

IDENTIFY HER2 ALTERATIONS TO INFORM ELIGIBILITY FOR TREATMENT WITH ENHERTU

ENHERTU is approved for certain previously treated adult patients with¹:

 HER2+ Metastatic Breast Cancer (IHC 3+ or ISH+)	 HER2-low Metastatic Breast Cancer (IHC 1+ or IHC 2+/ISH-)	 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.

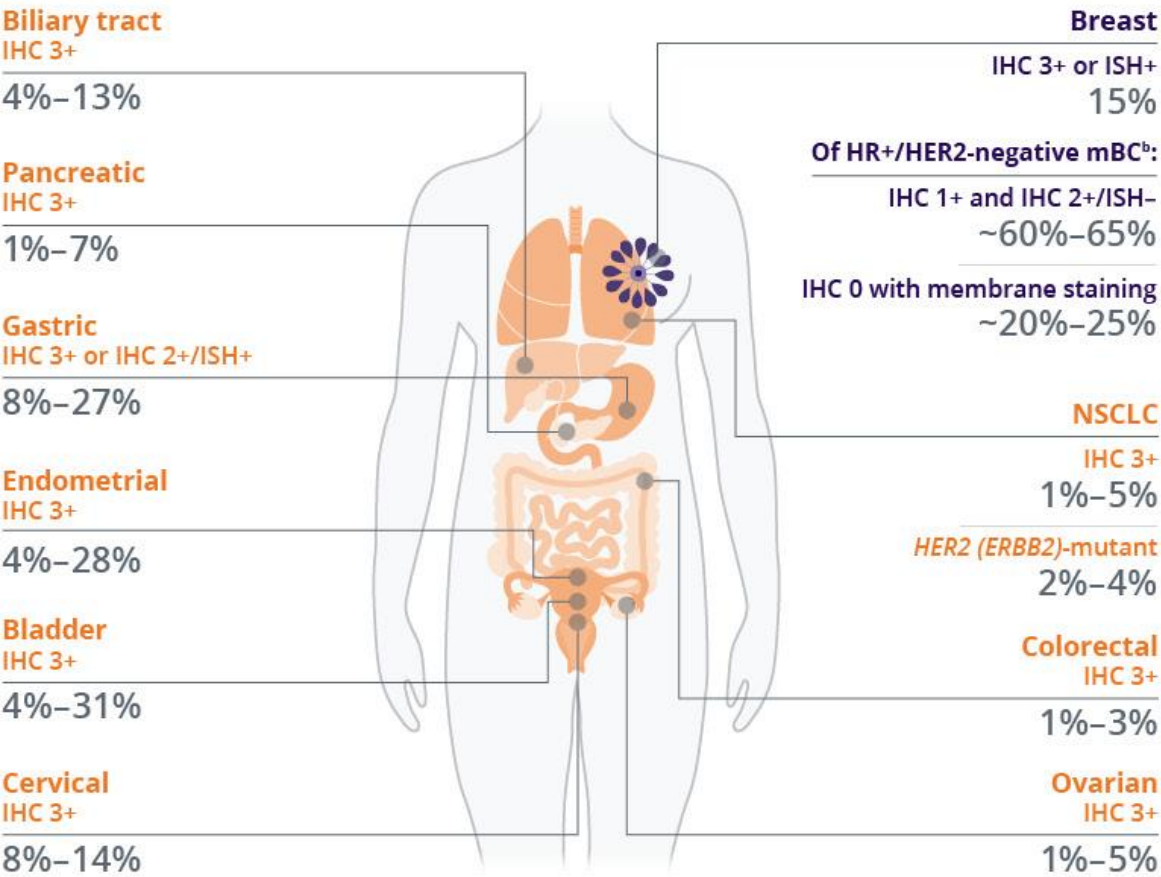
Please see Important Safety Information on pages 16-20 and throughout, and accompanying full [Prescribing Information](#), including **Boxed WARNINGS**, and [Medication Guide](#).



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

 HER2 overexpression^{2,3}	 HER2 (ERBB2) amplification⁴	 HER2 (ERBB2) mutation⁵
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 tumors³⁶⁻⁴¹

^aIndividual tumor prevalence numbers reflect US and ex-US populations. Due to limited testing of IHC in the US, data from a global population have been included.
^bAs demonstrated in DESTINY-Breast06 screening data.

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



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	✓		
	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/CompanionDiagnostics>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 ENHERTU¹

^aPlease see full indications for ENHERTU on page 1.
^bScoring criteria used in clinical trial.
^cDESTINY-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, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

Important Safety Information (cont'd)
Warnings and Precautions
Interstitial Lung Disease / Pneumonitis
Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with ENHERTU. A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment. Advise patients to immediately report cough, dyspnea, fever, and/or any new or worsening respiratory symptoms. Monitor patients for signs and symptoms of ILD. Promptly investigate evidence of ILD. Evaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist. For asymptomatic ILD/pneumonitis (Grade 1), interrupt ENHERTU until resolved to Grade 0, then if resolved in ≤28 days from date of onset, maintain dose. If resolved in >28 days from date of onset, reduce dose 1 level. Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥0.5 mg/kg/day prednisolone or equivalent). For symptomatic ILD/pneumonitis (Grade 2 or greater), permanently discontinue ENHERTU.



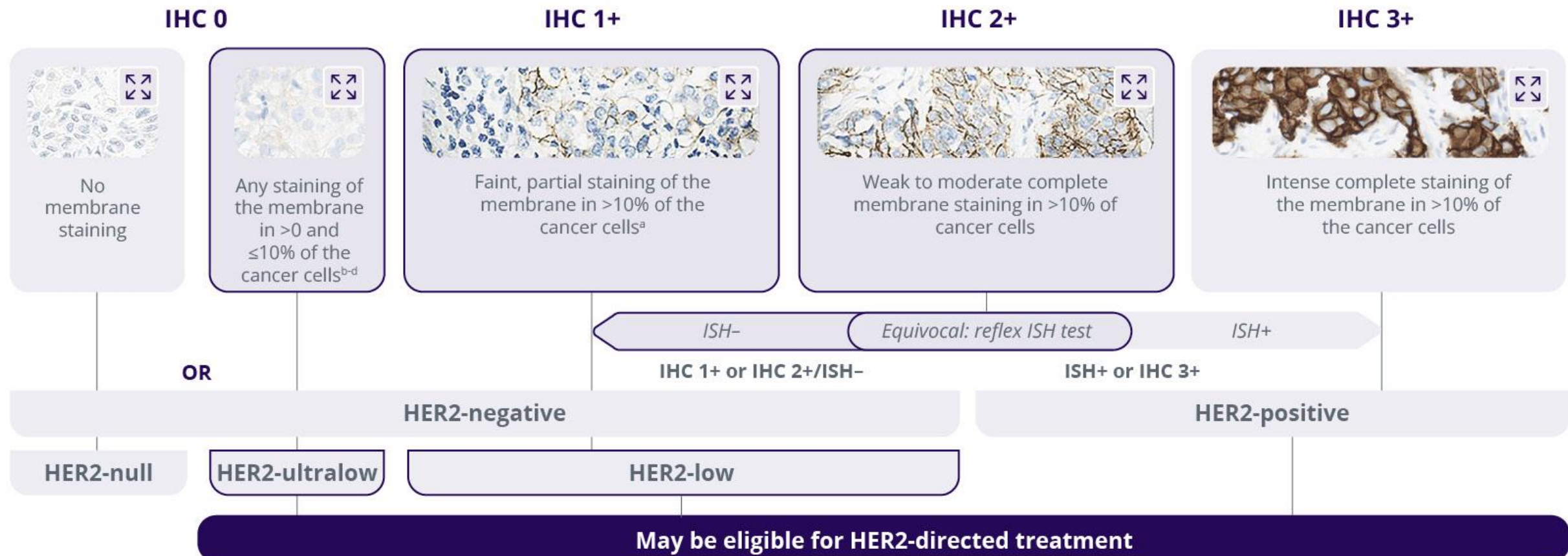
Perform HER2 IHC testing to identify HER2-ultralow and HER2-low patients who may be eligible for HER2-directed treatment in mBC

HER2-ultralow status is now actionable in certain patients with mBC¹

- HER2-ultralow is defined as IHC 0 with membrane staining

~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 PATHWAY HER2 (4B5) FDA-approved companion diagnostic scoring criteria for breast cancer^{1,42,48}



Study design: DESTINY-Breast06 is a Phase 3, international, multicenter, randomized, open-label trial of ENHERTU vs physician's choice of chemotherapy in 866 patients with HR+/HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining) mBC. Patients were eligible if they had disease progression on at least 2 lines of ET in the metastatic setting, or 1 line of ET in the metastatic setting and progressed within 24 months of the start of adjuvant ET or within 6 months of starting 1L ET + CDK4/6 inhibitor in the metastatic setting. Patients in the ENHERTU arm received 5.4 mg/kg IV Q3W and patients in the chemotherapy arm could receive capecitabine, nab-paclitaxel, or paclitaxel. Treatment was continued until unacceptable toxicity or disease progression. The primary endpoint was PFS in the HER2-low population (determined by BICR according to RECIST v1.1). Select secondary endpoints included PFS (BICR) in the overall study population (HER2-low and HER2-ultralow); OS in the HER2-low population and in the overall study population; ORR in the HER2-low population and in the overall study population; and DOR in the HER2-low population and in the overall study population.^{1,43,49,50}

^aAs demonstrated in DESTINY-Breast06 screening data. ^bReview at 40x is recommended to discern the presence or absence of any staining such as faint, partial staining.⁴² ^cRecommend re-reading by a second pathologist for cases with "faint, partial staining of the membrane" and %Tumor Cells (%TC) ≤5%.⁴² ^dIn the HER2-ultralow "IHC 0 with membrane staining" category, partial membranous staining is usually faint but may exhibit stronger intensities, and such rare cases are scored as HER2-ultralow if they do not otherwise qualify for a higher score. Refer to the PATHWAY HER2 (4B5) Interpretation Guide for case examples.⁴²

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

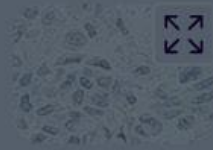
Perform HER2 IHC testing to identify HER2-ultralow and HER2-low patients who may be eligible for HER2-directed treatment in mBC

HER2-ultralow status is now actionable in certain patients with mBC¹

~60% of HR+/HER2-negative mBC tumors previously considered

• HER2-ultralow

Test for HER2
FDA-approved



No
membrane
staining

HER2-null

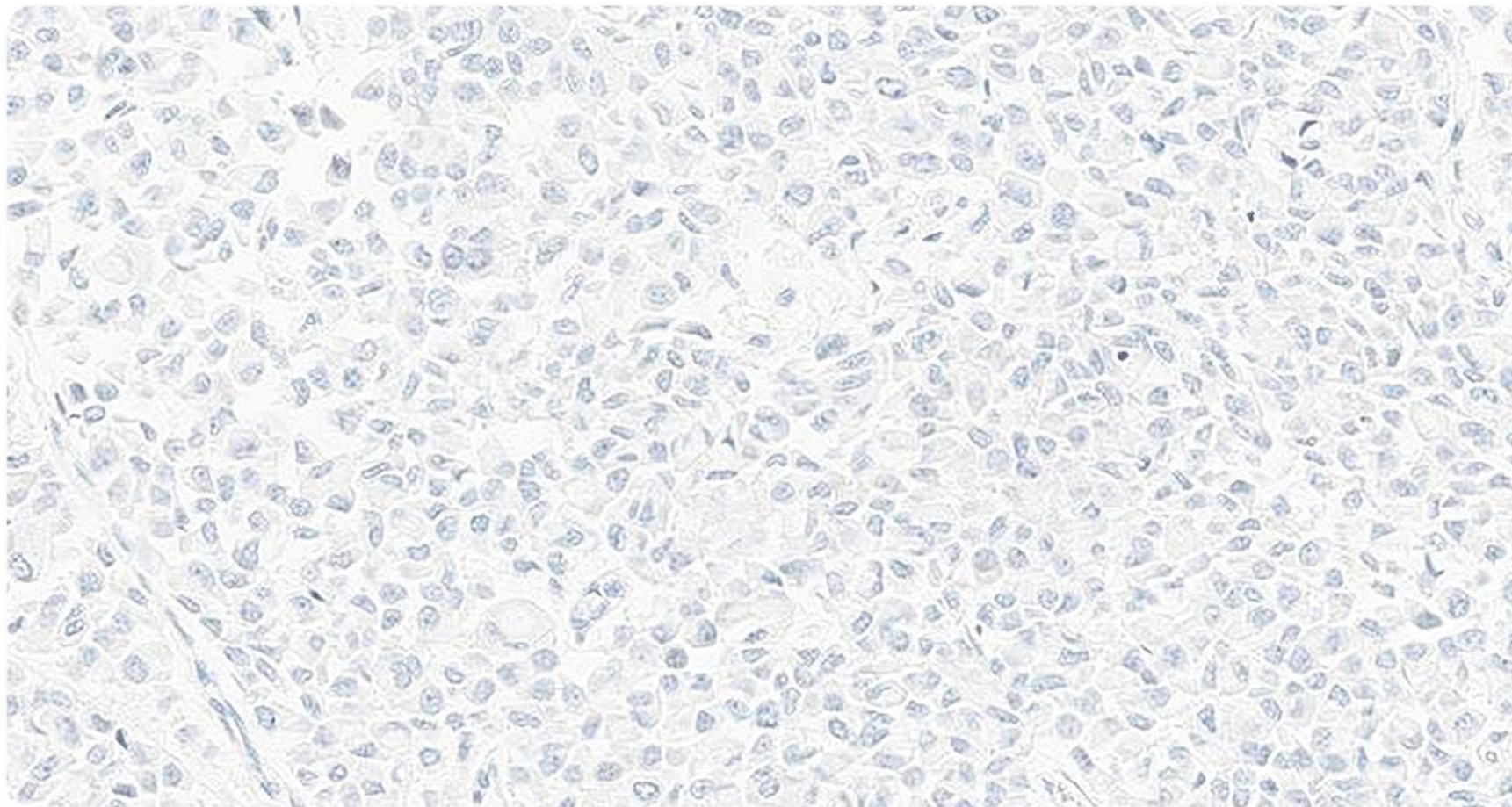
Study design: DESTINY-Breast06 screening data. HR+/HER2-low (IHC 1+ or 2+) in the metastatic setting; the metastatic setting.

Treatment was continued until unacceptable toxicity or disease progression. The primary endpoint was PFS in the HER2-low population (determined by BICR according to RECIST v1.1). Select secondary endpoints included PFS (BICR) in the overall study population (HER2-low and HER2-ultralow); OS in the HER2-low population and in the overall study population; ORR in the HER2-low population and in the overall study population; and DOR in the HER2-low population and in the overall study population.^{1,43,49,50}

^aAs demonstrated in DESTINY-Breast06 screening data. ^bReview at 40x is recommended to discern the presence or absence of any staining such as faint, partial staining.⁴² ^cRecommend re-reading by a second pathologist for cases with "faint, partial staining of the membrane" and %Tumor Cells (%TC) ≤5%.⁴² ^dIn the HER2-ultralow "IHC 0 with membrane staining" category, partial membranous staining is usually faint but may exhibit stronger intensities, and such rare cases are scored as HER2-ultralow if they do not otherwise qualify for a higher score. Refer to the PATHWAY HER2 (4B5) Interpretation Guide for case examples.⁴²

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

IHC 0



No membrane staining



(4B5)



Staining of
in >10% of
cells

56 patients with
2 lines of ET in the
DK4/6 inhibitor in
xel, or paclitaxel.

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

HER2-ultralow status is now actionable in certain patients with mBC¹

~60% of HR+/HER2-negative mBC tumors previously considered

• HER2-ultralow

Test for HER2
FDA-approved



No
membrane
staining

HER2-null

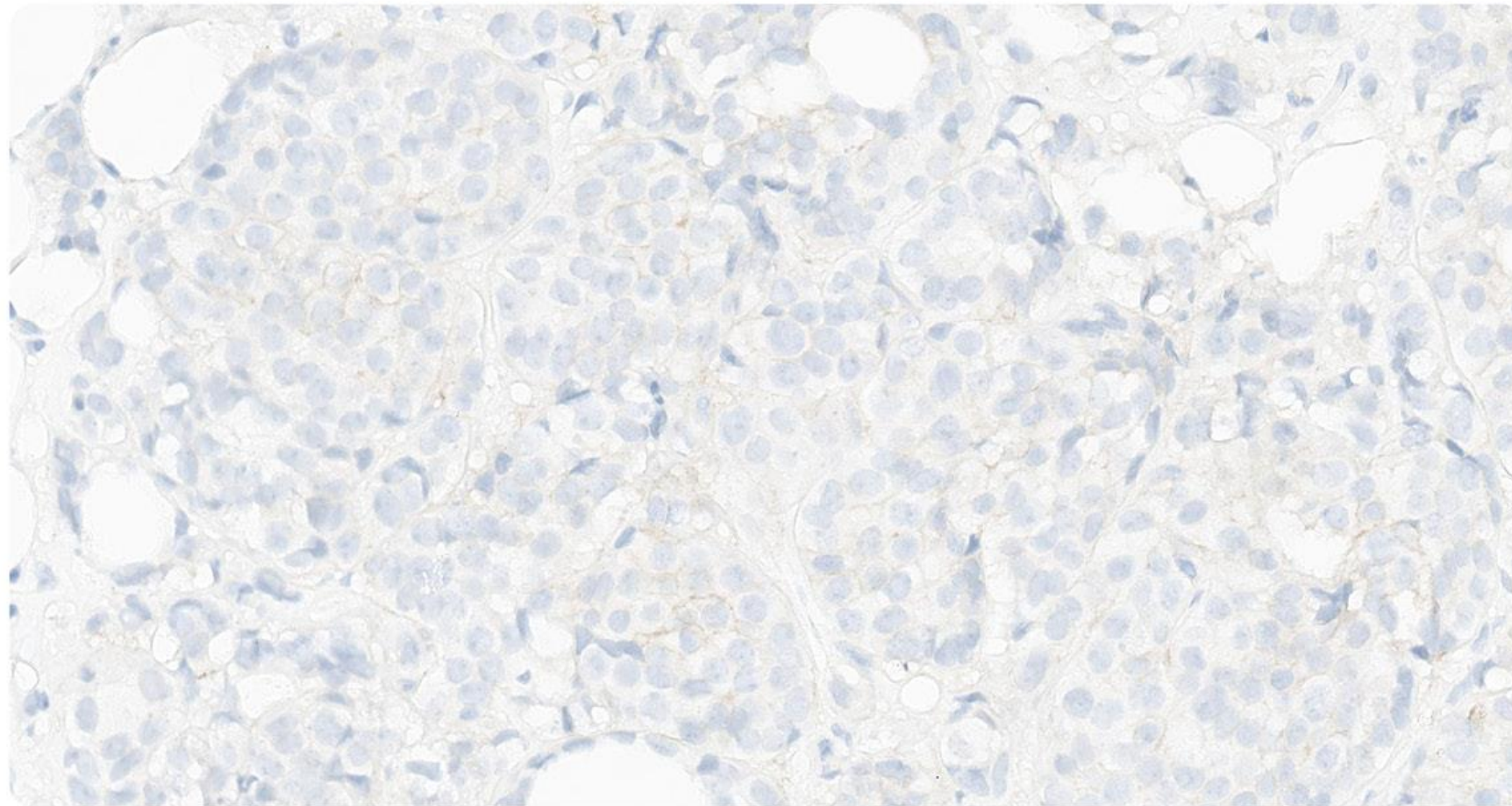
Study design: DESTINY-Breast06 screening data. ^aReview at 40x is recommended to discern the presence or absence of any staining such as faint, partial staining.⁴² ^cRecommend re-reading by a second pathologist for cases with "faint, partial staining of the membrane" and %Tumor Cells (%TC) ≤5%.⁴² ^dIn the HER2-ultralow "IHC 0 with membrane staining" category, partial membranous staining is usually faint but may exhibit stronger intensities, and such rare cases are scored as HER2-ultralow if they do not otherwise qualify for a higher score. Refer to the PATHWAY HER2 (4B5) Interpretation Guide for case examples.⁴²

Treatment was continued until unacceptable toxicity or disease progression. The primary endpoint was PFS in the HER2-low population (determined by BICR according to RECIST v1.1). Select secondary endpoints included PFS (BICR) in the overall study population (HER2-low and HER2-ultralow); OS in the HER2-low population and in the overall study population; ORR in the HER2-low population and in the overall study population; and DOR in the HER2-low population and in the overall study population.^{1,43,49,50}

^aAs demonstrated in DESTINY-Breast06 screening data. ^bReview at 40x is recommended to discern the presence or absence of any staining such as faint, partial staining.⁴² ^cRecommend re-reading by a second pathologist for cases with "faint, partial staining of the membrane" and %Tumor Cells (%TC) ≤5%.⁴² ^dIn the HER2-ultralow "IHC 0 with membrane staining" category, partial membranous staining is usually faint but may exhibit stronger intensities, and such rare cases are scored as HER2-ultralow if they do not otherwise qualify for a higher score. Refer to the PATHWAY HER2 (4B5) Interpretation Guide for case examples.⁴²

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

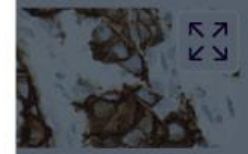
IHC 0



Any staining of the membrane in >0 and ≤10% of the cancer cells



(4B5)



Staining of
in >10% of
cells

56 patients with
2 lines of ET in the
DK4/6 inhibitor in
xel, or paclitaxel.

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

HER2-ultralow status is now actionable in certain patients with mBC¹

~60% of HR+/HER2-negative mBC tumors previously considered

• HER2-ultralow

Test for HER2
FDA-approved



No
membrane
staining

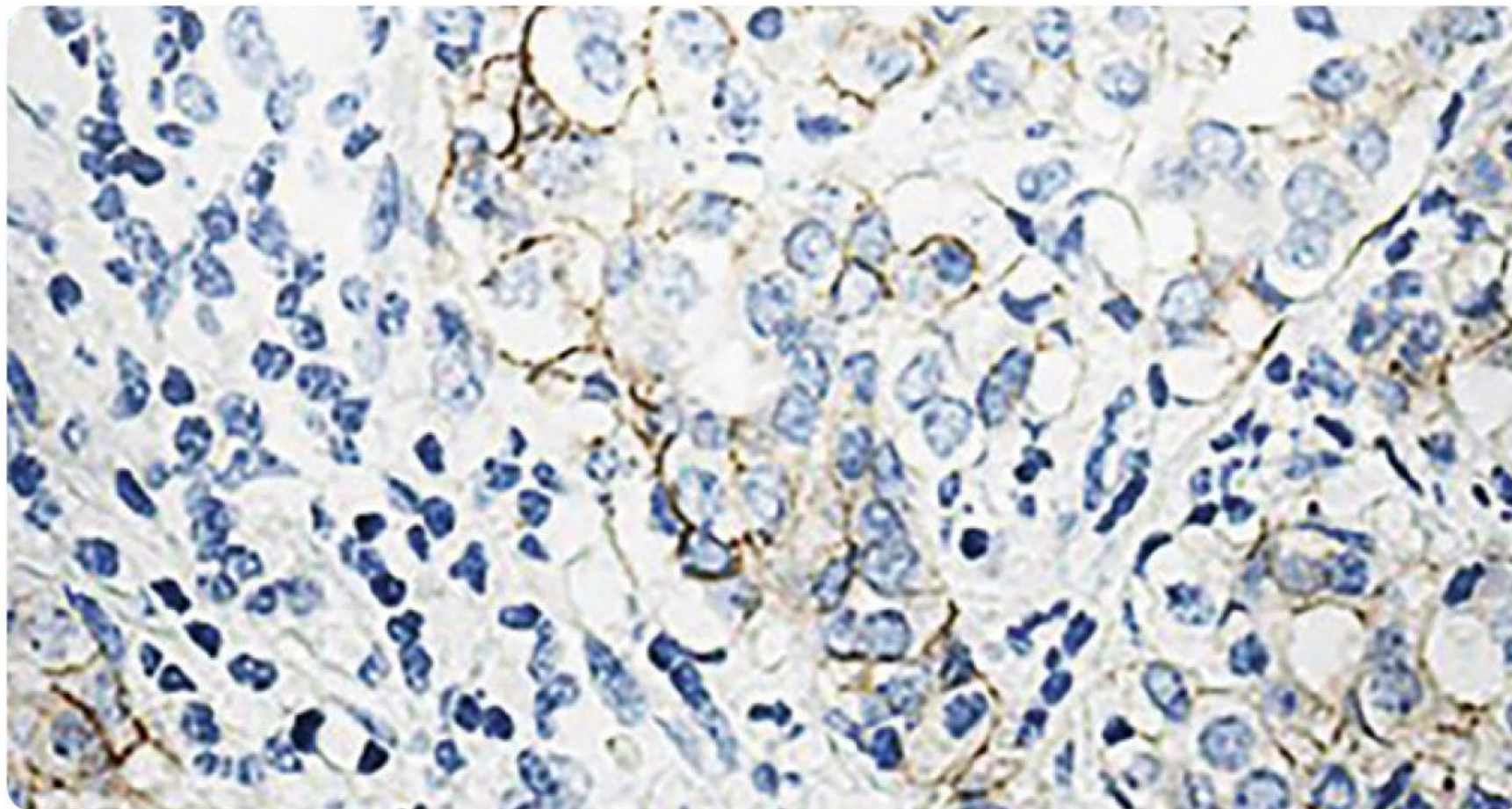
HER2-null

Study design: DESTINY-Breast06 screening data. ^aReview at 40x is recommended to discern the presence or absence of any staining such as faint, partial staining.⁴² ^cRecommend re-reading by a second pathologist for cases with "faint, partial staining of the membrane" and %Tumor Cells (%TC) ≤5%.⁴² ^dIn the HER2-ultralow "IHC 0 with membrane staining" category, partial membranous staining is usually faint but may exhibit stronger intensities, and such rare cases are scored as HER2-ultralow if they do not otherwise qualify for a higher score. Refer to the PATHWAY HER2 (4B5) Interpretation Guide for case examples.⁴²

Treatment was continued until unacceptable toxicity or disease progression. The primary endpoint was PFS in the HER2-low population (determined by BICR according to RECIST v1.1). Select secondary endpoints included PFS (BICR) in the overall study population (HER2-low and HER2-ultralow); OS in the HER2-low population and in the overall study population; ORR in the HER2-low population and in the overall study population; and DOR in the HER2-low population and in the overall study population.^{1,43,49,50}

^aAs demonstrated in DESTINY-Breast06 screening data. ^bReview at 40x is recommended to discern the presence or absence of any staining such as faint, partial staining.⁴² ^cRecommend re-reading by a second pathologist for cases with "faint, partial staining of the membrane" and %Tumor Cells (%TC) ≤5%.⁴² ^dIn the HER2-ultralow "IHC 0 with membrane staining" category, partial membranous staining is usually faint but may exhibit stronger intensities, and such rare cases are scored as HER2-ultralow if they do not otherwise qualify for a higher score. Refer to the PATHWAY HER2 (4B5) Interpretation Guide for case examples.⁴²

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



IHC 1+

Faint, partial staining of the membrane in >10% of the cancer cells



g)^{25,a}

(4B5)

+



e staining of
in >10% of
r cells

56 patients with
2 lines of ET in the
DK4/6 inhibitor in
xel, or paclitaxel.

Treatment was continued until unacceptable toxicity or disease progression. The primary endpoint was PFS in the HER2-low population (determined by BICR according to RECIST v1.1). Select secondary endpoints included PFS (BICR) in the overall study population (HER2-low and HER2-ultralow); OS in the HER2-low population and in the overall study population; ORR in the HER2-low population and in the overall study population; and DOR in the HER2-low population and in the overall study population.^{1,43,49,50}

^aAs demonstrated in DESTINY-Breast06 screening data. ^bReview at 40x is recommended to discern the presence or absence of any staining such as faint, partial staining.⁴² ^cRecommend re-reading by a second pathologist for cases with "faint, partial staining of the membrane" and %Tumor Cells (%TC) ≤5%.⁴² ^dIn the HER2-ultralow "IHC 0 with membrane staining" category, partial membranous staining is usually faint but may exhibit stronger intensities, and such rare cases are scored as HER2-ultralow if they do not otherwise qualify for a higher score. Refer to the PATHWAY HER2 (4B5) Interpretation Guide for case examples.⁴²

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

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

HER2-ultralow status is now actionable in certain patients with mBC¹

~60% of HR+/HER2-negative mBC tumors previously considered

• HER2-ultralow

Test for HER2
FDA-approved



No
membrane
staining

HER2-null

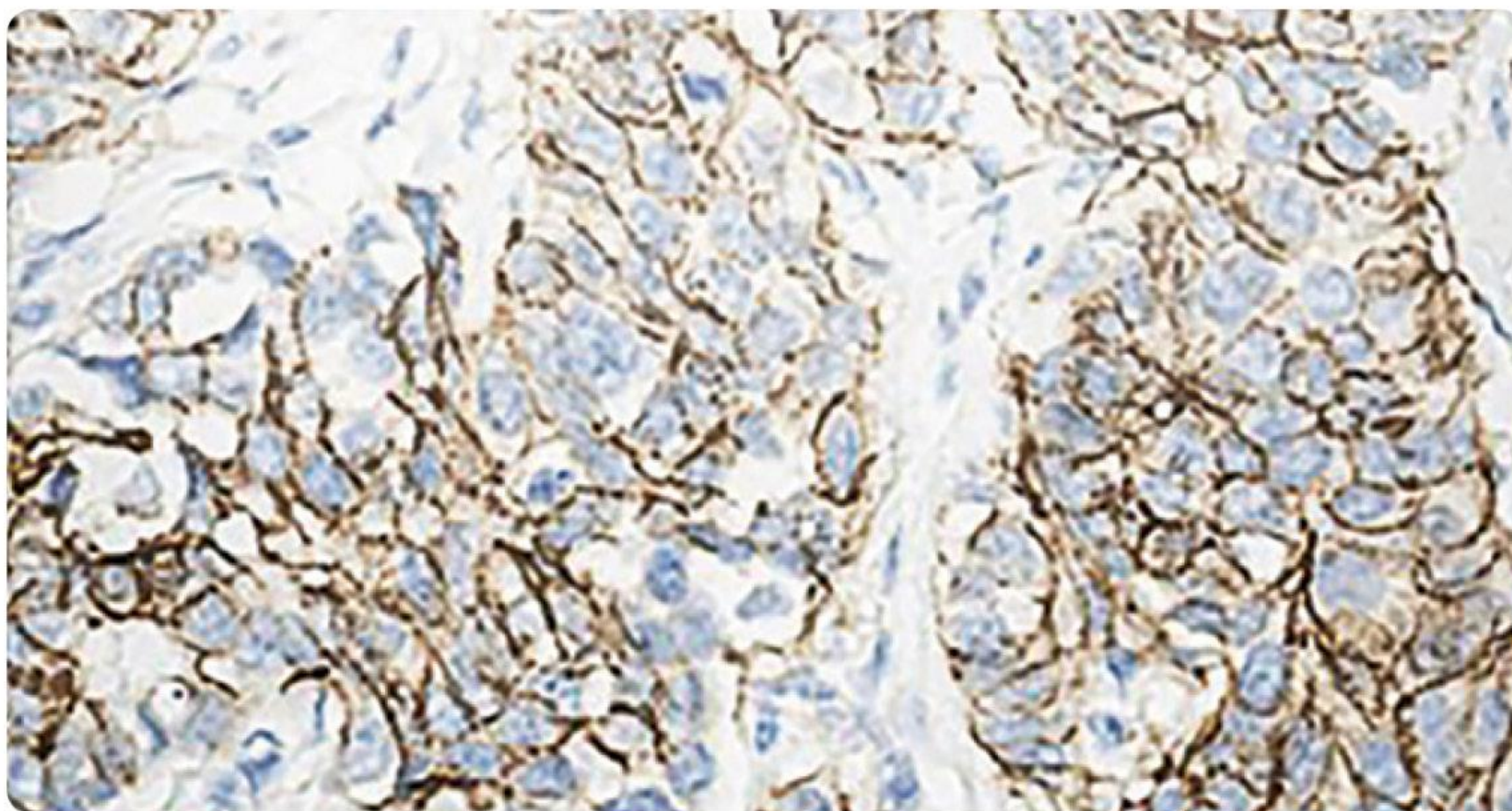
Study design: DESTINY-Breast06 screening data. HR+/HER2-low (IHC 1+) in the metastatic setting; the metastatic setting.

Treatment was continued until unacceptable toxicity or disease progression. The primary endpoint was PFS in the HER2-low population (determined by BICR according to RECIST v1.1). Select secondary endpoints included PFS (BICR) in the overall study population (HER2-low and HER2-ultralow); OS in the HER2-low population and in the overall study population; ORR in the HER2-low population and in the overall study population; and DOR in the HER2-low population and in the overall study population.^{1,43,49,50}

^aAs demonstrated in DESTINY-Breast06 screening data. ^bReview at 40x is recommended to discern the presence or absence of any staining such as faint, partial staining.⁴² ^cRecommend re-reading by a second pathologist for cases with "faint, partial staining of the membrane" and %Tumor Cells (%TC) ≤5%.⁴² ^dIn the HER2-ultralow "IHC 0 with membrane staining" category, partial membranous staining is usually faint but may exhibit stronger intensities, and such rare cases are scored as HER2-ultralow if they do not otherwise qualify for a higher score. Refer to the PATHWAY HER2 (4B5) Interpretation Guide for case examples.⁴²

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

IHC 2+



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



(4B5)

+



Faint, partial staining of
in >10% of
r cells

56 patients with
2 lines of ET in the
DK4/6 inhibitor in
xel, or paclitaxel.

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

HER2-ultralow status is now actionable in certain patients with mBC¹

~60% of HR+/HER2-negative mBC tumors previously considered

• HER2-ultralow

Test for HER2
FDA-approved



No
membrane
staining

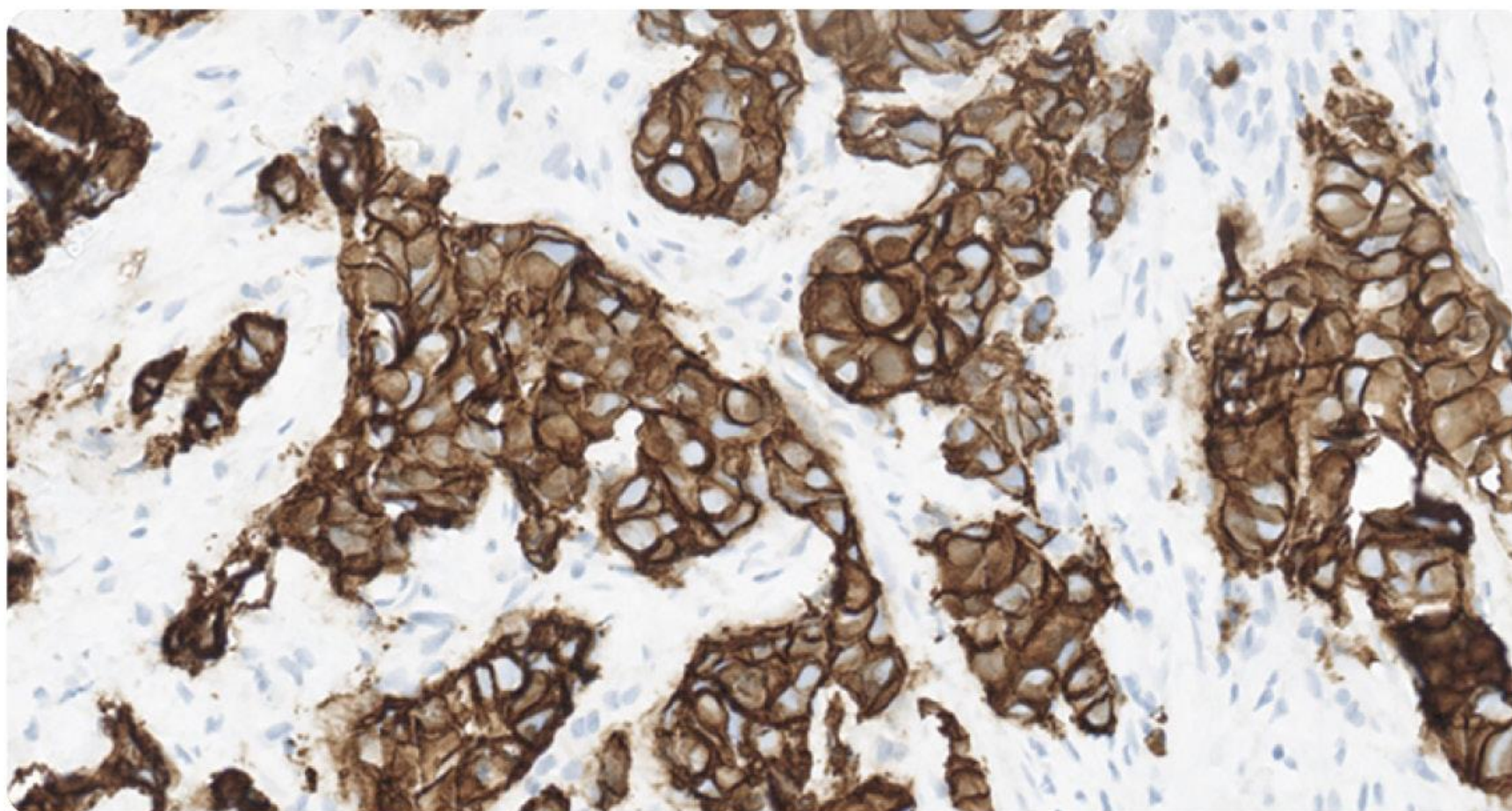
HER2-null

Study design: DESTINY-Breast06 screening data. HR+/HER2-low (IHC 1+ or 2+) in the metastatic setting; the metastatic setting.

Treatment was continued until unacceptable toxicity or disease progression. The primary endpoint was PFS in the HER2-low population (determined by BICR according to RECIST v1.1). Select secondary endpoints included PFS (BICR) in the overall study population (HER2-low and HER2-ultralow); OS in the HER2-low population and in the overall study population; ORR in the HER2-low population and in the overall study population; and DOR in the HER2-low population and in the overall study population.^{1,43,49,50}

^aAs demonstrated in DESTINY-Breast06 screening data. ^bReview at 40x is recommended to discern the presence or absence of any staining such as faint, partial staining.⁴² ^cRecommend re-reading by a second pathologist for cases with "faint, partial staining of the membrane" and %Tumor Cells (%TC) ≤5%.⁴² ^dIn the HER2-ultralow "IHC 0 with membrane staining" category, partial membranous staining is usually faint but may exhibit stronger intensities, and such rare cases are scored as HER2-ultralow if they do not otherwise qualify for a higher score. Refer to the PATHWAY HER2 (4B5) Interpretation Guide for case examples.⁴²

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



Intense complete staining of the membrane in >10% of the cancer cells



g)^{25,a}

(4B5)

+



e staining of
in >10% of
r cells

56 patients with
2 lines of ET in the
DK4/6 inhibitor in
xel, or paclitaxel.

Scoring and interpretation considerations in metastatic breast cancer



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

1

Screen entire tissue at low magnification⁵¹

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

2

Assess membrane staining pattern²:

- Incomplete/partial
- Complete/circumferential

AND

Assess staining intensity²:

- Faint
- Weak to moderate
- Intense

3

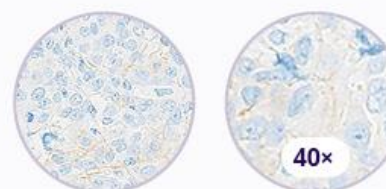
Assess relative percentages of stained cells using established cutoffs²:

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

4

Use high magnification (40x) to discern faint, incomplete staining, according to ASCO-CAP guidelines⁵¹

- Additional time may be needed to interpret and score cases with artifact, values near the 10% cutoff, and heterogeneous areas⁵¹
- Request a second pathologist review for cases with faint, incomplete staining of the membrane and percentage of tumor cells near the 10% threshold⁴²



You may be asked to re-evaluate previous HER2 IHC 0 results to identify the presence of any staining of the membrane in >0 and ≤10% of the cancer cells⁴²

Important Safety Information (cont'd)

Warnings and Precautions

Interstitial Lung Disease / Pneumonitis (cont'd)

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

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, 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^{2,42,51,52}



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
<i>ultraView</i> 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 detection²

The staining procedure is locked with a mild cell-conditioning step and a primary antibody incubation time of 12 minutes⁴²

- 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 use⁴²

- 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 *ultraView* 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, 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 $\leq 10\%$ of cells⁵²

Recommended reporting for
HER2-ultralow⁵²

HER2 by Immunohistochemistry (IHC) Status

✓ **Negative (Score 0)#**

— No membrane staining detected (0/absent membrane staining)

✓ **Membrane staining that is incomplete and is faint/barely perceptible and in $\leq 10\%$ of tumor cells (0+/with membrane staining)**

— Other (specify): _____

+Comment(s) on HER2 IHC Results#

Breast cancers with HER2 IHC scores of 0+, 1+, or 2+ (ISH negative) may be eligible for treatment targeting non-amplified levels of HER2 expression in the metastatic setting. Currently, patients with no membrane staining by IHC (0) are ineligible/excluded. Consider using the optional standardized HER2 IHC report comment to explain the clinical relevance of lower levels of HER2 IHC staining in the metastatic setting and definitions of "ultralow and low" HER2 used in clinical trials.

— In the DESTINY-Breast04 and 06 trials, "HER2 low" was considered IHC Score 1+ or 2+/ISH negative, and "HER2 ultralow" was HER2 IHC Score of 0 (pattern 0+) with membrane staining that is incomplete and faint/barely perceptible in less than or equal to 10% of tumor cells. Breast cancers with these staining patterns may be eligible for treatment with trastuzumab-deruxtecan in the metastatic setting (but those with no staining, IHC 0, are currently excluded)

Recommended reporting for HER2-low

- Check "Negative (Score 1+)" and "Membrane staining that is incomplete and is faint/barely perceptible and in greater than 10% of tumor cells" **or**
- Check "Equivocal (Score 2+)" and "Weak to moderate complete membrane staining observed in $>10\%$ of tumor cells" and check "Negative based on IHC and ISH results" in HER2 by In Situ Hybridization (ISH) Status

Although scoring criteria and descriptions of HER2 IHC status differ, all are consistent with the HER2-ultralow indication for ENHERTU^{1,2,42,52}

Study/guideline	Scoring criteria	HER2 IHC status description	ENHERTU indication
DESTINY-Breast06	Membrane staining that is seen in >0 and $\leq 10\%$ of tumor cells	IHC 0 with membrane staining	HER2-ultralow
PATHWAY HER2 (4B5) Roche/Ventana CDx	Any staining of the membrane in >0 and $\leq 10\%$ of the cancer cells	IHC 0 <u>with</u> membrane staining	
CAP Breast Reporting Template	Membrane staining that is incomplete and is faint/barely perceptible and $\leq 10\%$ of tumor cells	0+/with membrane staining	
ASCO-CAP Guidelines	Membrane staining that is incomplete and is faint/barely perceptible and in $\leq 10\%$ tumor cells	IHC 0	

Check with your multidisciplinary team about best practices for reporting HER2-ultralow status in mBC

[View CAP Reporting Template](#)

Please see Important Safety Information on pages 16-20 and throughout, and accompanying full [Prescribing Information](#), including **Boxed WARNINGS**, and [Medication Guide](#).

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 $0.5 \times 10^9/L$), interrupt ENHERTU until resolved to Grade 2 or less, then maintain dose. For Grade 4 neutropenia (ANC $<0.5 \times 10^9/L$), interrupt ENHERTU until resolved to Grade 2 or less, then reduce dose by 1 level. For febrile neutropenia (ANC $<1.0 \times 10^9/L$ and temperature $>38.3^\circ C$ or a sustained temperature of $\geq 38^\circ C$ 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)

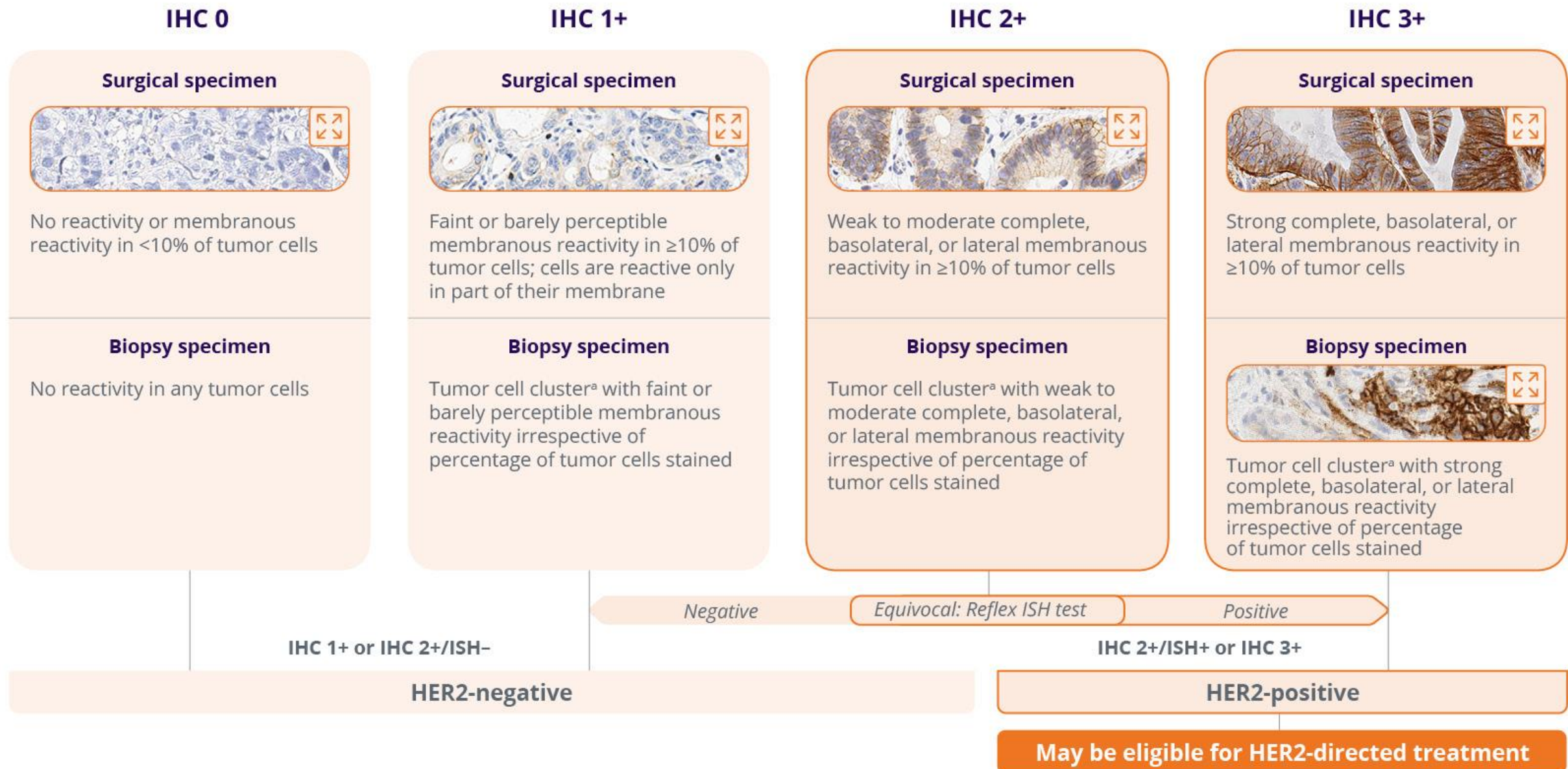
In patients with metastatic breast cancer, HER2-mutant NSCLC, and other solid tumors treated with ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in 65% of patients. Nineteen percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was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

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



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}



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}

^aTumor 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, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.



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}

Surgical

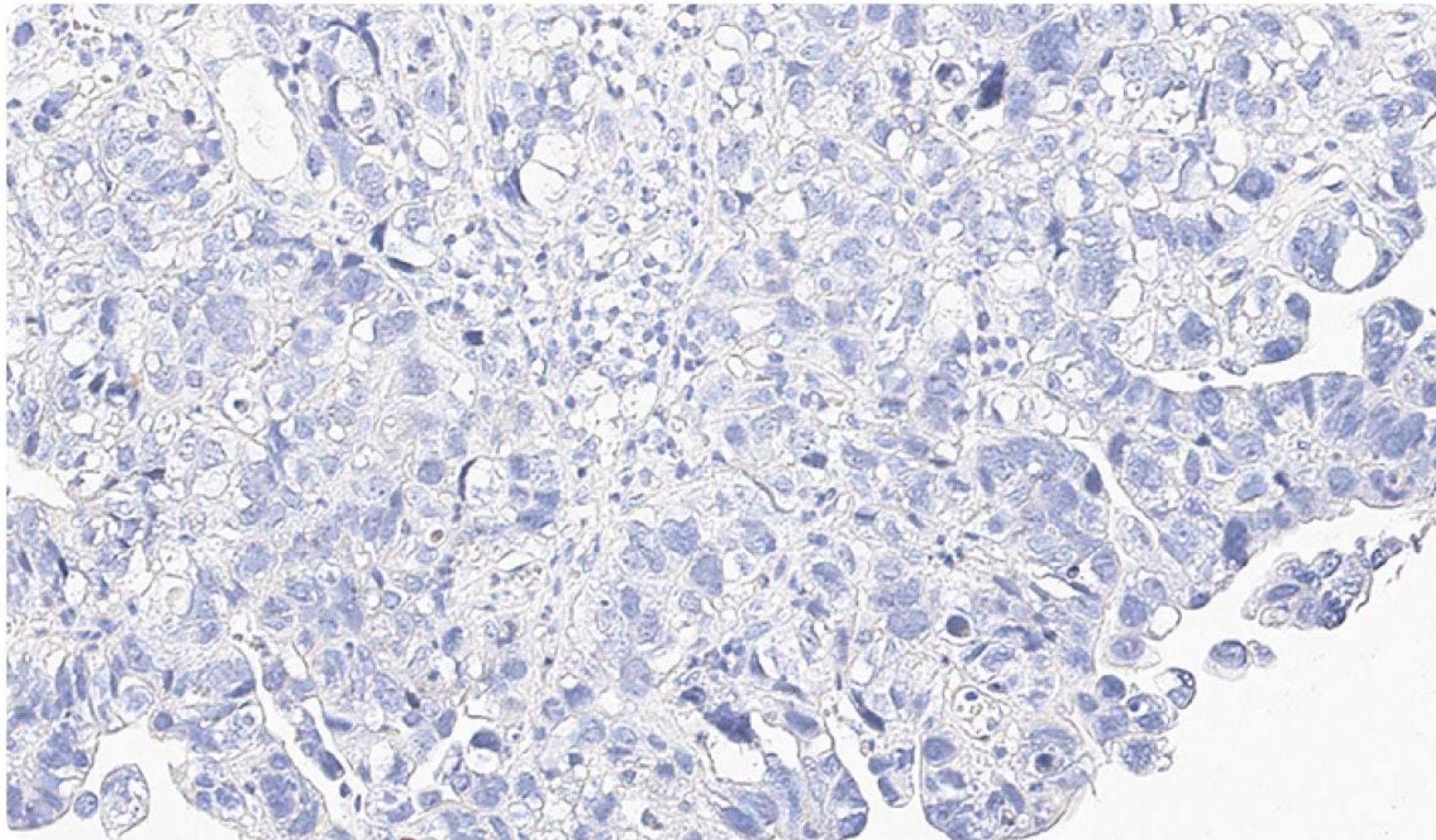


No reactivity or reactivity in <10%

Biopsy

No reactivity in

IHC 0



Specimen



Basolateral, or lateral reactivity in

Specimen



with strong basolateral, or lateral reactivity in percentage of tumor cells

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}

^aTumor 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, and accompanying full [Prescribing Information](#), including [Boxed WARNINGS](#), and [Medication Guide](#).

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}

Surgical

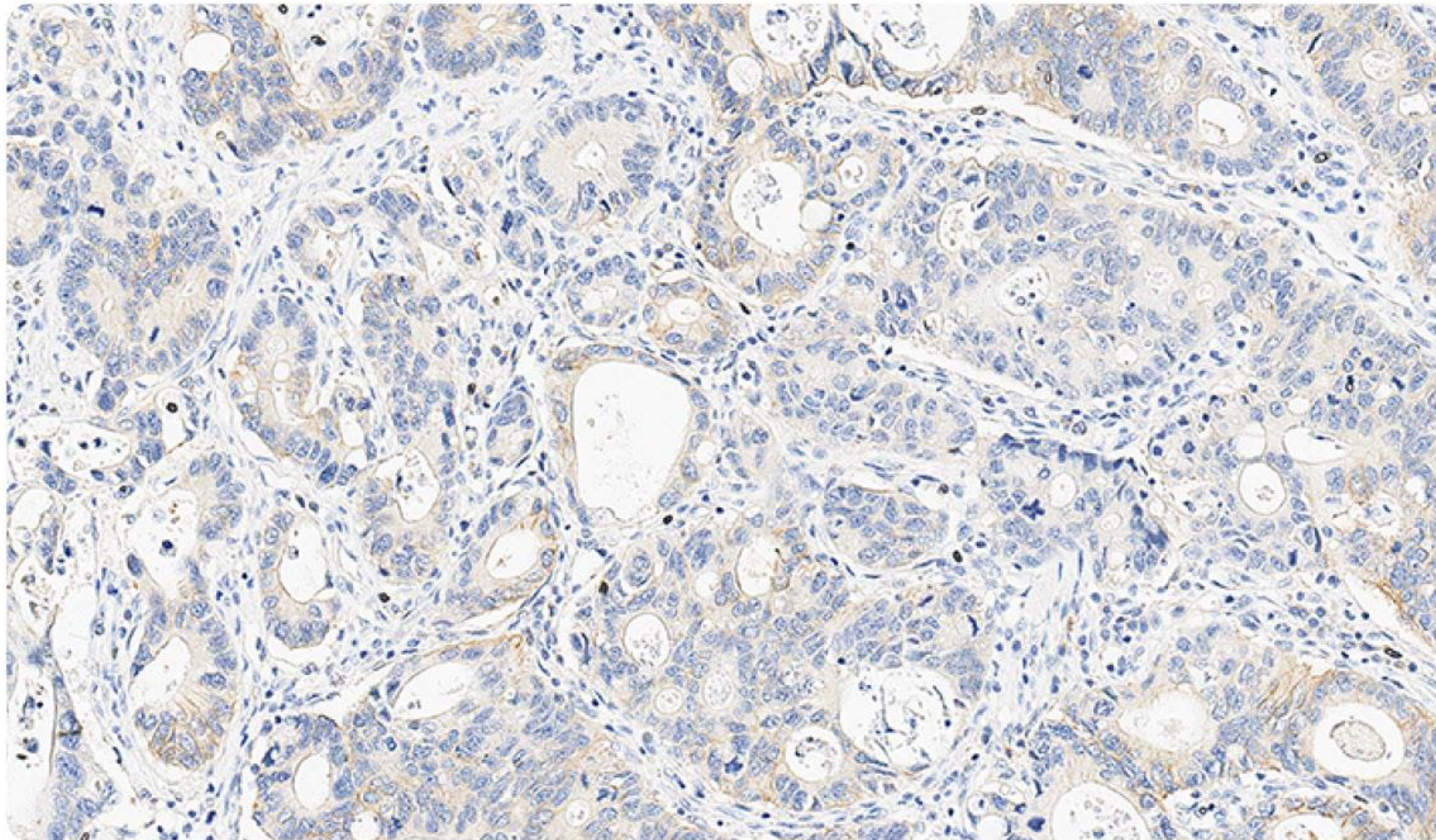


No reactivity or reactivity in <10%

Biopsy

No reactivity in

IHC 1+



Specimen



solateral, or reactivity in

Specimen



with strong reactivity, or lateral reactivity percentage

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}

*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, and accompanying full [Prescribing Information](#), including [Boxed WARNINGS](#), and [Medication Guide](#).

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}

Surgical

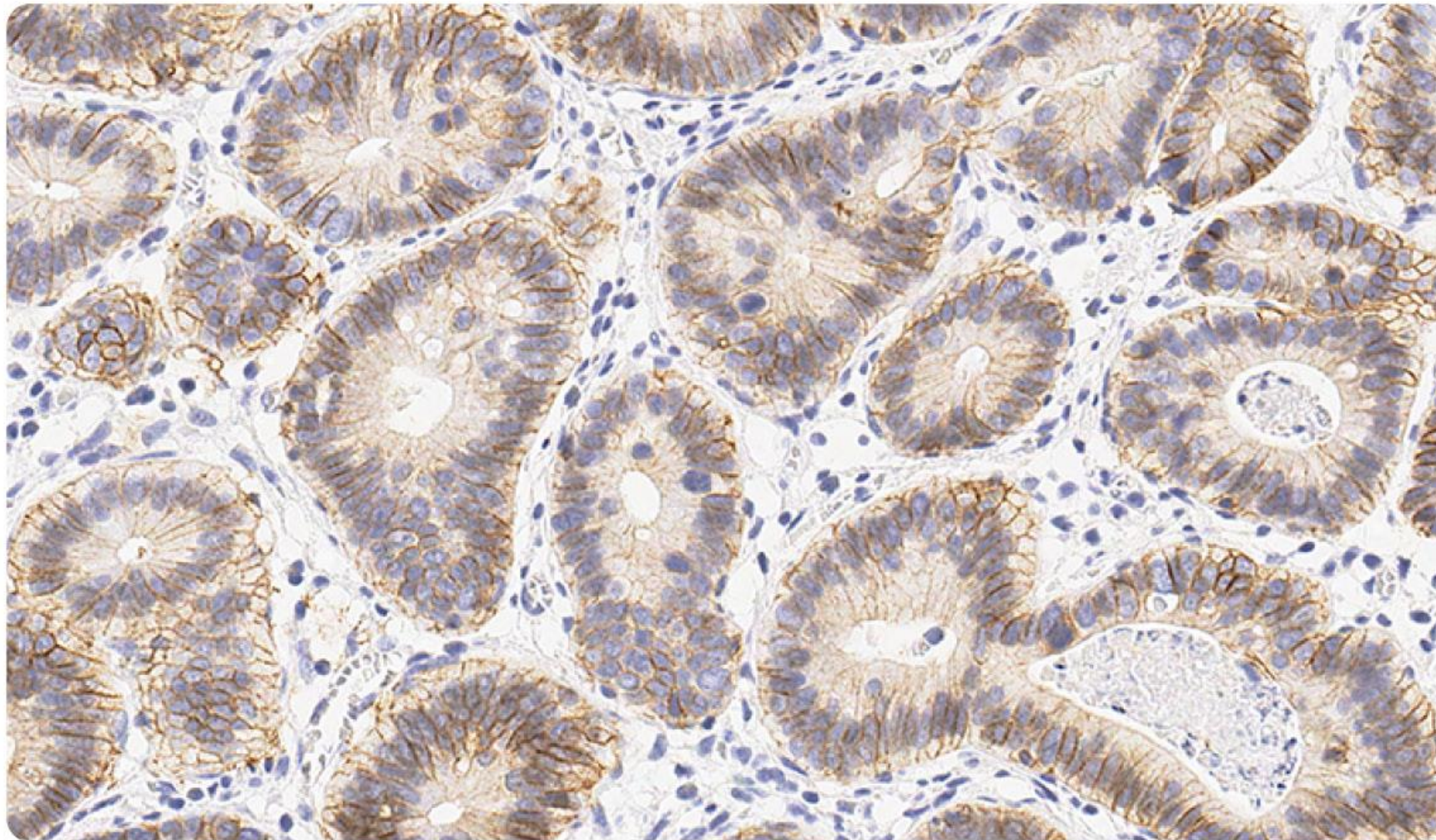


No reactivity or reactivity in <10%

Biopsy

No reactivity in

IHC 2+



Specimen



isolateral, or reactivity in

Specimen



with strong al, or lateral reactivity percentage ed

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}

^aTumor 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, and accompanying full [Prescribing Information](#), including [Boxed WARNINGS](#), and [Medication Guide](#).

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}

Surgical

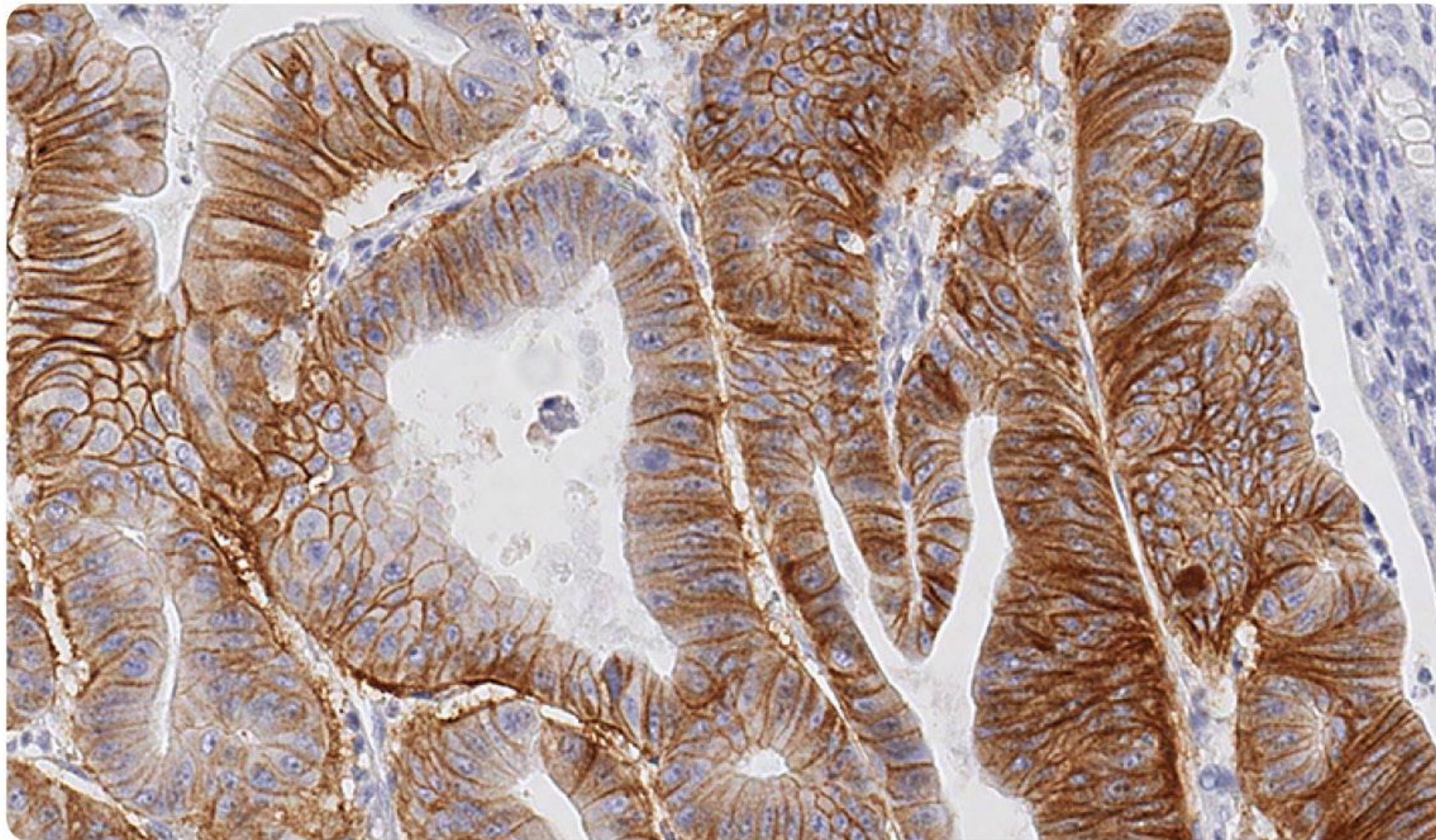


No reactivity or reactivity in <10%

Biopsy

No reactivity in

IHC 3+ (Surgical specimen)



Specimen



isolateral, or reactivity in

Specimen



with strong al, or lateral vity entage ed

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}

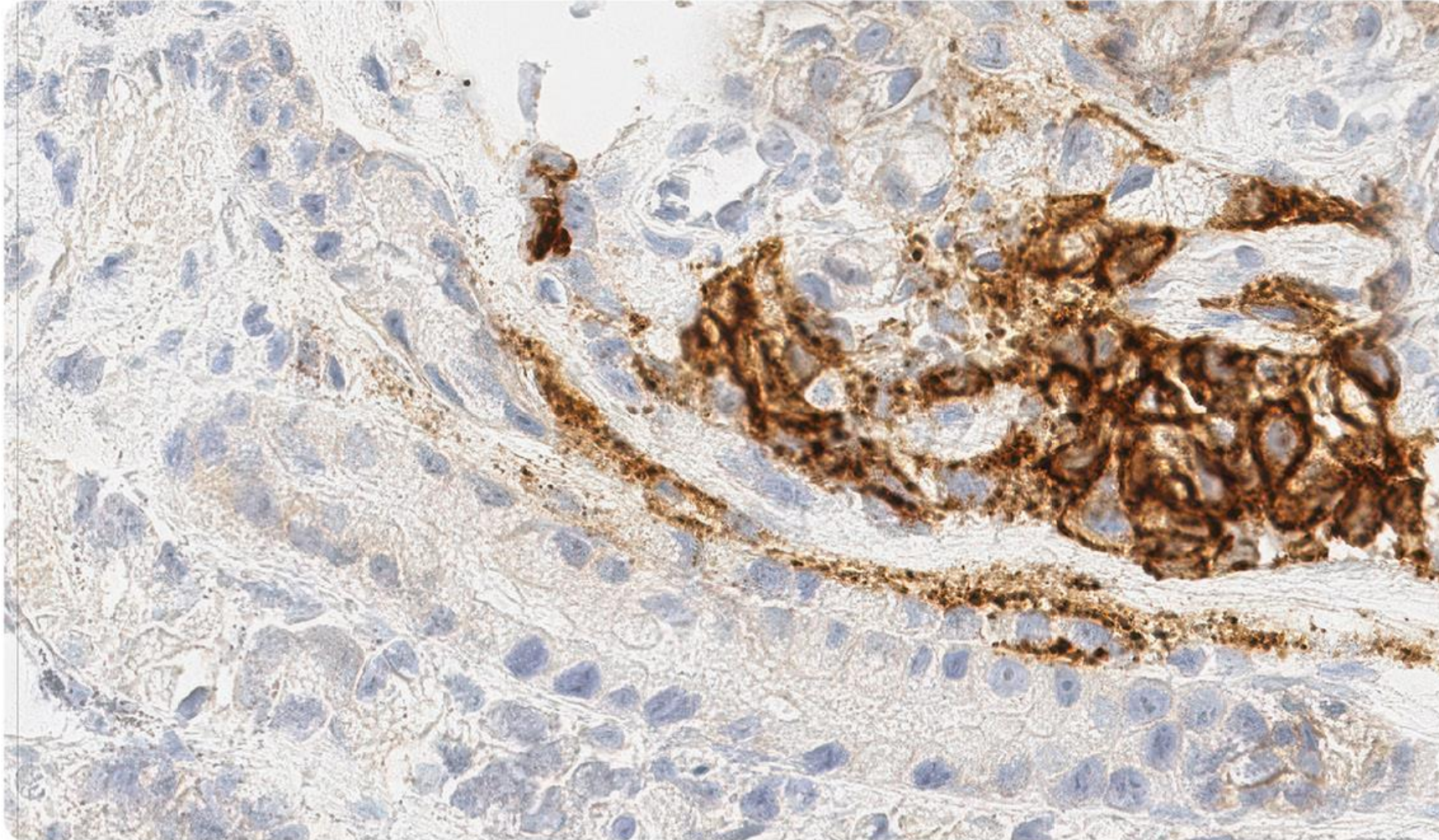
*Tumor cell cluster is defined as a cluster of 5 or more tumor cells.³

Please see Important Safety Information on pages 16-20 and throughout, and accompanying full [Prescribing Information](#), including [Boxed WARNINGS](#), and [Medication Guide](#).

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 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}

^aTumor 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, and accompanying full [Prescribing Information](#), including [Boxed WARNINGS](#), and [Medication Guide](#).



Scoring and interpretation considerations in aGC/GEJ adenocarcinoma



Surgical specimen³

- 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^{3,53}

- 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 cancer³

- Compared to breast, gastric tumors have:



Greater intratumoral heterogeneity



Lower incidence of complete membrane staining



Frequent basolateral patterns of HER2 expression

^aInconclusive 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, and accompanying full [Prescribing Information](#), including [Boxed WARNINGS](#), and [Medication Guide](#).





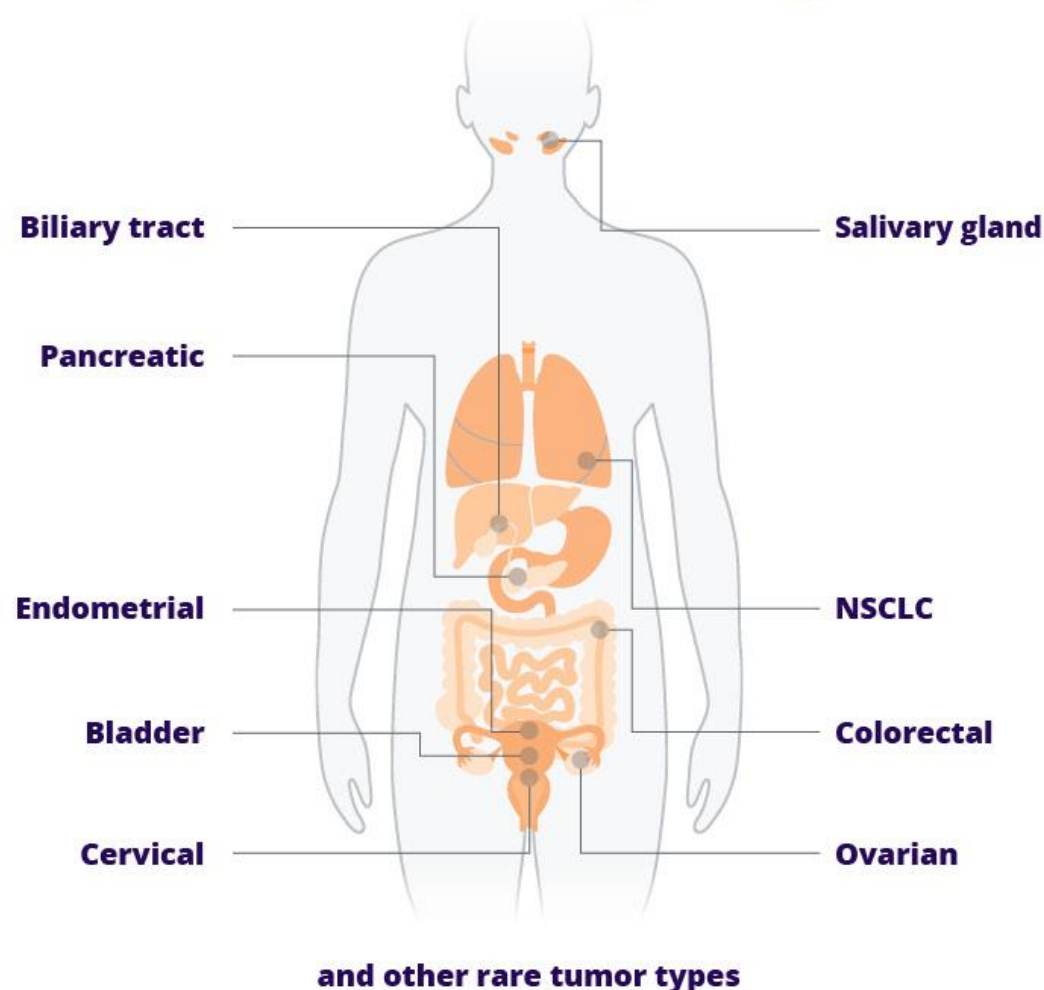
Metastatic Solid Tumors

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^{1,47,54}

- 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

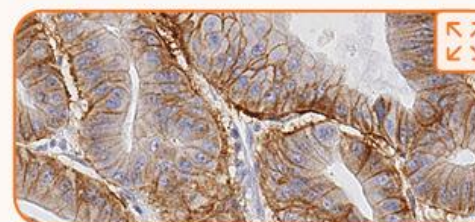
The clinical relevance of HER2+ (IHC 3+) was evaluated across 3 clinical trials^a in the following tumor types^{1,47}:



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

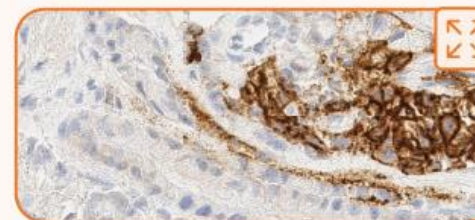
- Refer to page 8 for full gastric scoring criteria

ASCO-CAP Gastric Cancer Scoring Criteria for IHC 3+^{1,3,48}



Surgical specimen

Strong complete, basolateral, or lateral membranous reactivity in $\geq 10\%$ 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}

^aDESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02.¹

^bTumor 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, and accompanying full [Prescribing Information](#), including [Boxed WARNINGS](#), and [Medication Guide](#).





Metastatic Solid Tumors

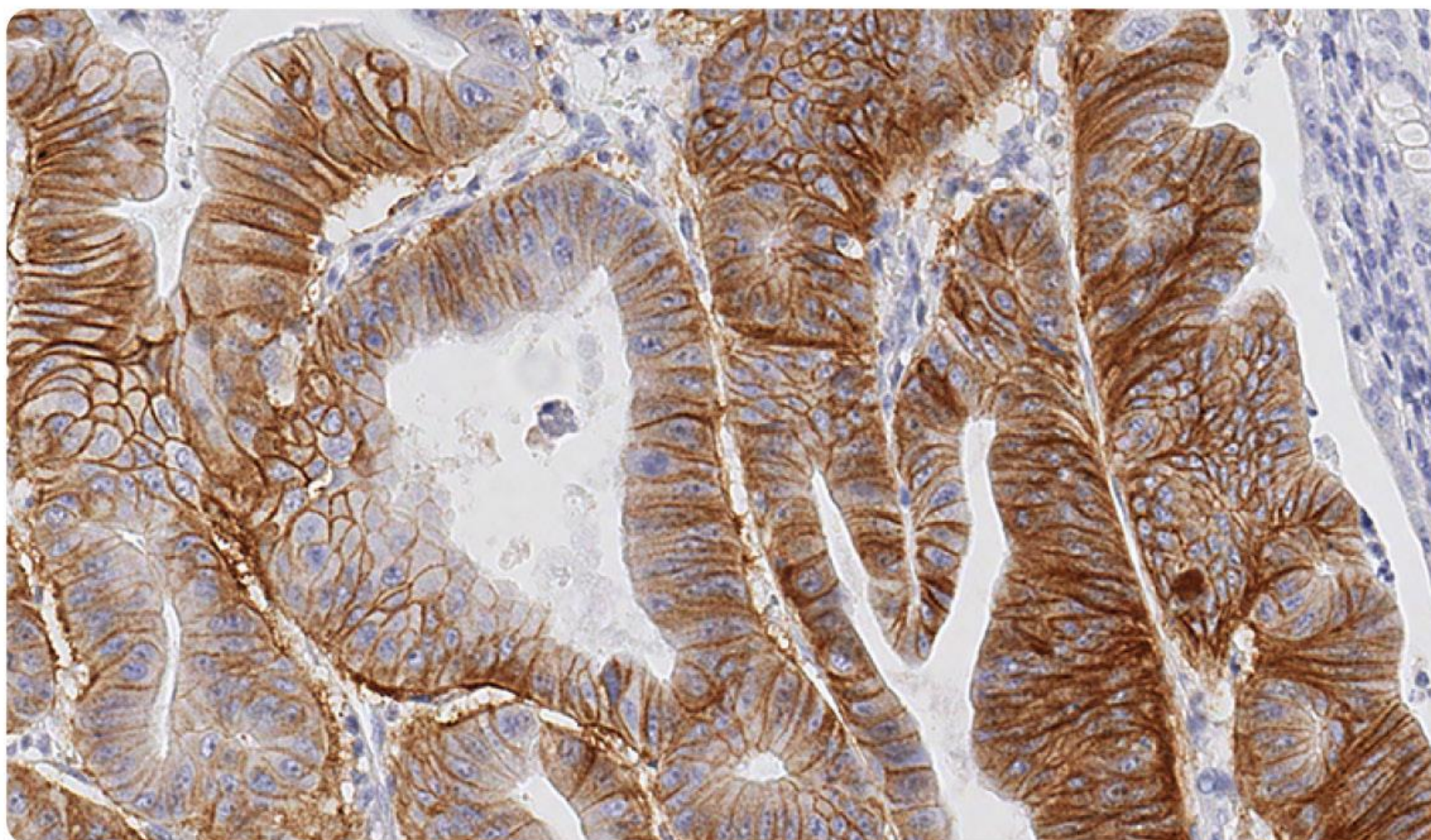
Perform HER2 IHC testing in all metastatic solid tumors

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

Surgical specimen



used in

or IHC 3+^{1,3,48}

n

basolateral, or
ous reactivity in
lls

^b with strong
eral, or
ous reactivity
centage of
d

ment

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

^aDESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02.¹

^bTumor 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, and accompanying full [Prescribing Information](#), including [Boxed WARNINGS](#), and [Medication Guide](#).





Metastatic Solid Tumors

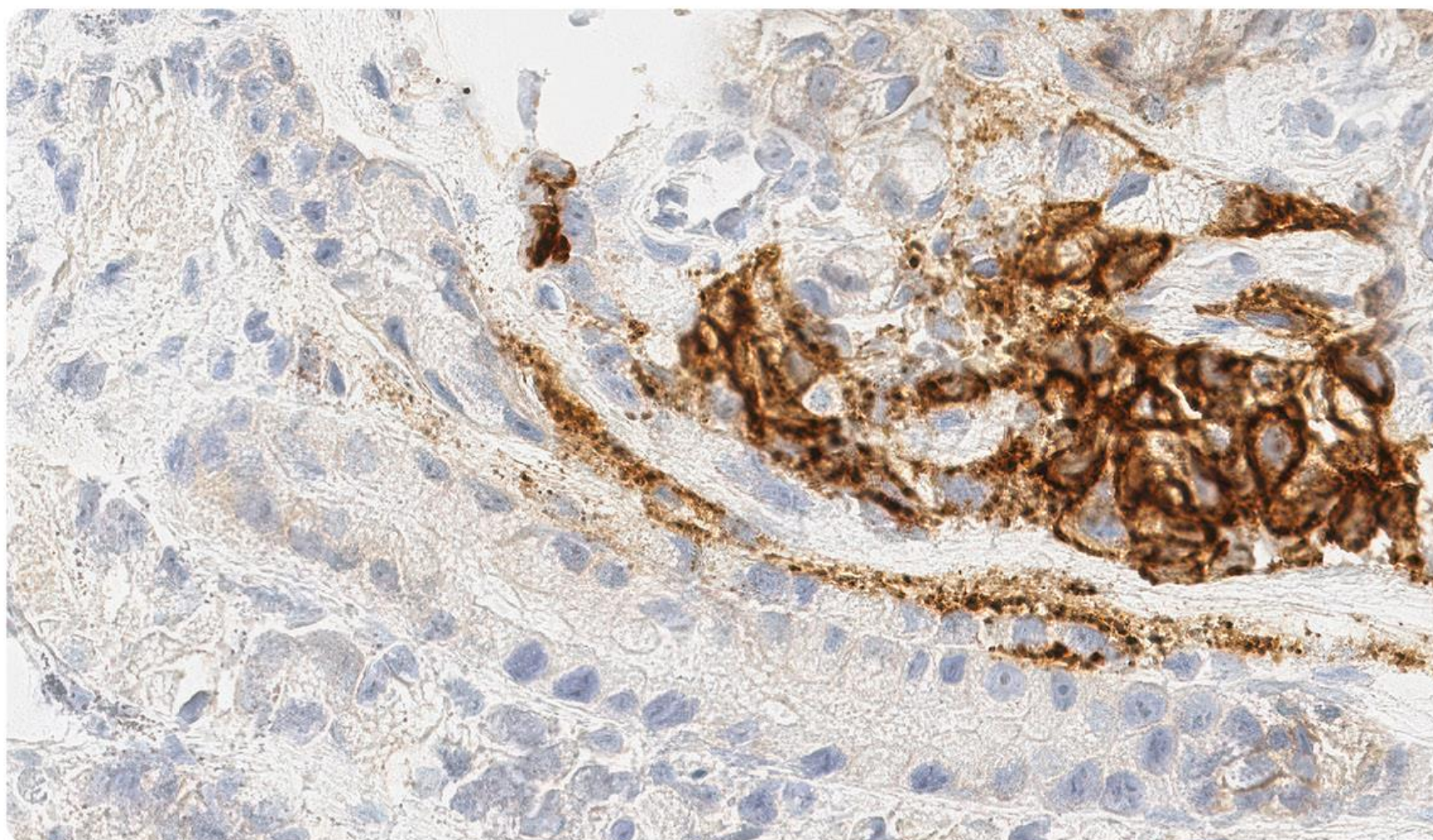
Perform HER2 IHC testing in all metastatic solid tumors

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

Biopsy specimen



used in

or IHC 3+^{1,3,48}

basolateral, or
ous reactivity in
lls

with strong
eral, or
ous reactivity
centage of
d

ment

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

^aDESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02.¹

^bTumor 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, and accompanying full [Prescribing Information](#), including [Boxed WARNINGS](#), and [Medication Guide](#).



HER2
ALTERATIONS

METASTATIC
BREAST CANCER

GASTRIC
CANCER

METASTATIC
SOLID TUMORS

mNSCLC

PRE-ANALYTICS
& REPORTING

ISI

ABBREVIATIONS
& REFERENCES

SUMMARY

PI



10



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



Control

Breast scoring



Circumferential



Lateral



Basolateral

Gastric scoring



In DESTINY-PanTumor02, tissue samples were⁴⁸:

- 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 testing³



Your oncology team may request that you test archived tissue to identify potentially eligible patients for HER2-targeted treatment^{3,55}

- 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^{52,56-60}

- For other tumor types, the CAP General IHC Quantitative Biomarkers Template is available⁶¹

Make HER2 IHC testing a standard part of your initial biomarker workup across solid tumors¹

^aDESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02.⁴⁵⁻⁴⁷

Please see Important Safety Information on pages 16-20 and throughout, 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-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^{1,29,40,62}

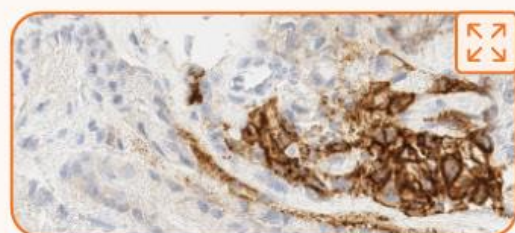
- NGS testing is the recommended method for efficiently utilizing limited biopsy tissue while maximizing diagnostic genomic information
- Sanger sequencing and targeted PCR techniques can also be utilized

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^{1,63}

Report summary

Tier 1: Variants of strong clinical significance

VARIANT	CLINICAL IMPACT
<i>ERBB2</i>	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}

^aTumor cell cluster is defined as a cluster of 5 or more tumor cells.³

^bFrom 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.⁶³

Please see Important Safety Information on pages 16-20 and throughout, 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}



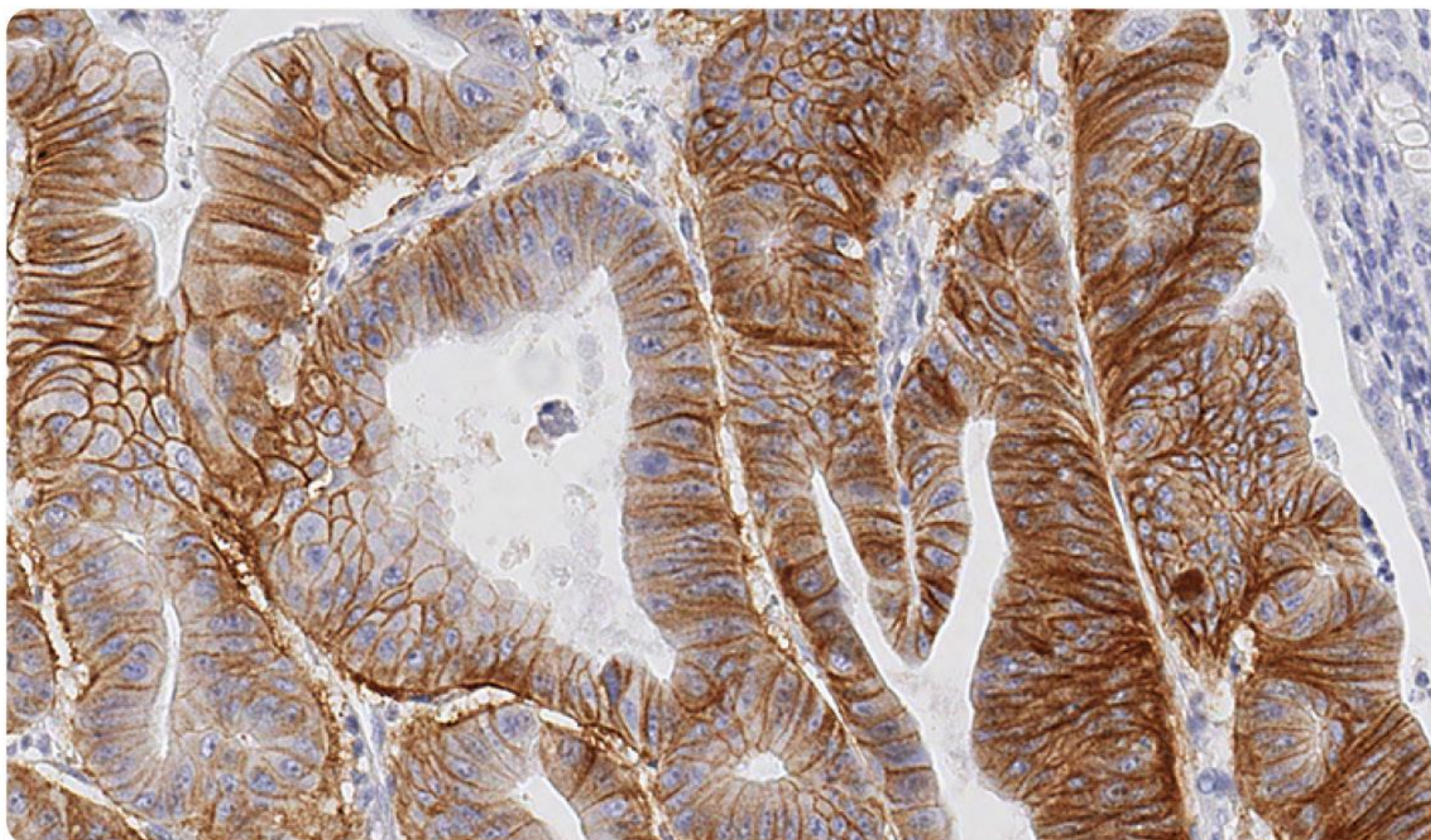
HER2 IHC testing can detect HER2-positive (IHC 3+) mNSCLC^{1,45}

- ASCO patient



NGS testing can detect *HER2 (ERBB2)*-mutant mNSCLC^{1,29,40,62}

Surgical specimen



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

^aTumor cell cluster is defined as a cluster of five or more tumor cells.³

^bFrom 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.⁶³

Please see Important Safety Information on pages 16-20 and throughout, 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}



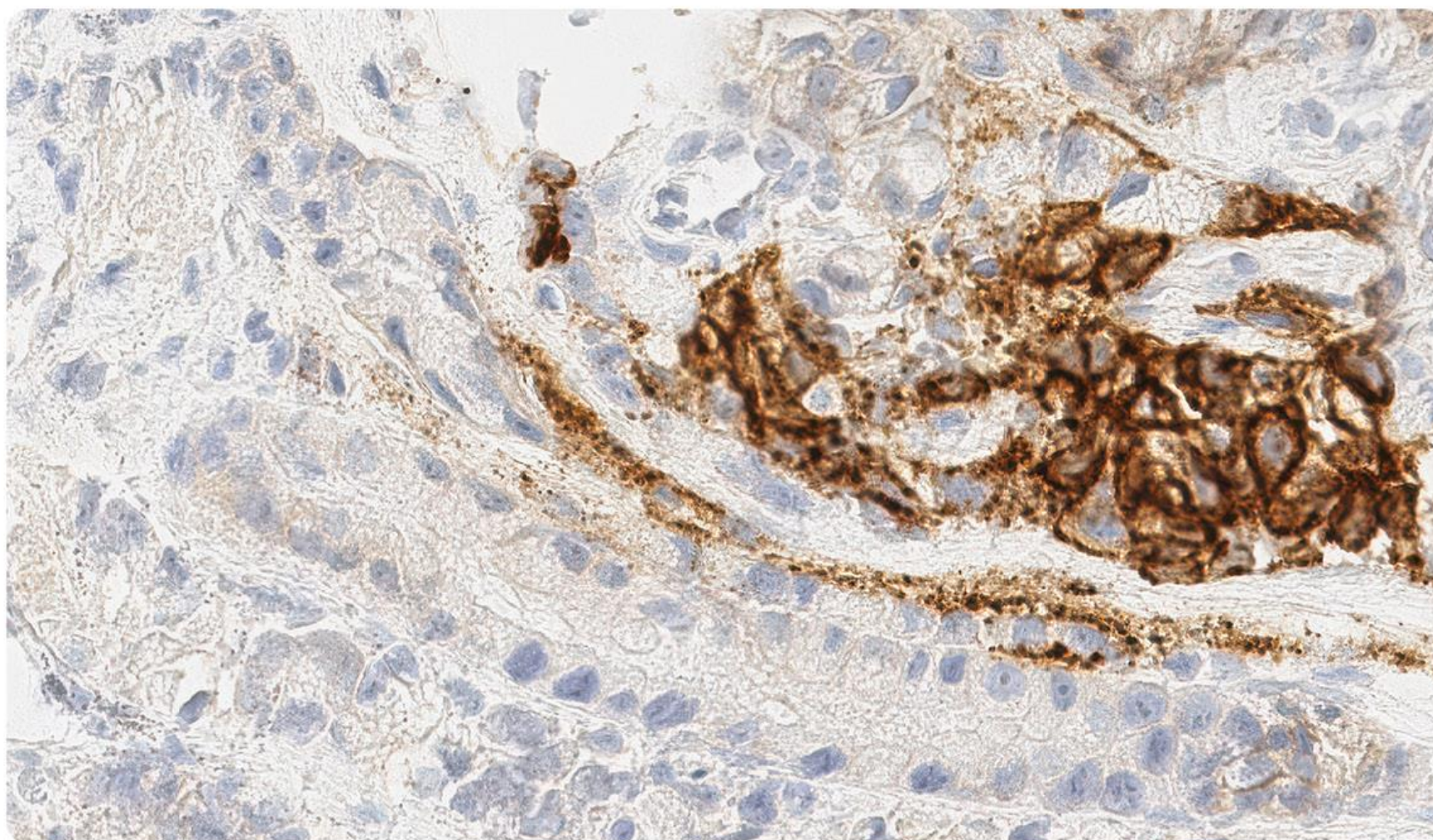
HER2 IHC testing can detect HER2-positive (IHC 3+) mNSCLC^{1,45}

- ASCO patient



NGS testing can detect *HER2 (ERBB2)*-mutant mNSCLC^{1,29,40,62}

Biopsy specimen



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

^aTumor cell cluster is defined as a cluster of five or more tumor cells.³

^bFrom 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.⁶³

Please see Important Safety Information on pages 16-20 and throughout, 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^{6,26-29,63,64}

HER2+ (IHC 3+) can still occur in the absence of a positive *HER2 (ERBB2)* amplification result detected via NGS/ISH testing²⁶

HER2 amplification ● ~1%

HER2+ (IHC 3+) ● 1%–5%

HER2 mutation ● 2%–4%

There is minimal to no overlap between *HER2 (ERBB2)* mutations and HER2 positivity (IHC 3+)⁶³



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 NGS⁴⁰

- Concurrent testing can reduce turnaround time and increase yield of targetable alteration detection⁴⁰
 - Testing with ctDNA can significantly reduce turnaround time for results⁶⁵
- Positive results with liquid biopsy are sufficient to confirm *HER2* mutations⁶⁶
- If no mutation is detected with plasma, tumor tissue should be tested¹



For mNSCLC patients, work with your MDT to ensure sufficient tissue is collected for both NGS and IHC testing³

- 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 NGS⁵⁶

- 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, and accompanying full [Prescribing Information](#), including **Boxed WARNINGS**, and [Medication Guide](#).





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^{2,3,52,67}

Cold ischemia time



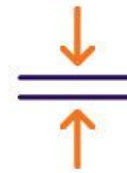
- Prolonged cold ischemia time may lead to false-negative IHC results
- Tissue acquisition to fixation time should be as short as possible
 - Specimens ideally should be placed in fixative within 1 hour

Incorrect fixation



- Specimens must be fixed in sufficient volume of 10% neutral buffered formalin for ≥6 hours
- Prolonged fixation in formalin (>72 hours) 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

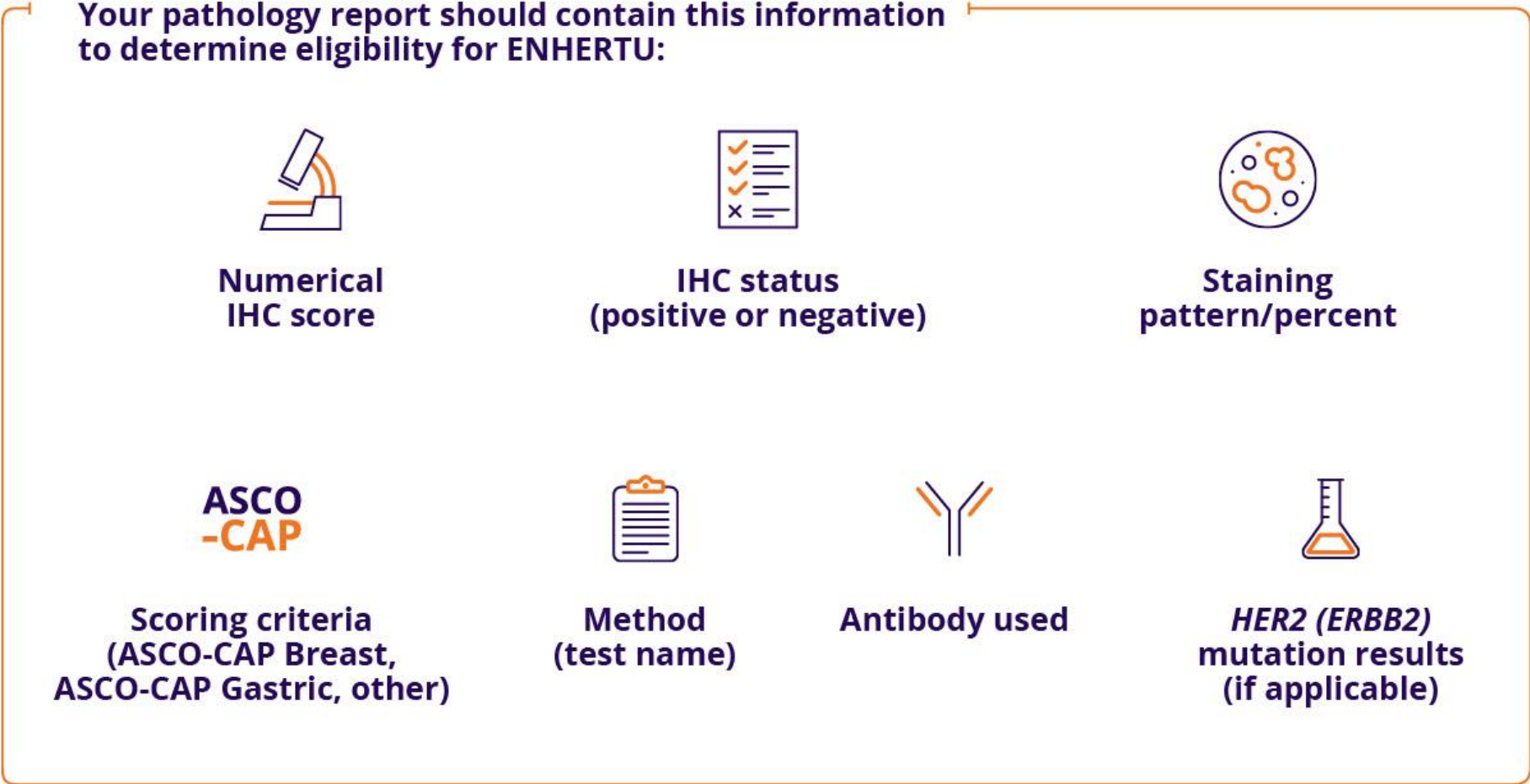
Revise reflexive protocols for new patients to add HER2 IHC testing for all solid tumors, including mNSCLC, and NGS testing for mNSCLC^{1,40}

Please see Important Safety Information on pages 16-20 and throughout, and accompanying full [Prescribing Information](#), including **Boxed WARNINGS**, and [Medication Guide](#).





Clearly report HER2 alterations and corresponding actionability for ENHERTU



Report any and all membrane staining in patients with mBC¹

- HER2-ultralow is defined as IHC 0 with membrane staining
- HER2-low is defined as IHC 1+ or IHC 2+/ISH-



HER2 IHC scores must be reported as part of any comprehensive biomarker analysis report, along with *HER2 (ERBB2)* mutation results in mNSCLC^{52,56}

- 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

Please see Important Safety Information on pages 16-20 and throughout, and accompanying full [Prescribing Information](#), including **Boxed WARNINGS**, and [Medication Guide](#).

Important Safety Information (cont'd)

Warnings and Precautions

Neutropenia (cont'd)

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

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

Left Ventricular Dysfunction

Patients treated with ENHERTU may be at increased risk of developing left ventricular dysfunction. Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies, including ENHERTU. Assess LVEF prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. Manage LVEF decrease through treatment interruption. When LVEF is >45% and absolute decrease from baseline is 10-20%, continue treatment with ENHERTU. When LVEF is 40-45% and absolute decrease from baseline is <10%, continue treatment with ENHERTU and repeat LVEF assessment within 3 weeks.



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](#).

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



HER2
ALTERATIONS

METASTATIC
BREAST CANCER

GASTRIC
CANCER

METASTATIC
SOLID TUMORS

mNSCLC

PRE-ANALYTICS
& REPORTING



ISI

ABBREVIATIONS
& REFERENCES

SUMMARY

PI



16



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 $0.5 \times 10^9/L$), interrupt ENHERTU until resolved to Grade 2 or less, then maintain dose. For Grade 4 neutropenia (ANC $<0.5 \times 10^9/L$), interrupt ENHERTU until resolved to Grade 2 or less, then reduce dose by 1 level. For febrile neutropenia (ANC $<1.0 \times 10^9/L$ and temperature $>38.3^\circ C$ or a sustained temperature of $\geq 38^\circ C$ 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 $25 \times 10^9/L$) interrupt ENHERTU until resolved to Grade 1 or less, then maintain dose. For Grade 4 thrombocytopenia (platelets $<25 \times 10^9/L$) 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 ($\geq 20\%$) 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](#).

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



HER2
ALTERATIONS

METASTATIC
BREAST CANCER

GASTRIC
CANCER

METASTATIC
SOLID TUMORS

mNSCLC

PRE-ANALYTICS
& REPORTING



ISI

ABBREVIATIONS
& REFERENCES

SUMMARY

PI



17



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](#).

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



HER2
ALTERATIONS

METASTATIC
BREAST CANCER

GASTRIC
CANCER

METASTATIC
SOLID TUMORS

mNSCLC

PRE-ANALYTICS
& REPORTING



ISI

ABBREVIATIONS
& REFERENCES

SUMMARY

PI



18



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/m² biweekly or paclitaxel (N=7) 80 mg/m² 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](#).

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



HER2
ALTERATIONS

METASTATIC
BREAST CANCER

GASTRIC
CANCER

METASTATIC
SOLID TUMORS

mNSCLC

PRE-ANALYTICS
& REPORTING



ISI

ABBREVIATIONS
& REFERENCES

SUMMARY

PI



19



Indications and Important Safety Information (cont'd)

Adverse Reactions (cont'd)

The most common ($\geq 20\%$) 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](https://www.fda.gov/medwatch).

Please see accompanying full [Prescribing Information](#), including **Boxed WARNINGS**, and [Medication Guide](#).

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



HER2
ALTERATIONS

METASTATIC
BREAST CANCER

GASTRIC
CANCER

METASTATIC
SOLID TUMORS

mNSCLC

PRE-ANALYTICS
& REPORTING



ISI

ABBREVIATIONS
& REFERENCES

SUMMARY

PI



20



Abbreviations and References

Abbreviations

1L, first line; aGC, advanced gastric cancer; ASCO, American Society of Clinical Oncology; BICR, blinded independent central review; CAP, College of American Pathologists; CDK4/6, cyclin-dependent kinases 4 and 6; CDx, companion diagnostics; CEP17, centromeric region of chromosome 17; ctDNA, circulating tumor DNA; DAB, 3,3'-diaminobenzidine tetrahydrochloride; DOR, duration of response; *ERBB2*, erb-b2 receptor tyrosine kinase 2; ET, endocrine therapy; FISH, fluorescence in situ hybridization; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor-positive; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenous; 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; ORR, objective response rate; OS, overall survival; PCR, polymerase chain reaction; PFS, progression-free survival; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

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. *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, Sancı 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.

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

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



HER2
ALTERATIONS

METASTATIC
BREAST CANCER

GASTRIC
CANCER

METASTATIC
SOLID TUMORS

mNSCLC

PRE-ANALYTICS
& REPORTING

ISI

ABBREVIATIONS
& REFERENCES

SUMMARY

PI



21



References (cont'd)

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. 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.1.2025. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed March 25, 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.4.2025. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed March 24, 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.4.2025. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed June 27, 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.2.2025. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed March 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. 40. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.7.2025. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed July 10, 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.4.2025. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed April 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. 42. PATHWAY anti-HER-2/neu (4B5) rabbit monoclonal primary antibody method sheet. 14427US Rev K. 25-01-29. 43. Bardia A, Hu X, Dent R, et al; DESTINY-Breast06 Trial Investigators. Protocol for: Trastuzumab deruxtecan after endocrine therapy in metastatic breast cancer. *N Engl J Med*. 2024;391(22):2110-2122. 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):2419-2430. 45. Li BT, Smit EF, Goto Y, et al; DESTINY-Lung01 Trial Investigators. Trastuzumab deruxtecan in HER2-mutant non-small-cell lung cancer. *N Engl J Med*. 2022;386(3):241-251. 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. Bardia A, Hu X, Dent R, et al; DESTINY-Breast06 Trial Investigators. Trastuzumab deruxtecan after endocrine therapy in metastatic breast cancer. *N Engl J Med*. 2024;391(22):2110-2122. 50. Bardia A, Hu X, Dent R, et al; DESTINY-Breast06 Trial Investigators. Supplement to: Trastuzumab deruxtecan after endocrine therapy in metastatic breast cancer. *N Engl J Med*. 2024;391(22):2110-2122. 51. PATHWAY anti-HER-2/neu (4B5) rabbit monoclonal primary antibody interpretation guide for breast cancer. 14991US Rev A. 25-01-28. 52. College of American Pathologists. Reporting template for reporting results of biomarker testing of specimens from patients with carcinoma of the breast. Accessed March 19, 2025. https://documents.cap.org/documents/New-Cancer-Protocols-March-2025/Breast.Bmk_1.6.0.0.REL_CAPCP.pdf 53. Ruschoff J, Hanna W, Bilous M, et al. HER2 testing in gastric cancer: a practical approach. *Mod Pathol*. 2012;25(5):637-650. 54. National Cancer Institute. NCI Dictionary of Cancer Terms. Accessed October 17, 2024. <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/tumor-agnostic-therapy> 55. 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. 56. College of American Pathologists. Template for reporting results of biomarker testing of specimens from patients with non-small cell carcinoma of the lung. Accessed October 21, 2024. https://documents.cap.org/protocols/Lung.Bmk_2.0.1.1.REL_CAPCP.pdf 57. College of American Pathologists. Template for reporting results of biomarker testing of specimens from patients with carcinoma of the colon and rectum. Accessed October 21, 2024. https://documents.cap.org/protocols/ColoRectal.Bmk_1.3.0.0.REL_CAPCP.pdf 58. College of American Pathologists. Template for reporting results of HER2 (ERBB2) biomarker testing of specimens from patients with adenocarcinoma of the stomach or gastroesophageal junction. Accessed October 21, 2024. <https://documents.cap.org/protocols/cp-gastric-HER2biomarker17-1001.pdf> 59. College of American Pathologists. Template for reporting results of biomarker testing of specimens from patients with carcinoma of gynecologic origin. Accessed October 21, 2024. https://documents.cap.org/documents/Gynecologic.Bmk_1.1.0.0.REL_CAPCP.pdf 60. College of American Pathologists. Head and neck biomarker reporting template. Accessed October 21, 2024. https://documents.cap.org/protocols/HN.Bmk_2.2.0.0.REL_CAPCP.pdf 61. College of American Pathologists. Template for reporting results of quantitative IHC biomarker testing of specimens from patients with carcinoma. Accessed October 21, 2024. https://documents.cap.org/protocols/IHC.Bmk_1.1.0.1.REL_CAPCP.pdf

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

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



HER2
ALTERATIONS

METASTATIC
BREAST CANCER

GASTRIC
CANCER

METASTATIC
SOLID TUMORS

mNSCLC

PRE-ANALYTICS
& REPORTING

ISI

ABBREVIATIONS
& REFERENCES

SUMMARY

PI



22



References (cont'd)

62. 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. 63. 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. 64. 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. 65. 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. 66. 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. 67. College of American Pathologists. Template for reporting results of biomarker testing of specimens from patients with carcinoma of the endometrium. 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, and accompanying full [Prescribing Information](#), including **Boxed WARNINGS**, and [Medication Guide](#).

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



HER2
ALTERATIONS

METASTATIC
BREAST CANCER

GASTRIC
CANCER

METASTATIC
SOLID TUMORS

mNSCLC

PRE-ANALYTICS
& REPORTING

ISI

ABBREVIATIONS
& REFERENCES

SUMMARY

PI

23

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-ultralow¹



Perform HER2 IHC testing AND NGS testing for patients with mNSCLC^{1,40}



HER2 IHC test ALL metastatic solid tumors¹

See the clinical data at [ENHERTUhcp.com](https://www.enherthu.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](#).