt ENHERTU**. * Repeat LVEF assessment within 3 weeks.	*
			If LVEF **recovers to within 10% from baseline.**	**Resume** treatment with ENHERTU at the **same dose**.
			If LVEF **has not recovered to within 10% from baseline.**	**Permanently discontinue ENHERTU.**
	LVEF less than 40% or absolute decrease from baseline is greater than 20%		**Interrupt ENHERTU**. * Repeat LVEF assessment within 3 weeks.	*
			If LVEF of **less than 40% or absolute decrease from baseline of greater than 20%** is confirmed.	**Permanently discontinue ENHERTU.**
	Symptomatic congestive heart failure (CHF)		**Permanently discontinue ENHERTU.**	

† Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v.5.0).

Adapted from the ENHERTU Product Monograph

Cases of infusion-related reactions (IRRs), including a serious case of hypersensitivity were reported in ENHERTU clinical trials. Patients should be monitored for IRRs and dose interruption or discontinuation of ENHERTU may be required based on IRR severity.

ILD=interstitial lung disease; IRR=infusion-related reaction; LVEF=left ventricular ejection.

References:

1. ENHERTU Product Monograph. AstraZeneca Canada Inc.

2. BC Cancer. Symptom Management Guidelines: Fever and Neutropenia. Available at: http://www.bccancer.bc.ca/nursing-site/Documents/7.%20Fever%20and%20Neutropenia.pdf. Accessed on November 19, 2024.

3. Ezekowitz JA, *et al*. *Can J Cardiol*. 2017;33(11):1342-1433.

4. Cancer Care Alberta. Acute Infusion-Related Adverse Events to Chemotherapy and Monoclonal Antibodies. Available at: https://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-supp019-infusionreactions.pdf. Accessed on November 19, 2024.

5. DeSancho MT and Rand JH. (2003). Bleeding Disorders. In: DW Kufe, et al. (Eds.), *Holland-Frei Cancer Medicine* (6th ed.). BC Decker. Available at: https://www.ncbi.nlm.nih.gov/books/NBK13623/.

AstraZeneca Daiichi-Sankyo

CA-10513E

MEMBER OF INNOVATIVE MEDICINES CANADA

REVIEWED BY PAAB

Pr ENHERTU® trastuzumab deruxtecan