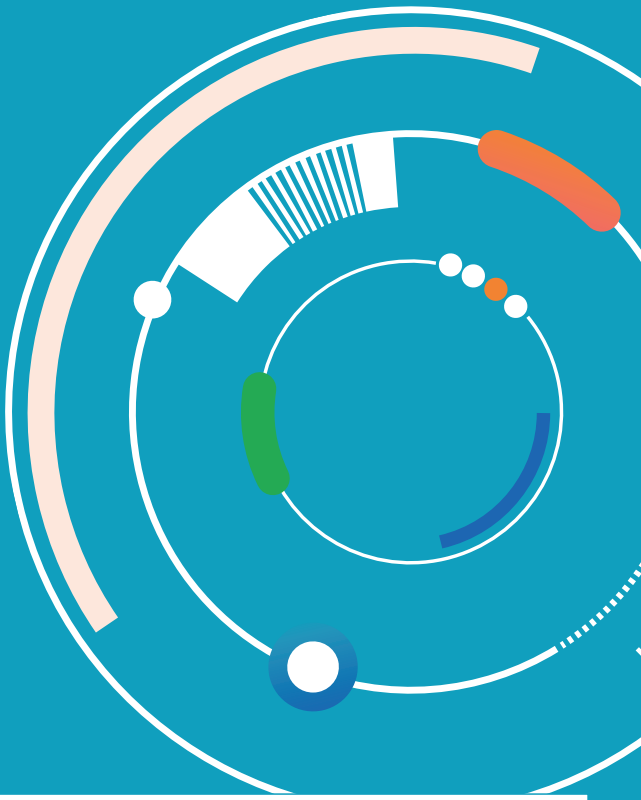
HER2 PRECISION MEDICINE

# **HER2-low testing** in breast cancer:

## A resource for oncologists



**ENHERTU▼ (trastuzumabderukstekan) is indicated as a monotherapy for the treatment of adult patients with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.**

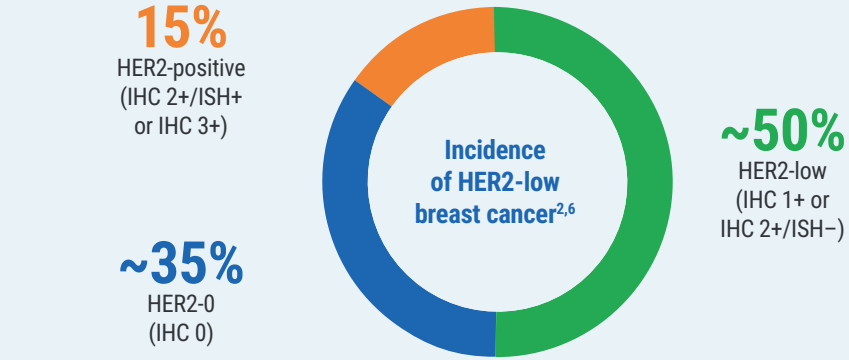
Daiichi-Sankyo | AstraZeneca

ENHERTU® trastuzumabderukstekan

# What is HER2-low and why is it important?

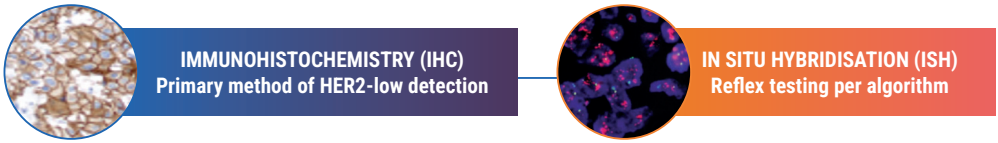
- Management of HER2-positive BC has advanced significantly over the last 25 years, emphasising the continued importance of targeting HER2 as the treatment landscape evolves[1]
- HER2 expression has been viewed historically as either negative or positive for treatment classification purposes. However, the HER2 gene is expressed along a continuum[2–6]
- Now, HER2-low, defined as IHC 1+ or IHC 2+/ISH-, has identified another patient population within the historical HER2-negative classification[2]
- Approximately 50% of all breast cancers may be categorised as HER2-low[2,7]

**Change to the HER2 testing paradigm is required to give patients a more precise HER2 designation that includes HER2-low and will impact eligibility for treatment[2,6,7]**




# How is HER2-low tested?

**Current HER2 diagnostics are based on two separate assays[3,4,8,9]**




- HER2 analysis is typically performed on the most recent suitable tumour sample. This may be a recent or archive biopsy sample, depending on availability[7]

# Why should I test for HER2-low?

- DESTINY-Breast04 is a Phase III clinical trial that evaluated ENHERTU▼, (trastuzumab deruxtecan) a HER2-targeted ADC, for previously treated patients with HER2-low mBC compared with treatment of physician's choice (TPC)*[7]
- Eligible patients with HR-positive or -negative disease (N=557) were randomised 2:1 to receive 5.4 mg/kg ENHERTU every 3 weeks or TPC[7]
- The primary endpoint was PFS among patients with HR-positive disease[7]
- This pivotal trial is the first to demonstrate the clinically meaningful benefit of a HER2-targeted therapy in HER2-low breast cancer, meeting the primary and other key endpoints[7]

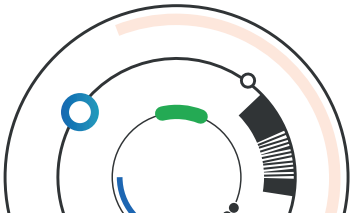
## DESTINY-Breast04 efficacy[7]

| | Cohort | Treatment | mPFS, months | HR (95% CI) | mOS, months | HR (95% CI) |
|---|---|---|---|---|---|---|
| HER2-low mBC treated with 1–2 prior lines of CT | HR+ patients | Enhertu (N=331) | 10.1 | 0.51 (0.40–0.64); P<0.001 | 23.9 | 0.64 (0.48–0.86); P=0.003 |
| | | TPC (N=163) | 5.4 | | 17.5 | |
| | Overall population | Enhertu (N=373) | 9.9 | 0.50 (0.40–0.63); P<0.001 | 23.4 | 0.64 (0.49–0.84); P=0.001 |
| | | TPC (N=184) | 5.1 | | 16.8 | |

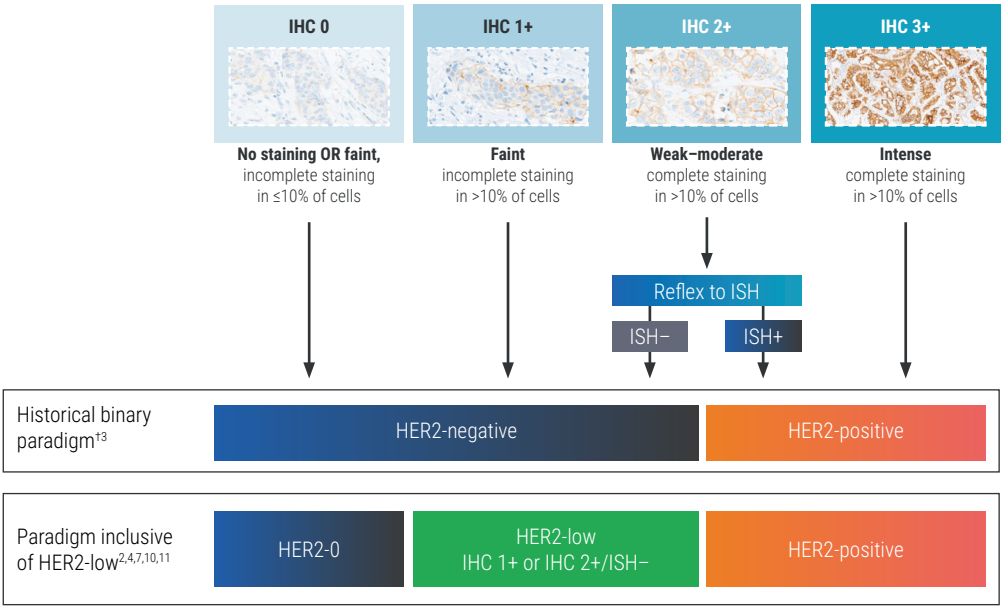
## Safety profile of ENHERTU in HER2-positive patients[7]

- The most common (≥20%) adverse reactions, including laboratory abnormalities, for ENHERTU were nausea (73.0%), fatigue (47.7%), alopecia (37.7%), vomiting (34.0%), anaemia (33.2%), constipation (21.3%), neutropenia (33.2%), increased aminotransferase levels (23.5%), decreased appetite (28.6%), diarrhoea (22.4%), thrombocytopenia (23.7%), and leukopenia (23.2%)
- The frequency of Grade ≥3 AEs was lower with ENHERTU (52.6%) vs. TPC (67.4%)
- Drug-related ILD or pneumonitis was reported in 12.1% of patients (Grade 5, 0.8%) in the ENHERTU arm and 0.6% of patients in the TPC arm

*TPC was either capecitabine, eribulin, gemcitabine, paclitaxel or nab-paclitaxel



# Proposed algorithm for defining HER2-low BC




Images provided by Dr. Corrado D'Arrigo and the team at Poundbury Cancer Institute, UK.

# Interpretation of the results

A retrospective analyses of patient mBC samples that were historically categorised as HER2-negative (N=789) were using the updated scoring paradigm. 67.2% of samples previously determined as HER2-negative were reclassified as HER2-low[12]

Under the binary paradigm, there was little need to invest time to definitively distinguish between IHC 0 and IHC 1+ as both scores were representative of HER2-negative and would be treated accordingly[7,12]

However, separating between these categories is now important in order to identify patients who are HER2-low and potentially eligible for ENHERTU treatment[7,12]

†Diagnosis as per 2018 ASCO/CAP HER2 guidelines

# When should HER2-low be tested?

**HER2 status should be determined using IHC and ISH when biopsy tissue is available for:**[4,13]

- All newly diagnosed patients with breast cancer
- All patients with metastatic breast cancer
- All cases of recurrent disease after initial treatment

**In DESTINY-Breast-04, 51% of biopsies were recent and 44% archive‡**[14]

When a biopsy is available, **re-testing HER2 status** in the metastatic setting is advised in the following situations:[15–17]

| 01 | 02 | 03 | 04 | 05 | 06 | 07 |
|---|---|---|---|---|---|---|
| In recurrent and / or stage IV HER2-negative BC patients | When the receptor status of the primary tumour is unknown or negative | If the primary tumour is heterogeneous for receptor expression | If a patient was assessed as IHC 0 using a non-clinically validated assay | If new therapies become available | If the initial test was performed >10 years previously | If the metastatic evolution is unusual compared with the tumour characteristics |

# Implications of precise HER2 designation

The landmark DESTINY-Breast04 trial has established HER2-low as a new targetable patient population in mBC who may benefit from HER2-targeted therapy with ENHERTU[7]

- The PATHWAY anti-HER2/neu (4B5) Rabbit Monoclonal Primary Antibody assay (Ventana [4B5]) is the only clinically validated and FDA-approved IHC assay for the identification HER2-low[7,17]

The indication for ENHERTU has been expanded to adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH−) breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy‡[18]

To determine your BC patients' HER2-low status and potential eligibility for ENHERTU, it is important to test biopsies using the Ventana (4B5) with the CDx protocol using the most recently available tissue[7,16,17]

‡See Prescribing information for full indication

# Challenges associated with HER2-low testing

In DESTINY-Breast04, HER2-low was centrally assessed exclusively with clinically validated Ventana (4B5) assay for IHC classification[7,17]

- A comparison between HER2 scores using the most commonly employed assays (Ventana [4B5] and HercepTest) demonstrated good concordance when assessing HER2 expression using the historical binary scoring system[16]
- However, greater discordance is observed between the assays when interpreting HER2 expression at the lower levels[11,16]
- In a direct comparison, approximately 73% concordance was reported between the Ventana (4B5) assay and HercepTest assay (N=500)[16]
- For this reason, re-testing of HER2 IHC 0 cases previously assessed using assays not equivocal to the performance of the 4B5 assay may be recommended[16]

Studies have reported that, pathologists are able to distinguish between IHC 2+ and IHC 3+ with greater confidence than IHC 0 and IHC 1+. Accuracy of HER2 scoring in samples with low levels of expression can be addressed with education[14,19]

Multidisciplinary coordination is needed to in order for HER2 testing to be carried out by a trained pathologist using the CDx protocol, with clear reporting to confirm HER2 status to oncologists[4,17]

HER2 intra- and inter-tumour heterogeneity is present in breast cancer tumours, but its effects may be more pronounced in HER2-low cases[2,3,4,10,20]

Due to faintness of staining in samples with low levels of HER2 expression, differences in tissue handling may greatly impact staining intensity and thus scoring[2,21]

**Please discuss these data with your local pathology service**

# Considerations for assessing HER2 status in clinical practice

## Re-score

- Consider re-scoring samples previously scored as HER2-negative[12]
- Some cases will be near the 10% staining cutoff (IHC 0 vs. IHC 1+) and require additional scrutiny for accurate assessment[12]

## Re-test

- Consider re-testing samples tested using an assay without equivalent concordance to the Ventana (4B5) assay to accurately determine the HER2 IHC score[17,19]
- Consider re-testing patients at disease progression or relapse prior to treatment as HER2 expression may change over time[15,22]

## New specimens

- ASCO/CAP recommend assessment of HER2 in newly diagnosed patients with BC and, where possible, in those who develop metastatic disease. HER2 status can change during disease progression[4,15,22]
- Adhere to the 2018 ASCO/CAP guidelines regarding preanalytical preparation of specimens to ensure high quality HER2 staining ahead of assessment[3,4]

ADC=antibody-drug conjugate; AE=adverse event; ASCO=American Society of Clinical Oncology; BC=breast cancer; CAP=College of American Pathologists; CDx=companion diagnostic; CI=confidence interval; CT=chemotherapy; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; IHC=immunohistochemistry; ILD=interstitial lung disease; ISH=in situ hybridisation; mBC=metastatic breast cancer; TPC=treatment of physician's choice.

**1.** Wang J, Xu B. *Signal Transduct Target Ther*. 2019;4:34. **2.** Tarantino P, et al. *J Clin Oncol*. 2020;38(17):1951–1962. **3.** Wolff AC, et al. *J Clin Oncol*. 2023;41(22):3867–3872. **4.** Tarantino P, et al. *Ann Oncol*. 2023;34(8):645–659. **5.** Pernas S, Tolaney SM. *Curr Opin Oncol*. 2020;32:545–554. **6.** Eiger D, et al. *Cancers*. 2021;13:1015. **7.** Modi S, et al. *New Engl J Med*. 2022;387:9–20. **8.** Gutierrez C, Schiff R. *Arch Pathol Lab Med*. 2011;135(1):55–62. **9.** Hanna WM, et al. *Modern Pathology*. 2014;27:4–18. **10.** Marchiò C, et al. *Semin Cancer Biol*. 2021;72:123–135. **11.** Franchet C, et al. *Ann Pathol*. 2021;41(6):507–520. **12.** Viale G, et al. *ESMO Open.* 2023 Aug;8(4)101615. **13.** Miglietta F, et al. *NPJ Breast Cancer*. 2021;7(1):137. **14.** Prat A, et al. *Cancer Res*. 2023;83(5 Suppl): HER2-18. **15.** Penault-Llorca F, et al. *Breast*. 2013;22(2):200–202. **16.** Scott M, et al. *J Clin Oncol.* 2021;39:1021. **17.** Roche Diagnostics. https://diagnostics.roche.com/ global/en/news-listing/2022/roche-receives-fda-approval-for-first-companion-diagnostic-to-id.html. Accessed August 2023. **18.** Enhertu® (fam-trastuzumab deruxtecan-nxki) for injection, for intravenous use. Prescribing Information. November 2022. **19.** Rüschoff J, et al. Cancer Res. 2023;83(5_Supplement): HER2-13. **20.** Modi S, et al. *J Clin Oncol*. 2020;38(17):1887–1896. **21.** Compton CC, et al. *Arch Pathol Lab Med*. 2019;143(11):1346–1363. **22.** Aurilio G, et al. *Eur J Cancer*. 2014;50(2):277–289.

# ▼ **ENHERTU** (trastuzumabderukstekan)

**Indikasjon:** Brystkreft: *HER2-positiv brystkreft:* Enhertu som monoterapi er indisert til behandling av voksne pasienter med inoperabel eller metastaserende HER2-positiv brystkreft som har fått ett eller flere tidligere anti-HER2-baserte regimer. *HER2-lav brystkreft:* Enhertu som monoterapi er indisert til behandling av voksne pasienter med inoperabel eller metastaserende HER2-lav brystkreft som har fått tidligere kjemoterapi ved metastaserende sykdom eller fått sykdomstilbakefall under eller innen 6 måneder etter fullført adjuvant kjemoterapi (se pkt. 4.2).

**Dosering:** Anbefalt dose brystkreft: 5,4 mg/kg. Gis som iv. infusjon (ikke som støtdose eller bolus) 1 gang hver 3. uke (21-dagerssyklus) frem til sykdomsprogresjon eller uakseptabel toksisitet. Før hver dose bør pasientene premedisineres med et kombinasjonsregime av 2 eller 3 legemidler (f.eks. deksametason med enten en 5-HT3-reseptorantagonist og/eller en NK1-reseptorantagonist, samt andre legemidler som indisert) til forebygging av kjemoterapiindusert kvalme og oppkast.

**Bivirkninger:** De vanligste bivirkningene var kvalme (75,0 %), fatigue (57,3 %) og oppkast (42,1%). Behandling av bivirkninger kan kreve midlertidig avbrudd, dosereduksjon eller seponering av behandling.

**Utvalgt sikkerhetsinformasjon:** Skal forskrives av lege og administreres under tilsyn av helsepersonell med erfaring innen bruk av kreftlegemidler. For å forebygge feilmedisinering skal hetteglassene sjekkes for å sikre at legemidlet som tilberedes og administreres er Enhertu (trastuzumabderukstekan) og ikke trastuzumab eller trastuzumabemtansin.
*Interstitiell lungesykdom (ILD)/pneumonitt:* Pasienter skal monitoreres for tegn og symptomer på ILD/pneumonitt og umiddelbart utredes ved mistanke om dette. Nøytropeni: Komplett blodtelling skal foretas før oppstart av behandling og før hver dose, og som klinisk indisert.
*Reduksjon i venstre ventrikkels ejeksjonsfraksjon (LVEF):* Standard hjertefunksjonsundersøkelse (EKG eller MUGA skanning) skal foretas for å vurdere LVEF før oppstart av behandling og regelmessig under behandling som klinisk indisert. *Graviditet:* Kan forårsake fosterskade.

Vi anbefaler at du leser preparatomtalen før oppstart av behandling.
Det er utarbeidet risikohåndteringsmateriell og pasientinformasjon for Enhertu. Dette finner du på www.felleskatalogen.no eller ved å kontakte oss.

Se preparatomtalen (SPC) for utfyllende informasjon om Enhertu.

**Reseptgruppe:** C.

**Pakninger, priser:** *100mg:* 1 stk. (hetteglass) 22341,00 NOK.

Besluttet innført 1) til behandling av pasienter med inoperabel eller metastatisk HER2-positiv brystkreft som har fått ett eller flere tidligere anti-HER2-baserte regimer 2) som monoterapi til behandling av voksne pasienter med inoperabel eller metastaserende HER2-lav brystkreft som har fått tidligere kjemoterapi ved metastaserende sykdom eller fått sykdomstilbakefall under eller innen 6 måneder etter fullført adjuvant kjemoterapi. Enhertu inngår i anbefalinger fra RHF spesialistgruppe, og rekvirering skal gjøres i tråd de regionale helseforetakenes anbefalinger:
Onkologi og kolonistimulerende legemidler. https://www.sykehusinnkjop.no/avtaler-legemidler/onkologi/

Enhertu markedsføres i Norge av Daiichi Sankyo Nordics Aps og AstraZeneca AS.

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