Trastuzumab deruxtecan (Enhertu®) in patients with previously treated HER2-positive breast cancer

General information

Drug description [1]	Indication [2]
Trastuzumab deruxtecan (DS-8201) is an antibody-drug conjugate composed of an anti-human epidermal growth factor receptor 2 (HER2) antibody, a cleavable tetrapeptide-based linker, and a cytotoxic topoisomerase I inhibitor.	Trastuzumab deruxtecan is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic HER2 positive breast cancer who have received two or more prior anti HER2 based regimens.

Current treatment [3]

There are some therapeutic approaches for the treatment of advanced HER2-positive breast cancer which include:

- First-line treatment:
  - Pertuzumab, in combination with trastuzumab and docetaxel.
  - Trastuzumab in combination with paclitaxel.
  - Trastuzumab monotherapy for people who have received at least two chemotherapy regimens for metastatic breast cancer.
- Second-line treatment:
  - 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.
- Third-line treatment:
  - Eribulin is recommended as an option for treating locally advanced or metastatic breast cancer in adults, only when:
    - it has progressed after at least 2 chemotherapy regimens (which may include an anthracycline or a taxane, and capecitabine).

Regulatory status

EMA [2]	FDA [4-6]
Approval status for this indication: On 10 December 2020, the CHMP adopted a positive opinion, recommending the granting of a conditional marketing authorisation for Enhertu®. Enhertu® was reviewed under EMA's accelerated assessment programme. UPDATE: Date of issue of marketing authorisation valid throughout the European Union: 18/01/2021 The full indication is: ❖ Enhertu® as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2 positive breast cancer who have received two or more prior anti HER2 based regimens. **Other indications**: none ✓ **Medicine under additional monitoring** ✓ **Medicine received a conditional marketing authorisation**	**Approval status for this indication**: On 20 December 2019, the FDA granted accelerated approval to fam-trastuzumab deruxtecan-nxki (Enhertu®) for patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting (this indication is approved under accelerated approval based on tumor response rate and duration of response). **Other indications**: ❖ On 15 January 2021, the FDA approved fam-trastuzumab deruxtecan-nxki (Enhertu®) for adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal adenocarcinoma who have received a prior trastuzumab-based regimen.

Costs

Enhertu® powder for concentrate for solution for infusion 100 mg = € 1,600.00 (ex-factory price) [7]

DESTINY-Breast01 patients received trastuzumab deruxtecan at a dose of 5.4 mg/kg IV every 3 weeks; the median treatment duration was 10.0 months [1].

Assuming an average body weight of 70 kg, one dose of Enhertu® would cost approx. € 6,400.00.

Special warnings and precautions for use [8]

- 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.
- 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.

❖ Interstitial lung disease (ILD)/pneumonitis:
- Cases of ILD, and/or pneumonitis, have been reported with Enhertu®. Fatal outcomes have been observed.
- Patients should be advised to immediately report cough, dyspnoea, fever, and/or any new or worsening respiratory symptoms. Patients should be monitored for signs and symptoms of ILD/pneumonitis. Evidence of ILD/pneumonitis should be promptly investigated.
- Patients with suspected ILD/pneumonitis should be evaluated by radiographic imaging, preferably a computed tomography (CT) scan. Consultation with a pulmonologist should be considered.
- For asymptomatic (Grade 1) ILD/pneumonitis, consider corticosteroid treatment (e.g. ≥ 0.5 mg/kg prednisolone or equivalent). Enhertu should be withheld until recovery to Grade 0 and may be resumed according to instructions (see label information).
- For symptomatic ILD/pneumonitis (Grade 2 or greater), promptly initiate corticosteroid treatment (e.g. ≥ 1 mg/kg prednisolone or equivalent) and continue for at least 14 days or until complete resolution of clinical and chest CT findings. Then gradually taper for at least 4 weeks.
- Enhertu® should be permanently discontinued in patients who are diagnosed with any symptomatic (Grade 2 or greater) ILD/pneumonitis. Patients with a history of ILD/pneumonitis may be at increased risk of developing ILD/pneumonitis.

❖ Neutropenia:
- Cases of neutropenia, including febrile neutropenia, were reported in clinical studies of Enhertu®. Complete blood counts should be monitored prior to initiation of Enhertu® and prior to each dose, and as clinically indicated.
- Based on the severity of neutropenia, Enhertu® may require dose interruption or reduction.

❖ Left ventricular ejection fraction (LVEF) decrease:
- LVEF decrease has been observed with anti-HER2 therapies.
- Standard cardiac function testing (echocardiogram or MUGA scanning) should be performed to assess LVEF prior to initiation of Enhertu® and at regular intervals during treatment as clinically indicated.
- Enhertu® should be permanently discontinued if LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed. Enhertu® should be permanently discontinued in patients with symptomatic congestive heart failure (CHF).

❖ Embryo-foetal toxicity:
- Enhertu® can cause foetal harm when administered to a pregnant woman.
- Females of reproductive potential should be advised to use effective contraception during treatment and for at least 7 months following the last dose of Enhertu®. Male patients with female partners of reproductive potential should be advised to use effective contraception during treatment with Enhertu® and for at least 4 months after the last dose of Enhertu®.

❖ 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.

Study characteristics [1, 9, 10]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
DESTINY-Breast01 NCT03248492	184	trastuzumab deruxtecan at a dose of 5.4 mg/kg IV every 3 weeks until unacceptable toxicity or disease progression	-	objective response (according to independent central review)	two-part[1], open-label, single-group, multicenter, phase II study	HER2	Daiichi Sankyo and AstraZeneca	Link Link (dose-expansion, phase I study)

Efficacy	Safety
Confirmed response rate (independent central review): 60.9% (95% CI, 53.4-68.0); of these patients: **Complete response:** 6.0% **Partial response:** 54.9% **Progressive disease:** 1.6%	**Any AEs grade 3**: n=89/184 (48.4%) **Any AEs grade 4**: n=7/184 (3.8%) **TEAEs grade ≥3:** n=105/184 (57.1%)

[1] In the first part of the study, three different doses of trastuzumab deruxtecan were evaluated to establish a recommended dose; in the second part, the efficacy and safety of the recommended dose were evaluated.

Reduction in tumor size: in most of the patients for whom both baseline and post-baseline data were available.
Disease-control rate: 97.3% (95% CI, 93.8-99.1)
Clinical-benefit rate: 76.1% (95% CI, 69.3-82.1)
Median time until response: 1.6 months (95% CI, 1.4-2.6), an interval that corresponded to the time until the first imaging after baseline.
Confirmed response among the 180 patients who had tumor progression during or after the administration of trastuzumab emtansine: 61.1% (95% CI, 53.6-68.3).
Median response duration: 14.8 months (95% CI, 13.8-16.9)
Median duration of PFS: 16.4 months (95% CI, 12.7-not reached) among all patients and 18.1 months (95% CI, 6.7-18.1) among the 24 patients who were enrolled with treated and asymptomatic brain metastases.
Estimated OS at 6 months: 93.9% (95% CI, 89.3-96.6)
Estimated OS at 12 months: 86.2% (95% CI, 79.8-90.7)
Median OS: not reached at the time of this report

UPDATE: Efficacy results from an updated data cut-off with median duration of follow-up of 20.5 months (ITT analysis set) [8]:
Confirmed objective response rate: 61.4% (95% CI, 54.0-68.5)
Complete response: 6.5%
Partial response: 54.9%
Median duration of response: 20.8 months (95% CI, 15.0-NR)
% with duration of response ≥ 6 months: 81.5% (95% CI. 72.2-88.0)

Drug-related TEAEs: n=89/184 (48.4%)
Serious TEAEs: n=42/184 (22.8%)
Drug-related serious TEAEs: n=23/184 (12.5%)
TEAEs leading to drug discontinuation: n=28/184 (15.2%)
Drug-related TEAEs leading to drug discontinuation: n=27/184 (14.7%)
TEAEs leading to death: n=9/184 (4.9%)
Drug-related TEAEs leading to death: n=2/184 (1.1%)

ESMO-MCBS version 1.1

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	3	-	ORR: 61.4%	54.0-68.5	ORR (PR+CR)≥60%	3	+52.2% grade ≥3 toxicity and 2% toxic fatalities	-	-1	2
Due to the low level of evidence (single-arm study design) the adapted scale was not applied.											

Risk of bias (study level)

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
no	no	no, open-label	unclear[2]	yes[3]	unclear

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Abbreviations: AE=adverse event, AJ=adjustment, C=comparator, CHF=congestive heart failure, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CR=complete response, CT=computed tomography, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HER2= human epidermal growth factor receptor 2, HR=hazard ratio, I=intervention, ILD= interstitial lung disease, Int.=intention, ITT=intention-to-treat, IV=intravenous, LVEF=left ventricular ejection fraction n=number, MG=median gain, n=number of patients, NR=not reached, ORR=overall response rate, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PR=partial response, QoL=quality of life, SAE=serious adverse event, ST=standard treatment, TEAE=treatment-emergent adverse event,

[2] DESTINY-Breast01 trial is ongoing until 03/2021
[3] Industry-funded; representatives from the sponsor were involved in study oversight and data interpretation. Data were analyzed and interpreted by the sponsor and the authors. Editorial assistance was financially supported by the sponsor.

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