ENHERTU THERAPY MANAGEMENT GUIDE

Efficacy & Safety | Management of Select Adverse Reactions | Dosing & Administration

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

A comprehensive resource with clinical data in the following indications[1]:

HER2+ eBC (IHC 3+ or ISH+)

- Neoadjuvant treatment followed by THP
- Post-neoadjuvant treatment for patients with residual invasive disease

HER2+ mBC (IHC 3+ or ISH+)

- 1L therapy in combination with pertuzumab
- 2L monotherapy

HER2-low and HER2-ultralow mBC

- HR+, HER2-low (IHC 1+ or IHC 2+/ISH–) or HER2-ultralow (IHC 0 with membrane staining) mBC
- Eligible previously treated HER2-low (IHC 1+ or IHC 2+/ISH–) mBC

2L *HER2*-mutant mNSCLC

2L HER2+ aGC (IHC 3+ or IHC 2+/ISH+)

HER2+ (IHC 3+) **metastatic solid tumors**

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.**

Indications

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
- 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-authorized 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
- HER2-Low and HER2-Ultralow Metastatic Breast Cancer
  - As monotherapy 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-authorized test, that has progressed on one or more endocrine therapies in the metastatic setting
  - As monotherapy for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-authorized test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy
- HER2-Mutant Unresectable or Metastatic Non-Small Cell Lung Cancer (NSCLC)
  - As monotherapy for the treatment of adult patients with unresectable or metastatic NSCLC whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-authorized test, and who have received a prior systemic therapy

    This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
- HER2-Positive Locally Advanced or Metastatic Gastric Cancer
  - As monotherapy for the treatment of adult patients with locally advanced or metastatic HER2-positive (IHC 3+ or IHC 2+/ISH positive) gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen
- HER2-Positive (IHC 3+) Unresectable or Metastatic Solid Tumors
  - As monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options

    This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

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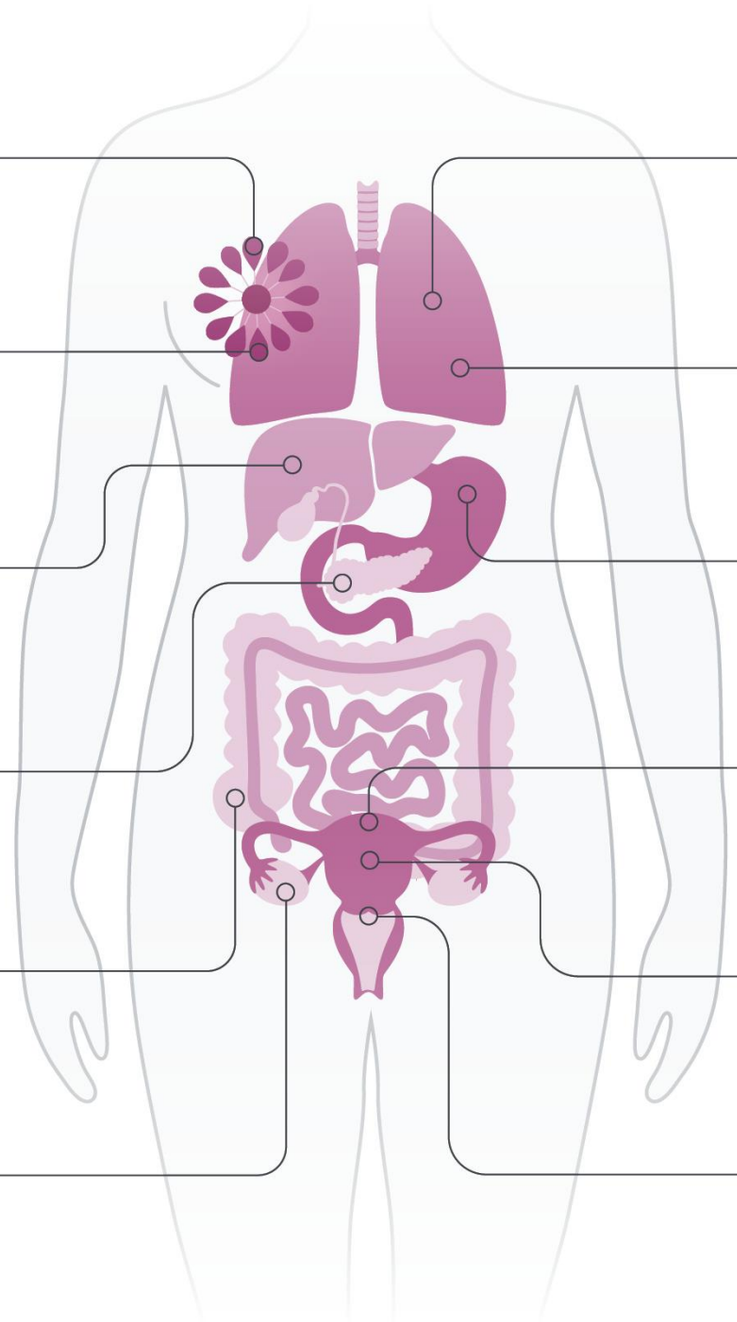
HER2 expression/alteration is found across many tumor types[2-29,a]



- ~15% — Breast HER2+ (IHC 3+ or ISH+)
- ~50% — Breast HER2-low (IHC 1+ or IHC 2+/ISH–)
- 4%-13% — Biliary tract HER2+ (IHC 3+)
- 1%-7% — Pancreatic HER2+ (IHC 3+)
- 1%-3% — Colorectal HER2+ (IHC 3+)
- 1%-5% — Ovarian HER2+ (IHC 3+)
- 2%-4% — Activating *HER2* (*ERBB2*)-mutant NSCLC
- 1%-5% — NSCLC HER2+ (IHC 3+)
- 18% — Gastric HER2+ (IHC 3+ or IHC 2+/ISH+)
- 4%-31% — Bladder HER2+ (IHC 3+)
- 4%-28% — Endometrial HER2+ (IHC 3+)
- 8%-14% — Cervical HER2+ (IHC 3+)

[a]Individual tumor prevalence numbers reflect US and ex-US populations. Due to limited testing of IHC in the US, data from a global population have been included.

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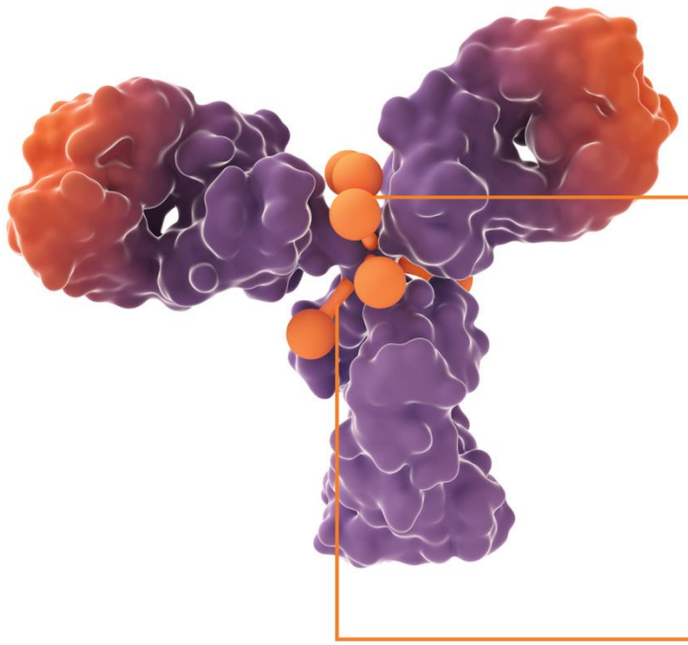
ENHERTU is a specifically engineered HER2-directed antibody-drug conjugate (ADC)[1,30]

HER2-directed mAb[1,30]

- Provides targeted delivery of cytotoxic agent
- Consists of the same amino acid sequence as trastuzumab



Topoisomerase I inhibitor payload[1,31,32,a]

- Highly potent payload is an exatecan derivative, known as DXd, with a short systemic half-life
- Upon release, membrane-permeable payload causes DNA damage and cell death, resulting in destruction of targeted tumor cells and neighboring cells present in the tumor microenvironment, known as the bystander antitumor effect

Tumor-selective cleavable linker[1,30,31,a]

- Attaches payload to the antibody
- Linker-payload is stable in plasma
- Linker selectively cleaved by enzymes that are upregulated in tumor cells

ENHERTU has a homogeneous and high drug-to-antibody ratio of ~8 molecules of cytotoxic agent per antibody[1,30,31,a,b]

[a]Based on in vitro and in vivo non-clinical studies. The clinical relevance of these features is under investigation.
[b]ADCs are a mixture of molecules in which the DAR is variable. Homogeneity of DAR refers to a mixture where there is low variability of DAR; the payload number per antibody falls into a narrow range.[31]

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ENHERTU has demonstrated efficacy across a range of HER2-expressing tumor types[1]

Indication		Study	Design	Population
Breast	HER2+ (IHC 3+ or ISH+) eBC as neoadjuvant treatment	DESTINY-Breast11	Multicenter, open-label, randomized, head-to-head trial of ENHERTU followed by THP vs ddAC-THP	927 adult patients with high-risk, HER2+, early-stage breast cancer or inflammatory breast cancer
	HER2+ (IHC 3+ or ISH+) eBC as post-neoadjuvant treatment	DESTINY-Breast05	Multicenter, open-label, randomized, head-to-head trial of ENHERTU vs T-DM1	1635 adult patients with HER2+ breast cancer with residual invasive disease following neoadjuvant therapy and at high risk of recurrence
	1L HER2+ mBC (IHC 3+ or ISH+)	DESTINY-Breast09	Multicenter, randomized, head-to-head trial of ENHERTU + pertuzumab vs THP	1157 adult patients with HER2+ advanced or mBC who had not received prior chemotherapy or HER2-targeted therapy for advanced or mBC and either had *de novo* mBC or had received (neo)adjuvant HER2-targeted therapy >6 months before diagnosis of advanced/ metastatic disease
	HER2-low mBC (IHC 1+ or IHC 2+/ISH–)	DESTINY-Breast04	Multicenter, open-label, randomized trial vs physician's choice of chemotherapy	557 adult patients with HER2-low mBC (IHC 1+ or IHC 2+/ISH–) with an HR+ cohort (n=494) and an HR– cohort (n=63) who received 1-2 prior lines of chemotherapy in the metastatic setting and, if HR+, had also progressed on or were refractory to endocrine therapy
	HR+/HER2-low (IHC 1+ or IHC 2+/ISH–) or HER2-ultralow (IHC 0 with membrane staining)	DESTINY-Breast06	Multicenter, open-label, randomized trial vs physician's choice of chemotherapy	866 adult patients with advanced or metastatic HR+ breast cancer with HER2-low (IHC 1+ or IHC 2+/ISH–) or HER2-ultralow (IHC 0 with membrane staining) expression who 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

Important Safety Information (cont'd)

Warnings and Precautions

Interstitial Lung Disease / Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with ENHERTU. A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment. Advise patients to immediately report cough, dyspnea, fever, and/or any new or worsening respiratory symptoms. Monitor patients for signs and symptoms of ILD. Promptly investigate evidence of ILD. Evaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist. For asymptomatic ILD/pneumonitis (Grade 1), interrupt ENHERTU until resolved to Grade 0, then if resolved in ≤28 days from date of onset, maintain dose. If resolved in >28 days from date of onset, reduce dose 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.

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ENHERTU has demonstrated efficacy across a range of HER2-expressing tumor types[1] (cont'd)

Indication		Study	Design	Population
Lung[a]	*HER2 (ERBB2)*-mutant mNSCLC	DESTINY-Lung02	Multicenter, multicohort, randomized, blinded, dose-optimization trial	102 adult patients with unresectable or metastatic non-squamous NSCLC who had activating *HER2 (ERBB2)* mutations and disease progression after a prior systemic therapy
Metastatic Solid Tumors[a]	HER2+ (IHC 3+) metastatic solid tumors	DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02	3 multicenter trials	192 adult patients with HER2+ (IHC 3+) unresectable or metastatic solid tumors that progressed after ≥1 prior treatment
Gastric	HER2+ aGC/GEJ (IHC 3+ or IHC 2+/ISH+)	DESTINY-Gastric01	Multicenter, open-label, randomized trial in Japan/South Korea	188 adult patients with HER2+ locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma who had progressed on ≥2 prior regimens, including trastuzumab, a fluoropyrimidine- and a platinum-containing chemotherapy regimen

Important Safety Information (cont'd)

Warnings and Precautions

Interstitial Lung Disease / Pneumonitis (cont'd)

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.

HER2-Positive, HER2-Low, and HER2-Ultralow Breast Cancer, HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (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.

[a]This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

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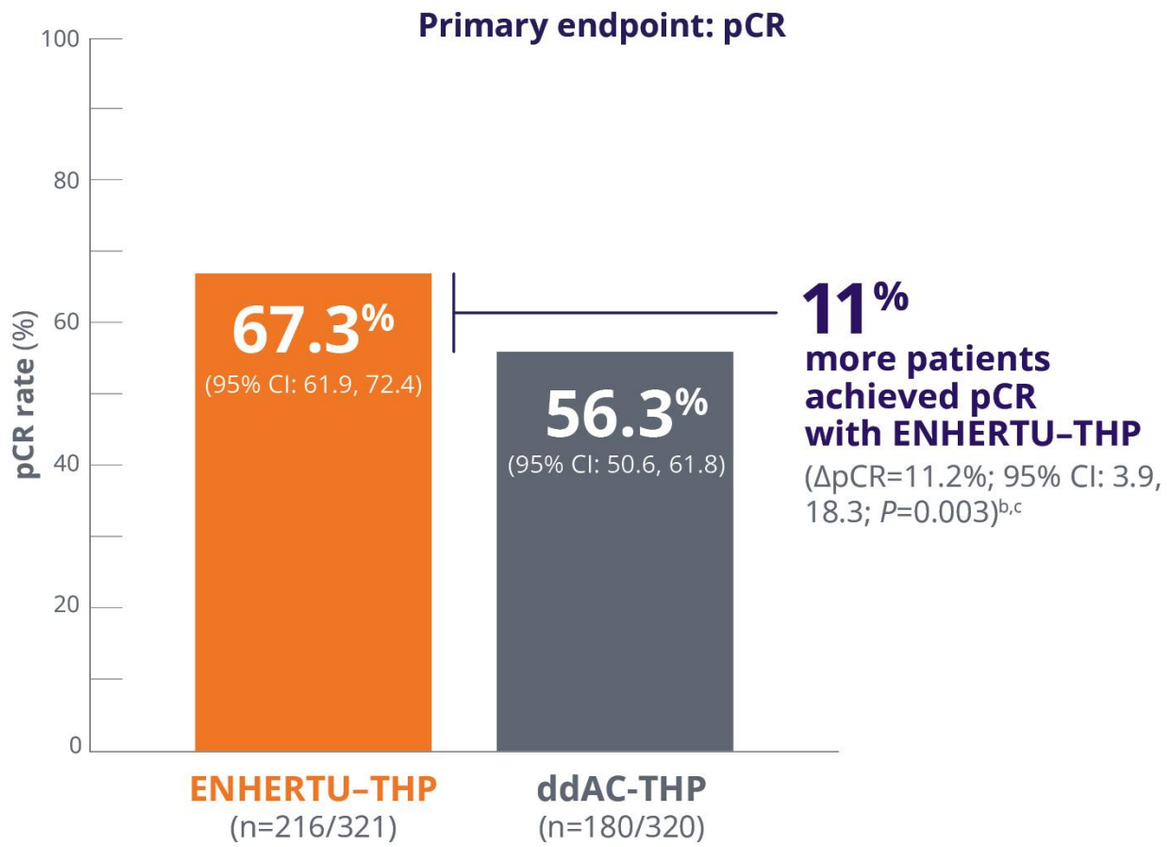
With ENHERTU followed by THP in patients with HER2+ eBC in the neoadjuvant setting

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



- At the time of the pCR analysis, 29 (4.5%) patients had EFS events and 12 (1.9%) patients had OS events[1,33]
  - 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]

Important Safety Information (cont'd)

Warnings and Precautions

Interstitial Lung Disease / Pneumonitis (cont'd)

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.

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.

HER2-Positive Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)

In patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, ILD occurred in 10% of patients. Median time to first onset was 2.8 months (range: 1.2 to 21).

[a]**Study design:** DESTINY-Breast11 is a Phase 3, global, multicenter, open-label, randomized study investigating neoadjuvant use of ENHERTU followed by THP (paclitaxel, trastuzumab, and pertuzumab) in adult patients with previously untreated HER2+, locally advanced high-risk (lymph node positive [N1-3] or with a primary tumor stage T3-4) or inflammatory early breast cancer. Patients (N=927) were randomly assigned 1:1:1 to receive 8 cycles of neoadjuvant treatment with ENHERTU 5.4 mg/kg IV Q3W for 4 cycles followed by THP for 4 cycles, ddAC for 4 cycles followed by THP for 4 cycles, or an additional investigational therapy. The primary endpoint was centrally assessed pCR rate (ypT0/Tis ypN0). Select secondary endpoints were EFS, iDFS, and OS.[1,33]
[b]Based on Miettinen and Nurminen method stratified by HER2 status and hormone receptor status.[1]
[c]The 2-sided stratified Miettinen and Nurminen test *P* value is compared with the allocated alpha of 0.03.[1]

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The benefit-risk profile of ENHERTU–THP was demonstrated in DESTINY-Breast11[1,33]

No new safety signals were identified in the ENHERTU–THP arm

- Median duration of neoadjuvant treatment: 5.6 months (range: 0.7-9.0) with ENHERTU–THP[1]

Clinically relevant AE considerations[33]	**ENHERTU 5.4 mg/kg followed by THP** (n=320)
Serious AEs	10.6%
AE leading to discontinuation	14.1%
AE leading to dose interruption	37.8%
AE leading to dose reduction	18.1%
ILD/pneumonitis (All Grades)[a]	4.4% (One Grade 5 event)[b]

Clinically relevant AR considerations 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

- Symptom identification is key to diagnosis; monitor patients and initiate management at first sign of ILD[1]
- The most common (≥20%) ARs, 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%)[1]

Incidence of select common adverse reactions in DESTINY-Breast11[1]

Adverse reactions	**ENHERTU 5.4 mg/kg followed by THP** (n=320)		**ddAC-THP** (n=312)	
	All Grades (%)	**Grades 3-4 (%)**	**All Grades (%)**	**Grades 3-4 (%)**
Nausea	65	1.9	52	0.3
Diarrhea	59	6	54	3.2
Alopecia	48	0	49	0
Fatigue[c]	41	0.6	55	2.2
Constipation	29	0.3	24	0
Vomiting	29	0.9	21	0.6
Decreased appetite	20	0	18	0.3

[a]Including interstitial lung disease, lung opacity, pneumonia fungal, pneumonitis.[1]
[b]Grade 5=fatal cases.[33]
[c]Including asthenia, fatigue, and malaise.[1]

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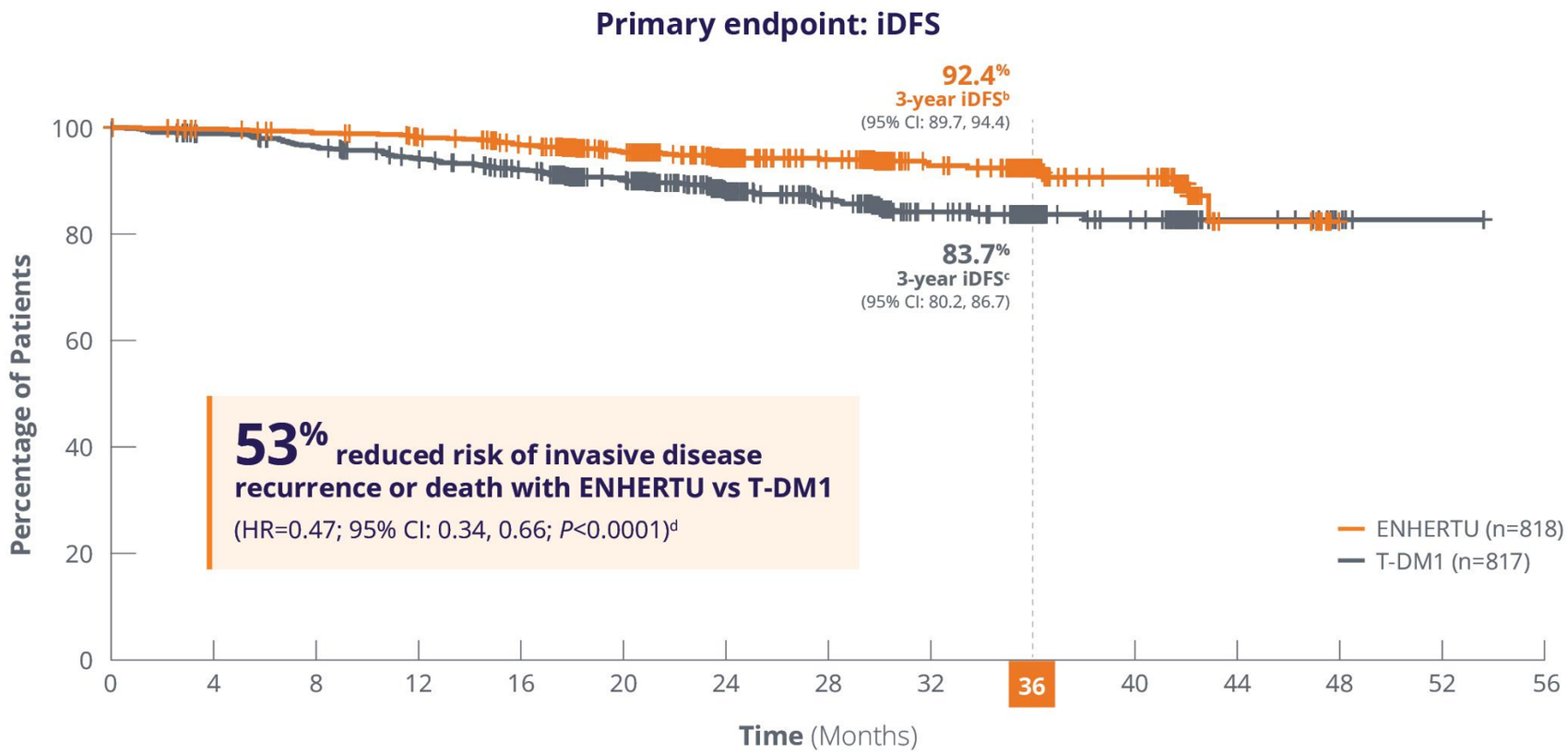
In patients with HER2+ residual invasive BC in the post-neoadjuvant setting

Superior iDFS with ENHERTU vs T-DM1 in a head-to-head trial in the curative-intent setting[1,a]



Number at Risk

ENHERTU	818	781	771	758	731	634	440	370	218	129	90	14	0	0	0
T-DM1	817	769	745	719	687	599	417	337	186	120	79	14	4	1	0

- Interim analysis (data cutoff July 2, 2025). Median duration of follow-up for ENHERTU: 29.9 months[34]
- **The analyses at 3 years are based on Kaplan-Meier estimates and are descriptive only; DESTINY-Breast05 was not powered to assess a statistical difference between treatment groups at this time point**

[a]**Study design:** DESTINY-Breast05 is a Phase 3, global, multicenter, open-label, randomized study investigating ENHERTU monotherapy in the adjuvant setting vs T-DM1 monotherapy in adult patients with HER2+ breast cancer with residual invasive disease in the breast or axillary nodes after neoadjuvant chemotherapy and trastuzumab-based treatment that was either inoperable disease at presentation or post-neoadjuvant positive nodal status. Patients (N=1635) were randomized 1:1 to receive 14 cycles of ENHERTU 5.4 mg/kg IV Q3W or 14 cycles of T-DM1 3.6 mg/kg IV Q3W. The primary endpoint was iDFS (defined as the time from randomization to the first occurrence of ipsilateral locoregional invasive breast cancer recurrence, distant recurrence, contralateral invasive BC, or death from any cause). The key secondary endpoint was DFS; additional secondary endpoints included OS, DRFI, and BMFI.[1,34]
[b]Number of events in the ENHERTU arm at 3 years: 51/818 (6%).[1]
[c]Number of events in the T-DM1 arm at 3 years: 102/817 (12%).[1]
[d]The stratified log-rank test *P* value is compared with the allocated alpha of 0.0183 for this interim analysis (with 74% of the planned number of events for final analysis).[1]

Important Safety Information (cont'd)

Warnings and Precautions

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.

HER2-Positive, HER2-Low, and HER2-Ultralow Breast Cancer, HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (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% of patients.

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The benefit-risk profile of ENHERTU was demonstrated in DESTINY-Breast05[1,34]

No new safety signals were identified in the ENHERTU arm

- Median duration of post-neoadjuvant treatment: 10 months (range: 0.7-16) with ENHERTU[1]

Clinically relevant AR considerations[1,34]	ENHERTU 5.4 mg/kg (n=806)	
Serious ARs	17%	• Serious ARs in ≥1% of patients who received ENHERTU were ILD/pneumonitis, radiation pneumonitis, pneumonia, and platelet count decreased. Fatal ARs occurred in 0.4% of patients including ILD/pneumonitis (2 patients) and respiratory tract infection (1 patient)
Permanent discontinuations due to ARs	18%	• The AR which resulted in permanent discontinuation of ENHERTU >2% included ILD/pneumonitis
Dose interruptions due to ARs	50%	• ARs 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 due to ARs	26%	• ARs which required dose reductions in >2% of patients included nausea, fatigue, platelet count decreased, ILD/pneumonitis, and neutrophil count decreased
Drug-related ILD/pneumonitis (All Grades)	9.6%[a]	• Majority of adjudicated drug-related ILD/pneumonitis events were Grade 1 or 2 (n=68/77) • Two Grade 5 adjudicated drug-related ILD/pneumonitis events were observed with ENHERTU[b]

- Symptom identification is key to diagnosis; monitor patients and initiate management at first sign of ILD[1]
- The most common (≥20%) ARs, including laboratory abnormalities, 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%)[1]

Incidence of select common adverse reactions in DESTINY-Breast05[1]

Adverse reactions	ENHERTU 5.4 mg/kg (n=806)		T-DM1 (n=801)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Nausea	71	4.5	29	0.1
Fatigue[c]	54	6	37	1
Constipation	32	0	16	0.1
Vomiting	31	1.1	9	0.1
Diarrhea	23	1.2	9	0.4
Decreased appetite	20	0.9	10	0
Alopecia	16	0	1.2	0

[a]Overall reported ILD rate was 17% for ENHERTU and 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).[1] [b]Grade 5=fatal cases.[34] [c]Including asthenia, fatigue, lethargy, and malaise.[1]

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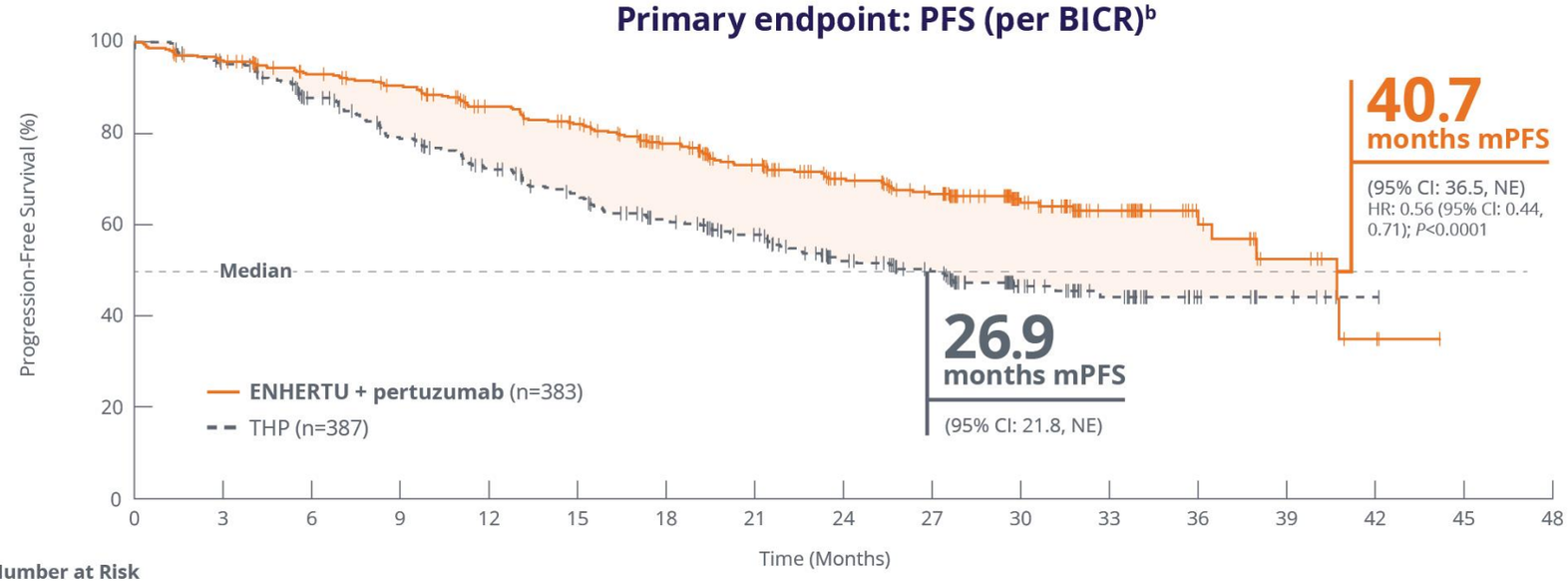
In DESTINY-Breast09, a **head-to-head study** vs THP

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

Primary endpoint: PFS (per BICR)[b]



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

HAZARD RATIO: 0.56
(95% CI: 0.44, 0.71); *P*<0.0001[b]

ENHERTU + pertuzumab—the first and only 1L HER2+ mBC treatment regimen in over a decade with superior PFS vs standard of care THP[1,35]

Secondary endpoint: Confirmed ORR (per BICR)[1,c,d]

- The DESTINY-Breast09 protocol was not powered for ORR (secondary endpoint, defined as CR+PR) to detect differences between treatment arms. Therefore, the clinical significance of these data cannot be determined

MAJORITY RESPONDED

ENHERTU + pertuzumab demonstrated a confirmed ORR of 87% (n=374; 95% CI: 83, 90), with CR achieved in 15% of patients (81% ORR with THP; n=371; 95% CI: 77, 85; 8% CR)

[a]**Study design:** DESTINY-Breast09 is the largest Phase 3, randomized, 3-arm, multicenter, global trial investigating first-line use of ENHERTU + pertuzumab compared with THP in 1157 patients with HER2+ mBC. Patients were randomized 1:1:1 to receive either ENHERTU 5.4 mg/kg + pertuzumab (n=383), THP (taxane [docetaxel or paclitaxel], trastuzumab, and pertuzumab) (n=387), or an investigational therapy (n=387) IV Q3W. All patients were treated until disease progression or unacceptable toxicity. The primary endpoint was PFS (BICR) according to RECIST v1.1. Secondary endpoints were OS and confirmed ORR.[1,36,37]
[b]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]
[c]95% CI was based on Clopper-Pearson method.[1]
[d]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).[1,38]

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Important Safety Information (cont'd)

Warnings and Precautions

Neutropenia (cont'd)

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.

ENHERTU followed by THP

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.

HER2-Positive Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)

In patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, a decrease in neutrophil count was reported in 72% of patients. Fifty-one percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 16 days (range: 4 to 187). Febrile neutropenia was reported in 4.8% of patients.

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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[36]

- Median duration of treatment: 22 months (range: 0.3-44.5) with ENHERTU + pertuzumab[1]

Clinically relevant AR considerations[1,39]	ENHERTU 5.4 mg/kg + pertuzumab (n=381)	
Serious ARs	27%	• 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%	• For ENHERTU + pertuzumab, most frequent AR (>2%) associated with permanent discontinuation was ILD/pneumonitis (6.6%)
Dose interruptions due to ARs	69%	• 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%	• 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
ILD/pneumonitis (All Grades)[a]	12%	• Majority of events were Grade 1 or 2 (n=44/46) • Two Grade 5 adjudicated drug-induced ILD/pneumonitis events were observed with ENHERTU[b]

- Symptom identification is key to diagnosis; monitor patients and initiate management at first sign of ILD[1]
- 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%), 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%)[1]

Incidence of select common adverse reactions in DESTINY-Breast09[1]

Adverse reactions	ENHERTU 5.4 mg/kg + pertuzumab (n=381)		THP (n=382)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Nausea	75	5	34	0.3
Diarrhea	64	8	62	6
Fatigue[c]	53	8	42	2.1
Alopecia	48	0	53	0.5
Vomiting	46	2.4	18	0.5
Constipation	33	0.3	12	0
Decreased appetite	32	2.4	18	0.8

[a]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] [b]Grade 5=fatal cases.[36] [c]Including asthenia, fatigue, lethargy, and malaise.[1]

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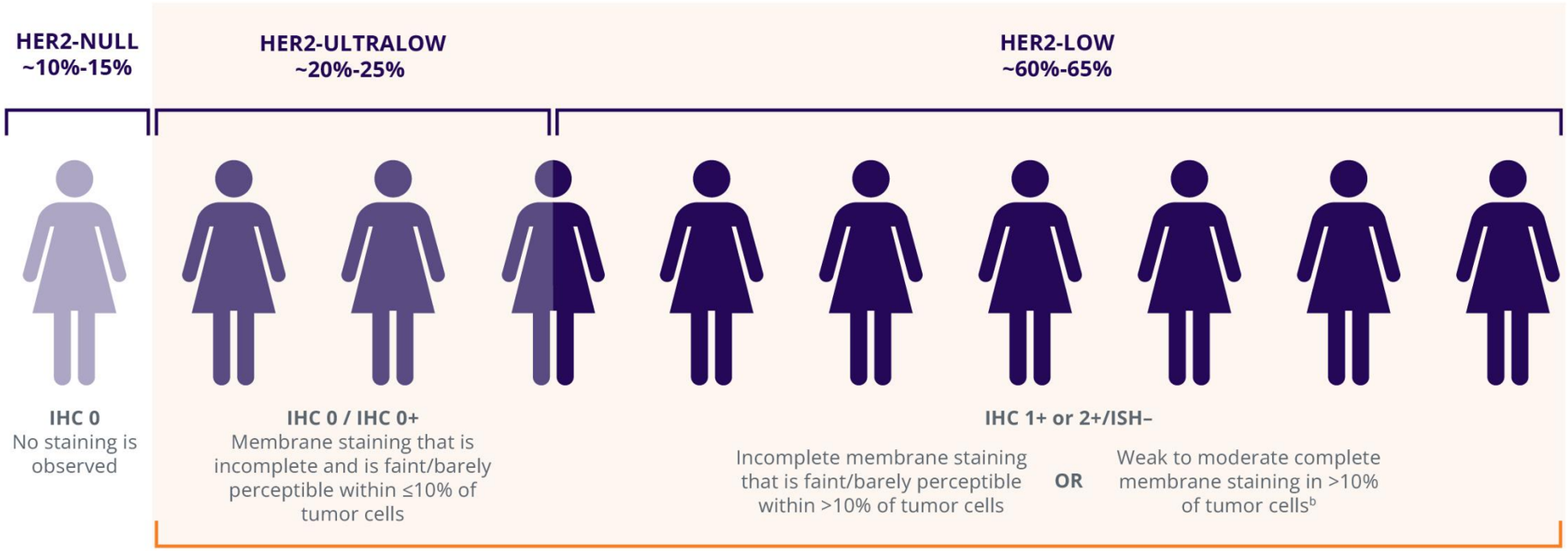
For eligible patients with HR+/HER2-low (IHC 1+ or IHC 2+/ISH–) or HER2-ultralow (IHC 0 with membrane staining) mBC who have received at least 1 line of ET in the metastatic setting[1]

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

HR+/HER2-negative mBC[40,41,a]



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

Important Safety Information (cont'd)

Warnings and Precautions

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.

[a]As demonstrated in DESTINY-Breast06 screening data. Among the 1856 patients screened for participation in the study, 12% (225 patients) had IHC 0 with absent membrane staining, while 22% (402 patients) were classified as HER2-ultralow, defined as IHC 0 with membrane staining. IHC 1+ was observed in 45% (829 patients), and IHC 2+/ISH– in 21% (385 patients).[40]
[b]Complete membrane staining that is intense but within ≤10% of tumor cells is also considered IHC 2+.[41]

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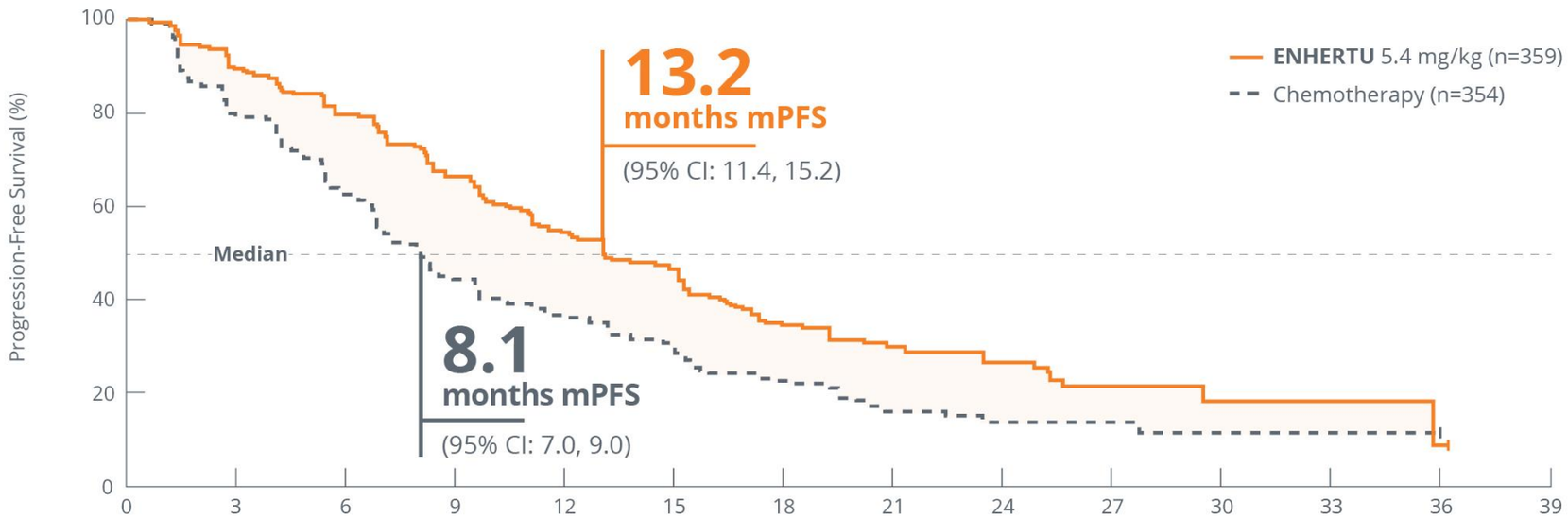
DESTINY-Breast06: In patients with HR+/HER2-low (IHC 1+ or IHC 2+/ISH–) mBC

ENHERTU provided 13.2 months median PFS vs 8.1 months with chemotherapy[a]

ENHERTU demonstrated a statistically significant and clinically meaningful PFS benefit in HR+/HER2-low mBC (primary endpoint, BICR)[1,42]



Number at Risk														
ENHERTU	359	310	265	213	163	131	72	49	28	17	10	6	1	0
Chemotherapy	354	254	192	118	85	65	37	19	10	6	2	1	1	0

- ENHERTU significantly improved mPFS vs physician-choice chemotherapy, including IV and oral options[1]
- At the time of the PFS final analysis, OS data were not yet mature[1]

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

Important Safety Information (cont'd)

Warnings and Precautions

Left Ventricular Dysfunction (cont'd)

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, HER2-Low, and HER2-Ultralow Breast Cancer, HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (5.4 mg/kg)

ENHERTU as Monotherapy

In patients treated with ENHERTU 5.4 mg/kg, LVD 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.

ENHERTU followed by THP

In patients treated with ENHERTU 5.4 mg/kg followed by THP in DESTINY-Breast11, LVD was reported in 1.3% of patients, of which 0.3% were Grade 3.

[a]**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 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); OS 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.[1,42-44]

[b]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]

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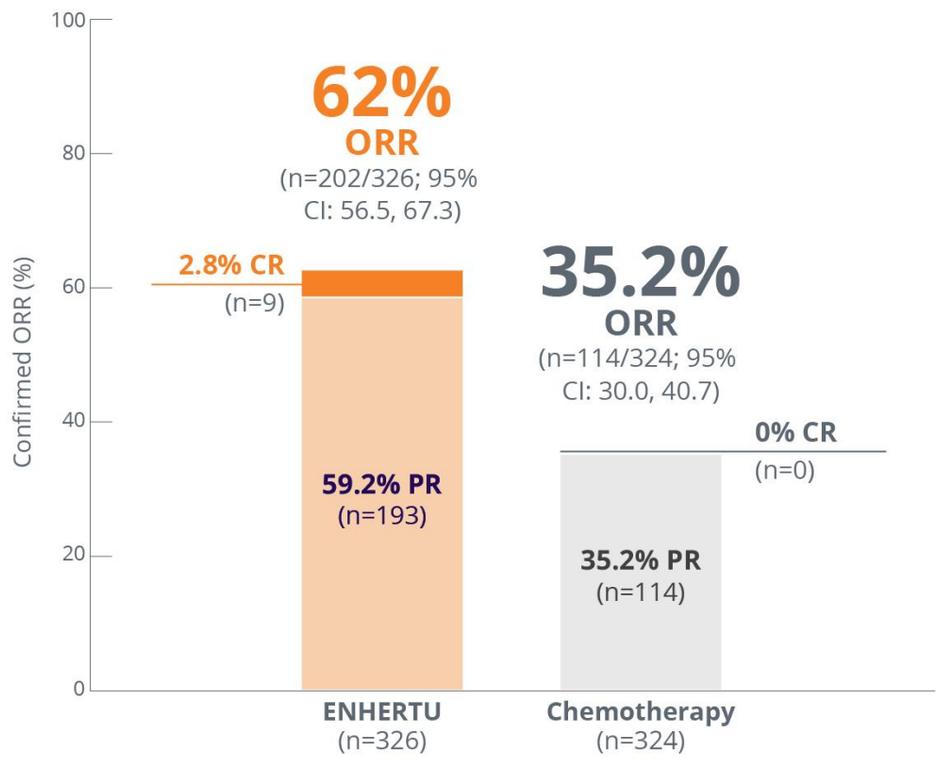
DESTINY-Breast06: In patients with HR+/HER2-low (IHC 1+ or IHC 2+/ISH–) mBC

Over 60% ORR with ENHERTU and 35.2% with chemotherapy

Secondary endpoint: confirmed objective response in the HER2-low mBC population (BICR)[1,44,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 and were not powered to show differences between treatment arms. Therefore, the clinical significance of these data cannot be determined

Additional results

- Median time to response (TTR) was **2.7** months with ENHERTU and **2.6** months with chemotherapy[38]

>90% (n=300/326) of patients achieved disease control (CR+PR+SD) with ENHERTU[38]

- DCR was 92% with ENHERTU (n=300/326) and 79.9% with chemotherapy (n=259/324)[38]
- **TTR and DCR were not tested for statistical significance and were not powered to show differences between treatment arms. Therefore, the clinical significance of these data cannot be determined**

[a]Analysis was performed based on the patients with measurable disease assessed by BICR at baseline.[1]

Important Safety Information (cont'd)

Warnings and Precautions

Left Ventricular Dysfunction (cont'd)

HER2-Positive Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)

In patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, no clinical adverse events of heart failure were reported; however, on echocardiography, 8% were found to have asymptomatic Grade 2 decrease in LVEF.

Embryo-Fetal Toxicity

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

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The ENHERTU benefit-risk profile in HER2-low mBC was further confirmed in DESTINY-Breast06 and was established in HER2-ultralow mBC[1,42]

• Median duration of treatment: 11 months (range: 0.4-39.6) with ENHERTU; 5.6 months (range: 0.1-35.9) with chemotherapy

Clinically relevant AR considerations	ENHERTU 5.4 mg/kg (n=434)	
Serious ARs	20%	• Serious ARs in >1% of patients 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, and general physical health deterioration (0.2% each)
Permanent discontinuations due to ARs	14%	• Most frequent (>2%) was ILD/pneumonitis. Per protocol, ENHERTU was discontinued in DESTINY-Breast06 in patients who were diagnosed with any symptomatic (Grade 2 or greater) ILD
Dose interruptions due to ARs	48%	• Most frequent (>2%) were COVID-19, decreased neutrophil count, anemia, pyrexia, pneumonia, decreased white blood cell count, and ILD
Dose reductions due to ARs	25%	• Most frequent (>2%) were nausea, fatigue, decreased platelet count, and decreased neutrophil count
ILD/pneumonitis (All Grades)[a]	11%	• Majority of events were Grade 1 or 2 (n=43/49) • Three Grade 5 adjudicated drug-induced ILD/pneumonitis events were observed with ENHERTU[b]

• Symptom identification is key to diagnosis; monitor patients and initiate management at first sign of ILD

• Most common (≥20%) ARs, including laboratory abnormalities, in patients receiving ENHERTU 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%)

Incidence of select common adverse reactions in DESTINY-Breast06

Adverse reactions	ENHERTU 5.4 mg/kg (n=434)		Chemotherapy (n=417)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Nausea	70	2.1	30	0.5
Fatigue[c]	53	4.4	40	2.4
Alopecia	48	0	21	0.5
Diarrhea	34	2.3	27	2.6
Vomiting	34	1.4	12	0.2
Constipation	32	0.7	15	0.5
Decreased appetite	26	1.4	12	0.5

[a]Including bronchiectasis, interstitial lung disease, lower respiratory tract infection, pneumonia, pneumonia bacterial, pneumonitis, and pulmonary toxicity.[1]
[b]Grade 5=fatal cases.[42]
[c]Including fatigue, asthenia, malaise, and lethargy.[1]

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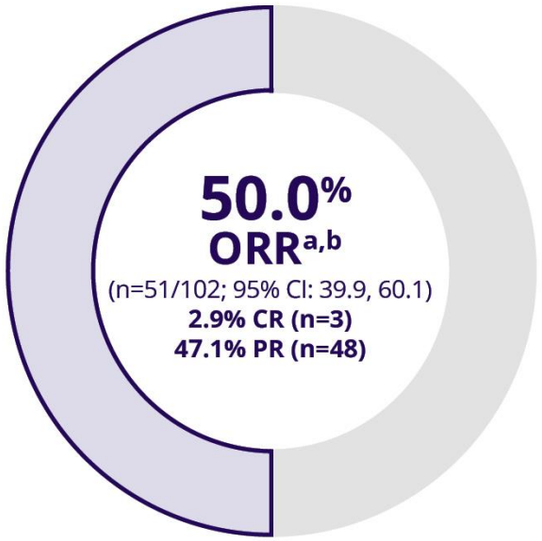
In activating *HER2*-mutant 2L mNSCLC at 5.4 mg/kg

Half of patients treated with ENHERTU achieved a durable response[1]

DESTINY-Lung02[1]



12.6 months mDOR[1,a,c]

(n=51; 95% CI: 6.4, NE)

- All responders had been followed for at least 6 months from the date of initial response or until disease progression or death, whichever came first[1]

- DESTINY-Lung02 is a Phase 2, multicenter, multicohort, randomized, blinded, dose-optimization trial of ENHERTU in adult patients with unresectable or metastatic non-squamous NSCLC who had activating *HER2 (ERBB2)* mutations and disease progression after a prior systemic therapy. Patients with a history of steroid-dependent ILD/pneumonitis, clinically significant cardiac disease, clinically active brain metastases, and ECOG performance status >1 were excluded. Patients were randomized to receive ENHERTU 5.4 mg/kg IV Q3W (n=102) or 6.4 mg/kg IV Q3W (n=50) until disease progression or unacceptable toxicity. Only the results for the recommended dose of 5.4 mg/kg are described due to increased toxicity observed with the higher dose in patients with NSCLC, including ILD/pneumonitis. The major efficacy outcomes were confirmed ORR by BICR using RECIST v1.1 and DOR. The final analysis occurred after all responders had been followed for at least 6 months from the date of initial response or until disease progression or death, whichever came first.[1,45,46]

ENHERTU was evaluated at two dose levels. While response rates were consistent across dose levels, increased rates of ILD/pneumonitis were observed at the higher dose in patients with NSCLC. The approved recommended dose of 5.4 mg/kg IV Q3W is described above[1]

This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

[a]Tumor imaging was obtained every 6 weeks.[1]
[b]Confirmed objective response was assessed by BICR based on RECIST v1.1. ORR 95% CI calculated using Clopper-Pearson method.[1]
[c]Median DOR based on Kaplan-Meier estimate; 95% CI calculated using Brookmeyer-Crowley method.[1]

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Important Safety Information (cont'd)

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, HER2-Low, and HER2-Ultralow Breast Cancer, HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (5.4 mg/kg)
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, DESTINY-Lung01, DESTINY-Lung02, DESTINY-CRC02, and DESTINY-PanTumor02. Among these patients, 67% were exposed for >6 months and 39% were exposed for >1 year. In this pooled safety population, the most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased white blood cell count (73%), nausea (72%), decreased hemoglobin (67%), decreased neutrophil count (65%), decreased lymphocyte count (60%),

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Safety data from DESTINY-Lung02 in activating *HER2*-mutant 2L mNSCLC[1]

- Only the results for the recommended dose of 5.4 mg/kg are described due to increased toxicity observed with the higher dose in patients with NSCLC, including ILD/pneumonitis
  - Median duration of treatment was 8 months (range: 0.7-28) for patients treated with ENHERTU in DESTINY-Lung02

Clinically relevant AR considerations	ENHERTU 5.4 mg/kg (n=101)	
Serious ARs	40%	• Serious ARs in >1% of patients were ILD/pneumonitis, pleural effusion, thrombocytopenia, dyspnea, nausea, pneumonia, vomiting, myocarditis, pulmonary embolism, and increased troponin I. Fatalities due to ARs occurred in 3% of patients, including ILD/pneumonitis, cerebrovascular accident, and pneumococcal sepsis (1 patient each)
Permanent discontinuations due to ARs	17%	• ARs which resulted in permanent discontinuation of ENHERTU were ILD/pneumonitis, pneumonia, blood bilirubin increased, hypokalemia, metastases to meninges, and myocarditis
Dose interruptions due to ARs	50%	• ARs which required dose interruption (>2%) included neutropenia, COVID-19, ILD/pneumonitis, fatigue, anemia, and pneumonia
Dose reductions due to ARs	20%	• The most frequent ARs (>2%) associated with dose reduction were neutropenia, fatigue, and decreased appetite
ILD/pneumonitis (All Grades)[a]	15%	• ILD occurred in 15% of patients and fatality occurred in 1 patient with adjudicated drug-induced ILD/pneumonitis (1%)

- Symptom identification is key to diagnosis; monitor patients and initiate management at first sign of ILD
- Most common (≥20%) ARs, including laboratory abnormalities, in patients receiving ENHERTU were decreased hemoglobin (68%), nausea (67%), decreased white blood cell count (66%), decreased neutrophil count (59%), decreased lymphocyte count (56%), increased aspartate aminotransferase (51%), decreased albumin (50%), decreased platelet count (49%), fatigue (48%), increased alanine aminotransferase (41%), decreased appetite (41%), constipation (38%), increased alkaline phosphatase (37%), vomiting (32%), decreased blood potassium (29%), diarrhea (24%), alopecia (22%), and musculoskeletal pain (21%)

Incidence of select common adverse reactions in DESTINY-Lung02[1]

Adverse reactions	ENHERTU 5.4 mg/kg (n=101)	
	All Grades (%)	Grades 3-4 (%)
Nausea	67	4
Fatigue[b]	48	8
Decreased appetite	41	2
Constipation	38	1
Vomiting[c]	32	3
Diarrhea	24	1
Alopecia	22	0

[a]Interstitial lung disease includes events that were adjudicated as drug-induced ILD for ENHERTU including pneumonitis, interstitial lung disease, pulmonary toxicity, and respiratory failure.
[b]Including asthenia, fatigue, and malaise.
[c]Including vomiting and retching.

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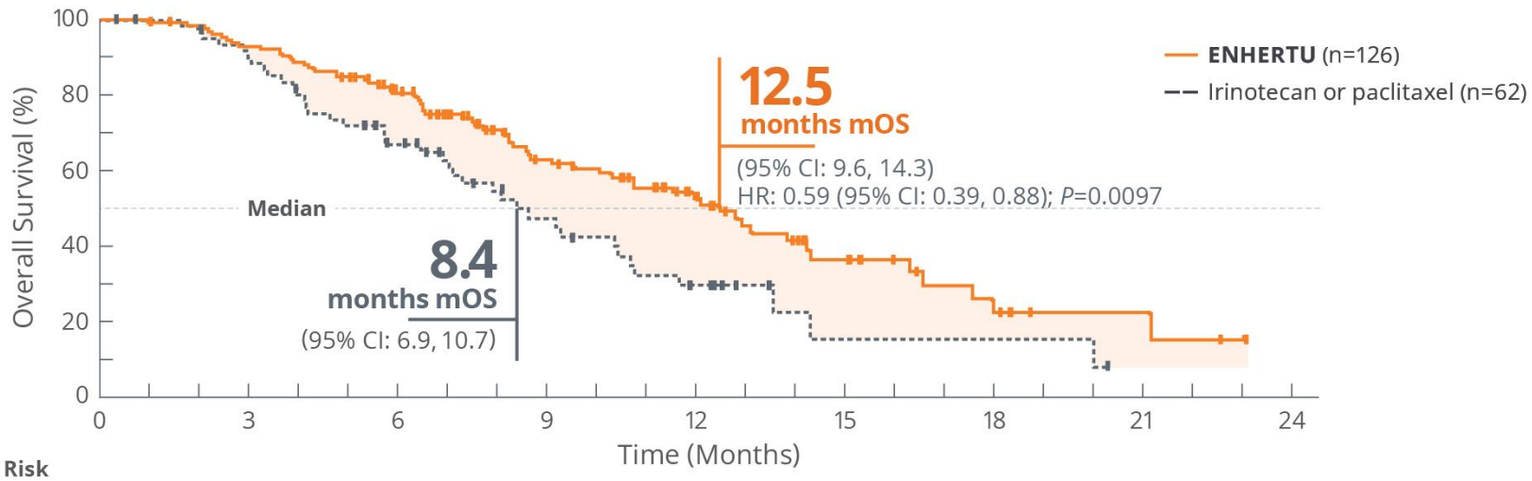
In DESTINY-Gastric01

ENHERTU is the first and only HER2-directed treatment to surpass 1 year mOS in aGC following progression on a trastuzumab-based regimen[1,47-49,a]

Superior overall survival vs irinotecan or paclitaxel[1,47,b-d]



Number at Risk

ENHERTU	126	115	88	54	33	14	7	3	0
Irinotecan or Paclitaxel	62	54	37	19	10	2	2	0	0

	ENHERTU	Irinotecan or paclitaxel
Primary endpoint **Confirmed ORR[1,e]**	**40.5%** (n=51/126; 95% CI: 31.8, 49.6; *P*<0.0001); 7.9% CR (n=10) + 32.5% PR (n=41)	**11.3%** (n=7/62; 95% CI: 4.7, 21.9); 0% CR + 11.3% PR (n=7)
Secondary endpoint **mPFS[1,f]**	**5.6 months** (95% CI: 4.3, 6.9)	**3.5 months** (95% CI: 2.0, 4.3)
	(HR=0.47; 95% CI: 0.31, 0.71)	
Secondary endpoint **mDOR[1,g,h]**	**11.3 months** (n=51/126; 95% CI: 5.6, NR)	**3.9 months** (n=7/62; 95% CI: 3.0, 4.9)

[a]**Study design:** DESTINY-Gastric01: A multicenter, open-label, randomized, Phase 2 trial in Japan/South Korea of 188 adult patients with HER2+ locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma who had progressed on ≥2 prior regimens, including trastuzumab, a fluoropyrimidine- and a platinum-containing chemotherapy regimen. Patients in the ENHERTU arm received 6.4 mg/kg IV once every 3 weeks, and those in the chemotherapy arm received either irinotecan monotherapy 150 mg/m^2 IV every 2 weeks or paclitaxel monotherapy 80 mg/m^2 IV weekly for 3 weeks. Treatment was administered until unacceptable toxicity or disease progression. The major efficacy outcomes were ORR assessed by ICR according to RECIST v1.1 and OS. Additional efficacy outcomes were PFS and DOR.[1,47]

[b]OS was evaluated following a statistically significant outcome of ORR. Interim OS analysis was conducted after all patients had tumor assessment at approximately 24 weeks or discontinued the study. At the time of analysis, 64 (51%) patients in the ENHERTU arm and 23 (37%) in the irinotecan or paclitaxel arm had their data censored, as noted by the tick marks. In the full analysis set of patients who received the study therapies (n=187), the two-sided *P* value of 0.01 crossed the O'Brien-Fleming boundary of significance (0.0202 on the basis of the number of deaths). Analysis was stratified by region. Data cutoff date November 8, 2019. Efficacy results of the final analysis from DESTINY-Gastric01 are consistent with the results of the primary analysis.[38,47,50]

[c]At the time of data cutoff, 49.2% of patients in the ENHERTU arm (n=62/126) had died vs 62.9% of patients in the irinotecan or paclitaxel arm (n=39/62).[38,47]

[d]The prespecified analysis was based on the full analysis set (n=125, all randomized patients who received at least one dose of ENHERTU); data shown are based on the intent-to-treat analysis set (n=126, all randomized patients in the ENHERTU arm).[38]

[e]Confirmed ORR was defined as a response (CR+PR according to RECIST v1.1) as confirmed on a follow-up scan ≥4 weeks after an initial response as designated by ICR.[47]

[f]PFS was not formally tested for statistical significance.[38]

[g]mDOR was measured for responding patients (PR or CR) only (ENHERTU, n=51; irinotecan, n=6; paclitaxel, n=1).[38]

[h]1.5 months (95% CI: 1.4, 1.7) TTR with ENHERTU and 1.6 months (95% CI: 1.3, 1.7) with irinotecan or paclitaxel. TTR is an exploratory endpoint.[47]

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Important Safety Information (cont'd)

Adverse Reactions (cont'd)

fatigue (55%), decreased platelet count (48%), increased aspartate aminotransferase (46%), increased alanine aminotransferase (43%), 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%),

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The benefit-risk profile of ENHERTU was established in DESTINY-Gastric01[1,47]

- Median duration of treatment was 4.6 months (range: 0.7-22.3) in ENHERTU-treated patients and 2.8 months (range: 0.5-13.1) in irinotecan/paclitaxel patients

Clinically relevant AR considerations	ENHERTU 6.4 mg/kg (n=125)	
Serious ARs	44%	• Serious adverse reactions in >2% of patients who received ENHERTU were decreased appetite, ILD, anemia, dehydration, pneumonia, cholestatic jaundice, pyrexia, and tumor hemorrhage. Fatalities due to adverse reactions occurred in 2.4% of patients, including disseminated intravascular coagulation, large intestine perforation, and pneumonia (1 patient each)
Permanent discontinuations due to ARs	15%	• ILD accounted for 6%
Dose interruptions due to ARs	62%	• Most frequent (>2%) were neutropenia, anemia, decreased appetite, leukopenia, fatigue, thrombocytopenia, ILD, pneumonia, lymphopenia, upper respiratory tract infection, diarrhea, and decreased blood potassium
Dose reductions due to ARs	32%	• Most frequent (>2%) were neutropenia, decreased appetite, fatigue, nausea, and febrile neutropenia
ILD/pneumonitis (All Grades)[a]	10%	• Majority of events were Grade 1 or 2 (n=9/12)

- Symptom identification is key to diagnosis; monitor patients and initiate management at first sign of ILD
- Most common (≥20%) ARs, including laboratory abnormalities, in patients receiving ENHERTU were decreased hemoglobin (75%), decreased white blood cell count (74%), decreased neutrophil count (72%), decreased lymphocyte count (70%), decreased platelet count (68%), nausea (63%), decreased appetite (60%), increased aspartate aminotransferase (58%), fatigue (55%), increased blood alkaline phosphatase (54%), increased alanine aminotransferase (47%), diarrhea (32%), decreased blood potassium (30%), vomiting (26%), constipation (24%), increased blood bilirubin (24%), pyrexia (24%), and alopecia (22%)

Incidence of select common adverse reactions in DESTINY-Gastric01

Adverse reactions	ENHERTU 6.4 mg/kg (n=125)		Irinotecan or paclitaxel (n=62)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Nausea	63	4.8	47	1.6
Decreased appetite	60	17	45	13
Fatigue[b]	55	9	44	4.8
Diarrhea	32	2.4	32	1.6
Vomiting	26	0	8	0
Constipation	24	0	23	0
Alopecia	22	0	15	0

[a]Includes events that were adjudicated as drug-induced ILD: pneumonitis, ILD, respiratory failure, organizing pneumonia, acute respiratory failure, lung infiltration, lymphangitis, and alveolitis.[1]
[b]Including fatigue, asthenia, and malaise.[1]

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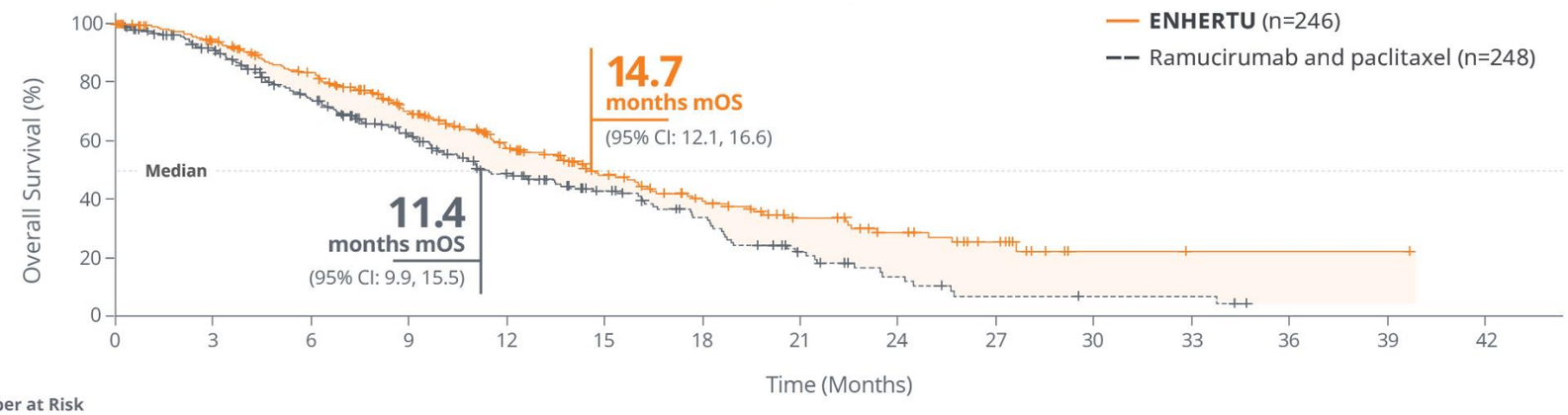
In DESTINY-Gastric04

Interim efficacy results in DESTINY-Gastric04 were consistent with DESTINY-Gastric01[1,51,a]

- Efficacy data based on a cutoff date of October 24, 2024. Median duration of follow-up was 16.8 months with ENHERTU and 14.4 months with ramucirumab and paclitaxel[51]
- These data are from a prespecified interim analysis of an ongoing clinical trial. A final analysis is planned when the trial has completed[51]

OS: primary endpoint[51,b]



Number at Risk

ENHERTU	246	219	185	134	94	65	45	30	21	12	2	1	1	1	0
Ramucirumab and paclitaxel	248	204	150	109	76	52	36	18	9	4	3	3	0		

Secondary endpoints[51]

6.7 months mPFS[c]
(n=246; 95% CI: 5.6, 7.1) vs 5.6 months (n=248; 95% CI: 4.9, 5.8) with ramucirumab and paclitaxel (HR=0.74; 95% CI: 0.59, 0.92; *P*=0.007)[d]

44.3% confirmed ORR[e]
(n=104/235; 95% CI: 37.8, 50.9) vs 29.1% (n=69/237; 95% CI: 23.4, 35.3) with ramucirumab and paclitaxel; *P*<0.001[f,g]

3% CR (n=7) vs 1.3% (n=3) with ramucirumab and paclitaxel[h]

41.3% PR (n=97) vs 27.8% (n=66) with ramucirumab and paclitaxel

7.4 months mDOR[c]
(95% CI: 5.7, 10.1) vs 5.3 months (95% CI: 4.1, 5.7) with ramucirumab and paclitaxel

These studies represent additional data to the safety and efficacy data in the PI and further support the approved 2L use of ENHERTU for eligible patients with HER2+ advanced gastric/GEJ adenocarcinoma

[a]**Study design:** DESTINY-Gastric04: A multicenter, open-label, randomized, confirmatory Phase 3 trial of 494 adult patients with HER2-positive, unresectable, locally advanced, recurrent, or metastatic gastric or gastroesophageal junction adenocarcinoma who had progressed on or after a trastuzumab-containing regimen, and had not received any additional systemic therapy in the metastatic setting. Patients had HER2-positive cancers, defined as IHC 3+ or IHC 2+/ISH+. Patients in the ENHERTU arm (n=246) received 6.4 mg/kg every 3 weeks, and those in the ramucirumab and paclitaxel arm (n=248) received 8 mg/kg of ramucirumab every 2 weeks, along with 80 mg/m^2 of paclitaxel weekly for 3 weeks. The primary endpoint was OS. Additional secondary endpoints included PFS, ORR, and DOR.[51] [b]Median OS and OS rates at specified timepoints were calculated using Kaplan-Meier analysis. CI for median was computed using the Brookmeyer-Crowley method. CIs for OS rates at specific timepoints were calculated using the Greenwood formulation.[51] [c]Median PFS was calculated using Kaplan-Meier analysis. CI for median was computed using the Brookmeyer-Crowley method. Estimates and CIs at the specified time points were calculated using Kaplan-Meier analysis.[51] [d]Two-sided *P* value was calculated using a stratified log-rank test, and stratified Cox proportional hazards model was adjusted for the HER2 status (IHC 3+ or IHC 2+/ISH+) stratification factor.[51] [e]ORR-eligible patients were those who were randomized at least 77 days (ie, 2 × 6 weeks − 1 week) before data cutoff date of interim analysis. Confirmed ORR and DCR are calculated using the eligible patients as the denominator (ENHERTU, n=235; ramucirumab and paclitaxel, n=237).[51] [f]CI calculated based on Clopper-Pearson method for single proportion.[51] [g]*P* value calculated using the Cochran-Mantel-Haenszel test adjusted for the HER2 status (IHC 3+ or IHC 2+/ISH+) stratification factor.[51] [h]Complete response patients without target lesions at baseline are included.[51]

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Important Safety Information (cont'd)

Adverse Reactions (cont'd)

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%), increased blood bilirubin (23%), and abdominal pain (22%).

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).

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In DESTINY-Gastric04

Safety results were consistent with DESTINY-Gastric01[1,51]

No Grade 4 or 5 ILD/pneumonitis was observed with ENHERTU in DESTINY-Gastric04 (n=244)[51]

	All Grades	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
% (n)	13.9 (34)	2.9 (7)	10.7 (26)	0.4 (1)	0	0

• All reported left ventricular dysfunction cases were Grade ≤3 (Grade 2, n=3/6; Grade 3, n=3/6)

The most common (≥10%) treatment-emergent adverse reactions in DESTINY-Gastric04, including lab abnormalities, were[51]:

Adverse reaction	**ENHERTU** (n=244)		**Ramucirumab and Paclitaxel** (n=233)	
	All Grades (%)	**Grade 3 or 4** (%)	**All Grades** (%)	**Grade 3 or 4** (%)
Fatigue[a]	48.0	7.0	37.8	2.6
Neutropenia[b]	48.0	28.7	48.9	35.6
Nausea	44.3	4.9	14.2	0
Anemia[c]	31.1	13.9	33.0	13.7
Decreased appetite	29.1	2.0	18.0	1.3
Leukopenia[d]	26.6	7.4	22.3	12.4
Thrombocytopenia[e]	26.6	8.6	13.7	3.0
Diarrhea	25.8	1.2	20.2	2.1
Alopecia	24.2	0	26.6	0
Aminotransferase level increased[f]	21.7	2.0	9.4	0.4
Vomiting	20.1	2.9	6.9	0.4
ILD or pneumonitis[g]	13.9	0.4	1.3	1.3
Weight decreased	11.1	1.2	3.9	0.4
Constipation	10.7	0	5.2	0
Lymphopenia[h]	10.2	2.0	5.6	1.3

• Median treatment duration was 5.4 months (range: 0.7-30.3) in patients treated with ENHERTU and 4.6 months (range: 0.9-34.9) in patients treated with ramucirumab and paclitaxel[51]

Shown are adverse events that emerged or worsened after the initiation of a trial drug until 47 days after the last dose of a trial drug. Adverse events that occurred in at least 10% of the patients with any grade of drug-related adverse event in either treatment group are listed according to preferred or grouped term. Adverse events were coded with the use of the *Medical Dictionary for Regulatory Activities*, version 27.1, and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. If a patient had more than one event according to a preferred term or grouped term, the patient was counted once at each level of summation.[51]

[a]Group term of fatigue includes fatigue, asthenia, malaise, and lethargy.[51]
[b]Group term of neutropenia includes neutrophil count decreased and neutropenia.[51]
[c]Group term of anemia includes hemoglobin decreased, red blood cell count decreased, anemia, and hematocrit decreased.[51]
[d]Group term of leukopenia includes white blood cell count decreased and leukopenia.[51]
[e]Group term of thrombocytopenia includes platelet count decreased and thrombocytopenia.[51]
[f]Group term of aminotransferase level increased includes aminotransferase levels increased, aspartate aminotransferase increased, alanine aminotransferase increased, γ-glutamyltransferase increased, liver function test abnormal, hepatic function abnormal, and liver function test increased.[51]
[g]Interstitial lung disease includes all events that were considered by the adjudication committee as being related to a trial drug.[51]
[h]The group term lymphopenia includes lymphocyte count decreased and lymphopenia.[51]

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About half of patients responded to treatment with ENHERTU, as shown below[1]

	ORR[a,b]	mDOR[a,c]
Metastatic solid tumors[1]	**51.4%** (n=57/111; 95% CI: 41.7, 61.0) **2.7% CR** (n=3) + **48.6% PR** (n=54)	**19.4 months** (n=57; range: 1.3, 27.9+)
mNSCLC[1]	**52.9%** (n=9/17; 95% CI: 27.8, 77.0) **5.9% CR** (n=1) + **47.1% PR** (n=8)	**6.9 months** (n=9; range: 4.0, 11.7+)
mCRC[1]	**46.9%** (n=30/64; 95% CI: 34.3, 59.8) **0% CR** (n=0) + **46.9% PR** (n=30)	**5.5 months** (n=30; range: 1.3+, 9.7+)

Median follow-up was 16 months for metastatic solid tumors, 11.17 months for mNSCLC, and 9.28 months for mCRC.[38]

This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Responses with ENHERTU in 3 clinical trials supported a tumor-agnostic accelerated approval[1]

ENHERTU was granted accelerated approval based on 3 trials. DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02 were multicenter clinical trials which included 192 adults with HER2+ (IHC 3+) unresectable or metastatic solid tumors that progressed after ≥1 prior treatment. Patients were treated with 5.4 mg/kg IV of ENHERTU every 3 weeks until disease progression, death, withdrawal of consent, or unacceptable toxicity. Confirmed ORR was the major efficacy outcome, DOR was an additional efficacy outcome, and both were assessed by ICR using RECIST v1.1.[1]

[a]Assessed by ICR based on RECIST v1.1.[1]
[b]CI is derived based on the Clopper-Pearson method.[1]
[c]Calculated using the Kaplan-Meier technique.[1]
+ denotes ongoing response.[1]

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Important Safety Information (cont'd)

Adverse Reactions (cont'd)

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%).

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Safety data from DESTINY-Breast01, DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02 in HER2+ (IHC 3+) metastatic solid tumors[1]

- Safety was evaluated in 347 adult patients with unresectable or metastatic HER2+ (IHC 3+) solid tumors who received ENHERTU 5.4 mg/kg in DB-01, DP-02, DL-01, and DC-02. Median duration of treatment was 8.3 months (range: 0.7-30.2)

Clinically relevant AR considerations	**ENHERTU 5.4 mg/kg** (N=347)	
Serious ARs	34%	• Serious adverse reactions in >1% of patients who received ENHERTU were sepsis, pneumonia, vomiting, urinary tract infection, abdominal pain, nausea, pneumonitis, pleural effusion, hemorrhage, COVID-19, fatigue, acute kidney injury, anemia, cellulitis, and dyspnea • Fatalities due to adverse reactions occurred in 6.3% of patients. Fatalities included ILD/pneumonitis (2.3%), cardiac arrest (0.6%), COVID-19 (0.6%), and sepsis (0.6%), and the following events occurred in one patient each (0.3%): acute kidney injury, cerebrovascular accident, general physical health deterioration, pneumonia, and hemorrhagic shock
Permanent discontinuations due to ARs	15%	• ILD/pneumonitis accounted for 10%
Dose interruptions due to ARs	48%	• Most frequent (>2%) were decreased neutrophil count, anemia, COVID-19, fatigue, decreased white blood cell count, and ILD/pneumonitis
Dose reductions due to ARs	27%	• Most frequent (>2%) were fatigue, nausea, decreased neutrophil count, ILD/pneumonitis, and diarrhea
ILD/pneumonitis (All Grades)[a]	16%	• ILD occurred in 16% of patients and fatality occurred in 2.3% of patients • 0.6% of events were Grade 3 or 4

- Symptom identification is key to diagnosis; monitor patients and initiate management at first sign of ILD
- Most common (≥20%) ARs, including laboratory abnormalities, were decreased white blood cell count (75%), nausea (69%), decreased hemoglobin (67%), decreased neutrophil count (66%), fatigue (59%), decreased lymphocyte count (58%), decreased platelet count (51%), increased aspartate aminotransferase (45%), increased alanine aminotransferase (44%), increased blood alkaline phosphatase (36%), vomiting (35%), decreased appetite (34%), alopecia (34%), diarrhea (31%), decreased blood potassium (29%), constipation (28%), decreased sodium (22%), stomatitis (20%), and upper respiratory tract infection (20%)

Incidence of select common adverse reactions in DESTINY-Breast01, DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02

Adverse reactions	**ENHERTU 5.4 mg/kg** (N=347)	
	All Grades (%)	**Grades 3-4 (%)**
Nausea	69	7
Fatigue[b]	59	10
Vomiting	35	3.5
Decreased appetite	34	2.6
Alopecia	34	0.3
Diarrhea	31	4.3
Constipation	28	0.6

[a]Interstitial lung disease includes events that were adjudicated as drug-induced ILD: pneumonitis, ILD, organizing pneumonia, respiratory failure, acute respiratory failure, alveolitis, lung opacity, lymphangitis, pneumonia, bacterial pneumonia, pulmonary fibrosis, and radiation pneumonitis. Grade 5 adjudicated drug-induced ILD events were pneumonitis, respiratory failure, acute respiratory failure, lymphangitis, pulmonary fibrosis.[1]

[b]Including fatigue, asthenia, malaise, lethargy.[1]

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ENHERTU select safety profile[1]

• A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment

ARs	Pooled studies of 5.4 mg/kg monotherapy[a]		Pooled studies of 5.4 mg/kg + pertuzumab[b]		Study of 5.4 mg/kg followed by THP[c]		Study of 6.4 mg/kg monotherapy[d]	
	Percent of patients	Median time to first onset	Percent of patients	Median time to first onset	Percent of patients	Median time to first onset	Percent of patients	Median time to first onset
ILD/pneumonitis	12% (fatal: 0.9%)	5.5 months (range: 0.9-31.5)	12% (fatal: 0.5%)	8.0 months (range: 0.6-33.8)	4.4% (fatal: 0.3%)	2.7 months (range: 1.1-6.0)	10%	2.8 months (range: 1.2-21)
Neutropenia[e]	65% (Grade 3-4: 19%)	22 days (range: 2-939)	79% (Grade 3-4: 29%)	22 days (range: 5-994)	58% (Grade 3-4: 17%)	42 days (range: 11-165)	72% (Grade 3-4: 51%)	16 days (range: 4-187)
Febrile neutropenia	1%	–	2.6%	–	0.9%	–	4.8%	–
Left ventricular dysfunction[f]	4.6% (Grade 3-4: 0.6%)	–	11% (Grade 3-4: 2.1%)	–	1.3% (Grade 3: 0.3%)	–	0 (Grade 2 asymptomatic: 8%)	–
Most common (≥20%) ARs	• Nausea (72%) • Fatigue (55%) • Vomiting (38%) • Alopecia (37%)	• Constipation (32%) • Decreased appetite (31%) • Diarrhea (30%) • Musculoskeletal pain (24%)	• Nausea (74%) • Diarrhea (64%) • 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%)	• Nausea (65%) • Diarrhea (59%) • Peripheral neuropathy (59%) • Alopecia (48%) • Fatigue (41%) • Rash (31%)	• Musculoskeletal pain (30%) • Constipation (29%) • Vomiting (29%) • Stomatitis (23%) • Decreased appetite (20%)	• Nausea (63%) • Decreased appetite (60%) • Fatigue (55%) • Diarrhea (32%) • Vomiting (26%) • Constipation (24%)	• Pyrexia (24%) • Alopecia (22%)
Most common (≥20%) laboratory abnormalities	• Decreased white blood cell count (73%) • Decreased hemoglobin (67%) • Decreased neutrophil count (65%) • Decreased lymphocyte count (60%) • Decreased platelet count (48%) • Increased aspartate aminotransferase (46%) • Increased alanine aminotransferase (43%) • Increased blood alkaline phosphatase (39%) • Decreased blood potassium (32%)		• Decreased white blood cell count (86%) • Decreased hemoglobin (80%) • Decreased neutrophil count (79%) • Increased alanine aminotransferase (65%) • Increased aspartate aminotransferase (63%) • Decreased lymphocyte count (61%) • Decreased platelet count (55%) • Increased blood alkaline phosphatase (54%) • Decreased blood potassium (54%) • Increased blood bilirubin (23%)		• Decreased hemoglobin (83%) • Increased alanine aminotransferase (79%) • Increased aspartate aminotransferase (74%) • Decreased white blood cell count (67%) • Decreased neutrophil count (58%) • Decreased lymphocyte count (40%) • Decreased blood potassium (29%)		• Decreased hemoglobin (75%) • Decreased white blood cell count (74%) • Decreased neutrophil count (72%) • Decreased lymphocyte count (70%) • Decreased platelet count (68%) • Increased aspartate aminotransferase (58%) • Increased blood alkaline phosphatase (54%) • Increased alanine aminotransferase (47%) • Decreased blood potassium (30%) • Increased blood bilirubin (24%)	

Please refer to the ENHERTU Prescribing Information for additional information on dose modifications for ARs.

[a]The pooled safety population reflects exposure to ENHERTU 5.4 mg/kg IV Q3W in 2233 patients in Study DS8201-A-J101 (NCT02564900), DB-01, DB-02, DB-03, DB-04, DB-06, DL-01, DL-02, DC-02, and DP-02.
[b]The pooled safety population reflects exposure to ENHERTU 5.4 mg/kg + pertuzumab IV Q3W in 431 patients in DB-07 and DB-09.
[c]Based on exposure to ENHERTU 5.4 mg/kg IV Q3W for 4 cycles followed by THP in 320 patients in DB-11.
[d]Based on exposure to ENHERTU 6.4 mg/kg IV Q3W in 125 patients in DG-01.
[e]Defined as a decrease in neutrophil count.
[f]Defined as LVEF decrease.

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Grade and description of select ARs observed with ENHERTU[52]

Severity	Description (NCI-CTCAE grading)
Alopecia	
Grade 1	• Grade 1: Hair loss of <50% of normal for that individual that is not obvious from a distance but only on close inspection; a different hair style may be required to cover the hair loss, but it does not require a wig or hair piece to camouflage
Grade 2	• Grade 2: Hair loss of ≥50% of normal for that individual that is readily apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss; associated with psychosocial impact
Constipation	
Grades 1 and 2	• Grade 1: Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema • Grade 2: Persistent symptoms with regular use of laxatives or enemas; limiting instrumental activities of daily living
Grades 3 and 4	• Grade 3: Obstipation with manual evacuation indicated; limiting self-care activities of daily living • Grade 4: Life-threatening consequences; urgent intervention indicated
Decreased appetite	
Grades 1 and 2	• Grade 1: Loss of appetite without alteration of eating habits • Grade 2: Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated
Grades 3 and 4	• Grade 3: Associated with significant weight loss or malnutrition (eg, inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated • Grade 4: Life-threatening consequences; urgent intervention indicated
Diarrhea	
Grades 1 and 2	• Grade 1: Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline • Grade 2: Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental activities of daily living
Grades 3 and 4	• Grade 3: Increase of ≥7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care activities of daily living • Grade 4: Life-threatening consequences; urgent intervention indicated
Fatigue	
Grades 1 and 2	• Grade 1: Fatigue relieved by rest • Grade 2: Fatigue not relieved by rest; limiting instrumental activities of daily living
Grades 3 and 4	• Grade 3: Fatigue not relieved by rest; limiting self-care activities of daily living • Grade 4: Not applicable
Nausea	
Grades 1 and 2	• Grade 1: Loss of appetite without alteration in eating habits • Grade 2: Oral intake decreased without significant weight loss, dehydration, or malnutrition
Grades 3 and 4	• Grade 3: Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated • Grade 4: Not applicable
Vomiting	
Grades 1 and 2	• Grade 1: Intervention not indicated • Grade 2: Outpatient IV hydration; medical intervention indicated
Grades 3 and 4	• Grade 3: Tube feeding, TPN, or hospitalization indicated • Grade 4: Life-threatening consequences

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

Nausea and Vomiting

Fam-trastuzumab deruxtecan-nxki (ENHERTU®) is classified as highly emetogenic, which includes delayed nausea and/or vomiting[1,53]

- This may be prevented and/or managed with prophylactic antiemetic protocols for high emetic risk agents
- Administer prophylactic antiemetic medications per local institutional guidelines for prevention of chemotherapy-induced nausea and vomiting

	Incidence of nausea (All Grades)[1]	Incidence of vomiting (All Grades)[1]
Pooled studies of 5.4 mg/kg monotherapy[a]	72%	38%
Pooled studies of 5.4 mg/kg in combination with pertuzumab[b]	74%	46%
Study of 5.4 mg/kg followed by THP[c]	65%	29%
Study of 6.4 mg/kg[d]	63%	26%

Prevention and Management

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Antiemesis[53]

- 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
- This includes an NCCN Category 1, preferred 4-drug regimen
  - Refer to next page for this regimen, and additional 3-drug regimens, for high emetic risk agents

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

Escalate
If emesis occurred during a previous cycle with a 3-drug regimen, consider escalating to a 4-drug regimen (if not used previously)

Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of ENHERTU. See page 37 for the ENHERTU dose reduction schedule.[1]

Set appropriate expectations and implement prophylactic interventions for nausea/vomiting for all patients to help manage patients' experience while on therapy

[a]The pooled safety population reflects exposure to ENHERTU 5.4 mg/kg IV Q3W in 2233 patients in Study DS8201-A-J101 (NCT02564900), DB-01, DB-02, DB-03, DB-04, DB-06, DL-01, DL-02, DC-02, and DP-02.[1] [b]The pooled safety population reflects exposure to ENHERTU 5.4 mg/kg + pertuzumab IV Q3W in 431 patients in DB-07 and DB-09.[1] [c]Based on exposure to ENHERTU 5.4 mg/kg IV Q3W for 4 cycles followed by THP in 320 patients in DB-11.[1] [d]Based on exposure to ENHERTU 6.4 mg/kg IV Q3W in 125 patients in DG-01.[1]

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The NCCN Guidelines® for Antiemesis recommends 3-4–drug prophylactic antiemetic regimens for high emetic risk agents to prevent both acute and delayed emesis during every cycle[53,a,b]

- Consider option A, B, or C
- All treatments are Category 1 and should be started **before** anticancer therapy[c]

	Day 1	Day 2	Day 3	Day 4
Option A Preferred	Olanzapine[d] NK1 RA 5-HT3 RA[e,f] Dexamethasone[g,h]	Olanzapine[d] Oral aprepitant (if oral aprepitant used on Day 1) ±Dexamethasone[g,h]	Olanzapine[d] Oral aprepitant (if oral aprepitant used on Day 1) ±Dexamethasone[g,h]	Olanzapine[d] ±Dexamethasone[g,h]
Option B[i]	Olanzapine[d] Palonosetron Dexamethasone[g,h]	Olanzapine[d]	Olanzapine[d]	Olanzapine[d]
Option C[i]	NK1 RA 5-HT3 RA[e,f] Dexamethasone[g,h]	Oral aprepitant (if oral aprepitant used on Day 1) Dexamethasone[g,h]	Oral aprepitant (if oral aprepitant used on Day 1) Dexamethasone[g,h]	Dexamethasone[g,h]

The high emetic risk protocol includes management for **4 total days**

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[a]For details regarding recommendations and specific dosing information, please refer to the NCCN Guidelines for Antiemesis. [b]Antiemetic regimens should be chosen based on the drug with the highest emetic risk as well as patient-specific risk factors. [c]Category 1 recommendations indicate uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate based on high-level evidence (≥1 randomized Phase 3 trials or high-quality, robust meta-analyses). [d]Once daily or bedtime on Day 1; bedtime on Days 2-4. Data suggest that a 2.5-mg dose of olanzapine may be efficacious, especially when used as part of a 4-drug regimen. Olanzapine doses of 2.5-5 mg may be less effective than 10 mg when used as part of a 3-drug regimen. Consider lower doses, especially for patients who are older or who are at high risk for oversedation. [e]If netupitant/palonosetron or fosnetupitant/palonosetron fixed combination product is used, no further 5-HT3 RA is required. [f]When used in combination with an NK1 RA, there is no preferred 5-HT3 RA. [g]Emerging data and clinical practice suggest dexamethasone doses may be individualized. Higher doses may be considered, especially when an NK1 RA is not given concomitantly. For patients receiving moderately or highly emetogenic chemotherapy, especially those patients with few identifiable chemotherapy-induced nausea and vomiting (CINV) risk factors or who are intolerant to corticosteroids, the use of lower doses, given for shorter durations, limiting the administration to day 1 or even elimination of dexamethasone on day 1 and/or subsequent days (for delayed nausea and emesis prevention) may be acceptable and may not compromise nausea or antiemesis control. If dexamethasone is eliminated on day 1 or subsequent days, consider the use of an antiemetic combination containing a 5-HT3 RA, NK1 RA, and olanzapine on day 1, and olanzapine for delayed CINV. [h]Use of corticosteroid premedications should be avoided with cellular therapies. Clinicians may wish to consider a dexamethasone-sparing approach with immune checkpoint inhibitor therapy as well. [i]If not used previously, consider escalating to a 4-drug regimen (option A) if emesis occurred during a previous cycle of anticancer therapy with a 3-drug regimen (olanzapine-containing regimen B or NK1 RA-containing regimen C). Olanzapine-containing regimens may be useful for patients with severe nausea.

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Fatigue

Approximately 1 out of every 2 patients receiving ENHERTU experienced fatigue across clinical trials[1]

- Fatigue was one of the most frequent ARs associated with dose interruption or reduction

	Incidence of Fatigue (All Grades)[1]
Pooled studies of 5.4 mg/kg monotherapy[a]	**55%**
Pooled studies of 5.4 mg/kg in combination with pertuzumab[b]	**53%**
Study of 5.4 mg/kg followed by THP[c]	**41%**
Study of 6.4 mg/kg[d]	**55%[e]**

Management

The NCCN Guidelines for Cancer-Related Fatigue recommendations[54]

- **Screen** regularly for fatigue, using tools such as the Numeric Rating Scale
- **Evaluate** for all possible causes (eg, current disease status and medications) and assess treatable contributing factors
- **Intervene** with management strategies (eg, exercise, psychosocial interventions, nutrition consultation, and bright white light therapy)
- **Re-evaluate** as needed

Additional Strategies

Set expectations around fatigue

- Tailor conversations around fatigue to each individual patient/situation
- Reiterate that fatigue is not linear—it may be more intense in the days post-treatment and lessen as the cycle wears on[55]
- Fatigue may be disease-, treatment-, or non-treatment–related[55]

Identify causes of fatigue that may be treatable, such as anemia, nutritional deficits, insomnia, and comorbidities[56,57]

- Addressing nausea and vomiting may also help address fatigue
- Dehydration-related vomiting can result in fatigue

ASCO Guidelines for cancer-related fatigue includes management strategies for fatigue, such as[58]

- Exercise (eg, movement)
- Cognitive behavioral therapy
- Mindfulness-based stress reduction

Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of ENHERTU. See page 37 for the ENHERTU dose reduction schedule.[1]

- The ENHERTU dose reduction schedule includes 2 dose reductions (efficacy observed in clinical trials was inclusive of patients who reduced doses)[1]
- Fatigue may be a symptom of left ventricular dysfunction. See page 34 for more information[1]

[a]The pooled safety population reflects exposure to ENHERTU 5.4 mg/kg IV Q3W in 2233 patients in Study DS8201-A-J101 (NCT02564900), DB-01, DB-02, DB-03, DB-04, DB-06, DL-01, DL-02, DC-02, and DP-02.[1] [b]The pooled safety population reflects exposure to ENHERTU 5.4 mg/kg + pertuzumab IV Q3W in 431 patients in DB-07 and DB-09.[1] [c]Based on exposure to ENHERTU 5.4 mg/kg IV Q3W for 4 cycles followed by THP in 320 patients in DB-11.[1] [d]Based on exposure to ENHERTU 6.4 mg/kg IV Q3W in 125 patients in DG-01.[1] [e]Including fatigue, asthenia, and malaise.[1]

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20 mg/mL INJECTION FOR INTRAVENOUS USE

Alopecia

Patients may experience alopecia while receiving ENHERTU; the clinical grade may vary

	Incidence of Alopecia (All Grades)[1]
Pooled studies of 5.4 mg/kg monotherapy[a]	37%
Pooled studies of 5.4 mg/kg in combination with pertuzumab[b]	48%
Study of 5.4 mg/kg followed by THP[c]	48%
Study of 6.4 mg/kg[d]	22%

Strategies

Set expectations

- Recognize that alopecia may be a greater concern for some patients more than others[59]
- Accurately characterize the alopecia experienced in clinical trials

A variety of strategies have been employed by certain patients for cancer treatment–induced alopecia[60]

- Preventive measures
- Concealment strategies (ie, wigs)
- Mental health support

Evaluate the benefit-risk profile of ENHERTU in the context of alopecia and patients' overall treatment goals[1]

[a]The pooled safety population reflects exposure to ENHERTU 5.4 mg/kg IV Q3W in 2233 patients in Study DS8201-A-J101 (NCT02564900), DB-01, DB-02, DB-03, DB-04, DB-06, DL-01, DL-02, DC-02, and DP-02.[1] [b]The pooled safety population reflects exposure to ENHERTU 5.4 mg/kg + pertuzumab IV Q3W in 431 patients in DB-07 and DB-09.[1] [c]Based on exposure to ENHERTU 5.4 mg/kg IV Q3W for 4 cycles followed by THP in 320 patients in DB-11.[1] [d]Based on exposure to ENHERTU 6.4 mg/kg IV Q3W in 125 patients in DG-01.[1]

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Interstitial Lung Disease (ILD) and pneumonitis

ILD/pneumonitis can occur with ENHERTU. Early identification is key to appropriately managing ILD.[1]

	Incidence of ILD/pneumonitis[1]	Median time to first onset[1]
Pooled metastatic studies of 5.4 mg/kg monotherapy[a]	**12%** (Fatal: 0.9%)	**5.5 months** (range: 0.9-31.5)
Pooled studies of 5.4 mg/kg in combination with pertuzumab[b]	**12%** (Fatal: 0.5%)	**8.0 months** (range: 0.6-33.8)
Study of 6.4 mg/kg[c]	**10%**	**2.8 months** (range: 1.2-21)

Management

Implement a protocol like the 5 "S" strategies[d] to help identify and manage ILD/pneumonitis in patients receiving ENHERTU

- **Screen:** Careful patient selection based on baseline risk and screening that continues during treatment are warranted (baseline pulse oximetry [SpO_2], PFT, and high-resolution CT)[61,62]
- **Scan:** Radiological scans—including high-resolution CT at least every 12 weeks—remain the fundamental diagnostic tool for ILD[61,62]
- **Synergy:** Work together with the patient, multidisciplinary care team, and staff[61]

If ILD/pneumonitis is suspected:

- **Suspend:** Promptly investigate evidence and interrupt ENHERTU treatment as soon as ILD is suspected, regardless of which grade is confirmed[1,61]
- **Steroids:** Corticosteroids can be initiated as soon as ILD is suspected, before a pulmonologist consultation[61,62]

See additional information about the 5 "S" strategies on the next page, including dosage modifications from the full Prescribing Information if ILD/pneumonitis is suspected.

Key Strategies

Proactive education is key to ensuring patients monitor for and report symptoms[1]:

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

Maintain vigilance with routine scanning to identify ILD early[1,62]

- Grade 1 ILD is asymptomatic—high-resolution CT scanning at regular intervals is critical to identifying Grade 1 ILD

ENHERTU can be restarted if ILD is identified as asymptomatic (Grade 1) and resolved to Grade 0 within[1,61]:

- ≤28 days from date of onset, restart at the same dose
- >28 days from date of onset, restart at reduced dose

Protocols may vary by institution, depending on what resources or infrastructure are available. The 5 "S" strategies above should be considered if feasible

[a]The pooled safety population reflects exposure to ENHERTU 5.4 mg/kg IV Q3W in 2233 patients in Study DS8201-A-J101 (NCT02564900), DB-01, DB-02, DB-03, DB-04, DB-06, DL-01, DL-02, DC-02, and DP-02.[1] [b]The pooled safety population reflects exposure to ENHERTU 5.4 mg/kg + pertuzumab IV Q3W in 431 patients in DB-07 and DB-09.[1] [c]Based on exposure to ENHERTU 6.4 mg/kg IV Q3W in 125 patients in DG-01.[1] [d]The 5 "S" strategies are adapted from a review article by Tarantino and Tolaney (*JCO Oncol Pract* 2023) based on the publication by Rugo et al. (*JCO Oncol Pract* 2023).

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Early identification of ILD/pneumonitis is key to appropriate management[1,61-63]

Follow the five "S" strategies to help detect and manage ILD/pneumonitis in patients receiving ENHERTU

KEY: ENHERTU Prescribing Information recommendation

1 SCREEN

Careful patient selection based on baseline risk and screening that continues during treatment are warranted[61]

Before initiating ENHERTU[62,63]

- Complete history and physical
- Consider baseline pulse oximetry (SpO_2), PFT, and high-resolution CT scans (see **Scan** below), if clinically indicated
- Educate patient and engage multidisciplinary team (see **Synergy** below)

Throughout treatment[1,62,63]

- Advise patients to immediately report signs and symptoms that may indicate ILD/pneumonitis
  - Cough
  - Fever
  - Dyspnea
  - New or worsening respiratory symptoms
- Continue to monitor vitals (SpO_2 and PFT, if clinically indicated)
- Investigate potential evidence:
  - Infectious disease evaluation
  - Bronchoscopy, BAL, and/or ABGs, if clinically indicated and feasible

2 SCAN

Radiological scans remain the fundamental diagnostic tool for ILD[61]

- Promptly investigate evidence of ILD. Evaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist[1]

CT scans[62]

- Consider CT scans of the chest for baseline prior to treatment, including high-resolution CT scans, if feasible
- Repeat at least every 12 weeks (or every 6-9 weeks if baseline respiratory symptoms are present), if feasible
- Consult your institution's guidelines for best practices

3 SYNERGY

Work together with the patient, multidisciplinary care team, and staff[61]

Patient[1]

- Inform patients of the risks of severe or fatal ILD
- Advise patients to contact their HCP immediately for any of the following: cough, shortness of breath, fever, or other new or worsening respiratory symptoms

Multidisciplinary team[62]

- Consider consulting pulmonologist/radiologist, including for patients with significant lung comorbidities
- Comprehensive education of staff, nurses, patient navigators, and advanced practice providers/clinicians is an important part of ILD monitoring and management

HCP staff[62]

- Help facilitate open communication with the patient
- Help assess signs/symptoms

If ILD/pneumonitis is suspected when[62,a]:

- Radiographic changes potentially consistent with ILD/pneumonitis are seen
- Patient experiences acute onset of new or worsening pulmonary signs/symptoms, such as dyspnea, cough, or fever

4 SUSPEND TREATMENT

Promptly investigate evidence and **interrupt ENHERTU treatment as soon as ILD is suspected, regardless of which grade is confirmed[1,61]**

Asymptomatic (Grade 1) ILD/pneumonitis[1]	Symptomatic (Grade ≥2) ILD/pneumonitis[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 1 dose level (see dose reductions at right)	**Permanently discontinue ENHERTU**

5 STEROIDS

Corticosteroids can be initiated as soon as ILD is suspected, before a pulmonologist consultation[61,62]

• Consider corticosteroid treatment (eg, ≥0.5 mg/kg/day prednisolone or equivalent) as soon as ILD/pneumonitis is suspected	• Promptly initiate systemic corticosteroid treatment (eg, ≥1 mg/kg/day prednisolone or equivalent) as soon as ILD/pneumonitis is suspected • Continue for ≥14 days followed by a gradual taper for ≥4 weeks

Dose Reduction Schedule[1]

	Breast cancer, NSCLC, and IHC 3+ solid tumors	Gastric cancer
Recommended starting dose	5.4 mg/kg	6.4 mg/kg
First dose reduction	4.4 mg/kg	5.4 mg/kg
Second dose reduction	3.2 mg/kg	4.4 mg/kg
Requirement for further dose reduction	Discontinue	Discontinue

Do not re-escalate the ENHERTU dose after a dose reduction is made

- **ILD can be severe, life-threatening, or fatal. Follow all ILD/pneumonitis events:** Regardless of severity or seriousness, all ILD/pneumonitis events should be followed until resolution, including after drug discontinuation[1,62,63]
- **Monitor patients with moderate renal impairment more frequently:** A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in these patients[1]
- **In patients with unresectable or mNSCLC:** The approved recommended dose of ENHERTU is 5 mg/kg Q3W due to increased toxicity, including ILD/pneumonitis, observed with a higher dose[1]
- Higher systemic exposure to fam-trastuzumab deruxtecan-nxki was associated with a higher incidence rate of any grade ILD[1]

[a]Evaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist.[1]

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

	Incidence of drug-related ILD/pneumonitis	Median time to first onset
Neoadjuvant study of 5.4 mg/kg followed by THP[a]	**4.4%[1]** (Fatal: 0.3%)	**2.7 months[1]** (range:1.1-6.0)
Post-neoadjuvant study of 5.4 mg/kg monotherapy	**9.6%[34,b]**	**123.5 days[64,c]** (range: 36-350)

Signs and symptoms of ILD/pneumonitis[1,38]

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

Promptly investigate evidence of ILD/pneumonitis[33,63]

- 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 benefits and risks of treatment and to contact their HCP immediately to report any of these symptoms

KEY: ENHERTU Prescribing Information recommendation

Patients and HCPs should be aware of ILD risk; regular monitoring and quickly identifying and reporting symptoms are needed for appropriate management[38,63,65]

- Frequency of CT scans was determined by the individual study protocols
  - In DESTINY-Breast11 (neoadjuvant), patients received high-resolution CT at screening, then additional scans every 6 weeks during neoadjuvant treatment and at 40-day follow-up
  - In DESTINY-Breast05 (post-neoadjuvant), patients received low-dose, non-contrast chest CT at screening. All patients who received adjuvant radiotherapy received low-dose chest CT at 6 weeks after the start of treatment, then every 12 weeks while on treatment, and again at a 40-day follow-up. Patients who received sequential radiotherapy had an additional low-dose chest CT after completing radiotherapy, prior to initiating treatment

Conduct routine 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[1,38]

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[d] 1 level
- Consider corticosteroid treatment (eg, ≥0.5 mg/kg/day prednisolone or equivalent)

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

In the post-neoadjuvant breast cancer setting, rule out radiotherapy-related pneumonitis. If only radiation pneumonitis is suspected, follow dose modifications for radiation pneumonitis on the following page.

[a]Based on exposure to ENHERTU 5.4 mg/kg IV Q3W for 4 cycles followed by THP in 320 patients in DB-11.[1] [b]Based on exposure to ENHERTU 5.4 mg/kg IV Q3W in 806 patients in DB-05.[1] [c]Includes all patients who received sequential or concurrent adjuvant radiotherapy and ≥1 dose of study treatment in DESTINY-Breast05. Time to first adjudicated ILD onset = onset date of first ILD adjudicated as drug related – first dose date + 1.[64] [d]Refer to dose reduction schedule in the dosing section.

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Radiation pneumonitis was observed in both arms of DESTINY-Breast05 since most[a] patients received sequential or concurrent radiotherapy[1,65,66]

- **Radiation pneumonitis is an AE associated with radiation therapy[67]**
- Symptoms of radiation pneumonitis (eg, low-grade fever, congestion, dry cough, pleuritic chest pain, sensation of chest fullness) usually develop 1-3 months following completion of radiation therapy[65]
- Identification of radiation pneumonitis should be based on the timing and location of radiographic abnormalities relative to the radiation treatment[65]
- Among patients receiving sequential or concurrent adjuvant radiotherapy in DESTINY-Breast05, radiation pneumonitis occurred in[1]:
  - 31% of patients receiving ENHERTU (N=757; all cases Grade 1 [27%] or Grade 2 [4.9%])
  - 31% of patients receiving T-DM1 (N=750; all cases Grade 1 [24%] or Grade 2 [7%])
- A higher incidence of radiation pneumonitis was reported for patients who received sequential vs concurrent adjuvant radiotherapy[1]:
  - ENHERTU arm: 34% sequential; 29% concurrent
  - T-DM1 arm: 37% sequential; 27% concurrent
- For patients treated with ENHERTU, median time to onset of first event of radiation pneumonitis was 4.1 months (range: 1.3–11.6)[1]

Dose modifications for radiotherapy-related pneumonitis in the post-neoadjuvant early breast cancer setting[65]

Severity	Grade 1: (asymptomatic)	Grade 2: (symptomatic)	Grade 3-4:
Treatment modification	1 **Continue** Treatment with ENHERTU	1 **Consider interruption of** ENHERTU 2 Recover to baseline or Grade ≤1 3 Manage per local institutional guidelines	2 **Permanently discontinue** ENHERTU

Toxicity grades are in accordance with NCI-CTCAE v.5.0.

[a]In DESTINY-Breast05, 93.4% of patients in the ENHERTU arm (n=764) and 92.9% of patients in the T-DM1 arm (n=759) received adjuvant radiotherapy.[34]

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Left ventricular dysfunction[1]

Severity

Treatment modification

LVEF >45%	LVEF 40%-45%		LVEF <40% or absolute decrease from baseline >20%
AND absolute decrease from baseline 10-20%	AND absolute decrease from baseline <10%	AND absolute decrease from baseline 10-20%	
1	1	1	1
Continue	**Continue**	**Interrupt**	**Interrupt**
Treatment with ENHERTU	Treatment with ENHERTU	ENHERTU	ENHERTU
	2	2	2
	Repeat LVEF assessment within 3 weeks	Repeat LVEF assessment within 3 weeks	Repeat LVEF assessment within 3 weeks
		3	3
		If LVEF recovers to within 10% from baseline,	If LVEF <40% or absolute decrease from baseline >20% is confirmed,
		Resume treatment with ENHERTU at the same dose	**Permanently discontinue ENHERTU**
		If LVEF has not recovered to within 10% from baseline,	
		Permanently discontinue ENHERTU	

Permanently discontinue ENHERTU in patients with symptomatic CHF

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Neutropenia[1,52]

- Monitor complete blood counts, based on the algorithm below, prior to initiation of ENHERTU and prior to each dose, and as clinically indicated
- Based on the severity of neutropenia, ENHERTU may require dose interruption or reduction

Severity	Grade ≤2: ANC ≥1.0 x 10^9/L	Grade 3: ANC <1.0 to 0.5 x 10^9/L	Grade 4: ANC <0.5 x 10^9/L	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
Treatment modification	1 **Continue** Treatment with ENHERTU	1 **Interrupt** ENHERTU	1 **Interrupt** ENHERTU	1 **Interrupt** ENHERTU
		2 Resolve to Grade ≤2 (ANC ≥1.0 x 10^9/L)	2 Resolve to Grade ≤2 (ANC ≥1.0 x 10^9/L)	2 Resolve
		3 **Resume ENHERTU treatment at the same dose**	3 **Reduce ENHERTU dose by one level and resume treatment** **See Dose Reduction Table on page 37**	3 **Reduce ENHERTU dose by one level and resume treatment** **See Dose Reduction Table on page 37**

Thrombocytopenia[1,52]

- Thrombocytopenia can occur in patients treated with ENHERTU
- **Based on the severity of thrombocytopenia, manage through treatment interruption or dose reduction using the algorithm below**

Severity	Grade ≤2: Platelets LLN to 50 x 10^9/L	Grade 3: Platelets <50 to 25 x 10^9/L	Grade 4: Platelets <25 x 10^9/L
Treatment modification	1 **Continue** Treatment with ENHERTU	1 **Interrupt** ENHERTU	1 **Interrupt** ENHERTU
		2 Resolve to Grade 1 or less (platelets ≥75 x 10^9/L)	2 Resolve to Grade 1 or less (platelets ≥75 x 10^9/L)
		3 **Resume ENHERTU treatment at the same dose**	3 **Reduce ENHERTU dose by one level and resume treatment** **See Dose Reduction Table on page 37**

Toxicity grades are in accordance with NCI-CTCAE v.5.0.

Please see Important Safety Information throughout as well as on pages 41-46, and click here for full Prescribing Information, including Boxed WARNINGS, and click here for Medication Guide.

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

Administration and management of ENHERTU[1]

INITIATE PROPHYLAXIS: ENHERTU is highly emetogenic, which can cause delayed nausea and/or vomiting. Administer prophylactic antiemetic medications per local institutional guidelines for prevention of chemotherapy-induced nausea and vomiting[1]

- Please see page 27 for more information on the management of nausea and/or vomiting

ADMINISTER: ENHERTU is administered as an IV infusion once every 3 weeks (21-day cycle)[1]

Recommended weight-based dosage and schedule

HER2+ eBC (neoadjuvant treatment)

ENHERTU 5.4 mg/kg over 90 minutes → IF WELL TOLERATED → **ENHERTU 5.4 mg/kg** over 30 minutes → FOLLOWED BY → **THP**
- Taxane
- Trastuzumab (6 mg/kg Q3W)
- Pertuzumab (840-mg loading dose followed by 420 mg Q3W)

CYCLE 1 | CYCLES 2-4 | CYCLES 5-8

4 CYCLES OF ENHERTU | 4 CYCLES OF THP

HER2+ eBC (post-neoadjuvant treatment)

ENHERTU 5.4 mg/kg over 90 minutes → IF WELL TOLERATED → **ENHERTU 5.4 mg/kg** over 30 minutes

CYCLE 1 | CYCLES 2-14

14 CYCLES OF ENHERTU

1L HER2+ mBC

ENHERTU 5.4 mg/kg over 90 minutes → Wait ~30 minutes → **Pertuzumab 840 mg** → IF WELL TOLERATED → **ENHERTU 5.4 mg/kg** over 30 minutes → Wait ~30 minutes → **Pertuzumab 420 mg** → **Continue until disease progression or unacceptable toxicity**

CYCLE 1 | SUBSEQUENT CYCLES

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

Administration and management of ENHERTU[1] (cont'd)

- 2L HER2+ mBC
- HER2-low or HER2-ultralow mBC
- *HER2*-mutant mNSCLC[a]
- HER2+ (IHC 3+) metastatic solid tumors

ENHERTU 5.4 mg/kg over 90 minutes → IF WELL TOLERATED → **ENHERTU 5.4 mg/kg** over 30 minutes → **Continue until disease progression or unacceptable toxicity**

INITIAL INFUSION — SUBSEQUENT INFUSIONS

[a]In patients with unresectable or metastatic *HER2*-mutant NSCLC, the approved recommended dose of ENHERTU is 5.4 mg/kg IV Q3W due to increased toxicity, including ILD/pneumonitis, observed with a higher dose.

HER2+ aGC

ENHERTU 6.4 mg/kg over 90 minutes → IF WELL TOLERATED → **ENHERTU 6.4 mg/kg** over 30 minutes → **Continue until disease progression or unacceptable toxicity**

INITIAL INFUSION — SUBSEQUENT INFUSIONS

MANAGE: Treatment with ENHERTU may require dose modifications to manage ARs[1]

- Refer to the guidance in the ENHERTU Prescribing Information for temporary interruption, dose reduction, or treatment discontinuation to manage potential ARs. Refer to the Prescribing Information for pertuzumab for dose modification recommendations. Pertuzumab is not to be administered as a single agent
- **Do not re-escalate the ENHERTU dose after a dose reduction is made**
- If a planned dose is delayed or missed, administer as soon as possible; do not wait until the next planned cycle. Adjust the schedule of administration to maintain a 3-week interval between doses. Administer the infusion at the dose and rate the patient tolerated in the most recent infusion

Dose reduction schedule[1]	Breast cancer, NSCLC, and IHC 3+ solid tumors	Gastric cancer
Recommended starting dose	5.4 mg/kg	6.4 mg/kg
First dose reduction	4.4 mg/kg	5.4 mg/kg
Second dose reduction	3.2 mg/kg	4.4 mg/kg
Requirement for further dose reduction	Discontinue treatment	

Patient selection considerations[1]

- **For HER2+ eBC:** Select patients based on HER2+ (IHC 3+ or ISH+) status
- **For HER2+ mBC:** Select patients for treatment with ENHERTU + pertuzumab based on confirmed HER2+ status or *HER2* gene amplification (IHC 3+ or ISH+)
- **For HER2-low or HER2-ultralow mBC:** Select patients for the treatment of unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH–) or HER2-ultralow (IHC 0 with membrane staining) breast cancer based on HER2 expression
- **For *HER2*-mutant mNSCLC:** Select patients based on the presence of activating *HER2 (ERBB2)* mutations in tumor or plasma specimens. If no mutation is detected in a plasma specimen, test tumor tissue
- **For HER2+ aGC:** Select patients based on HER2 protein overexpression or *HER2* gene amplification (IHC 3+ or IHC 2+/ISH+). Reassess HER2 status if it is feasible to obtain a new tumor specimen after prior trastuzumab-based therapy and before treatment with ENHERTU
- **For HER2+ (IHC 3+) unresectable or metastatic solid tumors:** Select patients based on HER2+ (IHC 3+) tumor specimens. An FDA-authorized test for the detection of HER2+ (IHC 3+) solid tumors for treatment with ENHERTU is not currently available
- Information on FDA-authorized tests for the detection of HER2 protein expression, *HER2* gene amplification, and activating *HER2* mutations is available at: http://www.fda.gov/CompanionDiagnostics

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ENHERTU preparation for administration

In order to prevent medication errors, check the vial labels to ensure that the drug being prepared and administered is ENHERTU **and not trastuzumab or ado-trastuzumab emtansine.**[1]

Reconstitute and further dilute ENHERTU prior to intravenous infusion. Use appropriate aseptic technique.[1]

ENHERTU is a hazardous drug. Follow applicable special handling and disposal procedures.[1]

Reconstitution[1]

- Reconstitute immediately before dilution
- More than one vial may be needed for a full dose. Calculate the dose (mg), the total volume of reconstituted ENHERTU solution required, and the number of vial(s) of ENHERTU needed
- Reconstitute each 100 mg vial by using a sterile syringe to slowly inject 5 mL of Sterile Water for Injection, USP into each vial to obtain a final concentration of 20 mg/mL
- Swirl the vial gently until completely dissolved. **Do not shake**
- If not used immediately, store the reconstituted ENHERTU vials in a refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours from the time of reconstitution, protect the vial from light. **Do not freeze**
- The product does not contain a preservative. Discard unused reconstituted ENHERTU after 24 hours refrigerated

Dilution[1]

- Withdraw the calculated amount from the vial(s) using a sterile syringe. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. The solution should be clear and colorless to light yellow. Do not use if visible particles are observed or if the solution is cloudy or discolored
- Dilute the calculated volume of reconstituted ENHERTU in an intravenous infusion bag containing **100 mL of 5% Dextrose Injection, USP**. DO NOT use Sodium Chloride Injection, USP. ENHERTU is compatible with an infusion bag made of polyvinylchloride or polyolefin (copolymer of ethylene and polypropylene)
- Gently invert the infusion bag to thoroughly mix the solution. **Do not shake**
- Cover the infusion bag to protect from light
- Discard any unused portion left in the vials

Administration[1,38]

- D5W is recommended for priming and flushing the administration line
- If not used immediately, store the diluted ENHERTU in a refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours or at room temperature between 20°C to 25°C (68°F to 77°F) for up to 4 hours including preparation and infusion time
- Protect from light. **Do not freeze**
- The maximum time from reconstitution of the vial through the end of administration should not exceed 24 hours
- If the prepared infusion solution was stored refrigerated (2°C to 8°C [36°F to 46°F]), allow the solution to reach room temperature prior to administration. Cover the infusion bag to protect from light
- Administer ENHERTU as an intravenous infusion only with an infusion set made of polyolefin or polybutadiene
- Administer ENHERTU with a 0.20 or 0.22 micron in-line polyethersulfone (PES) or polysulfone (PS) filter
- Do NOT administer as an intravenous push or bolus
- Cover the infusion bag to protect from light during administration
- Do not mix ENHERTU with other drugs or administer other drugs through the same intravenous line
- First infusion: Administer infusion over 90 minutes
- Subsequent infusions: Administer over 30 minutes if prior infusions were well tolerated

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ENHERTU4U provides support resources for patients prescribed ENHERTU

ENHERTU® 4U
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Comprehensive Access Support

- ENHERTU4U can help with benefit verification, prior authorization assistance, and pharmacy research and coordination
- If there is a delay in a patient's coverage decision, ENHERTU4U may be able to provide the first dose at no cost

Patient Savings Program

- Eligible commercial patients may pay as little as $0 per infusion in out-of-pocket costs for ENHERTU
- The annual benefit may also cover up to $100 in infusion costs per administration[a]
- There are no income requirements to participate in the program

Patient Assistance Programs

- Designed to help uninsured or underinsured patients who meet the financial requirements

To receive support for your patients and obtain more information about reimbursement, visit ENHERTU4U.com or call 1-833-ENHERTU (1-833-364-3788)

ENHERTU4U provides patients and their providers access and reimbursement support for ENHERTU.
ENHERTU4U is administered and sponsored by Daiichi Sankyo, Inc. only. Reimbursement and access are not guaranteed.

[a]Patients who are residents of Massachusetts or Rhode Island are not eligible for infusion assistance. Additional eligibility rules apply.

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ENHERTU patient savings program

Eligibility

The patient may be eligible for this offer if he or she is insured by commercial insurance and his or her insurance does not cover the full cost of his or her prescription.

Patients who are enrolled in a state or federally funded prescription insurance program are not eligible for this offer. This includes patients enrolled in Medicare Part B, Medicare Part D, Medicaid, Medigap, Veterans Affairs (VA), Department of Defense (DoD) programs or TriCare, and patients who are Medicare eligible and enrolled in an employer-sponsored group waiver health plan or government-subsidized prescription drug benefit program for retirees.

If the patient is enrolled in a state or federally funded prescription insurance program, he or she may not use this program even if he or she elects to be processed as an uninsured (cash paying) patient. This offer is not insurance and is restricted to residents of the United States and Puerto Rico.

Terms of use

Eligible patients with a valid prescription of ENHERTU may pay as little as $0 per infusion and $0 in out-of-pocket costs for ENHERTU. The out-of-pocket costs covered by the program can include the cost of the product itself and/or the cost of infusion of the product (program maximum of $100 per infusion assistance).[a,b] Other restrictions may apply. Patient is responsible for applicable taxes, if any. Patient must be enrolled in the program before use. If you have any questions regarding this offer, please call 833-364-3788 (833-ENHERTU).

Non-transferable, limited to one per person, cannot be combined with any other offer. Void where prohibited by law, taxed or restricted. Patients, pharmacists, and prescribers cannot seek reimbursement from health insurance or any third party for any part of the benefit received by the patient through this offer. Daiichi-Sankyo and AstraZeneca reserve the right to rescind, revoke, or amend this offer, eligibility and terms of use at any time without notice. This offer is not conditioned on any past, present or future purchase, including refills. Offer must be presented along with a valid prescription for ENHERTU at the time of purchase. Patients must have commercial health insurance that covers medication costs for ENHERTU, but not the full cost to the patient.

Program covers the cost of the drug and administration, and does not cover costs for office visits or any other associated costs.

Offer is invalid for claims or transactions more than 180 days from the date on the explanation of benefits.

BY USING THIS PROGRAM, YOU AND YOUR PHARMACIST AND/OR PHYSICIAN UNDERSTAND AND AGREE TO COMPLY WITH THESE ELIGIBILITY REQUIREMENTS AND TERMS OF USE.

ENHERTU4U provides patients and their providers access and reimbursement support for ENHERTU. ENHERTU4U is administered and sponsored by Daiichi Sankyo, Inc. only. Reimbursement and access are not guaranteed.

[a]Patients who are residents of Massachusetts or Rhode Island are not eligible for infusion assistance. Additional eligibility rules apply. [b]Patients are responsible for any cost associated with the infusion above the $100 per infusion assistance provided by the program.

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Important Safety Information

Indications

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
- 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-authorized 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
- HER2-Low and HER2-Ultralow Metastatic Breast Cancer
  - As monotherapy 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-authorized test, that has progressed on one or more endocrine therapies in the metastatic setting
  - As monotherapy for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-authorized test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy
- HER2-Mutant Unresectable or Metastatic Non-Small Cell Lung Cancer (NSCLC)
  - As monotherapy for the treatment of adult patients with unresectable or metastatic NSCLC whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-authorized test, and who have received a prior systemic therapy

    This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
- HER2-Positive Locally Advanced or Metastatic Gastric Cancer
  - As monotherapy for the treatment of adult patients with locally advanced or metastatic HER2-positive (IHC 3+ or IHC 2+/ISH positive) gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen
- HER2-Positive (IHC 3+) Unresectable or Metastatic Solid Tumors
  - As monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options

    This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

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.

HER2-Positive, HER2-Low, and HER2-Ultralow Breast Cancer, HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (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.

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.

HER2-Positive Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)

In patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, ILD occurred in 10% of patients. Median time to first onset was 2.8 months (range: 1.2 to 21).

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Important Safety Information (cont'd)

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.

HER2-Positive, HER2-Low, and HER2-Ultralow Breast Cancer, HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (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% 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.

ENHERTU followed by THP

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.

HER2-Positive Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)

In patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, a decrease in neutrophil count was reported in 72% of patients. Fifty-one percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 16 days (range: 4 to 187). Febrile neutropenia was reported in 4.8% of patients.

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, HER2-Low, and HER2-Ultralow Breast Cancer, HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (5.4 mg/kg)

ENHERTU as Monotherapy

In patients treated with ENHERTU 5.4 mg/kg, LVD 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.

ENHERTU followed by THP

In patients treated with ENHERTU 5.4 mg/kg followed by THP in DESTINY-Breast11, LVD was reported in 1.3% of patients, of which 0.3% were Grade 3.

HER2-Positive Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)

In patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, no clinical adverse events of heart failure were reported; however, on echocardiography, 8% were found to have asymptomatic Grade 2 decrease in LVEF.

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, HER2-Low, and HER2-Ultralow Breast Cancer, HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (5.4 mg/kg)

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, DESTINY-Lung01, DESTINY-Lung02, DESTINY-CRC02, and DESTINY-PanTumor02. Among these patients, 67% were exposed for >6 months and 39% were exposed for >1 year. In this pooled safety population, the most common (≥20%) adverse reactions, including laboratory abnormalities, were 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 (43%), 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.

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Important Safety Information (cont'd)

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%), increased blood bilirubin (23%), and abdominal pain (22%).

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%).

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.

HER2-Positive Metastatic Breast Cancer

DESTINY-Breast09

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 (1 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%). 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

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(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 DESTINY-Breast03. 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%).

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.

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%).

HER2-Mutant Unresectable or Metastatic NSCLC (5.4 mg/kg)
DESTINY-Lung02 evaluated 2 dose levels (5.4 mg/kg [n=101] and 6.4 mg/kg [n=50]); however, only the results for the recommended dose of 5.4 mg/kg intravenously every 3 weeks are described below due to increased toxicity observed with the higher dose in patients with NSCLC, including ILD/pneumonitis.

The safety of ENHERTU was evaluated in 101 patients with HER2-mutant unresectable or metastatic NSCLC who received ENHERTU 5.4 mg/kg intravenously once every 3 weeks until disease progression or unacceptable toxicity in DESTINY-Lung02. The median duration of treatment was 8 months (range: 0.7 to 28) for patients who received ENHERTU.

Serious adverse reactions occurred in 40% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were ILD/pneumonitis, pleural effusion, thrombocytopenia, dyspnea, nausea, pneumonia, vomiting, myocarditis, pulmonary embolism, and increased troponin I. Fatalities due to adverse reactions occurred in 3% of patients including ILD/pneumonitis, cerebrovascular accident, and pneumococcal sepsis (1 patient each).

ENHERTU was permanently discontinued in 17% of patients. Adverse reactions which resulted in permanent discontinuation of ENHERTU were ILD/pneumonitis, pneumonia, blood bilirubin increased, hypokalemia, metastases to meninges, and myocarditis. Dose interruptions of ENHERTU due to adverse reactions occurred in 50% of patients. Adverse reactions which

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required dose interruption (>2%) included neutropenia, COVID-19, ILD/pneumonitis, fatigue, anemia, and pneumonia. Dose reductions due to an adverse reaction occurred in 20% of patients. The most frequent adverse reactions (>2%) associated with dose reduction were neutropenia, fatigue, and decreased appetite.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased hemoglobin (68%), nausea (67%), decreased white blood cell count (66%), decreased neutrophil count (59%), decreased lymphocyte count (56%), increased aspartate aminotransferase (51%), decreased albumin (50%), decreased platelet count (49%), fatigue (48%), increased alanine aminotransferase (41%), decreased appetite (41%), constipation (38%), increased alkaline phosphatase (37%), vomiting (32%), decreased blood potassium (29%), diarrhea (24%), alopecia (22%), and musculoskeletal pain (21%).

HER2-Positive Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)

The safety of ENHERTU was evaluated in 187 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma in DESTINY-Gastric01. Patients intravenously received at least 1 dose of either ENHERTU (N=125) 6.4 mg/kg every 3 weeks or either irinotecan (N=55) 150 mg/m^2 biweekly or paclitaxel (N=7) 80 mg/m^2 weekly for 3 weeks. The median duration of treatment was 4.6 months (range: 0.7 to 22.3) for patients who received ENHERTU.

Serious adverse reactions occurred in 44% of patients receiving ENHERTU 6.4 mg/kg. Serious adverse reactions in >2% of patients who received ENHERTU were decreased appetite, ILD, anemia, dehydration, pneumonia, cholestatic jaundice, pyrexia, and tumor hemorrhage. Fatalities due to adverse reactions occurred in 2.4% of patients: disseminated intravascular coagulation, large intestine perforation, and pneumonia occurred in 1 patient each (0.8%).

ENHERTU was permanently discontinued in 15% of patients, of which ILD accounted for 6%. Dose interruptions due to adverse reactions occurred in 62% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, anemia, decreased appetite, leukopenia, fatigue, thrombocytopenia, ILD, pneumonia, lymphopenia, upper respiratory tract infection, diarrhea, and decreased blood potassium. Dose reductions occurred in 32% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were neutropenia, decreased appetite, fatigue, nausea, and febrile neutropenia.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased hemoglobin (75%), decreased white blood cell count (74%), decreased neutrophil count (72%), decreased lymphocyte count (70%), decreased platelet count (68%), nausea (63%), decreased appetite (60%), increased aspartate aminotransferase (58%), fatigue (55%), increased blood alkaline phosphatase (54%), increased alanine aminotransferase (47%), diarrhea (32%), decreased blood potassium (30%), vomiting (26%), constipation (24%), increased blood bilirubin (24%), pyrexia (24%), and alopecia (22%).

HER2-Positive (IHC 3+) Unresectable or Metastatic Solid Tumors

The safety of ENHERTU was evaluated in 347 adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who received ENHERTU 5.4 mg/kg intravenously once every 3 weeks in DESTINY-Breast01, DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02. The median duration of treatment was 8.3 months (range 0.7 to 30.2).

Serious adverse reactions occurred in 34% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were sepsis, pneumonia, vomiting, urinary tract infection, abdominal pain, nausea, pneumonitis, pleural effusion, hemorrhage, COVID-19, fatigue, acute kidney injury, anemia, cellulitis, and dyspnea. Fatalities due to adverse reactions occurred in 6.3% of patients including ILD/pneumonitis (2.3%), cardiac arrest (0.6%), COVID-19 (0.6%), and sepsis (0.6%). The following events occurred in 1 patient each (0.3%): acute kidney injury, cerebrovascular accident, general physical health deterioration, pneumonia, and hemorrhagic shock.

ENHERTU was permanently discontinued in 15% of patients, of which ILD/pneumonitis accounted for 10%. Dose interruptions due to adverse reactions occurred in 48% of patients. The most frequent adverse reactions (>2%) associated with dose interruption were decreased neutrophil count, anemia, COVID-19, fatigue, decreased white blood cell count, and ILD/pneumonitis. Dose reductions occurred in 27% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, nausea, decreased neutrophil count, ILD/pneumonitis, and diarrhea.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased white blood cell count (75%), nausea (69%), decreased hemoglobin (67%), decreased neutrophil count (66%), fatigue (59%), decreased lymphocyte count (58%), decreased platelet count (51%), increased aspartate aminotransferase (45%), increased alanine aminotransferase (44%), increased blood alkaline phosphatase (36%), vomiting (35%), decreased appetite (34%), alopecia (34%), diarrhea (31%), decreased blood potassium (29%), constipation (28%), decreased sodium (22%), stomatitis (20%), and upper respiratory tract infection (20%).

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 2233 patients treated with ENHERTU 5.4 mg/kg, 28% were ≥65 years and 6% were ≥75 years. No overall differences in efficacy within clinical studies were observed between patients ≥65 years compared to younger patients. There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged ≥65 years (56%) as compared to younger patients (49%). Of the 125 patients with HER2-positive locally advanced or metastatic gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg in DESTINY-Gastric01, 56% were ≥65 years and 14% were ≥75 years. No overall differences in efficacy or safety were observed between patients ≥65 years of age compared to younger patients. *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

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observed between patients ≥65 years compared to younger patients. *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%).

- **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.

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Abbreviations

1L, first line
2L, second line
5-HT3, 5-hydroxytryptamine 3
ABG, arterial blood gas
ADC, antibody-drug conjugate
AE, adverse event
aGC, advanced gastric cancer
ANC, absolute neutrophil count
AR, adverse reaction
ASCO, American Society of Clinical Oncology
BAL, bronchoalveolar lavage
BC, breast cancer
BICR, blinded independent central review
BMFI, brain metastases–free interval
CBR, clinical benefit rate
CDK4/6, cyclin-dependent kinases 4 and 6
CHF, congestive heart failure
CI, confidence interval
CR, complete response
CT, computed tomography
D5W, dextrose 5% in water
DAR, drug-to-antibody ratio
DCR, disease control rate
ddAC, dose-dense doxorubicin and cyclophosphamide
DFS, disease-free survival
DOR, duration of response
DRFI, distant recurrence–free interval
eBC, early breast cancer
ECOG, Eastern Cooperative Oncology Group
EFS, event-free survival
***ERBB2*,** erb-b2 receptor tyrosine kinase 2
ET, endocrine therapy
GEJ, gastroesophageal junction
HCP, healthcare professional
HER2, human epidermal growth factor receptor 2
HR, hazard ratio
HR–, hormone receptor-negative
HR+, hormone receptor-positive
ICR, independent central review
iDFS, invasive disease–free survival
IHC, immunohistochemistry
ILD, interstitial lung disease
ISH, in situ hybridization
IV, intravenous
LLN, lower limit of normal
LVEF, left ventricular ejection fraction
mAb, monoclonal antibody
mBC, metastatic breast cancer
mCRC, metastatic colorectal cancer
mDOR, median duration of response
mNSCLC, metastatic non-small cell lung cancer
mOS, median overall survival
mPFS, median progression-free survival
NCCN, National Comprehensive Cancer Network® (NCCN®)
NCI-CTCAE, National Cancer Institute–Common Terminology Criteria for Adverse Events
NE, not evaluable
NK1, neurokinin-1
NR, not reached
NSCLC, non-small cell lung cancer
ORR, objective response rate
OS, overall survival
pCR, pathological complete response
PFS, progression-free survival
PFT, pulmonary function test
PR, partial response
Q3W, every 3 weeks
RA, receptor antagonist
RECIST, Response Evaluation Criteria in Solid Tumors
SD, stable disease
SpO_2, saturation of peripheral oxygen
T-DM1, ado-trastuzumab emtansine
THP, taxane (docetaxel or paclitaxel), trastuzumab, and pertuzumab
TPN, total parenteral nutrition
TTR, time to response

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