Pr ENHERTU®
trastuzumab deruxtecan

Adverse Events
Management Handbook

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

ENHERTU (trastuzumab deruxtecan) as monotherapy, indicated for:

- the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH–) breast cancer who have received at least one prior line of chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Patients with hormone receptor positive (HR+) breast cancer should have received at least one and be no longer considered eligible for endocrine therapy,
- the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received at least one prior anti-HER2-based regimen either in the metastatic setting, or in the neoadjuvant or adjuvant setting and developed disease recurrence during or within 6 months of completing neoadjuvant or adjuvant therapy, and
- the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received prior treatment with trastuzumab emtansine (T-DM1),

have been issued market authorization without conditions.

HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; ISH=*in situ* hybridization; T-DM1=trastuzumab emtansine.

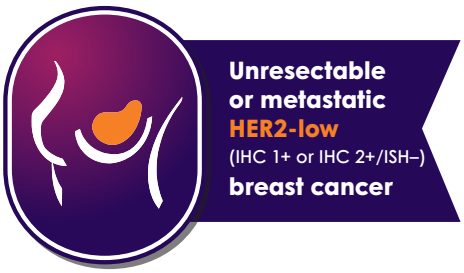
How to use this handbook

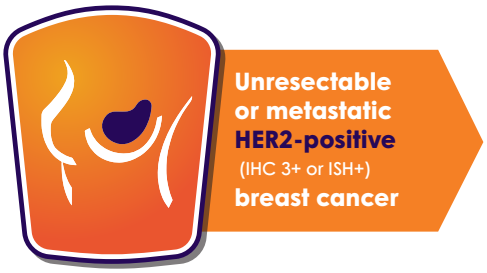
This handbook was created to inform you about adverse events (AEs) that may occur in your patients with breast cancer receiving ENHERTU and recommendations on how to help manage these AEs.

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 in both HER2-low and HER2-positive clinical trials
- AE signs and symptoms to recognize
- AE management and dosage adjustment information

The sections in this handbook include:





- Dose modifications
- Cardiovascular
- Respiratory
- Infusion-related reactions
- Hematologic

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; HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; ISH=*in situ* hybridization.

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The safety profile of ENHERTU was evaluated in DESTINY-Breast04 in 371 patients with unresectable or metastatic HER2-low breast cancer who received at least one dose of ENHERTU 5.4 mg/kg[1]*

The most common adverse reactions (frequency ≥20% All Grades) were:

Adverse Reaction	ENHERTU (N=371) 5.4 mg/kg	
	Any Grade (%)	Grade 3-4 (%)
Nausea	76	5
Fatigue	54	9
Vomiting	40	2
Alopecia	40	0
Anemia	39	10
Constipation	34	0.8
Neutropenia	34	14
Transaminases increased	32	6
Decreased appetite	32	2
Diarrhea	27	1
Musculoskeletal pain	27	1
Thrombocytopenia	26	6
Leukopenia	24	7

Adapted from the ENHERTU Product Monograph

The most common serious adverse reactions (frequency >1%) were ILD/pneumonitis, dyspnea, musculoskeletal pain, anemia, febrile neutropenia, nausea, pyrexia, and vomiting. There were 5 (1.3%) patients with adverse reactions leading to death, 3 attributed to ILD (0.8%) and 1 (0.3%) attributed to both dyspnea and febrile neutropenia.

Unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH–) breast cancer

Adverse reactions leading to dose modifications, dose reduction or treatment discontinuation in DESTINY-Breast04[1]

Dose interruption due to adverse reactions occurred in **26% of patients treated with ENHERTU**	The most frequent adverse reactions (>2%) associated with dose interruption were: • neutropenia (9.2%) • fatigue (5.1%) • anemia (4.6%) • leukopenia (3.5%) • ILD/pneumonitis (3.0%) • transaminases increased (3.0%) • blood bilirubin increased (2.2%)
Dose reductions due to adverse reactions occurred in **20% of patients treated with ENHERTU**	The most frequent adverse reactions (>2%) associated with dose reduction were: • fatigue (4.6%) • nausea (4.6%) • thrombocytopenia (3.5%) • neutropenia (3.0%)
Treatment discontinuation due to adverse reactions occurred in **11% of patients treated with ENHERTU**	The most frequent adverse reaction (>2%) associated with permanent discontinuation was: • ILD/pneumonitis (8.4%)

Adapted from the ENHERTU Product Monograph

Infusion-related reactions† occurred in 0.5% of patients treated with ENHERTU.

HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; ILD=interstitial lung disease; ISH=*in situ* hybridization.
* The safety profile of ENHERTU was evaluated in 371 patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH–) breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast04. The median duration of treatment was 8.2 months (range: 0.2 to 33.3) in the ENHERTU group and 3.5 months (range: 0.3 to 17.6) in the chemotherapy group.
† Grouped term includes injection site reaction and chills.

Common adverse events (≥1% all grades) reported in patients treated with ENHERTU in DESTINY-Breast04[1]*

System Organ Class[a]	ENHERTU 5.4 mg/kg N=371		Chemotherapy N=172	
	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)
Blood and Lymphatic System Disorders				
Anemia[b]	143 (39)	38 (10)	47 (27)	9 (5)
Neutropenia[c]	126 (34)	52 (14)	90 (52)	71 (41)
Thrombocytopenia[d]	95 (26)	22 (6)	16 (9)	1 (0.6)
Leukopenia[e]	89 (24)	25 (7)	56 (33)	33 (19)
Lymphopenia[f]	32 (9)	20 (5)	13 (8)	6 (3)
Febrile neutropenia	4 (1)	3 (0.8)	6 (3)	6 (3)
Cardiac Disorders				
Ejection fraction decreased	16 (4)	1 (0.3)	0	0
Eye Disorders				
Vision blurred[g]	18 (5)	0	5 (3)	0
Gastrointestinal Disorders				
Nausea	282 (76)	17 (5)	52 (30)	0
Vomiting	150 (40)	6 (2)	23 (13)	0
Constipation	126 (34)	3 (0.8)	38 (22)	0
Diarrhea	100 (27)	5 (1)	38 (22)	3 (2)
Abdominal pain[h]	65 (18)	2 (0.5)	23 (13)	0
Stomatitis[i]	49 (13)	1 (0.3)	19 (11)	1 (0.6)
Abdominal distension	20 (5)	0	5 (3)	1 (0.6)
Gastritis	10 (3)	1 (0.3)	1 (0.6)	0
Flatulence	9 (2)	0	0	0
General Disorders and Administration Site Conditions				
Fatigue[j]	199 (54)	32 (9)	83 (48)	8 (5)
Pyrexia	46 (12)	1 (0.3)	22 (13)	0
Hepatobiliary Disorders				
Transaminases increased[k]	120 (32)	21 (6)	54 (31)	17 (10)
Infections and Infestations				
Upper respiratory tract infection[l]	51 (14)	1 (0.3)	9 (5)	0
Investigations				
Weight decreased	60 (16)	1 (0.3)	14 (8)	0
Blood alkaline phosphatase increased	36 (10)	1 (0.3)	5 (3)	0
Metabolism and Nutrition Disorders				
Decreased appetite	118 (32)	9 (2)	33 (19)	2 (1)
Hypokalemia[m]	41 (11)	10 (3)	13 (8)	2 (1)
Dehydration	7 (2)	1 (0.3)	2 (1)	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[n]	99 (27)	5 (1)	45 (26)	0

System Organ Class[a]	ENHERTU 5.4 mg/kg N=371		Chemotherapy N=172	
	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)
Nervous System Disorders				
Headache[o]	55 (15)	1 (0.3)	11 (6)	0
Peripheral neuropathy[p]	50 (13)	0	50 (29)	9 (5)
Dizziness[q]	39 (11)	2 (0.5)	11 (6)	0
Dysgeusia	37 (10)	0	16 (9)	1 (0.6)
Respiratory, Thoracic and Mediastinal Disorders				
Interstitial lung disease[r]	45 (12)	5 (1)	1 (0.6)	0
Epistaxis	39 (11)	0	2 (1)	0
Dyspnea	38 (10)	5 (1)	16 (9)	2 (1)
Cough	36 (10)	0	14 (8)	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	147 (40)	0	57 (33)	0
Rash[s]	40 (11)	0	15 (9)	1 (0.6)
Pruritus	12 (3)	1 (0.3)	7 (4)	0
Skin hyperpigmentation[t]	10 (3)	0	1 (0.6)	0

Adapted from the ENHERTU Product Monograph

HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; ISH=*in situ* hybridization; PT=preferred term.

* The safety profile of ENHERTU was evaluated in 371 patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH–) breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast04. The median duration of treatment was 8.2 months (range: 0.2 to 33.3) in the ENHERTU group and 3.5 months (range: 0.3 to 17.6) in the chemotherapy group.

a National Cancer Institute Common Terminology Criteria for Adverse Events v.5.0 (NCI CTCAE v.5.0)

b Grouped term of anemia includes anemia, hemoglobin decreased, hematocrit decreased, and red blood cell count decreased.

c Grouped term of neutropenia includes neutropenia and neutrophil count decreased.

d Grouped term of thrombocytopenia includes thrombocytopenia and platelet count decreased.

e Grouped term of leukopenia includes leukopenia and white blood cell count decreased.

f Grouped term of lymphopenia includes lymphopenia and lymphocyte count decreased.

g Grouped term of vision blurred includes vision blurred and visual impairment.

h Grouped term of abdominal pain includes PTs of abdominal pain, abdominal discomfort, gastrointestinal pain, abdominal pain lower, and abdominal pain upper.

i Grouped term of stomatitis includes stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, oral mucosal blistering, and oral mucosal eruption.

j Grouped term of fatigue includes fatigue, asthenia, malaise and lethargy.

k Grouped term of transaminases increased includes transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, and hepatic function abnormal.

l Grouped term of upper respiratory tract infection includes upper respiratory tract infection, influenza, influenza like illness, nasopharyngitis, pharyngitis, sinusitis, and rhinitis.

m Grouped term of hypokalemia includes hypokalemia and blood potassium decreased.

n Grouped term of musculoskeletal pain includes back pain, myalgia, pain in extremity, musculoskeletal pain, muscle spasms, bone pain, neck pain, musculoskeletal chest pain, and limb discomfort.

o Grouped term of headache includes headache, migraine, and sinus headache.

p Group term of peripheral neuropathy includes neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy, polyneuropathy, paresthesia, hypoesthesia, dysesthesia, and neuralgia.

q Grouped term of dizziness includes dizziness, dizziness postural and vertigo.

r Interstitial lung disease includes events that were adjudicated as ILD for ENHERTU: pneumonitis, interstitial lung disease, organizing pneumonia, pneumonia, and radiation pneumonitis. Grade 1, Grade 2 and Grade 3 events were reported in 3.5%, 6.5% and 1.3% of patients in the ENHERTU arm, respectively. No Grade 4 events were reported in the ENHERTU arm. Grade 5 adjudicated drug-related ILD events were in 0.8% of patients in the ENHERTU arm.

s Grouped term of rash includes rash, rash pustular, rash maculo-papular, rash papular, rash macular, and rash pruritic.

t Grouped term includes skin hyperpigmentation, skin discoloration, and pigmentation disorder.

ENHERTU safety profile was evaluated in DESTINY-Breast03 in 257 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg[1†]

The most common adverse reactions (frequency ≥20%) were:

Adverse Reaction	ENHERTU (N=257) 5.4 mg/kg	
	Any Grade (%)	Grade 3-4* (%)
Nausea	76	7
Fatigue	49	6
Vomiting	49	2
Neutropenia	43	19
Alopecia	37	0.4
Constipation	34	0
Anemia	33	7
Transaminases increased	32	2
Musculoskeletal pain	31	1
Leukopenia	30	7
Decreased appetite	29	2
Diarrhea	29	1
Thrombocytopenia	26	7
Headache	22	0.4
Respiratory Infections	22	0.8
Abdominal pain	21	0.8

* No Grade 5 adverse reactions were reported in either arm.
Adapted from the ENHERTU Product Monograph

The most common serious adverse reactions (frequency >1%) were interstitial lung disease and vomiting. Fatalities due to adverse reactions occurred in 0.8% of patients including COVID-19 and sudden death (one patient each).

Adverse reactions leading to dose modifications, dose reduction or treatment discontinuation in DESTINY-Breast03

Dose interruption due to adverse events occurred in **34.2% of patients treated with ENHERTU**	The most frequent adverse events (>2%) associated with dose interruption were: • neutropenia (16.7%) • leukopenia (5.1%) • thrombocytopenia (4.3%) • fatigue (4.3%) • anemia (3.5%) • nausea (3.1%) • interstitial lung disease (2.7%)
Dose reductions due to adverse events occurred in **19.8% of patients treated with ENHERTU**	The most frequent adverse events (>2%) associated with dose reduction were: • nausea (6.2%) • neutropenia (3.5%) • fatigue (3.1%)
Treatment discontinuation due to adverse events occurred in **10.5% of patients treated with ENHERTU**	The most frequent adverse event (>2%) associated with permanent discontinuation was: • interstitial lung disease (8.2%)

Adapted from the ENHERTU Product Monograph

Febrile neutropenia occurred in 0.8% of patients treated with ENHERTU.

HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; ISH=*in situ* hybridization.
† The safety profile of ENHERTU was evaluated in 257 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast03. The median duration of treatment was 14.3 months (range: 0.7 to 29.8) in the ENHERTU group and 6.9 months (range: 0.7 to 25.1) in the trastuzumab emtansine group.

Common adverse events (≥1% All Grades) reported in patients treated with ENHERTU in DESTINY-Breast03[1]*

System Organ Class	ENHERTU 5.4 mg/kg N=257		Trastuzumab emtansine 3.6 mg/kg N=261	
	Any Grade n (%)	Grade 3-4 n (%)‡	Any Grade n (%)	Grade 3-4 n (%)‡
Blood and Lymphatic System Disorders				
Neutropenia[a]	110 (43)	49 (19)	31 (12)	8 (3)
Anemia[b]	84 (33)	19 (7)	45 (17)	15 (6)
Leukopenia[c]	78 (30)	17 (7)	22 (8)	1 (0.4)
Thrombocytopenia[d]	66 (26)	19 (7)	139 (53)	67 (26)
Lymphopenia[e]	29 (11)	10 (4)	9 (3)	3 (1)
Cardiac Disorders				
Ejection fraction decrease	6 (2)	0	1 (0.4)	0
Eye Disorders				
Vision blurred	9 (4)	0	3 (1)	0
Gastrointestinal Disorders				
Nausea	195 (76)	17 (7)	79 (30)	1 (0.4)
Vomiting	126 (49)	4 (2)	26 (10†)	2 (0.8)
Constipation	88 (34)	0	51 (20)	0
Diarrhea	75 (29)	3 (1)	18 (7)	1 (0.4)
Abdominal pain[f]	54 (21)	2 (0.8)	20 (8)	1 (0.4)
Stomatitis[g]	51 (20)	2 (0.8)	14 (5)	0
Dyspepsia	29 (11)	0	16 (6)	0
General Disorders and Administration Site Conditions				
Fatigue[h]	127 (49)	15 (6)	91 (35)	2 (0.8)
Hepatobiliary Disorders				
Transaminases increased[i]	81 (32)	6 (2)	121 (46)	20 (8)
Infections and Infestations				
Respiratory Infections[j]	56 (22)	2 (0.8)	32 (12)	3 (1)
Injury, Poisoning and Procedural Complications				
Infusion-related reactions[k]	6 (2)	0	7 (3)	0
Investigations				
Weight decreased	43 (17)	3 (1)	16 (6)	1 (0.4)
Blood alkaline phosphatase increased	35 (14)	1 (0.4)	30 (11)	0
Metabolism and Nutrition Disorders				
Decreased appetite	75 (29)	4 (2)	44 (17)	1 (0.4)
Hypokalemia[l]	33 (13)	9 (4)	26 (10†)	2 (0.8)
Dehydration	11 (4)	1 (0.4)	0	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[m]	80 (31)	3 (1)	66 (25)	1 (0.4)

System Organ Class	ENHERTU 5.4 mg/kg N=257		Trastuzumab emtansine 3.6 mg/kg N=261	
	Any Grade n (%)	Grade 3-4 n (%)‡	Any Grade n (%)	Grade 3-4 n (%)‡
Nervous System Disorders				
Headache[n]	56 (22)	1 (0.4)	42 (16)	0
Peripheral neurophathy[o]	33 (13)	1 (0.4)	37 (14)	1 (0.4)
Dizziness	32 (12)	1 (0.4)	22 (8)	0
Dysgeusia	15 (6)	0	8 (3)	0
Respiratory, Thoracic and Mediastinal Disorders				
Epistaxis	29 (11)	0	42 (16)	1 (0.4)
Cough	27 (11)	1 (0.4)	26 (10†)	0
Interstitial lung disease[p]	27 (11)	2 (0.8)	5 (2)	0
Dyspnea	21 (8)	1 (0.4)	13 (5)	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	95 (37)	1 (0.4)	8 (3)	0
Pruritus	21 (8)	0	18 (7)	1 (0.4)
Rash[q]	20 (8)	0	27 (10)	0
Skin hyperpigmentation[r]	15 (6)	0	0	0

Adapted from the ENHERTU Product Monograph

HER2=human epidermal growth factor receptor 2; PT=preferred term.

* The safety profile of ENHERTU was evaluated in 257 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast03. The median duration of treatment was 14.3 months (range: 0.7 to 29.8) in the ENHERTU group and 6.9 months (range: 0.7 to 25.1) in the trastuzumab emtansine group.

† Actual number prior to rounding = 9.96.

‡ No Grade 5 adverse reactions were reported in either arm.

a Grouped term of neutropenia includes PTs of neutropenia and neutrophil count decreased.

b Grouped term of anemia includes PTs of anemia, hemoglobin decreased, and red blood cell count decreased.

c Grouped term of leukopenia includes PTs of leukopenia and white blood cell count decreased.

d Grouped term of thrombocytopenia includes PTs of thrombocytopenia and platelet count decreased.

e Grouped term of lymphopenia includes PTs of lymphopenia and lymphocyte count decreased.

f Grouped term of abdominal pain includes PTs of abdominal pain, abdominal discomfort, abdominal pain lower, and abdominal pain upper.

g Grouped term of stomatitis includes PTs of stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosal eruption.

h Grouped term of fatigue includes PTs of fatigue, asthenia, malaise and lethargy.

i Grouped term of transaminases increased includes PTs of transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, and hepatic function abnormal.

j Grouped term includes PTs of respiratory tract infection, lower and upper respiratory tract infection, pneumonia, influenza, influenza-like illness, viral upper respiratory infection, bronchitis, and respiratory syncytial virus infection.

k Grouped term includes PTs of hypersensitivity, infusion-related reactions.

l Grouped term of hypokalemia includes PTs of hypokalemia and blood potassium decreased.

m Grouped term of musculoskeletal pain includes PTs of back pain, myalgia, pain in extremity, musculoskeletal pain, muscle spasms, bone pain, neck pain, musculoskeletal chest pain, and limb discomfort.

n Grouped term of headache includes headache and migraine.

o Grouped term includes PTs of neuropathy peripheral, peripheral sensory neuropathy, and paresthesia.

p Interstitial lung disease includes events that were adjudicated as ILD for ENHERTU: pneumonitis, interstitial lung disease, organizing pneumonia, pneumonia, and pulmonary mass. For trastuzumab emtansine: pneumonitis, interstitial lung disease, organizing pneumonia, and pulmonary embolism. Grade 1, Grade 2 and Grade 3 events were reported in 2.7%, 7.0% and 0.8% of subjects in the arm, respectively. No Grade 4 or Grade 5 adjudicated drug-related ILD events were reported either arm.

q Grouped term of rash includes PTs of rash, rash pustular and rash maculo-papular.

r Grouped term of skin hyperpigmentation includes PTs of skin hyperpigmentation, skin discoloration, and pigmentation disorder.

ENHERTU safety profile was also evaluated in a pooled analysis of 234 patients from DESTINY-Breast01 and Study DS8201-A-J101[1]*

The most common adverse events (frequency ≥20%) were:

Adverse Events	% (All Grades)
Nausea	80
Fatigue	60
Vomiting	49
Alopecia	46
Constipation	36
Decreased appetite	35
Anemia	34
Neutropenia	32
Diarrhea	31
Thrombocytopenia	23
Cough	21
Leukopenia	21
Headache	20

Adapted from the ENHERTU Product Monograph

Serious adverse events occurred in 20% of patients receiving ENHERTU.

Serious adverse events in >1% of patients who received ENHERTU were interstitial lung disease, vomiting, nausea, and hypokalemia. Fatalities due to adverse events occurred in 5.1% of patients, including interstitial lung disease (2.6%).

Dose interruption due to adverse events occurred in **25% of patients treated with ENHERTU**	The most frequent adverse events (>2%) associated with dose interruption were: • neutropenia (14.5%) • anemia (3.4%) • upper respiratory tract infection (3.0%) • leukopenia (3.0%) • interstitial lung disease (2.6%) • thrombocytopenia (2.6%) • fatigue (2.1%)
Dose reductions due to adverse events occurred in **15% of patients treated with ENHERTU**	The most frequent adverse events (>2%) associated with dose reduction were: • fatigue (3.8%) • nausea (3.4%) • neutropenia (3.4%)
Treatment discontinuation due to adverse events occurred in **11% of patients treated with ENHERTU**	The most frequent adverse event (>2%) associated with permanent discontinuation was: • interstitial lung disease (9.4%)

Adapted from the ENHERTU Product Monograph

Other clinically relevant adverse events reported in less than 10% of patients were:

- Injury, Poisoning and Procedural Complications: infusion-related events (2.6%)
- Blood and Lymphatic System Disorders: febrile neutropenia (1.7%)
- Cardiac Disorders: ejection fraction decrease (1.3%)
- Infections and Infestations: sepsis (0.9%)

* The safety profile of ENHERTU has been evaluated in a pooled analysis of 234 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in Phase 2 DESTINY-Breast01 and Phase 1 Study DS8201-A-J101. The median duration of treatment was 9.8 months (range: 0.7 to 37.1).

Adverse drug events reported in DESTINY-Breast01 and DS8201-A-J101 trials (≥10% all grades or ≥2% Grades 3 or 4)[1*]

System Organ Class[a]	ENHERTU 5.4 mg/kg N=234	
	All Grades n (%)	Grades 3 or 4 n (%)
Blood and Lymphatic System Disorders		
Anemia[b]	79 (34)	21 (9)
Neutropenia[c]	76 (32)	44 (19)
Thrombocytopenia[d]	54 (23)	10 (4)
Leucopenia[e]	48 (21)	13 (6)
Lymphopenia[f]	26 (11)	12 (5)
Eye Disorders		
Dry eye	27 (12)	1 (0.4)
Gastrointestinal Disorders		
Nausea	187 (80)	16 (7)
Vomiting	114 (49)	10 (4)
Constipation	84 (36)	2 (0.9)
Diarrhea	72 (31)	6 (3)
Abdominal pain[g]	46 (20)	3 (1)
Stomatitis[h]	35 (15)	2 (0.9)
Dyspepsia	33 (14)	0
General Disorders and Administration Site Conditions		
Fatigue[i]	141 (60)	15 (6)
Infections and Infestations		
Upper respiratory tract infections[j]	43 (18)	15 (6)
Investigations		
Aspartate aminotransferase increased	35 (15)	2 (0.9)
Alanine aminotransferase increased	25 (11)	3 (1)
Nervous System Disorders		
Headache[k]	47 (20)	0
Dizziness	25 (11)	0
Metabolism and Nutrition Disorders		
Decreased appetite	81 (35)	3 (1)
Hypokalemia	30 (13)	8 (3)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	50 (21)	0
Dyspnea	34 (15)	4 (2)
Epistaxis	33 (14)	0
Interstitial lung disease[l]	32 (14)	1 (0.4)
Skin and Subcutaneous Tissue Disorders		
Alopecia	108 (46)	1 (0.4)
Rash[m]	30 (13)	1 (0.4)

Adapted from the ENHERTU Product Monograph

HER2=human epidermal growth factor receptor 2; PT=preferred term.

* The safety profile of ENHERTU was evaluated in a pooled analysis of 234 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in Phase 2 DESTINY-Breast01 and Phase 1 Study DS8201-A-J101. ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 9.8 months (range: 0.7 to 37.1). The studies excluded patients with a history of treated ILD or ILD at screening, patients with untreated, symptomatic brain metastases and patients with a history of clinically significant cardiac disease.[1]

a Based on Medical Dictionary for Regulatory Activities (MedDRA) version 20.1; events were graded using NCI-CTCAE version 4.03.

b Grouped term of anemia includes PTs of anemia, hemoglobin decreased, red blood cell count decreased, and hematocrit decreased.

c Grouped term of neutropenia includes PTs of neutropenia and neutrophil count decreased.

d Grouped term of thrombocytopenia includes PTs of thrombocytopenia and platelet count decreased.

e Grouped term of leukopenia includes PTs of leukopenia and white blood cell count decreased.

f Grouped term of lymphopenia includes PTs of lymphopenia and lymphocyte count decreased.

g Grouped term of abdominal pain includes PTs of abdominal discomfort, gastrointestinal pain, abdominal 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 and asthenia.

j Upper respiratory tract infection (grouped term) includes PTs of upper respiratory tract infection, influenza, and influenza-like illness.

k Grouped term of headache includes PTs of headache, sinus headache, and migraine.

l Interstitial lung disease includes events that were adjudicated as ILD: pneumonitis, interstitial lung disease, respiratory failure, organizing pneumonia, acute respiratory failure, lung infiltration, lymphangitis, and alveolitis; includes 6 (2.6%) fatal events.

m Grouped term of rash includes PTs of rash, rash pustular, and rash maculo-papular.

ENHERTU safety profile was also evaluated in 404 patients from DESTINY-Breast02[1]*

The most common adverse events (frequency ≥20%) were:

Adverse Events	% (All Grades)
Nausea	73
Fatigue	62
Vomiting	38
Alopecia	37
Constipation	35
Neutropenia	34
Decreased appetite	31
Anemia	29
Diarrhea	27
Musculoskeletal pain	25
Transaminases increased	23
Abdominal pain	22
Thrombocytopenia	22
Headache	20

Adapted from the ENHERTU Product Monograph

Serious adverse events in >1% of patients who received ENHERTU were interstitial lung disease, vomiting, fatigue and nausea. Fatalities due to adverse events occurred in 2.5% of patients including 2 (0.5%) patients with fatal adverse reactions of ILD.

Dose interruption due to adverse events occurred in **30.7% of patients treated with ENHERTU**	The most frequent adverse events (>2%) associated with dose interruption were: • neutropenia (15.4%) • anemia (6.2%) • fatigue (5.0%) • leukopenia (4.0%) • thrombocytopenia (2.5%)
Dose reductions due to adverse events occurred in **21.8% of patients treated with ENHERTU**	The most frequent adverse events (>2%) associated with dose reduction were: • fatigue (7.4%) • nausea (5.7%) • neutropenia (3.7%) • vomiting (2.5%)
Treatment discontinuation due to adverse events occurred in **10.9% of patients treated with ENHERTU**	The most frequent adverse event (>2%) associated with permanent discontinuation was: • interstitial lung disease (8.7%)

Adapted from the ENHERTU Product Monograph

Febrile neutropenia occurred in 0.3% of patients treated with ENHERTU.

* The safety profile of ENHERTU has been evaluated in 404 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast02. The median duration of treatment was 11.3 months (range: 0.7 to 45.1) in the ENHERTU group and 4.6 months (range: 0.1 to 43.0) in the physician's choice group.

Adverse drug events reported in DESTINY-Breast02 trial (≥1% all grades)[1*]

System Organ Class	ENHERTU 5.4 mg/kg N=404		Treatment of physician's choice N=195	
	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)
Blood and Lymphatic System Disorders				
Neutropenia[a]	137 (34)	71 (18)	23 (12)	8 (4)
Anemia[b]	118 (29)	33 (8)	27 (14)	6 (3)
Thrombocytopenia[c]	87 (22)	8 (2)	23 (12)	4 (2)
Leukopenia[d]	79 (20)	27 (7)	12 (6)	0
Lymphopenia[e]	50 (12)	19 (5)	6 (3)	2 (1)
Cardiac Disorders				
Ejection fraction decrease	17 (4)	2 (0.5)	1 (0.5)	0
Eye Disorders				
Dry eye	23 (6)	1 (0.3)	9 (5)	0
Vision blurred[f]	12 (3)	0	2 (1)	0
Gastrointestinal Disorders				
Nausea	293 (73)	27 (7)	73 (37)	5 (3)
Vomiting	152 (38)	15 (4)	25 (13)	2 (1)
Constipation	142 (35)	1 (0.3)	21 (11)	1 (0.5)
Diarrhea	109 (27)	11 (3)	105 (54)	14 (7)
Abdominal pain[g]	88 (22)	4 (1)	39 (20)	4 (2)
Dyspepsia	48 (12)	0	18 (9)	0
Stomatitis[h]	47 (12)	4 (1)	40 (21)	2 (1)
General Disorders and Administration Site Conditions				
Fatigue[i]	249 (62)	38 (9)	72 (37)	2 (1)
Hepatobiliary Disorders				
Transaminases increased[j]	93 (23)	10 (2)	29 (15)	3 (2)
Injury, Poisoning and Procedural Complications				
Infusion-related reactions[k]	5 (1)	0	3 (2)	0
Investigations				
Weight decreased	71 (18)	1 (0.3)	7 (4)	0
Blood bilirubin increased[l]	31 (8)	2 (0.5)	25 (13)	3 (2)
Blood alkaline phosphatase increased	24 (6)	1 (0.3)	8 (4)	0
Blood creatinine increased	8 (2)	0	1 (0.5)	0
Metabolism and Nutrition Disorders				
Decreased appetite	125 (31)	7 (2)	35 (18)	1 (0.5)
Hypokalemia[m]	33 (8)	12 (3)	13 (7)	5 (3)
Dehydration	11 (3)	3 (0.7)	3 (2)	1 (0.5)
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[n]	101 (25)	3 (1)	35 (18)	1 (0.5)

System Organ Class	ENHERTU 5.4 mg/kg N=404		Treatment of physician's choice N=195	
	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)
Nervous System Disorders				
Headache[o]	82 (20)	1 (0.3)	12 (6)	0
Dizziness	33 (8)	1 (0.3)	13 (7)	0
Dysgeusia	33 (8)	0	12 (6)	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	53 (13)	0	20 (10)	0
Interstitial lung disease[p]	42 (10)	3 (0.7)	1 (0.5)	1 (0.5)
Dyspnea	34 (8)	1 (0.3)	32 (16)	0
Epistaxis	33 (8)	0	8 (4)	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	150 (37)	1 (0.3)	8 (4)	0
Rash[q]	34 (8)	0	32 (16)	0
Pruritus	22 (6)	0	8 (4)	0
Skin hyperpigmentation[r]	21 (5)	0	8 (4)	0

Adapted from the ENHERTU Product Monograph

HER2=human epidermal growth factor receptor 2; PT=preferred term.

* The safety profile of ENHERTU has been evaluated in 404 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast02. The median duration of treatment was 11.3 months (range: 0.7 to 45.1).[1]

a Grouped term of neutropenia includes PTs of neutropenia and neutrophil count decreased.

b Grouped term of anemia includes PTs of anemia, hemoglobin decreased and red blood cell count decreased.

c Grouped term of thrombocytopenia includes PTs of thrombocytopenia and platelet 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 vision blurred includes PTs of Vision blurred and Visual impairment.

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 and mouth ulceration.

i Grouped term of fatigue includes PTs of fatigue, asthenia, malaise, and lethargy

j Grouped term of transaminases increased includes PTs of transaminases increased, alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, hepatic function abnormal, liver function test increased, and hypertransaminasemia.

k Group term includes PT of infusion-related reaction (n=5).[2]

l Grouped term of blood bilirubin increased includes PTs of Blood bilirubin increased, Hyperbilirubinemia, Bilirubin conjugated increased, and Blood bilirubin unconjugated increased.

m Grouped term of hypokalemia includes PTs of hypokalemia and blood potassium decreased.

n Grouped term of musculoskeletal pain includes PTs of back pain, myalgia, pain in extremity, musculoskeletal pain, muscle spasms, bone pain, neck pain, musculoskeletal chest pain, and limb discomfort.

o Grouped term of headache includes PTs of headache and migraine.

p Grouped term of interstitial lung disease includes events that were adjudicated as drug-related ILD: interstitial lung disease, pneumonitis, lung disorder, pneumonia, idiopathic interstitial pneumonia, pulmonary toxicity, acute interstitial pneumonia and organizing pneumonia.

q Group term of rash includes PTs of Rash, Rash pustular, Rash maculo-papular, Rash papular, Rash macular, and Rash pruritic.

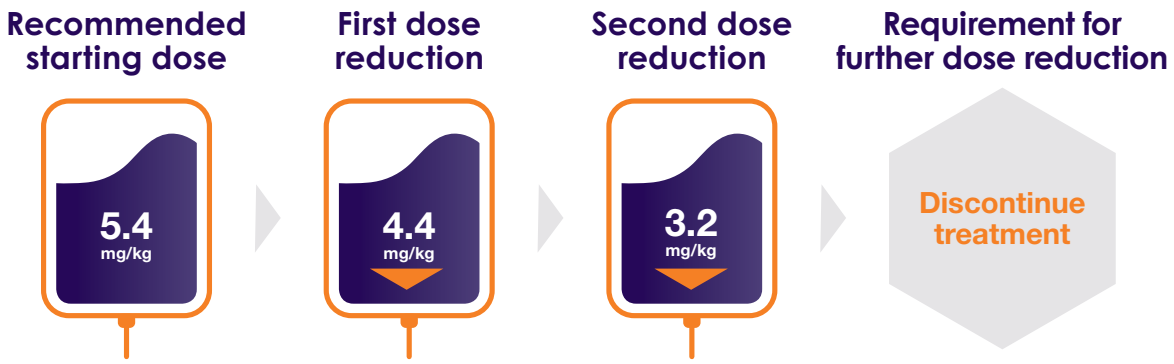
r Group term of skin hyperpigmentation includes PTs of Skin hyperpigmentation, Skin discolouration, and Pigmentation disorder.

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 27, 29, 31, and 34-35).

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

Dose reduction schedule for patients with breast cancer



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.

For more information on ENHERTU dosing and administration, please read the ENHERTU Dosing and Administration Handbook.

Please consult the ENHERTU Product Monograph 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]

ILD occurred in 165 (12.8%) of the 1287 patients with unresectable or metastatic breast cancer treated with 5.4 mg/kg of ENHERTU in clinical trials (all grades; fatal outcomes have been observed).*†‡§ ILD was more frequently reported in patients with moderate renal impairment (CrCl ≥30 and <60 mL/min) at baseline.

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

- Grade 1: 3.3%
- Grade 2: 7.6%
- Grade 3: 0.9%
- Grade 5: 1.0%

ILD occurred in 11% of the 257 patients with unresectable or metastatic HER2-positive breast cancer treated with 5.4 mg/kg of ENHERTU in DESTINY-Breast03 (all grades; fatal outcomes have been observed):*

- Grade 1: 2.7%
- Grade 2: 7.0%
- Grade 3: 0.8%
- No Grade 4 or Grade 5 adjudicated drug-related ILD events were reported in either arm

ILD occurred in 45 (12%) of the 371 patients with unresectable or metastatic HER2-low breast cancer treated with 5.4 mg/kg of ENHERTU in DESTINY-Breast04 (all grades; fatal outcomes have been observed):‡

- Grade 1: 3.5%
- Grade 2: 6.5%
- Grade 3: 1.3%
- No Grade 4 events were reported in the ENHERTU arm
- Grade 5 adjudicated drug-related ILD events were reported in 0.8% of patients in the ENHERTU arm

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 above.

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.

CrCl=creatinine clearance; HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; ILD=interstitial lung disease; ISH=*in situ* hybridization.

* The safety profile of ENHERTU was evaluated in 257 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast03. The median duration of treatment was 14.3 months (range: 0.7 to 29.8).

† The safety profile of ENHERTU was evaluated in a pooled analysis of 234 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in Phase 2 DESTINY-Breast01 and Phase 1 Study DS8201-A-J101. The median duration of treatment was 9.8 months (range: 0.7 to 37.1). Cases of ILD were determined by independent central review.

‡ The safety profile of ENHERTU was evaluated in 371 patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH–) breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast04. The median duration of treatment was 8.2 months (range: 0.2 to 33.3) in the ENHERTU group and 3.5 months (range: 0.3 to 17.6) in the chemotherapy group.

§ The safety profile of ENHERTU has been evaluated in 404 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast02. The median duration of treatment was 11.3 months (range: 0.7 to 45.1) in the ENHERTU group and 4.6 months (range: 0.1 to 43.0) in the physician's choice group.[1]

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 23).</td></tr>
<tr><td colspan="2">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).

Hematologic

Neutropenia[1]

Cases of neutropenia, including febrile neutropenia, were reported in patients with unresectable or metastatic breast cancer treated with 5.4 mg/kg of ENHERTU in clinical trials (n=1287).*†‡§

- A decrease in neutrophil count was reported in 35.7% (n=460) of patients
  - 17.5% (n=225) had Grade 3 or 4 events
- 0.9% developed febrile neutropenia

Signs and symptoms of an infection which may be caused by neutropenia[3]

- 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.

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

* The safety profile of ENHERTU was evaluated in 257 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast03. The median duration of treatment was 14.3 months (range: 0.7 to 29.8).

† The safety profile of ENHERTU was evaluated in a pooled analysis of 234 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in Phase 2 DESTINY-Breast01 and Phase 1 Study DS8201-A-J101. The median duration of treatment was 9.8 months (range: 0.7 to 37.1). Cases of ILD were determined by independent central review.

‡ The safety profile of ENHERTU was evaluated in 371 patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH–) breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast04. The median duration of treatment was 8.2 months (range: 0.2 to 33.3) in the ENHERTU group and 3.5 months (range: 0.3 to 17.6) in the chemotherapy group.

§ The safety profile of ENHERTU has been evaluated in 404 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast02. The median duration of treatment was 11.3 months (range: 0.7 to 45.1) in the ENHERTU group and 4.6 months (range: 0.1 to 43.0) in the physician's choice group.[1]

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 23).**
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 23).**

Adapted from the ENHERTU Product Monograph

Thrombocytopenia[1]

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 23).**

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]

Asymptomatic LVEF decrease occurred in 53 (4.1%) of the 1287 patients with unresectable or metastatic breast cancer treated with 5.4 mg/kg of ENHERTU in clinical trials.*†‡§

- Grade 2: 3.0% (n=38)
  - o Grade 2 LVEF decrease as abnormal laboratory findings was also observed
- Grade 3: 0.5% (n=6)

No decreases of LVEF to less than 20% were observed.

- Treatment with ENHERTU has not been studied in patients with a history of clinically significant cardiac disease or LVEF less than 50% prior to initiation of treatment

Signs and symptoms of LVEF decrease[4]

- 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.

HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; ISH=*in situ* hybridization; LVEF=left ventricular ejection fraction.
* The safety profile of ENHERTU was evaluated in 257 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast03. The median duration of treatment was 14.3 months (range: 0.7 to 29.8).
† The safety profile of ENHERTU was evaluated in a pooled analysis of 234 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in Phase 2 DESTINY-Breast01 and Phase 1 Study DS8201-A-J101. The median duration of treatment was 9.8 months (range: 0.7 to 37.1). Cases of ILD were determined by independent central review.
‡ The safety profile of ENHERTU was evaluated in 371 patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH–) breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast04. The median duration of treatment was 8.2 months (range: 0.2 to 33.3) in the ENHERTU group and 3.5 months (range: 0.3 to 17.6) in the chemotherapy group.
§ The safety profile of ENHERTU has been evaluated in 404 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast02. The median duration of treatment was 11.3 months (range: 0.7 to 45.1) in the ENHERTU group and 4.6 months (range: 0.1 to 43.0) in the physician's choice group.[1]

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

<table>
<tr><th>Adverse event</th><th colspan="2">Severity†</th><th colspan="2">Treatment modification</th></tr>
<tr><td rowspan="7">Left ventricular ejection fraction (LVEF) decreased</td><td colspan="2">LVEF greater than 45% and absolute decrease from baseline is 10% to 20%</td><td>• Continue treatment with ENHERTU.</td><td></td></tr>
<tr><td rowspan="4">LVEF 40% to 45%</td><td>And absolute decrease from baseline is less than 10%</td><td>• Continue treatment with ENHERTU.
* Repeat LVEF assessment within 3 weeks.</td><td>*</td></tr>
<tr><td rowspan="3">And absolute decrease from baseline is 10% to 20%</td><td>• Interrupt ENHERTU.
* Repeat LVEF assessment within 3 weeks.</td><td>*</td></tr>
<tr><td>• If LVEF recovers to within 10% from baseline.</td><td>Resume treatment with ENHERTU at the same dose.</td></tr>
<tr><td>• If LVEF has not recovered to within 10% from baseline.</td><td>Permanently discontinue ENHERTU.</td></tr>
<tr><td colspan="2" rowspan="2">LVEF less than 40% or absolute decrease from baseline is greater than 20%</td><td>• Interrupt ENHERTU.
* Repeat LVEF assessment within 3 weeks.</td><td>*</td></tr>
<tr><td>• If LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed.</td><td>Permanently discontinue ENHERTU.</td></tr>
<tr><td colspan="2">Symptomatic congestive heart failure (CHF)</td><td colspan="2">Permanently discontinue ENHERTU.</td></tr>
</table>

Adapted from the ENHERTU Product Monograph

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).

Infusion-related reactions (IRRs)

Cases of infusion-related reactions (IRRs), including a serious case of hypersensitivity, were reported in patients with unresectable or metastatic breast cancer treated with 5.4 mg/kg of ENHERTU in clinical trials (n=1287).*†‡§**

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

Signs and symptoms of IRRs[6]

- 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.

HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; IRR=infusion-related reaction; ISH=*in situ* hybridization; PT=preferred term.

* The safety profile of ENHERTU was evaluated in 257 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast03. The median duration of treatment was 14.3 months (range: 0.7 to 29.8).

† The safety profile of ENHERTU was evaluated in a pooled analysis of 234 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in Phase 2 DESTINY-Breast01 and Phase 1 Study DS8201-A-J101. The median duration of treatment was 9.8 months (range: 0.7 to 37.1). Cases of ILD were determined by independent central review.

‡ The safety profile of ENHERTU was evaluated in 371 patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH–) breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast04. The median duration of treatment was 8.2 months (range: 0.2 to 33.3) in the ENHERTU group and 3.5 months (range: 0.3 to 17.6) in the chemotherapy group.

§ IRRs occurred in 0.5%¶ of patients in the DESTINY-Breast04, 2.3% of patients in the DESTINY-Breast03, in 2.6% of patients in DESTINY-Breast01 and DS8201-A-J101 trials and in 1% of patients in DESTINY-Breast02.

¶ Grouped term includes PTs of hypersensitivity, infusion-related reactions in DESTINY-Breast03. Grouped term includes injection site reaction and chills in DESTINY-Breast04. In DESTINY-Breast02 , the group term includes PT of infusion-related reaction (n=5).[1,2]

** The safety profile of ENHERTU has been evaluated in 404 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast02. The median duration of treatment was 11.3 months (range: 0.7 to 45.1) in the ENHERTU group and 4.6 months (range: 0.1 to 43.0) in the physician's choice group.[1]

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 (T-DM1).

Other relevant warnings and precautions:

- Left ventricular ejection fraction (LVEF) decrease
- Anemia/thrombocytopenia
- Symptomatic congestive heart failure (CHF)
- Driving and operating machinery
- Neutropenia
- Infusion-related reactions (IRR)
- Interstitial lung disease (ILD)/pneumonitis
- Race (Asian populations)
- 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 23).**
		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 23).**
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 23).**
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 23).**

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.**	

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

Pr ENHERTU®
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References:

1. ENHERTU Product Monograph. AstraZeneca Canada Inc. January 17, 2025. **2.** Data on file. **3.** 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 June 21, 2022. **4.** Ezekowitz JA *et al. Can J Cardiol.* 2017;33(11):1342-1433. **5.** Data on file. **6.** 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 June 21, 2022.

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