Report ENHERTU® - trastuzumab deruxtecan

Product & Mechanism of action

Substance: trastuzumab deruxtecan

Brand Name: Enhertu

Originator/licensee: Daiichi Sankyo Europe GmbH

Classification: NI

ATC code: L01XC

Orphan Status:
Eu: No
Us: No

Mechanism of action:
trastuzumab deruxtecan, is made up of two active components:
Trastuzumab, a monoclonal antibody (a type of protein) that has been designed to attach to HER2, which is found in large quantities on some cancer cells. By attaching to HER2, trastuzumab activates cells of the immune system, which then kill the cancer cells. Trastuzumab also stops HER2 from stimulating the growth of cancer cells. About a quarter of breast cancers overexpress HER2.
Deruxtecan, a toxic substance that kills cells when they attempt to divide and grow. It becomes active once the trastuzumab component has attached to HER2 and enters the cancer cell. Deruxtecan blocks an enzyme called topoisomerase I, which is involved in copying cell DNA, which is needed to make new cells. By blocking the enzyme, cancer cells are prevented from multiplying and they eventually die [1].

Authorized indications Licensing status

Authorized Indication:
EMA: trastuzumab-deruxtecan 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 [1].
FDA: trastuzumab-deruxtecan is indicated for the treatment of adult patients with locally advanced or metastatic HER2-positive gastric or (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen [2].

Route of administration: iv

Licensing status
EU CHMP P.O. date: 10/11/2022
FDA M.A. date: 15/01/2022

EU Speed Approval Pathway: No
FDA Speed Approval Pathway: No

ABBREVIATIONS:
AE: adverse event
CI: Confidence Interval
ECOG: Eastern Cooperative Oncology Group
GEJ: gastroesophageal junction
M.A.: marketing authorization
ORR: objective response rate
P: p-value
P.O.: positive opinion
Pts: patients

Essential therapeutic features

Summary of clinical EFFICACY:
DESTINY-Gastric01 (NCT03329690) was an open-label, randomized, phase II trial to evaluate efficacy and safety of trastuzumab deruxtecan compared with chemotherapy.
Pts (N=187) had HER2-positive gastric or GEJ adenocarcinoma that had progressed while they were receiving at least two previous therapies*, were at least 20 years old and had an ECOG performance-status score of 0 or 1**.
The primary end-point was the objective response (complete or partial).
Pts were randomly assigned in a 2:1 ratio to receive trastuzumab deruxtecan (N=125) (6,4mg per kg of body weight every 3 weeks) or chemotherapy (N=62) (55 reiceved irinotecan and 7 paclitaxel).
Therapy with trastuzumab deruxtecan led to significant improvements in response as compared with standard therapies, among patients with HER2-positive gastric cancer [3].

Tabella 1: summary of efficacy

Variable	**Trastuzumab Deruxtecan (N=119)**	**Physician's Choice of Chemotherapy(N=56)**
Objective response (P<0.001)	51%	14%
Complete response	11%	0%
Partial response	50%	8%
Stable disease	42%	27%
Progressive disease	14%	17%
Confirmed disease control (95% CI)	86%	62%

Most patients (<80%) receiving trastuzumab deruxtecan had a reduction in tumor size, as compared with approximately half the pts receiving physician's choice of chemotherapy. The median duration of confirmed objective response was 11.3 months (95% CI) in the trastuzumab deruxtecan group, as compared with 3.9 months (95% CI, 3.0 to 4.9) in the physician's choice group [3].
*which included a fluoropyrimidine, a platinum agent, and trastuzumab (or approved biosimilar agent);
**on a scale from 0 to 5, with higher scores indicating greater disability.

Summary of clinical SAFETY:
The most common AE of grade 3 or higher were a decreased neutrophil count (in 51% of the trastuzumab deruxtecan group and 24% of the physician's choice group), anemia (38% and 23%, respectively), and decreased white-cell count (21% and 11%). A total of 12 patients had trastuzumab deruxtecan-related interstitial lung disease or pneumonitis (grade 1 or 2 in 9 patients and grade 3 or 4 in 3), as adjudicated by an independent committee. One drug-related death (due to pneumonia) was noted in the trastuzumab deruxtecan group; no drug-related deaths occurred in the physician's choice group [3].

Ongoing studies:

- ***For the same indication:***Yes(DESTINY-Gastric04) [4].
- ***For other indications:*** Yes [5].

Discontinued studies (for the same indication): No [5].

References:
[1]. https://www.ema.europa.eu/en/medicines/human/summaries-opinion/enhertu-1
[2]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761139s011lbl.pdf
[3]. Shitara K, Bang YJ, Iwasa S, Sugimoto N, Ryu MH, Sakai D, Chung HC, Kawakami H, Yabusaki H, Lee J, Saito K, Kawaguchi Y, Kamio T, Kojima A, Sugihara M, Yamaguchi K; DESTINY-Gastric01 Investigators. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer. N Engl J Med. 2020 Jun 18;382(25):2419-2430. doi: 10.1056/NEJMoa2004413. Epub 2020 May 29. PMID: 32469182.
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[5]. https://adisinsight.springer.com/drugs/800043383
[6]. https://gallery.farmadati.it/Home.aspx
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[8]. https://snlg.iss.it/wp-content/uploads/2022/01/LG-177_Stomaco_AIOM_agg2021.pdf
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NHS impact

Cost of therapy:
In Italy the ex-factory price of trastuzumab deruxctecan 100 mg is 2.344,81 € [6].

Epidemiology:
In Italy in the 2020, 14,500 new cases of gastric cancer and 8,700 deaths are estimated.
Approximately one of five gastric cancer is HER-2 positive [7-8].

POSSIBLE PLACE IN THERAPY
Lonsurf (trifluridine/tipiracil hydrochloride) is indicated as monotherapy for the treatment ofadult patients with metastatic gastric cancer including adenocarcinoma of the GEJ, who have been previously treated with at least two prior systemictreatment regimens for advanced disease [9].

OTHER INDICATIONS IN DEVELOPMENT
Uterine cancer, Solid tumors, Non-small cell lung cancer, Gastric cancer, Colorectal cancer, Breast cancer, Adenocarcinoma [5].

SAME INDICATION IN EARLIER LINE(S) OF TREATMENT:
Only trastuzumab(Herceptin) in combination with capecitabine or 5-fluorouracil and cisplatin is indicated in the treatment ofadult patients with metastatic adenocarcinoma of the stomach or gastroesophageal junction HER2positive, who have not previously received anticancer treatment for the diseasemetastatic disease [10].

OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION
*Service reorganization: Yes
*Possible off label use: Yes

Issued on: December 2022

		[10]. https://www.ema.europa.eu/en/documents/product-information/herceptin-epar-product-information_it.pdf	