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

ENHERTU is FDA approved in HR+/HER2-low and HR+/HER2-ultralow mBC who have received at least 1 line of ET in the metastatic setting

The approval of the new indication for ENHERTU was based on the results of the DESTINY-Breast06 trial—a global, Phase 3, randomized, multicenter, open-label study in patients with HR+/HER2-low and HER2-ultralow mBC

DESTINY-Breast06 is a multicenter, randomized, open-label, Phase 3 clinical trial that included 866 adults with HR+/HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining) unresectable or mBC with no prior chemotherapy who had received 1-2 lines of prior ET in the metastatic setting.[1,a]

- Patients were treated with ENHERTU 5.4 mg/kg Q3W (n=436) or physician's choice single-agent chemotherapy (n=430)[b] until disease progression, death, or unacceptable toxicity[1]

Indication and 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:

- Hormone receptor (HR)-positive, HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining) breast cancer, as determined by an FDA-approved test, that has progressed on one or more endocrine therapies in the metastatic setting
- 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

Contraindications

None.

Important Safety Information

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.**

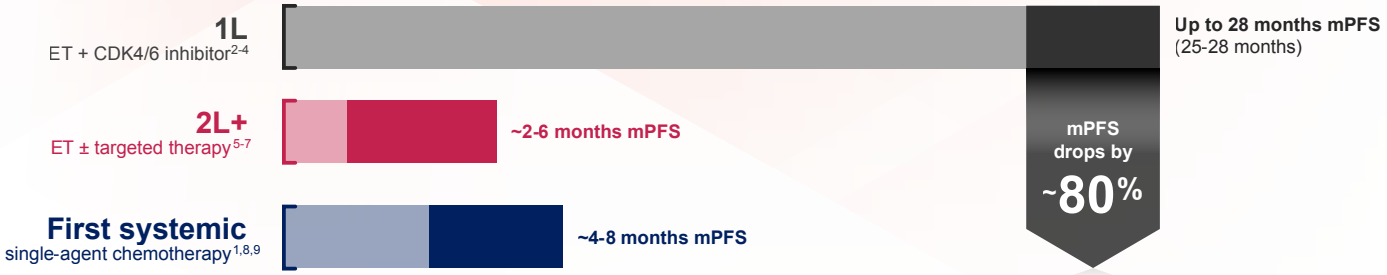
[a]Patients were eligible if they had disease progression on ≥2 lines of ET in the metastatic setting, or 1 line of ET in the metastatic setting and progressed within 24 months of adjuvant ET or within 6 months of starting 1L ET + CDK4/6i in the metastatic setting.[1]

[b]Patients received the physician's choice of chemotherapy (60% of patients received capecitabine, 24% nab-paclitaxel, and 16% paclitaxel).[1]

Abbreviations: ET, endocrine therapy; FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor-positive; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; Q3W, every 3 weeks.

Please see Important Safety Information throughout as well as on pages 8-10, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

Patients with HR+/HER2-negative mBC, including HER2-low mBC, need options that offer the potential for improved outcomes following 1-2 lines of ET



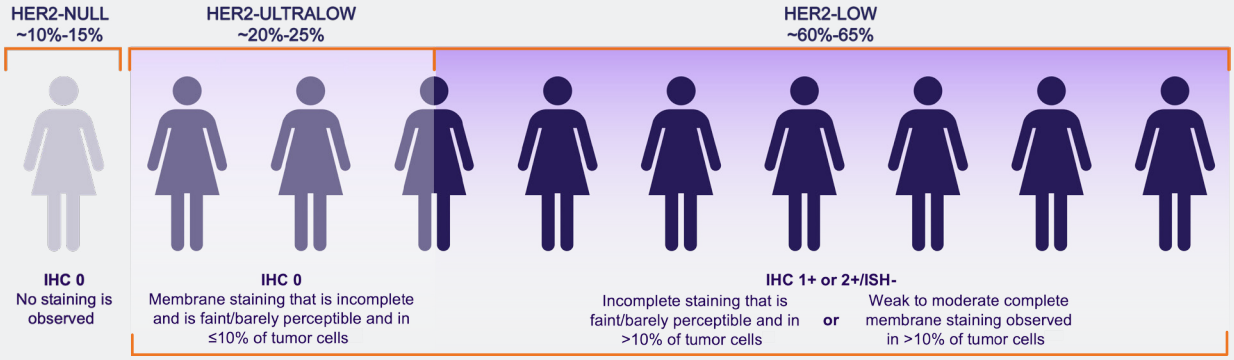
With few post-ET treatment options available, mPFS steeply declines in later lines of therapy[2-4]

Introducing HER2-ultralow: Traditionally classified as HER2-negative, identified by IHC 0 with membrane staining

For eligible patients with HR+/HER2-low (IHC 1+ or IHC 2+/ISH–) or HER2-ultralow (IHC 0 with membrane staining) mBC who have received at least 1 line of ET in the metastatic setting[1]

ENHERTU expands the opportunity for HER2-directed therapy for eligible patients with mBC

HR+/HER2-negative mBC[10,a]



~85%-90% of patients with HR+/HER2-negative mBC may have actionable levels of HER2 expression

[a]As demonstrated in DESTINY-Breast06 screening data.

- Assessment of HER2-low and -ultralow is based on IHC and/or ISH testing, which are standard tests used in clinical practice to evaluate BC patients and inform treatment decisions[11,12]

Previously treated patients with HR+ mBC classified as IHC 0 may be reevaluated to assess if they are potential candidates for HER2-directed treatment with ENHERTU

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.

Abbreviations: 1L, first line; 2L, second line; BC, breast cancer; CDK4/6, cyclin-dependent kinases 4 and 6; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor-positive; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; mPFS, median progression-free survival.

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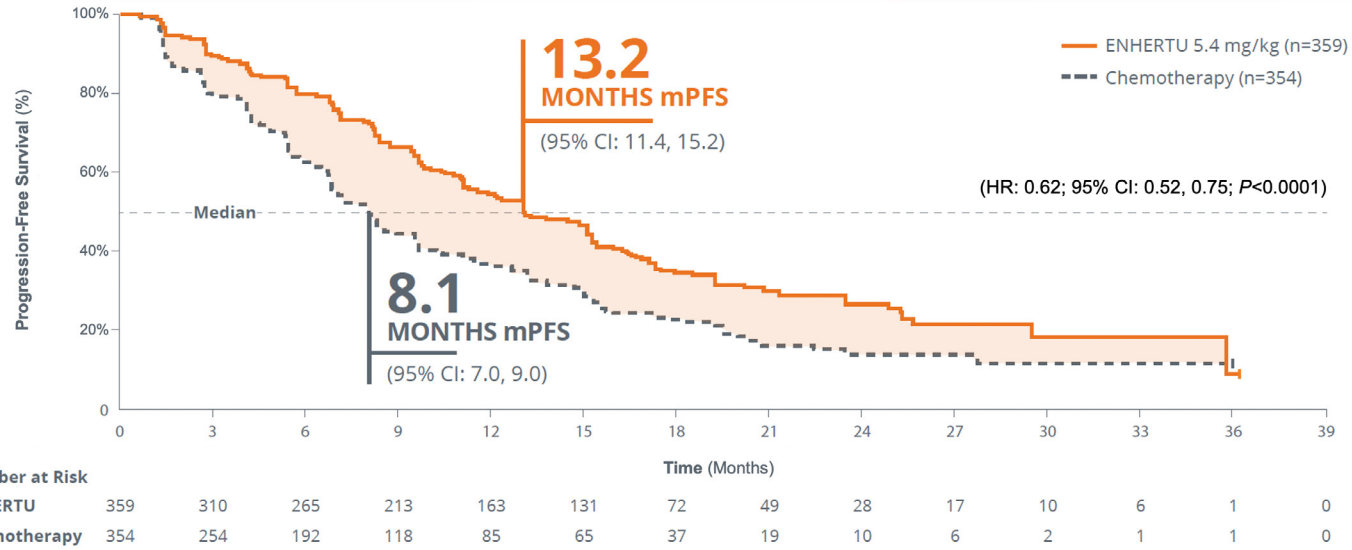
DESTINY-Breast06: In patients with HR+/HER2-low (IHC 1+ or IHC 2+/ISH-) mBC

ENHERTU significantly improved mPFS vs chemotherapy in chemotherapy-naïve patients with HR+/HER2-low mBC[1,13]

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



- Overall survival was not yet mature at the time of analysis

38% reduction in the risk of disease progression or death with ENHERTU vs chemotherapy (HR: 0.62; 95% CI: 0.52, 0.75; *P*<0.0001)[1,13,a]

Warnings and Precautions

Interstitial Lung Disease / Pneumonitis (cont'd)

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 1 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.

[a]Based on stratified analysis with stratification factors prior CDK4/6 inhibitor use (yes vs no) and HER2 IHC status of tumor samples (IHC 1+ vs IHC 2+/ISH-).[1]

Abbreviations: BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; HR+, hormone receptor-positive; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; mPFS, median progression-free survival; PFS, progression-free survival.

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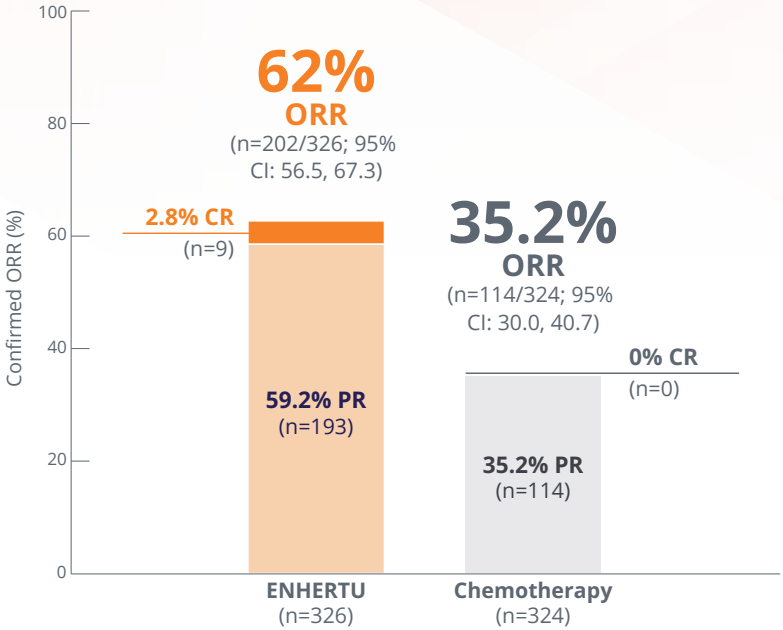
DESTINY-Breast06: In patients with HR+/HER2-low (IHC 1+ or IHC 2+/ISH-) mBC

Over 60% ORR with ENHERTU and 35.2% with chemotherapy[1]

Secondary endpoint: confirmed objective response in the HER2-low mBC population (BICR)[1,13,a]



- mDOR was **14.1 months** with ENHERTU and **8.6 months** with chemotherapy[1,a]
- ORR and DOR were not tested for statistical significance nor powered to show differences between treatment arms or subgroups. Therefore, the clinical significance is not known

Additional results

- Median TTR was **2.7** months with ENHERTU and **2.6** months with chemotherapy[14]
- **77.3%** CBR (CR + PR + SD at week 24) with ENHERTU (n=252/326) and **53.1%** with chemotherapy (n=172/324)[14]

OVER 90% (n=300/326) of patients achieved disease control (CR + PR + SD) with ENHERTU[14,b]

- TTR, CBR, and DCR were not tested for statistical significance nor powered to show differences between treatment arms or subgroups. Therefore, the clinical significance is not known

Warnings and Precautions (cont'd)

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. Median time to first onset was 5.5 months (range: 0.9 to 31.5). Fatal outcomes due to ILD and/or pneumonitis occurred in 0.9% of patients treated with ENHERTU.

Neutropenia

Severe neutropenia, including febrile neutropenia, can occur in patients treated with ENHERTU.

[a]Analysis was performed based on the patients with measurable disease assessed by BICR at baseline.[1]
[b]DCR was 92% with ENHERTU (n=300/326) and 79.9% with chemotherapy (n=259/324).[14]

Abbreviations: BICR, blinded independent central review; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; HER2, human epidermal growth factor receptor 2; mDOR, median duration of response; ORR, objective response rate; PR, partial response; SD, stable disease; TTR, time to response.

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Efficacy outcomes were consistent in the HER2-low and overall study populations, with similar results in the exploratory HER2-ultralow cohort

Summary of DESTINY-Breast06 efficacy results by patient population[1,13]

	HER2-low and HER2-ultralow (Overall study population) (N=866)		HER2-low cohort (IHC 1+ or IHC 2+/ISH-) (n=713)		Exploratory HER2-ultralow cohort (IHC 0 with membrane staining) (n=153)[a]	
	ENHERTU (n=436)	Chemotherapy (n=430)	**ENHERTU** (n=359)	Chemotherapy (n=354)	**ENHERTU** (n=77)	Chemotherapy (n=76)
mPFS (months) (95% CI)	**13.2 months** (12.0, 15.2)	**8.1 months** (7.0, 9.0)	**13.2 months** (11.4, 15.2)	**8.1 months** (7.0, 9.0)	**15.1 months** (10.0, 17.3)	**8.3 months** (5.8, 15.2)
HR (95% CI; *P*-value)	**0.64** (95% CI: 0.54, 0.76; *P*<0.0001)[b]		**0.62** (95% CI: 0.52, 0.75; *P*<0.0001)[c]		**0.76** (95% CI: 0.49, 1.17)	
ORR,[d] (n; 95% CI)	**62.6%** (246/293; 57.6, 67.4)	**34.4%** (134/389; 29.7, 39.4)	**62%** (202/326; 56.5, 67.3)	**35.2%** (114/324; 30.0, 40.7)	**65.7%** (44/67; 53.1, 76.8)	**30.8%** (20/65; 19.9, 43.4)

- ORR was not tested for statistical significance and was not powered to show differences between treatment arms. Therefore, the clinical significance of these data is not known
- In the overall population[9]:
  - 18% of patients had IHC 0 with membrane staining, 55% had IHC 1+, and 27% had IHC 2+/ISH-
  - Patients had a median of 2 prior lines of ET in the metastatic setting (range: 1 to 5) with 17% and 68% of patients having 1 and 2 lines of therapy, respectively
- At the time of analysis, overall survival data were not yet mature[1]

The PFS improvement with ENHERTU vs chemotherapy was similar in the HER2-low and overall study population[13]

Warnings and Precautions (cont'd)

Neutropenia (cont'd)

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 1 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 1 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. Nineteen percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 22 days (range: 2 to 939). Febrile neutropenia was reported in 1.2% of patients.

[a]Results for the HER2-ultralow cohort were not tested for statistical significance, and the study was not powered to show differences between treatment arms. Therefore, the clinical significance of these data is not known.
[b]Based on unstratified analysis.[1]
[c]Based on stratified analysis with stratification factors prior CDK4/6 inhibitor use (yes vs no) and HER2 IHC status of tumor samples (IHC 1+ vs IHC 2+/ISH-).[13]
[d]Analysis was performed based on the patients with measurable disease assessed by BICR at baseline.[1]

Abbreviations: CI, confidence interval; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IHC, immunohistochemistry; ISH, in situ hybridization; mPFS, median progression-free survival; NE, not estimable; ORR, objective response rate; PFS, progression-free survival.

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20 mg/mL INJECTION FOR INTRAVENOUS USE

Safety data from DESTINY-Breast06 further confirmed the benefit-risk profile in HER2-low and established it in HER2-ultralow mBC

The majority of adverse reactions were Grade 1 or 2[1,13]

- The median duration of treatment was 11 months (range: 0.4-39.6) with ENHERTU and 5.6 months (range: 0.1-35.9) with chemotherapy

Common adverse reactions (≥10% All Grades or ≥2% Grades 3 or 4) in patients treated with ENHERTU in DESTINY-Breast06[1]

Adverse reactions		ENHERTU 5.4 mg/kg (n=434)		Chemotherapy (n=417)	
		All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal disorders	Nausea	70	2.1	30	0.5
	Diarrhea	34	2.3	27	2.6
	Vomiting	34	1.4	12	0.2
	Constipation	32	0.7	15	0.5
	Abdominal pain[a]	20	0.5	14	0.2
	Stomatitis[b]	15	0	11	0.5
	Dyspepsia	12	0	4.8	0
General disorders and administration site conditions	Fatigue[c]	53	4.4	40	2.4
	Pyrexia	12	0.2	7	0
Skin and subcutaneous tissue disorders	Alopecia	48	0	21	0.5
	Rash[d]	12	0.2	43	0.5
Metabolism and nutrition disorders	Decreased appetite	26	1.4	12	0.5
Infections and infestations	COVID-19[e]	26	0.9	13	1
	Upper respiratory tract infection[f]	19	0	9	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[g]	24	0.5	23	1.9
Nervous system disorders	Headache[h]	18	0.5	10	0
	Dysgeusia	12	0.2	6	0
Respiratory, thoracic, and mediastinal disorders	Cough	16	0	9	0
	Interstitial lung disease[i]	11	0.7	0.2	0
	Epistaxis	10	0	3.6	0.2

ILD/pneumonitis, including Grade 5 cases, were reported with ENHERTU in DESTINY-Breast06[13]

Adjudicated as drug-induced ILD, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	All Grades
ENHERTU 5.4 mg/kg (n=434)	7 (1.6)	36 (8.3)	3 (0.7)	0	3 (0.7)	49 (11.3)
Chemotherapy (n=417)	0	1 (0.2)	0	0	0	1 (0.2)

- Of the 434 patients treated with ENHERTU 5.4 mg/kg, ILD occurred in 11.3% (n=49/434)[13]:
  - Three Grade 5 adjudicated drug-induced ILD/pneumonitis events were observed with ENHERTU[j]
  - 88% of the ILD cases were Grade 1 or 2 (n=43/49)
- In DESTINY-Breast06, median time to onset of adjudicated drug-induced ILD in patients treated with ENHERTU was 141 days (range: 37 to 835)[13]

Learn more about the 5 "S" strategies to help detect and manage ILD/pneumonitis in patients receiving ENHERTU

Events were graded using NCI-CTCAE version 5.0.[1]
[a]Including abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, and gastrointestinal pain.[1]
[b]Including stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, oral mucosal blistering, and oral mucosal eruption.[1]
[c]Including fatigue, asthenia, malaise, and lethargy.[1]
[d]Including dermatitis, dermatitis allergic, dermatitis contact, eczema, palmar-plantar erythrodysesthesia syndrome, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, and rash pustular.[1]
[e]Including COVID-19, COVID-19 pneumonia.[1]
[f]Including influenza, influenza like illness, upper respiratory tract infection, nasopharyngitis, pharyngitis, sinusitis, rhinitis, and laryngitis.[1]
[g]Including back pain, myalgia, pain in extremity, musculoskeletal pain, muscle spasms, bone pain, neck pain, musculoskeletal chest pain, and limb discomfort.[1]
[h]Including migraine, headache, and sinus headache.[1]
[i]Including bronchiectasis, interstitial lung disease, lower respiratory tract infection, pneumonia, pneumonia bacterial, pneumonitis, and pulmonary toxicity.[1]
[j]Grade 5=fatal cases.

Abbreviations: HER2, human epidermal growth factor receptor 2; HR+, hormone receptor-positive; ILD, interstitial lung disease; NCI-CTCAE, National Cancer Institute–Common Terminology Criteria for Adverse Events.

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ENHERTU is now approved for use in an additional eligible population: HR+/HER2-low and HER2-ultralow mBC—after at least one line of ET in the metastatic setting[1]

In DESTINY-Breast06, ENHERTU demonstrated superior PFS benefit vs chemotherapy in HR+/HER2-low chemotherapy-naïve mBC patients after 1-2 lines of ET

Primary endpoint: PFS (BICR) in HER2-low mBC
(HR: 0.62; 95% CI: 0.52, 0.75; *P*<0.0001)

13.2 months mPFS with ENHERTU (n=359; 95% CI: 11.4, 15.2) **VS** **8.1** months mPFS with chemotherapy[a] (n=354; 95% CI: 7.0, 9.0)

- 62% of patients achieved a confirmed objective response, and mDOR was 14.1 months with ENHERTU in the HER2-low population while 35.2% achieved a confirmed objective response and 8.6 months mDOR for chemotherapy
- ORR and DOR were not tested for statistical significance and were not powered to show differences between treatment arms. Therefore, the clinical significance of these data is not known
- **Consistent results were seen in the ITT population, which included patients with HER2-ultralow mBC**

Most common (≥20%) adverse reactions in DESTINY-Breast06, including laboratory abnormalities, of patients receiving ENHERTU

- Decreased white blood cell count (86%), decreased neutrophil count (75%), nausea (70%), decreased hemoglobin (69%), decreased lymphocyte count (66%), fatigue (53%), decreased platelet count (48%), alopecia (48%), increased alanine aminotransferase (44%), increased blood alkaline phosphatase (43%), increased aspartate aminotransferase (41%), decreased blood potassium (35%), diarrhea (34%), vomiting (34%), constipation (32%), decreased appetite (26%), COVID-19 (26%), and musculoskeletal pain (24%)

In DESTINY-Breast06, the majority of adverse reactions were Grade 1 or 2; Grade 5 ILD/pneumonitis events were observed in 0.7% of patients (n=3/434)[b]

- Of the 434 patients treated with ENHERTU 5.4 mg/kg, ILD occurred in 11% of patients (n=49/434)
- Symptom identification is key to diagnosis; monitor patients and initiate management at first sign of ILD

Study design: DESTINY-Breast06 is a Phase 3, international, multicenter, randomized, open-label trial of ENHERTU vs physician's choice of chemotherapy in 866 patients with HR+/HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining) mBC. Patients were eligible if they had disease progression on at least 2 lines of ET in the metastatic setting, or 1 line of ET in the metastatic setting and progressed within 24 months of the start of adjuvant ET or within 6 months of starting 1L ET + CDK4/6 inhibitor in the metastatic setting. Patients in the ENHERTU arm received 5.4 mg/kg IV Q3W and patients in the chemotherapy arm could receive capecitabine, nab-paclitaxel, or paclitaxel. Treatment was continued until unacceptable toxicity or disease progression. The primary endpoint was PFS (BICR) in the HER2-low population (determined by BICR according to RECIST v1.1). Select secondary endpoints included PFS (BICR) in the overall study population (HER2-low and HER2-ultralow); overall survival in the HER2-low population and in the overall study population; ORR in the HER2-low population and in the overall study population; and DOR in the HER2-low population and in the overall study population.

Warnings and Precautions (cont'd)

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.

[a]Patients received physician's choice of chemotherapy (single-agent capecitabine, nab-paclitaxel, or paclitaxel).
[b]Grade 5=fatal events.

Abbreviations: 1L, first line; BICR, blinded independent central review; CDK4/6, cyclin-dependent kinases 4 and 6; CI, confidence interval; DOR, duration of response; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; HR+, hormone receptor-positive; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, in situ hybridization; ITT, intent to treat; IV, intravenous; mBC, metastatic breast cancer; mDOR, median duration of response; mPFS, median progression-free survival; ORR, objective response rate; PFS, progression-free survival; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

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Indication and 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:

- Hormone receptor (HR)-positive, HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining) breast cancer, as determined by an FDA-approved test, that has progressed on one or more endocrine therapies in the metastatic setting
- 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

Important Safety Information

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 1 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. Median time to first onset was 5.5 months (range: 0.9 to 31.5). Fatal outcomes due to ILD and/or pneumonitis occurred in 0.9% of patients treated with ENHERTU.

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 1 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 1 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. Nineteen percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 22 days (range: 2 to 939). Febrile neutropenia was reported in 1.2% 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.

Please see Important Safety Information throughout as well as on pages 8-10, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

Left Ventricular Dysfunction (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, LVEF decrease was reported in 4.6% of patients, of which 0.6% were Grade 3 or 4.

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.

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 1 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 2233 patients in Study DS8201-A-J101 (NCT02564900), DESTINY-Breast01, DESTINY-Breast02, DESTINY-Breast03, DESTINY-Breast04, DESTINY-Breast06, and other clinical trials. Among these patients, 67% were exposed for >6 months and 38% were exposed for >1 year. In this pooled safety population, the most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased white blood cell count (73%), nausea (72%), decreased hemoglobin (67%), decreased neutrophil count (65%), decreased lymphocyte count (60%), fatigue (55%), decreased platelet count (48%), increased aspartate aminotransferase (46%), increased alanine aminotransferase (44%), increased blood alkaline phosphatase (39%), vomiting (38%), alopecia (37%), constipation (32%), decreased blood potassium (32%), decreased appetite (31%), diarrhea (30%), and musculoskeletal pain (24%).

HER2-Low and HER2-Ultralow Metastatic Breast Cancer

DESTINY-Breast06

The safety of ENHERTU was evaluated in 434 patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining) breast cancer who received ENHERTU 5.4 mg/kg intravenously once every 3 weeks in DESTINY-Breast06. The median duration of treatment was 11 months (range: 0.4 to 39.6) for patients who received ENHERTU.

Serious adverse reactions occurred in 20% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were ILD/pneumonitis, COVID-19, febrile neutropenia, and hypokalemia. Fatalities due to adverse reactions occurred in 2.8% of patients including ILD (0.7%); sepsis (0.5%); and COVID-19 pneumonia, bacterial meningoencephalitis, neutropenic sepsis, peritonitis, cerebrovascular accident, general physical health deterioration (0.2% each).

ENHERTU was permanently discontinued in 14% of patients. The most frequent adverse reaction (>2%) associated with permanent discontinuation was ILD/pneumonitis. Dose interruptions due to adverse reactions occurred in 48% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were COVID-19, decreased neutrophil count, anemia, pyrexia, pneumonia, decreased white blood cell count, and ILD. Dose reductions occurred in 25% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were nausea, fatigue, decreased platelet count, and decreased neutrophil count.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased white blood cell count (86%), decreased neutrophil count (75%), nausea (70%), decreased hemoglobin (69%), decreased lymphocyte count (66%), fatigue (53%), decreased platelet count (48%), alopecia (48%), increased alanine aminotransferase (44%), increased blood alkaline phosphatase (43%), increased aspartate aminotransferase (41%), decreased blood potassium (35%), diarrhea (34%), vomiting (34%), constipation (32%), decreased appetite (26%), COVID-19 (26%), and musculoskeletal pain (24%).

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 once 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.

Please see Important Safety Information throughout as well as on pages 8-10, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

Important Safety Information (cont'd)

Adverse Reactions (cont'd)

HER2-Low and HER2-Ultralow Metastatic Breast Cancer (cont'd)

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 decreased blood potassium (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 1741 patients with breast cancer treated with ENHERTU 5.4 mg/kg, 24% were ≥65 years and 4.9% 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 (61%) as compared to younger patients (52%).
- **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, DXd. 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 see accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

References: 1. ENHERTU. Prescribing Information. Daiichi Sankyo, Inc.; 2025. **2.** Finn RS, et al. *N Engl J Med.* 2016;375(20):1925-1936. **3.** Hortobagyi GN, et al. *Ann Oncol.* 2019;30(11):1842. **4.** Johnston S, et al. *NPJ Breast Cancer.* 2019;5:5. **5.** Bidard FC, et al. *J Clin Oncol.* 2022;40(28):3246-3256. **6.** Kalinsky K, et al. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; May 31-June 4, 2024; Chicago, IL. **7.** Turner NC, et al. *N Engl J Med.* 2023;388(22):2058-2070. **8.** Rugo HS, et al. *J Clin Oncol.* 2022;40(29):3365-3376. **9.** O'Shaughnessy J, et al. Presented at: San Antonio Breast Cancer Symposium; December 8-11, 2020; Virtual. **10.** Viale G, et al. Presented at: European Society for Medical Oncology (ESMO) Congress; October 20-24, 2023; Madrid, Spain. **11.** Atallah NM, et al. *Histopathology.* 2022;81(6):770-785. **12.** Franchina M, et al. *Int J Mol Sci.* 2023;24(16):12795. **13.** Bardia A, et al. *N Engl J Med.* 2024;391(22):2110-2122. **14.** Data on file. Daiichi Sankyo Inc., Basking Ridge, NJ.

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