Trastuzumab deruxtecan (Enhertu®) as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-low breast cancer

General information

Drug description	Indication [1]
Trastuzumab deruxtecan (Enhertu®; formerly DS-8201) is an antibody–drug conjugate consisting of a humanized 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-low[1] breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.

Current treatment [2]

Depending on if the breast cancer is HR+ or HR-, there are some therapeutic approaches for the treatment of advanced HER2-negative BC after chemotherapy which include:

- ❖ HR+:
  - Treatment options after chemotherapy
    - o Eribulin for treating locally advanced or metastatic breast cancer after 1 chemotherapy regimen.
    - o Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens. 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).
      - ▪ The company provides eribulin with the discount agreed in the patient access scheme.
- ❖ HR-:
  - Second-line treatment
    - o Eribulin for treating locally advanced or metastatic breast cancer after 1 chemotherapy regimen. Eribulin is not recommended for treating locally advanced or metastatic breast cancer in adults who have had only 1 chemotherapy regimen.
  - Third-line treatment
    - o Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens. 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).
      - ▪ The company provides eribulin with the discount agreed in the patient access scheme.

Regulatory status

EMA [1]	FDA [3, 4]
Approval status for this indication: On 15 December 2022, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Enhertu®. The CHMP adopted a new indication for the treatment of HER2-low breast cancer: ❖ Enhertu® as monotherapy is indicated 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. **Other indications**:	**Approval status for this indication**: On 5 August 2022, the FDA approved fam-trastuzumab deruxtecan-nxki (Enhertu®) for adult patients with unresectable or metastatic HER2-low breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy. **Other indications**: Enhertu® is indicated for the treatment of ❖ adult patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either: o in the metastatic setting, or o in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy. ❖ 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)

[1] HER2-low tumours are defined as those whose cells contain lower levels of the HER2 protein on their surface. These tumours account for about 50%–60% of all breast cancers [2].

❖ 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. ❖ Enhertu® as monotherapy is indicated for the treatment of adult patients with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen. ✓ **Medicine under additional monitoring** ✓ **Medicine received a conditional marketing authorisation**[2]	❖ adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction 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) [5].

Dosage and administration [3, 6]

- ❖ Do not substitute Enhertu® for or with trastuzumab or ado-trastuzumab emtansine.
- ❖ For intravenous infusion only. Do not administer as an intravenous push or bolus. DO NOT use Sodium Chloride Injection, USP.
- ❖ The recommended dosage of Enhertu® for breast cancer is 5.4 mg/kg given as an IV infusion once every 3 weeks (21- day cycle) until disease progression or unacceptable toxicity.
- ❖ Management of adverse reactions (ILD, neutropenia, thrombocytopenia, or left ventricular dysfunction) may require temporary interruption, dose reduction, or discontinuation of Enhertu®.
- ❖ 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 2 or 3 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) for prevention of chemotherapy-induced nausea and vomiting.

Warnings and precautions [3, 6]

- ❖ **Interstitial lung disease (ILD) and pneumonitis,** including fatal cases, have been reported with Enhertu®. Monitor for and promptly investigate signs and symptoms including cough, dyspnoea, 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**: 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.
- ❖ **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.
- ❖ **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, deruxtecan, Enhertu® should be administered with caution in patients with moderate and severe hepatic impairment.

Study characteristics [7-9]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
DESTINY-Breast04 NCT03734029	557 (2:1)	trastuzumab deruxtecan	physician's choice of chemotherapy	PFS in the hormone	**ongoing**[3], randomised, two-group, open-label, phase 3 trial	HER2	Daiichi Sankyo	DESTINY-Breast04 trial [8]

[2] 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.

[3] The DESTINY-Breast04 trial is currently ongoing; estimated study completion date is 03/2023.

		was administered IV every 3 weeks at a dose of 5.4 mg per kg of body weight	was administered in accordance with the local label or the National Comprehensive Cancer Network guidelines	receptor–positive cohort			and AstraZeneca	

Efficacy (I vs. C)	**Safety** (I vs. C)
<u>**Data-cutoff date for the primary efficacy analysis: 11 January 2022**</u> **Median PFS in the hormone receptor–positive cohort**: 10.1 months (95% CI, 9.5-11.5) vs. 5.4 months (95% CI, 4.4-7.1); HR for disease progression or death 0.51; 95% CI, 0.40-0.64; p<0.001 **Median PFS in the trastuzumab deruxtecan group among patients with a HER2 IHC score of 1+:** 10.3 months **Median PFS in the trastuzumab deruxtecan group among patients with a HER2 IHC score of 2+ and negative results on ISH**: 10.1 **Median PFS among patients who had received previous treatment with CDK4/6 inhibitors in the trastuzumab deruxtecan group:** 10.0 months **Median PFS without previous CDK4/6 inhibitor treatment:** 11.7 months **Median PFS among all patients**: 9.9 months (95% CI, 9.0-11.3) vs. 5.1 months (95% CI, 4.2 to 6.8); HR for disease progression or death 0.50; 95% CI, 0.40-0.63; p<0.001) **Median PFS in the hormone receptor–negative cohort**: 8.5 months (95% CI, 4.3-11.7) vs. 2.9 months (95% CI, 1.4-5.1); HR 0.46; 95% CI, 0.24-0.89) **Median OS among all patients**: 23.4 months (95% CI, 20.0-24.8) vs. 16.8 months (95% CI, 14.5-20.0); HR 0.64; 95% CI, 0.49-0.84; p= 0.001 **Median OS in the hormone receptor–positive cohort**: 23.9 months (95% CI, 20.8-24.8) vs. 17.5 months (95% CI, 15.2-22.4); HR for death 0.64; 95% CI, 0.48-0.86; p=0.003 **Median OS in the hormone receptor–negative cohort:** 18.2 months (95% CI, 13.6-not evaluable) vs. 8.3 months (95% CI, 5.6-20.6); HR 0.48; 95% CI, 0.24-0.95) **Patients with a confirmed objective response in the hormone receptor–positive cohort:** 52.6% (95% CI, 47.0-58.0) vs. 16.3% (95% CI, 11.0-22.8) **Patients with a complete response**: 3.6% vs. 0.6% **Patients with progressive disease as the best overall response**: 7.8% vs. 21.1% **Median duration of response**: 10.7 months vs. 6.8 months **Patients with a confirmed objective response among all patients**: 52.3% (95% CI, 47.1-57.4) vs. 16.3% (95% CI, 11.3-22.5) **Patients with a confirmed objective response in the hormone receptor–negative cohort**: 50.0% (95% CI, 33.8-66.2) and 16.7% (95% CI, 3.6-41.4)	**TEAEs:** n=369/371 (99.5%) vs. 169/172 (98.3%) **TEAEs grade ≥3:** n=195/371 (52.6%) vs. n=116/172 (67.4%) **Exposure-adjusted incidence rates**: 1.30 per patient-year and 2.66 per patient-year, respectively. **Serious TEAEs**: n=103/371 (27.8%) vs. n=43/172 (25.0%) **TEAEs associated with dose discontinuations**: n=60/371 (16.2%) vs. n=14/172 (8.1%) **Drug-related TEAEs associated with dose discontinuations**: n=56/371 (15.1%) vs. n=12/172 (7.0%) **TEAEs associated with dose interruptions:** n=143/371 (38.5%) vs. 72/172 (41.9%) **Drug-related TEAEs associated with dose interruptions:** n=106/371 (28.6%) vs. 62/172 (36.0%) **TEAEs associated with dose reductions:** n=84/371 (22.6%) vs. n=66/172 (38.4%) **Drug-related TEAEs associated with dose reductions**: n=77/371 (20.8%) vs. n=64/172 (37.2%) **TEAEs associated with deaths**: n=14/371 (3.8) vs. n=5/172 (2.9%) **Drug-related TEAEs associated with deaths[4]:** n=7/371 (1.9%)

Patient-reported outcomes – abstract data (PROs) [10]

- PROs were measured using the EORTC QLQ-C30 (primary variable: GHS/QoL scale score), EORTC QLQ-BR23 and the EQ-5D-5L visual analogue scale.
- PROs were assessed at prespecified timepoints per the protocol. CFB and TDD were assessed. Deterioration was defined as an increase of ≥10 points.

[4] Drug-related deaths in the trastuzumab deruxtecan group were due to pneumonitis (in 2 patients; 0.5%) and ischemic colitis, disseminated intravascular coagulation, dyspnoea, febrile neutropenia, and sepsis (in 1 patient - 0.3% - each); there were no drug-related deaths in the physician's choice group.

- In both arms, compliance for questionnaires was >92% at baseline and >80% for cycles 2-27.
- Baseline GHS score was 36.3 for trastuzumab deruxtecan and 37.8 for treatment of physician's choice.
- Mean CFB for GHS/QOL of the QLQ-C30 remained stable (within ± 10 points) over time for patients in the trastuzumab deruxtecan arm (n=331) up to 27 cycles and treatment of physician's choice arm (n=163) up to 13 cycles; beyond these cycles, the number of patients on treatment (n<10%) was too low to be informative.
- Median TDD of QLQ-C30 GHS/QoL was 7.6 months for trastuzumab deruxtecan vs. 5.1 months for treatment of physician's choice (HR 0.71; 95% CI, 0.56-0.92), and all prespecified QLQ-C30 subscales had longer TDD with trastuzumab deruxtecan, including pain (HR 0.51; 95% CI, 0.39-0.65) and physical functioning (HR 0.54; 95% CI, 0.42-0.70).
- For breast-specific arm symptoms of the QLQ-BR23, median TDD was 9.8 months for trastuzumab deruxtecan vs. 5.4 months for treatment of physician's choice (HR 0.67; 95% CI, 0.50-0.88).
- Median TDD of EQ-5D-5L VAS was 8.8 months for trastuzumab deruxtecan vs. 4.7 months for treatment of physician's choice (HR, 0.70; 0.54-0.91).

ESMO-MCBS version 1.1 [11]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2a	>12 months ≤24 months	OS: + 6.6 months	0.64 (0.49-0.84)	HR ≤0.70 AND gain ≥5 months	4	-	-	-	4
Adapted	NC	2a	>12 months ≤24 months	OS: + 6.6 months	0.64 (0.49-0.84)	HR ≤0.70 AND gain ≥5 months	4	-	-	-	4

Risk of bias (RCT) [12]

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	unclear	no, open-label	unclear[5]	yes[6]	unclear

First published: 01/2023
Last updated: 04/2023

Abbreviations: AE=adverse event, AJ=adjustment, C=comparator, CFB=Change from baseline, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, EMA=European Medicines Agency, EORTC-QLQ-C30=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, GEJ=gastroesophageal junction, GHS=global health status, HER2=human epidermal growth factor receptor 2, HR=hazard ratio, I=intervention, ILD= Interstitial lung disease, Int.=intention, LVEF=Left ventricular ejection fraction, MG=median gain, n=number of patients, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PRO=patient-reported outcome, QoL=quality of life, SAE=serious adverse event, ST=standard treatment, TDD=time to definitive deterioration, TEAE=treatment-emergent adverse event

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[5] DESTINY-Breast04 is ongoing; currently, primary analysis data is available.

[6] The trial was designed by Daiichi Sankyo, approved by the institutional review board at each site, and conducted in adherence with the International Council for Harmonisation Good Clinical Practice guidelines, the Declaration of Helsinki, and local regulations on the conduct of clinical research. Editorial and medical writing assistance with an earlier version of the manuscript was financially supported by Daiichi Sankyo.

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