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

ENHERTU in combination with pertuzumab is FDA-approved as a 1L treatment for HER2+ mBC

THE 1ST AND ONLY 1L mBC HER2-TARGETED TREATMENT REGIMEN IN OVER A DECADE WITH SUPERIOR PFS VS THP[1,2]

The approval of this indication for ENHERTU was based on the results of the DESTINY-Breast09 trial.

DESTINY-Breast09 is the largest Phase 3, randomized, 3-arm, multicenter, global trial investigating the 1L use of ENHERTU + pertuzumab compared with THP in patients with HER2+ mBC.[1,3,4]

- Eligibility criteria were ≥18 years of age, advanced or metastatic HER2+ BC, HR+ or HR– disease in the metastatic setting, no prior chemotherapy or anti-HER2 therapy or had received (neo)adjuvant HER2-targeted therapy >6 months prior to diagnosis of advanced or mBC, ≤1 previous line of ET in the metastatic setting,[a] ECOG performance status 0 or 1
- Patients were randomized 1:1:1 to receive either ENHERTU 5.4 mg/kg IV plus pertuzumab (n=383) Q3W,[b] THP (n=387) IV Q3W,[c] or investigational therapy (n=387) Q3W. All patients were treated until disease progression or unacceptable toxicity. ET allowed for HR+ disease after 6 cycles of ENHERTU or discontinuation of taxane with THP
- The primary endpoint was PFS (BICR) according to RECIST v1.1. Secondary endpoints were OS and confirmed ORR
  - Data for the ENHERTU monotherapy (ENHERTU + placebo) arm will remain blinded until the final PFS analysis

Indication and Important Safety Information

Indication

ENHERTU is a HER2-directed antibody and topoisomerase inhibitor conjugate indicated:

- HER2-Positive Metastatic Breast Cancer
  - In combination with pertuzumab as first-line treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH+) breast cancer, as determined by an FDA-approved test
  - As monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH+) breast cancer who have received a prior anti-HER2-based regimen either in the metastatic setting, or, in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy

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.

[a]Prior chemotherapy in the neoadjuvant or adjuvant setting was allowed with a disease-free interval from completion of systemic chemotherapy or HER2-targeted therapy to advanced or metastatic diagnosis of >6 months.[3] [b]After ENHERTU 5.4 mg/kg IV, patients received either pertuzumab (840 mg IV loading dose on Day 1, Cycle 1, followed by 420 mg IV Q3W thereafter) or placebo.[5] [c]THP was administered per local institutional standards. Patients received a taxane (either docetaxel [75 mg/m² IV Q3W for ≥6 cycles or until intolerable toxicity] or paclitaxel [80 mg/m² IV QW for ≥6 cycles or until intolerable toxicity] or paclitaxel [175 mg/m² IV Q3W for ≥6 cycles or until intolerable toxicity]) plus trastuzumab (8 mg/kg IV loading dose on Day 1, Cycle 1, followed by 6 mg/kg Q3W thereafter) plus pertuzumab (840 mg IV loading dose on Day 1, Cycle 1, followed by 420 mg thereafter).[3,5]

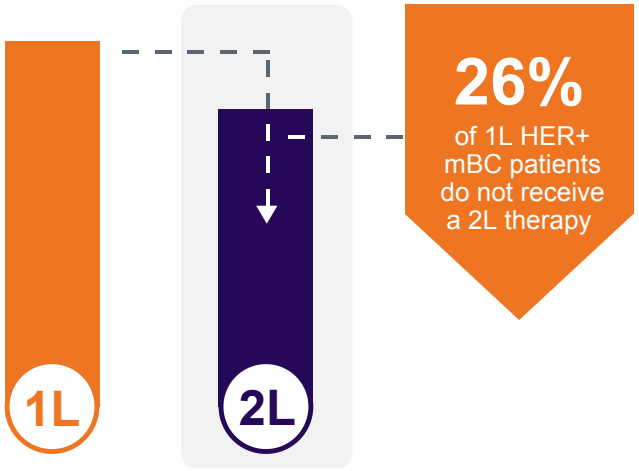
Abbreviations: 1L, first line; BC, breast cancer; BICR, blinded independent central review; ECOG, Eastern Cooperative Oncology Group; ET, endocrine therapy; FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IV, intravenous; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; THP, taxane + trastuzumab + pertuzumab.

Please see Important Safety Information throughout as well as on pages 9-12, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

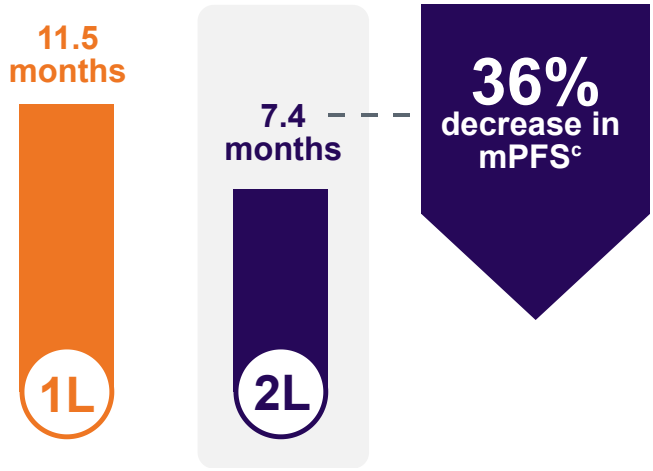
HER2+ is an aggressive subtype of mBC, and opportunities remain to help extend PFS[6]

Real-world data underscore the importance of 1L treatment selection in HER2+ mBC[6]

Not all patients go on to be treated after 1L[a,b]



mPFS significantly declines from 1L to 2L



Selecting the optimal 1L therapy delivers the greatest opportunity to extend PFS[6]

[a]This retrospective cohort included 2074 patients with HER2+ mBC who initiated 1L treatment between January 2013 and January 2021 using data from the US Flatiron Health database. Patients were followed through January 2022 to assess patient characteristics, treatment patterns, and clinical outcomes. These data do not reflect the most recent clinical trial results or regulatory approvals.[6]

[b]Of the 26% of patients who progressed but did not receive 2L treatment, 20.2% died and 5.8% discontinued treatment.[6]

[c]In the cohort of 2074 patients with HER2+ mBC from 2013 to 2021, mPFS declined from 11.5 months on 1L treatment to 7.4 months on 2L treatment.[6]

Abbreviations: 1L, first line; 2L, second line; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; mPFS, median progression-free survival; PFS, progression-free survival.

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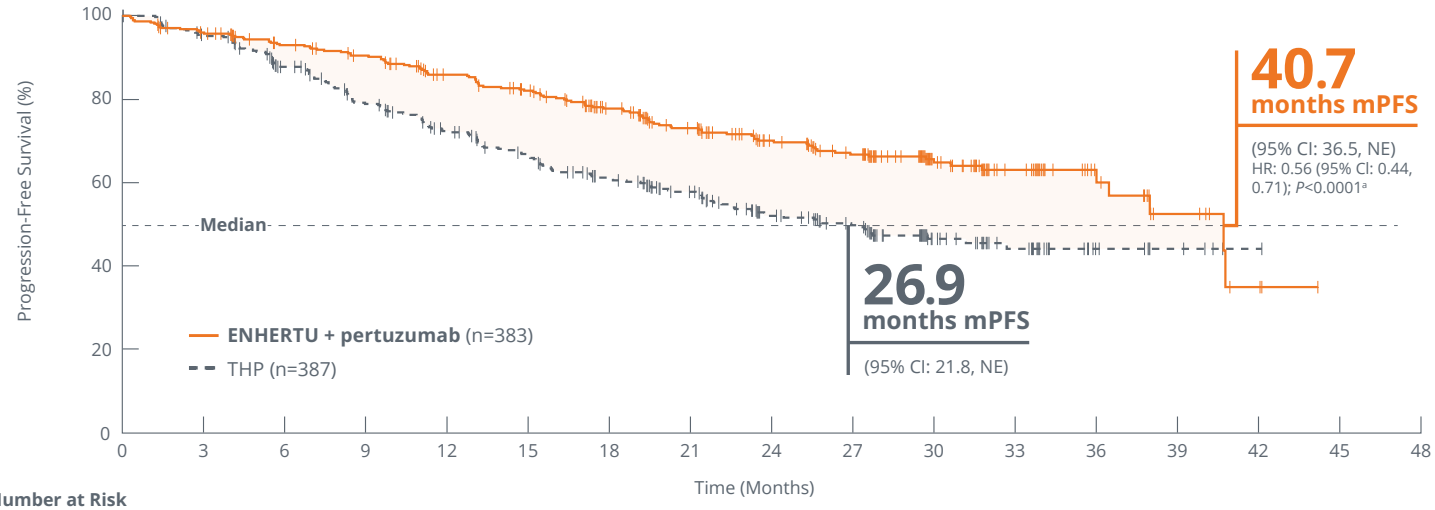
In DESTINY-Breast09, a **head-to-head study in 1L HER2+ mBC**

ENHERTU + pertuzumab delivered superior mPFS (40.7 months) vs THP (26.9 months)[1,5]

ENHERTU + pertuzumab demonstrated superior and statistically significant PFS vs THP in 1L HER2+ mBC (primary endpoint, BICR)[a]



Number at Risk

ENHERTU + pertuzumab	383	358	335	321	293	275	242	208	175	153	82	49	21	10	3	0
THP	387	353	312	273	241	215	187	160	124	106	51	32	12	5	1	0

44% reduction in the risk of death or progression with ENHERTU + pertuzumab vs THP[1]

Key secondary endpoint: Overall survival[1,5]

- OS was not yet mature at the time of analysis (16% maturity; HR: 0.84 [95% CI: 0.59, 1.19])

[a]The stratified log-rank test *P* value is compared with the allocated alpha of 0.00043 for this interim analysis (with 73% of the planned number of events for final analysis).[1]

Abbreviations: 1L, first line; BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; mBC, metastatic breast cancer; mPFS, median progression-free survival; NE, not estimable; OS, overall survival; PFS, progression-free survival; THP, taxane + trastuzumab + pertuzumab.

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

Interstitial Lung Disease / Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with ENHERTU monotherapy or ENHERTU in combination with pertuzumab. 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.

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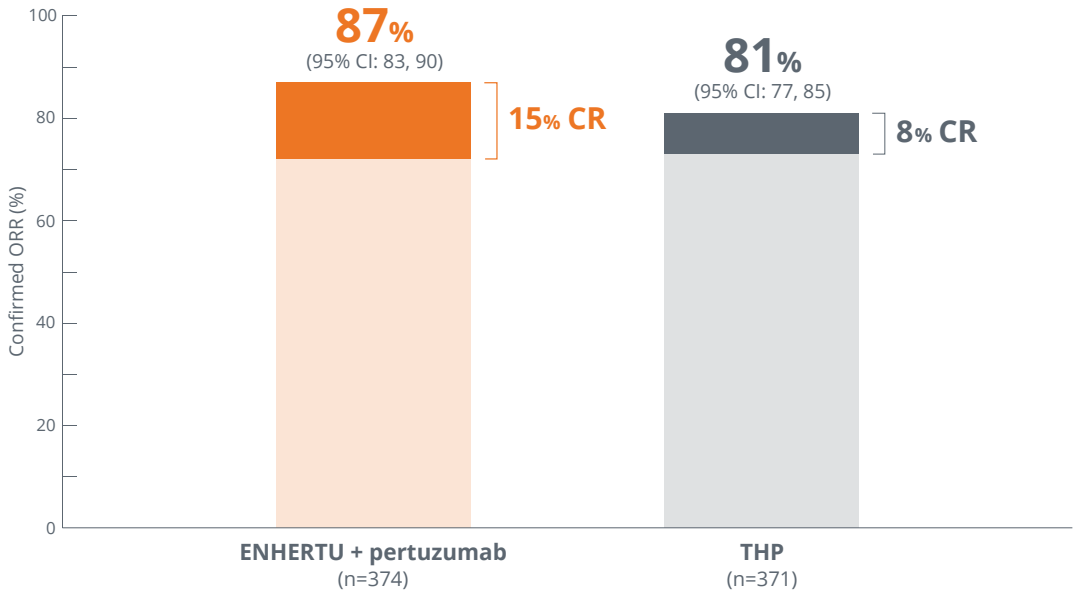
In DESTINY-Breast09, a **head-to-head study in 1L HER2+ mBC**

ENHERTU + pertuzumab demonstrated a confirmed ORR of 87%, with CR achieved in 15% of patients[1]

- The DESTINY-Breast09 protocol was not powered for ORR (secondary endpoint, defined as CR+PR) to detect differences between treatment arms. The graph is provided for illustrative purposes only as the clinical significance of these data is not known

Secondary endpoint: Confirmed ORR (per BICR)[a,b]



Majority responded: ~9 out of 10 patients achieved a confirmed ORR with ENHERTU + pertuzumab[1]

95% of patients achieved disease control with ENHERTU + pertuzumab
(95.3% DCR [15% CR (n=56) + 71.7% PR (n=268) + 8.6% SD (n=32)])[1,7]

[a]95% CI was based on Clopper-Pearson method.[1]
[b]Analysis was performed based on the patients with measurable disease assessed by BICR at baseline (n=374 patients randomized to receive ENHERTU + pertuzumab, n=371 for THP).[1]
Abbreviations: 1L, first line; CI, confidence interval; CR, complete response; DCR, disease control rate; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; ORR, objective response rate; PR, partial response; SD, stable disease; THP, taxane + trastuzumab + pertuzumab.

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

Interstitial Lung Disease / Pneumonitis (cont'd)

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).

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The majority of ARs were Grade 1 or 2 in the ENHERTU + pertuzumab arm[1]

Common ARs (≥10% all Grades or ≥2% Grade ≥3) in DESTINY-Breast09

Adverse reactions		ENHERTU 5.4 mg/kg + pertuzumab (n=381)		THP (n=382)	
		All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal disorders	Nausea	75	5	34	0.3
	Diarrhea	64	8	62	6
	Vomiting	46	2.4	18	0.5
	Constipation	33	0.3	12	0
	Abdominal pain[a]	23	0.3	13	0
	Stomatitis[b]	16	1.3	17	1.3
	Dyspepsia	12	0	6	0
General disorders and administration site conditions	Fatigue[c]	53	8	42	2.1
	Pyrexia	16	0	18	1.0
Skin and subcutaneous tissue disorders	Alopecia	48	0	53	0.5
	Rash[d]	17	0.3	22	0.3
	Pruritus	11	0	11	0.3
Infections and infestations	Upper respiratory tract infection[e]	33	1.6	30	0.5
	COVID-19	28	0.3	22	0.3
Metabolism and nutrition disorders	Decreased appetite	32	2.4	18	0.8
	Hypoalbuminemia	11	0.3	8	0.3
Investigations	Decreased weight	30	3.1	11	0.8
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[f]	24	1	33	0.3
Nervous system disorders	Headache[g]	19	0.3	14	0
	Dysgeusia	13	0	9	0
	Dizziness	12	0.3	10	0
Respiratory, thoracic, and mediastinal disorders	Cough	17	0.3	13	0
	Interstitial lung disease[h]	12	0	1	0
Eye disorders	Dry eye	11	0	6	0

Events were graded using NCI-CTCAE v.5.0.

[a]Including abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and gastrointestinal pain.[1] [b]Including aphthous ulcer, mouth ulceration, oral mucosal eruption, and stomatitis.[1] [c]Including asthenia, fatigue, lethargy, and malaise.[1] [d]Including rash, rash macular, rash maculo-papular, rash pruritic, and rash pustular.[1] [e]Including influenza, influenza-like illness, laryngitis, nasopharyngitis, pharyngitis, rhinitis, sinusitis, and upper respiratory tract infection.[1] [f]Including back pain, bone pain, muscle spasms, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, and pain in extremity.[1] [g]Including headache and migraine. [h]Interstitial lung disease (grouped term) includes PTs of chronic obstructive pulmonary disease (n=1), interstitial lung disease (n=23), pneumonia (n=3), and pneumonitis (n=22). These events were adjudicated as ILD and related to use of ENHERTU.[1]

Abbreviations: AR, adverse reaction; ILD, interstitial lung disease; NCI-CTCAE, National Cancer Institute–Common Terminology Criteria for Adverse Events; PT, preferred term; THP, taxane + trastuzumab + pertuzumab.

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No new safety signals were identified in the ENHERTU + pertuzumab arm when compared with the known profiles of the individual treatments

The median duration of treatment was 22 months (range: 0.3-44.5) for patients who received ENHERTU + pertuzumab and 16.9 months (range: 0.7-41.7) with THP[1,3]

Clinically relevant AR considerations	ENHERTU + pertuzumab (n=381)	THP (n=382)	
Serious ARs	27%	25.1%	• For ENHERTU + pertuzumab, serious ARs in >1% of patients were diarrhea, pneumonia, febrile neutropenia, hypokalemia, vomiting, ILD, pulmonary embolism, and sepsis. Fatalities due to ARs occurred in 3.4% of patients including pneumonia (n=3); ILD (n=2); sepsis (n=2); and pulmonary embolism, septic shock, acute kidney injury, dyspnea, febrile neutropenia, and intestinal ischemia (1 patient each)
Permanent discontinuations due to ARs	21%	28.3%	• For ENHERTU + pertuzumab, most frequent ARs (>2%) associated with permanent discontinuation was ILD/pneumonitis (6.6%)
Dose interruptions due to ARs	69%	49%	• For ENHERTU + pertuzumab, most frequent ARs (>2%) associated with dose interruption were COVID-19, neutropenia, upper respiratory tract infection, fatigue, anemia, hypokalemia, ILD/pneumonitis, thrombocytopenia, pneumonia, diarrhea, transaminase increased, leukopenia, cough, pyrexia, decreased appetite, and blood bilirubin increased
Dose reductions due to ARs	46%	19.9%	• For ENHERTU + pertuzumab, most frequent ARs (>2%) associated with dose reduction were fatigue, neutropenia, nausea, diarrhea, ILD/pneumonitis, thrombocytopenia, vomiting, transaminases increased, decreased weight, febrile neutropenia, and hypokalemia

- Other clinically relevant ARs reported in <10% of patients receiving ENHERTU + pertuzumab were increased blood bilirubin (9%), epistaxis (8%), abdominal distension (6%), dyspnea (6%), skin hyperpigmentation (6%), blurred vision (4.2%), gastritis (3.9%), increased blood creatinine (3.1%), dehydration (2.9%), febrile neutropenia (2.9%), flatulence (2.4%), and infusion related reaction (1.8%)[1]

Adjudicated as drug-related[3,5]	ENHERTU + pertuzumab (n=381)					
	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)	Grade 5, n (%)[a]	Any Grade, n (%)
ILD/pneumonitis	17 (4.5)	27 (7.1)	0	0	2 (0.5)	46 (12.1)

- **The most common selected laboratory abnormalities in patients receiving ENHERTU + pertuzumab** were decreased white blood cell count (87%), decreased hemoglobin (80%), decreased neutrophil count (78%), increased alanine aminotransferase (66%), increased aspartate aminotransferase (62%), decreased lymphocyte count (62%), decreased platelet count (56%), increased blood alkaline phosphatase (55%), decreased blood potassium (54%), increased blood bilirubin (23%), and increased blood creatinine (9%)[1]

[a]Grade 5=fatal cases.
Abbreviations: AR, adverse reaction; ILD, interstitial lung disease; THP, taxane + trastuzumab + pertuzumab.

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AR management strategies can support patients' experience while receiving ENHERTU + pertuzumab

Nausea & Vomiting

- **Nausea** (All Grades) occurred in **75%** of patients receiving ENHERTU + pertuzumab; Grades 3-4 events in 5%[1]
- **Vomiting** (All Grades) occurred in **46%** of patients receiving ENHERTU + pertuzumab; Grades 3-4 events in 2.4%[1]
- ENHERTU is classified as **highly emetogenic**, which includes delayed nausea and/or vomiting. **Administer prophylactic antiemetic medications** per local institutional guidelines for prevention of chemotherapy-induced nausea and vomiting[1]

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines)® for Antiemesis[8]

- Recommends **3-4-drug prophylactic antiemetic** regimens for **high emetic risk** agents, including fam-trastuzumab deruxtecan-nxki (ENHERTU), to prevent or decrease anticancer agent–induced acute and delayed emesis
- **Premedicate** with an antiemetic regimen for high emetic risk agents before infusion on Day 1, then **continue** for at least 3 days **(4 days total)** during every cycle, as it is harder to control nausea and/or vomiting once it has started

Management of ARs may require temporary interruption, dose reduction, or treatment discontinuation of ENHERTU[1]

Management strategies to help address clinically relevant ARs are available at ENHERTUhcp.com

Proactively manage nausea and vomiting

Review the 3-4 drug prophylactic antiemetic regimens for high emetic risk agents

Click here ▶

Detect and manage ILD/ pneumonitis

See how to implement protocols for ILD screening with the five "S" strategies

Click here ▶

Reduce dosage to manage select ARs

See the recommended dose modifications

Click here ▶

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Abbreviations: AR, adverse reaction; ILD, interstitial lung disease; NCCN, National Comprehensive Cancer Network.

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A potential new standard for HER2+ mBC treatment:

ENHERTU + pertuzumab offers superior PFS with no new safety signals vs THP[1]

SUPERIOR PFS

Superior mPFS of 40.7 months was achieved with ENHERTU + pertuzumab vs 26.9 months with THP[1]

- HR: 0.56 (95% CI: 0.44, 0.71); *P*<0.0001[a]

MAJORITY RESPONDED

ENHERTU + pertuzumab demonstrated a confirmed ORR of 87%, with CR achieved in 15% of patients[1]

- 87% with ENHERTU + pertuzumab (n=374; 95% CI: 83, 90; 15% CR + 72% PR); 81% with THP (n=371; 95% CI: 77, 85; 8% CR + 73% PR)[b]
- 15% CR with ENHERTU + pertuzumab; 8% CR with THP

In DESTINY-Breast09, ORR (secondary endpoint) was not powered to detect differences between treatment arms. Therefore, the clinical significance of these data is not known.

NO NEW SAFETY SIGNALS IDENTIFIED

The majority of ARs were Grade 1 or 2 in the ENHERTU + pertuzumab arm, with no new safety signals identified when compared with known profiles of each individual treatment[1,3]

Safety data from DESTINY-Breast09[1]

- The most common (≥20%) ARs, including laboratory abnormalities, in patients receiving ENHERTU + pertuzumab were decreased white blood cell count (87%), decreased hemoglobin (80%), decreased neutrophil count (78%), nausea (75%), increased alanine aminotransferase (66%), diarrhea (64%), decreased lymphocyte count (62%), increased aspartate aminotransferase (62%), decreased platelet count (56%), increased blood alkaline phosphatase (55%), decreased blood potassium (54%), fatigue (53%), alopecia (48%), vomiting (46%), constipation (33%), upper respiratory tract infection (33%), decreased appetite (32%), decreased weight (30%), COVID-19 (28%), musculoskeletal pain (24%), abdominal pain (23%), and increased blood bilirubin (23%)

ENHERTU + pertuzumab is now FDA-approved for **1L HER2+ mBC**.
Click here to learn more

[a]The stratified log-rank test *P* value is compared with the allocated alpha of 0.00043 for this interim analysis (with 73% of the planned number of events for final analysis).[1]

[b]Analysis was performed based on the patients with measurable disease assessed by BICR at baseline (n=374 patients randomized to receive ENHERTU + pertuzumab, n=371 for THP).[1]

Abbreviations: 1L, first line; AR, adverse reaction; CI, confidence interval; FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; mBC, metastatic breast cancer; mDOR, median duration of response; mPFS, median progression-free survival; NE, not estimable; ORR, objective response rate; PFS, progression-free survival; THP, taxane + trastuzumab + pertuzumab.

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

Interstitial Lung Disease / Pneumonitis (cont'd)

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.

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Indication and Important Safety Information

Indication

ENHERTU is a HER2-directed antibody and topoisomerase inhibitor conjugate indicated:

- HER2-Positive Metastatic Breast Cancer
  - In combination with pertuzumab as first-line treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH+) breast cancer, as determined by an FDA-approved test
  - As monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH+) breast cancer who have received a prior anti-HER2-based regimen either in the metastatic setting, or, in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy

Important Safety Information

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

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- **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 monotherapy or ENHERTU in combination with pertuzumab. 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)

ENHERTU as Monotherapy

In patients 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.

ENHERTU in Combination with Pertuzumab

In patients treated with ENHERTU 5.4 mg/kg in combination with pertuzumab (N=431), ILD occurred in 12% of patients. Median time to first onset was 8.0 months (range: 0.6 to 33.8). Fatal outcomes due to ILD and/or pneumonitis occurred in 0.5% of patients treated with ENHERTU in combination with pertuzumab.

Neutropenia

Severe neutropenia, including febrile neutropenia, can occur in patients treated with ENHERTU monotherapy or ENHERTU in combination with pertuzumab. 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)

ENHERTU as Monotherapy

In patients 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.

ENHERTU in Combination with Pertuzumab

In patients treated with ENHERTU 5.4 mg/kg in combination with pertuzumab (N=431), decreased neutrophil count occurred in 79% of patients. Median time to first onset was 22 days (range: 5 to 994). Twenty-nine percent had Grade 3 or 4 decreased neutrophil count. Febrile neutropenia was reported in 2.6% of patients.

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Important Safety Information (cont'd)

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. 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)

ENHERTU as Monotherapy

In patients 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.

ENHERTU in Combination with Pertuzumab

In patients treated with ENHERTU 5.4 mg/kg in combination with pertuzumab (N=431), LVEF decrease was reported in 11% of patients, of which 2.1% 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

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ENHERTU as Monotherapy

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%).

ENHERTU in Combination with Pertuzumab

The pooled safety population reflects exposure to ENHERTU 5.4 mg/kg in combination with pertuzumab intravenously every 3 weeks in 431 patients in DESTINY-Breast07 (n=50), and DESTINY-Breast09 (n=381). Among these patients, 86% were exposed for >6 months and 73% 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 (86%), decreased hemoglobin (80%), decreased neutrophil count (79%), nausea (74%), increased alanine aminotransferase (65%), diarrhea (64%), increased aspartate aminotransferase (63%), decreased lymphocyte count (61%), decreased platelet count (55%), increased blood alkaline phosphatase (54%), decreased blood potassium (54%), fatigue (53%), alopecia (48%), vomiting (46%), upper respiratory tract infection (32%), constipation (31%), decreased appetite (31%), decreased weight (28%), musculoskeletal pain (23%), abdominal pain (22%), and increased blood bilirubin (23%).

Important Safety Information (cont'd)

Adverse Reactions (cont'd)

HER2-Positive Metastatic Breast Cancer

DESTINY-Breast06

The safety of ENHERTU 5.4 mg/kg in combination with pertuzumab was evaluated in DESTINY-Breast09, a randomized, three-arm, multicenter study including 763 patients with HER2-positive (IHC 3+ or ISH+) unresectable or metastatic breast cancer. Three hundred eighty-one patients received ENHERTU in combination with pertuzumab and 382 patients received THP (taxane [docetaxel or paclitaxel], trastuzumab, and pertuzumab). Among patients who received ENHERTU in combination with pertuzumab, the median duration of treatment was 22 months (range: 0.3 months to 44.5 months).

Serious adverse reactions occurred in 27% of patients receiving ENHERTU in combination with pertuzumab. Serious adverse reactions in >1% of patients were diarrhea, pneumonia, febrile neutropenia, hypokalemia, vomiting, ILD, pulmonary embolism, and sepsis. Fatalities due to adverse reactions occurred in 3.4% of patients including pneumonia (n=3), ILD (n=2), sepsis (n=2), pulmonary embolism, septic shock, acute kidney injury, dyspnea, febrile neutropenia, and intestinal ischemia (one patient each).

ENHERTU was discontinued for adverse reactions in 21% of patients. The most frequent adverse reaction (>2%) associated with permanent discontinuation was ILD/pneumonitis (6.6%). Dose interruptions due to adverse reactions occurred in 69% of patients. The most frequent adverse reactions (>2%) associated with dose interruption were COVID-19, neutropenia, upper respiratory tract infection, fatigue, anemia, hypokalemia, ILD/pneumonitis, thrombocytopenia, pneumonia, diarrhea, transaminase increased, leukopenia, cough, pyrexia, decreased appetite, and blood bilirubin increased. Dose reductions occurred in 46% of patients treated with ENHERTU in combination with pertuzumab. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, neutropenia, nausea, diarrhea, ILD/pneumonitis, thrombocytopenia, vomiting, transaminases increased, decreased weight, febrile neutropenia, and hypokalemia.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased white blood cell count (87%), decreased hemoglobin (80%), decreased neutrophil count (78%), nausea (75%), increased alanine aminotransferase (66%), diarrhea (64%), increased aspartate aminotransferase (62%), decreased lymphocyte count (62%), decreased platelet count (56%), increased blood alkaline phosphatase (55%), decreased blood potassium (54%), fatigue (53%), alopecia (48%), vomiting (46%), upper respiratory tract infection (33%), constipation (33%), decreased appetite (32%), decreased weight (30%), COVID-19 (28%), musculoskeletal pain (24%), increased blood bilirubin (23%), and abdominal pain (23%).

DESTINY-Breast03

The safety of ENHERTU was evaluated in 257 patients with unresectable or metastatic HER2-positive breast cancer who received at least 1 dose of ENHERTU 5.4 mg/kg intravenously once every 3 weeks in DESTINYBreast03. The median duration of treatment was 14 months (range: 0.7 to 30) for patients who received ENHERTU.

Serious adverse reactions occurred in 19% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were vomiting, ILD, pneumonia, pyrexia, and urinary tract infection. Fatalities due to adverse reactions occurred in 0.8% of patients including COVID-19 and sudden death (1 patient each).

ENHERTU was permanently discontinued in 14% of patients, of which ILD/pneumonitis accounted for 8%. Dose interruptions due to adverse reactions occurred in 44% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, leukopenia, anemia, thrombocytopenia, pneumonia, nausea, fatigue, and ILD/pneumonitis. Dose reductions occurred in 21% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were nausea, neutropenia, and fatigue.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea (76%), decreased white blood cell count (74%), decreased neutrophil count (70%), increased aspartate aminotransferase (67%), decreased hemoglobin (64%), decreased lymphocyte count (55%), increased alanine aminotransferase (53%), decreased platelet count (52%), fatigue (49%), vomiting (49%), increased blood alkaline phosphatase (49%), alopecia (37%), decreased blood potassium (35%), constipation (34%), musculoskeletal pain (31%), diarrhea (29%), decreased appetite (29%), headache (22%), respiratory infection (22%), abdominal pain (21%), increased blood bilirubin (20%), and stomatitis (20%).

Important Safety Information (cont'd)

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:** *ENHERTU as Monotherapy*: Of the 2355 patients with breast cancer treated with ENHERTU 5.4 mg/kg, 23% were ≥65 years and 5% 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 (55%) as compared to younger patients (50%). *ENHERTU in Combination with Pertuzumab*: In patients with HER2-positive unresectable or metastatic breast cancer treated with ENHERTU 5.4 mg/kg in combination with pertuzumab (N=431), 17% were ≥65 years and 3% were ≥75 years. No overall differences in efficacy or safety were observed between patients ≥65 years of age compared to younger patients.
- **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.** Perjeta approved for HER2-positive metastatic breast cancer. Genentech. June 8, 2012. Accessed October 9, 2025. https://www.gene.com/media/news-features/perjeta-approved-for-her2-positive-metastatic-breast-cancer **3.** Tolaney SM, et al. *N Engl J Med*. Published online October 29, 2025. doi:10.1056/NEJMoa2508668 **4.** Swain SM, et al. *Ann Oncol*. 2014;25(6):1116-1121. **5.** Tolaney SM, et al. Presented at: 2025 American Society of Clinical Oncology (ASCO) Annual Meeting; May 30-June 3, 2025; Chicago, IL. **6.** Lam C, et al. *Oncologist*. 2025;30(4):oyae280. **7.** Data on file. Daiichi Sankyo, Inc. Basking Ridge, NJ. **8.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Antiemesis V.2.2025. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed November 19, 2025. 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.

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