Trastuzumab deruxtecan (Enhertu®) as monotherapy for the treatment of adult patients with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma

General information

Drug description	Indication [1]
Trastuzumab deruxtecan (Enhertu®, DS-8201; known as fam-trastuzumab deruxtecan-nxki in the United States) is an antibody-drug conjugate consisting of a humanised, monoclonal, anti-HER2 antibody bound to a cytotoxic topoisomerase I inhibitor (drug payload) by means of a cleavable, tetrapeptide-based linker.	Trastuzumab deruxtecan (Enhertu®) as monotherapy is indicated for the treatment of adult patients with advanced HER2-positive gastric or GEJ adenocarcinoma who have received a prior trastuzumab-based regimen.

Current treatment

- **Gastric cancer: Management of advanced and metastatic disease [2]**
  - Locally advanced unresectable or metastatic gastric cancer has a poor prognosis; survival in clinical trials assessing the value of chemotherapy has historically been <1 year in non-Asian countries.
  - Chemotherapy improves survival in comparison to best supportive care, and combination chemotherapy improves survival compared with single-agent 5-FU.
  - Additionally, the use of nivolumab with chemotherapy has recently improved survival for patients with advanced/metastatic disease and trastuzumab-chemotherapy has improved survival in patients with HER2-positive advanced/metastatic disease.
  - HER2-positive tumours
    - Adding trastuzumab to chemotherapy is recommended for patients with HER2-overexpressing (HER2 IHC 3þ or IHC 2þ/FISH positive) gastric cancer, based on the phase III ToGA study, which demonstrated higher response rates and longer OS (HR 0.74; 95% CI 0.60-0.91; p=0.0046) with trastuzumab-chemotherapy compared with chemotherapy alone; additional toxicity was low and manageable.
- **Second- and later-line treatment recommendations [2]:**
  - Ramucirumab-paclitaxel is recommended for second-line treatment of gastric cancer (I, A; ESMO-MCBS v1.1score: 2).
  - Ramucirumab monotherapy is also an option (I, B; ESMO-MCBS v1.1 score: 1).
  - Where ramucirumab is not available, paclitaxel, docetaxel or irinotecan monotherapy (I, A) or FOLFIRI (II, B) are recommended.
  - Treatment with trastuzumab is not recommended after first-line therapy in HER2-positive advanced gastric cancer (I, D), but trastuzumab deruxtecan may be considered (II, B; ESMO-MCBS v1.1 score: 4; FDA approved, not EMA approved).
  - Pembrolizumab is recommended for second-line treatment of patients with MSI-H/dMMR gastric cancer (II,A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-B).
  - For patients previously treated with two lines of therapy, trifluridine-tipiracil is recommended (I, A; ESMO-MCBS v1.1 score: 3).
  - Alternative treatments include a taxane or irinotecan (II, B).
- For the treatment of HER2-positive gastric carcinoma, Onkopedia recommends the following [3]:
  - HER2 diagnosis should be quality-controlled.
  - Trastuzumab should be added to chemotherapy in patients with HER2-positive advanced gastric cancer. The recommendation is based on data from the phase III ToGA trial, showing a higher response rate and prolonged survival for trastuzumab-cisplatin-fluoropyrimidine chemotherapy vs. chemotherapy alone with the above selection criteria; the additional trastuzumab side effects are minor and manageable.
  - Combinations of trastuzumb and oxaliplatin plus fluoropyrimidine produce comparable results to the historical cisplatin-containing ToGA regimen.

Regulatory status

EMA [1, 4]	FDA [5, 6]
Approval status for this indication: On 10 November 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 gastric cancer:	**Approval status for this indication**: On 15 January 2021, the FDA approved fam-trastuzumab deruxtecan-nxki (Enhertu®) for adult patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma who have received a prior trastuzumab-based regimen. ✓ **Priority review**

- ❖ Enhertu® as monotherapy is indicated for the treatment of adult patients with advanced HER2-positive gastric or GEJ adenocarcinoma who have received a prior trastuzumab-based regimen.

Other indications:

- ❖ 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 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.

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

✓ **Breakthrough therapy designation**
✓ **Orphan drug designation**
✓ **The approval of fam-trastuzumab deruxtecan-nxki is based on DESTINY-Gastric01; a trial that evaluated efficacy in patients with HER2-positive locally advanced or metastatic gastric or GEJ adenocarcinoma who had progressed on at least two prior regimens.**

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:
  - in the metastatic setting, or
  - in the neo-adjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy.
- ❖ adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-approved test, 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 (NSCLC) 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 concentrate for solution for infusion 100 mg = **€1,600.00** (ex-factory price) [7].

Posology [4]

- ❖ 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
- ❖ Patient selection
  - Patients treated with trastuzumab deruxtecan for gastric or gastroesophageal junction cancer should have documented HER2-positive tumour status, defined as a score of 3 + by immunohistochemistry or a ratio of ≥ 2 by in situ hybridisation or by fluorescence in situ hybridisation, assessed by a CE-marked in vitro diagnostic medical device. If a CE-marked IVD is not available, the HER2 status should be assessed by an alternate validated test.
- ❖ 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-HT_3 receptor antagonist and/or an NK1 receptor antagonist, as well as other medicinal products as indicated) for prevention of chemotherapy-induced nausea and vomit.

Warnings and precautions [4, 6]

- ❖ **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, 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.
- ❖ **Embryo-foetal toxicity**

[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.

- 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 [8-11]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
DESTINY-Gastric01 NCT03329690	188[2] (2:1)	trastuzumab deruxtecan at a dose of 6.4 mg per kg of body weight, administered IV every 3 weeks	physician's choice of chemotherapy[3]	objective response (according to independent central review)	open-label, randomised, multicenter, phase 2 trial	HER2	Daiichi Sankyo	Destiny-Gastric01 trial [10]

Efficacy (I vs. C)	**Safety** (I vs. C)
Data cut-off (8 November 2019) **Objective response**: 51% vs. 14%, p<0.001 **Confirmed objective response** (defined as a complete or partial response that was confirmed on a follow-up scan performed at least 4 weeks after the initial complete or partial response): 43% vs. 12% **Median duration of confirmed objective response**: 11.3 months (95% CI, 5.6-could not be estimated) vs. 3.9 months (95% CI, 3.0-4.9) **Median time to a response**: 1.5 months (95% CI, 1.4-1.7) vs. 1.6 months (95% CI, 1.3-1.7) **Patients with confirmed disease control**: 86% (95% CI,78-91) vs. 62% (95% CI, 49-75) **Median OS**: 12.5 months vs. 8.4 months; HR for death 0.59; 95% CI, 0.39-0.88; p=0.01 **Deaths:** 50% and 63% **Estimated OS at 6 months:** 80% vs. 66% **Estimated OS at 12 months**: 52% vs. 29% **Patients who received subsequent treatment after they discontinued the protocol treatment:** 48% vs. 74% **Median PFS:** 5.6 months (95% CI, 4.3-6.9) vs. 3.5 months (95% CI, 2.0-4.3); HR for progression or death 0.47; 95% CI, 0.31-0.71 **Estimated PFS at 6 months**: 43% vs. 21%	**TEAE of any grade**: n=125/125 (100%) vs. n=61/62 (98.4%) **Drug-related TEAEs**: n=122/125 (97.6%) vs. n=56/62 (90.3%) **TEAEs grade ≥3**: n=107/125 (85.6%) vs. n=35/62 (56.5%) **Drug-related TEAEs grade ≥3**: n=94/125 (75.2%) vs. n=27/62 (43.5%) **Serious TEAEs:** n=55/125 (44.0%) vs. n=15/62 (24.2%) **Drug-related serious TEAEs**: n=27/125 (21.6%) vs. n=5/62 (8.1%) **TEAEs leading to drug discontinuation**: n=19/125 (15.2%) vs. n=4/62 (6.5%) **Drug-related TEAEs leading to drug discontinuation**: n=12/125 (9.6%) vs. n=3/62 (4.8%) **TEAEs leading to death**: n=8/125 (6.4%) vs. n=2/62 (3.2%) **Drug-related TEAEs leading to death:** n=1/125 (0.8%)[5] vs. 0% **Exploratory cohort results (data cut-off 8 November 2019); cohort 1 and cohort 2 [13]:** **TEAEs grade ≥3**: 70.0% and 79.2%

[2] One patient in the trastuzumab deruxtecan group did not receive treatment because the patient was ineligible owing to an abnormal echocardiogram before the initiation of treatment.
[3] Patients in the physician's choice group received either irinotecan monotherapy, at a dose of 150 mg per square meter of body-surface area administered every 2 weeks, or paclitaxel monotherapy, at a dose of 80 mg per square meter administered on days 1, 8, and 15 every 4 weeks.
[5] This death occurred after the administration of cycle 6, and the patient did not have neutropenia at the time of the event. Details of the cause of pneumonia were not reported.

Estimated PFS at 12 months: 30% vs. 0%
Patients who died or had disease progression according to independent central review: 58% and 58%

Final OS results (at data cut-off 3 June 2020; median survival follow-up 18.5 months) [12]:
Median OS: 12.5 vs. 8.9 months; HR 0.60 (95% CI, 0.42-0.86)
12-month OS: 52.2% vs. 29.7%
ORR: 51.3% vs. 14.3%; p< 0.0001
Confirmed ORR: 42.0% vs. 12.5%; p= 0.0001
Disease control rate: 86.6% vs. 62.5%; p=0.0003
Confirmed median duration of response: 12.5 vs 3.9 months
Median PFS: 5.6 vs. 3.5 months; HR 0.47 (95% CI, 0.31-0.71); p=0.0003

Exploratory cohort[4] results (data cut-off 8 November 2019); cohort 1 and cohort 2 [13]:
Confirmed ORR: 26.3% (95% CI, 9.1-51.2) and 9.5% (95% CI, 1.2-30.4)
ORR by investigator assessment: 42.1% and 14.3%
Reduction in tumour size assessed by ICR: 68.4% and 60%
Disease control rate: 89.5% and 71.4%
Median duration of response in patients with confirmed ORR: 7.6 months and 12.5 months
Median OS: 17.8 (95% CI, 4.7-non-evaluable) months and 8.5 (95% CI, 4.3-10.9) months
PFS by ICR: 4.4 (95% CI, 2.7-7.1) months and 2.8 (95% CI, 1.5 to 4.3) months

TEAEs associated with study drug discontinuation: 10.0% and 4.2%
Drug-related ILD/pneumonitis: n=1 and n=1
Grade 1 TEAE of QT prolongation: n=0 and n=1

Patient-reported outcomes

According to the study protocol [8] of NCT03329690, the evaluation of secondary endpoints by the Functional Assessment of Cancer Therapy-Gastric (FACT-Ga), EuroQoL 5 Dimenstions 5 Levels (EQ-5D-5L) and Health care resource utilisation was planned. To date, there are **no results available**.

ESMO-MCBS version 1.1 [14]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2a	≤12 months	OS: +4.1 months	0.59 (0.39-0.88)	HR ≤0.65 AND gain ≥3 months	4	-	NA	-	4
Adapted	NC	2a	≤12 months	OS: +4.1 months	0.59 (0.39-0.88)	HR ≤0.65 AND gain ≥3 months	4	+31.5% drug-related TEAEs grade ≥3 +13.5 drug-related serious TEAEs	NA	-1	3

Risk of bias (RCT) [15]

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	yes[6]	**high**

First published: 12/2022
Last updated: 04/2023

[4] Cohort 1: HER2 IHC 21/ISH–, n=21; cohort 2: IHC 11, n=24.
[6] The trial was designed by the sponsor. Data were analysed and interpreted by the sponsor and authors. A professional writer participated in the preparation of the manuscript and was paid by the sponsor. In March 2019, AstraZeneca entered into a collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan. AstraZeneca was not involved in data collection but was involved in data interpretation as well as review of the manuscript and approval of its submission for publication.

Abbreviations: AE=adverse event, AJ=adjustment, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, dMMR=mismatch repair deficient, ESCAT= ESMO Scale for Clinical Actionability of Molecular Targets , EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FISH=fluorescence in situ hybridisation, FM=final magnitude of clinical benefit grade, GEJ=gastroesophageal junction, HER= human epidermal growth factor receptor 2, HR=hazard ratio, I=intervention, ICR=independent central review, IHC= immunohistochemical, ILD=interstitial lung disease, Int.=intention, LVEF=left ventricular ejection fraction, MG=median gain, MSI-H=microsatellite instability-high, n=number of patients, NA=not available, NSCLC=non small-cell lung cancer, ORR=objective response rate, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, ST=standard treatment, TEAE=treatment-emergent adverse event

References:

1. European Medicines Agency (EMA). Medicines. Enhertu. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/enhertu-1].
2. Lordick F, Carneiro F, Cascinu S, et al., on behalf of the ESMO Guidelines Committee. Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. [Available from: https://www.annalsofoncology.org/action/showPdf?pii=S0923-7534%2822%2901851-8].
3. Onkopedia. Onkopedia Guidelines. Gastric Cancer. [Available from: https://www.onkopedia-guidelines.info/en/onkopedia/guidelines/gastric-cancer/@@guideline/html/index.html#ID0EHDAG].
4. European Medicines Agency (EMA). Enhertu: EPAR - Product Information. [Available from: https://www.ema.europa.eu/en/documents/product-information/enhertu-epar-product-information_en.pdf].
5. US FDA. FDA approves fam-trastuzumab deruxtecan-nxki for HER2-positive gastric adenocarcinomas. [Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-fam-trastuzumab-deruxtecan-nxki-her2-positive-gastric-adenocarcinomas].
6. U.S. Food and Drug Administration (FDA). Enhertu. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761139s024lbl.pdf].
7. Österreichischer Apotheker-Verlag. Warenverzeichnis Online. [Available from: https://warenverzeichnis.apoverlag.at/].
8. Protocol for: Shitara K, Bang Y-J, Iwasa S, et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. N Engl J Med 2020;382:2419-30.
9. Supplement to: Shitara K, Bang Y-J, Iwasa S, et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. N Engl J Med 2020;382:2419-30.
10. Shitara K, Bang YL, Iwasa S, et al, for the DESTINY-Gastric01 Investigators. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer. N Engl J Med 2020;382:2419-30.
11. U.S. National Library of Medicine, ClinicalTrials.gov. DS-8201a in Human Epidermal Growth Factor Receptor 2 (HER2)-Expressing Gastric Cancer [DESTINY-Gastric01]. [Available from: https://clinicaltrials.gov/ct2/show/NCT03329690].
12. Yamaguchi K. Trastuzumab deruxtecan (T-DXd; DS-8201) in patients with HER2-positive advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma: Final overall survival (OS) results from a randomized, multicenter, open-label, phase 2 study (DESTINY-Gastric01). Journal of Clinical Oncology 39, no 15_suppl, 4048-4048 Abstract.
13. Yamaguchi K, Bang Y, Iwasa S, et al. Trastuzumab Deruxtecan in Anti–Human Epidermal Growth Factor Receptor 2 Treatment–Naive Patients With Human Epidermal Growth Factor Receptor 2–Low Gastric or Gastroesophageal Junction Adenocarcinoma: Exploratory Cohort Results in a Phase II Trial. J Clin Oncol 41:816-825, 2022.
14. Cherny NI, Dafni U, Bogaerts J., et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28: 2340–2366, 2017.
15. European Network for Health Technology Assessment (EUnetHTA). Levels of evidence. Internal validity of randomised controlled trials. Adapted version (2015). [Available from: https://www.eunethta.eu/wp-content/uploads/2018/01/Internal-validity-of-randomised-controlled-trials.pdf].