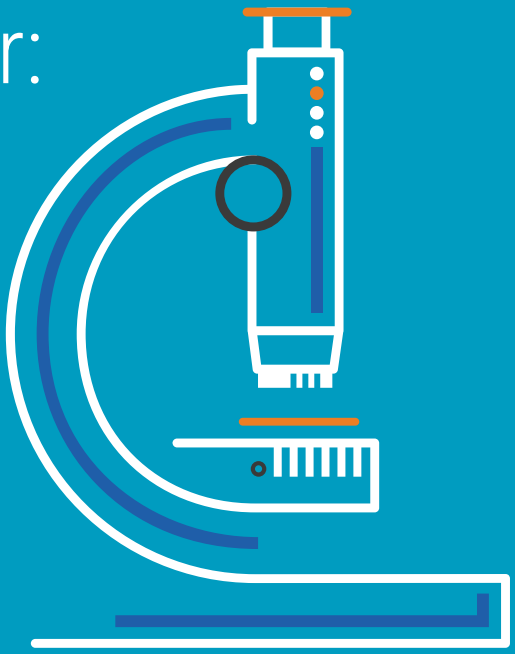
HER2 PRECISION MEDICINE

HER2-testing in metastatic breast cancer:

Pathology reporting guide



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.

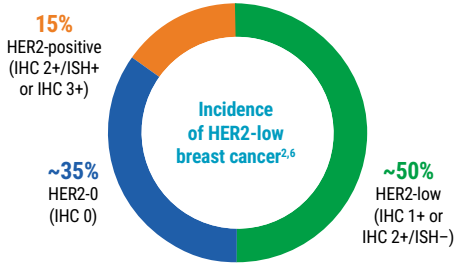
Daiichi-Sankyo | AstraZeneca

ENHERTU® trastuzumabderukstekan

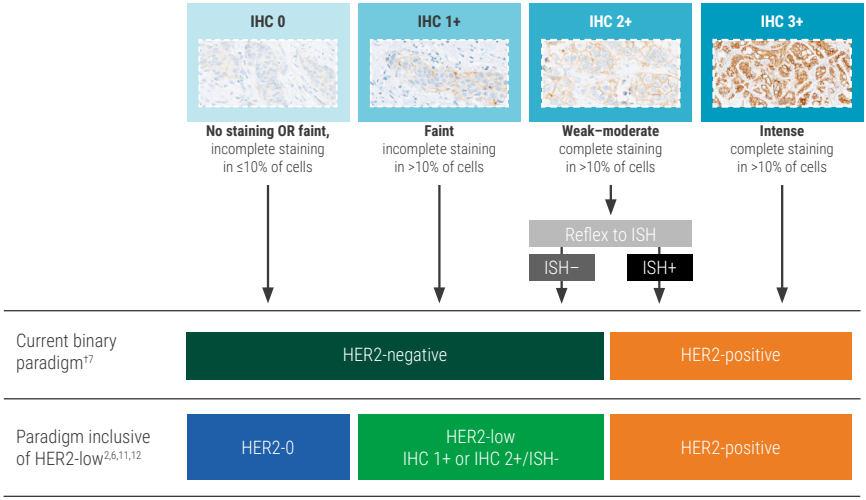
Have you updated your pathology reporting practice to include HER2-low?

- The treatment classification of HER2-negative* in breast cancer has changed with the approval of ENHERTU ▼ based on the results of the DESTINY-Breast04 trial[1,2]
- Consider updating your institution's pathology reporting template to record comprehensive details of the parameters assessed for HER2 to ensure that HER2 status is more accurately captured and to provide clarity when considering the best treatment options for patients[3–5]
- The revised HER2 treatment classification accounts for a new therapeutic option in patients with HER2-low metastatic breast cancer. IHC scoring criteria have not changed[1]

Approximately 50% of all breast cancers may be categorised as HER2-low, now a clinically actionable population[1,2,6]



Recent updates to country-specific guidelines recommend that specimens scored as IHC 1+ or IHC 2+/ISH- can now be categorised as HER2-low. HER2-low treatment classification utilises existing ASCO/CAP parameters for IHC assessment[1,5,7–9]



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

The protocol and interpretation guide utilised to identify patients with HER2-low metastatic breast cancer (mBC) in DESTINY-Breast04 are available[1]

*HER2-negative was defined as IHC 0, IHC 1+ or IHC 2+/ISH-.

HER2-low pathology report checklist

Consider including the following in the pathology report:

Specify the HER2 IHC assay used[1,4,6,10–13]

Assay selection can be an important factor when determining low levels of HER2 expression, as assays were historically optimised to detect high levels of HER2 expression. Ensure the HER2 IHC assay has been validated to detect HER2-low

Report the HER2 IHC score as 0, 1+, 2+ or 3+[3–5,7–9]

Categorisation of HER2 IHC score continues to be based on the current ASCO/CAP criteria[†]

Report the HER2 ISH result (if completed) as negative or positive, as well as the HER2 and CEP17 copy number and ratio[3,4,7–9]

Reflex ISH is performed on samples scored as HER2 IHC 2+ or indeterminate to assess final HER2 status

Include the estimated percentage of tumour cells stained[‡] and staining intensity[§3,4,7–9]

Documenting this level of detail for IHC staining is important in differentiating between IHC 0 and IHC 1+, and therefore HER2-0 or HER2-low status

Conclude the report with the final HER2 interpretation and estimated percentage staining[3–5,7–9]

Specify any notable specimen, pre-analytical, and IHC/ISH scoring factors that influenced the interpretation

Reporting commentary on HER2-low status maybe helpful for treatment decisions in patients with metastatic disease[7]

Pathologists and oncologists should discuss how commentary can be best modified to assist with patient management in this new era of HER2-low. ASCO/CAP recommend including the footnote "Patients with breast cancers that are HER2 IHC 3+ or IHC 2+/ISH amplified may be eligible for several therapies that disrupt HER2 signaling pathways. Invasive breast cancers that test 'HER2-negative' (IHC 0, 1+ or 2+/ISH not-amplified) are more specifically considered 'HER2-negative for protein overexpression/gene amplification' since non-overexpressed levels of the HER2 protein may be present in these cases. Patients with breast cancers that are HER2 IHC 1+ or IHC 2+/ISH not-amplified may be eligible for a treatment that targets non-amplified/non-overexpressed levels of HER2 expression for cytotoxic drug delivery (IHC 0 results do not result in eligibility currently)"

[†]IHC 0: no staining observed or incomplete and faint/barely perceptible in ≤10% tumour cells; IHC 1+: incomplete membrane staining that is faint/barely perceptible in >10% of tumour cells; IHC 2+: weak to moderate complete membrane staining observed in >10% of tumour cells; IHC 3+: circumferential membrane staining observed in >10% of tumour cells.
[‡]Range (1–10% or >10%) and actual percentage of staining.
[§]Partial, weak, moderate or strong staining.

Rationale for updated to HER2 reporting

The pivotal DESTINY-Breast04 study in HER2-low mBC has driven changes in the HER2 treatment classification paradigm[1]

DESTINY-Breast04 was a randomised, open-label, Phase III trial that met the primary endpoint of progression-free survival (PFS) among patients with hormone receptor-positive disease

Eligible patients with HR-positive or -negative disease (N=557) were randomised 2:1 to receive 5.4 mg/kg ENHERTU intravenously every 3 weeks or treatment of physician's choice (TPC)¶

HR+

The primary endpoint was PFS among patients with HR-positive disease

ENHERTU is the first HER2-targeted therapy to demonstrate a statistically significant and clinically meaningful improvement in median PFS and overall survival vs. TPC in patients classified as HER2-low¶

DESTINY-Breast04 efficacy[1]

	Cohort	Treatment	mPFS, months (95% CI)	HR (95% CI)	mOS, months (95% CI)	HR (95% CI)
HER2-low mBC treated with 1–2 prior lines of CT	HR+ patients	ENHERTU (N=331)	10.1 (9.5–11.5)	0.51 (0.40–0.64); P<0.001	23.9 (20.8–24.8)	0.64 (0.48–0.86); P=0.003
		TPC¶ (N=163)	5.4 (4.4–7.1)		17.5 (15.2–22.4)	
	Overall population	ENHERTU (N=373)	9.9 (9.0–11.3)	0.50 (0.40–0.63); P<0.001	23.4 (20.0–24.8)	0.64 (0.49–0.84); P=0.001
		TPC¶ (N=184)	5.1 (4.2–6.8)		16.8 (14.5–20.0)	

Safety was consistent with the known safety profile of ENHERTU in patients with HER2-positive mBC[1]

The most common (≥20%) adverse reactions, including laboratory abnormalities, for ENHERTU were nausea (73.0%), fatigue (47.7%), vomiting (34.0%), alopecia (37.7%), 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 (determined by an independent committee) 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.

Considerations for updating the HER2 treatment classification

Historically, there was no clinical need to invest time to definitively distinguish between IHC 0 and IHC 1+ as both scores were representative of HER2-negative*[7–9]

This distinction is now important to differentiate between HER2-0 and HER2-low, and therefore, potential eligibility for HER2-targeted treatment[2,7–9]

Consider re-scoring samples previously scored as HER2-negative*[10]

Some cases will be near to the 10% staining cutoff (IHC 0 vs. IHC 1+) and require additional scrutiny for accurate assessment[5,10]

In DESTINY-Breast04, HER2 status was centrally assessed with the Ventana on market 4B5 assay[1]

- The Ventana (4B5) assay is now a clinically validated companion diagnostic for HER2-low[13]

Re-testing HER2 IHC 0 cases previously assessed using assays not equivalent to the performance of the Ventana (4B5) assay may be recommended[11]

HER2 status can change during disease progression or relapse[14–16]

- The current ASCO/CAP guidelines recommend all newly diagnosed patients with breast cancer and patients who develop metastatic disease have a HER2 test performed[7]

Consider updating your institution's pathology reporting template for mBC in order to accurately record patients' HER2 status and determine potential eligibility for ENHERTU

*HER2-negataive was defined as IHC 0, IHC 1+ or IHC 2+/ISH-.
ASCO=American Society of Clinical Oncology; CAP=College of American Pathologists; CI=confidence interval; CT=chemotherapy; HER2=human epidermal growth factor receptor 2; HR=hazard ratio; IHC=immunohistochemistry; ISH=*in situ* hybridisation; mBC=metastatic breast cancer; mOS=median overall survival; mPFS=medial progression-free survival; TPC=treatment of physician's choice.

Notes

1. Modi S, et al. *New Engl J Med*. 2022;387(1):9–20. **2.** ENHERTU® (fam-trastuzumab deruxtecan-nxki) for injection, for intravenous use. Prescribing Information. November 2022. **3.** Royal College of Pathologists. Pathology reporting of breast disease in surgical excision specimens incorporating the dataset for histological reporting of breast cancer. *https://www.rcpath.org/resourceLibrary/g148-breastdataset-hires-jun16-pdf.html*. Accessed August 2023. **4.** College of American Pathologists. Template for reporting results of biomarker testing of specimens from patients with carcinoma of the breast. *March 2023. https://documents.cap.org/documents/Breast.Bmk_1.5.0.1.REL_CAPCP.pdf*. Accessed August 2023. **5.** Rakha EA, et al. *J Clin Pathol*. 2023;76(4):217–227. **6.** Tarantino P, et al. *J Clin Oncol*. 2020;38(17):1951–1962; **7.** Wolff AC, et al. *J Clin Oncol*. 2023:41(22):3867–3872. **8.** Tarantino P, et al. *Ann Oncol*. 2023;34(8):645–659. **9.** Franchet C, et al. *Ann Pathol*. 2021;41(6):507–520. **10.** Viale G, et al. *ESMO Open*. 2023 Aug;8(4)101615. **11.** Scott M, et al. *J Clin Oncol*. 2021;39:1021. **12.** Rüschoff J, et al. *Virchows Archiv*. 2022; 481:685–694. **13.** 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. **14.** Aurillo G, et al. *Eur J Cancer*. 2014;50(2):277–289. **15.** Miglietta F, et al. *NPJ Breast Cancer*. 2021;7(1):137. **16.** Penault-Llorca F, et al. *Breast*. 2013;22(2):200–202.

▼ **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 med 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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