Across solid tumors

IDENTIFY HER2 ALTERATIONS TO INFORM ELIGIBILITY FOR TREATMENT WITH ENHERTU

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

ENHERTU is approved for certain previously treated adult patients with[1]:

- **HER2+ Metastatic Breast Cancer (IHC 3+ or ISH+)**
- **HER2-low Metastatic Breast Cancer (IHC 1+ or IHC 2+/ISH–)**
- NEW **HER2-ultralow Metastatic Breast Cancer (IHC 0 with membrane staining)**
- ***HER2*-mutant mNSCLC** (accelerated approval)
- **HER2+ Advanced Gastric Cancer (IHC 3+ or IHC 2+/ISH+)**
- **HER2+ Metastatic Solid Tumors (IHC 3+)** (accelerated approval)

Indications and Important Safety Information

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**

Please see Important Safety Information on pages 16-20 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

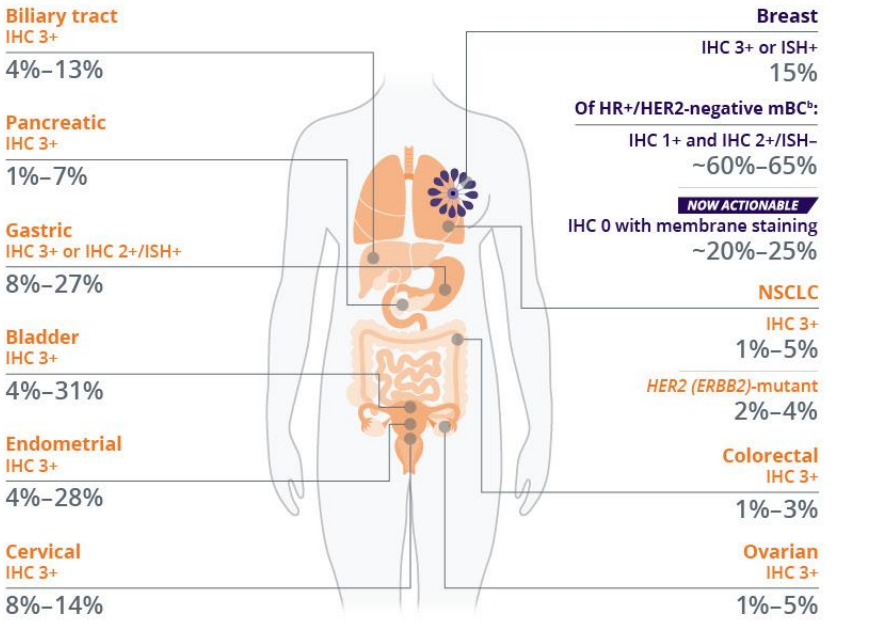
Daiichi-Sankyo | AstraZeneca

Across Tumor Types

Three distinct HER2 alterations have been identified, and each requires a specific method of testing

HER2 overexpression[2,3]	*HER2 (ERBB2)* amplification[4]	*HER2 (ERBB2)* mutation[5]
Overabundance of HER2 receptors on the surface of a cell	Abnormally high number of *HER2 (ERBB2)* gene copies	Mutation in the *HER2 (ERBB2)* gene
IHC test	FISH or NGS test	NGS test

Prevalence of relevant HER2 alterations in select solid tumors[6-35,a]



NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recognizes the clinical relevance of HER2 alterations across many solid tumors[36-41]

[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 has been included.

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

Please see Important Safety Information on pages 16-20 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

Across Tumor Types

ENHERTU is an FDA-approved treatment for eligible patients with certain HER2 alterations[a]

Tumor type	HER2 status	Key clinical trial(s)	ASCO-CAP breast scoring criteria[b]	ASCO-CAP gastric scoring criteria[b]	
Metastatic breast cancer[1,2,42,43]	HER2-positive (IHC 3+ or ISH+)	DESTINY-Breast03	✓		Consider using the FDA-approved PATHWAY HER2 (4B5) CDx for detecting HER2-low and HER2-ultralow mBC
	HER2-low (IHC 1+ or IHC 2+/ISH–)	DESTINY-Breast06[c]/ DESTINY-Breast04	✓		
	NOW ACTIONABLE HER2-ultralow (IHC 0 with membrane staining)	DESTINY-Breast06[c]	✓		
Advanced gastric cancer/GEJ adenocarcinoma[1,44]	HER2-positive (IHC 3+ or IHC 2+/ISH+)	DESTINY-Gastric01		✓	ASCO-CAP gastric HER2 scoring criteria were used to identify patients in these trials
Metastatic solid tumors, including NSCLC[1,45-47] (accelerated approval)	HER2-positive (IHC 3+)	DESTINY-PanTumor02/ DESTINY-Lung01/ DESTINY-CRC02		✓	
Metastatic non-small cell lung cancer[1,40] (accelerated approval)	*HER2 (ERBB2)*-mutant	DESTINY-Lung02	—	—	NGS testing can be used to detect *HER2 (ERBB2)* mutations

- There is no specific validation assay across metastatic solid tumors; however, 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/CcompanionDiagnostics[1]
- For patient selection criteria for ENHERTU, please see Section 2.1 of the Prescribing Information

Test for the appropriate HER2 alterations in each tumor type to identify eligible patients for treatment with ENHERTU[1]

[a]Please see full indications for ENHERTU on page 1.
[b]Scoring criteria used in clinical trial.
[c]DESTINY-Breast06 used a proposed scoring algorithm based on the ASCO-CAP scoring criteria for breast cancer.[43]

Please see Important Safety Information on pages 16-20 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

Important Safety Information

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.

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

mBC

Perform HER2 IHC testing to identify HER2-ultralow and HER2-low patients who may be eligible for HER2-directed treatment in mBC

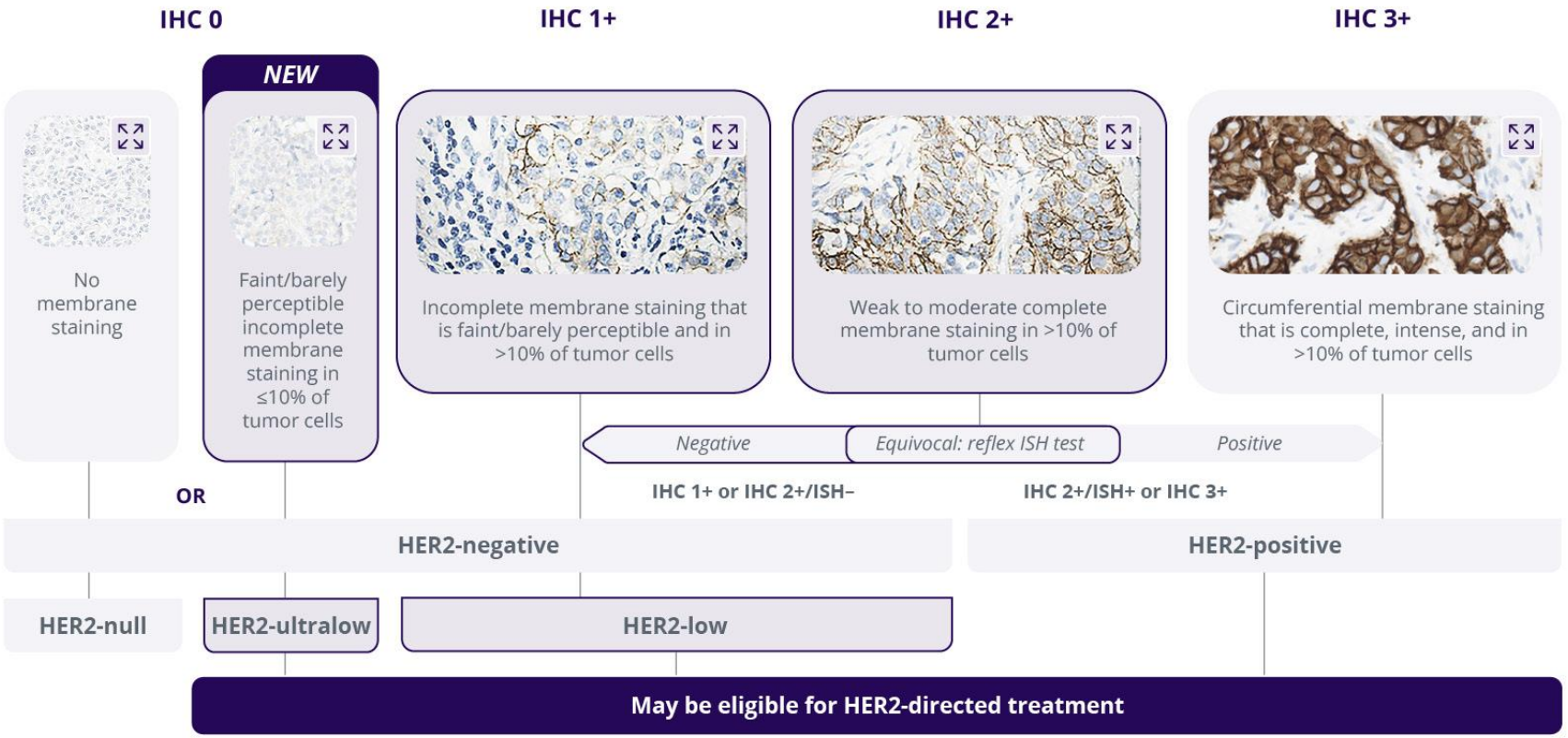
NOW ACTIONABLE

HER2-ultralow status is now actionable in certain patients with mBC[1]

- HER2-ultralow is defined as faint/barely perceptible, incomplete membrane HER2 staining that is seen in ≤10% of tumor cells[1,2]

~60% of HR+/HER2-negative mBC tumors previously considered IHC 0 are **HER2-ultralow** (IHC 0 with membrane staining)[25,a]

Test for HER2-ultralow and HER2-low with IHC using the proposed scoring algorithm based on the ASCO-CAP scoring criteria for breast cancer[1,2,48,49]



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

Please see Important Safety Information on pages 16-20 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

mBC

Perform HER2 IHC testing to identify HER2-ultralow and HER2-low patients who may be eligible for HER2-directed treatment in mBC

[NOW ACTIONABLE]

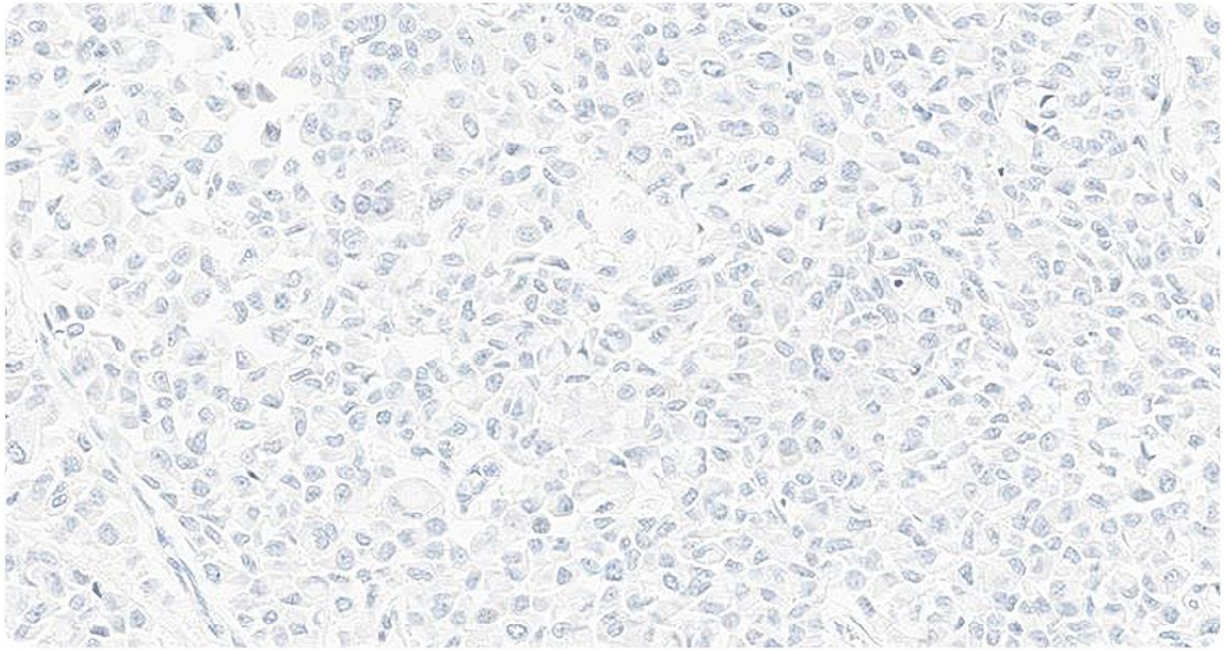
HER2-ultralow status is [now] actionable in certain patients with mBC[1]

- HER2-ultralow
  that is seen in

~60% of HR+/HER2-negative mB nors
ralow

Test for HER2
criteria for br

IHC 0



No membrane staining

No membrane staining

mbrane staining
ntense, and in
nor cells

HER2-null

May be eligible for HER2-directed treatment

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

Please see Important Safety Information on pages 16-20 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

mBC

Perform HER2 IHC testing to identify HER2-ultralow and HER2-low patients who may be eligible for HER2-directed treatment in mBC

[NOW ACTIONABLE]

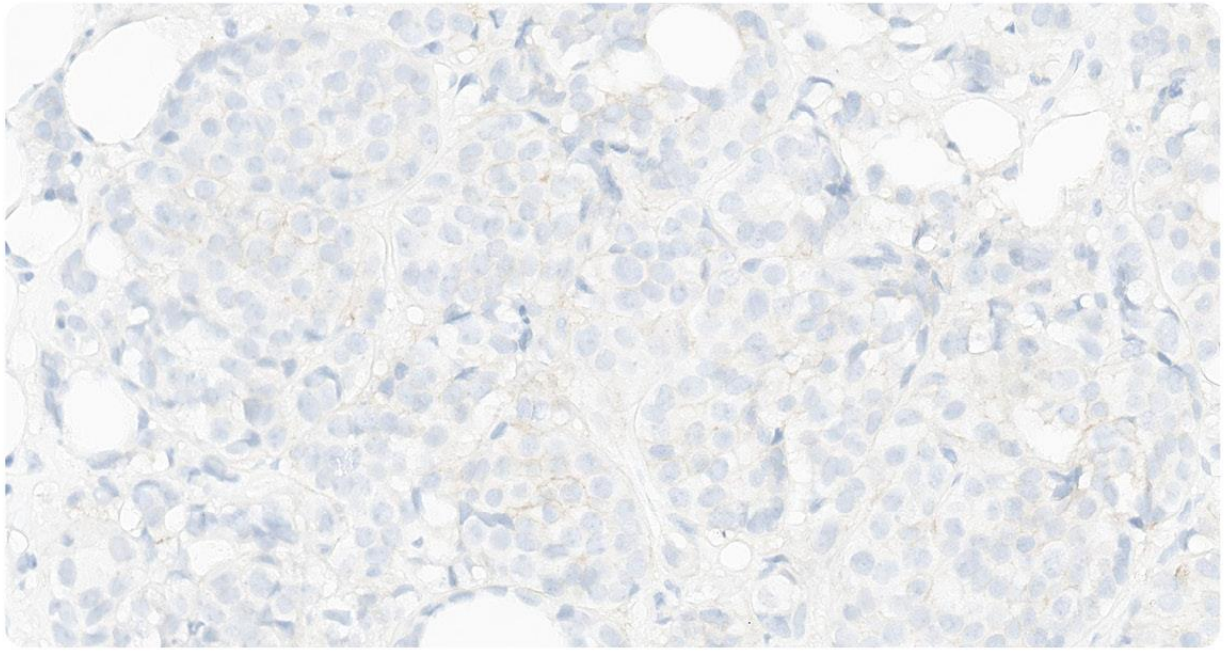
HER2-ultralow status is [now] actionable in certain patients with mBC[1]

- HER2-ultralow
  that is seen in

~60% of HR+/HER2-negative mB nors
ralow

Test for HER2
criteria for br

IHC 0



Faint/barely perceptible incomplete membrane staining in ≤10% of tumor cells

No membrane staining

mbrane staining
ntense, and in
or cells

HER2-null

May be eligible for HER2-directed treatment

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

Please see Important Safety Information on pages 16-20 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

mBC

Perform HER2 IHC testing to identify HER2-ultralow and HER2-low patients who may be eligible for HER2-directed treatment in mBC

[NOW ACTIONABLE]

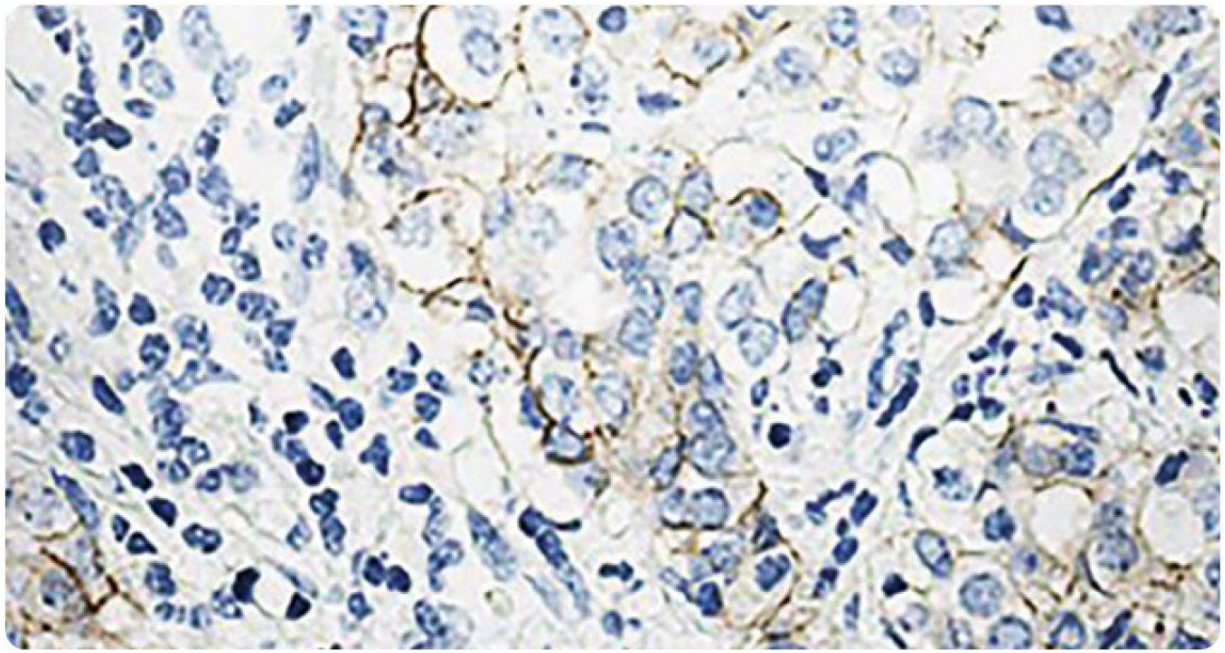
HER2-ultralow status is [now] actionable in certain patients with mBC[1]

- HER2-ultralow
  that is seen in

~60% of HR+/HER2-negative mB nors
ralow

Test for HER2
criteria for br

IHC 1+



Incomplete membrane staining that is faint/barely perceptible and in >10% of tumor cells

No membrane staining

mbrane staining
ntense, and in
nor cells

HER2-null

May be eligible for HER2-directed treatment

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

Please see Important Safety Information on pages 16-20 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

mBC

Perform HER2 IHC testing to identify HER2-ultralow and HER2-low patients who may be eligible for HER2-directed treatment in mBC

[NOW ACTIONABLE]

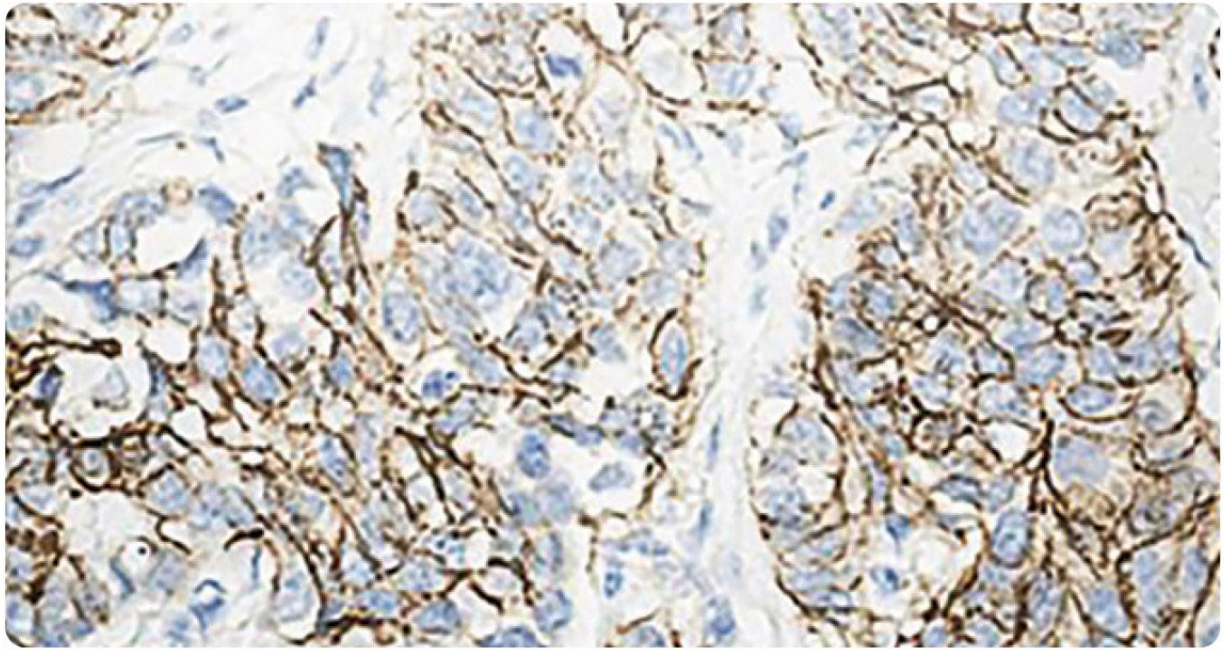
HER2-ultralow status is [now] actionable in certain patients with mBC[1]

- HER2-ultralow
  that is seen in

~60% of HR+/HER2-negative mB nors
ralow

Test for HER2
criteria for br

IHC 2+



Weak to moderate complete membrane staining in >10% of tumor cells

No membrane staining

mbrane staining
ntense, and in
nor cells

HER2-null

May be eligible for HER2-directed treatment

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

Please see Important Safety Information on pages 16-20 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

mBC

Perform HER2 IHC testing to identify HER2-ultralow and HER2-low patients who may be eligible for HER2-directed treatment in mBC

[NOW ACTIONABLE]

HER2-ultralow status is [now] actionable in certain patients with mBC[1]

- HER2-ultralow
- that is seen in

~60% of HR+/HER2-negative mB… nors …tralow

Test for HER2 … g
criteria for br…

I … +

No membrane staining

…mbrane staining …ntense, and in …nor cells

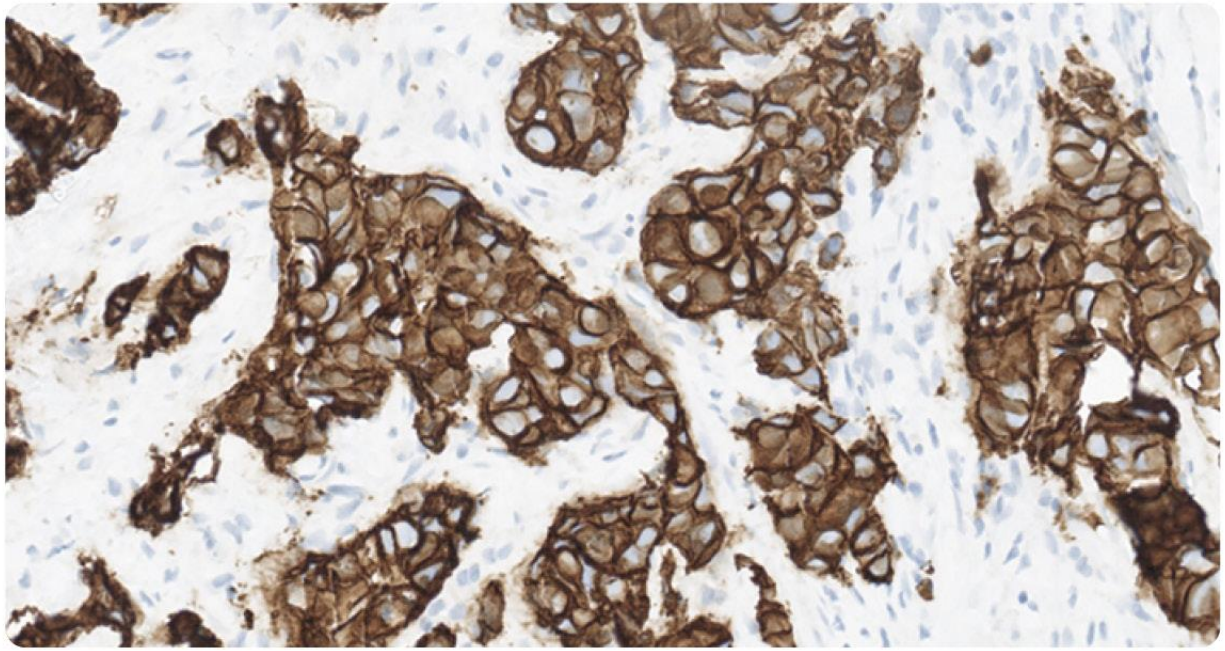
HER2-null

May be eligible for HER2-directed treatment

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

Please see Important Safety Information on pages 16-20 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

IHC 3+



Circumferential membrane staining that is complete, intense, and in >10% of tumor cells

mBC

Scoring and interpretation considerations in mBC

All levels of HER2 membrane staining in mBC should be scored following the same steps

1 Screen entire tissue at low magnification[50]

- Identify well-preserved areas and avoid areas of necrosis or crush artifact

2 Assess membrane staining pattern[2]:

- Incomplete/partial
- Complete/circumferential

AND

Assess staining intensity[2]:

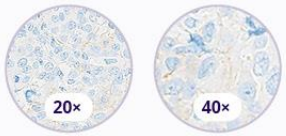
- Faint
- Weak to moderate
- Intense

3 Assess relative percentages of stained cells using established cutoffs[2]:

- 0%, no staining
- Less than or equal to 10%
- Greater than 10%

4 Use high magnification (40x) to discern faint, incomplete staining[50]

- Additional time may be needed to interpret and score cases with artifact, values near the 10% cutoff, and heterogeneous areas[50]
- Request a second pathologist review for cases with faint, incomplete staining of the membrane and percentage of tumor cells near the 10% threshold[42]



You may be asked to re-evaluate previous HER2 IHC 0 results to identify the presence of faint/barely perceptible, incomplete membrane staining in ≤10% of cells[1,2]

Important Safety Information

Warnings and Precautions

Interstitial Lung Disease / Pneumonitis (cont'd)

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

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).

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

Please see Important Safety Information on pages 16-20 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

The PATHWAY HER2 (4B5) CDx is clinically validated and FDA approved to detect HER2-low and HER2-ultralow mBC

The protocol and staining procedure is locked for HER2-low and HER2-ultralow, and there were no changes to the PATHWAY HER2 (4B5) CDx on market[2,42,50,51]

USE PATHWAY anti-HER2 (4B5) antibody + **ON** BenchMark ULTRA instrument + **WITH** the locked U PATHWAY HER2 4B5 staining procedure + **PER** 2023 ASCO-CAP HER2 testing scoring criteria ▶ **CLINICALLY VALIDATED** HER2-low and HER2-ultralow identification and reporting for HER2-directed treatment

Procedure type	Method
Staining Procedure	U PATHWAY HER2 4B5
Cell Conditioning	**ULTRA CC1, 36 minutes, Mild (95°C)**
Antibody (Primary)	**PATHWAY HER2 4B5 Ab– 12 minutes, 36°C** or Neg Ctl Rbt Ig– 12 minutes, 36°C
*ultra*View DAB Detection Kit	See Method Sheet for more information
Counterstain	Hematoxylin II, 4 minutes, 36°C
Post Counterstain	Bluing, 4 minutes, 36°C

- Use on-slide controls with a range of protein expression (including 1+) to help ensure the assay has an appropriate limit of detection[2]

The staining procedure is locked with a mild cell-conditioning step and a primary antibody incubation time of 12 minutes[42]

- U PATHWAY HER2 4B5 staining procedure should be used to assess HER2 in all breast cancer cases
- Deviations from the recommended cell conditioning or antibody incubation time may affect the HER2 score, particularly in cases with HER2-low and HER2-ultralow expression, which may impact treatment decisions

Intended use[42]

- PATHWAY anti-HER-2/neu (4B5) Rabbit Monoclonal Primary Antibody (PATHWAY anti-HER2 (4B5) antibody) is a rabbit monoclonal antibody intended for laboratory use for the semi-quantitative detection of HER2 antigen by immunohistochemistry (IHC) in sections of formalin-fixed, paraffin-embedded normal and neoplastic breast tissue using the *ultra*View Universal DAB Detection Kit on a BenchMark ULTRA instrument
- This IHC device is indicated for identifying breast cancer patients who are eligible for HER2-directed treatment (IHC 1+ or IHC 2+/ISH non-amplified and IHC 0 with membrane staining)
- This product should be interpreted by a qualified pathologist in conjunction with histological examination, relevant clinical information, and proper controls. This antibody is intended for in vitro diagnostic (IVD) use

Please see Important Safety Information on pages 16-20 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

Report any and all membrane staining

Report HER2-ultralow status by documenting IHC 0 score and faint/barely perceptible, incomplete membrane staining in ≤10% of cells[1,2]

- Update reporting templates or add a comment to existing reporting templates to highlight a patient's HER2-ultralow or HER2-low status by:
  - Adding the presence of faint/barely perceptible, incomplete membrane staining in ≤10% of cells
  - Utilizing the terms "HER2-ultralow" or "HER2-low"

Recommended reporting for HER2-ultralow[1,2,51]

HER2 by immunohistochemistry

- ✓ Negative (Score 0)
- ____ Negative (Score 1+)#
- ____ Equivocal (Score 2+)#
  Percentage of cells with uniform intense complete membrane staining: ____ %
- ____ Positive (Score 3+)
  Percentage of cells with uniform intense complete membrane staining: ____ %

Comment: Faint/barely perceptible, incomplete membrane staining in ≤10% of cells/HER2-ultralow

Recommended reporting for HER2-low[1,51]

HER2 by immunohistochemistry

- ____ Negative (Score 0)
- ✓ Negative (Score 1+)#
- ____ Equivocal (Score 2+)#
  Percentage of cells with uniform intense complete membrane staining: ____ %
- ____ Positive (Score 3+)
  Percentage of cells with uniform intense complete membrane staining: ____ %

Comment: HER2-low

Recommended comments for treating physician for low levels of HER2 expression[1,2,43]

Staining pattern	HER2 score	Recommended comments
No membrane staining observed	IHC 0 absent membrane staining	HER2-null
Faint/barely perceptible incomplete membrane staining in ≤10% of tumor cells	IHC 0 with membrane staining	HER2-ultralow
Incomplete membrane staining that is faint/barely perceptible and in >10% of tumor cells	IHC 1+	HER2-low
Weak to moderate complete membrane staining observed in >10% of tumor cells	IHC 2+/ISH–	HER2-low

Please see Important Safety Information on pages 16-20 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

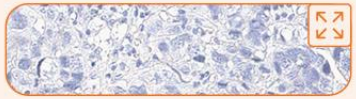
aGC

Test for HER2 using ASCO-CAP scoring criteria for gastric cancer in patients with aGC/GEJ adenocarcinoma

ASCO-CAP gastric cancer scoring criteria[1,3,48]

IHC 0

Surgical specimen



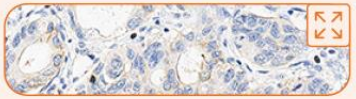
No reactivity or membranous reactivity in <10% of tumor cells

Biopsy specimen

No reactivity or in any tumor cells

IHC 1+

Surgical specimen



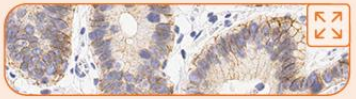
Faint or barely perceptible membranous reactivity in ≥10% of tumor cells; cells are reactive only in part of their membrane

Biopsy specimen

Tumor cell cluster[a] with faint or barely perceptible membranous reactivity irrespective of percentage of tumor cells stained

IHC 2+

Surgical specimen



Weak to moderate complete, basolateral, or lateral membranous reactivity in ≥10% of tumor cells

Biopsy specimen

Tumor cell cluster[a] with weak to moderate complete, basolateral, or lateral membranous reactivity irrespective of percentage of tumor cells stained

IHC 3+

Surgical specimen

Strong complete, basolateral, or lateral membranous reactivity in ≥10% of tumor cells

Biopsy specimen

Tumor cell cluster[a] with strong complete, basolateral, or lateral membranous reactivity irrespective of percentage of tumor cells stained

Negative | *Equivocal: Reflex ISH test* | *Positive*

IHC 1+ or IHC 2+/ISH− → **HER2-negative**

IHC 2+/ISH+ or IHC 3+ → **HER2-positive**

May be eligible for HER2-directed treatment

Unlike in breast cancer, complete circumferential membranous staining is not required for HER2-positive status, as basolateral (U-shaped) or lateral expression patterns are more typical in HER2-positive gastric cancer[2,3]

[a]Tumor cell cluster is defined as a cluster of 5 or more tumor cells.[3]

Please see Important Safety Information on pages 16-20 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

aGC

Test for HER2 using ASCO-CAP scoring criteria for gastric cancer in patients with aGC/GEJ adenocarcinoma

ASCO-CAP gastric cancer scoring criteria[1,3,48]

Surgica

No reactivity or
reactivity in <10

Biopsy

No reactivity or

ecimen

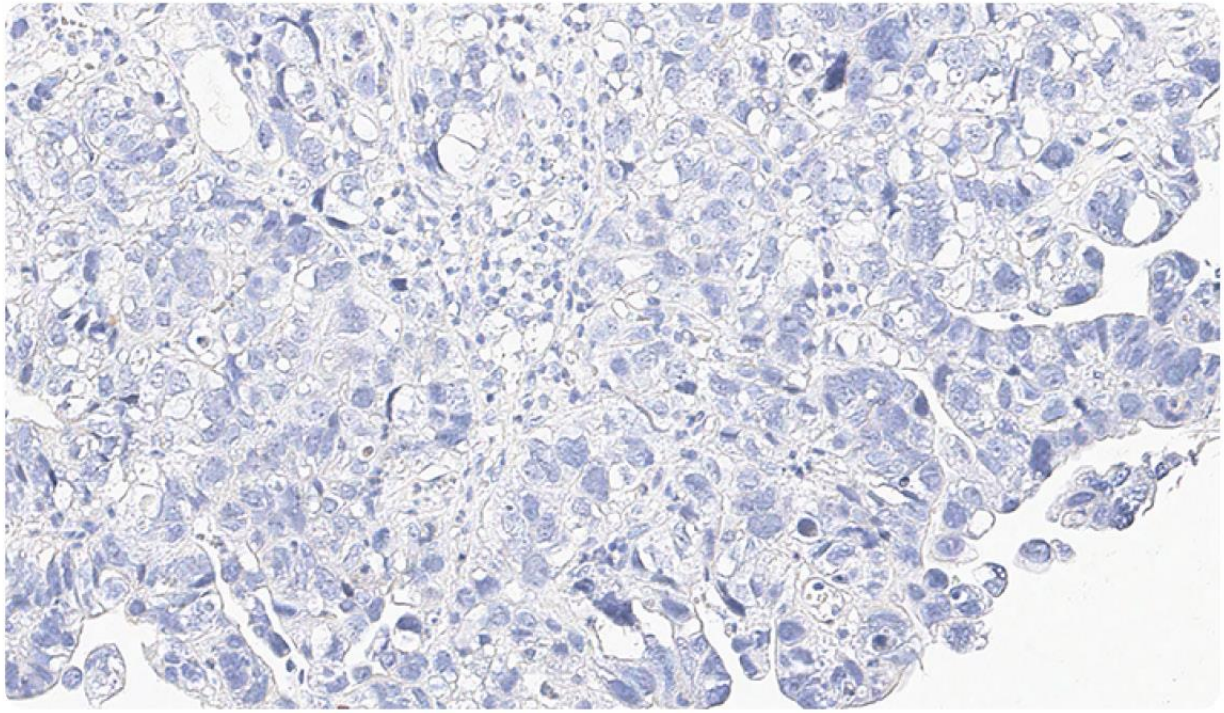
solateral, or
reactivity in

cimen

with strong
al, or lateral
vity
ntage
ed

treatment

IHC 0



Unlike in breast cancer, complete circumferential membranous staining is not required for HER2-positive status, as basolateral (U-shaped) or lateral expression patterns are more typical in HER2-positive gastric cancer[2,3]

[a]Tumor cell cluster is defined as a cluster of 5 or more tumor cells.[3]

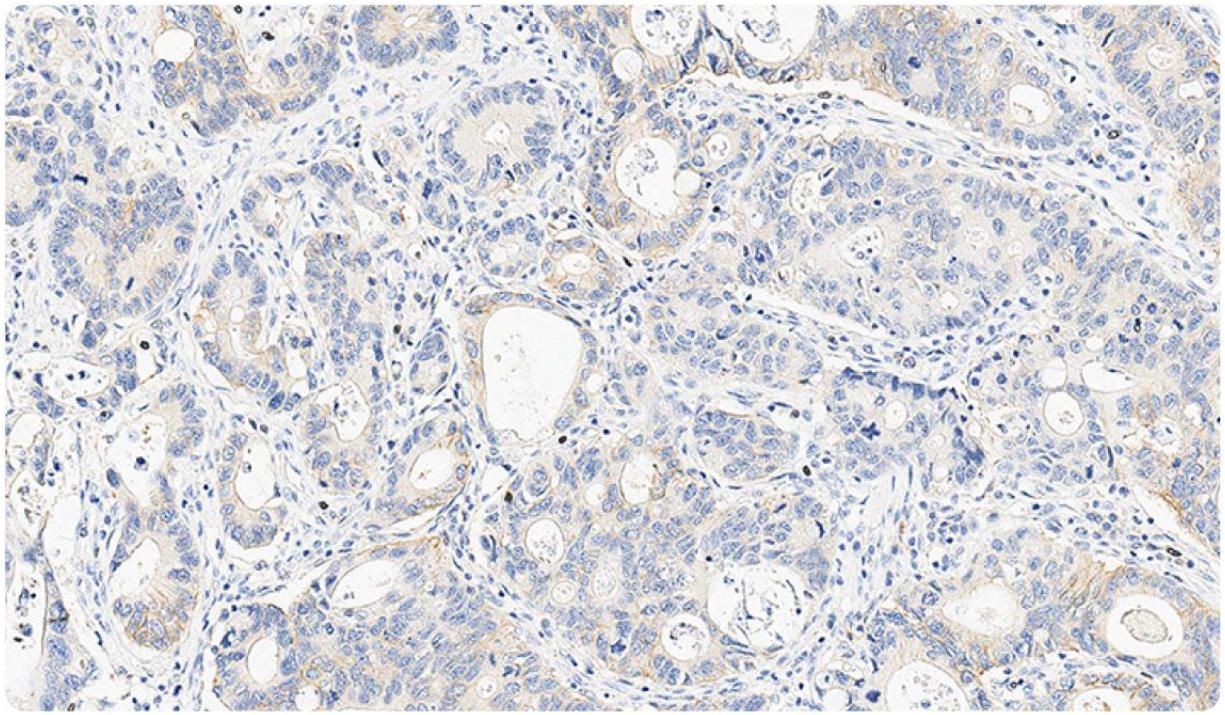
Please see Important Safety Information on pages 16-20 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

aGC

Test for HER2 using ASCO-CAP scoring criteria for gastric cancer in patients with aGC/GEJ adenocarcinoma

ASCO-CAP gastric cancer scoring criteria[1,3,48]

IHC 1+



Unlike in breast cancer, complete circumferential membranous staining is not required for HER2-positive status, as basolateral (U-shaped) or lateral expression patterns are more typical in HER2-positive gastric cancer[2,3]

[a]Tumor cell cluster is defined as a cluster of 5 or more tumor cells.[3]

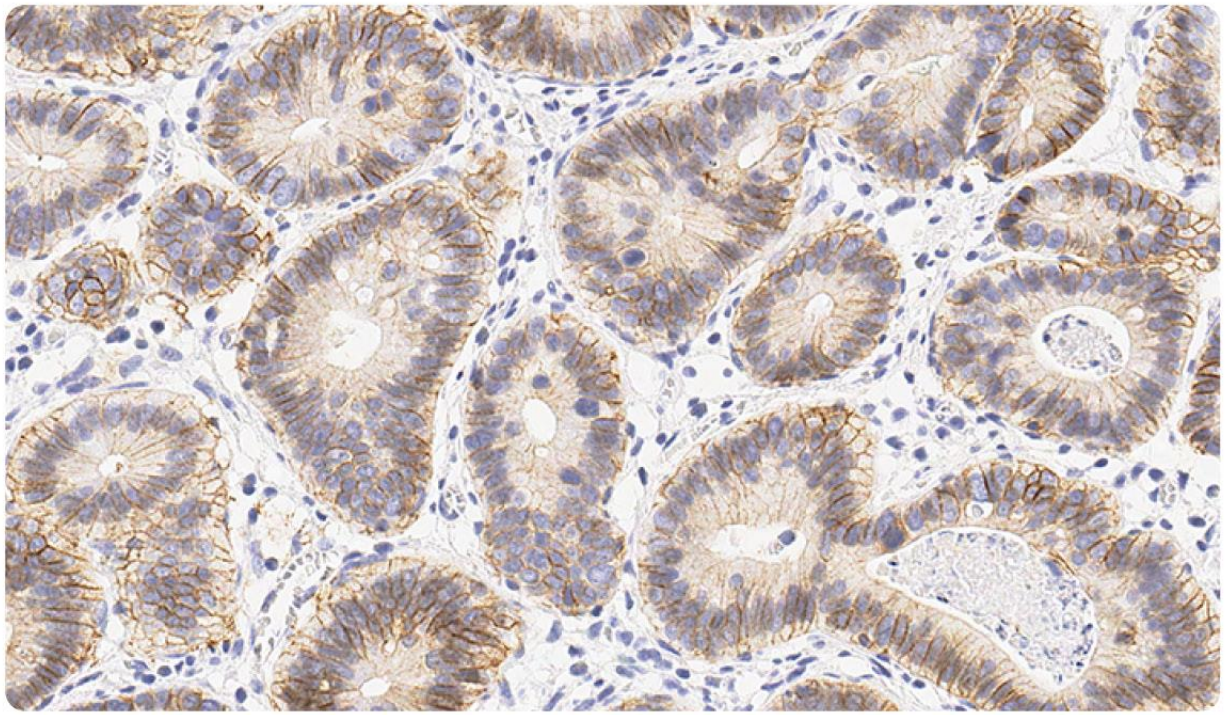
Please see Important Safety Information on pages 16-20 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

aGC

Test for HER2 using ASCO-CAP scoring criteria for gastric cancer in patients with aGC/GEJ adenocarcinoma

ASCO-CAP gastric cancer scoring criteria[1,3,48]

IHC 2+



Unlike in breast cancer, complete circumferential membranous staining is not required for HER2-positive status, as basolateral (U-shaped) or lateral expression patterns are more typical in HER2-positive gastric cancer[2,3]

[a]Tumor cell cluster is defined as a cluster of 5 or more tumor cells.[3]

Please see Important Safety Information on pages 16-20 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

aGC

Test for HER2 using ASCO-CAP scoring criteria for gastric cancer in patients with aGC/GEJ adenocarcinoma

ASCO-CAP gastric cancer scoring criteria[1,3,48]

Surgica

No reactivity or
reactivity in <10

Biopsy

No reactivity or

ecimen

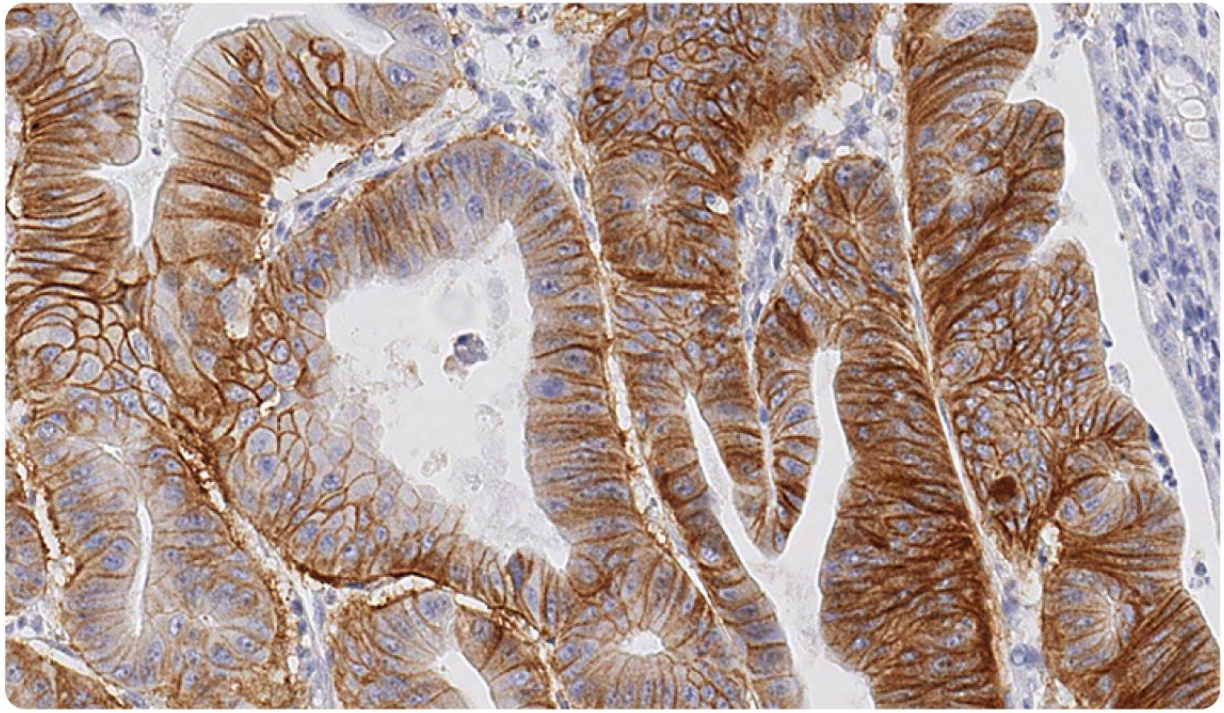
solateral, or
reactivity in

cimen

with strong
al, or lateral
vity
ntage
ed

treatment

IHC 3+ (Surgical specimen)



Unlike in breast cancer, complete circumferential membranous staining is not required for HER2-positive status, as basolateral (U-shaped) or lateral expression patterns are more typical in HER2-positive gastric cancer[2,3]

[a]Tumor cell cluster is defined as a cluster of 5 or more tumor cells.[3]

Please see Important Safety Information on pages 16-20 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

aGC

Test for HER2 using ASCO-CAP scoring criteria for gastric cancer in patients with aGC/GEJ adenocarcinoma

ASCO-CAP gastric cancer scoring criteria[1,3,48]

Surgica

No reactivity or
reactivity in <10

Biopsy

No reactivity or

ecimen

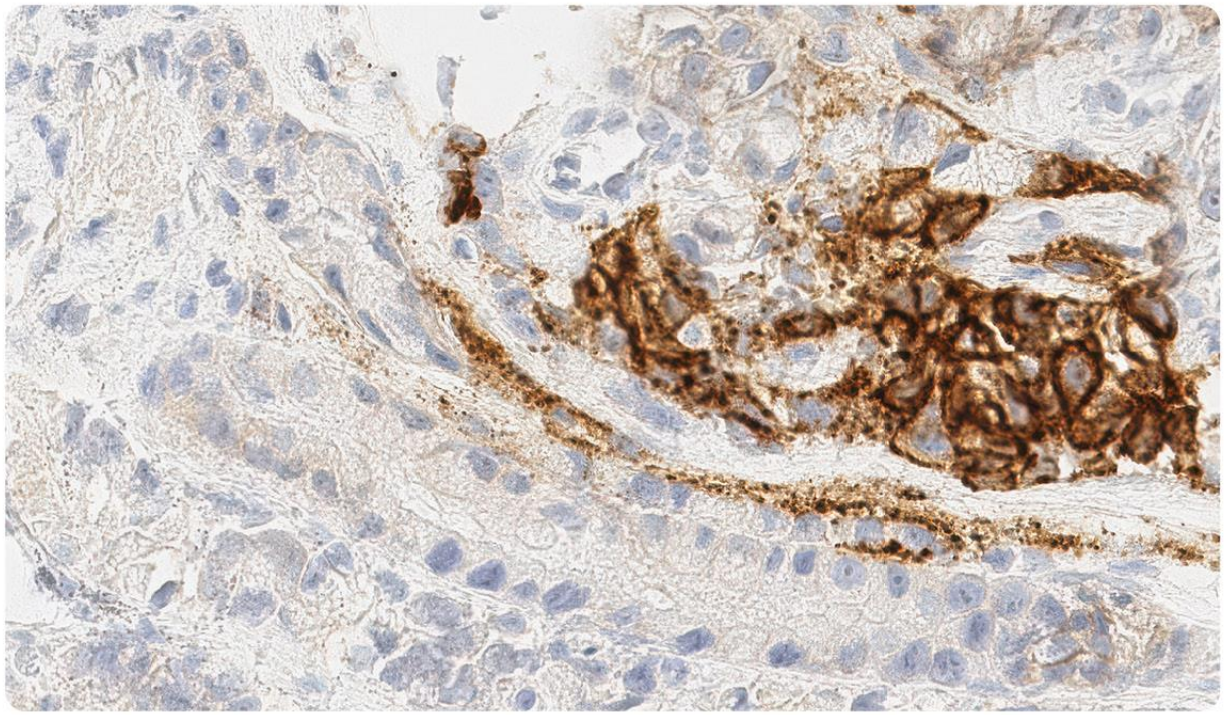
solateral, or
reactivity in

cimen

with strong
al, or lateral
vity
ntage
ed

treatment

IHC 3+ (Biopsy specimen)



Unlike in breast cancer, complete circumferential membranous staining is not required for HER2-positive status, as basolateral (U-shaped) or lateral expression patterns are more typical in HER2-positive gastric cancer[2,3]

[a]Tumor cell cluster is defined as a cluster of 5 or more tumor cells.[3]

Please see Important Safety Information on pages 16-20 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

aGC

Scoring and interpretation considerations in aGC/GEJ adenocarcinoma

Surgical specimen[3]

- When possible, select the tissue block with the areas of lowest grade of intestinal morphology
  - More than 1 tissue block may be selected if different morphologic patterns are present
- Use 4 µm thick paraffin sections unless the kit specifies another thickness
- Work with surgeons, nurses, and operating room personnel to minimize cold ischemic time and facilitate appropriate handling

Biopsy specimen[3,52]

- Testing multiple biopsy samples is preferable to account for increased heterogeneity in gastric tumors—defined as <30% of tumor cells staining positive or only focal staining of tumor cell
  - A minimum of 5 biopsy specimens and, optimally, 6-8, should be obtained
- Communicate with gastroenterology colleagues to ensure prompt fixation and documentation—immediately place into formalin in the endoscopy suite

Consider retesting if IHC is 2+ and ISH is inconclusive[3,a]

ASCO-CAP UPDATE

In 2016, ASCO-CAP developed guidelines to address the important nuances of HER2 expression, scoring, and outcomes in gastric cancer[3]

- Compared to breast, gastric tumors have:
  - Greater intratumoral heterogeneity
  - Lower incidence of complete membrane staining
  - Frequent basolateral patterns of HER2 expression

[a]Inconclusive ISH is defined as an average of ≥3 CEP17 signals with a ratio of <2 and 4 to 6 HER2 signals, not resolved by scoring an additional 20 cells in a different target area.[3]

Please see Important Safety Information on pages 16-20 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

HER2 ALTERATIONS | BREAST CANCER | GASTRIC CANCER | METASTATIC SOLID TUMORS | mNSCLC | PRE-ANALYTICS & REPORTING | ISI | ABBREVIATIONS & REFERENCES | SUMMARY | PI

9

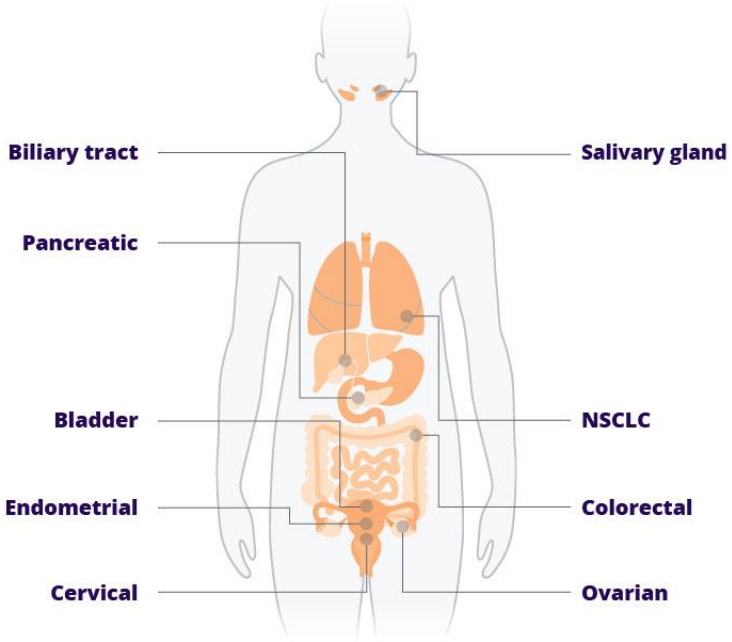
Metastatic Solid Tumors

Perform HER2 IHC testing in all metastatic solid tumors

HER2-positive (IHC 3+) is actionable across metastatic solid tumors due to a tumor-agnostic indication for HER2-directed treatment that is FDA approved under accelerated approval[1,47,53]

- A tumor-agnostic therapy is a type of targeted treatment that is used to treat all solid tumors with the targeted biomarker without regard to where in the body the tumor originated

The clinical relevance of HER2+ (IHC 3+) was evaluated across 3 clinical trials[a] in the following tumor types[1,47]:

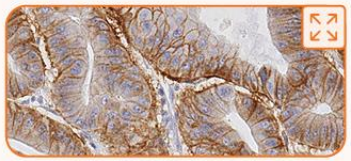


and other rare tumor types

ASCO-CAP gastric cancer scoring criteria were used in 3 clinical trials[a] across metastatic solid tumors (outside of breast cancer)[45-47]

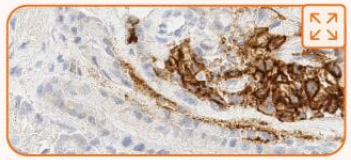
- Refer to page 8 for full gastric scoring criteria

ASCO-CAP Gastric Cancer Scoring Criteria for IHC 3+[1,3,48]



Surgical specimen

Strong complete, basolateral, or lateral membranous reactivity in ≥10% of tumor cells



Biopsy specimen

Tumor cell cluster[b] with strong complete, basolateral, or lateral membranous reactivity irrespective of percentage of tumor cells stained

HER2-positive (IHC 3+)

May be eligible for HER2-directed treatment

ASCO-CAP guidelines for gastric cancer were used to assess HER2 IHC status in DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02[3,45-47]

[a]DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02.[1]
[b]Tumor cell cluster is defined as a cluster of 5 or more tumor cells.[3]

Please see Important Safety Information on pages 16-20 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

Metastatic Solid Tumors

Perform HER2 IHC testing in all metastatic solid tumors

HER2-positive (IHC 3+) is actionable across metastatic solid tumors due to a tumor-agnostic indication for HER2-directed treatment that is FDA approved under accelerated approval[1,47,53]

- A tumor-agnostic therapy is a type of targeted treatment that is used to treat all solid tumors with the targeted biomarker without regard to where in the body the tumor originated

The clinical re… used in across 3 clinic…

Biliary tra…

Pancreat…

Bladd…

Endometri…

Cervic…

…or IHC 3+[1,3,48]

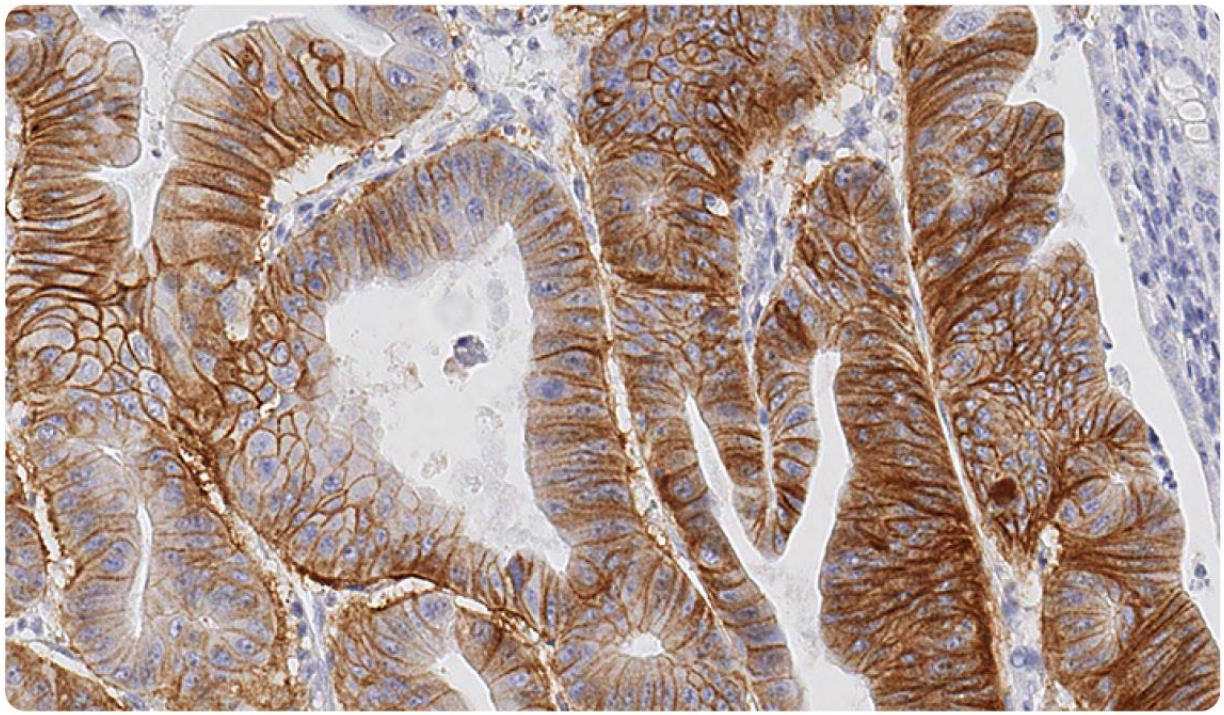
…n

…basolateral, or …ous reactivity in …lls

…[b] with strong …eral, or …ous reactivity …rcentage of …d

…ment

Surgical specimen



…ASCO-CAP guidelines for gastric cancer were used to assess HER2 IHC status in DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02[3,45-47]

[a]DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02.[1]
[b]Tumor cell cluster is defined as a cluster of 5 or more tumor cells.[3]

Please see Important Safety Information on pages 16-20 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

Metastatic Solid Tumors

Perform HER2 IHC testing in all metastatic solid tumors

HER2-positive (IHC 3+) is actionable across metastatic solid tumors due to a tumor-agnostic indication for HER2-directed treatment that is FDA approved under accelerated approval[1,47,53]

- A tumor-agnostic therapy is a type of targeted treatment that is used to treat all solid tumors with the targeted biomarker without regard to where in the body the tumor originated

The clinical re… across 3 clinic… …used in …

Biliary tra…

Pancreat…

Bladd…

Endometri…

Cervic…

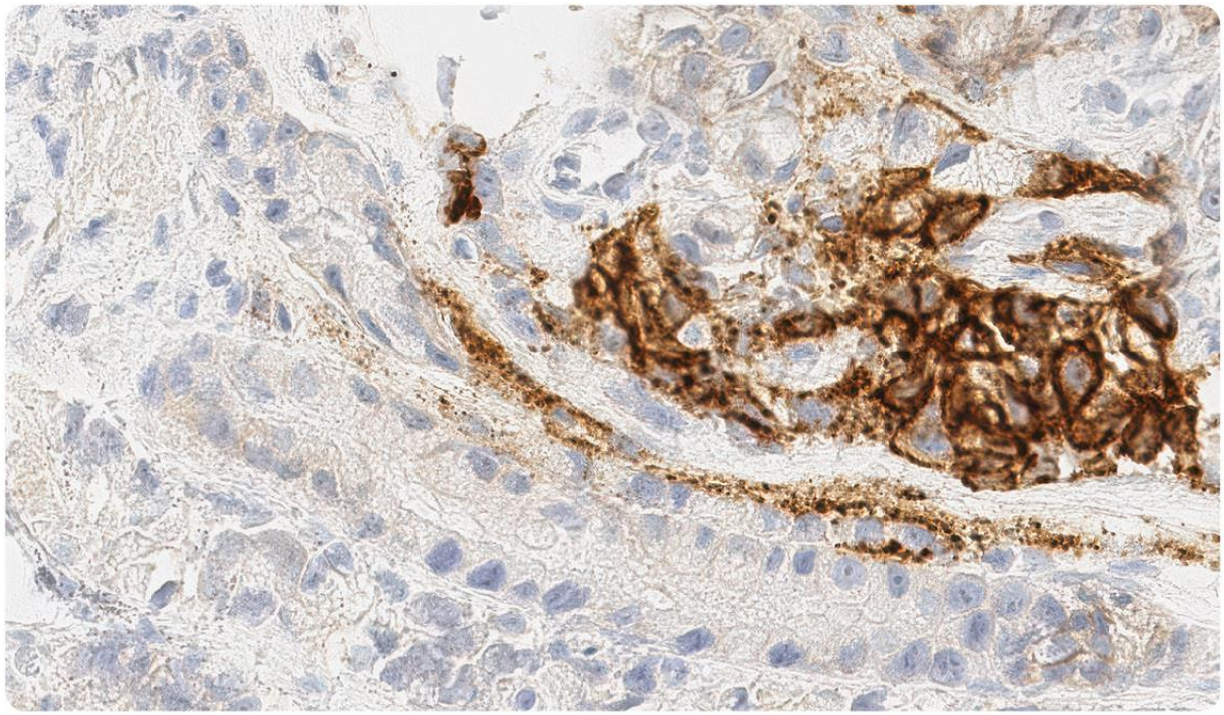
…or IHC 3+[1,3,48]

…basolateral, or …ous reactivity in …lls

…[b] with strong …eral, or …ous reactivity …rcentage of …d

…ment

Biopsy specimen



…ASCO-CAP guidelines for gastric cancer were used to assess HER2 IHC status in DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02[3,45-47]

[a]DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02.[1]
[b]Tumor cell cluster is defined as a cluster of 5 or more tumor cells.[3]

Please see Important Safety Information on pages 16-20 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

Metastatic Solid Tumors

Scoring and interpretation considerations in metastatic solid tumors

Consider applying the ASCO-CAP gastric scoring criteria to metastatic solid tumors, as employed in the clinical trial setting[2,3,48,a]

Breast criteria

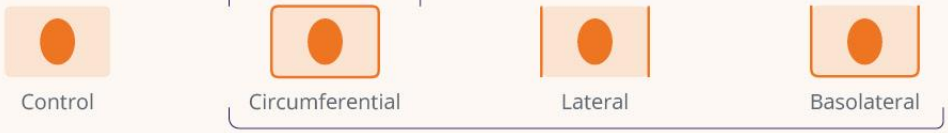
Circumferential membrane staining that is complete, intense, and in >10% of tumor cells

VS

Gastric criteria

Strong, complete basolateral or lateral membranous reactivity in ≥10% of tumor cells

Staining patterns required for IHC 3+ with each set of scoring criteria



In DESTINY-PanTumor02, tissue samples were[48,54]:

- Acquired from non-target lesions, if feasible
- Collected via a core needle (excisional or incisional tumor biopsy samples were also accepted)
- Not more than 3 years old from the time of the biopsy or resection/excision, but preferably no older than 1 year
- More than 100 tumor cells/section for resection specimen and at least 1 tumor cell cluster (defined as a cluster of ≥5 tumor cells) for biopsy specimen

Fine needle aspirations are also acceptable samples for IHC testing[3]

Your oncology team may request that you test archived tissue to identify potentially eligible patients for HER2-targeted treatment[3,54]

- If archived tissue is not available, consider re-biopsy, if feasible, to obtain fresh tissue for HER2 IHC testing

HER2 IHC is part of the CAP Biomarkers Reporting Templates for breast, gastric, colorectal, gynecological, head and neck, and lung specimens[51,55-59]

- For other tumor types, the CAP General IHC Quantitative Biomarkers Template is available[60]

Make HER2 IHC testing a standard part of your initial biomarker workup across solid tumors[1]

[a]DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02.[1]

Please see Important Safety Information on pages 16-20 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

mNSCLC

Perform HER2 IHC and NGS testing to detect 2 distinct HER2 alterations in mNSCLC[1,40]

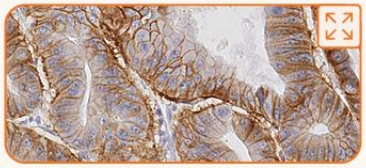
HER2 IHC testing can detect HER2-positive (IHC 3+) mNSCLC[1,45]

- ASCO-CAP gastric cancer scoring criteria were used to identify patients with HER2+ (IHC 3+) tumors in the DESTINY-Lung01 trial

NGS testing can detect *HER2 (ERBB2)*-mutant mNSCLC[1,29,40,61]

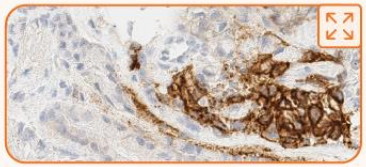
- NGS testing is the recommended method for efficiently utilizing limited biopsy tissue while maximizing diagnostic genomic information
- Sanger sequencing and targeted PCR techniques can also be utilized

ASCO-CAP Gastric Cancer Scoring Criteria for IHC 3+[1,3,48]



Surgical specimen

Strong complete, basolateral, or lateral membranous reactivity in ≥10% of tumor cells



Biopsy specimen

Tumor cell cluster[a] with strong complete, basolateral, or lateral membranous reactivity irrespective of percentage of tumor cells stained

HER2-positive (IHC 3+)

May be eligible for HER2-directed treatment

HER2 (ERBB2) mutations[1,62]

Report summary

Tier 1: Variants of strong clinical significance

VARIANT	CLINICAL IMPACT
ERBB2	**Associated with sensitivity to HER2-directed therapy**

HER2 (ERBB2) mutations are not associated with HER2-positive (IHC 3+) status

- In study of 1126 patients with NSCLC, none were both *HER2 (ERBB2)*-mutant and HER2-positive (IHC 3+)[b]

HER2 (ERBB2)-mutant

May be eligible for HER2-directed treatment

Both HER2 IHC testing and NGS testing are needed to identify actionable HER2 alterations in mNSCLC[1,40]

[a]Tumor cell cluster is defined as a cluster of five or more tumor cells.[3]
[b]From February 2015 to December 2016, a prospective analysis screened 1126 patients with advanced NSCLC to determine the frequency of patients with HER2-aberrant NSCLC tumors. HER2 was defined as positive if there was an IHC score of 3+, both an IHC score of 2+ and a positive FISH result, or if there were exon 20 insertion mutations in the HER2 gene.[62]

Please see Important Safety Information on pages 16-20 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

Perform HER2 IHC and NGS testing to detect 2 distinct HER2 alterations in mNSCLC[1,40]

HER2 IHC testing can detect HER2-positive (IHC 3+) mNSCLC[1,45]

- ASCO
  patie

NGS testing can detect *HER2 (ERBB2)*-mutant mNSCLC[1,29,40,61]

y utilizing
enomic

n also be utilized

ASCO-CA

ed therapy

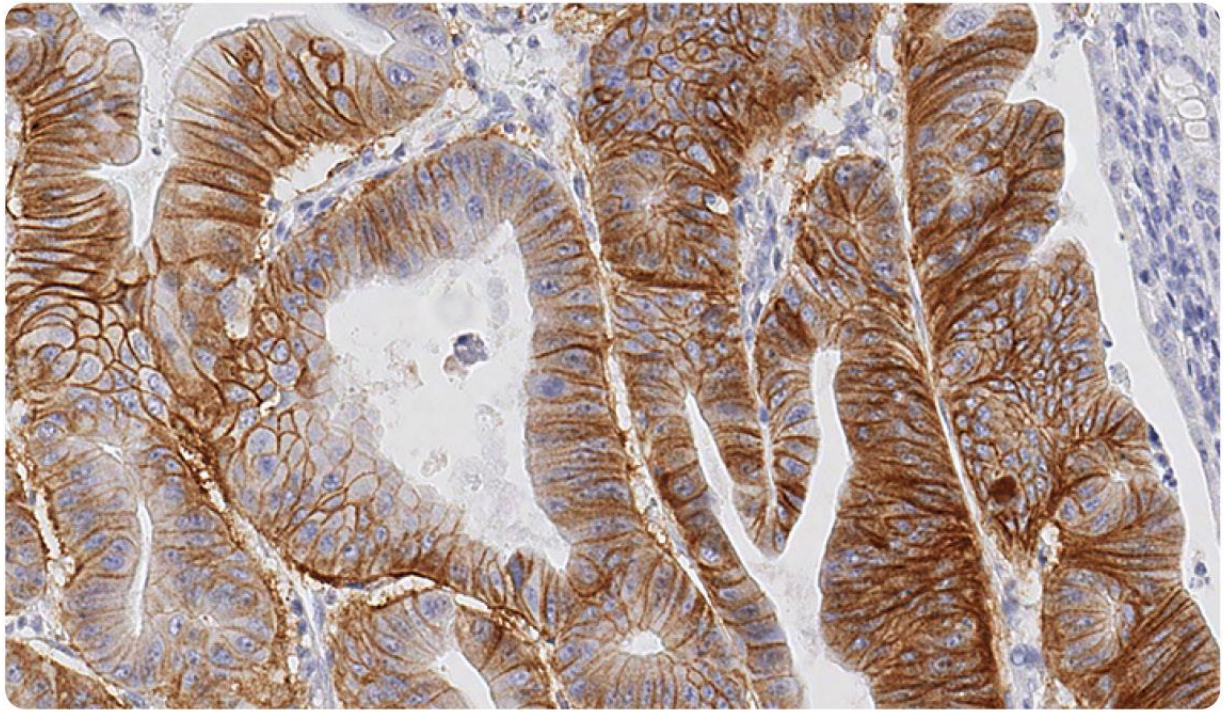
(IHC 3+) status

May

ent

Both HER2 IHC testing and NGS testing are needed to identify actionable HER2 alterations in mNSCLC

Surgical specimen



[a]Tumor cell cluster is defined as a cluster of five or more tumor cells.[3]
[b]From February 2015 to December 2016, a prospective analysis screened 1126 patients with advanced NSCLC to determine the frequency of patients with HER2-aberrant NSCLC tumors. HER2 was defined as positive if there was an IHC score of 3+, both an IHC score of 2+ and a positive FISH result, or if there were exon 20 insertion mutations in the HER2 gene.[62]

Please see Important Safety Information on pages 16-20 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

mNSCLC

Perform HER2 IHC and NGS testing to detect 2 distinct HER2 alterations in mNSCLC[1,40]

HER2 IHC testing can detect HER2-positive (IHC 3+) mNSCLC[1,45]

- ASCO
  patie

NGS testing can detect *HER2 (ERBB2)*-mutant mNSCLC[1,29,40,61]

y utilizing
enomic

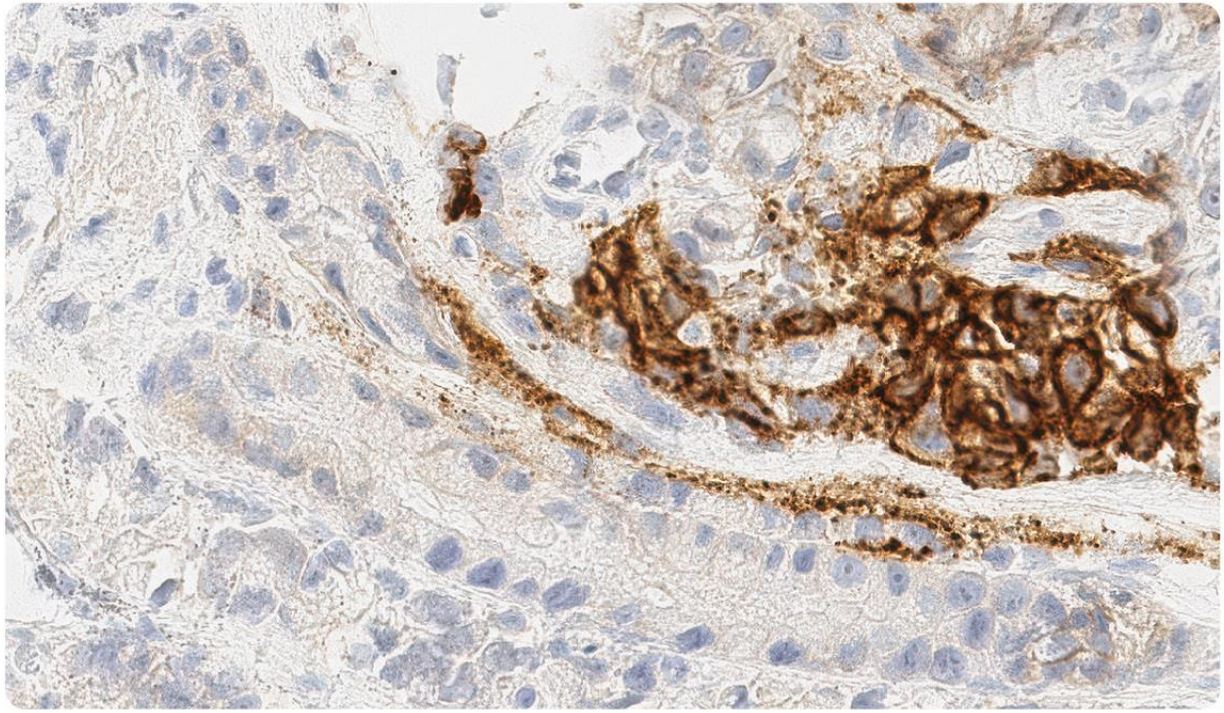
n also be utilized

ASCO-CA

ed therapy

(IHC 3+) status

Biopsy specimen



Both HER2 IHC testing and NGS testing are needed to identify actionable HER2 alterations in mNSCLC

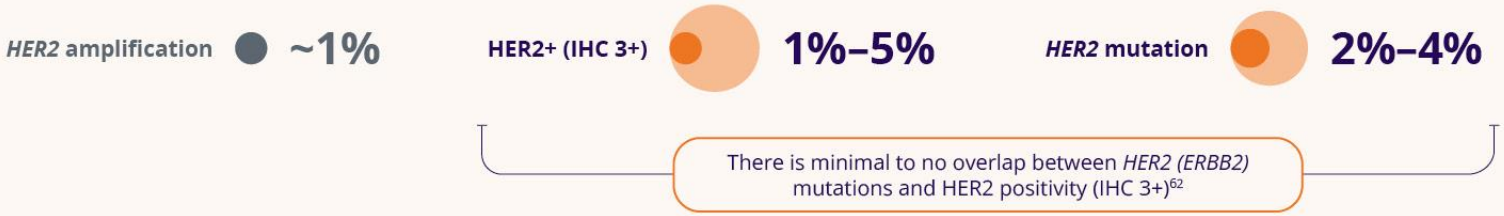
[a]Tumor cell cluster is defined as a cluster of five or more tumor cells.[3]
[b]From February 2015 to December 2016, a prospective analysis screened 1126 patients with advanced NSCLC to determine the frequency of patients with HER2-aberrant NSCLC tumors. HER2 was defined as positive if there was an IHC score of 3+, both an IHC score of 2+ and a positive FISH result, or if there were exon 20 insertion mutations in the HER2 gene.[62]

Please see Important Safety Information on pages 16-20 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

Scoring and interpretation considerations in mNSCLC

HER2-positive (IHC 3+) status, *HER2 (ERBB2)* amplifications, and *HER2 (ERBB2)* mutations can occur independently and at different levels of prevalence in NSCLC[6,26-29,62,63]

HER2+ (IHC 3+) can still occur in the absence of a positive *HER2 (ERBB2)* amplification result detected via NGS/ISH testing[26]



There is minimal to no overlap between *HER2 (ERBB2)* mutations and HER2 positivity (IHC 3+)[62]

ASCO-CAP gastric scoring criteria were used in DESTINY-Lung01 to identify HER2+ (IHC 3+) in mNSCLC[2,3,45]

- Unlike breast cancer, complete circumferential membranous staining is not required for HER2-positive status in gastric cancer. Instead, basolateral (U-shaped) or lateral expression patterns are more typical in HER2-positive gastric cancer
- Refer to page 8 for gastric scoring criteria

Use tissue and liquid/ctDNA as complementary sample types to identify *HER2 (ERBB2)* mutations via NGS[40]

- Concurrent testing can reduce turnaround time and increase yield of targetable alteration detection[40]
  - Testing with ctDNA can significantly reduce turnaround time for results[64]
- Positive results with liquid biopsy are sufficient to confirm *HER2* mutations[65]
- If no mutation is detected with plasma, tumor tissue should be tested[1]

For mNSCLC patients, work with your MDT to ensure sufficient tissue is collected for both NGS and IHC testing[3]

- Surgical resection and biopsy specimens are preferred for HER2 IHC testing
- Fine needle aspirations/cytology specimens are acceptable alternatives for HER2 IHC testing

Report both HER2-positive (IHC 3+) results from IHC and *HER2 (ERBB2)* mutation results from NGS[55]

- CAP confirms that each HER2 alteration is independently associated with response to HER2-directed therapy
- The CAP NSCLC biomarker reporting template includes fields for reporting HER2 IHC results and *HER2 (ERBB2)* NGS results

Please see Important Safety Information on pages 16-20 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

Across Tumor Types

Standardize HER2 IHC testing by adopting best practices across all solid tumors

Pre-analytic variables of tissue samples are important to consider, as they may impact HER2 staining and subsequent scoring[2,3,51,66]

Cold ischemia time

- Prolonged cold ischemia time may lead to false-negative IHC results
- Tissue acquisition to fixation time should be as short as possible
  - Specimens ideally should be placed in fixative within 1 hour

Incorrect fixation

- Specimens must be fixed in sufficient volume of 10% neutral buffered formalin for ≥6 hours
- Prolonged fixation in formalin (>1 week) or fixation in non-formalin fixatives may cause failure to obtain ISH results
- Procedures or fixation involving acid (eg, decalcification) may degrade DNA and affect tissue immunoreactivity

Inadequate tissue sample

- Thinner sections can yield greater sampling error and less intense counterstain
  - Small sample size may lead to false-negative results if tumor heterogeneity is present
- Thicker sections can lead to the presence of overlapping nuclei and more difficulty with deparaffinization, protease digestion, and probe or detection reagent dispersion

Improper antibody titration

- Overconcentrated solution can cause overstaining, which may lead to false-positive IHC results

Revise reflexive protocols for new patients to add HER2 IHC testing for all solid tumors, including mNSCLC, and NGS testing for mNSCLC[1,40]

Please see Important Safety Information on pages 16-20 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

Across Tumor Types

Clearly report HER2 alterations and corresponding actionability for ENHERTU

Your pathology report should contain this information to determine eligibility for ENHERTU:

- Numerical IHC score
- IHC status (positive or negative)
- Staining pattern/percent
- Scoring criteria (ASCO-CAP Breast, ASCO-CAP Gastric, Other)
- Method (test name)
- Antibody used
- *HER2 (ERBB2)* mutation results (if applicable)

HER2 IHC scores must be reported as part of any comprehensive biomarker analysis report, along with *HER2 (ERBB2)* mutation results in mNSCLC[51,55]

- If a score cannot be determined, note the reason, such as inadequate specimen handling, presence of artifacts (crush or edge) that make interpretation difficult, or failure of analytic testing

Important Safety Information

Warnings and Precautions

Neutropenia

Severe neutropenia, including febrile neutropenia, can occur in patients treated with ENHERTU. Monitor complete blood counts prior to initiation of ENHERTU and prior to each dose, and as clinically indicated. For Grade 3 neutropenia (Absolute Neutrophil Count [ANC] <1.0 to 0.5 x 10^9/L), interrupt ENHERTU until resolved to Grade 2 or less, then maintain dose. For Grade 4 neutropenia (ANC <0.5 x 10^9/L), interrupt ENHERTU until resolved to Grade 2 or less, then reduce dose by 1 level. For febrile neutropenia (ANC <1.0 x 10^9/L and temperature >38.3° C or a sustained temperature of ≥38° C for more than 1 hour), interrupt ENHERTU until resolved, then reduce dose by 1 level.

HER2-Positive, HER2-Low, and HER2-Ultralow 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.

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

Please see Important Safety Information on pages 16-20 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

Indications and Important Safety Information

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).

Please see accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

Indications and Important Safety Information (cont'd)

Warnings and Precautions (cont'd)
Neutropenia
Severe neutropenia, including febrile neutropenia, can occur in patients treated with ENHERTU. Monitor complete blood counts prior to initiation of ENHERTU and prior to each dose, and as clinically indicated. For Grade 3 neutropenia (Absolute Neutrophil Count [ANC] <1.0 to 0.5 x 10^9/L), interrupt ENHERTU until resolved to Grade 2 or less, then maintain dose. For Grade 4 neutropenia (ANC <0.5 x 10^9/L), interrupt ENHERTU until resolved to Grade 2 or less, then reduce dose by 1 level. For febrile neutropenia (ANC <1.0 x 10^9/L and temperature >38.3° C or a sustained temperature of ≥38° C for more than 1 hour), interrupt ENHERTU until resolved, then reduce dose by 1 level.

HER2-Positive, HER2-Low, and HER2-Ultralow 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.

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%).

Please see accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

Indications and Important Safety Information (cont'd)

Adverse Reactions (cont'd)

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. 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%).

Please see accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

Indications and Important Safety Information (cont'd)

Adverse Reactions (cont'd)

HER2-Mutant Unresectable or Metastatic NSCLC (5.4 mg/kg)

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

The safety of ENHERTU was evaluated in 101 patients with HER2-mutant unresectable or metastatic NSCLC who received ENHERTU 5.4 mg/kg intravenously once every 3 weeks until disease progression or unacceptable toxicity in DESTINY-Lung02. 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.

Please see accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

Indications and Important Safety Information (cont'd)

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

Use in Specific Populations

- **Pregnancy:** ENHERTU can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risks to a fetus. There are clinical considerations if ENHERTU is used in pregnant women, or if a patient becomes pregnant within 7 months after the last dose of ENHERTU.
- **Lactation:** There are no data regarding the presence of ENHERTU in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with ENHERTU and for 7 months after the last dose.
- **Females and Males of Reproductive Potential:** Pregnancy testing: Verify pregnancy status of females of reproductive potential prior to initiation of ENHERTU. Contraception: *Females*: ENHERTU can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with ENHERTU and for 7 months after the last dose. *Males*: Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for 4 months after the last dose. Infertility: ENHERTU may impair male reproductive function and fertility.
- **Pediatric Use:** Safety and effectiveness of ENHERTU have not been established in pediatric patients.
- **Geriatric Use:** 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.

Please see accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

Abbreviations and References

Abbreviations

aGC, advanced gastric cancer; ASCO, American Society of Clinical Oncology; BC, breast cancer; CAP, College of American Pathologists; CDx, companion diagnostics; CEP17, centromeric region of chromosome 17; ctDNA, circulating tumor DNA; *ERBB2*, erb-b2 receptor tyrosine kinase 2; FISH, fluorescence in situ hybridization; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; MDT, multidisciplinary team; mNSCLC, metastatic non-small cell lung cancer; NCCN, National Comprehensive Cancer Network® (NCCN®); NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; PCR, polymerase chain reaction.

References

1. ENHERTU. Prescribing Information. Daiichi Sankyo, Inc.; 2025. **2.** Wolff AC, Somerfield MR, Dowsett M, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology-College of American Pathologists guideline update. *Arch Pathol Lab Med*. 2023;147(9):993-1000. **3.** Bartley AN, Washington MK, Colasacco C, et al. HER2 testing and clinical decision making in gastroesophageal adenocarcinoma: guideline from the College of American Pathologists, American Society for Clinical Pathology, and the American Society of Clinical Oncology. *J Clin Oncol*. 2017;35(4):446-464. **4.** Morsberger L, Pallavajjala A, Long P, et al. HER2 amplification by next-generation sequencing to identify HER2-positive invasive breast cancer with negative HER2 immunohistochemistry. *Cancer Cell Int*. 2022;22(1):350. **5.** Ren S, Wang J, Ying J, et al. Consensus for HER2 alterations testing in non-small-cell lung cancer [published correction appears in *ESMO Open*. 2022;7(3):100482]. *ESMO Open*. 2022;7(1):100395. Published online February 8, 2022. doi:10.1016/j.esmoop.2022.100395 **6.** 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. **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.** 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. **9.** Chou A, Waddell N, Cowley MJ, et al. Clinical and molecular characterization of HER2 amplified-pancreatic cancer. *Genome Med*. 2013;5(8):78. **10.** 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. **11.** Subasinghe D, Acott N, Mahesh PKB, et al. Human epidermal growth factor receptor-2 gene expression positivity determined by silver in situ hybridization/immunohistochemistry methods and associated factors in a cohort of Sri Lankan patients with gastric adenocarcinoma: a prospective study. *J Int Med Res*. 2023;51(2):3000605231154403. doi:10.1177/03000605231154403 **12.** Gao X, Zhao L, Zhang N, et al. Impact of HER2 on prognosis and benefit from adjuvant chemotherapy in stage II/III gastric cancer patients: a multicenter observational study. *Int J Surg*. 2023;109(5):1330-1341. **13.** 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. **14.** 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. **15.** 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. **16.** 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. **17.** 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. **18.** 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. **19.** 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. **20.** 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. **21.** 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. **22.** 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. **23.** 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. **24.** Tarantino P, Hamilton E, Tolaney S, et al. HER2-low breast cancer: pathological and clinical landscape. *J Clin Oncol*. 2020;38(17):1951-1962. **25.** 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 13-17, 2024; Barcelona, Spain. **26.** 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. **27.** 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. **28.** 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. **29.** Zhao J, Xia Y. Targeting HER2 alterations in non–small-cell lung cancer: a comprehensive review. *JCO Precis Oncol*. 2020;4:411-425. doi:10.1200/PO.19.00333 **30.** Heppner BI, Behrens H-M, Balschun K, et al. HER2/neu testing in primary colorectal carcinoma. *Br J Cancer*. 2014;111(10):1977-1984. **31.** 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. **32.** 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.

Please see Important Safety Information on pages 16-20 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

References (cont'd)

33. 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. **34.** Pils D, Pinter A, Reibenwein J, et al. In ovarian cancer the prognostic influence of HER2/neu is not dependent on the CXCR4/SDF-1 signalling pathway. *Br J Cancer*. 2007;96(3):485-491. **35.** 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. **36.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Bladder Cancer V.6.2024. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed January 17, 2025. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **37.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Cervical Cancer V.2.2025. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed January 31, 2025. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **38.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Colon Cancer V.6.2024. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed January 17, 2025. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **39.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Rectal Cancer V.5.2024. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed January 17, 2025. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **40.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.3.2025. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed January 14, 2025. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **41.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.6.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed November 11, 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. **42.** PATHWAY anti-HER-2/neu (4B5) rabbit monoclonal primary antibody method sheet. 14427US Rev H. 25-01-27. **43.** Bardia A, Hu X, Dent R, et al. Protocol for: Trastuzumab deruxtecan after endocrine therapy in metastatic breast cancer. *N Engl J Med*. 2024. Published online ahead of print. doi:10.1056/NEJMoa2407086 **44.** Shitara K, Bang Y-J, Iwasa S, et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. *N Engl J Med*. 2020;382(2):419-2430. **45.** Li BT, Smit EF, Goto Y, et al. Trastuzumab deruxtecan in HER2-mutant non–small-cell lung cancer. *N Engl J Med*. 2022;386(3):241-251. **46.** Protocol for: Trastuzumab deruxtecan in participants with HER2-overexpressing advanced or metastatic colorectal cancer (DESTINY-CRC02). ClinicalTrials.gov identifier: NCT04744831. Updated January 22, 2024. Accessed January 24, 2024. https://storage.googleapis.com/ctgov2-large-docs/31/NCT04744831/Prot_SAP_000.pdf **47.** Meric-Bernstam F, Makker V, Oaknin A, et al. Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: primary results from the DESTINY-PanTumor02 phase II trial. *J Clin Oncol*. 2024;42(1):47-58. **48.** Data on file. Daiichi Sankyo, Inc. Basking Ridge, NJ. **49.** Tarantino P, Viale G, Press MF, et al. ESMO expert consensus statements (ECS) on the definition, diagnosis, and management of HER2-low breast cancer. *Ann Oncol*. 2023;34(8):645-659. **50.** PATHWAY anti-HER-2/neu (4B5) rabbit monoclonal primary antibody interpretation guide for breast cancer. 1449100 Rev L. 22-09-29. **51.** Fitzgibbons PL, Connolly JL. Template for reporting results of biomarker testing of specimens from patients with carcinoma of the breast. Version 1.5.0.1. Published March 2023. Accessed July 19, 2023. https://documents.cap.org/documents/Breast.Bmk_1.5.0.1.REL_CAPCP.pdf **52.** Ruschoff J, Hanna W, Bilous M, et al. HER2 testing in gastric cancer: a practical approach. *Mod Pathol*. 2012;25(5):637-650. **53.** National Cancer Institute. NCI Dictionary of Cancer Terms. Accessed October 17, 2024. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/tumor-agnostic-therapy **54.** Meric-Bernstam F, Makker V, Oaknin A, et al. Protocol for: Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: primary results from the DESTINY-PanTumor02 phase II trial. *J Clin Oncol*. 2024;42(1):47-58. **55.** Baskovich BW, Fitzgibbons PL, Birdsong GG, et al. Template for reporting results of biomarker testing of specimens from patients with non-small cell carcinoma of the lung. Version 2.0.1.1. Published September 2023. Accessed October 21, 2024. https://documents.cap.org/protocols/Lung.Bmk_2.0.1.1.REL_CAPCP.pdf **56.** Burgart LJ, Chopp WV, Jain D, et al. Template for reporting results of biomarker testing of specimens from patients with carcinoma of the colon and rectum. Version 1.3.0.0. Published June 2021. Accessed October 21, 2024. https://documents.cap.org/protocols/ColoRectal.Bmk_1.3.0.0.REL_CAPCP.pdf **57.** Bartley AN, Christ J, Fitzgibbons P, et al. Template for reporting results of HER2 (ERBB2) biomarker testing of specimens from patients with adenocarcinoma of the stomach or gastroesophageal junction. Version 1.0.0.1. Published June 2017. Accessed October 21, 2024. https://documents.cap.org/protocols/cp-gastric-HER2biomarker17-1001.pdf **58.** Crothers BA, Harik MD, Bartley AN, et al. Template for reporting results of biomarker testing of specimens from patients with carcinoma of gynecologic origin. Version 1.1.0.0. Published March 2023. Accessed October 21, 2024. https://documents.cap.org/documents/Gynecologic.Bmk_1.1.0.0.REL_CAPCP.pdf **59.** Seethala RR, Schneider F, Baras A, et al. Head and neck biomarker reporting template. Version 2.2.0.0. Published September 2023. Accessed October 21, 2024. https://documents.cap.org/protocols/HN.Bmk_2.2.0.0.REL_CAPCP.pdf **60.** Baras A, Khoury JD, Baskovich BW, et al. Template for reporting results of quantitative IHC biomarker testing of specimens from patients with carcinoma. Version 1.0.0.0. Published June 2021. Accessed October 21, 2024. https://documents.cap.org/protocols/IHC.Bmk_1.1.0.1.REL_CAPCP.pdf **61.** 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. doi:10.1016/j.ctrv.2020.101996 **62.** Ninomiya K, Hata T, Yoshioka H, et al. A prospective cohort study to define the clinical features and outcome of lung cancers harboring HER2 aberration in Japan (HER2-CS STUDY). *Chest*. 2019;156(2):357-366.

Please see Important Safety Information on pages 16-20 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

References (cont'd)

63. Odintsov I, Makarem M, Nishino M, et al. Prevalence and therapeutic targeting of high-level ERBB2 amplification in NSCLC. *J Thorac Oncol*. 2024;19(5):732-748. **64.** Leighl NB, Page RD, Raymond VM, et al. Clinical utility of comprehensive cell-free DNA analysis to identify genomic biomarkers in patients with newly diagnosed metastatic non–small cell lung cancer. *Clin Cancer Res*. 2019;25(15):4691-4700. **65.** Merker J, Oxnard G, Compton C, et al. Circulating tumor DNA analysis in patients with cancer: American Society of Clinical Oncology and College of American Pathologists joint review. *J Clin Oncol*. 2018;36(16):1631-1641. **66.** Fitzgibbons PL, Bartley AN, Longacre TA, et al. Template for reporting results of biomarker testing of specimens from patients with carcinoma of the endometrium. Version 1.2.0.0. Published August 2019. Accessed January 2, 2024. https://documents.cap.org/protocols/cp-femalereproductive-endometrium-biomarker-19-1200.pdf

Please see Important Safety Information on pages 16-20 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

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

Test for HER2 status in solid tumors to inform eligibility for treatment with ENHERTU

- **Measure and report ALL levels of HER2 expression for mBC, including HER2-low and HER2-ultralow[1]**
- **Perform HER2 IHC testing AND NGS testing for patients with mNSCLC[1,40]**
- **HER2 IHC test ALL metastatic solid tumors[1]**

See the clinical data at ENHERTUhcp.com to learn why ENHERTU may be a HER2-directed treatment option for your eligible patients

Indications and Important Safety Information

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**

Please see Important Safety Information on pages 16-20 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

Daiichi-Sankyo | AstraZeneca