HER2 PRECISION MEDICINE

HER2-low patient identification: A resource for pathologists

HER2-LOW BREAST CANCER IS NOW CLINICALLY ACTIONABLE

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.

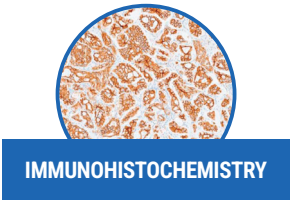
Daiichi-Sankyo | AstraZeneca

ENHERTU® trastuzumabderukstekan

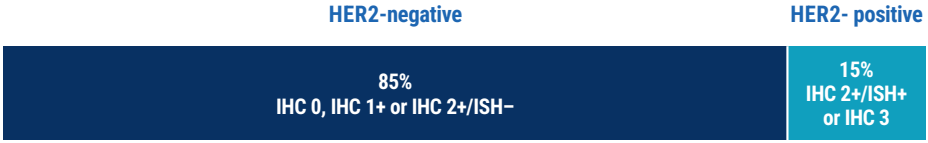
HER2-low breast cancer is now clinically actionable

Globally, breast cancer is the leading cause of cancer-related deaths in women[1]

- Breast cancer is classified by multiple histologic and molecular subtypes for the purpose of prognosis and treatment identification[2]
- Status of hormone receptor (HR; oestrogen and progesterone) and HER2 are used to make treatment decisions[2]
- HER2 status is primarily assessed by immunohistochemistry (IHC)[3,4]



Historically, classification of HER2 expression in order to make treatment decisions in breast cancer has been binary; either HER2-positive or HER2-negative[5–9]



- However, using the current ASCO/CAP criteria for HER2 scoring in breast cancer samples, those assessed as IHC 1+ or IHC 2+ with a negative in situ hybridisation (ISH) result are regarded as HER2-low under a new treatment classification paradigm[5–10]

- The HER2-low population is heterogenous, including both luminal-type HR-positive and HR-negative breast cancers[9]

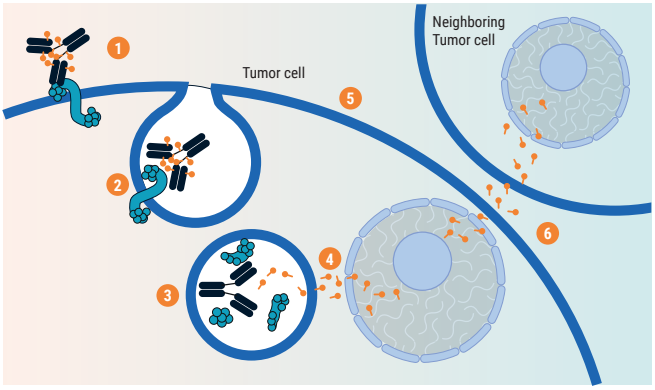
Antibody drug conjugates (ADC), have enabled effective targeting of breast cancer tumours with low levels of HER2 expression[9,10]

As patients with HER2-low breast cancer tumours were previously regarded as HER2-negative, they were not eligible for HER2-targeted treatments[9,10]

- However, HER2-targeted treatments have been shown to have a statistically significant benefit in the HER2-low metastatic breast cancer (mBC) population compared with standard-of-care[10]

Pivotal DESTINY-Breast04 study in HER2-low metastatic breast cancer

Mechanism of action for ENHERTU ▼, a HER2-targeted ADC[9,10]



1. T-DXd binds to HER2
2. T-DXd internalized
3. Linker cleaved, releasing topoisomerase I inhibitor
4. Topoisomerase I inhibitor enters nucleus
5. Tumor cell death
6. Membrane permeable payload results in bystander effect

T-DXd
HER2 protein
Topoisomerase I inhibitor payload

ENHERTU has demonstrated significant clinical benefits in HER2-low mBC[10]

- DESTINY-Breast04 was the first Phase III randomised, controlled clinical trial of ENHERTU vs. treatment of physician's choice (TPC) for HER2-low mBC[10]
- ENHERTU is the first HER2-targeted therapy to demonstrate a statistically significant and clinically meaningful improvement in progression-free survival (PFS) and overall survival (OS) vs.TPC in patients with HER2-low mBC[10]
  - The primary endpoint was PFS by blinded independent central review (BICR) in the HR+ population. For ENHERTU, mPFS was 10.1 months (95% CI, 9.5–11.5) vs. 5.4 months (95% CI, 4.4–7.1) with TPC. The hazard ratio was 0.51 (95% CI, 0.40–0.64); P<0.001[10]
  - A key secondary endpoint was OS by BICR in the HR+ population. With ENHERTU, mOS was 23.9 months (95% CI, 20.8–24.8) vs 17.5 months (95% CI, 15.2–22.4) with TPC. The hazard ratio was 0.64 (95% CI, 0.48–0.86); P=0.003[10]
- Safety in DESTINY-Breast04 was consistent with the previously reported safety profile of ENHERTU in mBC, and showed an overall positive benefit–risk[10]
  - The most common (≥20%) drug-related 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%)[10]
  - The frequency of Grade ≥3 AEs was lower with ENHERTU (52.6%) vs. TPC (67.4%)[10]
  - 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[10]

HER2-low identification: implementation into clinical practice

DESTINY-Breast04 established HER2-low (IHC 1+, IHC 2+/ISH−) mBC as a new targetable patient population, and suggests that ENHERTU may be a potential new standard of care in this setting[10]

It is important to replicate the histological processes used in DESTINY-Breast04 to ensure accurate identification of patients who may benefit from ENHERTU[10]

The protocol and interpretation guide utilised to identify patients with HER2-low mBC in DESTINY-Breast04 are available[10]

- Adequate tumour tissue was assessed for HER2 status at central laboratories. For IHC, the PATHWAY anti-HER2/neu (4B5) Rabbit Monoclonal Primary Antibody (VENTANA [4B5]) assay was used*[10]
- IHC and ISH scoring was based on the ASCO/CAP HER2 2018 guidelines[10]
- To accurately score low levels of HER2 expression, pathologists were trained in staining pattern identification and microscope magnification techniques[10]

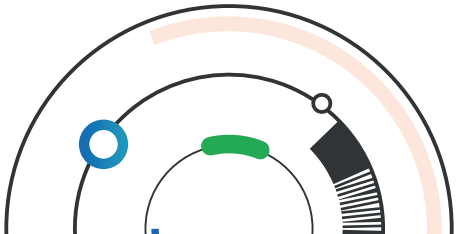
Preanalytical considerations for HER2 assessment

Tissue selection

- Primary or most metastatic biopsies can be used for assessing HER2 status[10]
- HER2 expression can evolve between primary and metastatic tumours[11,12]
- Decalcified bone metastases, fine needle aspirates or other cytological specimens were not used in DESTINY-Breast04[10]
- In DESTINY-Breast-04, 51% of biopsies were recent (2019 or later) and 44% archive (2018 or earlier).† The majority of archived specimens used were acquired within five years[10]

Tissue processing

- Routinely processed, FFPE tissues are suitable for use with the validated IHC and ISH assays[10]
- Fix specimens in 10% neutral buffered formalin for 6–72 hours. Duration affects the extent of tissue penetration, level of fixation and the subsequent quality of staining[10,13]
- Mount serial sections (~4-µm) of FFPE specimens on glass microscope slides[10]
- Using the VENTANA HER2 (4B5) assay and BenchMark ULTRA instrument, incubate the primary antibody for 12 minutes at 36°C[10,15]



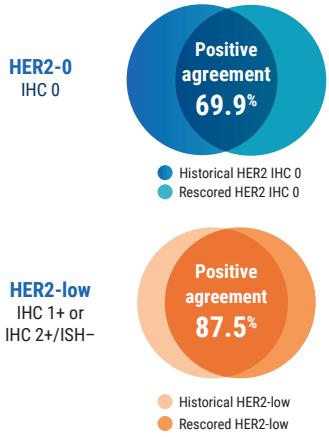
*When reflex ISH was required, the INFORM HER2 Dual ISH assay was used.
†Data on tumour collection data were missing for the remaining specimens.

Reclassification of HER2 scoring

- Reclassification of HER2 expression has the potential to change the treatment landscape for patients with mBC who have previously been categorised as HER2-negative[9,10]
- Under the binary paradigm, there was little need to invest time to definitively distinguish between IHC 0 and IHC 1+ as both scores were classed as HER2-negative and treated accordingly[10,15]
- Retrospective analyses of samples scored as IHC 0 showed that up to 1 in 3 could be re-scored with a different IHC value[15]
- However, differentiating between IHC 0 and IHC 1+ is now important in order to identify patients who are HER2-low and potentially eligible for HER2-targeted treatments[10,15]

Scoring concordance‡[15]

Overall concordance 81.3% (n=639/786)



Adapted from Viale G, et al. 2022[15]

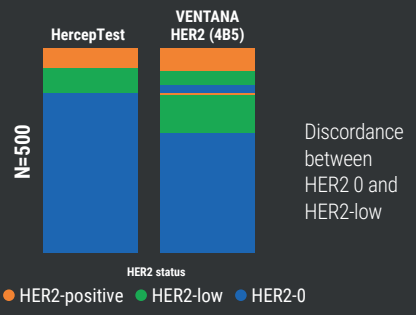
The importance of using a clinically validated assay

- PATHWAY HER2 (4B5) CDx is the only clinically validated and FDA-approved protocol to identify HER2-low in mBC[10,16]

USE PATHWAY anti-HER2 (4B5) antibody + **ON BenchMark ULTRA instrument** + **WITH U PATHWAY HER2 4B5 staining procedure** + **PER 2018 ASCO/CAP HER2 testing scoring criteria** → **Clinically validated HER2-LOW identification and reporting**

- HER2 IHC assays were originally optimised to identify high levels of HER2 expression[6]
- Use of a validated HER2 IHC assay is recommended to most accurately determine biopsies that are HER2-low vs. IHC 0[10,15–17]
- In a direct comparison of commonly used HER2 IHC assays, the VENTANA HER2 (4B5) assay identified a higher proportion of HER2-low samples than the HercepTest assay[17]

Alignment in patient status[17]



Adapted from Scott M, et al. 2021.[17]

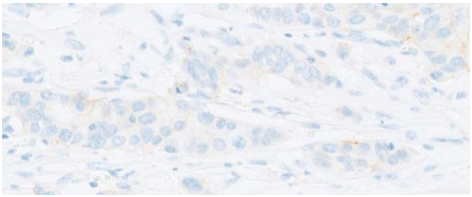
‡Concordance includes only patients with both historical and rescored IHC scores available.

Interpretation of HER2 staining patterns

HER2 IHC score interpretation remains the same between the 2018 and 2023 ASCO/CAP guidelines for HER2 testing[5,18]

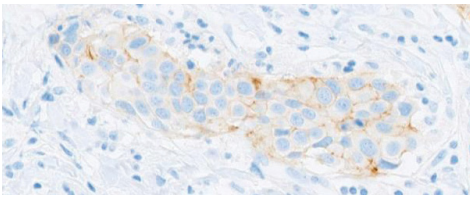
0

No staining is observed or membrane staining that is incomplete and is faint/barely perceptible and in ≤10% of tumour cells



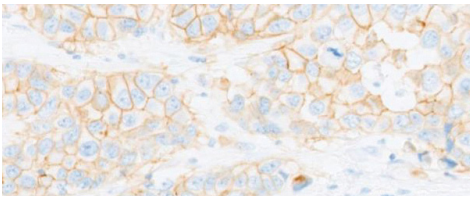
1+

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



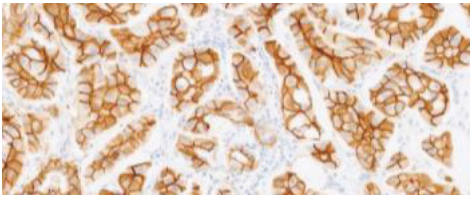
2+

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



3+

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



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

Key considerations when assessing HER2 status in clinical practice

Introduction of HER2-low as a HER2 treatment classification may require updates to pathology practices.

Re-score

- Consider re-scoring samples previously scored as HER2-negative[15]
- Some cases will be near the 10% staining cutoff (IHC 0 vs. IHC 1+) and require additional scrutiny for accurate assessment[3,10,15]

Re-test

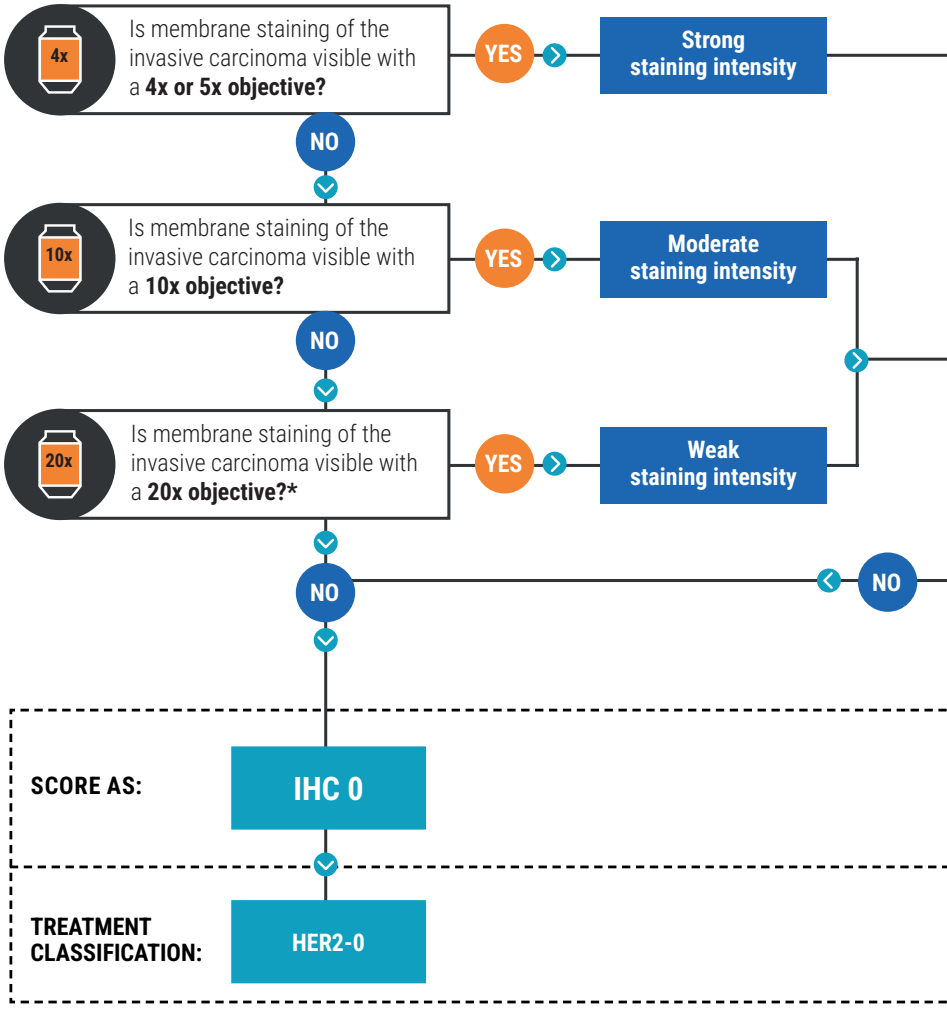
- Consider re-testing samples stained using an assay without equivalent concordance to the VENTANA HER2 (4B5) assay to accurately determine the HER2 IHC score[17]
- Consider re-testing patients at disease progression or relapse prior to treatment as HER2 expressions may change over time[11,12]

New specimens

- ASCO/CAP recommend assessment of HER2 status in newly diagnosed patients with BC and, where possible, in those who develop metastatic disease. HER2 status can change during disease progression[5,11,12]
- Adhere to the 2018 ASCO/CAP guidelines regarding preanalytical preparation of specimens to ensure high quality HER2 staining ahead of assessment[18]

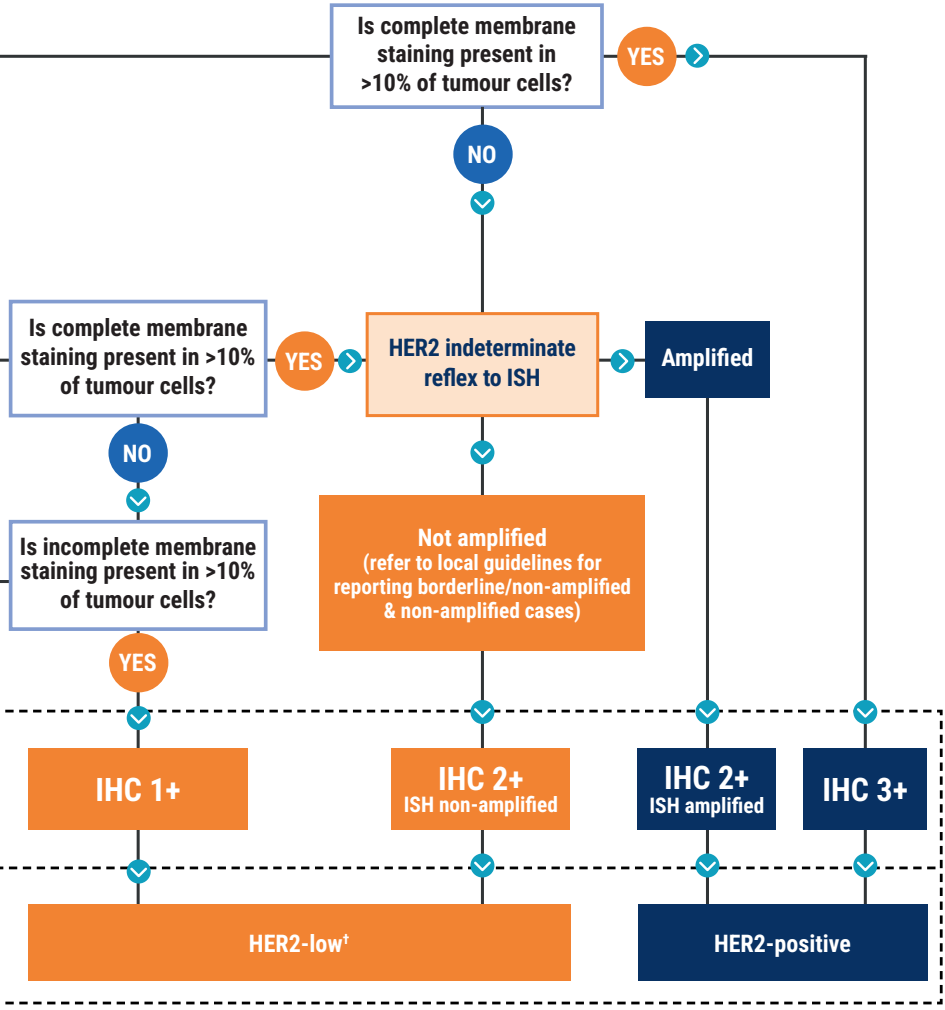
Scoring algorithm

This algorithm was developed in collaboration with Dr Corrado D'Arrigo and the team at Poundbury Cancer Institute, UK.



†Assuming >10% complete or incomplete membrane staining of any intensity for IHC 2+/ISH not amplified.

Determine HER2 status (invasive component) by a validated IHC assay on any invasive breast carcinoma at the time of diagnosis or at relapse. Ensure appropriate staining of on-slide controls before proceeding[5,18]



Notes

ADC=antibody-drug conjugate; ASCO=American Society of Clinical Oncology; CAP=College of American Pathologists; CDx=companion diagnostic; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; IHC=immunohistochemistry; ISH=in situ hybridisation; IUO=investigational use only; mBC=metastatic breast cancer; TPC=treatment of physician's choice.

1. Sung H, et al. *CA Cancer J Clin*. 2021;71:209–249. **2.** Nascimento RG, Otoni KM. *Mastol.* 2020;30:e20200024. **3.** Gutierrez C, Schiff R. *Arch Pathol Lab Med*. 2011;135:55–62. **4.** Hanna WM, et al. *Modern Pathology*. 2014;27:4–18. **5.** Wolff AC, et al. *J Clin Oncol*. 2023;41:3867–3872. **6.** Tarantino P, et al. *Ann Oncol*. 2023;S0923-7534(23)00693-2. **7.** Marchiò C, et al. *Semin Cancer Biol*. 2021;72:123–135. **8.** Tarantino P, et al. *J Clin Oncol*. 2020;38:1951–1962. **9.** Schettini F, et al. *NPJ Breast Cancer*. 2021;7:1. **10.** Modi S, et al. *New Engl J Med*. 2022;387:9–20. **11.** Aurilio G, et al. *Eur J Cancer*. 2014;50:277–289. **12.** Miglietta F, et al. *NPJ Breast Cancer*. 2021;7:149. **13.** Compton CC, et al. *Arch Pathol Lab Med*. 2019;143:1346–1363. **14.** PATHWAY anti-HER-2/neu (4B5) Rabbit Monoclonal Primary Antibody Package Insert. **15.** Viale G, et al. *ESMO Open*. 2023 Aug;8(4)101615. **16.** 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. **17.** Scott M, et al. *J Clin Oncol.* 2021;39:1021. **18.** Wolff AC, et al. *J Clin Oncol*. 2018;36:2105–2122.

▼ **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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