For eligible previously treated patients with **HER2-low (IHC 1+ or IHC 2+/ISH–)** mBC[1]

ENHERTU®
fam-trastuzumab deruxtecan-nxki
20 mg/mL INJECTION FOR INTRAVENOUS USE

GROUNDBREAKING SURVIVAL
DEFINING THE POSSIBILITIES IN HER2-LOW mBC[1]

ENHERTU significantly improved mPFS and mOS vs chemotherapy in HR+/HER2-low mBC[1]

Primary Endpoint[1]

Nearly doubled mPFS

10.1 months mPFS
ENHERTU
(n=331; 95% CI: 9.5, 11.5)

vs

5.4 months mPFS
Chemotherapy
(n=163; 95% CI: 4.4, 7.1)

(HR=0.51; 95% CI: 0.40, 0.64; *P*<0.0001)

Secondary Endpoint[1]

>6-month increase in mOS

23.9 months mOS
ENHERTU
(n=331; 95% CI: 20.8, 24.8)

vs

17.5 months mOS
Chemotherapy
(n=163; 95% CI: 15.2, 22.4)

(HR=0.64; 95% CI: 0.48, 0.86; *P*=0.0028)

Survival benefit observed in the overall study population (HR+ and HR–)[1]

- 9.9 months mPFS with ENHERTU (n=373; 95% CI: 9.0, 11.3) vs 5.1 months (n=184; 95% CI: 4.2, 6.8) with chemotherapy (secondary endpoint; HR=0.50; 95% CI: 0.40, 0.63; *P*<0.0001)
- 23.4 months mOS with ENHERTU (n=373; 95% CI: 20.0, 24.8) vs 16.8 months (n=184; 95% CI: 14.5, 20.0) with chemotherapy (secondary endpoint; HR=0.64; 95% CI: 0.49, 0.84; *P*=0.001)

NCCN CATEGORY 1, Preferred Systemic Therapy Regimen—NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommends fam-trastuzumab deruxtecan-nxki (ENHERTU) as the Category 1 preferred systemic therapy option for recurrent unresectable (local or regional) or stage IV HER2-negative disease, for patients with tumors that are HER2 IHC 1+ or 2+ and ISH negative.[2,a]

[a]For patients with tumors that are HER2 IHC 1+ or 2+ and ISH negative, who have received at least 1 prior line of chemotherapy for metastatic disease and, if tumor is HR+, are refractory to endocrine therapy.

DESTINY-Breast04 is a phase 3, international, multicenter, randomized, open-label trial of ENHERTU vs physician's choice of chemotherapy in 557 patients with HER2-low mBC (IHC 1+ or IHC 2+/ISH–). The study included 2 cohorts: 494 HR+ and 63 HR–. Patients had 1 or 2 prior lines of chemotherapy in the metastatic setting, and if HR+, had also progressed on or were refractory to endocrine therapy. Patients in the ENHERTU arm received 5.4 mg/kg IV Q3W and patients in the chemotherapy arm could receive eribulin, capecitabine, gemcitabine, nab-paclitaxel, or paclitaxel. Treatment was continued until unacceptable toxicity or disease progression. The primary endpoint was PFS in the HR+ population (determined by BICR according to mRECIST v1.1). Select secondary endpoints included PFS (BICR) in the overall study population (HR+ and HR–), OS in the HR+ population, OS in the overall study population (HR+ and HR–), ORR in the HR+ population, and DOR in the HR+ population.[1,3]

Important Safety Information

Indication

ENHERTU is a HER2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of adult patients with:

- Unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

- **Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU. 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 to immediately report symptoms.**
- **Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception.**

Please see Important Safety Information throughout as well as on pages 6-7, and click here for full Prescribing Information, including Boxed WARNINGS, and click here for Medication Guide.

HR+
(n=494)

In patients with **HR+/HER2-low mBC**

Nearly doubled mPFS vs chemotherapy with the first and only HER2-directed therapy for HER2-low mBC[1]

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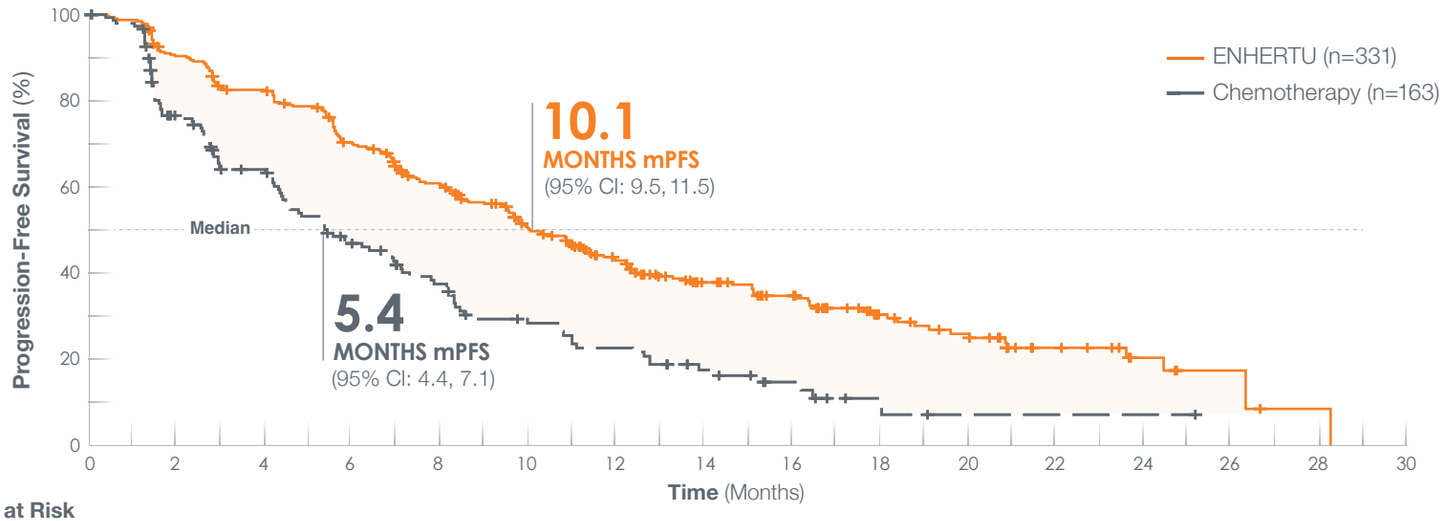
ENHERTU demonstrated a statistically significant and clinically meaningful PFS benefit in HR+/HER2-low mBC (primary endpoint, BICR)[1,4]



Number at Risk

ENHERTU	331	290	262	218	182	142	107	78	64	37	28	14	7	4	1	0
Chemotherapy	163	105	84	57	43	30	24	14	8	3	1	1	1	0		

ENHERTU reduced the risk of disease progression or death by 49% vs chemotherapy (HR=0.51; 95% CI: 0.40, 0.64; *P*<0.0001)[1]

mPFS in select prespecified exploratory patient subgroups[5]

HER2 IHC Score	ENHERTU	Chemotherapy
IHC 1+ (n=288; HR=0.48; 95% CI: 0.35, 0.65)	10.3 months (n=119/192; 95% CI: 8.6, 12.3)	5.3 months (n=66/96; 95% CI: 4.1, 7.8)
IHC 2+/ISH– (n=206; HR=0.55; 95% CI: 0.38, 0.80)	10.1 months (n=92/139; 95% CI: 8.2, 12.2)	5.9 months (n=44/67; 95% CI: 4.3, 7.9)

- Prespecified exploratory patient subgroups were not tested for statistical significance and not powered to show differences between treatment arms or between subgroups

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Important Safety Information (cont'd)

Warnings and Precautions

Interstitial Lung Disease / Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with ENHERTU. A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment. Advise patients to immediately report cough, dyspnea, fever, and/or any new or worsening respiratory symptoms. Monitor patients for signs and symptoms of ILD. Promptly investigate evidence of ILD. Evaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist. For asymptomatic ILD/pneumonitis (Grade 1), interrupt ENHERTU until resolved to Grade 0, then if resolved in ≤28 days from date of onset, maintain dose. If resolved in >28 days from date of onset, reduce dose one level. Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥0.5 mg/kg/day prednisolone or equivalent). For symptomatic ILD/pneumonitis (Grade 2 or greater), permanently discontinue ENHERTU. Promptly initiate systemic corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥1 mg/kg/day prednisolone or equivalent) and continue for at least 14 days followed by gradual taper for at least 4 weeks.

In patients with **HER2-low mBC**

Survival benefit observed in the overall study population (HR+ and HR–)[1,4]

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Summary of DESTINY-Breast04 efficacy results by patient population[1,4,6,a,b]

	Overall study population (N=557)		HR+/HER2-low cohort (n=494)		Exploratory HR–/HER2-low cohort (n=58)	
	ENHERTU (n=373)	Chemotherapy (n=184)	ENHERTU (n=331)	Chemotherapy (n=163)	ENHERTU (n=40)	Chemotherapy (n=18)
mPFS (mo)	**9.9** (95% CI: 9.0, 11.3)	**5.1** (95% CI: 4.2, 6.8)	**10.1** (95% CI: 9.5, 11.5)	**5.4** (95% CI: 4.4, 7.1)	**8.5** (95% CI: 4.3, 11.7)	**2.9** (95% CI: 1.4, 5.1)
HR (*P*-value)	**0.50 (95% CI: 0.40, 0.63)** (*P*<0.0001)		**0.51 (95% CI: 0.40, 0.64)** (*P*<0.0001)		**0.46 (95% CI: 0.24, 0.89)**	
mOS (mo)	**23.4** (95% CI: 20.0, 24.8)	**16.8** (95% CI: 14.5, 20.0)	**23.9** (95% CI: 20.8, 24.8)	**17.5** (95% CI: 15.2, 22.4)	**18.2** (95% CI: 13.6, NE)	**8.3** (95% CI: 5.6, 20.6)
HR (*P*-value)	**0.64 (95% CI: 0.49, 0.84)** (*P*=0.001)		**0.64 (95% CI: 0.48, 0.86)** (*P*=0.0028)		**0.48 (95% CI: 0.24, 0.95)**	
ORR	**52.3%** (n=195) (95% CI: 47.1, 57.4)	**16.3%** (n=30) (95% CI: 11.3, 22.5)	**52.9%** (n=175) (95% CI: 47.3, 58.4)	**16.6%** (n=27) (95% CI: 11.2, 23.2)	**50.0%** (n=20) (95% CI: 33.8, 66.2)	**16.7%** (n=3) (95% CI: 3.6, 41.4)
CR	**3.5%** (n=13)	**1.1%** (n=2)	**3.6%** (n=12)	**0.6%** (n=1)	**2.5%** (n=1)	**5.6%** (n=1)
PR	**49.1%** (n=183)	**15.2%** (n=28)	**49.5%** (n=164)	**16.0%** (n=26)	**47.5%** (n=19)	**11.1%** (n=2)
mDOR (mo)	**10.7** (95% CI: 8.5, 13.2)	**6.8** (95% CI: 6.0, 9.9)	**10.7** (95% CI: 8.5, 13.7)	**6.8** (95% CI: 6.5, 9.9)	**8.6** (95% CI: 7.1, 13.9)	**4.9** (95% CI: 3.7, 6.0)

[a]For the primary and secondary endpoints, the hormone receptor status is based on data collected using the interactive web/voice response system at the time of randomization, which includes mis-stratified patients.[4] [b]For other endpoints, hormone receptor status is based on data from the electronic data capture corrected for mis-stratification.[4]

- The HR– cohort was an exploratory population. The data are descriptive and were not tested for statistical significance, nor powered to show a difference between treatment arms
- ORR and mDOR were not tested for statistical significance, and were not powered to show differences between treatment arms

Important Safety Information (cont'd)

Warnings and Precautions

Interstitial Lung Disease / Pneumonitis (cont'd)

Metastatic Breast Cancer and Other Solid Tumors (5.4 mg/kg)
In patients with metastatic breast cancer and other solid tumors treated with ENHERTU 5.4 mg/kg, ILD occurred in 12% of patients. Fatal outcomes due to ILD and/or pneumonitis occurred in 1.0% of patients treated with ENHERTU. Median time to first onset was 5 months (range: 0.9 to 23).

Neutropenia

Severe neutropenia, including febrile neutropenia, can occur in patients treated with ENHERTU. Monitor complete blood counts prior to initiation of ENHERTU and prior to each dose, and as clinically indicated. For Grade 3 neutropenia (Absolute Neutrophil Count [ANC] <1.0 to 0.5 x 10^9/L), interrupt ENHERTU until resolved to Grade 2 or less, then maintain dose. For Grade 4 neutropenia (ANC <0.5 x 10^9/L), interrupt ENHERTU until resolved to Grade 2 or less, then reduce dose by one level. For febrile neutropenia (ANC <1.0 x 10^9/L and temperature >38.3° C or a sustained temperature of ≥38° C for more than 1 hour), interrupt ENHERTU until resolved, then reduce dose by one level.

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Safety data from DESTINY-Breast04 further established the benefit-risk profile in HER2-low mBC[1]

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The majority of adverse reactions were Grade 1 or 2[1]

- The median duration of treatment was 8 months (range: 0.2 to 33) with ENHERTU and 3.5 months (range: 0.3 to 18) with chemotherapy[1,4]
- Prophylactic or supportive treatment of treatment-induced adverse reactions was at the discretion of the treating physician[6]

Common adverse reactions (≥10% all Grades or ≥2% Grades 3 or 4) in patients treated with ENHERTU in DESTINY-Breast04[1]

Adverse reactions		ENHERTU 5.4 mg/kg (n=371)		Chemotherapy (n=172)	
		All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Gastrointestinal disorders	Nausea	76	4.6	30	0
	Vomiting	40	1.6	13	0
	Constipation	34	0.8	22	0
	Diarrhea	27	1.3	22	1.7
	Abdominal pain[a]	18	0.5	13	0
	Stomatitis[b]	13	0.3	12	0.6
General disorders and administration site conditions	Fatigue[c]	54	9	48	4.7
	Pyrexia	12	0.3	13	0
Skin and subcutaneous tissue disorders	Alopecia	40	0	33	0
	Rash[d]	13	0	23	4.7
Blood and lymphatic system disorders	Anemia[e]	39	10	27	5
Metabolism and nutrition disorders	Decreased appetite	32	2.4	19	1.2
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[f]	32	1.3	31	0.6
Investigations	Decreased weight	16	0.3	8	0
Vascular disorders	Hemorrhage[g]	16	0	3.5	0
Nervous system disorders	Headache[h]	15	0.3	6	0
	Peripheral neuropathy[i]	13	0	29	5
	Dizziness[j]	11	0.5	6	0
Infections and infestations	Upper respiratory tract infection[k]	14	0.3	5	0
Respiratory, thoracic, and mediastinal disorders	Interstitial lung disease[l]	12	1.3	0.6	0
	Dyspnea	10	1.3	9	1.2

Events were graded using NCI-CTCAE version 5.0.

[a]Including abdominal pain, abdominal discomfort, lower abdominal pain, and upper abdominal pain. [b]Including stomatitis, aphthous ulcer, mouth ulceration, and pharyngeal inflammation. [c]Including fatigue, asthenia, and malaise. [d]Including rash, pustular rash, pruritic rash, maculo-papular rash, palmar-plantar erythrodysesthesia syndrome, papular rash, macular rash, eczema, erythema multiforme, dermatitis, urticarial dermatitis, drug eruption, and dermatitis bullous. [e]Including anemia, decreased hemoglobin, and decreased red blood cell count. [f]Including back pain, myalgia, pain in extremity, musculoskeletal pain, bone pain, musculoskeletal chest pain, arthralgia, noncardiac chest pain, musculoskeletal stiffness, arthritis, spinal pain, and neck pain. [g]Including esophageal varices, hemorrhage, hemorrhoidal hemorrhage, epistaxis, hematuria, conjunctival hemorrhage, vaginal hemorrhage, gingival bleeding, genital hemorrhage, eye hemorrhage, hemoptysis, hemorrhagic cystitis, pharyngeal hemorrhage, rectal hemorrhage, upper gastrointestinal hemorrhage, and esophageal hemorrhage. [h]Including headache and migraine. [i]Including peripheral neuropathy, peripheral sensory neuropathy, peripheral motor neuropathy, polyneuropathy, paresthesia, hypoesthesia, dysesthesia, and neuralgia. [j]Including dizziness, postural dizziness, and vertigo. [k]Including upper respiratory tract infection, influenza, influenza-like illness, nasopharyngitis, pharyngitis, sinusitis, and rhinitis. [l]Interstitial lung disease includes events that were adjudicated as ILD for ENHERTU: interstitial lung disease, pneumonitis, organizing pneumonia, pneumonia, and radiation pneumonitis.

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Adverse reactions may require dose modifications[1]

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- The median duration of treatment was 8 months (range: 0.2 to 33) with ENHERTU and 3.5 months (range: 0.3 to 18) with chemotherapy[1,4]

	ENHERTU 5.4 mg/kg (n=371)	Chemotherapy (n=172)	
Serious adverse reactions[1,4,6]	28%	25%	• For ENHERTU, serious ARs in >1% of patients were ILD/pneumonitis, pneumonia, dyspnea, musculoskeletal pain, sepsis, anemia, febrile neutropenia, hypercalcemia, nausea, pyrexia, and vomiting. Fatalities due to adverse reactions occurred in 4.0% of patients, including ILD/pneumonitis (3 patients); sepsis (2 patients); and ischemic colitis, disseminated intravascular coagulation, dyspnea, febrile neutropenia, general physical health deterioration, pleural effusion, and respiratory failure (1 patient each)[1] • For chemotherapy, the most frequent in >1% of patients were dyspnea, febrile neutropenia, fatigue, pleural effusion, neutropenia, disease progression, hepatic failure, hyponatremia, overdose, medication error, colitis, and femur fracture[6]
Discontinuations due to adverse reactions[1,4,7]	16%	8%	• For ENHERTU, the most frequent adverse reaction associated with discontinuation was ILD/pneumonitis (8%).[1] Per protocol, ENHERTU was discontinued in DESTINY-Breast04 in patients who were diagnosed with any symptomatic (Grade 2 or greater) ILD[1] • For chemotherapy, the most frequent was peripheral sensory neuropathy (2.3%)[7]
Dose interruptions due to adverse reactions[1,5,6]	39%	42%	• For ENHERTU, the most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, fatigue, anemia, leukopenia, COVID-19, ILD/pneumonitis, increased transaminases, and hyperbilirubinemia[1] • For chemotherapy, the most frequent (>2%) were neutropenia, leukopenia, increased transaminases, palmar-plantar erythrodysesthesia syndrome, fatigue, anemia, nausea, diarrhea, and peripheral sensory neuropathy[6]
Dose reductions due to adverse reactions[1,5,6]	23%	38%	• For ENHERTU, the most frequent adverse reactions (>2%) associated with dose reduction were fatigue, nausea, thrombocytopenia, and neutropenia[1] • For chemotherapy, the most frequent (>2%) were neutropenia, palmar-plantar erythrodysesthesia syndrome, increased transaminases, fatigue, leukopenia, nausea, and peripheral sensory neuropathy[6]

- Other clinically relevant adverse reactions reported in ≤10% of patients treated with ENHERTU were cough (10%), dysgeusia (10%), abdominal distension (5%), blurred vision (4.9%), pruritus (3.2%), gastritis (2.7%), skin hyperpigmentation (2.7%), flatulence (2.4%), dehydration (1.9%), febrile neutropenia (1.1%), and infusion-related reactions (0.5%)[1]

In DESTINY-Breast04, Grade 5 ILD/pneumonitis events were observed in 0.8% of patients (n=3/371)[1,4,a]

- Of the 371 patients treated with ENHERTU 5.4 mg/kg, ILD occurred in 12.1% of patients (n=45/371)
- Symptom identification is key to diagnosis; monitor patients and initiate management at first sign of ILD

[a]Grade 5=fatal events.[6]

Refer to the full Prescribing Information for full dose modifications for adverse reactions.

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Important Safety Information

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Indication

ENHERTU is a HER2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of adult patients with:

- Unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

- **Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU. 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 to immediately report symptoms.**
- **Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception.**

Contraindications

None.

Warnings and Precautions

Interstitial Lung Disease / Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with ENHERTU. A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment. Advise patients to immediately report cough, dyspnea, fever, and/or any new or worsening respiratory symptoms. Monitor patients for signs and symptoms of ILD. Promptly investigate evidence of ILD. Evaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist. For asymptomatic ILD/pneumonitis (Grade 1), interrupt ENHERTU until resolved to Grade 0, then if resolved in ≤28 days from date of onset, maintain dose. If resolved in >28 days from date of onset, reduce dose one level. Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥0.5 mg/kg/day prednisolone or equivalent). For symptomatic ILD/pneumonitis (Grade 2 or greater), permanently discontinue ENHERTU. Promptly initiate systemic corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥1 mg/kg/day prednisolone or equivalent) and continue for at least 14 days followed by gradual taper for at least 4 weeks.

Metastatic Breast Cancer and Other Solid Tumors (5.4 mg/kg)
In patients with metastatic breast cancer and other solid tumors treated with ENHERTU 5.4 mg/kg, ILD occurred in 12% of patients. Fatal outcomes due to ILD and/or pneumonitis occurred in 1.0% of patients treated with ENHERTU. Median time to first onset was 5 months (range: 0.9 to 23).

Neutropenia

Severe neutropenia, including febrile neutropenia, can occur in patients treated with ENHERTU. Monitor complete blood counts prior to initiation of ENHERTU and prior to each dose, and as clinically indicated. For Grade 3 neutropenia (Absolute Neutrophil Count [ANC] <1.0 to 0.5 x 10^9/L), interrupt ENHERTU until resolved to Grade 2 or less, then maintain dose. For Grade 4 neutropenia (ANC <0.5 x 10^9/L), interrupt ENHERTU until resolved to Grade 2 or less, then reduce dose by one level. For febrile neutropenia (ANC <1.0 x 10^9/L and temperature >38.3° C or a sustained temperature of ≥38° C for more than 1 hour), interrupt ENHERTU until resolved, then reduce dose by one level.

Metastatic Breast Cancer and Other Solid Tumors (5.4 mg/kg)
In patients with metastatic breast cancer and other solid tumors treated with ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in 65% of patients. Sixteen percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 22 days (range: 2 to 664). Febrile neutropenia was reported in 1.1% of patients.

Left Ventricular Dysfunction

Patients treated with ENHERTU may be at increased risk of developing left ventricular dysfunction. Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies, including ENHERTU. Assess LVEF prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. Manage LVEF decrease through treatment interruption. When LVEF is >45% and absolute decrease from baseline is 10-20%, continue treatment with ENHERTU. When LVEF is 40-45% and absolute decrease from baseline is <10%, continue treatment with ENHERTU and repeat LVEF assessment within 3 weeks. When LVEF is 40-45% and absolute decrease from baseline is 10-20%, interrupt ENHERTU and repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within 10% from baseline, permanently discontinue ENHERTU. If LVEF recovers to within 10% from baseline, resume treatment with ENHERTU at the same dose. When LVEF is <40% or absolute decrease from baseline is >20%, interrupt ENHERTU and repeat LVEF assessment within 3 weeks. If LVEF of <40% or absolute decrease from baseline of >20% is confirmed, permanently discontinue ENHERTU. Permanently discontinue ENHERTU in patients with symptomatic congestive heart failure. Treatment with ENHERTU has not been studied in patients with a history of clinically significant cardiac disease or LVEF <50% prior to initiation of treatment.

Metastatic Breast Cancer and Other Solid Tumors (5.4 mg/kg)
In patients with metastatic breast cancer and other solid tumors treated with ENHERTU 5.4 mg/kg, LVEF decrease was reported in 3.6% of patients, of which 0.4% were Grade 3.

Embryo-Fetal Toxicity

ENHERTU can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risks to a fetus. Verify the pregnancy status of females of reproductive potential prior to the initiation of ENHERTU. Advise females of reproductive potential to use effective contraception during treatment and for 7 months after the last dose of ENHERTU. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for 4 months after the last dose of ENHERTU.

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Important Safety Information (cont'd)

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Additional Dose Modifications

Thrombocytopenia

For Grade 3 thrombocytopenia (platelets <50 to 25 x 10^9/L) interrupt ENHERTU until resolved to Grade 1 or less, then maintain dose. For Grade 4 thrombocytopenia (platelets <25 x 10^9/L) interrupt ENHERTU until resolved to Grade 1 or less, then reduce dose by one level.

Adverse Reactions

Metastatic Breast Cancer and Other Solid Tumors (5.4 mg/kg)
The pooled safety population reflects exposure to ENHERTU 5.4 mg/kg intravenously every 3 weeks in 984 patients in Study DS8201-A-J101 (NCT02564900), DESTINY-Breast01, DESTINY-Breast03, DESTINY-Breast04, and another clinical trial. Among these patients 65% were exposed for >6 months and 39% were exposed for >1 year. In this pooled safety population, the most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea (76%), decreased white blood cell count (71%), decreased hemoglobin (66%), decreased neutrophil count (65%), decreased lymphocyte count (55%), fatigue (54%), decreased platelet count (47%), increased aspartate aminotransferase (48%), vomiting (44%), increased alanine aminotransferase (42%), alopecia (39%), increased blood alkaline phosphatase (39%), constipation (34%), musculoskeletal pain (32%), decreased appetite (32%), hypokalemia (28%), diarrhea (28%), and respiratory infection (24%).

HER2-Low Metastatic Breast Cancer
DESTINY-Breast04
The safety of ENHERTU was evaluated in 371 patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who received ENHERTU 5.4 mg/kg intravenously every 3 weeks in DESTINY-Breast04. The median duration of treatment was 8 months (range: 0.2 to 33) for patients who received ENHERTU.

Serious adverse reactions occurred in 28% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were ILD/pneumonitis, pneumonia, dyspnea, musculoskeletal pain, sepsis, anemia, febrile neutropenia, hypercalcemia, nausea, pyrexia, and vomiting. Fatalities due to adverse reactions occurred in 4% of patients including ILD/pneumonitis (3 patients); sepsis (2 patients); and ischemic colitis, disseminated intravascular coagulation, dyspnea, febrile neutropenia, general physical health deterioration, pleural effusion, and respiratory failure (1 patient each).

ENHERTU was permanently discontinued in 16% of patients, of which ILD/pneumonitis accounted for 8%. Dose interruptions due to adverse reactions occurred in 39% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, fatigue, anemia, leukopenia, COVID-19, ILD/pneumonitis, increased transaminases, and hyperbilirubinemia. Dose reductions occurred in 23% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, nausea, thrombocytopenia, and neutropenia.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea (76%), decreased white blood cell count (70%), decreased hemoglobin (64%), decreased neutrophil count (64%), decreased lymphocyte count (55%), fatigue (54%), decreased platelet count (44%), alopecia (40%), vomiting (40%), increased aspartate aminotransferase (38%), increased alanine aminotransferase (36%), constipation (34%), increased blood alkaline phosphatase (34%), decreased appetite (32%), musculoskeletal pain (32%), diarrhea (27%), and hypokalemia (25%).

Use in Specific Populations

- **Pregnancy:** ENHERTU can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risks to a fetus. There are clinical considerations if ENHERTU is used in pregnant women, or if a patient becomes pregnant within 7 months after the last dose of ENHERTU.
- **Lactation:** There are no data regarding the presence of ENHERTU in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with ENHERTU and for 7 months after the last dose.
- **Females and Males of Reproductive Potential:** Pregnancy testing: Verify pregnancy status of females of reproductive potential prior to initiation of ENHERTU. Contraception: *Females*: ENHERTU can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with ENHERTU and for 7 months after the last dose. *Males*: Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for 4 months after the last dose. Infertility: ENHERTU may impair male reproductive function and fertility.
- **Pediatric Use:** Safety and effectiveness of ENHERTU have not been established in pediatric patients.
- **Geriatric Use:** Of the 883 patients with breast cancer treated with ENHERTU 5.4 mg/kg, 22% were ≥65 years and 3.6% were ≥75 years. No overall differences in efficacy within clinical studies were observed between patients ≥65 years of age compared to younger patients. There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged ≥65 years (60%) as compared to younger patients (48%).
- **Renal Impairment:** A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment. Monitor patients with moderate renal impairment more frequently. The recommended dosage of ENHERTU has not been established for patients with severe renal impairment (CLcr <30 mL/min).
- **Hepatic Impairment:** In patients with moderate hepatic impairment, due to potentially increased exposure, closely monitor for increased toxicities related to the topoisomerase inhibitor. The recommended dosage of ENHERTU has not been established for patients with severe hepatic impairment (total bilirubin >3 times ULN and any AST).

To report SUSPECTED ADVERSE REACTIONS, contact Daiichi Sankyo, Inc. at 1-877-437-7763 or FDA at 1-800-FDA-1088 or fda.gov/medwatch.

Please click here for full Prescribing Information, including Boxed WARNINGS, and click here for Medication Guide.

Proven survival benefit with ENHERTU in DESTINY-Breast04 has established the need to identify patients with HER2-low (IHC 1+ or IHC 2+/ISH–) mBC[1]

Most common (≥20%) ARs, including laboratory abnormalities, in the pooled safety population of patients with mBC and other solid tumors treated with ENHERTU 5.4 mg/kg (N=984)[1]

- Nausea (76%), decreased white blood cell count (71%), decreased hemoglobin (66%), decreased neutrophil count (65%), decreased lymphocyte count (55%), fatigue (54%), decreased platelet count (47%), increased aspartate aminotransferase (48%), vomiting (44%), increased alanine aminotransferase (42%), alopecia (39%), increased blood alkaline phosphatase (39%), constipation (34%), musculoskeletal pain (32%), decreased appetite (32%), hypokalemia (28%), diarrhea (28%), and respiratory infection (24%)

Abbreviations
AR, adverse reaction
BICR, blinded independent central review
CI, confidence interval
CR, complete response
DOR, duration of response
HER2, human epidermal growth factor receptor 2
HR, hazard ratio
HR–, hormone receptor-negative
HR+, hormone receptor-positive
IHC, immunohistochemistry
ILD, interstitial lung disease
ISH, in situ hybridization
IV, intravenous
mBC, metastatic breast cancer
mDOR, median duration of response
mOS, median overall survival
mPFS, median progression-free survival
mRECIST, Modified Response Evaluation Criteria in Solid Tumors
NCCN, National Comprehensive Cancer Network
NCI-CTCAE, National Cancer Institute–Common Terminology Criteria for Adverse Events
NE, not evaluable
ORR, objective response rate
OS, overall survival
PFS, progression-free survival
PR, partial response
Q3W, every 3 weeks

References 1. ENHERTU. Prescribing information. Daiichi Sankyo, Inc.; 2022. **2.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V4.2022. © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed June 21, 2022. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **3.** Modi S, Jacot W, Yamashita T, et al; DESTINY-Breast04 Trial Investigators. Protocol for: Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. *N Engl J Med.* 2022;387(1):9-20. **4.** Modi S, Jacot W, Yamashita T, et al; DESTINY-Breast04 Trial Investigators. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. *N Engl J Med.* 2022;387(1):9-20. **5.** Modi S, Jacot W, Yamashita T, et al; DESTINY-Breast04 Trial Investigators. Supplement to: Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. *N Engl J Med.* 2022;387(1):9-20. **6.** Data on file. Daiichi Sankyo, Inc. Basking Ridge, NJ. **7.** Modi S, Jacot W, Yamashita T, et al; DESTINY-Breast04 Trial Investigators. Trastuzumab deruxtecan (T-DXd) vs treatment of physician's choice in patients with HER2-low unresectable and/or metastatic breast cancer: results of DESTINY-Breast04, a randomized, phase 3 study. Presented at: the American Society of Clinical Oncology; June 3-7, 2022; Chicago, IL.

Please see Important Safety Information throughout as well as on pages 6-7, and click here for full Prescribing Information, including Boxed WARNINGS, and click here for Medication Guide.

Daiichi-Sankyo | AstraZeneca

Important Safety Information

Indication

ENHERTU is a HER2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of adult patients with:

- Unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

- **Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU. 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 to immediately report symptoms.**
- **Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception.**