Across solid tumors

IDENTIFY HER2 ALTERATIONS TO INFORM ELIGIBILITY FOR TREATMENT WITH ENHERTU

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

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

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

[a]Indicated for certain previously treated adults.[1]

Indications and Important Safety Information

Indications

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

- HER2-Positive Early Breast Cancer
  - As neoadjuvant treatment of adult patients with HER2-positive (IHC 3+ or ISH+) Stage II or III breast cancer, as determined by an FDA-authorized test followed by a taxane, trastuzumab, and pertuzumab (THP)
  - As adjuvant treatment of adult patients with HER2-positive (IHC 3+ or ISH+) breast cancer who have residual invasive disease following neoadjuvant trastuzumab (with or without pertuzumab) and taxane-based treatment
- HER2-Positive Metastatic Breast Cancer
  - In combination with pertuzumab as first-line treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH+) breast cancer, as determined by an FDA-authorized test
  - As monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH+) breast cancer who have received a prior anti-HER2-based regimen either in the metastatic setting, or, in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy
- HER2-Low and HER2-Ultralow Metastatic Breast Cancer
  - As monotherapy for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining) breast cancer, as determined by an FDA-authorized test, that has progressed on one or more endocrine therapies in the metastatic setting
  - As monotherapy for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-authorized test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy
- HER2-Mutant Unresectable or Metastatic Non-Small Cell Lung Cancer (NSCLC)
  - As monotherapy for the treatment of adult patients with unresectable or metastatic NSCLC whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-authorized test, and who have received a prior systemic therapy

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

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

Important Safety Information

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

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

Please see Important Safety Information on pages 16-22 and throughout, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

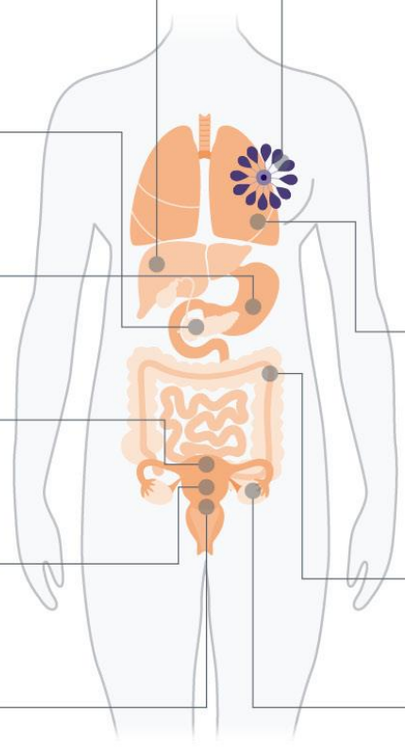
Daiichi-Sankyo | AstraZeneca

Across Tumor Types

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

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

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



Biliary tract
IHC 3+
4%–13%

Pancreatic
IHC 3+
1%–7%

Gastric
IHC 3+ or IHC 2+/ISH+
8%–27%

Endometrial
IHC 3+
4%–28%

Bladder
IHC 3+
4%–31%

Cervical
IHC 3+
8%–14%

Breast
IHC 3+ or ISH+
15%

Of HR+/HER2-negative mBC[b]:
IHC 1+ and IHC 2+/ISH–
~60%–65%

IHC 0 with membrane staining
~20%–25%

NSCLC
IHC 3+
1%–5%

HER2 (ERBB2)-mutant
2%–4%

Colorectal
IHC 3+
1%–3%

Ovarian
IHC 3+
1%–5%

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

[a]Individual tumor prevalence numbers reflect US and ex-US populations. Due to limited testing of IHC in the US, data from a global population have been included.
[b]As demonstrated in DESTINY-Breast06 screening data.

Please see Important Safety Information on pages 16-22 and throughout, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

Across Tumor Types

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

Tumor type	HER2 status	Key clinical trial(s)	ASCO-CAP breast scoring criteria[b]	ASCO-CAP gastric scoring criteria[b]	
Early breast cancer[1,36,37]	HER2-positive (IHC 3+ or ISH+)	DESTINY-Breast11/ DESTINY-Breast05	✓		Consider using the FDA-authorized PATHWAY HER2 (4B5) and VENTANA HER2 Dual ISH DNA Probe Cocktail CDx for detecting HER2 status, as used in the DESTINY-Breast trials[d]
Metastatic breast cancer[1,2,38,39]	HER2-positive (IHC 3+ or ISH+)	DESTINY-Breast09/ DESTINY-Breast03	✓		
	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[1,40,41]	HER2-positive (IHC 3+ or IHC 2+/ISH+)	DESTINY-Gastric04[e]/ DESTINY-Gastric01		✓	ASCO-CAP gastric HER2 scoring criteria were used to identify patients in these trials
Metastatic solid tumors, including NSCLC[1,42-44] (accelerated approval)	HER2-positive (IHC 3+)	DESTINY-PanTumor02/ DESTINY-Lung01/ DESTINY-CRC02		✓	
Metastatic non-small cell lung cancer[1,45] (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-authorized tests for the detection of HER2 protein expression, *HER2* gene amplification, and activating *HER2* mutations is available at http://www.fda.gov/CcompanionDiagnostics[1]
- For patient selection criteria for ENHERTU, please see Section 2.1 of the Prescribing Information

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

[a]Please see full indications for ENHERTU on page 1.
[b]Scoring criteria used in clinical trial.
[c]DESTINY-Breast06 used a proposed scoring algorithm based on the ASCO-CAP scoring criteria for breast cancer.[39]
[d]The PATHWAY HER2 (4B5) was not used in DB-03; the VENTANA HER2 Dual ISH DNA Probe Cocktail CDx was used in DB-09, DB-05, and DB-11.[1]
[e]This study provides additional data to the safety and efficacy data in the PI and further supports the approved 2L use of ENHERTU for eligible patients with HER2+ advanced gastric/GEJ adenocarcinoma.

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Important Safety Information (cont'd)

Warnings and Precautions

Interstitial Lung Disease / Pneumonitis

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

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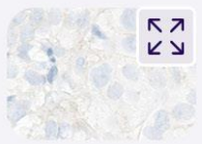
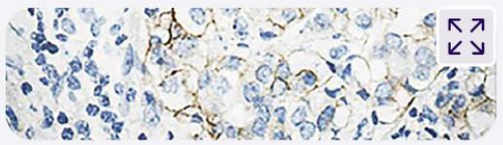
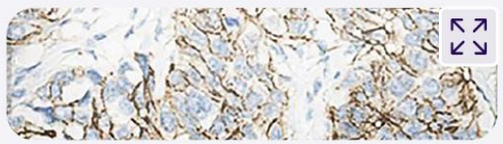
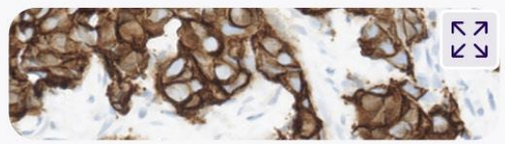
Perform HER2 IHC testing to identify HER2-ultralow and HER2-low patients who may be eligible for HER2-directed treatment in mBC

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

- 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-authorized companion diagnostic scoring criteria for breast cancer[1,44,51]

IHC 0	IHC 1+	IHC 2+	IHC 3+
				
No membrane staining	Any staining of the membrane in >0 and ≤10% of the cancer cells[b-d]	Faint, partial staining of the membrane in >10% of the cancer cells[b]	Weak to moderate complete membrane staining in >10% of the cancer cells	Intense complete staining of the membrane in >10% of the cancer cells
		ISH–	*Equivocal: reflex ISH test*	*ISH+*
		IHC 1+ or IHC 2+/ISH–		**ISH+ or IHC 3+**
OR		**HER2-negative**		**HER2-positive**
HER2-null	**HER2-ultralow**	**HER2-low**		

May be eligible for HER2-directed treatment

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.[1,45,52,53]

[a]As demonstrated in DESTINY-Breast06 screening data. Among the 1856 patients screened for participation in the study, 12% (255 patients) had IHC 0 with absent membrane staining, while 22% (402 patients) were classified as HER2-ultralow, defined as IHC 0 with membrane staining. IHC 1+ was observed in 45% (829 patients), and IHC 2+/ISH- in 21% (385 patients).[25]
[b]Review at 40x is recommended to discern the presence or absence of any staining such as faint, partial staining.[44]
[c]Recommend re-reading by a second pathologist for cases classified as HER2-null or as HER2-ultralow expression with % of tumor cells ≤5%.[44]
[d]In 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.[44]

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BC

Scoring and interpretation considerations in breast cancer

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

1

Screen entire tissue at low magnification[49]

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

2

Assess membrane staining pattern[2]:

- Incomplete/partial
- Complete/circumferential

AND

Assess staining intensity[2]:

- Faint
- Weak to moderate
- Intense

3

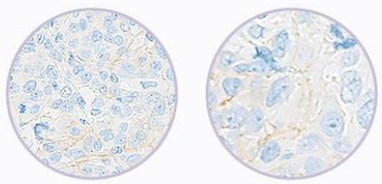
Assess relative percentages of stained cells using established cutoffs[2]:

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

4

Use high-power magnification (40x) to discern faint, incomplete membrane staining, according to ASCO-CAP guidelines[49]

- Additional time may be needed to interpret and score cases with artifact, values near the 10% cutoff, and heterogeneous areas[49]
- Request a second pathologist review for cases classified as HER2-null or as HER2-ultralow expression with % of tumor cells ≤5%[38]



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 cells[38]

Important Safety Information (cont'd)

Warnings and Precautions

Interstitial Lung Disease/ Pneumonitis (cont'd)

Promptly initiate systemic corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥1 mg/kg/day prednisolone or equivalent) and continue for at least 14 days followed by gradual taper for at least 4 weeks. In the adjuvant HER2+ breast cancer setting, if drug-induced ILD is suspected, rule out radiotherapy-related pneumonitis. If only radiotherapy-related pneumonitis is suspected, consider interruption of ENHERTU for Grade 2 and permanently discontinue ENHERTU for Grade ≥3.

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

ENHERTU as Monotherapy

In patients treated with ENHERTU 5.4 mg/kg, ILD occurred in 12% of patients. Median time to first onset was 5.5 months (range: 0.9 to 31.5). Fatal outcomes due to ILD and/or pneumonitis occurred in 0.9% of patients treated with ENHERTU.

ENHERTU in Combination with Pertuzumab

In patients treated with ENHERTU 5.4 mg/kg in combination with pertuzumab (N=431), ILD occurred in 12% of patients. Median time to first onset was 8.0 months (range: 0.6 to 33.8). Fatal outcomes due to ILD and/or pneumonitis occurred in 0.5% of patients treated with ENHERTU in combination with pertuzumab.

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The PATHWAY HER2 (4B5) CDx is clinically validated and FDA authorized to detect HER2 status in BC

The PATHWAY HER2 (4B5) CDx can be used to detect HER2-expressing BC, including HER2-low and HER2-ultralow mBC, and there have been no changes to the on-market protocol[2,38,49,50]

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

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

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

The staining procedure is pre-programmed with a mild cell-conditioning step and a primary antibody incubation time of 12 minutes[38]

- 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 produce invalid results, particularly in cases with HER2-low and HER2-ultralow expression, which may impact treatment decisions

Intended use[38]

- 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 breast carcinoma tissue using the *ultraView* Universal DAB Detection Kit on a BenchMark *ULTRA* or BenchMark *ULTRA* PLUS instrument
- This IHC device is indicated for identifying metastatic breast cancer patients who are eligible for HER2-directed treatment (IHC 0 with membrane staining, IHC 1+ or IHC 2+/ISH non-amplified, and IHC 3+ or ISH amplified)
- Test results 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 16-22 and throughout, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

BC

Report any and all membrane staining

Report HER2-ultralow by documenting IHC 0 score and faint/barely perceptible, incomplete membrane staining in ≤10% of cells[50]

Recommended reporting for HER2-ultralow[55]

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 ≤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 in mBC[1,2,38,50]

Study/guideline	Scoring criteria	HER2 IHC status description	ENHERTU indication
DESTINY-Breast06	Membrane staining that is seen in >0 and ≤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 ≤10% of the cancer cells	IHC 0 with membrane staining	
CAP Breast Reporting Template	Membrane staining that is incomplete and is faint/barely perceptible and in ≤10% of tumor cells	0+/with membrane staining	
ASCO-CAP Guidelines	Membrane staining that is incomplete and is faint/barely perceptible and in ≤10% of tumor cells	IHC 0	

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

View CAP Reporting Template

Please see Important Safety Information on pages 16-21 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 (cont'd)

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

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

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

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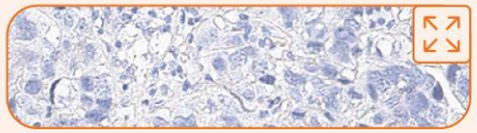
aGC

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

ASCO-CAP gastric cancer scoring criteria[1,3,46]

IHC 0

Surgical specimen



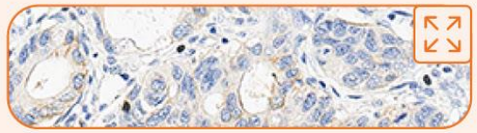
No reactivity or membranous reactivity in <10% of tumor cells

Biopsy specimen

No reactivity in any tumor cells

IHC 1+

Surgical specimen



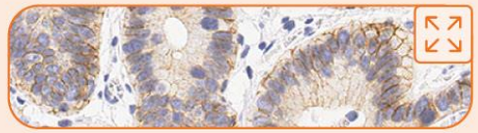
Faint or barely perceptible membranous reactivity in ≥10% of tumor cells; cells are reactive only in part of their membrane

Biopsy specimen

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

IHC 2+

Surgical specimen



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

Biopsy specimen

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

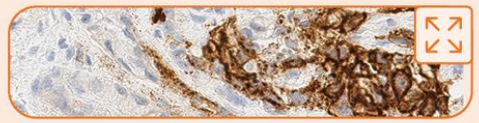
IHC 3+

Surgical specimen



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

Biopsy specimen



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

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

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

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

May be eligible for HER2-directed treatment

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

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

Please see Important Safety Information on pages 16-22 and throughout, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

aGC

Scoring and interpretation considerations in aGC/GEJ adenocarcinoma

Surgical specimen[3]

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

Biopsy specimen[3,51]

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

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

ASCO-CAP UPDATE

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

- Compared to breast, gastric tumors have:

Greater intratumoral heterogeneity

Lower incidence of complete membrane staining

Frequent basolateral patterns of HER2 expression

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

Please see Important Safety Information on pages 16-22 and throughout, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

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

9

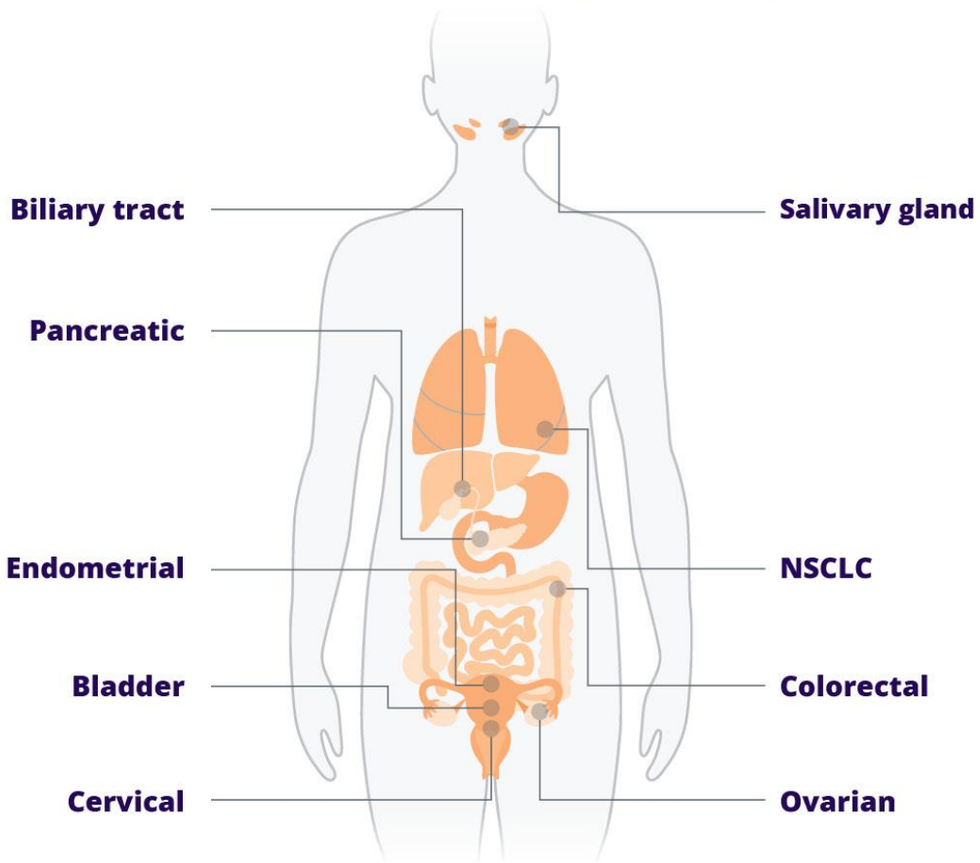
Metastatic Solid Tumors

Perform HER2 IHC testing in all metastatic solid tumors

HER2-positive (IHC 3+) is actionable across metastatic solid tumors due to a tumor-agnostic indication for HER2-directed treatment that is FDA approved under accelerated approval[1,44,52]

- 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[1,44]:

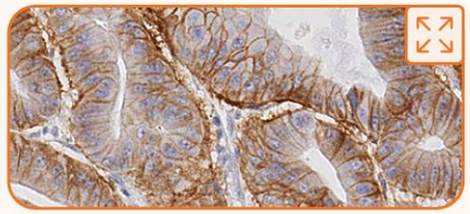


and other rare tumor types

ASCO-CAP gastric cancer scoring criteria were used in 3 clinical trials[a] across metastatic solid tumors (outside of breast cancer)[42-44]

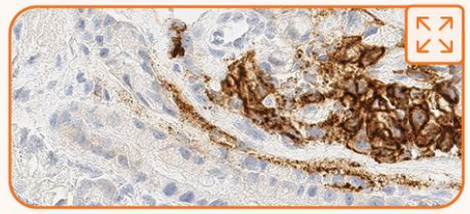
- Refer to page 8 for full gastric scoring criteria

ASCO-CAP Gastric Cancer Scoring Criteria for HER2+ (IHC 3+)[1,3,46]



Surgical specimen

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



Biopsy specimen

Tumor cell cluster (5 or more tumor cells) 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

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

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

Please see Important Safety Information on pages 16-22 and throughout, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

Scoring and interpretation considerations in metastatic solid tumors

ASCO-CAP guidelines for gastric cancer were used to assess HER2 IHC status in DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02[3,42-44]

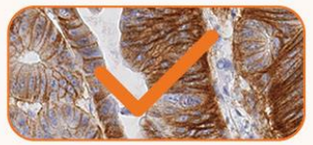
Breast criteria[2,46]



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

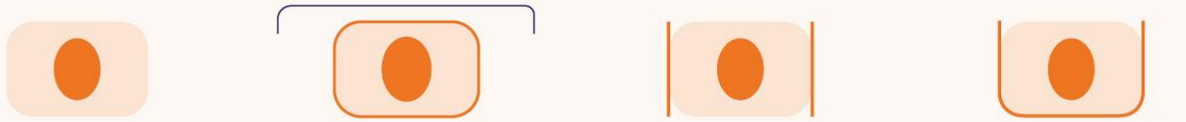
VS

Gastric criteria[3,46]



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

Staining patterns required for IHC 3+ with each set of scoring criteria[2,3]





The CAP Gynecologic Biomarkers Reporting Template includes HER2 IHC scoring criteria for cervical, endometrial, and ovarian tumors, which align with the ASCO-CAP gastric scoring criteria used in DESTINY-PanTumor02[3,53]

Review CAP gynecologic template here

Tissue Considerations: In DESTINY-PanTumor02, tissue samples were[54,55]:

- 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

Archival tissue, if fresh biopsy is not available, or fine needle aspirations are also acceptable samples for HER2 IHC testing[3,54]

Reporting Tools: The CAP includes guidance for reporting HER2 IHC results in their Biomarker Reporting Templates for breast, gastric, colon & rectum, gynecologic, head & neck, and lung specimens[49,53,56-59]

Review CAP templates here

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

Please see Important Safety Information on pages 16-22 and throughout, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

Perform NGS and HER2 IHC testing to detect 2 distinct HER2 alterations in mNSCLC[1,45]

NGS testing can detect *HER2 (ERBB2)*-mutant mNSCLC[1,29,45,61]

- NGS testing is recommended for efficiently utilizing limited biopsy tissue while maximizing diagnostic genomic information
- Targeted PCR can also be utilized

HER2 IHC testing can detect HER2-positive (IHC 3+) mNSCLC[1,42]

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

HER2 (ERBB2) mutations[1]

Report summary

Tier 1: Variants of strong clinical significance

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

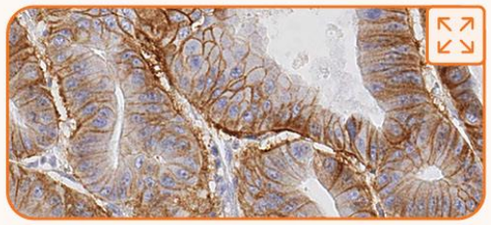
DESTINY-Lung02 supported the accelerated approval of HER2-directed treatment across activating *HER2* mutations, without limitation regarding location in the tyrosine kinase domain[1]

- Patients with HER2 mutations in both the kinase domain (97%) and extracellular domain (3%) were included in this study

***HER2 (ERBB2)*-mutant**

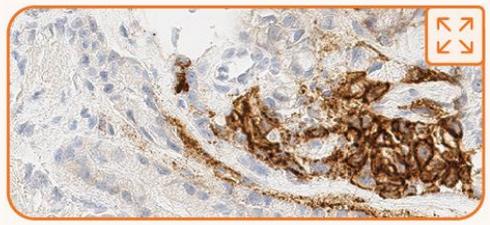
May be eligible for HER2-directed treatment

ASCO-CAP Gastric Cancer Scoring Criteria for HER2+ (IHC 3+)[1,3,46]



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

Both HER2 IHC testing and NGS testing are needed to identify actionable HER2 alterations in mNSCLC[1,45,b]

[a]Tumor cell cluster is defined as a cluster of 5 or more tumor cells.[3]
[b]Targeted PCR can also be used to identify *HER2 (ERBB2)* mutations.[45]

Please see Important Safety Information on pages 16-22 and throughout, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

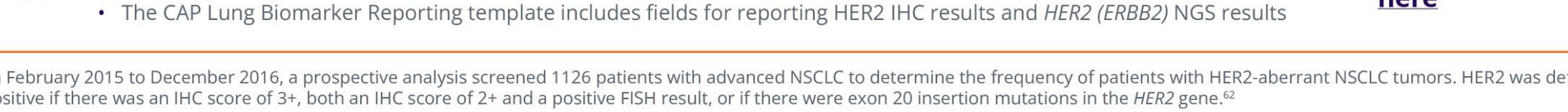
HER2 testing considerations in mNSCLC

2 actionable alterations

Activating *HER2 (ERBB2)* mutations and HER2-positive (IHC 3+) are actionable biomarkers in certain previously treated patients with mNSCLC[1]

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

HER2 (ERBB2) mutations generally do not occur concurrently with HER2-positive (IHC 3+) status[62]
- There is minimal to no overlap between *HER2 (ERBB2)* mutations and HER2-positive (IHC 3+)
- In a study of 1126 patients with NSCLC, none were both *HER2 (ERBB2)*-mutant and HER2-positive (IHC 3+)[a]



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

2 tests

Conduct both NGS and HER2 IHC testing at diagnosis of mNSCLC to inform treatment decisions in later lines[1,5]

HER2 IHC testing considerations[42]
- ASCO-CAP gastric scoring criteria were used in DESTINY-Lung01 to identify HER2+ (IHC 3+) status in mNSCLC
- Refer to page 8 for gastric scoring criteria

NGS testing considerations[1,45,64]
- Use complementary tissue and blood sample types to identify *HER2 (ERBB2)* mutations via NGS
- Positive results with liquid biopsy are sufficient to confirm *HER2 (ERBB2)* mutations
- If no mutation is detected with liquid biopsy, tumor tissue should be tested

2 results

Report HER2-positive (IHC 3+) results from IHC and *HER2 (ERBB2)* mutation results from NGS[56]

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

Review CAP lung template here

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

Please see Important Safety Information on pages 16-22 and throughout, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

Across Tumor Types

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

Pre-analytic variables of tissue samples are important to consider, as they may impact HER2 staining and subsequent scoring[2,3,50,65]

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[1,45]

Please see Important Safety Information on pages 16-22 and throughout, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

Across Tumor Types

Clearly report HER2 alterations and corresponding actionability for ENHERTU

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

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

Report any and all membrane staining in patients with mBC[1]

- 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[50,56]

- 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 16-21 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, HER2-Low, and HER2-Ultralow Breast Cancer, HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (5.4 mg/kg)

ENHERTU as Monotherapy

In patients treated with ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in 65% of patients. Nineteen percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 22 days (range: 2 to 939). Febrile neutropenia was reported in 1% of patients.

ENHERTU in Combination with Pertuzumab

In patients treated with ENHERTU 5.4 mg/kg in combination with pertuzumab (N=431), decreased neutrophil count occurred in 79% of patients. Median time to first onset was 22 days (range: 5 to 994). Twenty-nine percent had Grade 3 or 4 decreased neutrophil count. Febrile neutropenia was reported in 2.6% of patients.

ENHERTU followed by THP

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

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

Indications and Important Safety Information

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

- HER2-Positive Early Breast Cancer
  - As neoadjuvant treatment of adult patients with HER2-positive (IHC 3+ or ISH+) Stage II or III breast cancer, as determined by an FDA-authorized test followed by a taxane, trastuzumab, and pertuzumab (THP)
  - As adjuvant treatment of adult patients with HER2-positive (IHC 3+ or ISH+) breast cancer who have residual invasive disease following neoadjuvant trastuzumab (with or without pertuzumab) and taxane-based treatment
- HER2-Positive Metastatic Breast Cancer
  - In combination with pertuzumab as first-line treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH+) breast cancer, as determined by an FDA-authorized test
  - As monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH+) breast cancer who have received a prior anti-HER2-based regimen either in the metastatic setting, or, in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy
- HER2-Low and HER2-Ultralow Metastatic Breast Cancer
  - As monotherapy for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining) breast cancer, as determined by an FDA-authorized test, that has progressed on one or more endocrine therapies in the metastatic setting
  - As monotherapy for the treatment of adult patients with unresectable or metastatic
    HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-authorized test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy
- HER2-Mutant Unresectable or Metastatic Non-Small Cell Lung Cancer (NSCLC)
  - As monotherapy for the treatment of adult patients with unresectable or metastatic NSCLC whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-authorized test, and who have received a prior systemic therapy

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

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

Important Safety Information

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

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

Contraindications
None.

Warnings and Precautions
Interstitial Lung Disease / Pneumonitis
Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with ENHERTU. A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment. Advise patients to immediately report cough, dyspnea, fever, and/or any new or worsening respiratory symptoms. Monitor patients for signs and symptoms of ILD. Promptly investigate evidence of ILD. Evaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist. For asymptomatic ILD/pneumonitis (Grade 1), interrupt ENHERTU until resolved to Grade 0, then if resolved in ≤28 days from date of onset, maintain dose. If resolved in >28 days from date of onset, reduce dose 1 level. Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥0.5 mg/kg/day prednisolone or equivalent). For symptomatic ILD/pneumonitis (Grade 2 or greater), permanently discontinue ENHERTU. Promptly initiate systemic corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥1 mg/kg/day prednisolone or equivalent) and continue for at least 14 days followed by gradual taper for at least 4 weeks. In the adjuvant HER2+ breast cancer setting, if drug-induced ILD is suspected, rule out radiotherapy-related pneumonitis.

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

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

Indications and Important Safety Information (cont'd)

If only radiotherapy-related pneumonitis is suspected, consider interruption of ENHERTU for Grade 2 and permanently discontinue ENHERTU for Grade ≥3.

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

ENHERTU as Monotherapy
In patients treated with ENHERTU 5.4 mg/kg, ILD occurred in 12% of patients. Median time to first onset was 5.5 months (range: 0.9 to 31.5). Fatal outcomes due to ILD and/or pneumonitis occurred in 0.9% of patients treated with ENHERTU.

ENHERTU in Combination with Pertuzumab
In patients treated with ENHERTU 5.4 mg/kg in combination with pertuzumab (N=431), ILD occurred in 12% of patients. Median time to first onset was 8.0 months (range: 0.6 to 33.8). Fatal outcomes due to ILD and/or pneumonitis occurred in 0.5% of patients treated with ENHERTU in combination with pertuzumab.

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

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

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

HER2-Positive, HER2-Low, and HER2-Ultralow Breast Cancer, HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (5.4 mg/kg)
ENHERTU as Monotherapy
In patients treated with ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in 65% of patients. Nineteen percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 22 days (range: 2 to 939). Febrile neutropenia was reported in 1% of patients.

ENHERTU in Combination with Pertuzumab
In patients treated with ENHERTU 5.4 mg/kg in combination with pertuzumab (N=431), decreased neutrophil count occurred in 79% of patients. Median time to first onset was 22 days (range: 5 to 994). Twenty-nine percent had Grade 3 or 4 decreased neutrophil count. Febrile neutropenia was reported in 2.6% of patients.

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

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

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

HER2-Positive, HER2-Low, and HER2-Ultralow Breast Cancer, HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (5.4 mg/kg)
ENHERTU as Monotherapy
In patients treated with ENHERTU 5.4 mg/kg, LVD was reported in 4.6% of patients, of which 0.6% were Grade 3 or 4.

ENHERTU in Combination with Pertuzumab
In patients treated with ENHERTU 5.4 mg/kg in combination with pertuzumab (N=431), LVEF decrease was reported in 11% of patients, of which 2.1% were Grade 3 or 4.

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

ENHERTU®
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20 mg/mL INJECTION FOR INTRAVENOUS USE

Indications and Important Safety Information (cont'd)

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

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

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

Additional Dose Modifications
Thrombocytopenia
For Grade 3 thrombocytopenia (platelets <50 to 25 x 10^9/L) interrupt ENHERTU until resolved to Grade 1 or less, then maintain dose. For Grade 4 thrombocytopenia (platelets <25 x 10^9/L) interrupt ENHERTU until resolved to Grade 1 or less, then reduce dose by 1 level.

Adverse Reactions
HER2-Positive, HER2-Low, and HER2-Ultralow Breast Cancer, HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (5.4 mg/kg)
ENHERTU as Monotherapy
The pooled safety population reflects exposure to ENHERTU 5.4 mg/kg intravenously every 3 weeks in 2233 patients in Study DS8201-A-J101 (NCT02564900), DESTINY-Breast01, DESTINY-Breast02, DESTINY-Breast03, DESTINY-Breast04, DESTINY-Breast06, DESTINY-Lung01, DESTINY-Lung02, DESTINY-CRC02, and DESTINY-PanTumor02. Among these patients, 67% were exposed for >6 months and 39% were exposed for >1 year. In this pooled safety population, the most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased white blood cell count (73%), nausea (72%), decreased hemoglobin (67%), decreased neutrophil count (65%), decreased lymphocyte count (60%), fatigue (55%), decreased platelet count (48%), increased aspartate aminotransferase (46%), increased alanine aminotransferase (43%), increased blood alkaline phosphatase (39%), vomiting (38%), alopecia (37%), constipation (32%), decreased blood potassium (32%), decreased appetite (31%), diarrhea (30%), and musculoskeletal pain (24%).

ENHERTU in Combination with Pertuzumab
The pooled safety population reflects exposure to ENHERTU 5.4 mg/kg in combination with pertuzumab intravenously every 3 weeks in 431 patients in DESTINY-Breast07 (n=50), and DESTINY-Breast09 (n=381). Among these patients, 86% were exposed for >6 months and 73% were exposed for >1 year. In this pooled safety population, the most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased white blood cell count (86%), decreased hemoglobin (80%), decreased neutrophil count (79%), nausea (74%), increased alanine aminotransferase (65%), diarrhea (64%), increased aspartate aminotransferase (63%), decreased lymphocyte count (61%), decreased platelet count (55%), increased blood alkaline phosphatase (54%), decreased blood potassium (54%), fatigue (53%), alopecia (48%), vomiting (46%), upper respiratory tract infection (32%), constipation (31%), decreased appetite (31%), decreased weight (28%), musculoskeletal pain (23%), increased blood bilirubin (23%), and abdominal pain (22%).

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

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

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

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

DESTINY-Breast05
The safety of ENHERTU was evaluated in 806 patients with HER2-positive breast cancer with residual invasive disease following neoadjuvant HER2-targeted therapy who then received at least one dose of ENHERTU 5.4 mg/kg. ENHERTU was administered by intravenous infusion once every three weeks for 14 cycles. The median duration of treatment was 10 months (range: 0.7 to 16) for patients who received ENHERTU.

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

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

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

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

HER2-Positive Metastatic Breast Cancer

DESTINY-Breast09

The safety of ENHERTU 5.4 mg/kg in combination with pertuzumab was evaluated in DESTINY-Breast09, a randomized, three-arm, multicenter study including 763 patients with HER2-positive (IHC 3+ or ISH+) unresectable or metastatic breast cancer. Three hundred eighty-one patients received ENHERTU in combination with pertuzumab and 382 patients received THP (taxane [docetaxel or paclitaxel], trastuzumab, and pertuzumab). Among patients who received ENHERTU in combination with pertuzumab, the median duration of treatment was 22 months (range: 0.3 months to 44.5 months).

Serious adverse reactions occurred in 27% of patients receiving ENHERTU in combination with pertuzumab. Serious adverse reactions in >1% of patients were diarrhea, pneumonia, febrile neutropenia, hypokalemia, vomiting, ILD, pulmonary embolism, and sepsis. Fatalities due to adverse reactions occurred in 3.4% of patients including pneumonia (n=3), ILD (n=2), sepsis (n=2), pulmonary embolism, septic shock, acute kidney injury, dyspnea, febrile neutropenia, and intestinal ischemia (1 patient each).

ENHERTU was discontinued for adverse reactions in 21% of patients. The most frequent adverse reaction (>2%) associated with permanent discontinuation was ILD/pneumonitis (6%). Dose interruptions due to adverse reactions occurred in 69% of patients. The most frequent adverse reactions (>2%) associated with dose interruption were COVID-19, neutropenia, upper respiratory tract infection, fatigue, anemia, hypokalemia, ILD/pneumonitis, thrombocytopenia, pneumonia, diarrhea, transaminase increased, leukopenia, cough, pyrexia, decreased appetite, and blood bilirubin increased. Dose reductions occurred in 46% of patients treated with ENHERTU in combination with pertuzumab. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, neutropenia, nausea, diarrhea, ILD/pneumonitis, thrombocytopenia, vomiting, transaminases increased, decreased weight, febrile neutropenia, and hypokalemia.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased white blood cell count (87%), decreased hemoglobin (80%), decreased neutrophil count (78%), nausea (75%), increased alanine aminotransferase (66%), diarrhea (64%), increased aspartate aminotransferase (62%), decreased lymphocyte count (62%), decreased platelet count (56%), increased blood alkaline phosphatase (55%), decreased blood potassium (54%), fatigue (53%), alopecia (48%), vomiting (46%), upper respiratory tract infection (33%), constipation (33%), decreased appetite (32%), decreased weight (30%), COVID-19 (28%), musculoskeletal pain (24%), increased blood bilirubin (23%), and abdominal pain (23%).

DESTINY-Breast03

The safety of ENHERTU was evaluated in 257 patients with unresectable or metastatic HER2-positive breast cancer who received at least 1 dose of ENHERTU 5.4 mg/kg intravenously once every 3 weeks in DESTINY-Breast03. The median duration of treatment was 14 months (range: 0.7 to 30) for patients who received ENHERTU.

Serious adverse reactions occurred in 19% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were vomiting, ILD, pneumonia, pyrexia, and urinary tract infection. Fatalities due to adverse reactions occurred in 0.8% of patients including COVID-19 and sudden death (1 patient each). ENHERTU was permanently discontinued in 14% of patients, of which ILD/pneumonitis accounted for 8%. Dose interruptions due to adverse reactions occurred in 44% of patients treated with ENHERTU.

The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, leukopenia, anemia, thrombocytopenia, pneumonia, nausea, fatigue, and ILD/pneumonitis. Dose reductions occurred in 21% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were nausea, neutropenia, and fatigue.

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The most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea (76%), decreased white blood cell count (74%), decreased neutrophil count (70%), increased aspartate aminotransferase (67%), decreased hemoglobin (64%), decreased lymphocyte count (55%), increased alanine aminotransferase (53%), decreased platelet count (52%), fatigue (49%), vomiting (49%), increased blood alkaline phosphatase (49%), alopecia (37%), decreased blood potassium (35%), constipation (34%), musculoskeletal pain (31%), diarrhea (29%), decreased appetite (29%), headache (22%), respiratory infection (22%), abdominal pain (21%), increased blood bilirubin (20%), and stomatitis (20%).

HER2-Low and HER2-Ultralow Metastatic Breast Cancer

DESTINY-Breast06

The safety of ENHERTU was evaluated in 434 patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining) breast cancer who received ENHERTU 5.4 mg/kg intravenously once every 3 weeks in DESTINY-Breast06. The median duration of treatment was 11 months (range: 0.4 to 39.6) for patients who received ENHERTU.

Serious adverse reactions occurred in 20% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were ILD/pneumonitis, COVID-19, febrile neutropenia, and hypokalemia. Fatalities due to adverse reactions occurred in 2.8% of patients including ILD (0.7%); sepsis (0.5%); and COVID-19 pneumonia, bacterial meningoencephalitis, neutropenic sepsis, peritonitis, cerebrovascular accident, general physical health deterioration (0.2% each).

ENHERTU was permanently discontinued in 14% of patients. The most frequent adverse reaction (>2%) associated with permanent discontinuation was ILD/pneumonitis. Dose interruptions due to adverse reactions occurred in 48% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were COVID-19, decreased neutrophil count, anemia, pyrexia, pneumonia, decreased white blood cell count, and ILD. Dose reductions occurred in 25% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were nausea, fatigue, decreased platelet count, and decreased neutrophil count.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased white blood cell count (86%), decreased neutrophil count (75%), nausea (70%), decreased hemoglobin (69%), decreased lymphocyte count (66%), fatigue (53%), decreased platelet count (48%), alopecia (48%), increased alanine aminotransferase (44%), increased blood alkaline phosphatase (43%), increased aspartate aminotransferase (41%), decreased blood potassium (35%), diarrhea (34%), vomiting (34%), constipation (32%), decreased appetite (26%), COVID-19 (26%), and musculoskeletal pain (24%).

DESTINY-Breast04

The safety of ENHERTU was evaluated in 371 patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who received ENHERTU 5.4 mg/kg intravenously once every 3 weeks in DESTINY-Breast04. The median duration of treatment was 8 months (range: 0.2 to 33) for patients who received ENHERTU.

Serious adverse reactions occurred in 28% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were ILD/pneumonitis, pneumonia, dyspnea, musculoskeletal pain, sepsis, anemia, febrile neutropenia, hypercalcemia, nausea, pyrexia, and vomiting. Fatalities due to adverse reactions occurred in 4% of patients including ILD/pneumonitis (3 patients); sepsis (2 patients); and ischemic colitis, disseminated intravascular coagulation, dyspnea, febrile neutropenia, general physical health deterioration, pleural effusion, and respiratory failure (1 patient each).

ENHERTU was permanently discontinued in 16% of patients, of which ILD/pneumonitis accounted for 8%. Dose interruptions due to adverse reactions occurred in 39% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, fatigue, anemia, leukopenia, COVID-19, ILD/pneumonitis, increased transaminases, and hyperbilirubinemia. Dose reductions occurred in 23% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, nausea, thrombocytopenia, and neutropenia.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea (76%), decreased white blood cell count (70%), decreased hemoglobin (64%), decreased neutrophil count (64%), decreased lymphocyte count (55%), fatigue (54%), decreased platelet count (44%), alopecia (40%), vomiting (40%), increased aspartate aminotransferase (38%), increased alanine aminotransferase (36%), constipation (34%), increased blood alkaline phosphatase (34%), decreased appetite (32%), musculoskeletal pain (32%), diarrhea (27%), and decreased blood potassium (25%).

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

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

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

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

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ENHERTU was permanently discontinued in 17% of patients. Adverse reactions which resulted in permanent discontinuation of ENHERTU were ILD/pneumonitis, pneumonia, blood bilirubin increased, hypokalemia, metastases to meninges, and myocarditis. Dose interruptions of ENHERTU due to adverse reactions occurred in 50% of patients. Adverse reactions which required dose interruption (>2%) included neutropenia, COVID-19, ILD/pneumonitis, fatigue, anemia, and pneumonia. Dose reductions due to an adverse reaction occurred in 20% of patients. The most frequent adverse reactions (>2%) associated with dose reduction were neutropenia, fatigue, and decreased appetite.

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

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

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

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

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

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

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

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

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

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Use in Specific Populations

- **Pregnancy:** ENHERTU can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risks to a fetus. There are clinical considerations if ENHERTU is used in pregnant women, or if a patient becomes pregnant within 7 months after the last dose of ENHERTU.
- **Lactation:** There are no data regarding the presence of ENHERTU in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with ENHERTU and for 7 months after the last dose.
- **Females and Males of Reproductive Potential:** Pregnancy testing: Verify pregnancy status of females of reproductive potential prior to initiation of ENHERTU. Contraception: *Females*: ENHERTU can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with ENHERTU and for 7 months after the last dose. *Males*: Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for 4 months after the last dose. Infertility: ENHERTU may impair male reproductive function and fertility.
- **Pediatric Use:** Safety and effectiveness of ENHERTU have not been established in pediatric patients.
- **Geriatric Use:** *ENHERTU as Monotherapy*: Of the 2233 patients treated with ENHERTU 5.4 mg/kg, 28% were ≥65 years and 6% were ≥75 years. No overall differences in efficacy within clinical studies were observed between patients ≥65 years compared to younger patients. There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged ≥65 years (56%) as compared to younger patients (49%). Of the 125 patients with HER2-positive locally advanced or metastatic gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg in DESTINY-Gastric01, 56% were ≥65 years and 14% were ≥75 years. No overall differences in efficacy or safety were observed between patients ≥65 years of age compared to younger patients. *ENHERTU in Combination with Pertuzumab*: In patients with HER2-positive unresectable or metastatic breast cancer treated with ENHERTU 5.4 mg/kg in combination with pertuzumab (N=431), 17% were ≥65 years and 3% were ≥75 years. No overall differences in efficacy or safety were observed between patients ≥65 years compared to younger patients. *ENHERTU followed by THP*: Of the 320 patients with HER2-positive early breast cancer treated with ENHERTU 5.4 mg/kg followed by THP, 12% were ≥65 years and 1.6% were ≥75 years. No overall differences in efficacy were observed between patients ≥65 years compared to younger patients. There was a higher incidence of Grade 3-4 adverse reactions observed in patients ≥65 years (38%) as compared to younger patients (30%).
- **Renal Impairment:** A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment. Monitor patients with moderate renal impairment more frequently. The recommended dosage of ENHERTU has not been established for patients with severe renal impairment (CLcr <30 mL/min).
- **Hepatic Impairment:** In patients with moderate hepatic impairment, due to potentially increased exposure, monitor for increased adverse reactions related to the topoisomerase inhibitor, DXd. The recommended dosage of ENHERTU has not been established for patients with severe hepatic impairment (total bilirubin >3 times ULN and any AST).

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

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Abbreviations and References

Abbreviations

1L, first line; 2L, second line; aGC, advanced gastric cancer; ASCO, American Society of Clinical Oncology; BC, breast cancer; 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; 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; 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.

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

Measure and report ALL levels of HER2 expression for BC, including HER2-low and HER2-ultralow mBC[1]

Perform HER2 IHC testing AND NGS testing for patients with mNSCLC[1,45]

HER2 IHC test ALL metastatic solid tumors[1]

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

Indications and Important Safety Information

Indications

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

- HER2-Positive Early Breast Cancer
  - As neoadjuvant treatment of adult patients with HER2-positive (IHC 3+ or ISH+) Stage II or III breast cancer, as determined by an FDA-authorized test followed by a taxane, trastuzumab, and pertuzumab (THP)
  - As adjuvant treatment of adult patients with HER2-positive (IHC 3+ or ISH+) breast cancer who have residual invasive disease following neoadjuvant trastuzumab (with or without pertuzumab) and taxane-based treatment
- HER2-Positive Metastatic Breast Cancer
  - In combination with pertuzumab as first-line treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH+) breast cancer, as determined by an FDA-authorized test
  - As monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH+) breast cancer who have received a prior anti-HER2-based regimen either in the metastatic setting, or, in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy
- HER2-Low and HER2-Ultralow Metastatic Breast Cancer
  - As monotherapy for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining) breast cancer, as determined by an FDA-authorized test, that has progressed on one or more endocrine therapies in the metastatic setting
  - As monotherapy for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-authorized test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy
- HER2-Mutant Unresectable or Metastatic Non-Small Cell Lung Cancer (NSCLC)
  - As monotherapy for the treatment of adult patients with unresectable or metastatic NSCLC whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-authorized test, and who have received a prior systemic therapy

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

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

Important Safety Information

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

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

Please see Important Safety Information on pages 16-21 and throughout this brochure, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

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20 mg/mL INJECTION FOR INTRAVENOUS USE

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 actionable in certain patients with mBC[1]

- 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 s…g)[25,a]

Test for HER2 … (4B5)
FDA-authoriz…



No membrane staining



…e staining of … in >10% of …r cells

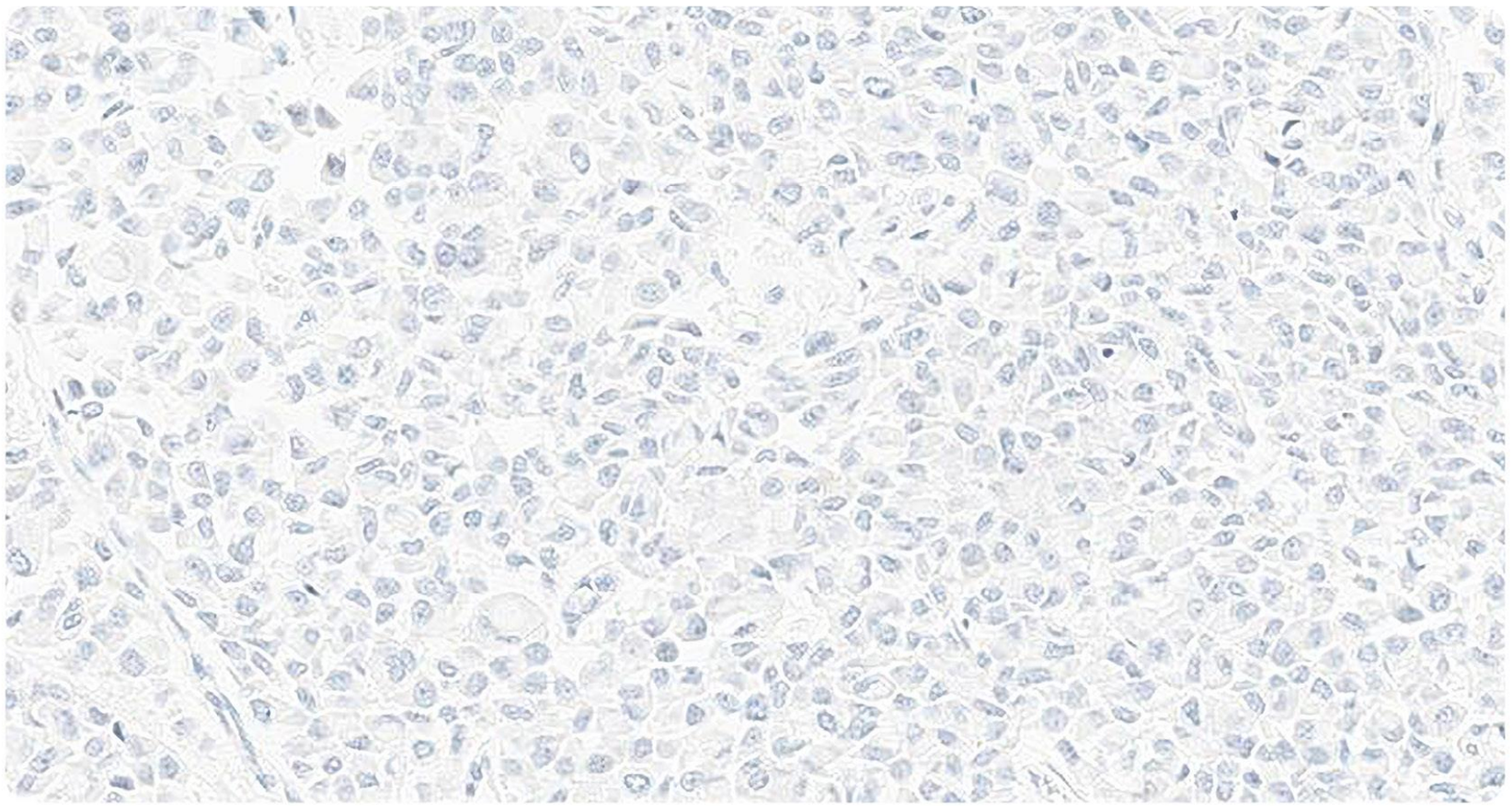
HER2-null

Study design: DES… …56 patients with HR+/HER2-low (IH… …t 2 lines of ET in the metastatic setting, … …DK4/6 inhibitor in the metastatic set… …xel, or paclitaxel. Treatment was co… …according to RECIST v1.1). Select secon… …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.[1,38,47,48]

[a]As demonstrated in DESTINY-Breast06 screening data. Among the 1856 patients screened for participation in the study, 12% (255 patients) had IHC 0 with absent membrane staining, while 22% (402 patients) were classified as HER2-ultralow, defined as IHC 0 with membrane staining. IHC 1+ was observed in 45% (829 patients), and IHC 2+/ISH- in 21% (385 patients).[25]
[b]Review at 40x is recommended to discern the presence or absence of any staining such as faint, partial staining.[38]
[c]Recommend re-reading by a second pathologist for cases classified as HER2-null or as HER2-ultralow expression with % of tumor cells ≤5%.[38]
[d]In 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.[38]

Please see Important Safety Information on pages 16-22 and throughout, and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

IHC 0



No membrane staining

BC

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

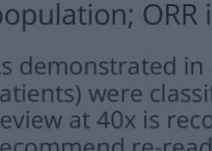
HER2-ultralow status is actionable in certain patients with mBC[1]

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

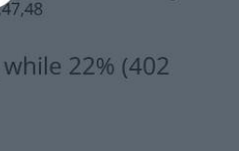
~60% of HR+/HER2-negative mBC tumors previously considered IHC 0 are **HER2-ultralow** (IHC 0 with membrane s…g)[25,a]

Test for HER2 … (4B5)
FDA-authoriz…

I **+**



No membrane staining



…e staining of … in >10% of …r cells

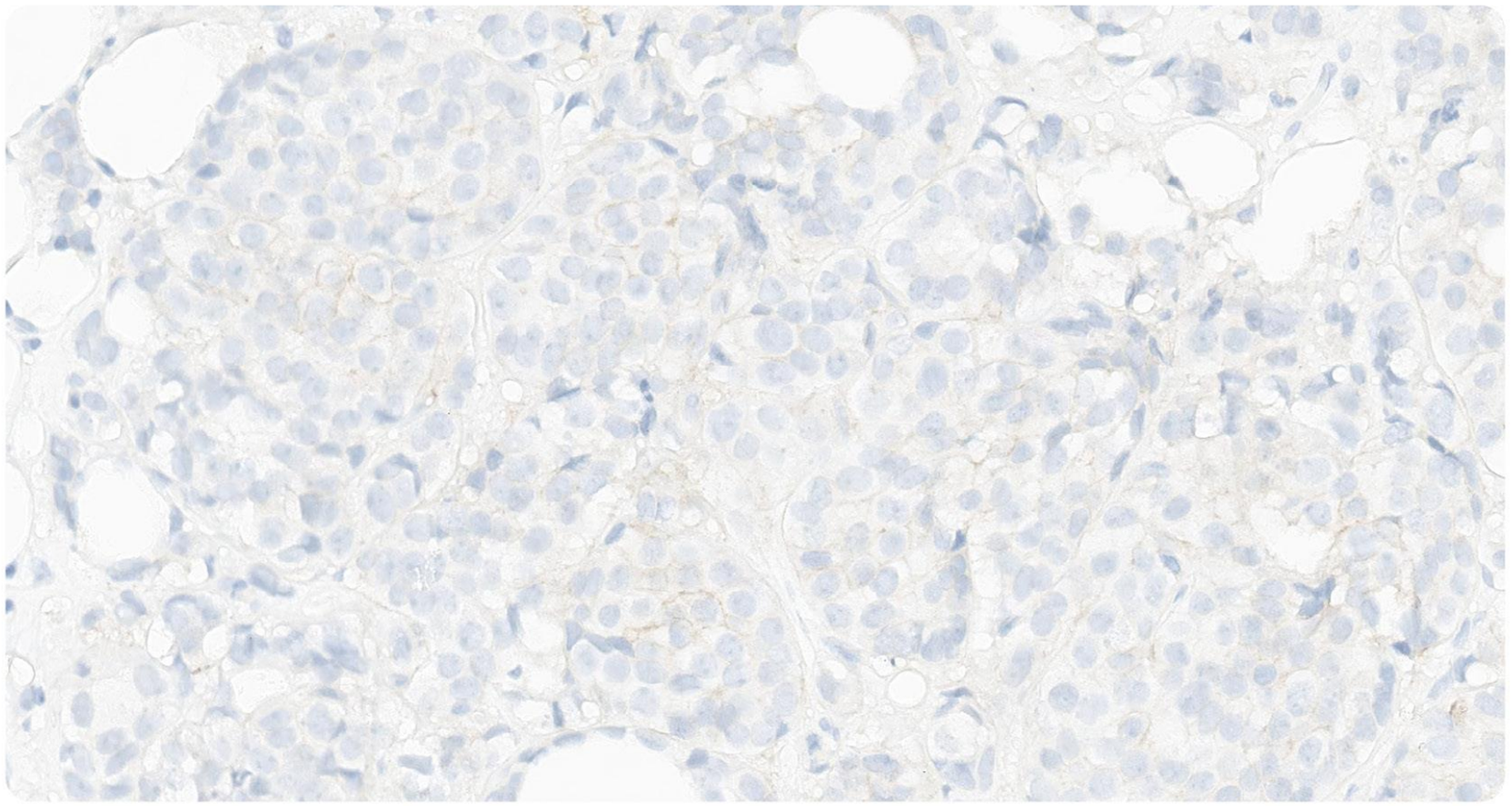
HER2-null

Study design: DES… 56 patients with HR+/HER2-low (IH… 2 lines of ET in the metastatic setting, … DK4/6 inhibitor in the metastatic set… …xel, or paclitaxel. Treatment was co… …according to RECIST v1.1). Select secon… …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.[1,30,47,48]

[a]As demonstrated in DESTINY-Breast06 screening data. Among the 1856 patients screened for participation in the study, 12% (255 patients) had IHC 0 with absent membrane staining, while 22% (402 patients) were classified as HER2-ultralow, defined as IHC 0 with membrane staining. IHC 1+ was observed in 45% (829 patients), and IHC 2+/ISH- in 21% (385 patients).[25]
[b]Review at 40x is recommended to discern the presence or absence of any staining such as faint, partial staining.[38]
[c]Recommend re-reading by a second pathologist for cases classified as HER2-null or as HER2-ultralow expression with % of tumor cells ≤5%.[38]
[d]In 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.[38]

Please see Important Safety Information on pages 16-22 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

BC

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

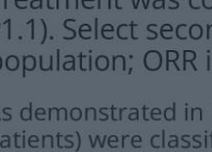
HER2-ultralow status is actionable in certain patients with mBC[1]

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

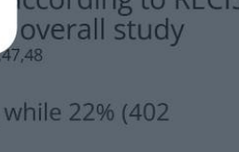
~60% of HR+/HER2-negative mBC tumors previously considered IHC 0 are **HER2-ultralow** (IHC 0 with membrane s…g)[25,a]

Test for HER2 … (4B5)
FDA-authoriz…

I… 1+



No membrane staining



…e staining of … in >10% of …r cells

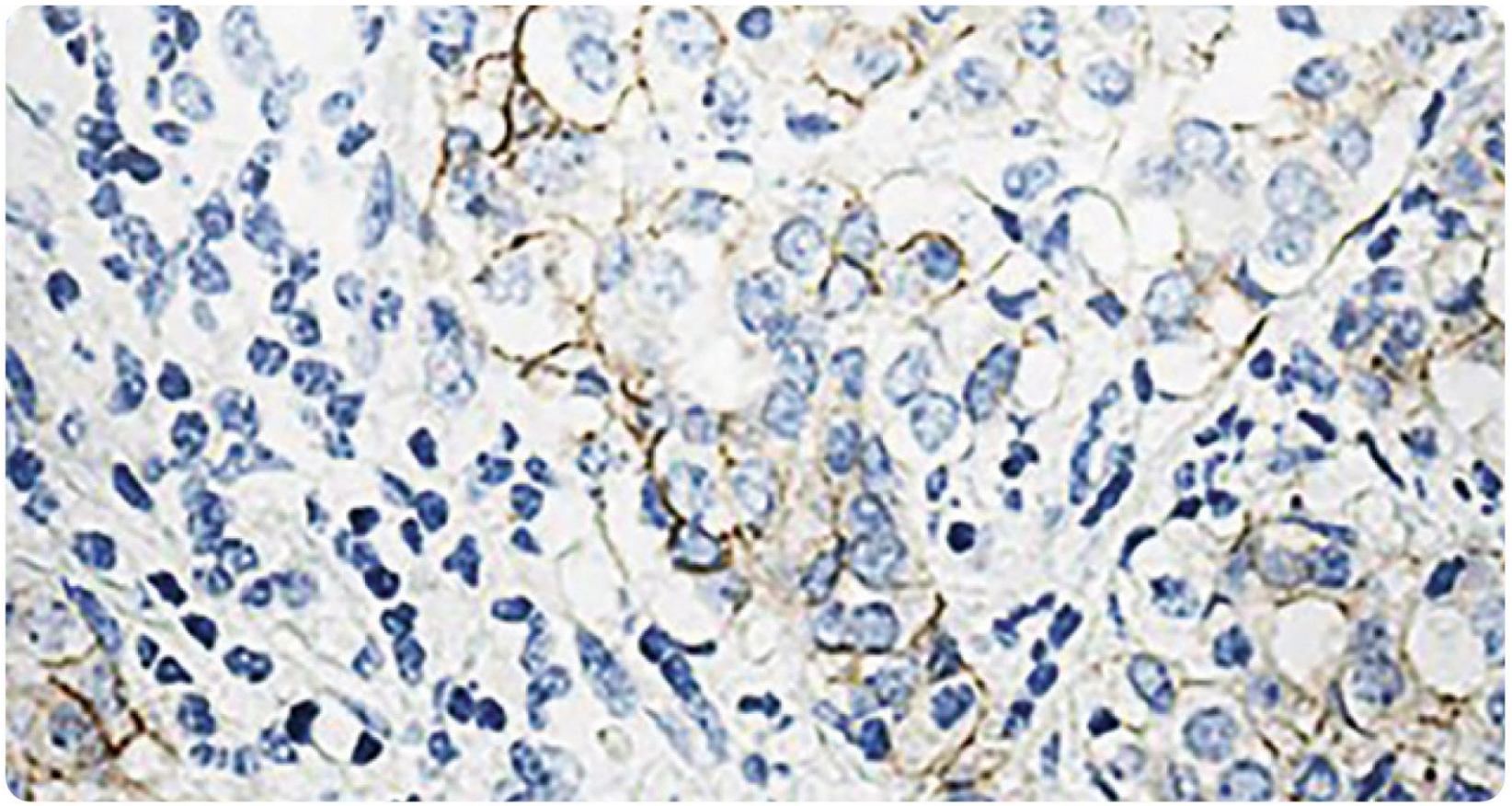
HER2-null

Study design: DES… 56 patients with HR+/HER2-low (IH… 2 lines of ET in the metastatic setting, … DK4/6 inhibitor in the metastatic set… …xel, or paclitaxel. Treatment was co… …cording to RECIST v1.1). Select secon… …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.[1,30,47,48]

[a]As demonstrated in DESTINY-Breast06 screening data. Among the 1856 patients screened for participation in the study, 12% (255 patients) had IHC 0 with absent membrane staining, while 22% (402 patients) were classified as HER2-ultralow, defined as IHC 0 with membrane staining. IHC 1+ was observed in 45% (829 patients), and IHC 2+/ISH- in 21% (385 patients).[25]
[b]Review at 40x is recommended to discern the presence or absence of any staining such as faint, partial staining.[38]
[c]Recommend re-reading by a second pathologist for cases classified as HER2-null or as HER2-ultralow expression with % of tumor cells ≤5%.[38]
[d]In 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.[38]

Please see Important Safety Information on pages 16-22 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

BC

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 actionable in certain patients with mBC[1]

- 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 s…g)[25,a]

Test for HER2 … (4B5)
FDA-authoriz…



No membrane staining



…e staining of … in >10% of …r cells

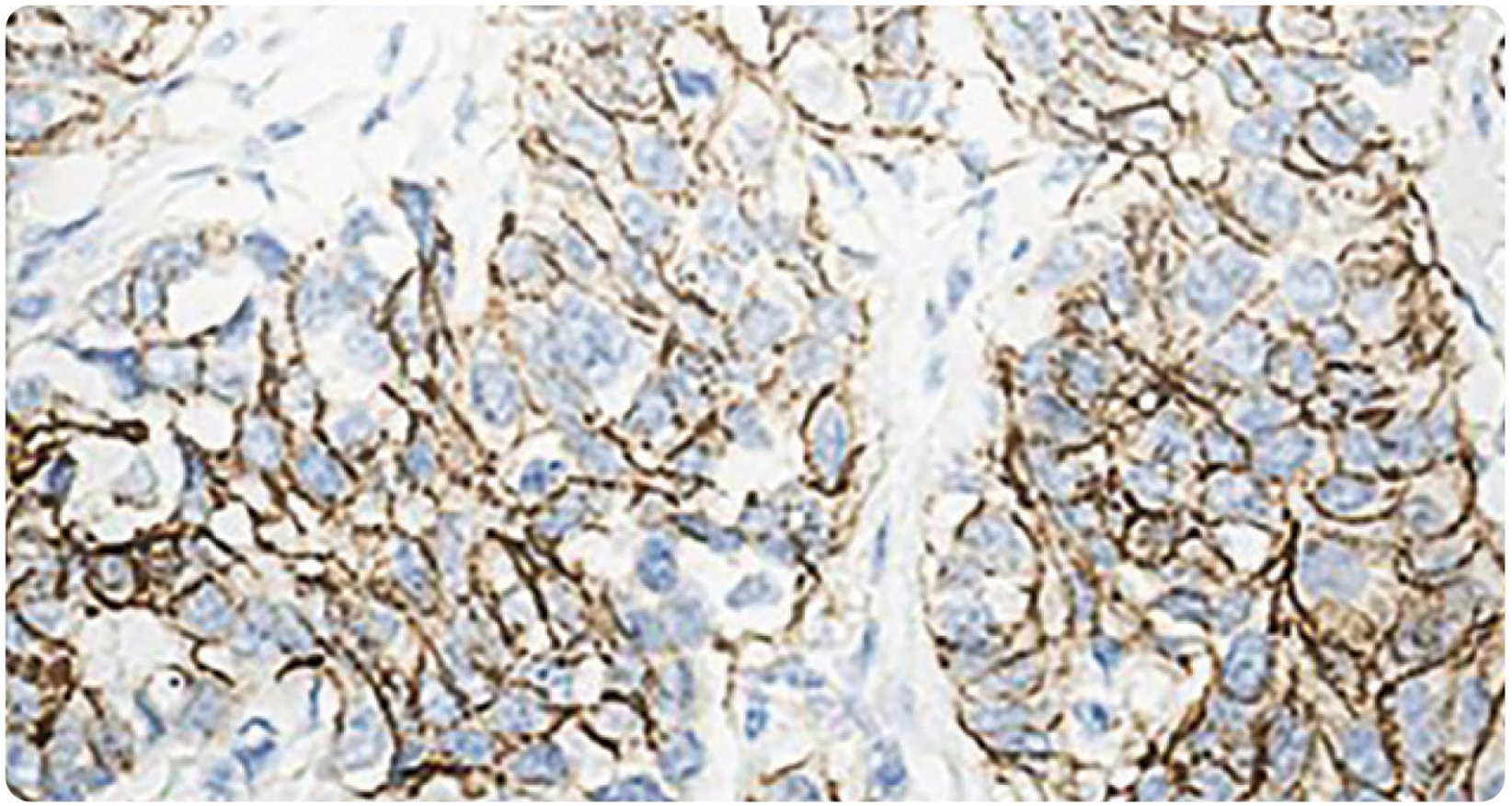
HER2-null

Study design: DES… 56 patients with HR+/HER2-low (IH… : 2 lines of ET in the metastatic setting, … DK4/6 inhibitor in the metastatic set… …xel, or paclitaxel. Treatment was co… …according to RECIST v1.1). Select secon… …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.[1,36,47,48]

[a]As demonstrated in DESTINY-Breast06 screening data. Among the 1856 patients screened for participation in the study, 12% (255 patients) had IHC 0 with absent membrane staining, while 22% (402 patients) were classified as HER2-ultralow, defined as IHC 0 with membrane staining. IHC 1+ was observed in 45% (829 patients), and IHC 2+/ISH- in 21% (385 patients).[25]
[b]Review at 40x is recommended to discern the presence or absence of any staining such as faint, partial staining.[38]
[c]Recommend re-reading by a second pathologist for cases classified as HER2-null or as HER2-ultralow expression with % of tumor cells ≤5%.[38]
[d]In 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.[38]

Please see Important Safety Information on pages 16-22 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

BC

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 actionable in certain patients with mBC[1]

- 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 s…g)[25,a]

Test for HER2 … (4B5)
FDA-authoriz…

I… 3+



No membrane staining



…e staining of … in >10% of …r cells

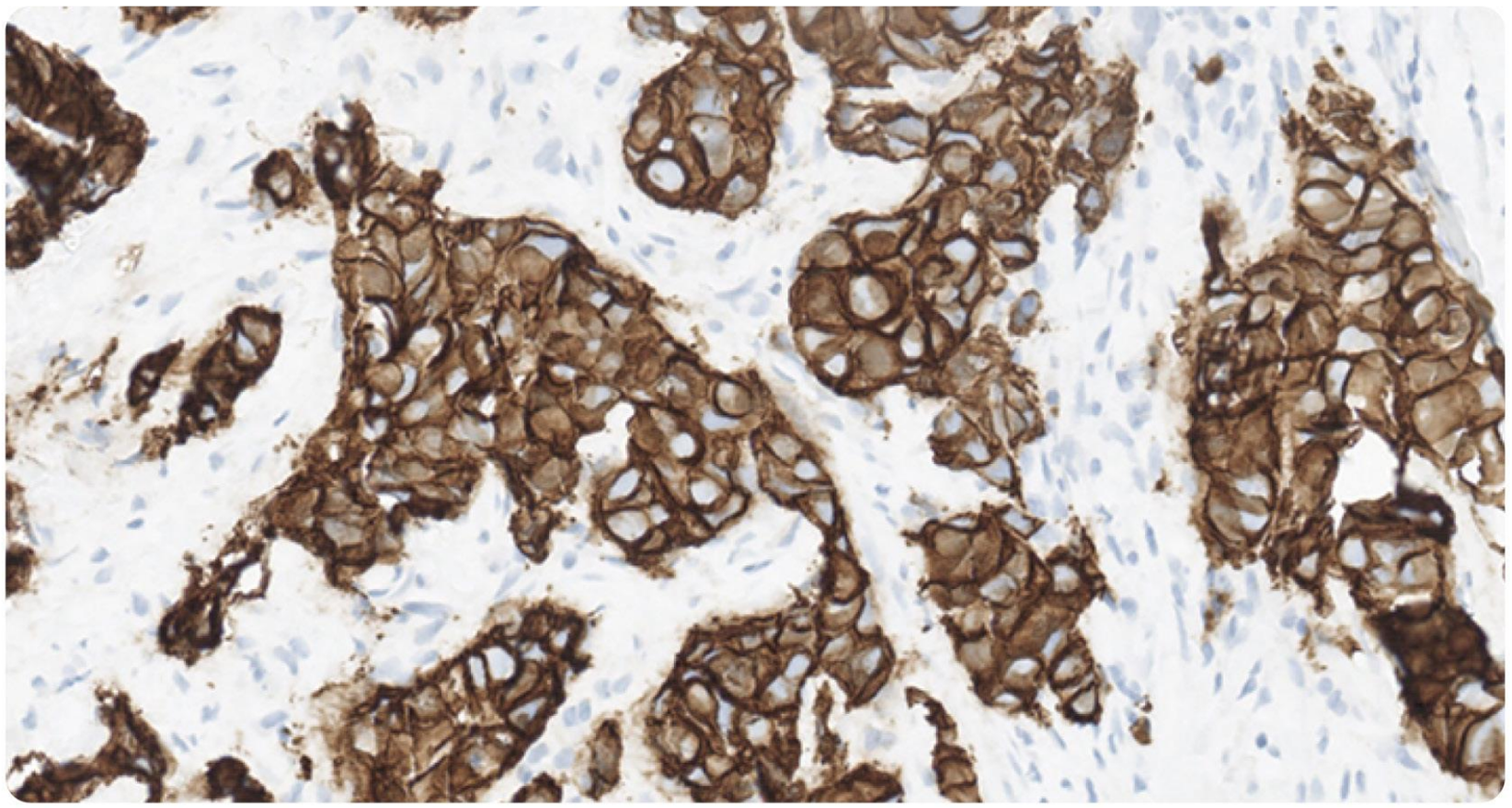
HER2-null

Study design: DES… …56 patients with HR+/HER2-low (IH… …t 2 lines of ET in the metastatic setting, … …DK4/6 inhibitor in the metastatic set… …xel, or paclitaxel. Treatment was co… …according to RECIST v1.1). Select secon… …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.[1,36,47,48]

[a]As demonstrated in DESTINY-Breast06 screening data. Among the 1856 patients screened for participation in the study, 12% (255 patients) had IHC 0 with absent membrane staining, while 22% (402 patients) were classified as HER2-ultralow, defined as IHC 0 with membrane staining. IHC 1+ was observed in 45% (829 patients), and IHC 2+/ISH- in 21% (385 patients).[25]
[b]Review at 40x is recommended to discern the presence or absence of any staining such as faint, partial staining.[38]
[c]Recommend re-reading by a second pathologist for cases classified as HER2-null or as HER2-ultralow expression with % of tumor cells ≤5%.[38]
[d]In 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.[38]

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IHC 3+



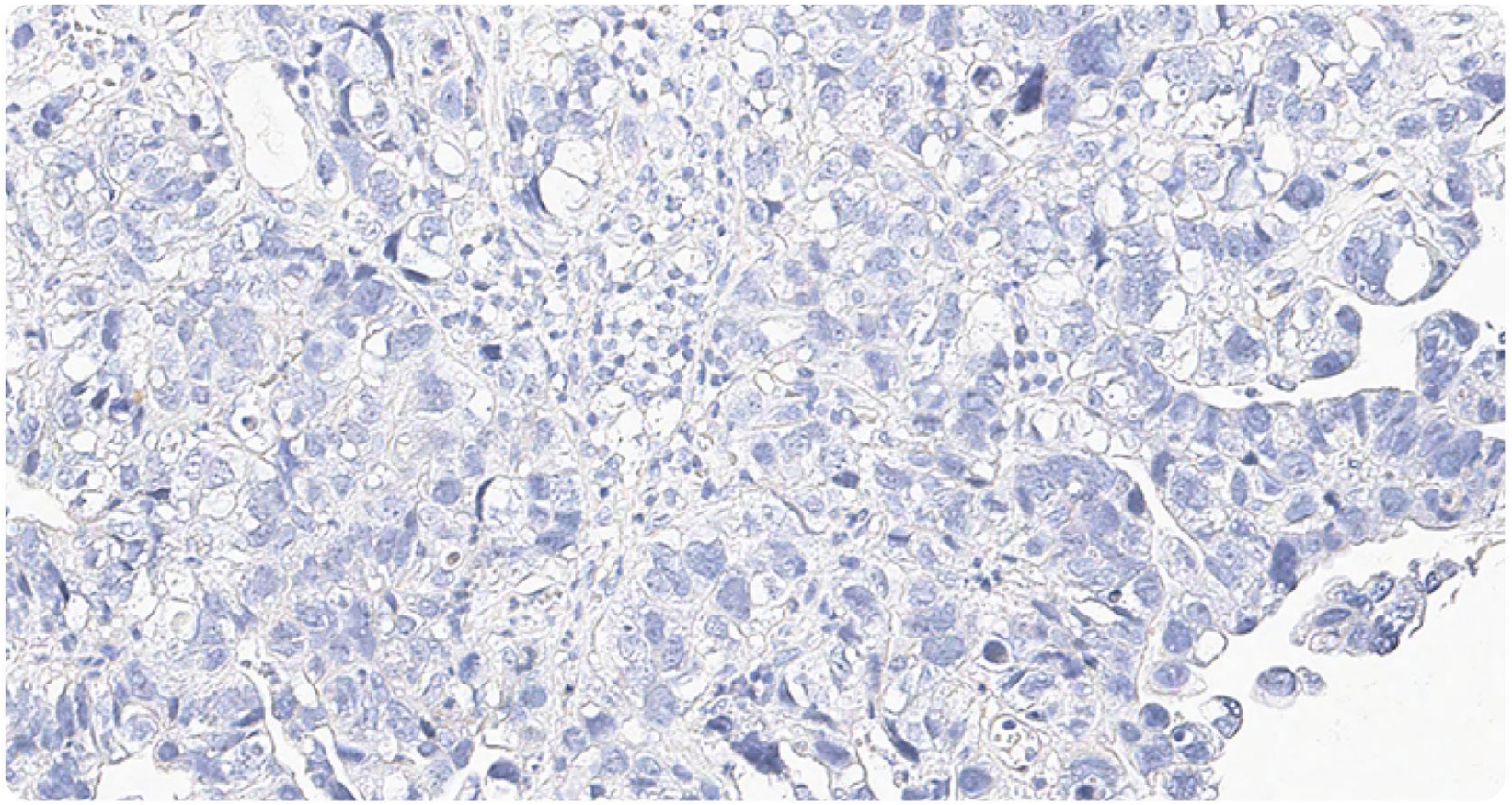
Intense complete staining of the membrane in >10% of the cancer cells

aGC

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

ASCO-CAP gastric cancer scoring criteria[1,3,46]

IHC 0



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

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

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

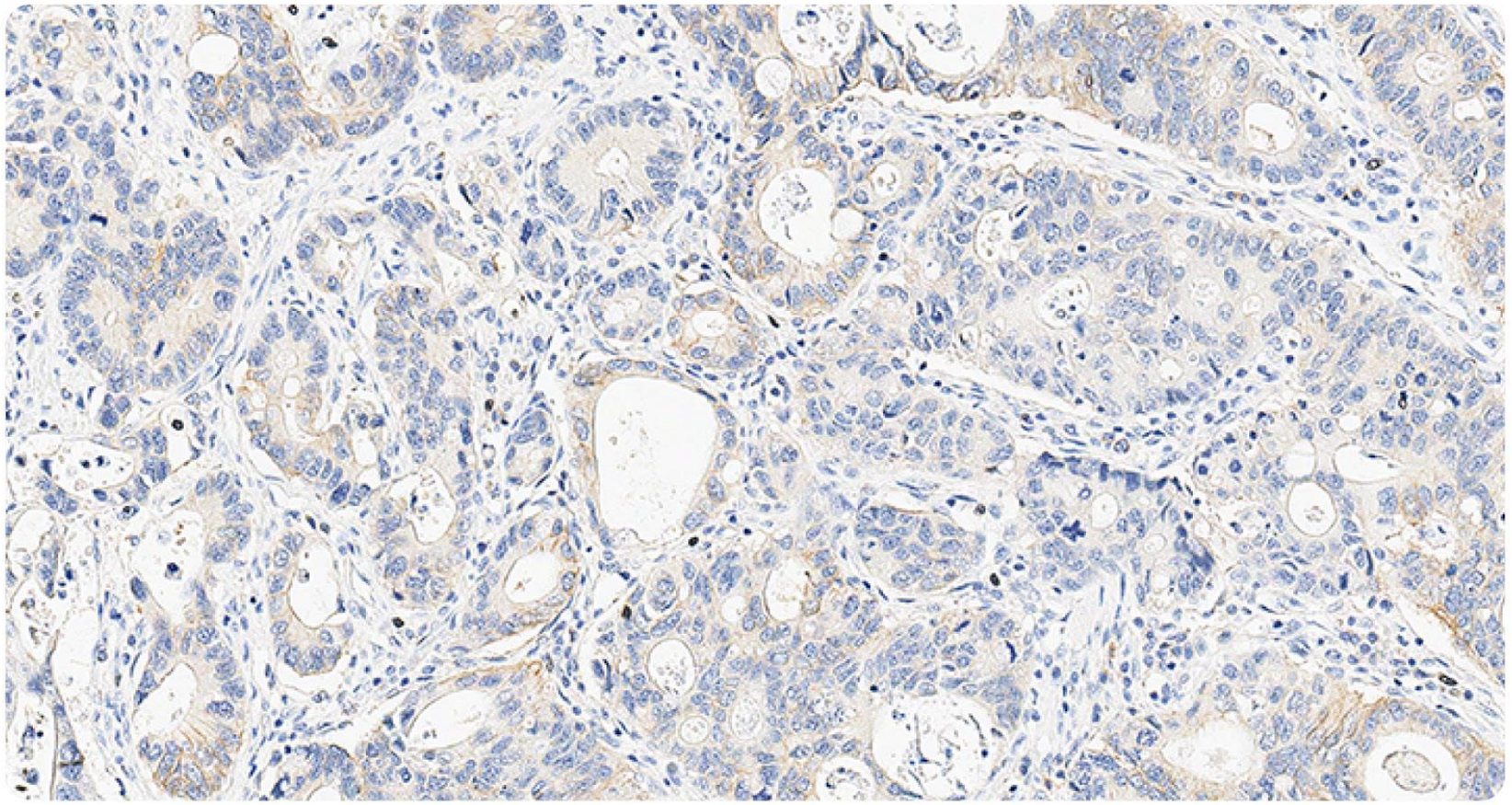
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aGC

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

ASCO-CAP gastric cancer scoring criteria[1,3,46]

IHC 1+



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

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]

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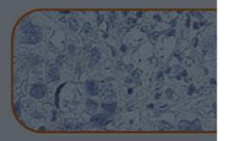
HER2 ALTERATIONS | BREAST CANCER | GASTRIC CANCER | METASTATIC SOLID TUMORS | mNSCLC | PRE-ANALYTICS & REPORTING | ISI | ABBREVIATIONS & REFERENCES | SUMMARY | PI | 8

aGC

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

ASCO-CAP gastric cancer scoring criteria[1,3,46]

Surgica



No reactivity or
reactivity in <10

Biopsy

No reactivity in

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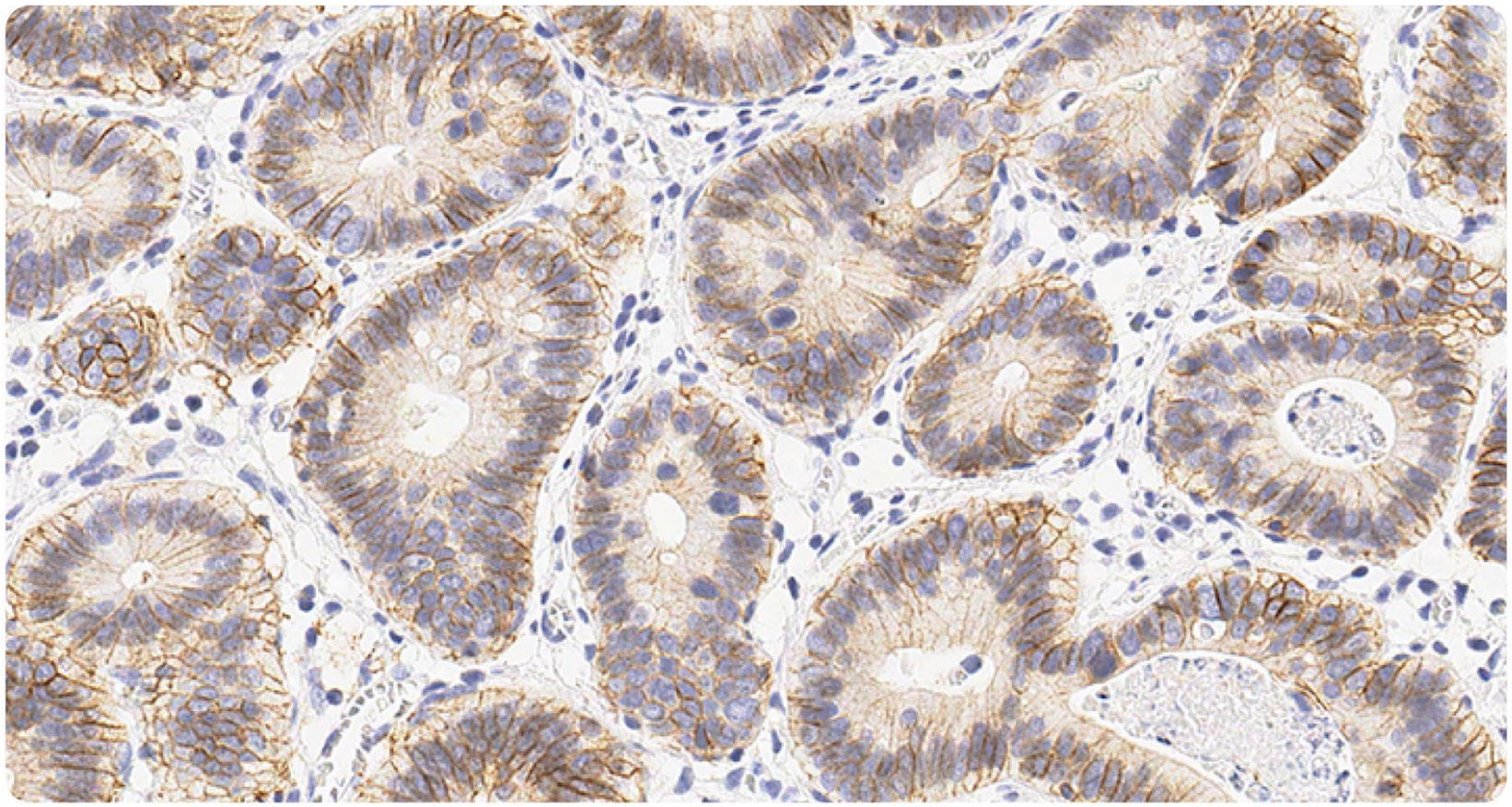
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IHC 2+



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

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]

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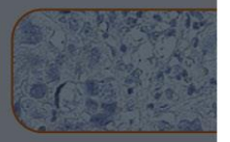
HER2 ALTERATIONS | BREAST CANCER | GASTRIC CANCER | METASTATIC SOLID TUMORS | mNSCLC | PRE-ANALYTICS & REPORTING | ISI | ABBREVIATIONS & REFERENCES | SUMMARY | PI | 8

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ASCO-CAP gastric cancer scoring criteria[1,3,46]

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Biopsy

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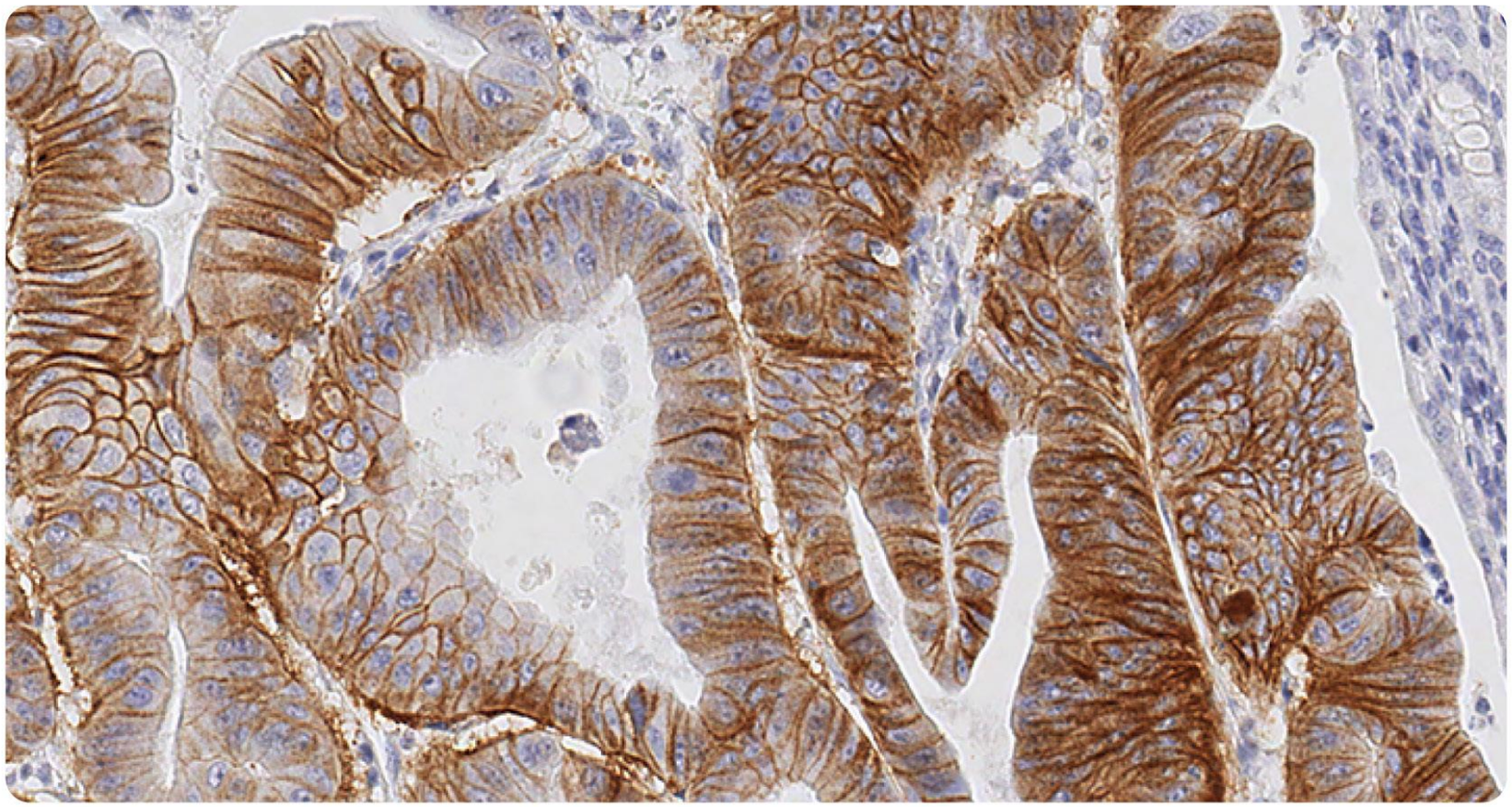
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IHC 3+ (Surgical specimen)



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

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]

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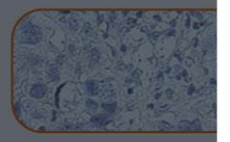
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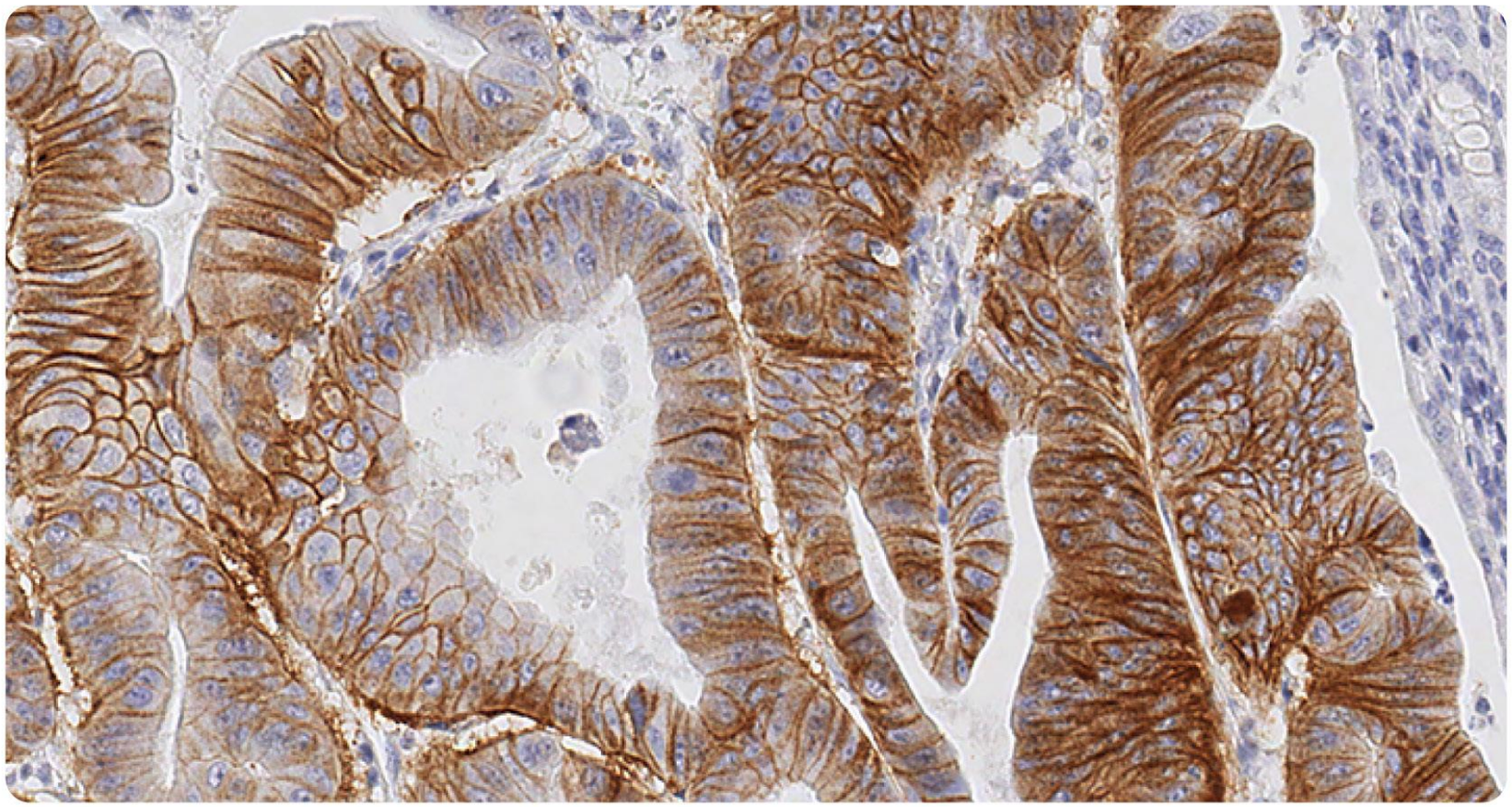
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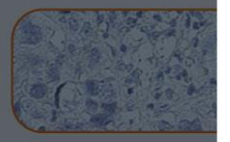
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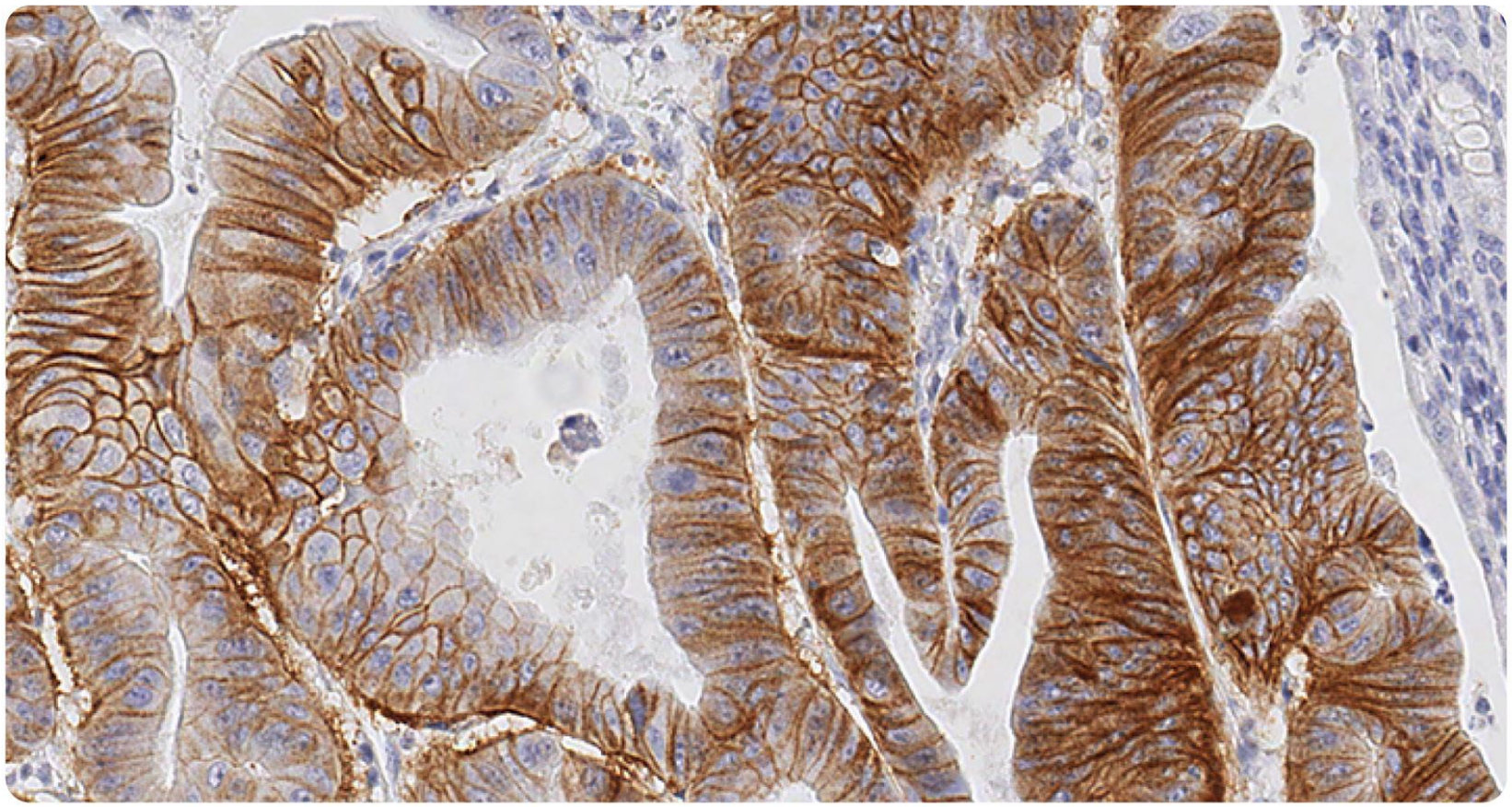
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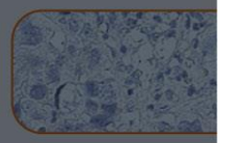
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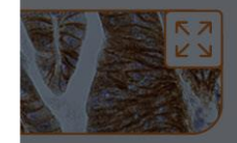


No reactivity or
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Biopsy

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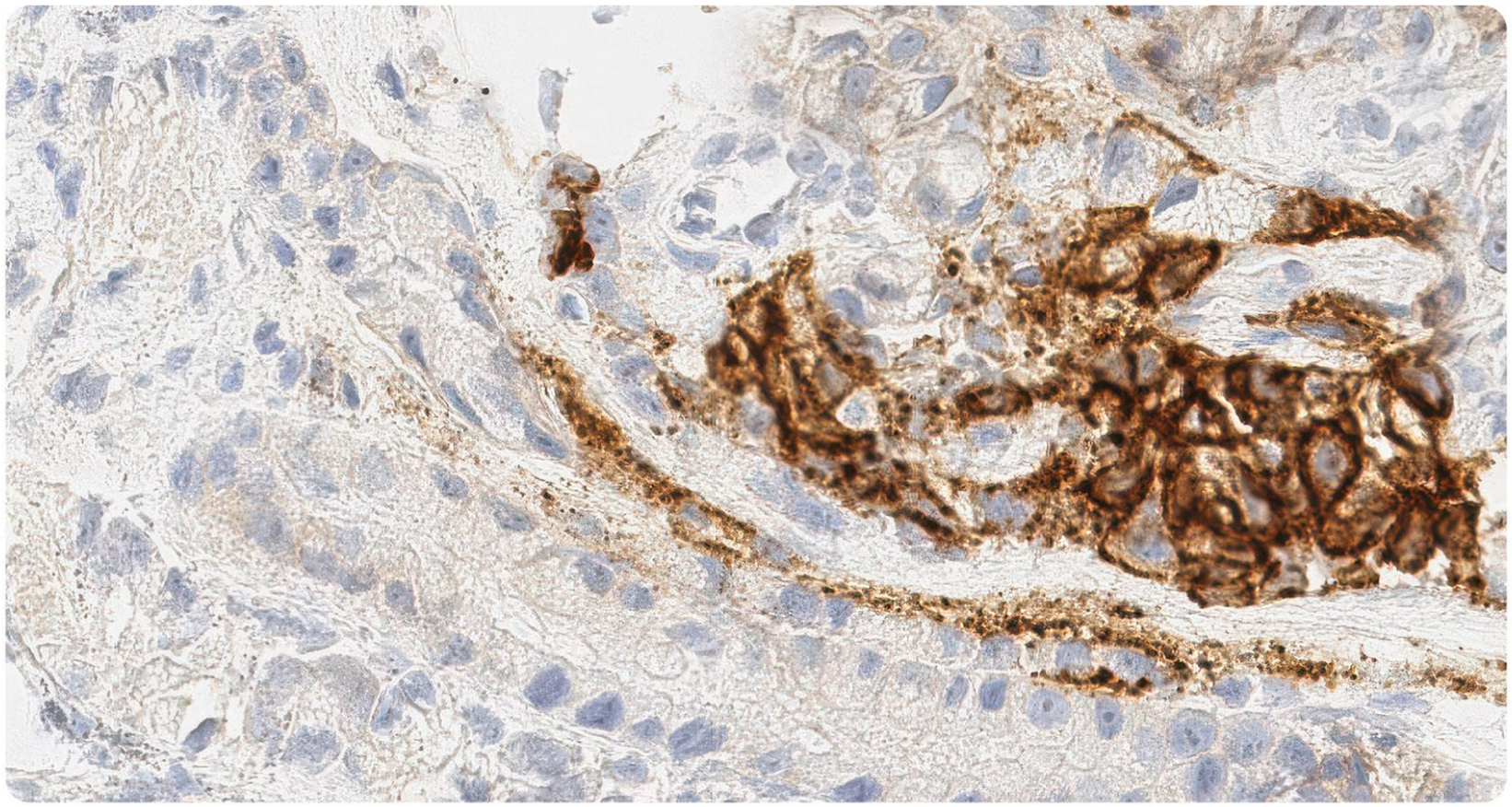
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IHC 3+ (Biopsy specimen)



Tumor cell cluster (5 or more tumor cells) with strong complete, basolateral, or lateral membranous reactivity irrespective of percentage of tumor cells stained

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]

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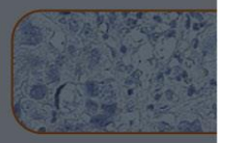
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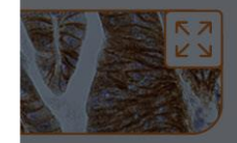


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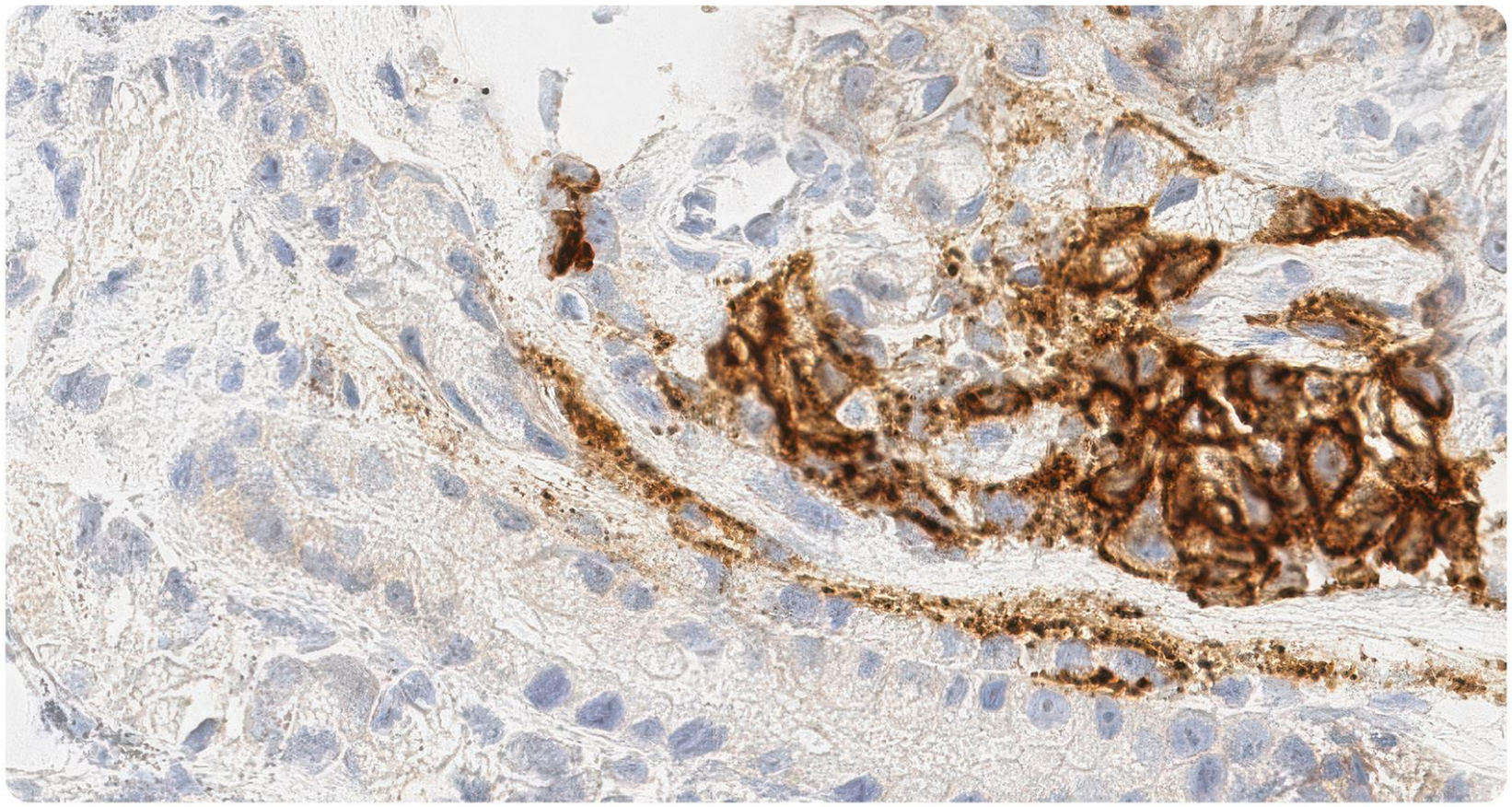
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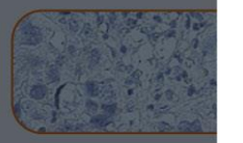
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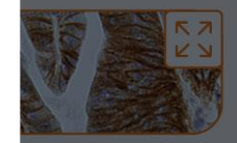


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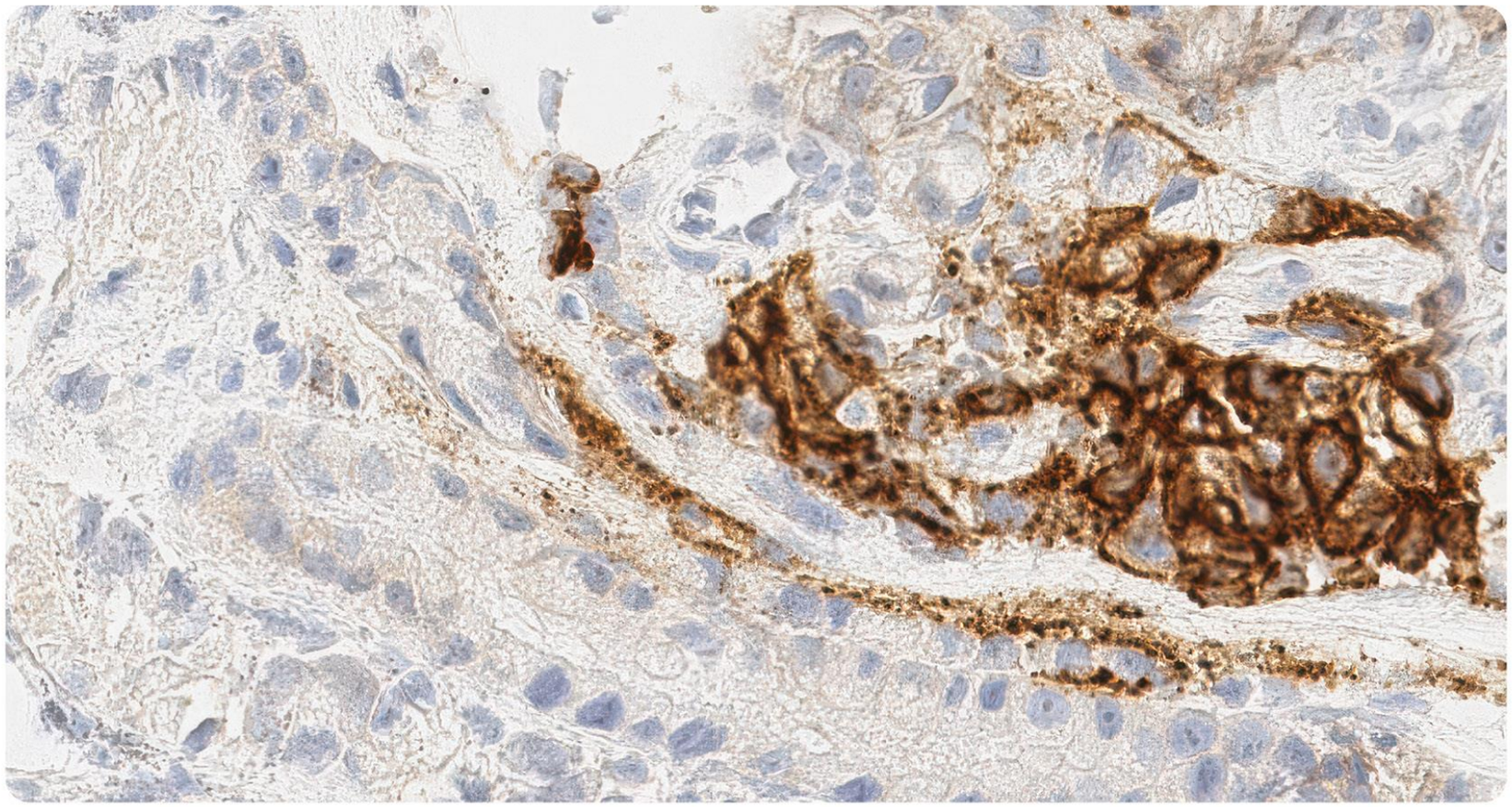
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