Trastuzumab deruxtecan (Enhertu®) as monotherapy for the treatment of unresectable or metastatic HER2 positive breast cancer

General information

Drug description [1]	Indication [2]
Trastuzumab deruxtecan (Enhertu®, also known as T-DXd and DS-8201) is an antibody–drug conjugate consisting of a humanised anti-HER2 monoclonal antibody linked to a topoisomerase I inhibitor payload through a tetrapeptide-based cleavable linker.	Trastuzumab deruxtecan (Enhertu®) as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2 positive breast cancer who have received one or more prior anti HER2 based regimens.

Current treatment [3]

- Trastuzumab emtansine is recommended, as an option for treating HER2-positive, unresectable, locally advanced or metastatic breast cancer in adults who previously received trastuzumab and a taxane, separately or in combination.
- Patients should have either received prior therapy for locally advanced or metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy.

Regulatory status

EMA [2]

Approval status for this indication: On 23 June 2022, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Enhertu®.

The CHMP adopted a **change** to an existing indication as follows:

- Enhertu® as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2 positive breast cancer who have received ~~two~~ **one** or more prior anti HER2 based regimens.

Other indications: none

✓ **Medicine under additional monitoring**
✓ **Medicine received a conditional marketing authorisation**[1]

FDA [4, 5]

Approval status for this indication: On 4 May 2022, the FDA approved fam-trastuzumab deruxtecan-nxki (Enhertu®) for adult patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either in the metastatic setting, or in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within 6 months of completing therapy.

✓ **Priority review**
✓ **Breakthrough designation**

Other indications: Enhertu® is indicated for the treatment of:

- Adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen.
- 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.
- Adult patients with unresectable or metastatic non-small cell lung cancer whose tumours have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy (this indication is approved under accelerated approval based on objective response rate and duration of response).

Costs

Enhertu® powder for concentrate for solution for infusion 100 mg = € 1,600.00 (ex-factory price) [6].

Additional information [7]

- Enhertu® should be prescribed by a physician and administered under the supervision of a healthcare professional experienced in the use of anticancer medicinal products.
- In order to prevent medicinal product errors, it is important to check the vial labels to ensure that the medicinal product being prepared and administered is Enhertu® (trastuzumab deruxtecan) and not trastuzumab or trastuzumab emtansine.
- Enhertu® should not be substituted with trastuzumab or trastuzumab emtansine.

[1] The approval of a medicine that address unmet medical needs of patients on the basis of less comprehensive data than normally required. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide the comprehensive clinical data in the future.

- Patients treated with trastuzumab deruxtecan should have documented HER2-positive tumour status, defined as a score of 3 + by IHC or a ratio of ≥ 2.0 by ISH or by fluorescence in situ hybridization assessed by a CE-marked IVD medical device. If a CE-marked IVD is not available, the HER2 status should be assessed by an alternate validated test.
- **Posology**
  - The recommended dose of Enhertu® is 5.4 mg/kg given as an IV infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.
  - The initial dose should be administered as a 90-minute IV infusion. If the prior infusion was well tolerated, subsequent doses of Enhertu® may be administered as 30-minute infusions.
  - The infusion rate of Enhertu® should be slowed or interrupted if the patient develops infusion-related symptoms.
  - Enhertu® should be permanently discontinued in case of severe infusion reactions.
- **Premedication**
  - Enhertu® is emetogenic, which includes delayed nausea and/or vomiting.

    Prior to each dose of Enhertu®, patients should be premedicated with a combination regimen of two or three medicinal products (e.g., dexamethasone with either a 5-HT3 receptor antagonist and/or an NK1 receptor antagonist, as well as other medicinal products as indicated

Warnings and precautions [4, 7]

- **Interstitial lung disease (ILD) and pneumonitis**
  - ILD and pneumonitis, including fatal cases, have been reported with Enhertu®.
  - Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms.
  - Permanently discontinue Enhertu® in all patients with Grade 2 or higher ILD/pneumonitis.
  - Advise patients of the risk and to immediately report symptoms.
- **Exposure to Enhertu® during pregnancy can cause embryo-foetal harm.**
  - Advise patients of these risks and the need for effective contraception.
- **Neutropenia**
  - Monitor complete blood counts prior to initiation of Enhertu® and prior to each dose, and as clinically indicated.
  - Manage through treatment interruption or dose reduction.
- **Left ventricular dysfunction (LVEF)**
  - Assess LVEF prior to initiation of Enhertu® and at regular intervals during treatment as clinically indicated.
  - Manage through treatment interruption or discontinuation.
  - Permanently discontinue Enhertu® in patients with symptomatic congestive heart failure.
- **Patients with moderate or severe hepatic impairment**
  - There are limited data in patients with moderate hepatic impairment and no data in patients with severe hepatic impairment.
  - As metabolism and biliary excretion are the primary routes of elimination of the topoisomerase I inhibitor, DXd, Enhertu® should be administered with caution in patients with moderate and severe hepatic impairment.
- **Traceability**
  - In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Study characteristics [1, 8-10]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
DESTINY-Breast03 NCT03529110	524 1:1	trastuzumab deruxtecan IV every 3 weeks at a dose of	trastuzumab emtansine IV every 3 weeks at a dose of 3.6 mg/kg	PFS (as determined by BICR)	ongoing[2], multicenter, open-label, randomised, active-controlled trial, phase 3 trial	HER2	Daiichi Sankyo and AstraZeneca	[1]

[2] The DESTINY-Breast03 trial is currently ongoing; estimated study completion date is 04/2023.

		5.4 mg/kg of body weight						

Efficacy (I vs. C)	**Safety** (I vs. C)
Median PFS: not reached (95% CI, 18.5-could not be estimated) vs. 6.8 months (95% CI, 5.6-8.2) **Percentage of patients who were alive without disease progression at 12 months (by BICR):** 75.8% (95% CI, 69.8-80.7) vs. 34.1% (95% CI, 27.7-40.5); HR for disease progression or death from any cause was 0.28 (95% CI, 0.22-0.37; p<0.001) **Median PFS (investigator-assessed):** 25.1 months (95% CI, 22.1-could not be estimated) vs. 7.2 months (95% CI, 6.8-8.3); HR 0.26; 95% CI, 0.20-0.35; p<0.001 **HR for disease progression or death from any cause among the patients who had received no lines or one line of previous therapy**: 0.33 **HR for disease progression or death from any cause among those who had received two or more lines of previous therapy:** 0.28 **Percentage of patients who were alive at 12 months** (at the time of data cutoff for the interim analysis): 94.1% (95% CI, 90.3-96.4) vs. 85.9% (95% CI, 80.9-89.7). The difference between the treatment groups did **not reach** the prespecified cutoff for significance (p<0.000265) (HR for death, 0.55; 95% CI, 0.36-0.86; p= 0.007) **Patients who had died as of the date of data cutoff**: 12.6% vs. 20.2% **Overall response**: 79.7% (95% CI, 74.3-84.4) vs. 34.2% (95% CI, 28.5-40.3) **Complete response**: 16.1% vs. 8.7% **Progressive disease was the best overall response in**: 1.1% vs. 17.5% **Patients who had disease control (defined as complete response, partial response, or stable disease)**: 96.6% vs. 76.8% Median duration of response per BICR: NR (20.3-NE) vs. NR (12.6-NE) PROs (data cutoff 21 May, 2021, abstract only) [11]: ❖ PRO endpoints were assessed before infusion on day 1 of the first 3 21-day cycles, then every 2 cycles, at end of treatment, at 40-days' follow-up, then every 3 months until end of follow-up. ❖ Endpoints included European Organization for Research and Treatment of Cancer QoL questionnaires (EORTC QLQ-C30; primary variable: GHS/QoL scale score) and the EuroQol 5-dimension 5-level (EQ-5D-5L) VAS. ❖ Analyses included change from baseline (CFB) and time to definitive deterioration (TDD). ❖ Hospitalisation-related endpoints were also measured. ❖ Compliance for questionnaires was >97% at baseline and >80% for cycles 3-29. ❖ QLQ-C30 baseline GHS scores recorded for I (n = 253) and C (n = 260) were similar. ❖ At end of treatment, mean CFB was not meaningfully different vs baseline (<10-point CFB) in both arms. ❖ Median TDD of QLQ-C30 GHS was 9.7 months vs. 8.3 months; HR 0.88 (95% CI, 0.70-1.11), and all prespecified QLQ-C30 subscales presented longer TDD with I, including emotional functioning; HR 0.69 (95% CI, 0.53-0.89) and pain; HR 0.75 (95% CI, 0.59-0.95). ❖ Median TDD of EQ-5D-5L VAS was 13.2 months for I vs. 8.5 months for T-DM1; HR 0.77 (95% CI, 0.61-0.98). ❖ 6.9% vs. 7.2% of patients were hospitalised; median time to first hospitalization was 219.5 vs. 60.0 days, respectively.	**TEAEs:** 256/257 (99.6%) vs. 249/261 (95.4%) **TEAEs grade ≥3:** n=134/257 (52.1%) vs. 126/261 (48.3%) **Drug-related TEAEs grade ≥3:** n=116/257 (45.1%) vs. n=104/261 (39.8%) **Serious TEAEs:** n=49/257 (19.1%) vs. n=47/261 (18.0%) **Serious drug-related TEAEs:** n=28/257 (10.9%) vs. n=16/261 (6.1%) **Drug-related TEAEs associated with dose discontinuations:** n=33/257 (12.8%) vs. n=13 (5.0%) **TEAEs associated with deaths:** n=5/257 (1.9%) vs. n=5/261 (1.9%)

ESMO-MCBS version 1.1 [12]

ESMO-MCBS not applicable as median PFS (as determined by BICR) was not reached.

Risk of bias (RCT) [13]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**

yes	-	no, open-label	unclear[3]	yes[4]	unclear
					First published: 07/2022 **Last updated**: 11/2022

Abbreviations: AE=adverse event, AJ=adjustment, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CFB=change from baseline, EMA=European Medicines Agency, EORTC-QLQ=European Organization for Research and Treatment of Cancer QoL questionnaires, EQ-5D-5L= EuroQol 5-dimension 5-level, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, GHS=global health status, HER"=human epidermal growth factor receptor 2, HR=hazard ratio, I=intervention, IHC=immunohistochemistry, ILD=interstitial lung disease, Int.=intention, ISH=in situ hybridization, IVD= in vitro diagnostic, LVEF=left ventricular ejection fraction, MG=median gain, n=number of patients, NE= not estimable, NR=not reached, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, ST=standard treatment, TDD=time to definitive deterioration, TEAE=treatment-emergent adverse event, VAS=visual analog scale

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[3] The DESTINY-Breast03 trial is currently ongoing.

[4] The trial was designed by one of the sponsors. Editorial and medical writing assistance with an earlier version of the manuscript was financially supported by Daiichi Sankyo.

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