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

ENHERTU–THP is FDA-approved as a neoadjuvant therapy for patients with HER2+ (IHC 3+ or ISH+) early breast cancer (Stage II or III)[1]

The approval of this indication for ENHERTU was based on the results of the DESTINY-Breast11 trial

Indication and Important Safety Information

Indication

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

- HER2-Positive Early Breast Cancer
  - As neoadjuvant treatment of adult patients with HER2-positive (IHC 3+ or ISH+) Stage II or III breast cancer, as determined by an FDA-authorized test followed by a taxane, trastuzumab, and pertuzumab (THP)
  - As adjuvant treatment of adult patients with HER2-positive (IHC 3+ or ISH+) breast cancer who have residual invasive disease following neoadjuvant trastuzumab (with or without pertuzumab) and taxane-based treatment

Important Safety Information

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

- **Interstitial lung disease (ILD) and pneumonitis, including severe, life-threatening, and 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

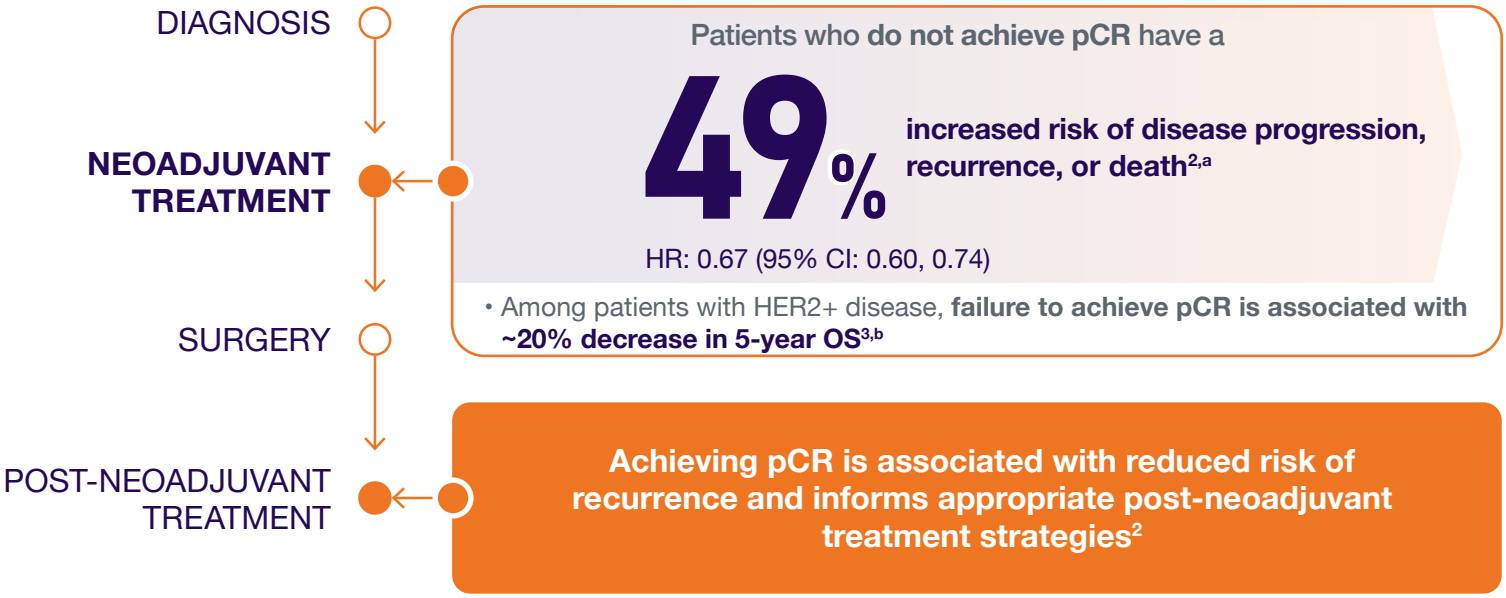
None.

Abbreviations: FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, *in situ* hybridization; THP, paclitaxel + trastuzumab + pertuzumab.

Please see Important Safety Information throughout as well as on pages 12-15, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

Achieving pCR is one of the primary treatment goals in the eBC setting for patients receiving neoadjuvant treatment[2]

pCR has been positively associated with increased EFS, which is the time elapsed between treatment randomization and disease progression that precludes surgery, local or distant recurrence, or death due to any cause[2-4]



For HER2+ patients, neoadjuvant and adjuvant therapy are recommended by the guidelines due to improvement in survival rates and reduction in risk of recurrence. Real-world evidence shows that 37% of high-risk HER2+ eBC patients did not receive neoadjuvant treatment per guideline recommendations, potentially contributing to worse outcomes[5,c]

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[a]Risk is calculated using the reciprocal of the HR to evaluate risk between negative and positive directions (1/0.67=1.49). Based on 51 studies of 12,535 patients that reported outcomes relating to pCR as an indicator of EFS, from a systemic review and meta-analysis of 78 observational HER2+ neoadjuvant breast cancer clinical trials published between 2009 and 2020. Data from 25,150 patients were included in the trial-level analysis. pCR was defined as no evidence of invasive and/or *in situ* disease in the breast and/or axillary lymph nodes.[2]

[b]Based on a 5-year OS of 95% (95% PI: 89%–99%) for pCR vs 76% (95% PI: 63%–88%) for non-pCR. Based on an evaluation of the association between pCR and clinical outcomes by 3 major clinical subtypes of breast cancer. Data are from 52 studies published from 1999 to 2016. The sample size for analysis ranged from 27 to 11,955 and featured a global patient population. Patient data were obtained by Kaplan-Meier (KM) curves or a measure of median survival or landmark event. pCR was defined as ypT0 ypN0 and ypT0/is ypN0.[3]

[c]Based on a retrospective, observational cohort study of 5,487 patients with HER2+ eBC within The US Oncology Network between January 2017-March 2023. High-risk patients (n=1,567) were included, and defined as the following: T0-T4, N1-N3, M0 or ≥T3, N0, M0.[5]

Abbreviations: CI, confidence interval; eBC, early breast cancer; EFS, event-free survival; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; NCCN, National Comprehensive Cancer Network; OS, overall survival; pCR, pathological complete response; PI, prediction interval.

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DESTINY-Breast11 is a Phase 3 global superiority trial evaluating neoadjuvant ENHERTU–THP vs ddAC-THP in HER2+ eBC[1,6]

DESTINY-Breast11: global, open-label, multicenter, randomized clinical trial

Patients with HER2+, locally advanced, inflammatory, or early-stage breast cancer (N=927)

Select eligibility criteria:
- ≥18 years of age
- ECOG PS 0-1
- A primary tumor stage of:
  - cT0-T4/N1-N3/M0 (node-positive), or
  - ≥cT3/N0-N3/M0 (tumor size >5 cm)

RANDOMIZED 1:1:1

Neoadjuvant treatment

- **ENHERTU Q3W**[a] 8 cycles (n=286)
- **ENHERTU Q3W** 4 cycles (n=321) → **THP Q3W** 4 cycles (n=321) →
- **ddAC Q2W** 4 cycles (n=320) → **THP Q3W** 4 cycles (n=320) →

→ **SURGERY**[b]

Primary Efficacy Endpoint	• pCR (ypT0/Tis ypN0)[c]
Select Secondary Efficacy Endpoints	• EFS • OS • iDFS

Stratification factors
- Hormone receptor status
- Central assessment of HER2+ status

Select exclusion criteria
- History of ILD/pneumonitis requiring treatment with steroids
- ILD/pneumonitis at screening
- ECOG PS >1

ddAC-THP is an NCCN Category 2A recommended treatment option for patients with HER2+ breast cancer, with studies showing similar efficacy rates for ddAC-THP and TCHP in the neoadjuvant setting[3,7]

[a]The ENHERTU monotherapy arm was prematurely closed by IDMC recommendations. The reasons for closure were multifactorial, including a lower pCR rate, low likelihood that ENHERTU alone would be superior to ddAC-THP, and the timing of surgery. The IDMC recommendation was not based on new safety findings. Patients already receiving ENHERTU monotherapy could continue treatment until completion of 8 cycles or meeting any discontinuation criteria, or switch to investigator's choice of local SOC.[6]

[b]Following surgery, treatment was determined by investigator and administered as part of the standard of care. Study protocol recommended radiotherapy with concomitant trastuzumab ± pertuzumab as post-neoadjuvant treatment in patients who achieved pCR and radiotherapy with T-DM1 in patients who did not achieve pCR.[6]

[c]ypT0/Tis ypN0 is defined as the absence of invasive disease in the breast and the axillary lymph nodes following surgery.[1]

Abbreviations: ddAC-THP, dose-dense doxorubicin + cyclophosphamide + trastuzumab + pertuzumab + taxane; eBC, early breast cancer; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; HER2, human epidermal growth factor receptor 2; iDFS, invasive disease-free survival; IDMC, Independent Data Monitoring Committee; ILD, interstitial lung disease; NCCN, National Comprehensive Cancer Network; OS, overall survival; pCR, pathological complete response; PS, performance status; Q2W, every 2 weeks; Q3W, every 3 weeks; SOC, standard of care; T-DM1, ado-trastuzumab emtansine; THP, paclitaxel + trastuzumab + pertuzumab.

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.

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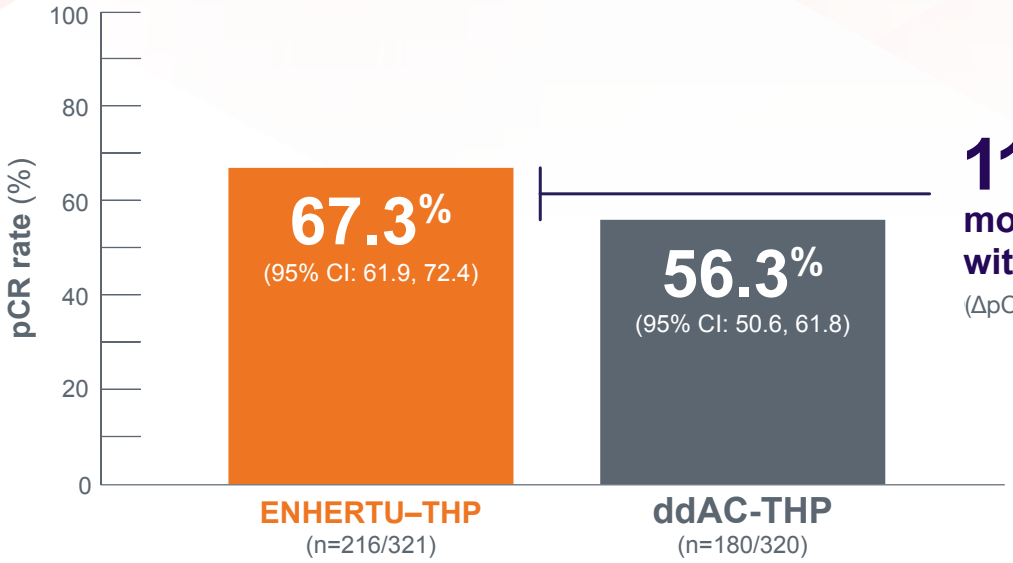
With ENHERTU followed by THP in patients with HER2+ eBC in the neoadjuvant setting

Superior pCR rates were achieved in the curative-intent setting[1]

Primary endpoint: pCR



11%
more patients achieved pCR with ENHERTU–THP
(ΔpCR=11.2%; 95% CI: 3.9, 18.3; *P*=0.003)[a,b]

- At the time of the pCR analysis, 29 (4.5%) patients had EFS events and 12 (1.9%) patients had OS events[1,6]
  - EFS HR was 0.56 (95% CI: 0.26, 1.17)
- **In DESTINY-Breast11, EFS and OS (secondary endpoints) were not powered to detect differences between treatment arms. Therefore, the clinical significance of these data cannot be determined**

2 out of 3 patients treated with ENHERTU–THP achieved pCR in DESTINY-Breast11[1]

[a]Based on Miettinen and Nurminen method stratified by HER2 status and hormone receptor status.[1]

[b]The 2-sided stratified Miettinen and Nurminen test *P* value is compared with the allocated alpha of 0.03.[1]

Abbreviations: CI, confidence interval; ddAC-THP, dose-dense doxorubicin + cyclophosphamide + trastuzumab + pertuzumab + taxane; eBC, early breast cancer; EFS, event-free survival; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; OS, overall survival; pCR, pathological complete response; THP, paclitaxel + trastuzumab + pertuzumab.

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

Interstitial Lung Disease / Pneumonitis (cont'd)

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.

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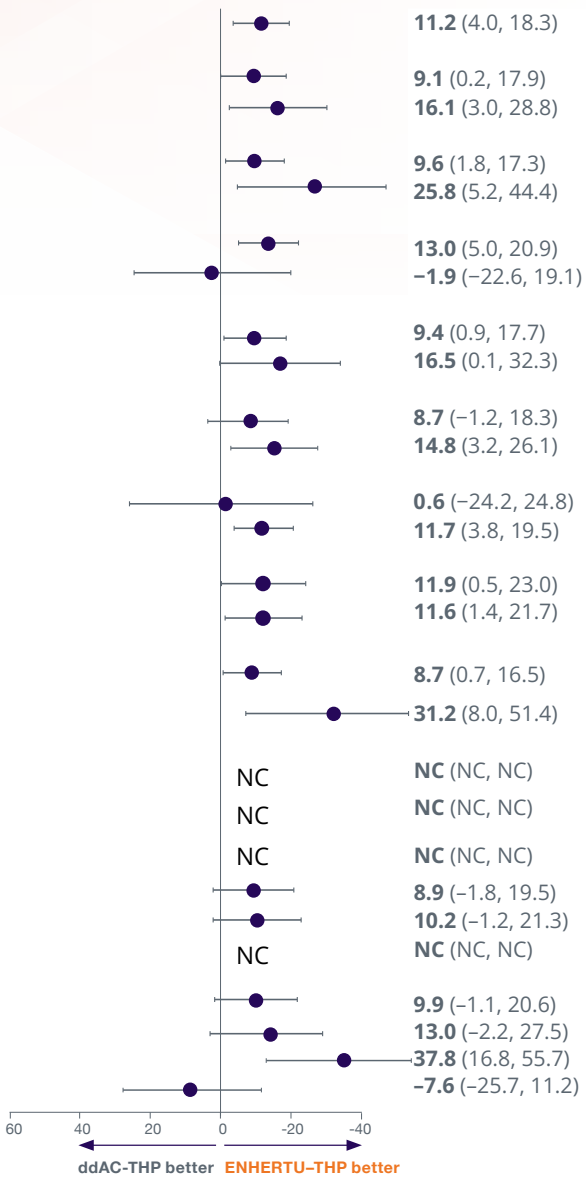
With ENHERTU followed by THP in patients with HER2+ eBC in the neoadjuvant setting

pCR rates measured in prespecified subgroups[6]

	ENHERTU–THP pCR (%)	ddAC-THP pCR (%)	ΔpCR (95% CI)
All patients (N=641)	**67.3** (n=216/321)	**56.3** (n=180/320)	**11.2** (4.0, 18.3)
Hormone receptor status			
HR+ (n=471)	**61.4** (n=145/236)	**52.3** (n=123/235)	**9.1** (0.2, 17.9)
HR– (n=168)	**83.1** (n=69/83)	**67.1** (n=57/85)	**16.1** (3.0, 28.8)
HER2 IHC status (by central lab)			
IHC 3+ (n=563)	**71.1** (n=199/280)	**61.5** (n=174/283)	**9.6** (1.8, 17.3)
Other (n=76)[a]	**42.5** (n=17/40)	**16.7** (n=6/36)	**25.8** (5.2, 44.4)
ECOG PS			
0 (n=558)	**68.7** (n=191/278)	**55.7** (n=156/280)	**13.0** (5.0, 20.9)
1 (n=83)	**58.1** (n=25/43)	**60.0** (n=24/40)	**–1.9** (–22.6, 19.1)
AJCC clinical stage			
II-IIIA (n=507)	**65.7** (n=163/248)	**56.4** (n=146/259)	**9.4** (0.9, 17.7)
IIIB-IIIC (n=133)	**72.2** (n=52/72)	**55.7** (n=34/61)	**16.5** (0.1, 32.3)
Clinical tumor stage			
cT0-2 (n=364)	**69.3** (n=122/176)	**60.6** (n=114/188)	**8.7** (–1.2, 18.3)
cT3-4 (n=277)	**64.8** (n=94/145)	**50.0** (n=66/132)	**14.8** (3.2, 26.1)
Nodal status			
N0 (n=61)	**57.7** (n=15/26)	**57.1** (n=20/35)	**0.6** (–24.2, 24.8)
N+ (n=568)	**68.3** (n=196/287)	**56.6** (n=159/281)	**11.7** (3.8, 19.5)
Menopausal status			
Postmenopausal (n=278)	**68.8** (n=86/125)	**56.9** (n=87/153)	**11.9** (0.5, 23.0)
Premenopausal (n=347)	**66.9** (n=123/184)	**55.2** (n=90/163)	**11.6** (1.4, 21.7)
Age			
<65 years (n=570)	**66.7** (n=188/282)	**58.0** (n=167/288)	**8.7** (0.7, 16.5)
≥65 years (n=71)	**71.8** (n=28/39)	**40.6** (n=13/32)	**31.2** (8.0, 51.4)
Race			
Black/African American (n=12)	**60.0** (n=3/5)	**28.6** (n=2/7)	NC **NC** (NC, NC)
Native American/other Pacific Islander (n=2)	**100.0** (n=1/1)	**100.0** (n=1/1)	NC **NC** (NC, NC)
American Indian/ Alaska Native (n=2)	**0.0** (n=0/2)	**NC** (n=0/0)	NC **NC** (NC, NC)
Asian (n=317)	**66.3** (n=106/160)	**57.3** (n=90/157)	**8.9** (–1.8, 19.5)
White (n=277)	**68.6** (n=96/140)	**58.4** (n=80/137)	**10.2** (–1.2, 21.3)
Other (n=18)	**66.7** (n=6/9)	**55.6** (n=5/9)	NC **NC** (NC, NC)
Geographical region			
Asia (n=304)	**66.5** (n=101/152)	**56.6** (n=86/152)	**9.9** (–1.1, 20.6)
Western Europe (n=146)	**75.4** (n=52/69)	**62.3** (n=48/77)	**13.0** (–2.2, 27.5)
North America (n=84)	**74.4** (n=32/43)	**36.6** (n=15/41)	**37.8** (16.8, 55.7)
Rest of world (n=107)	**54.4** (n=31/57)	**62.0** (n=31/50)	**–7.6** (–25.7, 11.2)



- **The DESTINY-Breast11 study protocol did not power the prespecified exploratory patient subgroup analysis to detect treatment effect differences between subgroups. Therefore, the clinical significance of these data cannot be determined**

[a]Other is defined as ISH+ in the absence of IHC 3+ status.[6]

Abbreviations: CI, confidence interval; ddAC-THP, dose-dense doxorubicin + cyclophosphamide + trastuzumab + pertuzumab + taxane; eBC, early breast cancer; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, *in situ* hybridization; NC, not calculated; pCR, pathological complete response; THP, paclitaxel + trastuzumab + pertuzumab.

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

Interstitial Lung Disease / Pneumonitis (cont'd)

In the adjuvant HER2+ breast cancer setting, if drug-induced ILD is suspected, rule out radiotherapy-related pneumonitis. If only radiotherapy-related pneumonitis is suspected, consider interruption of ENHERTU for Grade 2 and permanently discontinue ENHERTU for Grade ≥3.

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With ENHERTU followed by THP in patients with HER2+ eBC in the neoadjuvant setting

The majority of ARs were Grade 1 or 2 in the ENHERTU–THP arm[1]

Common ARs (≥10% all Grades or ≥2% Grade ≥3) in DESTINY-Breast11

Adverse reactions		ENHERTU–THP (n=320)		ddAC-THP (n=312)	
		All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal disorders	Nausea	65	1.9	52	0.3
	Diarrhea	59	6	54	3.2
	Constipation	29	0.3	24	0
	Vomiting	29	0.9	21	0.6
	Stomatitis[a]	23	0.3	36	1
	Abdominal Pain[b]	16	0	12	0
Nervous system disorders	Peripheral neuropathy[c]	59	2.5	47	2.2
	Headache[d]	18	0	16	0
Skin and subcutaneous tissue disorders	Alopecia	48	0	49	0
	Rash[e]	31	0.9	25	1
General disorders and administration site conditions	Fatigue[f]	41	0.6	55	2.2
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[g]	30	0	28	0.3
Metabolism and nutrition disorders	Decreased appetite	20	0	18	0.3
Respiratory, thoracic, and mediastinal disorders	Epistaxis	15	0	10	0
	Cough	10	0	14	0
Infections and infestations	Upper respiratory tract infection[h]	13	0.6	20	0.3
	COVID-19	10	0.9	11	0.3

ENHERTU–THP rates of serious AEs vs ddAC-THP[6]

	ENHERTU–THP (n=320)	ddAC-THP (n=312)
Any AE, %	98.1	98.7
Treatment-related	95.9	96.5
Grade ≥3 AEs, %	37.5	55.8
Treatment-related	31.6	51.0
Serious AEs, %	10.6	20.2
Treatment-related	7.2	15.4
AEs associated with death, %	0.6	0.6
Treatment-related	0.3	0.6

Events were graded using NCI-CTCAE v.5.0.

[a]Including aphthous ulcer, cheilitis, glossitis, mouth ulceration, mucosal inflammation, and stomatitis.[1]
[b]Including abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and gastrointestinal pain.[1]
[c]Including dysesthesia, hypoesthesia, neuropathy peripheral, paresthesia, peripheral motor neuropathy, peripheral sensory neuropathy, and polyneuropathy.[1]
[d]Including headache, migraine, and sinus headache.[1]
[e]Including dermatitis, dermatitis acneiform, dermatitis bullous, eczema, palmar-plantar erythrodysesthesia syndrome, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, skin exfoliation, and urticarial dermatitis.[1]
[f]Including asthenia, fatigue, and malaise.[1]
[g]Including arthralgia, back pain, bone pain, muscle spasms, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, and pain in extremity.[1]
[h]Including influenza, influenza-like illness, laryngitis, nasopharyngitis, pharyngitis, rhinitis, sinusitis, and upper respiratory tract infection.[1]

Abbreviations: AE, adverse event; AR, adverse reaction; ddAC-THP, dose-dense doxorubicin + cyclophosphamide + trastuzumab + pertuzumab + taxane; eBC, early breast cancer; HER2, human epidermal growth factor receptor 2; NCI-CTCAE, National Cancer Institute–Common Terminology Criteria for Adverse Events; NK1, neurokinin-1; RA, receptor antagonist; THP, paclitaxel + trastuzumab + pertuzumab.

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With ENHERTU followed by THP in patients with HER2+ eBC in the neoadjuvant setting

No new safety signals were identified in the ENHERTU–THP arm[1,6]

• Median duration of neoadjuvant treatment: 5.6 months (range: 0.7-9.1) with ENHERTU–THP

Clinically relevant AE considerations	ENHERTU–THP (n=320)	ddAC-THP (n=312)
Serious AEs	10.6%	20.2%
AE leading to discontinuation	14.1%	9.9%
AE leading to dose interruption	37.8%	54.5%
AE leading to dose reduction	18.1%	19.2%

10.6% **of patients experienced an SAE with ENHERTU–THP[6]**

- 20.2% of patients in the ddAC-THP arm experienced an SAE

97.2% **of patients underwent surgery following treatment with ENHERTU–THP[6]**

- 93.7% of patients in the ddAC-THP arm underwent surgery following treatment
- No patients failed to undergo surgery due to an AE

Clinically relevant AR considerations for ENHERTU in patients treated with ENHERTU–THP[1]:

- Serious ARs included COVID-19 (0.9%) and ILD/pneumonitis (0.6%). Fatal ARs occurred in 0.6% of patients, including ILD/pneumonitis and death not otherwise specified (1 patient each)
- The permanent discontinuation of ENHERTU due to ARs was 1.3%, of which ILD/pneumonitis accounted for 0.6%
- Dose interruptions of ENHERTU due to ARs occurred in 11% of patients. The most frequent ARs (>2%) associated with dose interruption of ENHERTU were decreased neutrophil count and COVID-19
- Dose reductions of ENHERTU occurred in 2.5% of patients

Abbreviations: AE, adverse event; ddAC-THP, dose-dense doxorubicin + cyclophosphamide + trastuzumab + pertuzumab + taxane; eBC, early breast cancer; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; SAE, serious adverse event; THP, paclitaxel + trastuzumab + pertuzumab.

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With ENHERTU followed by THP in patients with HER2+ eBC in the neoadjuvant setting

Early identification of ILD/pneumonitis is key to appropriate management

The majority of ILD/pneumonitis cases were Grade 1 or 2 in DESTINY-Breast11[6]

Incidence of ILD/pneumonitis in DESTINY-Breast11	**ENHERTU–THP** (n=320)	**ddAC-THP** (n=312)
All grades, n (%)	14 (4.4)	16 (5.1)
Grade 1, n (%)	4 (1.3)	4 (1.3)
Grade 2, n (%)	8 (2.5)	6 (1.9)
Grade 3, n (%)	1 (0.3)	5 (1.6)
Grade 4, n (%)	0 (0)	0 (0)
Grade 5, n (%)[a]	1 (0.3)	1 (0.3)

In the neoadjuvant setting, ILD/pneumonitis occurred in 4.4% of patients, with less than 1% experiencing Grade ≥3 events with ENHERTU–THP[6]

- Per DESTINY-Breast11 study protocol, patients received high-resolution CT at screening, then additional scans every 6 weeks during neoadjuvant treatment and at 40-day follow-up[8]
- Scans were reviewed for evidence of ILD/pneumonitis prior to administering each new cycle of ENHERTU–THP[8]

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

AR management strategies can support patients' experience while receiving ENHERTU–THP

Nausea & Vomiting

- Premedication: Antiemetics were administered in accordance with standard medical practice and patient tolerance for prophylaxis or management[1]
- In DESTINY-Breast11, use of 2 or 3 of the following was recommended by the study protocol: a glucocorticoid, serotonin (5-HT3) RA, and a NK1 RA. 16.9% of patients received 3 recommended prophylactic antiemetics before Cycle 1 of ENHERTU–THP (39.7% before Cycle 1 of ddAC-THP); 57.2% of patients received 2 recommended antiemetics before Cycle 1 of ENHERTU–THP (40.4% before Cycle 1 of ddAC-THP). The incidence of nausea events was higher in Cycles 1-4 than in Cycles 5-8 across both treatment arms[9]

The NCCN Guidelines® for Antiemesis[11]

- Recommends **3-4-drug prophylactic antiemetic** regimens for **high emetic risk** agents, including fam-trastuzumab deruxtecan-nxki (ENHERTU), to help 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

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Abbreviations: AR, adverse reaction; ddAC-THP, dose-dense doxorubicin + cyclophosphamide + trastuzumab + pertuzumab + taxane; NCCN, National Comprehensive Cancer Network; THP, paclitaxel + trastuzumab + pertuzumab.

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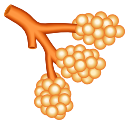
Monitoring for potential symptoms of ILD/pneumonitis is critical for proper management

Signs and symptoms of ILD/pneumonitis[1,8]

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

Promptly investigate evidence of ILD/pneumonitis[6,11]



- Diagnosis of ILD/pneumonitis requires exclusion of other causes
- All events of ILD/pneumonitis, regardless of severity or seriousness, should be followed until resolution, including after drug discontinuation
- Advise patients of the potential risks of treatment and to contact their HCP immediately to report any of these symptoms

Patients and HCPs should be aware of ILD risk; regular monitoring and quickly identifying and reporting symptoms are needed for appropriate management[8,10]

- Frequency of CT scans was determined by the DESTINY-Breast11 study protocol (see page 8 for more information)

Conduct routine review of scans to determine the presence of asymptomatic or symptomatic ILD/pneumonitis; identification based on scans, along with reporting of potential symptoms, may lead to modifying or discontinuing treatment[1,8]

For asymptomatic ILD (Grade 1)

- Interrupt ENHERTU until resolved to Grade 0, then:
  - If resolved in 28 days or less from date of onset, maintain dose
  - If resolved in greater than 28 days from date of onset, reduce dose 1 level
- Consider corticosteroid treatment (eg, ≥0.5 mg/kg/day prednisolone or equivalent)[a]

For symptomatic ILD (Grade 2 or greater)

- Promptly initiate systemic corticosteroid treatment (eg, ≥1 mg/kg/day prednisolone or equivalent)
  - Continue for at least 14 days followed by gradual taper for at least 4 weeks
- Permanently discontinue ENHERTU in patients who are diagnosed with any symptomatic ILD/pneumonitis

[a]Refer to Section 2.3 of the Prescribing Information for dose reduction schedule.
Abbreviations: CT, computed tomography; HCP, healthcare provider; ILD, interstitial lung disease; THP, paclitaxel + trastuzumab + pertuzumab.

Please see Important Safety Information throughout as well as on pages 12-15, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

ENHERTU–THP defines the next era in HER2+ eBC with superior pCR in the curative-intent setting[1,6]

11% HIGHER pCR

67.3% pCR rate with ENHERTU–THP vs 56.3% pCR rate with ddAC-THP
(95% CI: 3.9, 18.3; *P*=0.003)

- pCR rates measured in prespecified subgroups
- 4.5% of patients had EFS events at the time of analysis (HR: 0.56; 95% CI: 0.26, 1.17)
  - EFS was not powered to detect differences between treatment arms. Therefore, the clinical significance of these data cannot be determined

DEMONSTRATED BENEFIT-RISK PROFILE

DESTINY-Breast11 established the benefit-risk profile for ENHERTU–THP

- 97.2% of patients underwent surgery following treatment with ENHERTU–THP (93.7% with ddAC-THP)

NO NEW SAFETY SIGNALS IDENTIFIED

The majority of ARs were Grade 1 or 2 in the ENHERTU–THP arm, with no new safety signals identified

- Serious AEs with ENHERTU–THP was 10.6% vs 20.2% with ddAC-THP

Safety data from DESTINY-Breast11[1]

- The most common (≥20%) ARs, including laboratory abnormalities, in patients receiving ENHERTU–THP were decreased hemoglobin (83%), increased alanine aminotransferase (79%), increased aspartate aminotransferase (74%), decreased white blood cell count (67%), nausea (65%), peripheral neuropathy (59%), diarrhea (59%), decreased neutrophil count (58%), alopecia (48%), fatigue (41%), decreased lymphocyte count (40%), rash (31%), musculoskeletal pain (30%), decreased blood potassium (29%), constipation (29%), vomiting (29%), stomatitis (23%), and decreased appetite (20%)

ENHERTU–THP is FDA-approved for certain patients with HER2+ eBC in the neoadjuvant setting. Click here to learn more

Abbreviations: AE, adverse event; AR, adverse reaction; CI, confidence interval; ddAC-THP, dose-dense doxorubicin + cyclophosphamide + trastuzumab + pertuzumab + taxane; EFS, event-free survival; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; THP, paclitaxel + trastuzumab + pertuzumab.

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

Interstitial Lung Disease / Pneumonitis (cont'd)

HER2-Positive Breast Cancer and Other Solid Tumors (5.4 mg/kg)

ENHERTU followed by THP

In patients treated with ENHERTU 5.4 mg/kg followed by THP in DESTINY-Breast11, ILD occurred in 4.4% of patients. Median time to first onset was 2.7 months (range: 1.1 to 6.0). Fatal outcomes due to ILD and/or pneumonitis occurred in 1 patient (0.3%) treated with ENHERTU followed by THP.

Please see Important Safety Information throughout as well as on pages 12-15, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

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 severe, life-threatening, and 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. In the adjuvant HER2+ breast cancer setting, if drug-induced ILD is suspected, rule out radiotherapy-related pneumonitis. If only radiotherapy-related pneumonitis is suspected, consider interruption of ENHERTU for Grade 2 and permanently discontinue ENHERTU for Grade ≥3.

Metastatic Breast Cancer and Other Solid Tumors (5.4 mg/kg)

ENHERTU as Monotherapy

In patients treated with ENHERTU 5.4 mg/kg followed by THP in DESTINY-Breast11, ILD occurred in 4.4% of patients. Median time to first onset was 2.7 months (range: 1.1 to 6.0). Fatal outcomes due to ILD and/or pneumonitis occurred in 1 patient (0.3%) treated with ENHERTU followed by THP.

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)

ENHERTU as Monotherapy

In patients treated with ENHERTU 5.4 mg/kg followed by THP in DESTINY-Breast11, a decrease in neutrophil count was reported in 58% of patients. Seventeen percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 42 days (range: 11 to 165). Febrile neutropenia was reported in 0.9% of patients.

Please see Important Safety Information throughout as well as on pages 12-15, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

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 dysfunction (LVD) has been observed with anti-HER2 therapies, including ENHERTU. Assess left ventricular ejection fraction (LVEF) prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. Manage LVD 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.

HER2-Positive Breast Cancer and Other Solid Tumors (5.4 mg/kg)

ENHERTU followed by THP

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.

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

HER2-Positive Early Breast Cancer

DESTINY-Breast11

The safety of ENHERTU followed by THP was evaluated in 320 patients with HER2-positive (IHC 3+ or ISH+) early breast cancer who received at least 1 dose of ENHERTU 5.4 mg/kg followed by THP in DESTINY-Breast11. ENHERTU was administered by intravenous infusion once every three weeks for 4 cycles followed by THP for 4 cycles. The median duration of treatment was 5.6 months (range: 0.7 to 9.1) for patients who received ENHERTU followed by THP.

Serious adverse reactions occurred in 11% of patients receiving ENHERTU followed by THP, including COVID-19 (0.9%) and ILD/pneumonitis (0.6%). Fatal adverse reactions occurred in 0.6% of patients, including ILD/pneumonitis and death not otherwise specified (1 patient each).

In patients treated with ENHERTU followed by THP, the permanent discontinuation of ENHERTU due to adverse reactions occurred in 1.3%, of which ILD/pneumonitis accounted for 0.6%. Dose interruptions of ENHERTU due to adverse reactions occurred in 11% of patients. The most frequent adverse reactions (>2%) associated with dose interruption were decreased neutrophil count and COVID-19. Dose reductions of ENHERTU occurred in 2.5% of patients treated with ENHERTU.

The most common (≥20%) adverse reactions in patients treated with ENHERTU followed by THP, including laboratory abnormalities, were decreased hemoglobin (83%), increased alanine aminotransferase (79%), increased aspartate aminotransferase (74%), decreased white blood cell count (67%), nausea (65%), peripheral neuropathy (59%), diarrhea (59%), decreased neutrophil count (58%), alopecia (48%), fatigue (41%), decreased lymphocyte count (40%), rash (31%), musculoskeletal pain (30%), decreased blood potassium (29%), constipation (29%), vomiting (29%), stomatitis (23%), and decreased appetite (20%).

Important Safety Information (cont'd)

Adverse Reactions (cont'd)

HER2-Positive Early Breast Cancer

DESTINY-Breast05

The safety of ENHERTU was evaluated in 806 patients with HER2-positive breast cancer with residual invasive disease following neoadjuvant HER2-targeted therapy who then received at least one dose of ENHERTU 5.4 mg/kg. ENHERTU was administered by intravenous infusion once every three weeks for 14 cycles. The median duration of treatment was 10 months (range: 0.7 to 16) for patients who received ENHERTU.

Serious adverse reactions occurred in 17% of patients receiving ENHERTU. Serious adverse reactions in ≥1% of patients who received ENHERTU were ILD/pneumonitis, radiation pneumonitis, pneumonia, and platelet count decreased. Fatal adverse reactions occurred in 0.4% of patients including ILD/pneumonitis (2 patients) and respiratory tract infection (1 patient).

Permanent discontinuation of ENHERTU due to an adverse reaction occurred in 18% of patients. The adverse reaction which resulted in permanent discontinuation of ENHERTU >2% included ILD/pneumonitis. Dose interruptions of ENHERTU due to an adverse reaction occurred in 50% of patients. Adverse reactions which required dosage interruptions in >2% included radiation pneumonitis, neutrophil count decreased, COVID-19, white blood cell count decreased, ILD/pneumonitis, platelet count decreased, upper respiratory tract infection, fatigue, cough, and pyrexia. Dose reductions of ENHERTU due to an adverse reaction occurred in 26% of patients. Adverse reactions which required dose reductions in >2% of patients included nausea, fatigue, platelet count decreased, ILD/pneumonitis, and neutrophil count decreased.

The most common (≥20%) adverse reactions, including laboratory abnormalities, in patients receiving ENHERTU were decreased white blood cell count (80%), decreased lymphocyte count (72%), decreased neutrophil count (72%), nausea (71%), decreased hemoglobin (61%), increased aspartate aminotransferase (60%), fatigue (54%), increased alanine aminotransferase (53%), decreased platelet count (46%), increased blood alkaline phosphatase (39%), constipation (32%), vomiting (31%), decreased blood potassium (27%), diarrhea (23%), musculoskeletal pain (23%), and decreased appetite (20%).

ILD was reported in 17% of patients receiving ENHERTU, which included COVID-19 pneumonia, interstitial lung disease, lung opacity, organizing pneumonia, pneumocystis jirovecii pneumonia, pneumonia, and pneumonitis which was adjudicated as ILD (irrespective of causality). Adjudicated drug-related ILD for ENHERTU was 10% for all Grades and 0.9% for Grades 3 or 4.

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 followed by THP*: Of the 320 patients with HER2-positive early breast cancer treated with ENHERTU 5.4 mg/kg followed by THP, 12% were ≥65 years and 1.6% were ≥75 years. No overall differences in efficacy were observed between patients ≥65 years compared to younger patients. There was a higher incidence of Grade 3-4 adverse reactions observed in patients ≥65 years (38%) as compared to younger patients (30%).

Important Safety Information (cont'd)

Use in Specific Populations (cont'd)

- **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, monitor for increased adverse reactions 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.; 2026. **2.** Davey MG, et al. *BJS Open*. 2022;6(3):zrac028. **3.** Spring LM, et al. *Clin Cancer Res*. 2020;26(12):2838-2848. **4.** US Food and Drug Administration. July 2020. Accessed May 11, 2026. https://www.fda.gov/media/83507/download **5.** Mehta S, et al. Presented at: San Antonio Breast Cancer Symposium; December 12, 2024; San Antonio, TX. P3-11-09. **6.** Harbeck N, et al. *Ann Oncol*. 2026;37(2):166-179. **7.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.2.2026. © National Comprehensive Cancer Network, Inc. 2026. All rights reserved. Accessed May 11, 2026. 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. **8.** Data on file. Daiichi Sankyo, Inc. Basking Ridge, NJ. **9.** Curigliano G, et al. Presented at: San Antonio Breast Cancer Symposium; December 10, 2025; San Antonio, TX. RF6-02. **10.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Antiemesis V.1.2026. © National Comprehensive Cancer Network, Inc. 2026. All rights reserved. Accessed May 11, 2026. 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. **11.** Swain SM, et al. *Cancer Treat Rev*. 2022;106:102378.

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