YOUR CLINICAL GUIDE FOR ENHERTU

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

A comprehensive resource with clinical data, including:

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

2L HER2+ mBC (IHC 3+ or ISH+)[1]

HER2-low and HER2-ultralow mBC[1]
- 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[1]

2L HER2+ aGC (IHC 3+ or IHC 2+/ISH+)[1]

HER2+ (IHC 3+) **metastatic solid tumors**[1]

Important Safety Information

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY
- **Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue ENHERTU in all patients with Grade 2 or higher ILD/pneumonitis. Advise patients of the risk and to immediately report symptoms.**
- **Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception.**

Indications

ENHERTU is a HER2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of adult patients with:
- Unresectable or metastatic HER2-positive (IHC 3+ or ISH positive) 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
- Unresectable or metastatic:
  - Hormone receptor (HR)-positive, HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining) breast cancer, as determined by an FDA-approved test, that has progressed on one or more endocrine therapies in the metastatic setting
  - HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy
- Unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved 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.
- 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
- 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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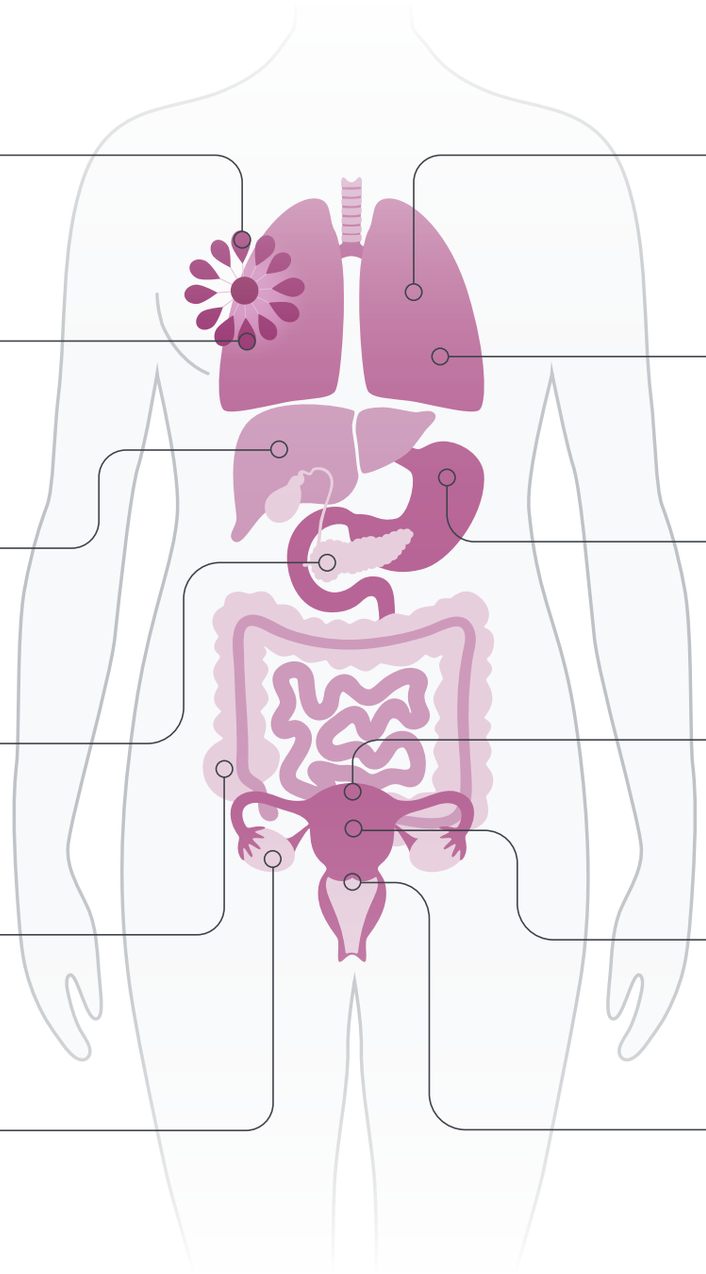
HER2 expression/alteration is found across many tumor types[2-29,a]



- ~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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BACKGROUND | HER2-EXPRESSING mBC | *HER2*-MUTANT 2L mNSCLC | 2L HER2+ aGC | HER2+ (IHC 3+) SOLID TUMORS | SAFETY | AR MANAGEMENT | DOSING & ADMIN | ACCESS & SUPPORT | ISI | PI | REF

2

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Patients with *HER2 (ERBB2)*-mutant mNSCLC are a distinct subgroup with a considerable unmet need

There are important differences between *HER2* mutations and other HER2 alterations in NSCLC[3,30]

***HER2* mutations occur in the *HER2 (ERBB2)* gene and are synonymous with *ERBB2* mutations[31]**

Other HER2 alterations:

- *HER2* amplifications are distinct from *HER2* mutations in that they result in abnormally high *HER2 (ERBB2)* gene copies[3]
- HER2 overexpression is characterized by an overabundance of HER2 receptors on the surface of cancer cells[3]

HER2 mutations have been observed in 2-4% of patients with NSCLC[3]

***HER2* mutations occur at a similar frequency to many other actionable biomarkers in NSCLC[32]**

Other actionable biomarkers[32]:

ALK fusion ≈3.8%

MET splice (*MET* exon 14) ≈3%

ROS1 fusion ≈2.6%

BRAF V600E ≈2.1%

Patients with *HER2*-mutant mNSCLC need additional treatment options[33]

Patients with *HER2*-mutant mNSCLC often have tumors that respond poorly to non-targeted treatment options[34-38]

- *HER2* mutations may be a driver of aggressive disease in mNSCLC[33]

Activating *HER2* mutations are an actionable biomarker in mNSCLC[1]

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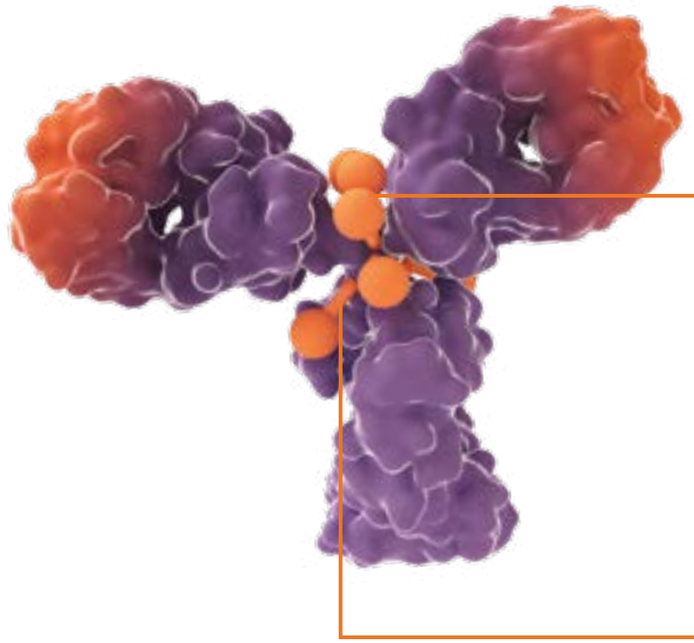
ENHERTU is a specifically engineered HER2-directed antibody-drug conjugate (ADC)[1,39]

HER2-directed mAb[1]

- Provides targeted delivery of cytotoxic agent[1,39]
- Consists of the same amino acid sequence as trastuzumab[40]



Topoisomerase I inhibitor payload[1,39,a]

- Highly potent payload is an exatecan derivative, known as DXd, with a short systemic half-life[1,40]
- 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[1,40,41]

Tumor-selective cleavable linker[1,39,40,a]

- Attaches payload to the antibody[1]
- Linker-payload is stable in plasma[39,40]
- Linker selectively cleaved by enzymes that are upregulated in tumor cells[1,40]

ENHERTU has a homogeneous and high drug-to-antibody ratio of ~8 molecules of cytotoxic agent per antibody[1,39,40,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.[40]

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

Indication		Study	Design	Population
Breast	2L HER2+ mBC (IHC 3+ or ISH+)	DESTINY-Breast03	Multicenter, open-label, randomized, head-to-head trial vs T-DM1	524 adult patients with HER2+ unresectable and/or mBC who received prior trastuzumab and taxane therapy for metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy
	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
Lung[a]	*HER2 (ERBB2)*-mutant mNSCLC	DESTINY-Lung02	Multicenter, multicohort, randomized, blinded, dose-optimization trial	101 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+)	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+ GC/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

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).

[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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In DESTINY-Breast03, a **head-to-head study** vs T-DM1,

ENHERTU demonstrated superior PFS vs T-DM1[1,a]

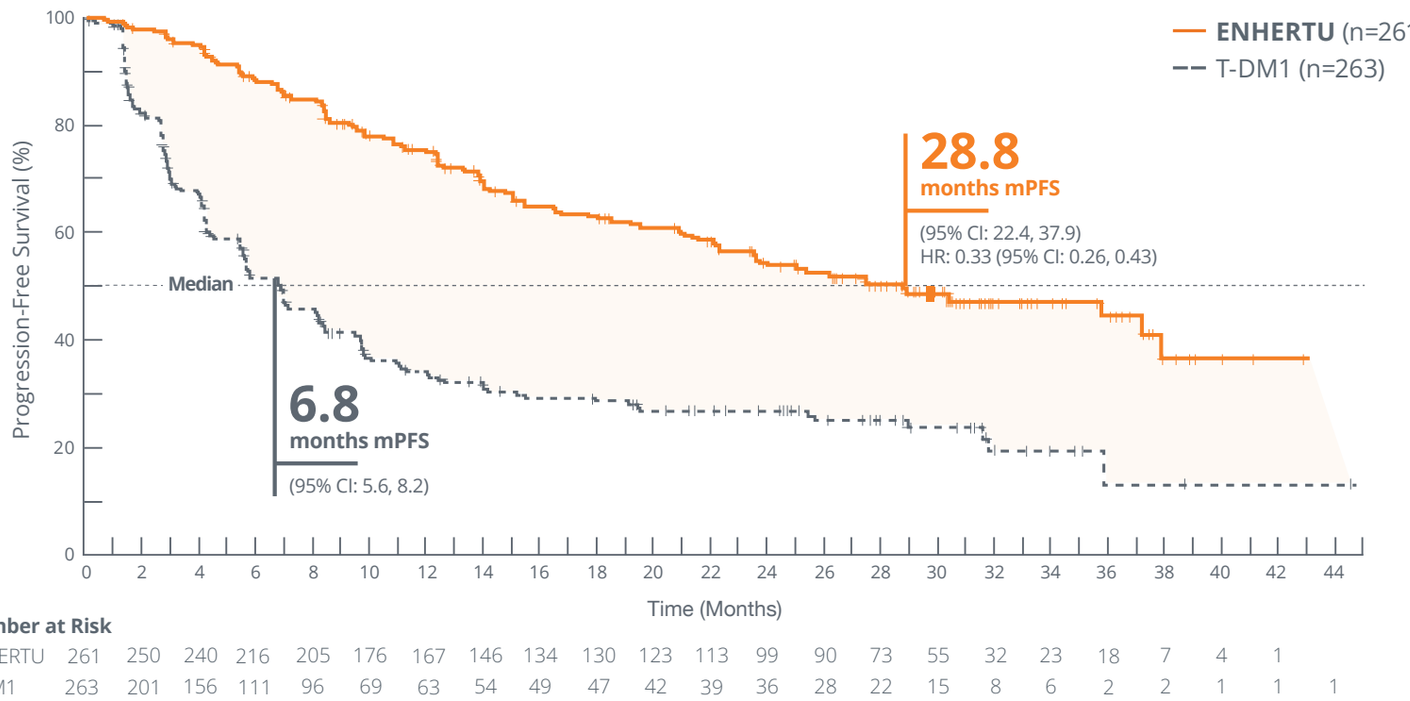
PRIMARY ENDPOINT
MAY 2021

HAZARD RATIO: 0.28 (95% CI: 0.22, 0.37); *P*<0.0001; **NR mPFS with ENHERTU** (95% CI: 18.5 months, NE) **vs 6.8 months with T-DM1** (95% CI: 5.6, 8.2)[1,42,b,c]

EXPLORATORY ANALYSIS
JULY 2022

- These data are from an exploratory PFS analysis conducted in July 2022, which was based on an open-label study and was not tested for statistical significance or powered to show a difference between treatment arms. Therefore, the clinical significance of these data is not known. Statistical significance of PFS was determined at the May 2021 analysis[1,42,43]

Progression-free survival[43,d]



Number at Risk

ENHERTU	261	250	240	216	205	176	167	146	134	130	123	113	99	90	73	55	32	23	18	7	4	1
T-DM1	263	201	156	111	96	69	63	54	49	47	42	39	36	28	22	15	8	6	2	2	1	1

[a]**Study design:** DESTINY-Breast03 is a Phase 3, multicenter, open-label, randomized, head-to-head study to compare efficacy and safety of ENHERTU vs T-DM1 of 524 adults with HER2+ unresectable and/or mBC who received prior trastuzumab and taxane therapy for metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy. ENHERTU patients received 5.4 mg/kg IV Q3W until unacceptable toxicity or disease progression. Primary endpoint was PFS (BICR) according to RECIST v1.1. Secondary endpoints included OS and ORR.[1,42]
[b]Median duration of follow-up for PFS (BICR) at the May 2021 analysis: 16.2 months (range: 0-32.7) for ENHERTU and 15.3 months (range: 0-31.3) for T-DM1.[42]
[c]The stratified log-rank test *P* value is compared with the allocated alpha of 0.0002 for this interim analysis (with 73% of the planned number of events for final analysis).[1]
[d]Median duration of follow-up for PFS (BICR) at the July 2022 analysis: 28.4 months (IQR: 22.1-32.9) for ENHERTU and 26.5 months (IQR: 14.5-31.3) for T-DM1.[43]

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

Interstitial Lung Disease / Pneumonitis (cont'd)

For symptomatic ILD/pneumonitis (Grade 2 or greater), permanently discontinue ENHERTU. Promptly initiate systemic corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥1 mg/kg/day prednisolone or equivalent) and continue for at least 14 days followed by gradual taper for at least 4 weeks.

HER2-Positive, HER2-Low, and HER2-Ultralow Metastatic Breast Cancer, HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (5.4 mg/kg)
In patients with metastatic breast cancer, HER2-mutant NSCLC, and other solid tumors treated with ENHERTU 5.4 mg/kg, ILD occurred in 12% of patients. Median time to first onset was 5.5 months (range: 0.9 to 31.5). Fatal outcomes due to ILD and/or pneumonitis occurred in 0.9% of patients treated with ENHERTU.

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In DESTINY-Breast03, a **head-to-head study** vs T-DM1,

ENHERTU demonstrated superior OS vs T-DM1[1]

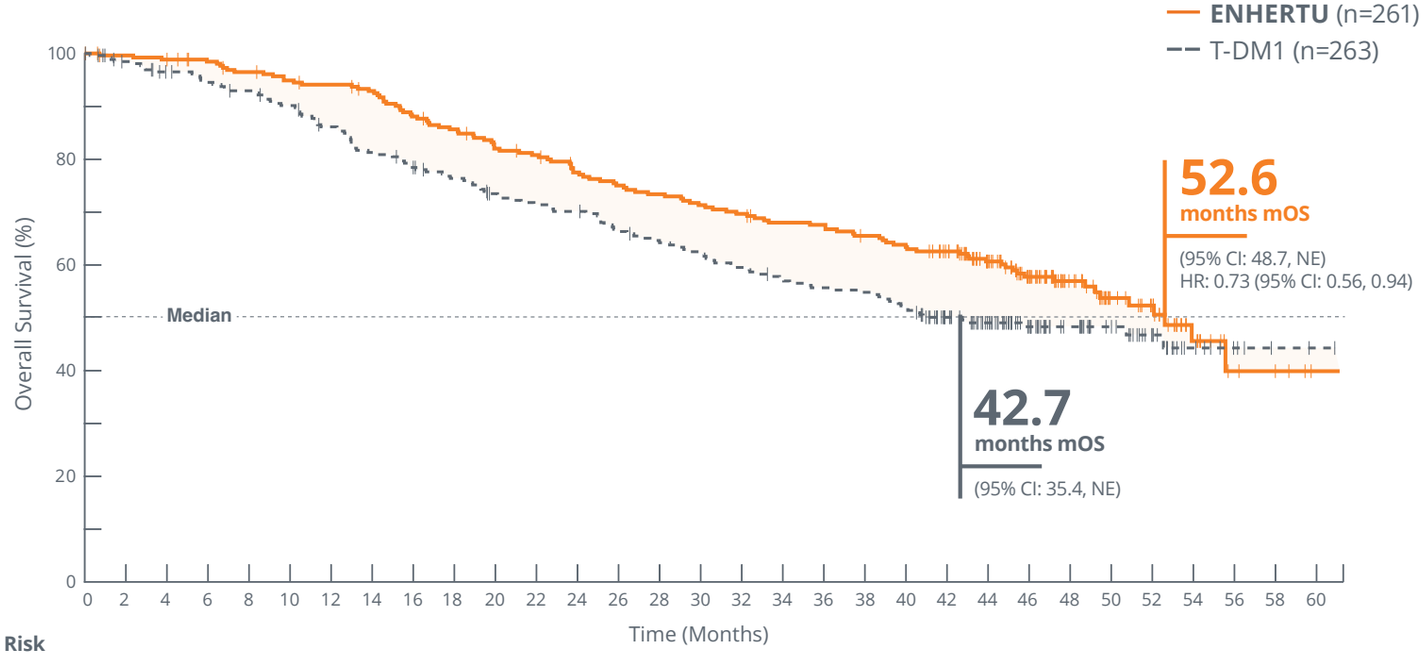
KEY SECONDARY ENDPOINT
JULY 2022

HAZARD RATIO: 0.64 (95% CI: 0.47, 0.87); *P*=0.0037; **NR mOS with ENHERTU** (95% CI: 40.5 months, NE) **vs NR with T-DM1** (95% CI: 34.0 months, NE)[1,43,a]

EXPLORATORY ANALYSIS
NOVEMBER 2023

- These data are from an exploratory OS analysis conducted in November 2023, which was based on an open-label study and was not tested for statistical significance or powered to show a difference between treatment arms. Therefore, the clinical significance of these data is not known. Statistical significance of OS was determined at the July 2022 analysis[1,43,44]

Overall survival[44,b]



Number at Risk

ENHERTU	255	244	236	219	202	188	178	169	162	151	115	60	32	6	1
T-DM1	244	233	213	193	175	167	151	140	130	121	85	45	21	5	1

[a]The stratified log-rank test *P* value is compared with the allocated alpha of 0.013 for this interim analysis (with 68% of the planned number of events for final analysis).[1]
[b]Median duration of follow-up at the November 2023 analysis: 43 months (range: 0-62.9) for ENHERTU and 35.4 months (range: 0-60.9) for T-DM1.[44]

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

Interstitial Lung Disease / Pneumonitis (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, ILD occurred in 10% of patients. Median time to first onset was 2.8 months (range: 1.2 to 21).

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.

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The benefit-risk profile of ENHERTU was established in DESTINY-Breast03

May 2021 analysis in DESTINY-Breast03 (n=257)[1,42]

- Median duration of treatment: 14 months (range: 0.7-30) with ENHERTU; 7 months (range: 0.7-25) with T-DM1

	May 2021 analysis of ENHERTU 5.4 mg/kg (n=257)[1,42]		NOVEMBER 2023 ANALYSIS[44]
Serious ARs	19%	• Serious ARs in >1% of patients were vomiting, ILD, pneumonia, pyrexia, and urinary tract infection. Fatalities occurred in 2 patients (1 due to COVID-19 and 1 due to sudden death)	27.6%
Permanent discontinuations due to ARs	14%	• Most frequent (>2%) was ILD/pneumonitis (8%)	24.5%
Dose interruptions due to ARs	44%	• Most frequent (>2%) were neutropenia, leukopenia, anemia, thrombocytopenia, pneumonia, nausea, fatigue, and ILD/pneumonitis	56.8%
Dose reductions due to ARs	21%	• Most frequent (>2%) were nausea, neutropenia, and fatigue	28.4%
ILD/pneumonitis (All Grades)[a]	10.5%	• Majority of events were Grade 1 or 2 (n=25/27) • No Grade 4 or 5 adjudicated drug-induced ILD/pneumonitis events were observed[b]	16.7%

- 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 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%), respiratory infection (22%), headache (22%), abdominal pain (21%), increased blood bilirubin (20%), and stomatitis (20%)[1]

Incidence of select common adverse reactions in DESTINY-Breast03 (May 2021)[1,42]

Adverse reactions	ENHERTU 5.4 mg/kg (n=257)		T-DM1 3.6 mg/kg (n=261)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Nausea	76	7	30	0.4
Fatigue[c]	49	6	35	0.8
Vomiting	49	1.6	10	0.8
Alopecia[d]	37	0.4	3.1	0
Constipation	34	0	20	0
Decreased appetite	29	1.6	17	0.4
Diarrhea	29	1.2	7	0.4

November 2023 analysis: No new safety signals were observed for ENHERTU[44]

- The median duration of treatment increased to 18.2 months for ENHERTU (range: 0.7 to 56.6) and remained 6.9 months for T-DM1 (range: 0.7 to 55.2)

[a]Includes events that were adjudicated as drug-induced ILD: pneumonitis, ILD, organizing pneumonia, pneumonia, and pulmonary mass.[1]
[b]Grade 5=fatal cases.[45]
[c]Including fatigue, asthenia, malaise, and lethargy.[1]
[d]This Grade 3 event was reported by the investigator. Per NCI-CTCAE v.5.0, the highest NCI-CTCAE grade for alopecia is Grade 2.[1]

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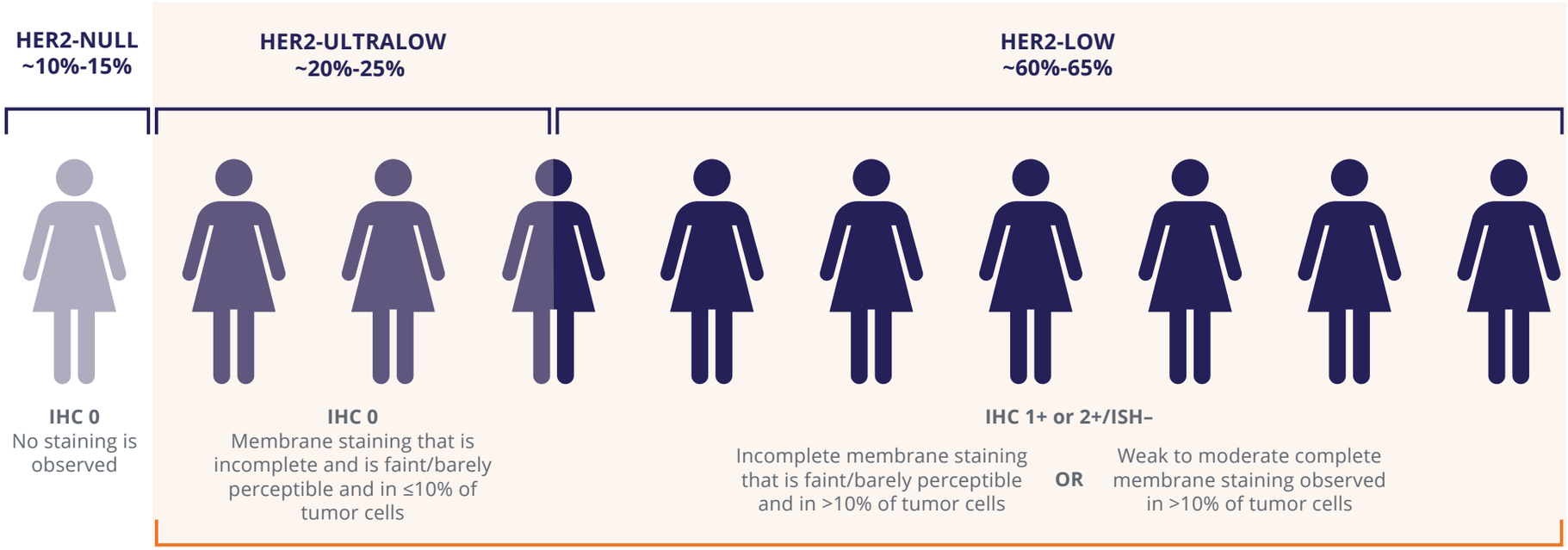
For eligible patients with HR+/HER2-low (IHC 1+ or IHC 2+/ISH–) or HER2-ultralow (IHC 0 with membrane staining) mBC who have received at least 1 line of ET in the metastatic setting,[1]

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

HR+/HER2-negative mBC[46,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 (cont'd)

Neutropenia (cont'd)

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 Metastatic Breast Cancer, HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (5.4 mg/kg)
In patients with metastatic breast cancer, HER2-mutant NSCLC, and other solid tumors treated with ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in 65% of patients. Nineteen percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 22 days (range: 2 to 939). Febrile neutropenia was reported in 1.2% of patients.

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

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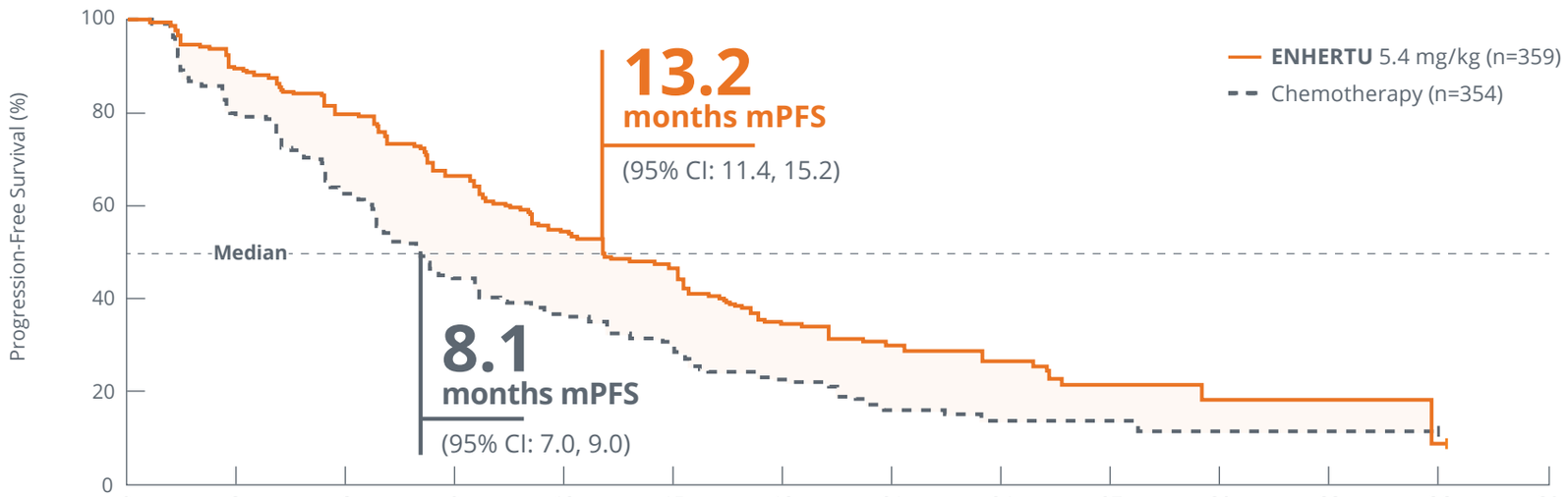
DESTINY-Breast06: In patients with HR+/HER2-low (IHC 1+ or IHC 2+/ISH–) mBC,

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)[1,47]



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]**

[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.[1,47-49]

[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]

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

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

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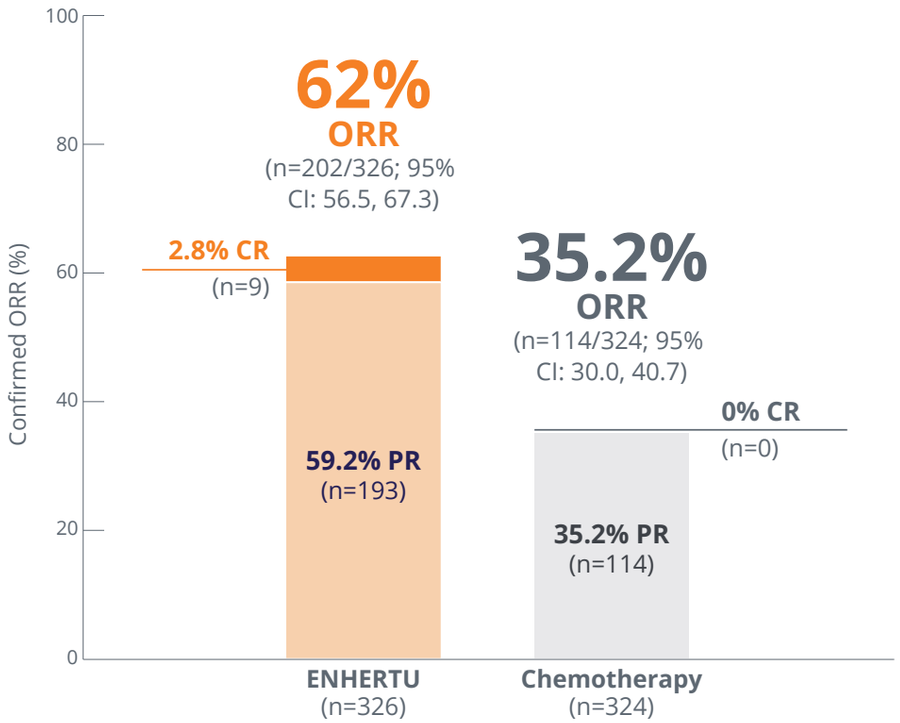
DESTINY-Breast06: In patients with HR+/HER2-low (IHC 1+ or IHC 2+/ISH–) mBC,

Over 60% ORR with ENHERTU and 35.2% with chemotherapy

Secondary endpoint: confirmed objective response in the HER2-low mBC population (BICR)[1,49,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 is not known

Additional results

- Median time to response (TTR) was **2.7** months with ENHERTU and **2.6** months with chemotherapy[45]
- **77.3%** clinical benefit rate (CBR) (CR+PR+SD at week 24) with ENHERTU (n=252/326) and **53.1%** with chemotherapy (n=172/324)[45]

OVER 90% **(n=300/326)** **of patients achieved disease control (CR+PR+SD) with ENHERTU[45,b]**

- TTR, CBR, 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 is not known

[a]Analysis was performed on the patients with measurable disease assessed by BICR at baseline.[1]
[b]DCR was 92% with ENHERTU (n=300/326) and 79.9% with chemotherapy (n=259/324).[45]

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

Left Ventricular Dysfunction (cont'd)

Manage LVEF decrease through treatment interruption. When LVEF is >45% and absolute decrease from baseline is 10-20%, continue treatment with ENHERTU. When LVEF is 40-45% and absolute decrease from baseline is <10%, continue treatment with ENHERTU and repeat LVEF assessment within 3 weeks. When LVEF is 40-45% and absolute decrease from baseline is 10-20%, interrupt ENHERTU and repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within 10% from baseline, permanently discontinue ENHERTU. If LVEF recovers to within 10% from baseline, resume treatment with ENHERTU at the same dose. When LVEF is <40% or absolute decrease from baseline is >20%, interrupt ENHERTU and repeat LVEF assessment within 3 weeks.

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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[1,47]

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

		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, 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.[1,45]
[c]Including fatigue, asthenia, malaise, and lethargy.[1]

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DESTINY-Breast04: In patients with HER2-low (IHC 1+ or IHC 2+/ISH–) mBC,

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

Summary of DESTINY-Breast04 efficacy results by patient population[1,45,50,b,c]

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

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

[a]**Study design:** DESTINY-Breast04 is a Phase 3, international, multicenter, randomized, open-label trial of ENHERTU vs physician's choice of chemotherapy in 557 patients with HER2-low mBC (IHC 1+ or IHC 2+/ISH–). The study included 2 cohorts: 494 HR+ and 63 HR–. Patients had 1 or 2 prior lines of chemotherapy in the metastatic setting, and if HR+, had also progressed on or were refractory to endocrine therapy. Patients in the ENHERTU arm received 5.4 mg/kg IV Q3W and patients in the chemotherapy arm could receive eribulin, capecitabine, gemcitabine, nab-paclitaxel, or paclitaxel. Treatment was continued until unacceptable toxicity or disease progression. The primary endpoint was PFS in the HR+ population (determined by BICR according to mRECIST v1.1). Select secondary endpoints included PFS (BICR) in the overall study population (HR+ and HR–), OS in the HR+ population, OS in the overall study population (HR+ and HR–), ORR in the HR+ population, and DOR in the HR+ population.[1,51]

[b]For the primary and secondary endpoints, the hormone receptor status is based on data collected using the interactive web/voice response system at the time of randomization, which includes mis-stratified patients.[50]

[c]For other endpoints, hormone receptor status is based on data from the electronic data capture corrected for mis-stratification.[50]

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

Left Ventricular Dysfunction (cont'd)

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

In patients with metastatic breast cancer, HER2-mutant NSCLC, and other solid tumors treated with ENHERTU 5.4 mg/kg, LVEF decrease was reported in 4.6% of patients, of which 0.6% were Grade 3 or 4.

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Safety data from DESTINY-Breast04 further established the benefit-risk profile in HER2-low mBC[1,50]

- Median duration of treatment: 8 months (range: 0.2-33) with ENHERTU; 3.5 months (range: 0.3-17.6) with chemotherapy

	ENHERTU 5.4 mg/kg (n=371)	
Serious ARs	28%	• Serious ARs in >1% of patients were ILD/pneumonitis, pneumonia, dyspnea, musculoskeletal pain, sepsis, anemia, febrile neutropenia, hypercalcemia, nausea, pyrexia, and vomiting. Fatalities 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)
Permanent discontinuations due to ARs	16%	• Most frequent (>2%) was ILD/pneumonitis (8%)
Dose interruptions due to ARs	39%	• Most frequent (>2%) were neutropenia, fatigue, anemia, leukopenia, COVID-19, ILD/pneumonitis, increased transaminases, and hyperbilirubinemia
Dose reductions due to ARs	23%	• Most frequent (>2%) were fatigue, nausea, thrombocytopenia, and neutropenia
ILD/pneumonitis (All Grades)[a]	12.1%	• Majority of events were Grade 1 or 2 (n=37/45) • 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 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%)

Incidence of select common adverse reactions in DESTINY-Breast04

Adverse reactions	ENHERTU 5.4 mg/kg (n=371)		Chemotherapy (n=172)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Nausea	76	4.6	30	0
Fatigue[c]	54	9	48	4.7
Vomiting	40	1.6	13	0
Alopecia	40	0	33	0
Constipation	34	0.8	22	0
Decreased appetite	32	2.4	19	1.2
Diarrhea	27	1.3	22	1.7

[a]Includes events that were adjudicated as drug-induced ILD: ILD, pneumonitis, organizing pneumonia, pneumonia, and radiation pneumonitis.[1]
[b]Grade 5=fatal cases.[45]
[c]Including fatigue, asthenia, and malaise.[1]

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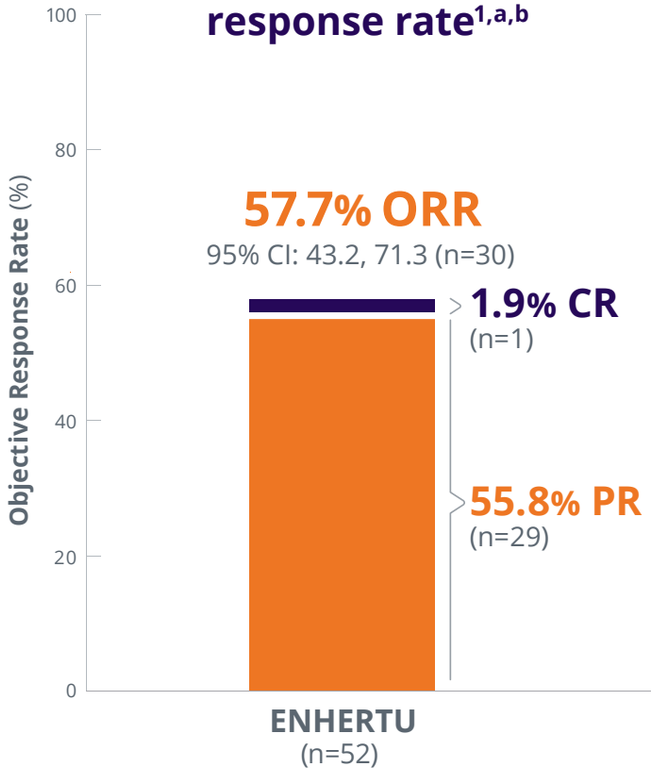
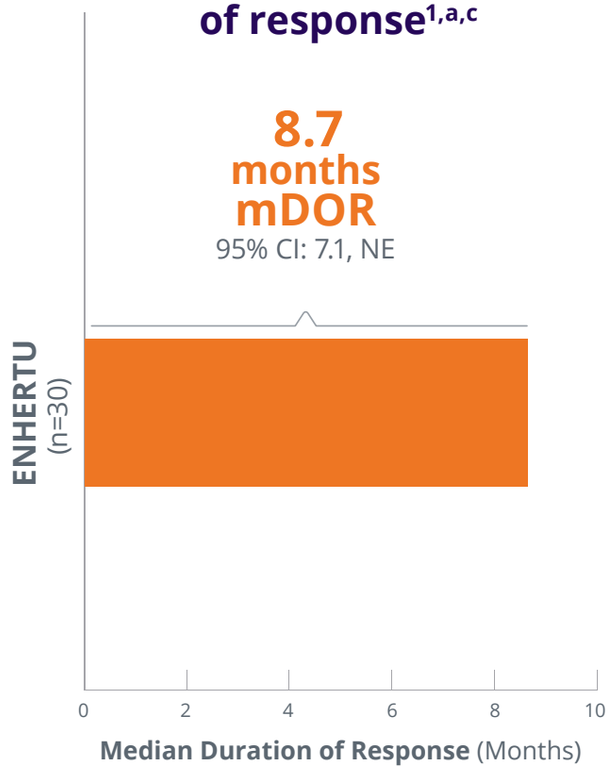
In activating *HER2*-mutant 2L mNSCLC at 5.4 mg/kg,

The majority of patients treated with ENHERTU achieved a durable response

Confirmed objective response rate[1,a,b]



Median duration of response[1,a,c]



- The cutoff date for efficacy data was June 22, 2022[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 received ENHERTU 5.4 mg/kg IV Q3W (n=101) 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 interim efficacy analysis included a prespecified cohort of 52 out of 101 patients.[1,52,53]

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]Radiographic tumor assessments were 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]

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

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.

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Safety data from DESTINY-Lung02 in activating *HER2*-mutant 2L mNSCLC[1,45]

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- 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
  - 19% of the 101 patients treated with ENHERTU in DESTINY-Lung02 were exposed for >6 months
  - The cutoff date for safety data was March 24, 2022

	ENHERTU 5.4 mg/kg (n=101)	
Serious ARs	30%	• Serious ARs in >1% of patients were ILD/pneumonitis, thrombocytopenia, dyspnea, nausea, pleural effusion, and increased troponin I. Fatality due to adverse reactions occurred in 1 patient with suspected ILD/pneumonitis (1%)
Permanent discontinuations due to ARs	8%	• ARs which resulted in permanent discontinuation of ENHERTU were ILD/pneumonitis, diarrhea, decreased blood potassium, hypomagnesemia, myocarditis, and vomiting
Dose interruptions due to ARs	23%	• Most frequent (>2%) were neutropenia and ILD/pneumonitis
Dose reductions due to ARs	11%	• 11 patients experienced dose reductions
ILD/pneumonitis (All Grades)[a]	6%	• ILD occurred in 6% of patients and fatality occurred in 1 patient with suspected 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 nausea (61%), decreased white blood cell count (60%), decreased hemoglobin (58%), decreased neutrophil count (52%), decreased lymphocyte count (43%), decreased platelet count (40%), decreased albumin (39%), increased aspartate aminotransferase (35%), increased alanine aminotransferase (34%), fatigue (32%), constipation (31%), decreased appetite (30%), vomiting (26%), increased alkaline phosphatase (22%), and alopecia (21%)

Incidence of select common adverse reactions in DESTINY-Lung02

Adverse reactions	ENHERTU 5.4 mg/kg (n=101)	
	All Grades (%)	Grades 3-4 (%)
Nausea	61	3
Fatigue[b]	32	4
Constipation	31	1
Decreased appetite	30	1
Vomiting[c]	26	2
Alopecia	21	0
Diarrhea	19	1

[a]Includes events that were adjudicated as drug-induced ILD: pneumonitis, ILD, pulmonary toxicity, and respiratory failure.[1]
[b]Including asthenia, fatigue, and malaise.[1]
[c]Including vomiting and retching.[1]

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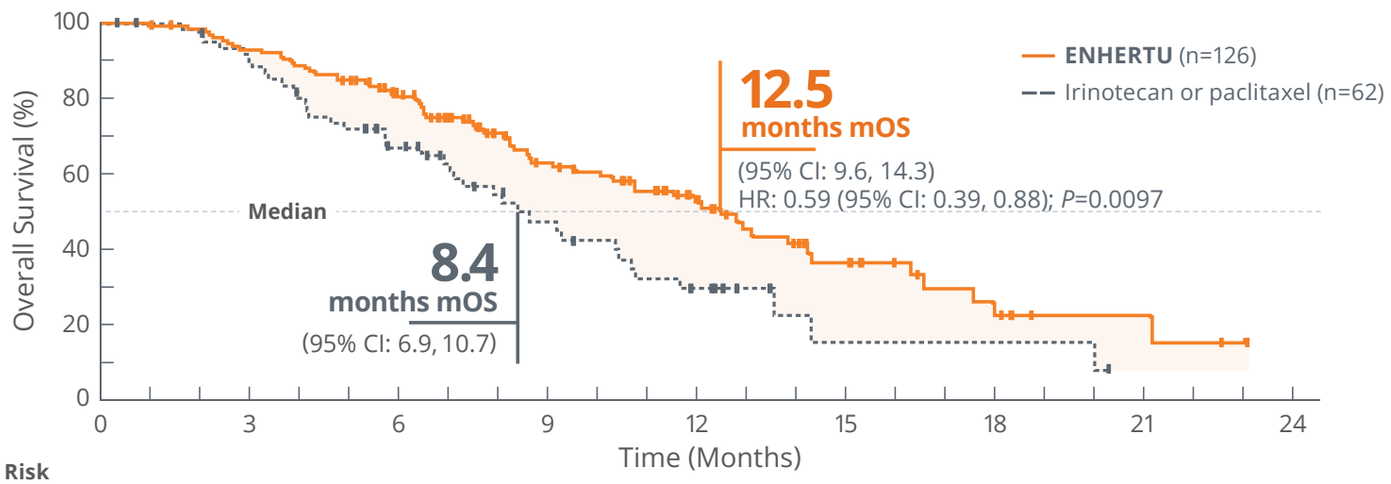
In DESTINY-Gastric01,

ENHERTU is the first and only HER2-directed treatment to surpass 1 year mOS in aGC following progression on a trastuzumab-based regimen[1,54-56,a]

Superior overall survival vs irinotecan or paclitaxel[1,54,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.[1,54]

[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.[45,54,57]

[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).[45,54]

[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).[45]

[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.[54]

[f]PFS was not formally tested for statistical significance.[45]

[g]mDOR was measured for responding patients (PR or CR) only (ENHERTU, n=51; irinotecan, n=6; paclitaxel, n=1).[45]

[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.[54]

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Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

Embryo-Fetal Toxicity (cont'd)

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

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Safety data from DESTINY-Gastric01 established the benefit-risk profile in HER2+ aGC[1,54]

- 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

	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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Responses with ENHERTU across clinical trials

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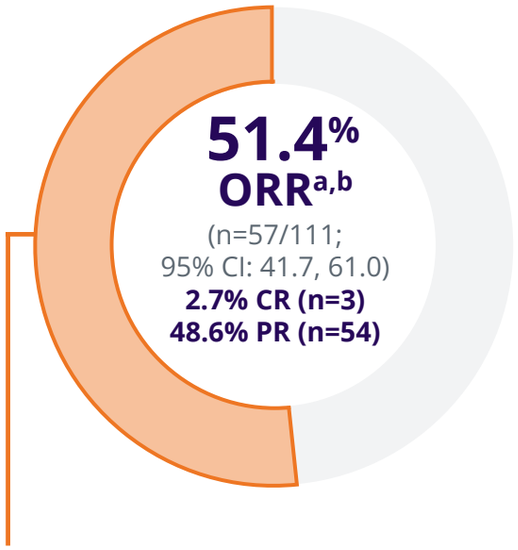
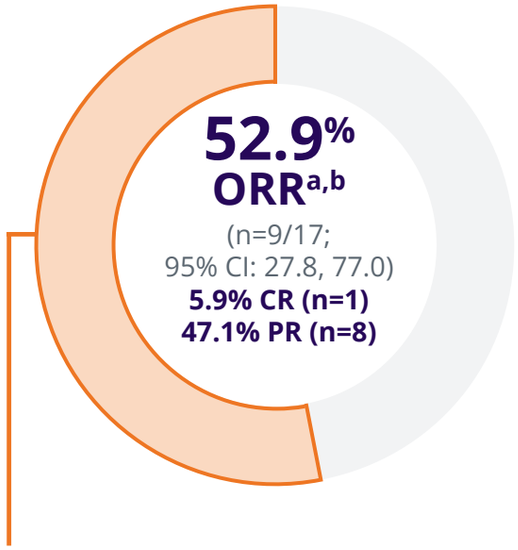
Metastatic solid tumors[1]



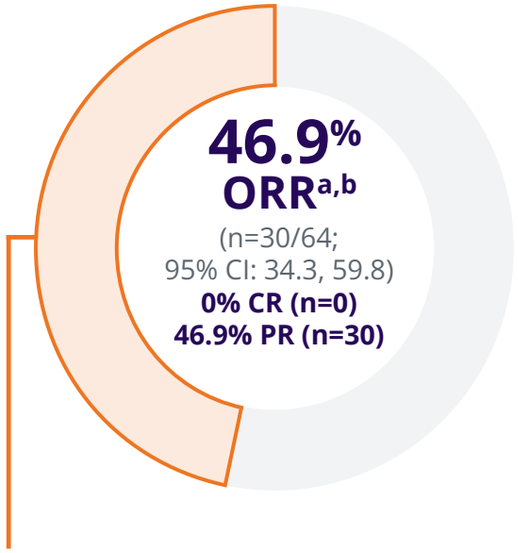
19.4 months mDOR[a,c]
(n=57; range: 1.3, 27.9+)

mNSCLC[1]



6.9 months mDOR[a,c]
(n=9; range: 4.0, 11.7+)

mCRC[1]



5.5 months mDOR[a,c]
(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.[4,5]

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]

Important Safety Information (cont'd)

Adverse Reactions (cont'd)

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 38% were exposed for >1 year. In this pooled safety population, the most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased white blood cell count (73%), nausea (72%), decreased hemoglobin (67%), decreased neutrophil count (65%), decreased lymphocyte count (60%), fatigue (55%), decreased platelet count (48%), increased aspartate aminotransferase (46%), increased alanine aminotransferase (44%), increased blood alkaline phosphatase (39%), vomiting (38%), alopecia (37%), constipation (32%), decreased blood potassium (32%), decreased appetite (31%), diarrhea (30%), and musculoskeletal pain (24%).

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Safety data from 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)

	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%	• 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 pooled safety data

Select adverse reactions from clinical studies[1,45]

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

	Metastatic Breast Cancer, *HER2*-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (5.4 mg/kg; N=2233)[a]	Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg; N=125)
ILD	• ILD occurred in 12% of patients (n=265/2233) • Median time to first onset was 5.5 months (range: 0.9-31.5) • Fatal outcomes due to ILD and/or pneumonitis occurred in 0.9% of patients treated with ENHERTU	• ILD occurred in 10% of patients • Median time to first onset was 2.8 months (range: 1.2-21)
Neutropenia	• Decrease in neutrophil count was reported in 65% of patients • 19% had Grade 3 or 4 decreased neutrophil count • Median time to first onset was 22 days (range: 2-939) • Febrile neutropenia was reported in 1.2% of patients	• Decrease in neutrophil count was reported in 72% of patients • 51% had Grade 3 or 4 decreased neutrophil count • Median time to first onset was 16 days (range: 4-187) • Febrile neutropenia was reported in 4.8% of patients
Left ventricular dysfunction	• LVEF decrease was reported in 4.6% of patients, of which 0.6% were Grade 3 or 4	• No clinical adverse events of heart failure were reported • 8% were found to have asymptomatic Grade 2 decrease in LVEF
Most common (≥20%) ARs, including laboratory abnormalities	• Decreased white blood cell count (73%), nausea (72%), decreased hemoglobin (67%), decreased neutrophil count (65%), decreased lymphocyte count (60%), fatigue (55%), decreased platelet count (48%), increased aspartate aminotransferase (46%), increased alanine aminotransferase (44%), increased blood alkaline phosphatase (39%), vomiting (38%), alopecia (37%), constipation (32%), decreased blood potassium (32%), decreased appetite (31%), diarrhea (30%), and musculoskeletal pain (24%)	• 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%)

[a]The pooled safety population reflects exposure to ENHERTU 5.4 mg/kg IV every 3 weeks 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]

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Early identification of ILD/pneumonitis is key to appropriate management[1,58-60]

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[58]

Before initiating ENHERTU[59,60]

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

Throughout treatment[1,59,60]

- 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[58]

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

CT scans[59]

- 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[58]

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[59]

- 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[59]

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

If ILD/pneumonitis is suspected when[59,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

	Asymptomatic (Grade 1) ILD/pneumonitis[1]	Symptomatic (Grade ≥2) ILD/pneumonitis[1]
4 SUSPEND TREATMENT Promptly investigate evidence and **interrupt ENHERTU treatment as soon as ILD is suspected, regardless of which grade is confirmed**[1,58]	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 one 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[58,59]	• 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[1,59,60]
- **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 5.4 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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Grade and description of select ARs observed with ENHERTU[61]

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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 (e.g., 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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NCCN Guidelines for prophylactic management of nausea and/or vomiting

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

Premedication is recommended prior to infusion of fam-trastuzumab deruxtecan-nxki (ENHERTU)[62]

- The NCCN Guidelines for Antiemesis recommends 3-4 prophylactic antiemetic regimens for high emetic risk agents, including fam-trastuzumab deruxtecan-nxki (ENHERTU), to help decrease potential nausea/vomiting[a-c]
- Consider option A, B, or C
- All treatments are Category 1 and should be started before anticancer therapy[d]

Treatment option	Day 1	Days 2, 3, and 4
A (Preferred)[e]	Use the following: • Olanzapine[f] • NK1 RA • 5-HT3 RA[g,h] • Dexamethasone[i,j]	Use the following: • Olanzapine[f] on days 2-4 • Oral aprepitant on days 2-3 (if oral aprepitant is used on day 1) • Dexamethasone[i,j] on days 2-4
B	Use the following: • Olanzapine[f] • Palonosetron • Dexamethasone[i,j]	Use the following: • Olanzapine[f] on days 2-4
C	Use the following: • NK1 RA • 5-HT3 RA[g,h] • Dexamethasone[i,j]	Use the following: • Oral aprepitant on days 2-3 (if oral aprepitant is used on day 1) • Dexamethasone[i,j] on days 2-4

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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]Especially for patients with anticipatory, anxiety-related, or breakthrough nausea, may consider adding lorazepam 0.5–1 mg by mouth (PO) or IV or sublingual (SL) every 6 hours as needed on days 1–4. Use the lowest effective dose and dosage interval possible. May be administered with or without H_2 blocker or proton pump inhibitor (PPI) if patient exhibits reflux symptoms.
[d]Category 1 recommendations indicate uniform NCCN consensus that the intervention is appropriate based on high-level evidence.
[e]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.
[f]Data suggest that a 5-mg dose of olanzapine is efficacious. Consider this dose especially for patients who are older or who are over sedated.
[g]If netupitant/palonosetron or fosnetupitant/palonosetron fixed combination product is used, no further 5-HT3 RA is required.
[h]When used in combination with an NK1 RA, there is no preferred 5-HT3 RA.
[i]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. Lower doses, given for shorter durations, or even elimination of dexamethasone on subsequent days (for delayed nausea and emesis prevention) may be acceptable based on patient characteristics. If dexamethasone is eliminated on subsequent days for delayed nausea and emesis prevention, consider other alternative antiemetics (eg, olanzapine).
[j]Use of corticosteroid premedications should be avoided with cellular therapies.

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Management of other select adverse reactions with ENHERTU

Left ventricular dysfunction[1]

Severity

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%	

Treatment modification

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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Management of other select adverse reactions with ENHERTU (cont'd)

Neutropenia[1,61]

- 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
1				
Treatment modification	**Continue** Treatment with ENHERTU	**Interrupt** ENHERTU	**Interrupt** ENHERTU	**Interrupt** ENHERTU
2		Resolve to Grade ≤2 (ANC ≥1.0 x 10^9/L)	Resolve to Grade ≤2 (ANC ≥1.0 x 10^9/L)	Resolve
3		**Resume ENHERTU treatment at the same dose**	**Reduce ENHERTU dose by one level and resume treatment** **See Dose Reduction Table on page 27**	**Reduce ENHERTU dose by one level and resume treatment** **See Dose Reduction Table on page 27**

Thrombocytopenia[1,61]

- 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
1			
Treatment modification	**Continue** Treatment with ENHERTU	**Interrupt** ENHERTU	**Interrupt** ENHERTU
2		Resolve to Grade 1 or less (platelets ≥75 x 10^9/L)	Resolve to Grade 1 or less (platelets ≥75 x 10^9/L)
3		**Resume ENHERTU treatment at the same dose**	**Reduce ENHERTU dose by one level and resume treatment** **See Dose Reduction Table on page 27**

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

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ENHERTU dosing and administration[1]

Recommended weight-based dosage and schedule

- ENHERTU is always given as a monotherapy

HER2+ mBC
HER2-low or HER2-ultralow mBC
***HER2*-mutant mNSCLC**
HER2+ (IHC 3+) metastatic solid tumors

5.4 mg/kg IV

HER2+ aGC

6.4 mg/kg IV

3 weeks
ONCE EVERY 3 WEEKS
(21-day cycle)

90 minutes
INITIAL INFUSION

IF WELL TOLERATED

30 minutes
SUBSEQUENT INFUSIONS

Continue until disease progression or unacceptable toxicity

In patients with unresectable or metastatic NSCLC, the approved recommended dose of ENHERTU is 5.4 mg/kg Q3W due to increased toxicity, including ILD/pneumonitis, observed with a higher dose

- **Do not substitute ENHERTU for or with trastuzumab or ado-trastuzumab emtansine**
- Slow or interrupt the infusion rate if the patient develops infusion-related symptoms
- Permanently discontinue ENHERTU in case of severe infusion reactions
- Premedication: ENHERTU is highly emetogenic, which includes delayed nausea and/or vomiting. Administer prophylactic antiemetic medications per local institutional guidelines for prevention of chemotherapy-induced nausea and vomiting

Recommended dose modifications for ENHERTU for adverse reactions

- Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of ENHERTU per dose modifications
- **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	Breast cancer, NSCLC, and IHC 3+ solid tumors starting dose 5.4 mg/kg	Gastric cancer starting dose 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

- **For HER2-low or HER2-ultralow unresectable or metastatic breast cancer:** select patients for treatment with ENHERTU based on HER2 expression that is either HER2-low (IHC 1+ or IHC 2+/ISH–) or HER2-ultralow (IHC 0 with membrane staining)
- **For *HER2*-mutant unresectable or metastatic NSCLC:** select patients for treatment with ENHERTU 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+ locally advanced or metastatic gastric cancer:** 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 for treatment with ENHERTU based on HER2+ (IHC 3+) specimens. An FDA-approved test for the detection of HER2+ (IHC 3+) solid tumors for treatment with ENHERTU is not currently available
- Information on FDA-approved tests for the detection of HER2 protein expression, *HER2* gene amplification, and activating *HER2* mutations is available at: http://www.fda.gov/CompanionDiagnostics

Please see Important Safety Information throughout as well as on pages 31-35, 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

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 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[1,45]

- 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

Please see Important Safety Information throughout as well as on pages 31-35, and click here for full Prescribing Information, including Boxed WARNINGS, and click here for Medication Guide.

BACKGROUND | HER2-EXPRESSING mBC | *HER2*-MUTANT 2L mNSCLC | 2L HER2+ aGC | HER2+ (IHC 3+) SOLID TUMORS | SAFETY | AR MANAGEMENT | DOSING & ADMIN | ACCESS & SUPPORT | ISI | PI | REF 28

ENHERTU4U provides support resources for patients prescribed ENHERTU

ENHERTU® 4U
fam-trastuzumab deruxtecan-nxki
20 mg/mL INJECTION FOR INTRAVENOUS USE

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)

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

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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.

[a]Patients who are residents of Massachusetts or Rhode Island are not eligible for infusion assistance.
[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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BACKGROUND | HER2-EXPRESSING mBC | *HER2*-MUTANT 2L mNSCLC | 2L HER2+ aGC | HER2+ (IHC 3+) SOLID TUMORS | SAFETY | AR MANAGEMENT | DOSING & ADMIN | ACCESS & SUPPORT | ISI | PI | REF 30

Indications and Important Safety Information

ENHERTU®
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Indications

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

- Unresectable or metastatic HER2-positive (IHC 3+ or ISH positive) 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
- Unresectable or metastatic:
  - Hormone receptor (HR)-positive, HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining) breast cancer, as determined by an FDA-approved test, that has progressed on one or more endocrine therapies in the metastatic setting
  - HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy
- Unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved 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.
- 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
- 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 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.

HER2-Positive, HER2-Low, and HER2-Ultralow Metastatic Breast Cancer, HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (5.4 mg/kg)
In patients with metastatic breast cancer, HER2-mutant NSCLC, and other solid tumors treated with ENHERTU 5.4 mg/kg, ILD occurred in 12% of patients. Median time to first onset was 5.5 months (range: 0.9 to 31.5). Fatal outcomes due to ILD and/or pneumonitis occurred in 0.9% of patients treated with ENHERTU.

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).

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 Metastatic Breast Cancer, HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (5.4 mg/kg)
In patients with metastatic breast cancer, HER2-mutant NSCLC, and other solid tumors treated with ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in 65% of patients. Nineteen percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 22 days (range: 2 to 939). Febrile neutropenia was reported in 1.2% of patients.

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Important Safety Information (cont'd)

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Warnings and Precautions (cont'd)

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

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

In patients with metastatic breast cancer, HER2-mutant NSCLC, and other solid tumors treated with ENHERTU 5.4 mg/kg, LVEF decrease was reported in 4.6% of patients, of which 0.6% were Grade 3 or 4.

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

The pooled safety population reflects exposure to ENHERTU 5.4 mg/kg intravenously every 3 weeks in 2233 patients in Study DS8201-A-J101 (NCT02564900), DESTINY-Breast01, DESTINY-Breast02, DESTINY-Breast03, DESTINY-Breast04, DESTINY-Breast06, DESTINY-Lung01, DESTINY-Lung02, DESTINY-CRC02, and DESTINY-PanTumor02. Among these patients, 67% were exposed for >6 months and 38% were exposed for >1 year. In this pooled safety population, the most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased white blood cell count (73%), nausea (72%), decreased hemoglobin (67%), decreased neutrophil count (65%), decreased lymphocyte count (60%), fatigue (55%), decreased platelet count (48%), increased aspartate aminotransferase (46%), increased alanine aminotransferase (44%), increased blood alkaline phosphatase (39%), vomiting (38%), alopecia (37%), constipation (32%), decreased blood potassium (32%), decreased appetite (31%), diarrhea (30%), and musculoskeletal pain (24%).

HER2-Positive Metastatic Breast Cancer

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.

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Important Safety Information (cont'd)

Adverse Reactions (cont'd)

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

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Important Safety Information (cont'd)

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Adverse Reactions (cont'd)

every 3 weeks until disease progression or unacceptable toxicity in DESTINY-Lung02. Nineteen percent of patients were exposed for >6 months.

Serious adverse reactions occurred in 30% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were ILD/pneumonitis, thrombocytopenia, dyspnea, nausea, pleural effusion, and increased troponin I. Fatality occurred in 1 patient with suspected ILD/pneumonitis (1%).

ENHERTU was permanently discontinued in 8% of patients. Adverse reactions which resulted in permanent discontinuation of ENHERTU were ILD/pneumonitis, diarrhea, decreased blood potassium, hypomagnesemia, myocarditis, and vomiting. Dose interruptions of ENHERTU due to adverse reactions occurred in 23% of patients. Adverse reactions which required dose interruption (>2%) included neutropenia and ILD/pneumonitis. Dose reductions due to an adverse reaction occurred in 11% of patients.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea (61%), decreased white blood cell count (60%), decreased hemoglobin (58%), decreased neutrophil count (52%), decreased lymphocyte count (43%), decreased platelet count (40%), decreased albumin (39%), increased aspartate aminotransferase (35%), increased alanine aminotransferase (34%), fatigue (32%), constipation (31%), decreased appetite (30%), vomiting (26%), increased alkaline phosphatase (22%), and alopecia (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%).

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Important Safety Information (cont'd)

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

Use in Specific Populations

- **Pregnancy:** ENHERTU can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risks to a fetus. There are clinical considerations if ENHERTU is used in pregnant women, or if a patient becomes pregnant within 7 months after the last dose of ENHERTU.
- **Lactation:** There are no data regarding the presence of ENHERTU in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with ENHERTU and for 7 months after the last dose.
- **Females and Males of Reproductive Potential:** Pregnancy testing: Verify pregnancy status of females of reproductive potential prior to initiation of ENHERTU. Contraception: *Females*: ENHERTU can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with ENHERTU and for 7 months after the last dose. *Males*: Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for 4 months after the last dose. Infertility: ENHERTU may impair male reproductive function and fertility.
- **Pediatric Use:** Safety and effectiveness of ENHERTU have not been established in pediatric patients.
- **Geriatric Use:** Of the 1741 patients with HER2-positive, HER2-low, or HER2-ultralow breast cancer treated with ENHERTU 5.4 mg/kg, 24% were ≥65 years and 4.9% were ≥75 years. No overall differences in efficacy within clinical studies were observed between patients ≥65 years of age compared to younger patients. There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged ≥65 years (61%) as compared to younger patients (52%). Of the 101 patients with HER2-mutant unresectable or metastatic NSCLC treated with ENHERTU 5.4 mg/kg, 40% were ≥65 years and 8% were ≥75 years. No overall differences in efficacy or safety were observed between patients ≥65 years of age compared to younger patients. 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. Of the 192 patients with HER2-positive (IHC 3+) unresectable or metastatic solid tumors treated with ENHERTU 5.4 mg/kg in DESTINY-PanTumor02, DESTINY-Lung01, or DESTINY-CRC02, 39% were ≥65 years and 9% were ≥75 years. No overall differences in efficacy or safety were observed between patients ≥65 years of age compared to younger patients.
- **Renal Impairment:** A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment. Monitor patients with moderate renal impairment more frequently. The recommended dosage of ENHERTU has not been established for patients with severe renal impairment (CLcr <30 mL/min).
- **Hepatic Impairment:** In patients with moderate hepatic impairment, due to potentially increased exposure, closely monitor for increased toxicities related to the topoisomerase inhibitor, DXd. The recommended dosage of ENHERTU has not been established for patients with severe hepatic impairment (total bilirubin >3 times ULN and any AST).

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

Abbreviations

1L, first line
2L, second line
5-HT3, 5-hydroxytryptamine 3
ABG, arterial blood gas
aGC, advanced gastric cancer
***ALK*,** anaplastic lymphoma kinase
ANC, absolute neutrophil count
AR, adverse reaction
BAL, bronchoalveolar lavage
BICR, blinded independent central review
***BRAF*,** v-Raf murine sarcoma viral oncogene homolog B
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
DOR, duration of response
DXd, deruxtecan
ECOG, Eastern Cooperative Oncology Group
***ERBB2*,** erb-b2 receptor tyrosine kinase 2
ET, endocrine therapy
GC, gastric cancer
GEJ, gastroesophageal junction
H_2, histamine type 2
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
IHC, immunohistochemistry
ILD, interstitial lung disease
IQR, interquartile range
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
mRECIST, Modified Response Evaluation Criteria in Solid Tumors
***MET*,** mesenchymal-epithelial transition
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
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
***ROS1*,** ROS proto-oncogene 1, receptor tyrosine kinase
SD, stable disease
SpO_2, saturation of peripheral oxygen
T-DM1, ado-trastuzumab emtansine
TPN, total parenteral nutrition

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References: 1. ENHERTU. Prescribing information. Daiichi Sankyo, Inc.; 2025. **2.** Tarantino P, Hamilton E, Tolaney SM, et al. HER2-low breast cancer: pathological and clinical landscape. *J Clin Oncol*. 2020;38(17):1951-1962. **3.** Zhao J, Xia Y. Targeting HER2 alterations in non–small-cell lung cancer: a comprehensive review. *JCO Precis Oncol*. 2020;4:411-425. **4.** Hofmann M, Stoss O, Shi D, et al. Assessment of a HER2 scoring system for gastric cancer: results from a validation study. *Histopathology*. 2008;52(7):797-805. **5.** Van Cutsem E, Bang YJ, Feng-Yi F, et al. HER2 screening data from ToGA: targeting HER2 in gastric and gastroesophageal junction cancer. *Gastric Cancer*. 2015;18(3):476-484. **6.** Halle MK, Tangen IL, Berg HF, et al. HER2 expression patterns in paired primary and metastatic endometrial cancer lesions. *Br J Cancer*. 2018;118(3):378-387. **7.** Vivaldi C, Fornaro L, Ugolini C, et al. HER2 overexpression as a poor prognostic determinant in resected biliary tract cancer. *Oncologist*. 2020;25(10):886-893. **8.** Uzunparmak B, Haymaker C, Raso G, et al. HER2-low expression in patients with advanced or metastatic solid tumors. *Ann Oncol*. 2023;34(11):1035-1046. **9.** Roa I, de Toro G, Schalper K, de Aretxabala X, Churi C, Javle M. Overexpression of the HER2/neu gene: a new therapeutic possibility for patients with advanced gallbladder cancer. *Gastrointest Cancer Res*. 2014;7(2):42-48. **10.** Chou A, Waddell N, Cowley MJ, et al. Clinical and molecular characterization of HER2 amplified-pancreatic cancer. *Genome Med*. 2013;5(8):78. **11.** Han SH, Ryu KH, Kwon AY. The prognostic impact of HER2 genetic and protein expression in pancreatic carcinoma—HER2 protein and gene in pancreatic cancer. *Diagnostics (Basel)*. 2021;11(4):653. **12.** Fleischmann A, Rotzer D, Seiler R, Studer UE, Thalmann GN. Her2 amplification is significantly more frequent in lymph node metastases from urothelial bladder cancer than in the primary tumours. *Eur Urol*. 2011;60(2):350-357. **13.** Gårdmark T, Wester K, De la Torre M, Carlsson J, Malmström P-U. Analysis of HER2 expression in primary urinary bladder carcinoma and corresponding metastases. *BJU Int*. 2005;95(7):982-986. **14.** Moustakas G, Kampantais S, Nikolaidou A, et al. HER-2 overexpression is a negative predictive factor for recurrence in patients with non-muscle-invasive bladder cancer on intravesical therapy. *J Int Med Res*. 2020;48(1):300060519895847. **15.** Moktefi A, Pouessel D, Liu J, et al. Reappraisal of HER2 status in the spectrum of advanced urothelial carcinoma: a need of guidelines for treatment eligibility. *Mod Pathol*. 2018;31(8):1270-1281. **16.** Semiz HS, Pala EE, Can B, Atag E, Gungor H, Sanci M. cERBB-2/Her-2 neu overexpression and prognostic significance in uterine carcinoma. *Turk Patoloji Derg*. 2023;39(1):55-63. **17.** Buza N, English DP, Santin AD, Hui P. Toward standard HER2 testing of endometrial serous carcinoma: 4-year experience at a large academic center and recommendations for clinical practice. *Mod Pathol*. 2013;26(12):1605-1612. **18.** Vermij L, Singh N, Leon-Castillo A, et al. Performance of a HER2 testing algorithm specific for p53-abnormal endometrial cancer. *Histopathology*. 2021;79(4):533-543. **19.** Heinmöller P, Gross C, Beyser K, et al. HER2 status in non-small cell lung cancer: results from patient screening for enrollment to a phase II study of herceptin. *Clin Cancer Res*. 2003;9(14):5238-5244. **20.** Zinner RG, Glisson BS, Fossella FV, et al. Trastuzumab in combination with cisplatin and gemcitabine in patients with Her2-overexpressing, untreated, advanced non-small cell lung cancer: report of a phase II trial and findings regarding optimal identification of patients with Her2-overexpressing disease. *Lung Cancer*. 2004;44(1):99-110. **21.** Takenaka M, Hanagiri T, Shinohara S, et al. The prognostic significance of HER2 overexpression in non-small cell lung cancer. *Anticancer Res*. 2011;31(12):4631-4636. **22.** Heppner BI, Behrens H-M, Balschun K, et al. HER2/neu testing in primary colorectal carcinoma. *Br J Cancer*. 2014;111(10):1977-1984. **23.** Wang X-Y, Zheng Z-X, Sun Y, et al. Significance of HER2 protein expression and HER2 gene amplification in colorectal adenocarcinomas. *World J Gastrointest Oncol*. 2019;11(4):335-347. **24.** Tuefferd M, Couturier J, Penault-Llorca F, et al. HER2 status in ovarian carcinomas: a multicenter GINECO study of 320 patients. *PLoS One*. 2007;2(11):e1138. **25.** Ersoy E, Cao QJ, Otis CN. HER2 protein overexpression and gene amplification in tubo-ovarian high-grade serous carcinomas. *Int J Gynecol Pathol*. 2022;41(4):313-319. **26.** Pils D, Pinter A, Reibenwein J, et al. In ovarian cancer the prognostic influence of HER2/nu is not dependent on the CXCR4/SDF-1 signalling pathway. *Br J Cancer*. 2007;96(3):485-491. **27.** Chung YW, Kim S, Hong JH, et al. Overexpression of HER2/HER3 and clinical feature of ovarian cancer. *J Gynecol Oncol*. 2019;30(5):e75. **28.** Shi H, Shao Y, Lu W, Lu B. An analysis of HER2 amplification in cervical adenocarcinoma: correlation with clinical outcomes and the International Endocervical Adenocarcinoma Criteria and Classification. *J Pathol Clin Res*. 2021;7(1):86-95. **29.** Panek G, Ligaj M. Prognostic significance of HER-2/neu expression in patients at early clinical stages of invasive cervical cancer. *Gin Onkol*. 2007;5(4):218-235. **30.** Jebbink M, de Langen AJ, Boelens MC, Monkhorst K, Smit EF. The force of HER2 - a druggable target in NSCLC? *Cancer Treat Rev*. 2020;86:101996. **31.** Li BT, Smit EF, Goto Y, et al; DESTINY-Lung01 Trial Investigators. Trastuzumab deruxtecan in HER2-mutant non–small-cell lung cancer. *N Engl J Med*. 2022;386(3):241-251. **32.** Jordan EJ, Kim HR, Arcila ME, et al. Prospective comprehensive molecular characterization of lung adenocarcinomas for efficient patient matching to approved and emerging therapies. *Cancer Discov*. 2017;7(6):596-609. **33.** Pillai RN, Behera M, Berry LD, et al. HER2 mutations in lung adenocarcinomas: a report from the Lung Cancer Mutation Consortium. *Cancer*. 2017;123(21):4099-4105. **34.** Auliac J-B, Dô P, Bayle S, et al. Non-small cell lung cancer patients harboring HER2 mutations: clinical characteristics and management in a real-life setting. Cohort HER2 EXPLORE GFPC 02-14. *Adv Ther*. 2019;36:2161-2166. **35.** Wang Y, Zhang S, Wu F, et al. Outcomes of pemetrexed-based chemotherapies in HER2-mutant lung cancers. *BMC Cancer*. 2018;18(1):326. **36.** Xu F, Yang G, Xu H, Yang L, Qiu W, Wang Y. Treatment outcome and clinical characteristics of HER2 mutated advanced non-small cell lung cancer patients in China. *Thorac Cancer*. 2020;11(3):679-685. **37.** Guisier F, Dubos-Arvis C, Viñas F, et al. Efficacy and safety of anti–PD-1 immunotherapy in patients with advanced NSCLC with BRAF, HER2, or MET mutations or RET translocation: GFPC 01-2018. *J Thorac Oncol*. 2020;15(4):628-636. **38.** Dudnik E, Bshara E, Grubstein A, et al. Rare targetable drivers (RTDs) in non-small cell lung cancer (NSCLC): outcomes with immune check-point inhibitors (ICPi). *Lung Cancer*. 2018;124:117-124. **39.** Ogitani Y, Aida T, Hagihara K, et al. DS-8201a, a novel HER2-targeting ADC with a novel DNA topoisomerase I inhibitor, demonstrates a promising antitumor efficacy with differentiation from T-DM1. *Clin Cancer Res*. 2016;22(20):5097-5108. **40.** Nakada T, Sugihara K, Jikoh T, Abe Y, Agatsuma T. The latest research and development into the antibody–drug conjugate, [fam-] trastuzumab deruxtecan (DS-8201a), for HER2 cancer therapy. *Chem Pharm Bull (Tokyo)*. 2019;67(3):173-185. **41.** Ogitani Y, Hagihara K, Oitate M, Naito H, Agatsuma T. Bystander killing effect of DS-8201a, a novel anti-human epidermal growth factor receptor 2 antibody–drug conjugate, in tumors with human epidermal growth factor receptor 2 heterogeneity. *Cancer Sci*. 2016;107(7):1039-1046. **42.** Cortés J, Kim SB, Chung WP, et al; DESTINY-Breast03 Trial Investigators. Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. *N Engl J Med*. 2022;386(12):1143-1154. **43.** Hurvitz SA, Hegg R, Chung WP, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. *Lancet*. 2023;401(10371):105-117. **44.** Cortés J, Hurvitz SA, Im S-A, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in HER2-positive metastatic breast cancer: long-term survival analysis of the DESTINY-Breast03 trial. *Nat Med*. 2024;30(8):2208-2215. **45.** Data on file. Daiichi Sankyo, Inc. Basking Ridge, NJ. **46.** Viale G, Salgado R, Bardia A, et al. HER2-low and HER2-ultralow status determination in tumors of patients with hormone receptor-positive metastatic breast cancer in DESTINY-Breast06. Presented at: European Society for Medical Oncology; September 15, 2024; Barcelona, Spain. **47.** Bardia A, Hu X, Dent R, et al. Trastuzumab deruxtecan after endocrine therapy in metastatic breast cancer. *N Engl J Med*. 2024;391(22):2110-2122. **48.** Bardia A, Hu X, Dent R, et al. Supplement to: Trastuzumab deruxtecan after endocrine therapy in metastatic breast cancer. *N Engl J Med*. 2024;391(22):2110-2122. **49.** Bardia A, Hu X, Dent R, et al. Protocol for: Trastuzumab deruxtecan after endocrine therapy in metastatic breast cancer. *N Engl J Med*. 2024;391(22):2110-2122. **50.** Modi S, Jacot W, Yamashita T, et al; DESTINY-Breast04 Trial Investigators. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. *N Engl J Med*. 2022;387(1):9-20. **51.** Modi S, Jacot W, Yamashita T, et al; DESTINY-Breast04 Trial Investigators. Protocol for: Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. *N Engl J Med*. 2022;387(1):9-20. **52.** Trastuzumab deruxtecan in participants with HER2-mutated metastatic non-small cell lung cancer (NSCLC) (DESTINY-LUNG02). ClinicalTrials.gov identifier: NCT04644237. Updated April 29, 2022. Accessed August 11, 2022. https://clinicaltrials.gov/ct2/show/NCT04644237 **53.** Smit EF, Li BT, Mazieres J, et al. Trastuzumab deruxtecan (T-DXd) in patients with HER2-mutated (HER2m) metastatic non–small cell lung cancer (NSCLC): a phase 2 study (DESTINY-Lung02). Poster presented at: ESMO Congress 2021; September 16-21, 2021. **54.** Shitara K, Bang YJ, Iwasa S, et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. *N Engl J Med*. 2020;382(25):2419-2430. **55.** Curea FG, Hebbar M, Ilie SM, et al. Current targeted therapies in HER2-positive gastric adenocarcinoma. *Cancer Biother Radiopharm*. 2017;32(10):351-363. **56.** Zhao D, Klempner SJ, Chao J. Progress and challenges in HER2-positive gastroesophageal adenocarcinoma. *J Hematol Oncol*. 2019;12(1):50. **57.** Yamaguchi K, Bang YJ, Iwasa S, et al. Trastuzumab deruxtecan (T-DXd; DS-8201) in patients with human epidermal growth factor

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BACKGROUND | HER2-EXPRESSING mBC | *HER2*-MUTANT 2L mNSCLC | 2L HER2+ aGC | HER2+ (IHC 3+) SOLID TUMORS | SAFETY | AR MANAGEMENT | DOSING & ADMIN | ACCESS & SUPPORT | ISI | PI | REF | 36

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receptor 2–positive advanced gastric cancer or gastroesophageal junction adenocarcinoma: final overall survival results from a randomized, multicenter, open-label, phase 2 study (DESTINY-Gastric01). Presented at: American Society of Clinical Oncology (ASCO) 2021 Annual Meeting; June 4-8, 2021. **58.** Tarantino P, Tolaney SM. Detecting and managing T-DXd-related interstitial lung disease: the five "S" rules. *JCO Oncol Pract*. 2023;19(8):526-527. **59.** Rugo HS, Crossno CL, Gesthalter YB, et al. Real-world perspectives and practices for pneumonitis/interstitial lung disease associated with trastuzumab deruxtecan use in human epidermal growth factor receptor 2–expressing metastatic breast cancer. *JCO Oncol Pract*. 2023;19(8):539-546. **60.** Swain SM, Nishino M, Lancaster LH, et al. Multidisciplinary clinical guidance on trastuzumab deruxtecan (T-DXd)–related interstitial lung disease/pneumonitis—focus on proactive monitoring, diagnosis, and management. *Cancer Treat Rev*. 2022;106:102378. **61.** National Cancer Institute, National Institutes of Health, US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. Published November 27, 2017. **62.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Antiemesis V.2.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed September 27, 2024. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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