swissmedic

Date: 14 July 2025
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Enhertu

International non-proprietary name:	trastuzumab deruxtecan
Pharmaceutical form:	powder for concentrate for solution for infusion
Dosage strength(s):	100 mg
Route(s) of administration:	intravenous
Marketing authorisation holder:	Daiichi Sankyo (Schweiz) AG
Marketing authorisation no.:	67967
Decision and decision date:	extension of therapeutic indication as a temporary authorisation in accordance with Art. 9a TPA approved on 26 May 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
AE	Adverse event
API	Active pharmaceutical ingredient
CI	Confidence interval
CNS	Central nervous system
DoR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
HER2	Human epidermal growth factor receptor 2
ICH	International Council for Harmonisation
IHC 3+	Immunohistochemistry score 3+
INN	International non-proprietary name
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
T-DXd	Trastuzumab deruxtecan
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

Temporary authorisation for human medicinal products
The authorisation was granted by Swissmedic as an "ex officio" temporary authorisation in accordance with Article 9*a* TPA.

Project Orbis
The applicant requested a marketing authorisation procedure within the framework of Project Orbis. Project Orbis is coordinated by the FDA and provides a framework for concurrent submission and review of oncology products among international partners.

2.2 Indication and dosage

2.2.1 Requested indication

Enhertu is used to treat adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumours who have received prior treatment or for whom no satisfactory alternative treatment options are available.

2.2.2 Approved indication

Other Unresectable or Metastatic Solid Tumours
Enhertu is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumours who show progression after at least one prior systemic treatment and who have no satisfactory alternative treatment options (see section "Clinical Efficacy").
Enhertu has not been studied in patients with sarcomas or primary CNS tumours.

These indications have been granted temporary authorisation as the clinical data were incomplete at the time the application was assessed (Art. 9a Therapeutic Products Act). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be converted into a standard authorisation.

2.2.3 Requested dosage

No change to the dosage recommendation was requested with the application for extension of indication.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	1 July 2024
Formal control completed	5 July 2024
List of Questions (LoQ)	25 October 2024
Response to LoQ	13 January 2025
Preliminary decision	26 February 2025
Response to preliminary decision	24 April 2025
Final decision	26 May 2025
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

3 Medical context

Human epidermal growth factor receptor 2 (HER2) is a tyrosine kinase receptor that belongs to the human epidermal growth factor receptor (EGFR) family. It is an important driver of carcinogenesis due to its role in regulating cell growth, survival, and differentiation[1]. HER2 (ERBB2) gene amplification and HER2 overexpression drive excessive cell growth and tumorigenesis across multiple tumour types. HER2 overexpression or mutations can be detected across solid tumours (breast cancer [15–20%], gastric or gastro-oesophageal junction adenocarcinomas [10–20%], colorectal cancer [5%], and in 3–4% of non-small-cell lung carcinomas)[2]. Notably, compared to other molecular alterations, HER2 overexpression is relatively simple to assess by immunohistochemistry (IHC) or in situ hybridisation (ISH), techniques that are generally more widely available than next generation sequencing (NGS)[3]. Multiple HER2-targeting drugs have been approved over the past two decades for treating breast cancer, including monoclonal antibodies like trastuzumab and pertuzumab; tyrosine kinase inhibitors (TKIs) like lapatinib, neratinib, tucatinib, and pyrotinib; and more recently antibody-drug conjugates (ADCs), including trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd)[4].
The majority of patients with HER2 (IHC 3+) expressing or amplified tumours (including ovarian, endometrial, lung, bladder, and biliary tract cancer) receive standard chemotherapy treatments that are not specifically targeted against HER2-expressing tumours and thus provide limited clinical benefit. The current NCCN guidelines on the most common tumour types list T-DXd as a useful treatment option in certain circumstances in second-line or further-line situations.

[1] Yamaguchi K 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. 2023;41:816–25
[2] Indini A et al. Trastuzumab deruxtecan: changing the destiny of HER2 expressing solid tumors. Int J Mol Sci. 2021;22(9):4774
[3] Wolf AC et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/ College of American Pathologists Clinical Practice Guideline Focused Update. JCO. 2018;36(20):2105–22
[4] Neupane N et al. Opportunities and Challenges for a Histology-Agnostic Utilization of Trastuzumab Deruxtecan. Curr Oncol Rep. 2023 Dec;25(12):1467-1482

4 Nonclinical aspects

The applicant did not submit new nonclinical studies to support the requested extension of the indication. This was considered acceptable since there are no changes with regard to posology or method of administration.
Based on the ERA, the extension of the indication will not be associated with a significant risk for the environment.
From the nonclinical point of view, there are no objections to approval of the proposed extension of indication.

5 Clinical aspects

The evaluation of the clinical and clinical pharmacology data of this application has been carried out in reliance on the previous regulatory decision by the FDA. The available assessment from this authority was used as a basis for the clinical and clinical pharmacology evaluation (Multi-discipline Review - 761139Orig1s028).

The efficacy assessment was primarily based on the results from 192 patients with HER2-positive IHC 3+ advanced or metastatic solid tumours pooled from the open-label, phase 2 studies DESTINY-PanTumor02, DESTINY-CRC02, and DESTINY-Lung01.
In total, 15 different tumour types were included (biliary tract, bladder, cervical, endometrial, ovarian, pancreatic, colorectal, NSCLC, and the rare cancers of the salivary gland, oropharynx, vulva, extramammary Paget's disease, lacrimal gland, lip and/or oral cavity, oesophagus [squamous and non-squamous]), with sample sizes ranging from 1-64.
The primary endpoint objective response rate (ORR) assessed by independent central review was 51.4% (95%CI 41.7, 61.0) in DESTINY-PanTumor02, 52.9% (95%CI 27.8, 77.0) in DESTINY-Lung01, and 46.9% (95%CI 34.3, 59.8) in DESTINY-CRC02. The median duration of response (DoR) varied from 5.5 months (95%CI 4.2, 8.1) in the DESTINY-CRC02 trial to 19.4 months (95%CI 10.0, NE) in the DESTINY-PanTumor02 trial. The ORR and DoR according to tumour type can be found in the Information for healthcare professionals.

The toxicities observed in a pooled population of 347 patients with HER2 IHC 3+ solid tumours treated with T-DXd 5.4 mg/kg were consistent with the known safety profile of T-DXd.

Due to the heterogenous study population with limited numbers in some tumour types and the short median duration of follow-up, only a temporary authorisation ex officio was granted.

The indication was adapted based on the studied population, which did not include patients with sarcoma or primary tumours of the central nervous system.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Enhertu was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

Interstitial lung disease (ILD) and/or 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. Patients with moderate renal impairment are at increased risk of developing ILD including fatal cases (see sections “Warnings and precautions” and “Undesirable Effects”).

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.
Enhertu has indications that have been granted temporary authorisation, see the “Indications/Uses” section.

ENHERTU® 100 mg powder for concentrate for solution for infusion

Composition

Active substances

Trastuzumabum deruxtecanum is composed of an antibody (produced in Chinese hamster ovary cells by recombinant DNA technology) conjugated via a linker to the topoisomerase I inhibitor DXd.

Excipients

L-histidinum, L-histidini hydrochloridum monohydricum, Saccharum, Polysorbatum 80.

Pharmaceutical form and active substance quantity per unit

Powder for concentrate for solution for infusion.
White to yellowish white lyophilised powder.
One vial of lyophilised powder for concentrate for solution for infusion contains 100 mg of trastuzumab deruxtecan.

Indications/Uses

Indications with standard authorisation

Breast cancer

HER2-positive breast cancer

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, including trastuzumab and a taxane, and had a progression either in the metastatic setting or within 6 months after finalization of an adjuvant or neoadjuvant therapy (see section "Properties/Effects").

HER2-low breast cancer

Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.
Patients with hormone receptor positive (HR+) breast cancer must additionally have received or be ineligible for endocrine therapy (see section "Properties/Effects").

Indication(s) with temporary authorisation

Gastric cancer
Enhertu as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have disease progression on or after a first-line regimen with trastuzumab and chemotherapy.

Other Unresectable or Metastatic Solid Tumors
Enhertu is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors who show progression after at least one prior systemic treatment and who have no satisfactory alternative treatment options (see section "Clinical Efficacy").
Enhertu has not been studied in patients with sarcomas and primary CNS tumors.

These indications have been granted temporary authorisation as the clinical data were incomplete at the time the application was assessed (Art. 9a Therapeutic Products Act). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be converted into a standard authorisation.

Dosage/Administration

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.
Do not substitute Enhertu for or with trastuzumab or trastuzumab emtansine.

Patient selection for HER2-low metastatic breast cancer

Select patients for treatment of unresectable or metastatic HER2-low breast cancer based on IHC 1+ or IHC 2+/ISH- tumor status, as assessed by a validated test (see section “Properties/Effects”).

Patient Selection for other unresectable or metastatic solid tumors

Select patients for treatment of unresectable or metastatic solid tumors based on HER2-positive (IHC 3+) tumor status, as assessed by a validated test.

Patient selection for gastric cancer

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 (IHC) or a ratio of ≥ 2 by *in situ* hybridization (ISH) or by fluorescence *in situ* hybridization (FISH), assessed by a validated test. Whenever possible a new tumor specimen is to be obtained to reassess the HER2 status before treatment with Enhertu.

Premedication

Enhertu is moderately emetogenic (see section “Undesirable Effects”), which includes delayed nausea and/or vomiting. Prior to each dose of Enhertu, patients can take antiemetic drugs in accordance with consensus-based and/or local guidelines as per tolerance for prophylaxis or management.

Posology

The initial dose should be administered as a 90-minute intravenous 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.

To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Recommended Dosage for Metastatic Breast Cancer and Other Unresectable or Metastatic Solid Tumors

The recommended dose of Enhertu is 5.4 mg/kg given as an intravenous infusion once every three weeks (21-day cycle) until disease progression or unacceptable toxicity.

*Recommended Dosage for Locally Advanced or Metastatic Gastric Cancer*The recommended dose of Enhertu is 6.4 mg/kg given as an intravenous infusion once every three weeks (21-day cycle) until disease progression or unacceptable toxicity.

Dose modifications

Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of Enhertu per guidelines provided in Tables 1 and 2.
Enhertu dose should not be re-escalated after a dose reduction is made.

Table 1: Dose reduction schedule

Dose reduction schedule	**Breast cancer and other solid tumors**	**Gastric cancer**
Starting dose	5.4 mg/kg	6.4 mg/kg
First dose reduction	4.4 mg/kg	5.4 mg/kg
Second dose reduction	3.2 mg/kg	4.4 mg/kg
Requirement for further dose reduction	Discontinue treatment.	Discontinue treatment

Table 2: Dose modifications for adverse reactions

Adverse reaction	**Severity**	**Treatment modification**
Interstitial lung disease (ILD)/pneumonitis	Asymptomatic ILD/pneumonitis (Grade 1)	Interrupt Enhertu until resolved to Grade 0, then: • if resolved in 28 days or less from date of onset, maintain dose. • if resolved in greater than 28 days from date of onset, reduce dose one level (see Table 1). • consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (see section “Warnings and precautions”).

Adverse reaction	Severity		Treatment modification
	Symptomatic ILD/pneumonitis (Grade 2 or greater)		• Permanently discontinue Enhertu. • Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected (see section “Warnings and precautions”).
Neutropenia	Grade 3 (less than 1.0-0.5 × 10^9/L)		• Interrupt Enhertu until subsided to Grade 2 or less, then maintain dose.
	Grade 4 (less than 0.5 × 10^9/L)		• Interrupt Enhertu until subsided to Grade 2 or less. • Reduce dose by one level (see Table 1).
Febrile neutropenia	Absolute neutrophil count of less than 1.0 × 10^9/L and temperature greater than 38.3°C or a sustained temperature of 38°C or greater for more than one hour.		• Interrupt Enhertu until resolved. • Reduce dose by one level (see Table 1).
Left ventricular ejection fraction (LVEF) decreased	LVEF greater than 45% and absolute decrease from baseline is 10% to 20%		• Continue treatment with Enhertu.
	LVEF 40% to 45%	And absolute decrease from baseline is less than 10%	• Continue treatment with Enhertu. • Repeat LVEF assessment within 3 weeks.
		And absolute decrease from baseline is 10% to 20%	• Interrupt Enhertu. • Repeat LVEF assessment within 3 weeks. • If LVEF has not recovered to within 10% from baseline, permanently discontinue Enhertu. • If LVEF recovers to within 10% from baseline, resume treatment with Enhertu at the same dose.

Adverse reaction	Severity	Treatment modification
	LVEF less than 40% or absolute decrease from baseline is greater than 20%	• Interrupt Enhertu. • Repeat LVEF assessment within 3 weeks. • If LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed, permanently discontinue Enhertu.
	Symptomatic congestive heart failure (CHF)	• Permanently discontinue Enhertu.

Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v.5.0).

Delayed or missed dose

If a planned dose is delayed or missed, it should be administered as soon as possible without waiting until the next planned cycle. The schedule of administration should be adjusted to maintain a 3-week interval between doses. The infusion should be administered at the dose and rate the patient tolerated in the most recent infusion.

Special populations

Elderly patients

No dose adjustment of Enhertu is required in patients aged 65 years or older. Limited data are available in patients ≥75 years of age.

Patients with renal impairment

No dose adjustment is required in patients with mild (creatinine clearance [CLcr] ≥60 and <90 mL/min) or moderate (CLcr ≥30 and <60 mL/min) renal impairment (see section “Pharmacokinetics”). Limited data are available in patients with severe renal impairment. A higher incidence of ILD/pneumonitis leading to an increase in discontinuation of therapy has been observed in patients with moderate renal impairment. Patients with moderate or severe renal impairment should be monitored carefully (see section “Warnings and precautions”).

Patients with hepatic impairment

No dose adjustment is required in patients with mild (total bilirubin ≤ upper limit of normal [ULN] and any aspartate transaminase [AST] >ULN or total bilirubin >1 to 1.5 times ULN and any AST) hepatic impairment. There are limited data to make a recommendation on dose adjustment in patients with moderate (total bilirubin >1.5 to 3 times ULN and any AST) hepatic impairment (see section

“Pharmacokinetics”). No data are available in patients with severe (total bilirubin >3 times ULN and any AST) hepatic impairment.

Children and adolescents

The safety and efficacy in children and adolescents below 18 years of age have not been established as there is no relevant use in the paediatric population.

Mode of administration

Enhertu is for intravenous use. It must be reconstituted and diluted by a healthcare professional and administered as an intravenous infusion. Enhertu must not be administered as an intravenous push or bolus.
For instructions on reconstitution and dilution of the medicinal product before administration, see section “Other information”, “Instructions and special precautions for handling and disposal”.

Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section “Composition”.

Warnings and precautions

Interstitial lung disease/pneumonitis

Cases of interstitial lung disease (ILD), and/or pneumonitis, have been reported with Enhertu (see section “Undesirable effects”). Fatal outcomes have been observed.
Patients with a history of ILD/pneumonitis requiring steroid treatment or present or suspected ILD/pneumonitis at the time of screening and patients with clinically severe pulmonary impairment were not included in clinical studies with Enhertu.
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 further evaluation of the lung using imaging techniques. Consultation with a pulmonologist should be considered. For asymptomatic (Grade 1) ILD/pneumonitis, consider corticosteroid treatment (e.g. ≥0.5 mg/kg/day prednisolone or equivalent). Enhertu should be withheld until recovery to Grade 0 and may be resumed according to instructions in Table 2 (see section “Dosage/Administration”). For symptomatic ILD/pneumonitis (Grade 2 or greater), promptly initiate systemic corticosteroid treatment (e.g. ≥1 mg/kg/day prednisolone or equivalent) and continue for at least 14 days followed by gradual taper for at least 4 weeks. Enhertu should be permanently discontinued in patients who are diagnosed with symptomatic (Grade 2 or greater) ILD/pneumonitis (see section “Dosage/Administration”). Patients with a history of ILD/pneumonitis or moderate or severe renal impairment may be at increased risk of developing

ILD/pneumonitis and, therefore, should be monitored carefully (see section “Properties/Effects” and “Dosage/Administration”).

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 (see section “Dosage/Administration”).

Left ventricular ejection fraction decrease

Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies. LVEF should be assessed prior to initiation of Enhertu and at regular intervals during treatment as clinically indicated. LVEF decrease should be managed through treatment interruption. Enhertu should be permanently discontinued if LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed. Treatment with Enhertu has not been studied in patients with LVEF less than 50% prior to initiation of treatment. Enhertu should be permanently discontinued in patients with symptomatic congestive heart failure (CHF) (see section “Dosage/Administration”).

Embryo-foetal toxicity

Enhertu can cause foetal harm when administered to a pregnant woman. In postmarketing reports, use of trastuzumab, a HER2 receptor antagonist, during pregnancy resulted in cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Based on findings in animals and its mechanism of action, the topoisomerase I inhibitor component of Enhertu, DXd, can also cause embryo-foetal harm when administered to a pregnant woman (see section “Pregnancy, lactation”).
The pregnancy status of females of reproductive potential should be verified prior to the initiation of Enhertu. The patient should be informed of the potential risks to the foetus. 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 (see section “Pregnancy, lactation”).

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 (see section “Dosage/Administration” and “Pharmacokinetics”).

Interactions

Effects of other medicinal products on the pharmacokinetics of Enhertu

In vitro, DXd was a substrate of P-gp, OATP1B1, OATP1B3, MATE2-K, MRP1, and BCRP.

Co-administration with ritonavir, a dual inhibitor of OATP1B/CYP3A, or with itraconazole, a strong CYP3A inhibitor, resulted in no clinically meaningful increase in exposures of Enhertu or the released topoisomerase I inhibitor, DXd. No dose adjustment is required during co-administration of Enhertu with medicinal products that are inhibitors of OATP1B or CYP3A.

No clinically meaningful interaction is expected with medicinal products that are inhibitors of P-glycoprotein (P-gp), MATE2-K, MRP1, or BCRP transporters.

Effects of Enhertu on the pharmacokinetics of other medicinal products

In vitro studies indicate DXd does not inhibit or induce major CYP450 enzymes including CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A. *In vitro* studies indicate that DXd does not inhibit OAT1, OAT3, OCT1, OCT2, OATP1B3, MATE1, MATE2-K, P-gp, BCRP, or BSEP transporters. No clinically meaningful drug-drug interaction is expected with medicinal products that are substrates of OAT1 or OATP1B1 transporters.

Pregnancy, lactation

Women of childbearing potential/contraception in males and females

Pregnancy status of women of childbearing potential should be verified prior to initiation of Enhertu.

Women of childbearing potential should use effective contraception during treatment with Enhertu and for at least 7 months following the last dose.

Men with female partners of childbearing potential should use effective contraception during treatment with Enhertu and for at least 4 months following the last dose.

Pregnancy

There are no available data on the use of Enhertu in pregnant women. However, in postmarketing reports, use of trastuzumab, a HER2 receptor antagonist, during pregnancy resulted in cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Based on findings in animals and its mechanism of action, the topoisomerase I inhibitor component of Enhertu, DXd, can also cause embryo-foetal harm when administered to a pregnant woman (see section “Preclinical data”).

Enhertu must not be used during pregnancy unless clearly necessary. If Enhertu is administered during pregnancy, or if a woman becomes pregnant during treatment or within 7 months following the last dose of Enhertu, it is necessary to point out the possibility of harm to the foetus.

Lactation

It is not known if trastuzumab deruxtecan is excreted in human milk. Due to the potential for serious adverse reactions in breast-feeding infants, women should discontinue breast-feeding prior to initiating treatment with Enhertu and breast-feeding must not take place during treatment. Women may begin breast-feeding 7 months after concluding treatment.

Fertility

No dedicated fertility studies have been conducted with Enhertu. Based on results from animal toxicity studies, Enhertu may impair male reproductive function and fertility (see section “Preclinical data”). It is not known whether trastuzumab deruxtecan or its metabolites are found in seminal fluid. Before starting treatment, male patients should be advised to seek counselling on sperm storage. Male patients must not freeze or donate sperm throughout the treatment period, and for at least 4 months after the final dose of Enhertu.

Effects on ability to drive and use machines

Enhertu is not expected to affect patients’ ability to drive or use machines. Because of potential adverse reactions such as fatigue, headache and dizziness (see section “Undesirable effects”), patients should be advised to use caution when driving or operating machinery.

Undesirable effects

Summary of the safety profile

The pooled safety population has been evaluated for patients who received at least one dose of Enhertu 5.4 mg/kg and above (n = 3156) across multiple tumour types in clinical studies. The median duration of treatment in this pool was 8.25 months (range: 0.2 to 76.0 months).

- The most common adverse reactions were nausea (70.8%), fatigue (56.4%), anaemia (38.3%), vomiting (37.4%) , neutropenia (37.6%), decreased appetite (35.5%), alopecia (35.5%), constipation (31.5%), diarrhoea (31.5%), transaminases increased (26.2 %), thrombocytopenia (25.9%), leukopenia (23.4%) and musculoskeletal pain (22.7%).The most common serious adverse reactions were ILD/pneumonitis (4.0%), pneumonia (2.2%), vomiting (1.5%), anaemia (1.4%), nausea (1.3%), fatigue (1.1%), decreased appetite (1.1%) and thrombocytopenia (1.0 %).
- The most common National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v.5.0) Grade 3 or 4 adverse reactions were neutropenia (20.8%), anaemia (13.6%), fatigue (8.1%), leukopenia (7.8%), thrombocytopenia (6.7%), nausea (5.1%), lymphopenia (4.6%), hypokalaemia (4.1%), transaminases increased (3.6%), decreased appetite (3.0%), vomiting (2.3%), diarrhoea (2.3%), pneumonia (1.7%), febrile neutropenia

(1.4%), ejection fraction decreased (1.1%), dyspnoea (1.0%), abdominal pain (1.0%), blood bilirubin increased (1.0%) and ILD/pneumonitis (1.0%),
Grade 5 adverse reactions occurred in 1.8% of patients, including ILD (1.4%).

- Dose interruptions due to adverse reactions occurred in 42.7% of patients treated with Enhertu. The most frequent adverse reactions associated with dose interruption were ejection fraction decreased (13.8%), neutropenia (13.5%), anaemia (5.5%), fatigue (5.1%), leukopenia (3.5%), upper respiratory tract infection (3.2%), ILD (2.9%), thrombocytopenia (2.9%) and pneumonia (2.5%).
- Dose reductions occurred in 33.4% of patients treated with Enhertu. The most frequent adverse reactions associated with dose reduction were ejection fraction decreased (13.7%), fatigue (6.5%), nausea (5.2%), neutropenia (4.4%), thrombocytopenia (2.4%) and decreased appetite (2.0%).
- Discontinuation of therapy due to an adverse reaction occurred in 25.0% of patients treated with Enhertu. The most frequent adverse reaction associated with permanent discontinuation were ejection fraction decreased (13.8 %) andILD/pneumonitis (9.4%).

Tabulated list of adverse reactions

The adverse reactions in patients who received at least one dose of Enhertu in clinical studies are presented in Table 3. The adverse reactions are listed by MedDRA system organ class (SOC) and categories of frequency. Frequency categories are defined as very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3: Adverse reactions in patients treated with trastuzumab deruxtecan 5.4 mg/kg and above in multiple tumour types

System organ class/preferred term or grouped term	**Any Grade (%)**		**Grade 3-4 (%)**
Infections and infestations			
Upper respiratory tract infection[a]	Very common	16.5	0.2
Pneumonia	Common	6.8	1.7
Blood and lymphatic system disorders			
Anaemia[b]	Very common	38.3	13.6
Neutropenia[c]	Very common	37.6	20.8

System organ class/preferred term or grouped term	Any Grade (%)		Grade 3-4 (%)
Thrombocytopenia[d]	Very common	25.9	6.7
Leukopenia[e]	Very common	23.4	7.8
Lymphopenia[f]	Very Common	10.2	4.6
Febrile neutropenia	Common	1.5	1.4
Metabolism and nutrition disorders			
Decreased appetite	Very common	35.5	3.0
Hypokalaemia[g]	Very common	12.5	4.1
Dehydration	Common	2.8	0.4
Nervous system disorders			
Headache[h]	Very common	14.8	0.2
Peripheral neuropathy[i]	Common	9.5	0.2
Dizziness	Common	8.8	0.3
Dysgeusia	Common	8.3	0.0
Eye disorders			
Dry eye	Common	5.0	0.2
Vision blurred[j]	Common	3.6	0.1
Cardiac disorders			
Ejection fraction decreased[k]	Very common	14.1	1.1
Respiratory, thoracic and mediastinal disorders			
Cough	Very common	14.0	0.1
Interstitial lung disease[l]	Very common	13.5	1.0
Dyspnoea	Common	9.5	1.0
Epistaxis	Common	8.8	0.1
Gastrointestinal disorders			
Nausea	Very common	70.8	5.1
Vomiting	Very common	37.4	2.3

System organ class/preferred term or grouped term	Any Grade (%)		Grade 3-4 (%)
Constipation	Very common	31.5	0.5
Diarrhoea	Very common	31.5	2.3
Abdominal pain[m]	Very common	18.5	1.0
Stomatitis[n]	Very common	14.3	0.5
Dyspepsia	Common	9.3	0.0
Abdominal distension	Common	3.7	0.1
Flatulence	Common	1.8	0
Gastritis	Common	1.6	0.1
Hepatobiliary disorders			
Transaminases increased[o]	Very common	26.2	3.6
Blood alkaline phosphatase increased	Common	8.6	0.8
Blood bilirubin increased[p]	Common	7.7	1.0
Skin and subcutaneous tissue disorders			
Alopecia	Very common	35.5	0.1
Rash[q]	Common	8.5	0.1
Pruritus	Common	5.0	0.0
Skin hyperpigmentation[r]	Common	3.2	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain[s]	Very Common	22.7	0.8
Renal and urinary disorders			
Blood creatinine increased	Common	4.1	0.3
General disorders and administration site conditions			
Fatigue[t]	Very common	56.4	8.1
Pyrexia	Very common	14.5	0.4
Weight decreased	Very common	14.4	0.9
Oedema peripheral	Common	8.8	0.1

System organ class/preferred term or grouped term	Any Grade (%)		Grade 3-4 (%)
Injury, poisoning and procedural complications			
Infusion-related reactions[u]	Common	1.0	0.0

[a] Upper respiratory tract infection (grouped term) includes PTs of Influenza, Influenza like illness, Upper respiratory tract infection, Nasopharyngitis, Pharyngitis, Sinusitis, Rhinitis, Laryngitis..

[b] Aneamia (grouped term) includes PTs of Haemoglobin decreased, Red blood cell count decreased, Anaemia, Haematocrit decreased.

[c] Neutropenia (grouped term) includes PTs of Neutrophil count decreased, Neutropenia.

[d] Thrombocytopenia (grouped term) includes PTs of Platelet count decreased, Thrombocytopenia.

[e] Leukopenia (grouped term) includes PTs of White blood cell count decreased, Leukopenia.

[f] Lymphopenia (grouped term) includes PTs of Lymphocyte count decreased, Lymphopenia.

[g] Hypokalaemia (grouped term) includes PTs of Hypokalaemia, Blood potassium decreased.

[h] Headache (grouped term) includes PTs of Migraine, Headache, Sinus headache.

[i] Peripheral neuropathy (grouped term) includes PTs of Neuropathy peripheral, Peripheral sensory neuropathy, Paraesthesia.

[j] Vision blurred (grouped term) includes PTs of Vision blurred, Visual impairment.

[k] Ejection fraction decreased (grouped term) includes Laboratory parameters of LVEF decrease (n=432) and PTs of Cardiac failure (n=5), Cardiac failure acute (n=1), Cardiac failure chronic (n=1), Cardiac failure congestive (n=1), Ejection fraction decreased (n=112), Left ventricular dysfunction (n=4).

[l] Interstitial lung disease (grouped term) includes PTs of Acute respiratory failure (n=1), Alveolitis (n=2), Bronchiectasis (n=1), Hypersensitivity pneumonitis (n=1), Idiopathic interstitial pneumonia (n=1), Interstitial lung disease (n=161), Lower respiratory tract infection (n=1), Lung disorder (n=1), Lung infiltration (n=1), Lung opacity (n=6), Lymphangitis (n=1), Organising pneumonia (n=13), Pneumonia (n=8), Pneumonia bacterial (n=2), Pneumonia fungal (n=1), Pneumonitis (n=220), Pulmonary fibrosis (n=1), Pulmonary mass (n=1), Pulmonary toxicity (n=4), Radiation pneumonitis (n=4), Respiratory failure (n=11). These events were adjudicated as drug-related ILD for T-DXd.

[m] Abdominal pain (grouped term) includes PTs of Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Gastrointestinal pain.

[n] Stomatitis (grouped term) includes PTs of Stomatitis, Aphthous ulcer, Mouth ulceration, Oral mucosa erosion, Oral mucosal blistering, Oral mucosal eruption

[o] Transaminases increased (grouped term) includes PTs of Transaminases increased, Aspartate aminotransferase increased, Alanine aminotransferase increased, Gamma-glutamyltransferase increased, Liver function test abnormal, Hepatic function abnormal, Liver function test increased.

[p] Blood bilirubin increased (grouped term) includes PTs of Blood bilirubin increased, Hyperbilirubinaemia, Bilirubin conjugated increased, Blood bilirubin unconjugated increased.

[q] Rash (grouped term) includes PTs of Rash, Rash pustular, Rash maculo-papular, Rash papular, Rash macular, Rash pruritic.

[r] Skin hyperpigmentation (grouped term) includes PTs of Skin hyperpigmentation, Skin discolouration, Pigmentation disorder.

[s] Musculoskeletal pain (grouped term) includes PTs of Back pain, Myalgia, Pain in extremity, Musculoskeletal pain, Muscle spasms, Bone pain, Neck pain, Musculoskeletal chest pain, Limb discomfort.

[t] Fatigue (grouped term) includes PTs of Fatigue, Asthenia, Malaise, Lethargy.

[u] Infusion related reaction (grouped term) includes PTs of Hypersensitivity (n=3), Infusion related reaction (n=29).

Description of selected undesirable effects

Interstitial lung disease/pneumonitis

In clinical studies across multiple tumour types (n = 3156), ILD occurred in 13.5% of patients treated with Enhertu 5.4 mg/kg and above. Median time to first onset was 5.3 months (range: -0.5 to 40.2). Most ILD cases were Grade 1 (3.3%) and Grade 2 (7.8%). Grade 3 cases occurred in 0.9% and Grade 4 cases occurred in 0.0% of patients. Grade 5 events occurred in 1.4% of patients. In clinical studies with patients treated with Enhertu 5.4 mg/kg and above across multiple tumour types, the incidence of ILD with moderate renal impairment (19.3%) was higher compared to patients with normal renal function (12.3%).

Neutropenia

In clinical studies (n = 3156) across multiple tumour types in patients treated with Enhertu 5.4 mg/kg and above, neutropenia was reported in 37.6% of patients and 20.8% had Grade 3 or 4 events. Median time to first onset was 22 days (range: 0 day to 51.5 months), and median duration of the first event was 15 days (range: 1 day to 30.9 months). Febrile neutropenia was reported in 1.5% of patients and 0.1% were Grade 5 (see section “Warnings and precautions”).

Left ventricular ejection fraction decrease

In the 3156 patients, across multiple tumour types in clinical studies who received Enhertu 5.4 mg/kg and above, LVEF decrease was reported in 112 patients (3.5%), of which 11 (0.3%) were Grade 1, 88 (2.8%) were Grade 2, and 13 (0.4%) were Grade 3. The observed frequency of LVEF decreased based on laboratory parameters (echocardiogram or multigated acquisition [MUGA] scanning) was 407/2801 (14.5%) for Grade 2, and 25/2801 (0.9%) for Grade 3. Treatment with Enhertu has not been studied in patients with LVEF less than 50% prior to initiation of treatment.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The measurement of antibodies is dependent on assay sensitivity and specificity. The rate of antibody positivity found is dependent on numerous factors; therefore, comparison of the rates with other therapies may be misleading. Across 5.4 mg/kg and 6.4 mg/kg doses evaluated in clinical studies, 2.2% (70/3124) of evaluable patients developed antibodies against trastuzumab deruxtecan following treatment with

Enhertu. The incidence of treatment-emergent neutralising antibodies against trastuzumab deruxtecan was 0.1% (3/3124).
Due to the limited number of patients who tested positive for ADA, the effect of ADA on safety and efficacy of Enhertu is unknown.

Children and adolescents

Safety has not been established in this population.

Elderly patients

Of the 3156 patients across multiple tumour types in clinical studies treated with Enhertu 5.4 mg/kg and above, 31.4% were 65 years or older and 6.5% were 75 years or older. The incidence of Grade 3-4 adverse reactions observed in patients 65 years or older was 51.2% and in younger patients was 47.2%.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is no information on overdose with trastuzumab deruxtecan. In the event of overdose, patients should be monitored and appropriate supportive care should be given.

Properties/Effects

ATC code

L01FD04

Mechanism of action

Enhertu, trastuzumab deruxtecan, is a HER2-targeted antibody-drug conjugate (ADC). The antibody is a humanised anti-HER2 IgG1 attached to deruxtecan, a topoisomerase I inhibitor (DXd), bound by a tetrapeptide-based cleavable linker. The ADC is stable in plasma. Following binding to HER2 on tumour cells, trastuzumab deruxtecan undergoes internalisation and intracellular linker cleavage by lysosomal enzymes that are upregulated in cancer cells. Upon release, the membrane-permeable DXd causes DNA damage and apoptotic cell death. DXd, an exatecan derivative, is approximately 10 times more potent than SN-38, the active metabolite of irinotecan.

Pharmacodynamics

The administration of multiple doses of trastuzumab deruxtecan (6.4 mg/kg every 3 weeks) did not show any clinically meaningful effect on the QTc interval (i.e., >20 ms) in an open-label, single-arm study in 51 patients with HER2-expressing metastatic breast cancer.
In the DESTINY-Breast04 study, it was observed that 21.6% of patients had a QTcF prolongation > 30 ms from baseline, 5.7% of patients had a QTcF prolongation > 60 ms from baseline and 1.9% of patients had a QTcF measurement of > 500 ms.

Clinical efficacy

DESTINY-Breast03
The efficacy and safety of Enhertu were studied in DESTINY-Breast03, a multicentre, open-label, active controlled, randomised, two-arm phase 3 study that enrolled patients with HER2-positive, unresectable or metastatic breast cancer who received prior trastuzumab and taxane therapy for metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy.
Archival breast tumour samples were required to show HER2 positivity defined as HER2 IHC 3+ or ISH-positive. The study excluded patients with a history of (non-infectious) ILD/pneumonitis requiring treatment with steroids or ILD/pneumonitis at screening, patients with untreated and symptomatic brain metastases, patients with a history of clinically significant cardiac disease, patients with an Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2 and patients with prior treatment with an anti-HER2 antibody-drug conjugate in the metastatic setting. Patients were randomized 1:1 to receive either Enhertu 5.4 mg/kg (n=261) or trastuzumab emtansine 3.6 mg/kg (n=263) administered by intravenous infusion once every three weeks. Randomization was stratified by hormone receptor status, prior treatment with pertuzumab, and history of visceral disease. Treatment was administered until disease progression, death, withdrawal of consent, or unacceptable toxicity.
The primary efficacy outcome measure was progression-free survival (PFS) as evaluated by blinded independent central review (BICR) according to RECIST v1.1. Overall survival (OS) was a key secondary efficacy outcome measure.
Patient demographics were balanced between treatment arms. Of the 524 patients randomised, the baseline demographic and disease characteristics were: median age 54 years (range: 20 to 83); 65 years or older (20.2%); 75 years or older (3.1%), female (99.6%); Asian (59.9%), White (27.3%), Black or African-American (3.6%); ECOG performance status 0 (62.8%) or 1 (36.8%); hormone receptor status (positive: 51.9%); presence of visceral disease (73.3%); presence of brain metastases at baseline (15.6%); and (48.3%) patients received one line of prior systemic therapy in the metastatic setting. The percentage of patients who were previously treated with pertuzumab was 61.1%. The percentage of patients who had not received prior treatment for metastatic disease was 9.5% and

6.7% of patients had received exactly one prior anti-HER2 therapy that was intended for the neoadjuvant or adjuvant therapy and experienced disease progression during or within 6 months of completing treatment (12 months for pertuzumab).

At the prespecified interim analysis for PFS (data cutoff 21 May 2021) based on 245 events (73% of total events planned for final analysis), the study demonstrated a statistically significant improvement in PFS per BICR in patients randomized to Enhertu compared to trastuzumab emtansine. At the prespecified OS analysis based on 169 events (data cutoff 25 July 2022), the study also demonstrated statistically significant improvement in OS. An updated PFS per BICR was provided at the time of this OS analysis.[1]

Table 4: Efficacy results in DESTINY Breast03[1]

Efficacy Parameter	**Enhertu N=261**	**trastuzumab emtansine N=263**
Progression-Free Survival (PFS) Primary end-point (BICR)[a]		
Number of events (%)	87 (33.3)	158 (60.1)
Median, months (95% CI)	NR (18.5, NE)	6.8 (5.6, 8.2)
Hazard ratio (95% CI)	0.28 (0.22, 0.37)	
p-value	p< 0.0001	
Overall Survival (OS)[b]		
Number of events (%)	72 (27.6)	97 (36.9)
Median, months (95% CI)	NR (40.5, NE)	NR (34.0, NE)
Hazard ratio (95% CI)	0.64 (0.47, 0.87)	
p-value[c]	p=0.0037	
Survival at 12 months (95% CI)	94.1% (90.4, 96.4)	86.0% (81.1, 89.8)
Survival at 24 months (95% CI)	77.4 (71.7, 82.1)	69.9 (63.7, 75.2)
PFS (BICR) (updated)[b]		
Number of events (%)	117 (44.8)	171 (65.0)
Median, months (95% CI)	28.8 (22.4, 37.9)	6.8 (5.6, 8.2)
Hazard ratio (95% CI)	0.33 (0.26, 0.43)	

CI = confidence interval; NE=not estimable; NR = not reached

[a] Data cutoff 21 May 2021
[b] Data cutoff 25 July 2022 for a pre-planned OS interim analysis
[c] The p-value is based on a stratified log-rank test; crossed the efficacy boundary of 0.013.

DESTINY-Breast02

The efficacy and safety of Enhertu were evaluated in study DESTINY-Breast02, a Phase 3, randomised, multicenter, open-label, active-controlled study that enrolled patients with unresectable or metastatic HER2-positive breast cancer.

The study included adult patients with unresectable or metastatic HER2-positive breast cancer who were resistant or refractory to prior trastuzumab emtansine. Archival breast tumor samples were required to show HER2 positivity defined as HER2 IHC 3+ or ISH-positive. The study excluded patients with a history of ILD/pneumonitis requiring treatment with steroids or ILD/pneumonitis at screening, patients with untreated and symptomatic brain metastases and patients with a history of clinically significant cardiac disease. Patients were randomized 2:1 to receive either Enhertu 5.4 mg/kg (N=406) by intravenous infusion every three weeks or treatment of physician's choice (N=202, trastuzumab plus capecitabine or lapatinib plus capecitabine). Randomization was stratified by hormone receptor status, prior treatment with pertuzumab, and history of visceral disease. Treatment was administered until disease progression, death, withdrawal of consent, or unacceptable toxicity.

The primary efficacy outcome measure was progression-free survival (PFS) as assessed by blinded independent central review (BICR) based on RECIST v1.1. Overall survival (OS) was a key secondary efficacy outcome measure.

Demographic and baseline disease characteristics were similar between treatment arms. Of the 608 patients randomized, the median age was 54 years (range 22 to 88); female (99.2%); White (63.2%), Asian (29.3%), Black or African American (2.8%); ECOG performance status 0 (57.4%) or 1 (42.4%); hormone receptor status (positive: 58.6%); presence of visceral disease (78.3%); presence of brain metastases at baseline (18.1%), and 4.9% of patients received one line of prior systemic therapy in the metastatic setting.

The study demonstrated a statistically significant improvement in PFS per BICR and OS in patients randomized to Enhertu compared to treatment of physician's choice.
Efficacy results are summarized in Table 5.

Table 5: Efficacy Results in DESTINY-Breast02

Efficacy Parameter	**Enhertu N=406**	**Treatment of Physician's Choice N=202**
PFS per BICR		
Number of events (%)	200 (49.3)	125 (61.9)
Median, months (95% CI)	17.8 (14.3, 20.8)	6.9 (5.5, 8.4)
Hazard ratio (95% CI)	0.36 (0.28, 0.45)	
p-value	p<0.000001†	

Efficacy Parameter	Enhertu N=406	Treatment of Physician's Choice N=202
Overall Survival (OS)		
Number of events (%)	143 (35.2)	86 (42.6)
Median, months (95% CI)	39.2 (32.7, NE)	26.5 (21.0, NE)
Hazard ratio (95% CI)	0.66 (0.50, 0.86)	
p-value[a]	p=0.0021	
Survival at 12 months (95% CI)	89.4% (85.9, 92.1)	74.7% (67.6, 80.4)
Survival at 24 months (95% CI)	65.9% (60.7, 70.7)	54.3% (46.3, 61.6)

CI = confidence interval; NE=not estimable
†presented as 6 decimal places
[a] The p-value is based on a stratified log-rank test; crossed the efficacy boundary of 0.004

At an updated exploratory analysis (cut-off 29 September 2023) with a median follow-up of 26.8 months, OS results as well as subgroup analysis for OS were consistent with the primary analysis. Median OS was 35.7 months (95% CI: 30.9, 40.8) in the T-DXd arm versus 25.0 months (95% CI: 20.4, 31.5) in the TPC arm (stratified HR: 0.69 [95% CI: 0.55, 0.86]).

DESTINY-Breast01

The efficacy and safety of Enhertu were demonstrated in DESTINY-Breast01, a multicentre, open-label, single-arm Phase 2 study that enrolled patients with HER2-positive, unresectable and/or metastatic breast cancer who had received two or more prior anti-HER2-based regimens, including trastuzumab emtansine (100%), trastuzumab (100%), and pertuzumab (65.8%). Archival breast tumour samples were required to show HER2-positivity defined as HER2 IHC 3+ or ISH-positive. The study excluded patients with a history of treated ILD or ILD at screening, patients with a history of clinically significant cardiac disease as well as patients with clinically unstable brain metastases. Enhertu was administered by intravenous infusion at 5.4 mg/kg once every three weeks until disease progression or unacceptable toxicity. The primary efficacy outcome measure was confirmed objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) in the intent-to-treat (ITT) population as evaluated by independent central review. Secondary efficacy outcome measures were duration of response (DOR) and progression-free survival (PFS).
Of the 184 patients enrolled in DESTINY-Breast01, baseline demographic and disease characteristics were: median age 55 years (range 28 to 96); female (100%); White (54.9%), Asian (38.0%), Black or African-American (2.2%); Eastern Cooperative Oncology Group (ECOG) performance status 0 (55.4%) or 1 (44.0%); hormone receptor status (positive: 52.7%); presence of visceral disease

(91.8%); median number of prior therapies in the metastatic setting: 5 (range: 2 to 17); prior pertuzumab therapy (65.8%); sum of diameters of target lesions (<5 cm: 42.4%, ≥5 cm: 50.0%). Efficacy results are summarised in Table 6.

Table 6: Efficacy results in DESTINY-Breast01 (intent-to-treat analysis set)

	DESTINY-Breast01 N = 184
Confirmed objective response rate (95% CI)	61.4% (54.0, 68.5)
Complete response (CR)	6.5%
Partial response (PR)	54.9%
Duration of response‡	
Median, months (95% CI)	20.8 (15.0, NR)
% with duration of response ≥6 months (95% CI)§	81.5% (72.2, 88.0)

ORR 95% CI calculated using Clopper-Pearson method
CI = confidence interval
95% CIs calculated using Brookmeyer-Crowley method
‡Includes 73 patients with censored data
§Based on KaplanMeier estimation
NR = not reached

Consistent anti-tumour activity was observed across pre-specified subgroups based on prior pertuzumab therapy and hormone receptor status.

DESTINY-Breast04

The efficacy of Enhertu was studied in DESTINY-Breast04, a phase 3, randomised, multicentre, open-label study that enrolled 557 adult patients with unresectable or metastatic HER2-low breast cancer. The study included 2 cohorts: 494 hormone receptor positive (HR+) patients and 63 hormone receptor negative (HR-) patients. HER2-low expression was defined as IHC 1+ or IHC 2+/ISH-, as determined by the PATHWAY/VENTANA anti-HER-2/neu (4B5) and when applicable, the INFORM HER2 Dual ISH assay, evaluated at a central laboratory. Patients must have received chemotherapy in the metastatic setting or have developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Patients who were HR+ must have received at least one endocrine therapy or be ineligible for endocrine therapy. Patients were randomised 2:1 to receive either Enhertu 5.4 mg/kg (N = 373) by intravenous infusion every three weeks or physician's choice of chemotherapy (N = 184, eribulin 51.1%, capecitabine 20.1%, gemcitabine 10.3%, nab paclitaxel 10.3%, or paclitaxel 8.2%). Randomisation was stratified by HER2 IHC status of tumour samples (IHC 1+ or IHC 2+/ISH-), number of prior lines of chemotherapy in the metastatic setting (1 or 2), and HR status/prior CDK4/6i treatment (HR+ with prior CDK4/6 inhibitor treatment, HR+ without prior CDK4/6 inhibitor treatment, or HR-). Treatment was administered until disease progression, death,

withdrawal of consent, or unacceptable toxicity. The study included patients with LVEF ≥50%. The study excluded patients with a history of ILD/pneumonitis requiring treatment with steroids or current or suspected ILD/pneumonitis at screening and patients with clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses. Patients were also excluded for clinically significant cardiac disease including corrected QT interval (QTc) prolongation >470 ms for female patients or > 450 ms in male patients, untreated or symptomatic brain metastases or ECOG performance status > 1.

The primary efficacy outcome measure was progression-free survival (PFS) in patients with HR+ breast cancer assessed by BICR based on RECIST v1.1. Key secondary efficacy outcome measures were PFS assessed by BICR based on RECIST v1.1 in the overall population (all randomised HR+ and HR- patients), overall survival (OS) in HR+ patients, and OS in the overall population.

Demographics and baseline tumour characteristics were similar between treatment arms. Of the 557 patients randomised, the median age was 57 years (range: 28 to 81); 23.5% were age 65 or older; 4.1% were age 75 or older; 99.6% were female and 0.4% were male; 47.9% were White, 40.0% were Asian, and 1.8% were Black or African American. Patients had an ECOG performance status of 0 (54.8%) or 1 (45.2%) at baseline; 57.6% were IHC 1+, 42.4% were IHC 2+/ISH-; 69.8% had liver metastases, 32.9% had lung metastases, and 5.7% had brain metastases. In the metastatic setting, patients had a median of 3 prior lines of systemic therapy (range: 1 to 9) with 57.6% having 1 and 40.9% having 2 prior chemotherapy regimens; 3.9% were early progressors (progression in the neo/adjuvant setting). In HR+ patients, the median number of prior lines of endocrine therapy was 2 (range: 0 to 9) and 70% had prior CDK4/6 inhibitor treatment.

The study demonstrated a statistically significant and clinically meaningful improvement in OS and PFS in patients randomised to Enhertu compared to chemotherapy in both the HR+ cohort and the overall population. Efficacy results are summarized in Table 7.

Table 7: Efficacy results in DESTINY-Breast04

Efficacy parameter	**HR+ cohort**	
	Enhertu (N = 331)	**Chemotherapy (N = 163)**
Overall survival*		
Number of events (%)	126 (38.1)	73 (44.8)
Median, months (95% CI)	23.9 (20.8, 24.8)	17.5 (15.2, 22.4)
Hazard ratio (95% CI)	0.64 (0.48, 0.86)	
p-value	0.0028	
Progression-free survival per BICR		
Number of events (%)	211 (63.7)	110 (67.5)
Median, months (95% CI)	10.1 (9.5, 11.5)	5.4 (4.4, 7.1)

Efficacy parameter	HR+ cohort	
	Enhertu (N = 331)	**Chemotherapy (N = 163)**
Hazard ratio (95% CI)	0.51 (0.40, 0.64)	
p-value	< 0.0001	

CI = confidence interval
* Data cut-off: 11 January 2022

The results in the HR-negative cohort are consistent with the results in the HR+ cohort. In the full analysis set (FAS), median OS was 23.4 months (95% CI: 20.0, 24.8) in patients randomised to Enhertu compared to 16.8 months (95% CI: 14.5, 20.0) in patients randomised to chemotherapy with a hazard ratio of 0.64 (95% CI: 0.49, 0.84). Median PFS was 9.9 months (95% CI: 9.0, 11.3) in patients randomised to Enhertu and 5.1 months (95% CI: 4.2, 6.8) in patients randomised to chemotherapy with a hazard ratio of 0.50 (95% CI: 0.40, 0.63).

In an updated descriptive analysis (cut-off 01 March 2023), with a median follow-up of 32 months, OS results were consistent with the primary analysis. The hazard ratio in the HR-positive cohort was 0.69 (95% CI: 0.55-0.87) with a median OS of 23.9 months (95% CI: 21.7-25.2) in the Enhertu arm versus 17.6 months (95% CI: 15.1-20.2) in the chemotherapy arm. The hazard ratio in the overall population was 0.69 (95% CI: 0.55, 0.86) with a median OS of 22.9 months (95% CI: 21.2, 24.5) in the Enhertu arm versus 16.8 months (95% CI: 14.1, 19.5) in the chemotherapy arm.

DESTINY-Gastric02

The efficacy and safety of Enhertu were studied in DESTINY-Gastric02, a Phase 2, multicenter, open-label, single-arm study conducted at sites in Europe and the United States. The study enrolled patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma who had progressed on a prior trastuzumab-containing regimen, including subjects who progressed on or within 6 months of completing a trastuzumab-containing adjuvant therapy. Patients were required to have centrally confirmed HER2 positivity defined as IHC 3+ or IHC 2+/ISH-positive based on a tumor biopsy obtained after progression on or after a first-line trastuzumab-containing regimen. The study included patients with LVEF ≥50%. The study excluded patients with a history of ILD/pneumonitis requiring treatment with steroids or ILD/pneumonitis at screening, patients with a history of clinically significant cardiac disease [including patients with QT interval corrected for heart rate (QTc) prolongation to >470 milliseconds (ms) for females or >450 ms for males and patients with a history of symptomatic congestive heart failure (New York Heart Association Class II to IV)], and patients with active brain metastases. Enhertu was administered by intravenous infusion at 6.4 mg/kg every three weeks until disease progression, death, withdrawal of consent, or unacceptable toxicity. The primary efficacy outcome measure was confirmed ORR assessed by ICR based on RECIST v1.1. DOR, PFS, and OS were secondary endpoints.

Of the 79 patients enrolled in DESTINY-Gastric02, demographic and baseline disease characteristics were: median age 61 years (range 20 to 78); 72% were male; 87% were White, 5.0% were Asian, and 1.0% were Black or African American. Patients had an ECOG performance status of either 0 (37%) or 1 (63%); 34% had gastric adenocarcinoma and 66% had GEJ adenocarcinoma; 86% were IHC 3+ and 13% were IHC 2+/ISH-positive, and 63% had liver metastases.

Efficacy results for ORR, DOR, PFS, and OS are summarized in Table 8.

Table 8: Efficacy Results in DESTINY-Gastric02 (Full Analysis Set[*])

Efficacy Parameter	**DESTINY-Gastric02** **N=79**
Data cut-off date 8 November 2021	
Confirmed Objective Response Rate (ORR)[†] % (95% CI)[‡]	 41.8 (30.8, 53.4)
Complete response n (%)	4 (5.1)
Partial response n (%)	29 (36.7)
Duration of Response (DOR) Median[§], months (95% CI)[¶]	 8.1 (5.9, NE)

*Includes all patients who received at least one dose of Enhertu

[†]Assessed by independent central review

[‡]Calculated using Clopper-Pearson method

[§]Based on Kaplan-Meier estimate

[¶]Calculated using the Brookmeyer and Crowley method

Additional efficacy results (data cutoff date 8 November 2021) for Enhertu (n=79) were median progression-free survival (PFS) of 5.6 months (95% CI: 4.2, 8.3) and median overall survival (OS) of 12.1 months (95% CI: 9.4, 15.4).

DESTINY-Gastric01

The efficacy and safety of Enhertu were studied in DESTINY-Gastric01, a Phase 2, multicenter, open-label, randomised study conducted at sites in Japan and South Korea. The study included adult patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma who had progressed on at least two prior regimens, including trastuzumab, a fluoropyrimidine agent, and a platinum agent. Patients were randomised 2:1 to receive either Enhertu (N=126) or physician's choice of chemotherapy: either irinotecan (N=55) or paclitaxel (N=7). Randomization was stratified by HER2 status (IHC 3+ or IHC 2+/ISH-positive), ECOG performance status (0 or 1), and region (Japan or South Korea). Enhertu was administered by intravenous infusion at 6.4 mg/kg every three weeks.

Irinotecan monotherapy was administered by intravenous infusion biweekly at 150 mg/m^2. Paclitaxel monotherapy was administered by intravenous infusion weekly at 80 mg/m^2. Tumour samples were required to have centrally confirmed HER2 positivity defined as IHC 3+ or IHC 2+/ISH-positive. The study excluded patients with a history of ILD/pneumonitis requiring treatment with steroids or ILD/pneumonitis at screening, patients with a history of clinically significant cardiac disease, and patients with active brain metastases. Treatment was administered until disease progression, death, withdrawal of consent, or unacceptable toxicity. The primary efficacy outcome measure was unconfirmed ORR assessed by ICR based on RECIST v1.1. OS, PFS, DOR, and confirmed ORR were secondary outcome measures.

Demographic and baseline disease characteristics were similar between treatment arms. Of the 188 patients, the median age was 66 years (range 28 to 82); 76% were male; 100% were Asian. Patients had an ECOG performance status of either 0 (49%) or 1 (51%); 87% had gastric adenocarcinoma and 13% had GEJ adenocarcinoma; 76% were IHC 3+ and 23% were IHC 2+/ISH-positive; 65% had inoperable advanced cancer; 35% had postoperative recurrent cancer; 54% had liver metastases; 29% had lung metastases; 55% had two and 45% had three or more prior regimens in the locally advanced or metastatic setting.

At the time of the primary analysis (data cut-off: 8 November 2019), the study demonstrated a statistically significant and clinically meaningful improvement in ORR and OS in the Enhertu-treated group compared to the chemotherapy-treated group. Efficacy results (data cut-off: 3 June 2020) are summarized in Table 9.

Table 9: Efficacy Results in DESTINY-Gastric01 (Intent-to-Treat Analysis Set)

Efficacy Parameter	**Enhertu N=126**	**Physician's Choice of Chemotherapy N=62**
Confirmed Objective Response Rate (ORR)[§]		
n (%)	50 (39.7)	7 (11.3)
95% CI[¶]	(31.1, 48.8)	(4.7, 21.9)
p-value[‡,#,**]	p<0.0001	
Complete Response n (%)	10 (7.9)	0 (0.0)
Partial Response n (%)	40 (31.7)	7 (11.3)
Stable Disease n (%)	57 (45.2)	31 (50.0)
Progressive Disease n (%)	15 (11.9)	18 (29.0)
Not Evaluable n (%)	4 (3.2)	6 (9.7)
Overall Survival (OS)[*]		
Median, months (95% CI)[†]	12.5 (10.3, 15.2)	8.9 (6.4,10.4)

Efficacy Parameter	Enhertu N=126	Physician's Choice of Chemotherapy N=62
Hazard ratio (95% CI)‡	0.60 (0.42, 0.86)	
Stratified Log-rank p-value‡,**	p=0.0051	
Progression-free Survival (PFS)§		
Median, months (95% CI)†	5.6 (4.3, 6.9)	3.5 (2.0, 4.3)
Hazard ratio (95% CI)‡	0.47 (0.31, 0.71)	
Duration of Confirmed Response (DOR)§		
Median, months (95% CI)†	12.5 (5.6, NE)	3.9 (3.0, 4.9)

CI = confidence interval; NE = not estimable
§Assessed by independent central review
¶95% exact binomial confidence interval
‡Stratified by region
#Based on the Cochran-Mantel-Haenszel test
**Nominal p-value provided for descriptive purposes. Statistical significance was established at the primary analysis for OS (p=0.0097) and unconfirmed ORR (p<0.0001)
*OS was evaluated following a statistically significant outcome of ORR.
†Median based on Kaplan-Meier estimate; 95% CI for median calculated using Brookmeyer-Crowley method

Other Unresectable or Metastatic Solid Tumors

The efficacy and safety of Enhertu were evaluated in adult patients n=192 with previously treated unresectable or metastatic HER2-positive (IHC 3+) solid tumors who were enrolled in one of three Phase 2, multicenter, studies: DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02.

The studies excluded patients with a history of (non-infectious) ILD/pneumonitis requiring treatment with steroids, or patients with ILD/pneumonitis at screening, patients with untreated and symptomatic brain metastases, patients with a history of clinically significant cardiac disease or patients with an Eastern Cooperative Oncology Group (ECOG) performance status >1. Patients received Enhertu 5.4 mg/kg by intravenous infusion every three weeks. Treatment was administered until disease progression, death, withdrawal of consent, or unacceptable toxicity. In all three studies, the primary efficacy outcome measure was confirmed objective response rate (ORR). Secondary efficacy outcome measure was duration of response (DOR). All outcomes were assessed by independent central review (ICR) based on RECIST v1.1.

DESTINY-PanTumor02

DESTINY-PanTumor02 was a Phase 2, multicenter, open-label study that enrolled 267 adult patients with locally advanced, unresectable, or metastatic HER2-expressing (IHC3+, IHC2+) solid tumors

who have progressed following at least one prior systemic regimen or who have no satisfactory alternative treatment option.

Efficacy was assessed in the subgroup of patients (N=111) with centrally or locally confirmed HER2-positive (IHC3+) solid tumors.

Of the 111 patients in the HER2-positive (IHC3+) subgroup enrolled in DESTINY-PanTumor02, demographic and baseline disease characteristics were: median age 64 years (range 23 to 85); 59 % were female; 58 % were White, 34 % were Asian, and 4.0 % were Black or African American; 3% of patients were of Hispanic/Latino ethnicity. Patients had an ECOG performance status of either 0 (49 %) or 1 (51 %) at baseline. The median number of prior regimens was 2.

DESTINY-Lung01

DESTINY-Lung01 was a Phase 2, multicenter, open-label, 2-cohort study that enrolled 181 patients with previously treated, unresectable or metastatic, HER2-expressing (IHC3+ or IHC2+) or HER2-mutant non-small cell lung cancer (NSCLC).

Efficacy was assessed in the subgroup of patients (N=17) with HER2-positive (IHC3+) non-small cell lung cancer.

Of the 17 patients in the HER2-positive (IHC3+) subgroup, demographic and baseline disease characteristics were: median age 59 years (range 31 to 74); 58.8% were male; 64.7% were White, 17.6% were Asian, and 11.8% were Black or African American. Patients had an ECOG performance status of either 0 (11.8%) or 1 (88.2%) at baseline. The median number of prior regimens was 3.

DESTINY-CRC02

DESTINY-CRC02 was a Phase 2, multicenter, randomized, 2-arm study that enrolled 122 patients with previously treated, unresectable or metastatic HER2-expressing (IHC3+ or IHC2+/ISH+) colorectal cancer (CRC).

Efficacy was assessed in the subgroup of patients (N=64) with HER2-positive (IHC3+) CRC.

Of the 64 patients in the HER2-positive (IHC3+) subgroup, demographic and baseline disease characteristics were: median age 58 years (range 25 to 78); 53.1% were male; 54.7 % were Asian, and 40.6% were White. Patients had an ECOG performance status of either 0 (57.8%) or 1 (42.2%) at baseline. The median number of prior regimens was 4.

Efficacy results are summarized in Table 10 and Table 11.

Table 10: Efficacy Results in HER2-positive (IHC3+) Patients in DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02

Efficacy Parameter	DESTINY-PanTumor02 N=111	DESTINY-Lung01 N=17	DESTINY-CRC02 N=64
Confirmed Objective Response Rate†			
n (%)	57 (51.4)	9 (52.9)	30 (46.9)
95% CI‡	(41.7, 61.0)	(27.8, 77.0)	(34.3, 59.8)
Complete Response, n (%)	3 (2.7)	1 (5.9)	0 (0)
Partial Response, n (%)	54 (48.6)	8 (47.1)	30 (46.9)
Duration of Response			
Median§, months (95% CI)	19.4 (10.0, NE)	6.9 (4.0, 9.8)	5.5 (4.2, 8.1)

CI = Confidence interval

§Calculated using the Kaplan-Meier technique.

‡CI is derived based on the Brookmeyer-Crowley method.

Table 11: Efficacy Results in HER2-positive (IHC3+) Patients by Tumor Type in DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02

Tumor Type	Patients N	Confirmed ORR† % (95% CI) ‡	DOR Median§, months (95% CI) ‡
Colorectal cancer	64	46.9 (34.3, 59.8)	5.5 (4.2, 8.1)
Bladder cancer	27	37.0 (19.4, 57.6)	5.7 (4.1, 10.0)
Biliary tract cancer	22	45.5 (24.4, 67.8)	10.9 (2.1, NE)
NSCLC	17	52.9 (27.8, 77.0)	6.9 (4.0, 9.8)
Endometrial cancer	16	56.3 (29.9, 80.2)	NE (5.8, NE)
Ovarian cancer	15	66.7 (38.4, 88.2)	NE (5.1, NE)
Cervical cancer	10	70.0 (34.8, 93.3)	NE (9.3, NE)
Salivary gland cancer	9	66.7 (29.9, 92.5)	20.1 (5.6, 20.1)
Pancreatic cancer	5	0	NA
Oropharyngeal neoplasm	1	PR	15.3
Vulvar cancer	1	PR	2.6
Extramammary Paget's Disease	1	PR	19.4
Lacrimal Gland Cancer	1	PR	19.8+
Lip and/or Oral Cavity Cancer	1	SD	NA

Esophageal Adenocarcinoma	1	PR	2.8
Esophageal Squamous Cell Carcinoma	1	PD	NA

CI = Confidence interval, NE = Not estimable, NA = not applicable

PD=Progressive disease, PR=Partial response, SD=Stable disease

[†]Assessed by independent central review

[‡]CI is derived based on the Clopper-Pearson method

[§]Calculated using the Kaplan-Meier technique

+ Denotes ongoing response

Pharmacokinetics

At the recommended dosage of trastuzumab deruxtecan for patients with various types of cancer: breast cancer, gastric cancer, non-small cell lung cancer and various solid cancers, the geometric mean (coefficient of variation [CV]%) C_{max} of trastuzumab deruxtecan and DXd were 133 µg/mL (20%) and 4.9 ng/mL (52%), respectively, and the AUC of trastuzumab deruxtecan and DXd were 806 µg·day/mL (27%) and 31 ng·day/mL (55%), respectively, based on population pharmacokinetic analysis.

Moderate accumulation (approximately 35% in cycle 3 compared to cycle 1) of trastuzumab deruxtecan was observed.

Absorption

Trastuzumab deruxtecan is administered intravenously. There have been no studies performed with other routes of administration.

Distribution

Based on population pharmacokinetic analysis, the volume of distribution of the central compartment (Vc) of trastuzumab deruxtecan and topoisomerase I inhibitor, DXd, was estimated to be 2.68 L and 28.0 L, respectively.

In vitro, the mean human plasma protein binding of the topoisomerase I inhibitor, DXd, was approximately 97%.

In vitro, the blood to plasma concentration ratio of DXd was approximately 0.6.

Metabolism

Trastuzumab deruxtecan undergoes intracellular cleavage by lysosomal enzymes to release the DXd. The humanised HER2 IgG1 monoclonal antibody is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

In vitro metabolism studies in human liver microsomes indicate that DXd is metabolised mainly by CYP3A4 via oxidative pathways.

Elimination

Following intravenous administration of trastuzumab deruxtecan in patients with metastatic HER2-positive, HER2-low breast cancer or HER2-mutant NSCLC, the clearance of trastuzumab deruxtecan in population pharmacokinetic analysis was calculated to be 0.45 L/day and the clearance of DXd was 17.9 L/h.
In patients with locally advanced or metastatic gastric or GEJ adenocarcinoma, trastuzumab deruxtecan clearance was 20% higher than in patients with metastatic HER2-positive breast cancer.
In cycle 3, the apparent elimination half-life (t1/2) of trastuzumab deruxtecan and released DXd was approximately 7 days. Moderate accumulation (approximately 35% in cycle 3 compared to cycle 1) of trastuzumab deruxtecan was observed.
Following intravenous administration of DXd to rats, the major excretion pathway was faeces via the biliary route. DXd was the most abundant component in urine, faeces, and bile. Following single intravenous administration of trastuzumab deruxtecan (6.4 mg/kg) to monkeys, unchanged released DXd was the most abundant component in urine and faeces. DXd excretion was not studied in humans.

Linearity/non-linearity

The exposure of trastuzumab deruxtecan and released DXd when administered intravenously increased in proportion to dose in the 3.2 mg/kg to 8.0 mg/kg dose range (approximately 0.6 to 1.5 times the recommended dose) with low to moderate interindividual variability.

Special populations

Based on population pharmacokinetic analysis, race, ethnicity, sex and body weight (27.3-125.4 kg) did not have a clinically meaningful effect on exposure of trastuzumab deruxtecan or released DXd.

Elderly patients

The population pharmacokinetic analysis showed that age (range 20-96 years) did not affect the pharmacokinetics of trastuzumab deruxtecan.

Patients with renal impairment

No dedicated renal impairment study was conducted. Based on population pharmacokinetic analysis including patients with mild (creatinine clearance [CLcr] ≥60 and <90 mL/min) or moderate (CLcr ≥30 and <60 mL/min) renal impairment (estimated by Cockcroft-Gault), the pharmacokinetics of the released DXd was not affected by mild or moderate renal impairment as compared to normal renal function (CLcr ≥90 mL/min).

Patients with hepatic impairment

No dedicated hepatic impairment study was conducted. Based on population pharmacokinetic analysis, the impact of changes on pharmacokinetics of trastuzumab deruxtecan in patients with mild

(total bilirubin ≤ULN and any AST >ULN or total bilirubin >1 to 1.5 times ULN and any AST) or moderate (total bilirubin >1.5 to 3 times ULN and any AST) hepatic impairment is not clinically meaningful.

Children and adolescents

No studies have been conducted to investigate the pharmacokinetics of trastuzumab deruxtecan in children or adolescents.

Preclinical data

Safety Pharmacology

In telemetered male cynomolgus monkeys treated with a single intravenous dose of trastuzumab deruxtecan, no effects on the cardiovascular, respiratory, or central nervous systems were observed at dose levels up to 78.8 mg/kg.

Repeated Dose Toxicity

In a six-week repeat-dose toxicity study, up to 197 mg/kg of trastuzumab deruxtecan was administered to rats once every three weeks. Toxicities were observed in intestines, lymphatic/haematopoietic organs (thymus, lymph nodes, bone marrow), kidneys, skin, testes, and incisor teeth. All changes observed, except for kidney, testicular and incisor teeth changes, were reversible following a nine-week recovery period. The severely toxic dose in 10% of the rats (STD_{10}) was determined to be >197 mg/kg (approximately 31 times the clinical dose of 5.4 mg/kg based on AUC).
In a three-month repeat-dose toxicity study, trastuzumab deruxtecan was administered to monkeys once every three weeks at 3, 10, and 30 mg/kg. Toxicities were observed in intestines, testes, skin, bone marrow, kidneys, and lungs. Pulmonary toxicity was observed at the highest dose (30 mg/kg) and was histopathologically characterised by aggregation of foamy alveolar macrophages and focal alveolus and/or interstitial inflammation, which showed reversibility after a three-month recovery period. The highest non-severely toxic dose was determined to be 30 mg/kg (approximately 7 times the clinical dose of 5.4 mg/kg based on AUC).Changes observed in other organs, except for those in the skin and kidney, also showed reversibility or a trend toward reversibility by the end of a three-month recovery period.

Genotoxicity

The topoisomerase I inhibitor component of trastuzumab deruxtecan, DXd, was clastogenic in both an *in vivo* rat bone marrow micronucleus assay and an *in vitro* Chinese hamster lung chromosome aberration assay and was not mutagenic in an *in vitro* bacterial reverse mutation assay.

Carcinogenicity

Carcinogenicity studies have not been conducted with trastuzumab deruxtecan.

Reproductive toxicity

Dedicated fertility studies have not been conducted with trastuzumab deruxtecan. Based on results from general animal toxicity studies, trastuzumab deruxtecan may impair male reproductive function and fertility.
There were no animal reproductive or developmental toxicity studies conducted with trastuzumab deruxtecan. Based on results from general animal toxicity studies, trastuzumab deruxtecan and DXd were toxic to rapidly dividing cells (lymphatic/haematopoietic organs, intestine, or testes), and DXd was genotoxic, suggesting the potential for embryotoxicity and teratogenicity.

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.
Sodium chloride solution for infusion must not be used for reconstitution or dilution since it may cause particulate formation.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Shelf life after opening

Reconstituted solution
The reconstituted preparation is not preserved. It is recommended that the reconstituted solution be used immediately. If not used immediately, the reconstituted solution may be stored in a refrigerator at 2-8ºC for up to 24 hours from the time of reconstitution, protected from light.
Diluted solution
It is recommended that the diluted solution be used immediately. If not used immediately, the diluted solution may be stored at room temperature for up to 4 hours or in a refrigerator at 2-8ºC for up to 24 hours, protected from light. These storage times start from the time of reconstitution.

Special precautions for storage

Store in the refrigerator (2-8°C) until time of reconstitution.
Do not freeze.
Keep out of the reach of children.
For storage conditions after reconstitution and dilution of the medicinal product, see section “Other information”, “Shelf life after opening”.

Instructions and special precautions for handling and disposal

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.
Appropriate procedures for the preparation of chemotherapeutic medicinal products should be used.
Appropriate aseptic technique should be used for the following reconstitution and dilution procedures.

Reconstitution

- Reconstitute immediately before dilution.
- More than one vial may be needed for a full dose. Calculate the dose (mg), the total volume of reconstituted Enhertu solution required, and the number of vial(s) of Enhertu needed (see section “Dosage/Administration”).
- Reconstitute each 100 mg vial using a sterile syringe to slowly inject 5 mL of sterile water for injection into each vial to obtain a final concentration of 20 mg/mL.
- Swirl the vial gently until completely dissolved. Do not shake.
- If not used immediately, store the reconstituted Enhertu vials in a refrigerator at 2-8ºC for up to 24 hours from the time of reconstitution, protected from light. Do not freeze.
- The product does not contain a preservative. Discard unused Enhertu after 24 hours refrigerated.
- Dilution
- Withdraw the calculated amount from the vial(s) using a sterile syringe. Inspect the reconstituted solution for particulates and discoloration. The solution should be clear and colorless to light yellow. Do not use if visible particles are observed or if the solution is cloudy or discolored.
- Dilute the calculated volume of reconstituted Enhertu in an infusion bag containing 100 mL of 5% glucose solution. Do not use sodium chloride solution (see section “Other information”, “Incompatibilities”). An infusion bag made of polyvinylchloride or polyolefin (copolymer of ethylene and polypropylene) is recommended.
- Gently invert the infusion bag to thoroughly mix the solution. Do not shake.
- Cover the infusion bag to protect from light.
- If not used immediately, store at room temperature for up to 4 hours including preparation and infusion or in a refrigerator at 2-8ºC for up to 24 hours, protected from light. Do not freeze.
- Discard any unused portion left in the vial.

Administration

- If the prepared infusion solution was stored refrigerated (2-8ºC), it is recommended that the solution be allowed to equilibrate to room temperature prior to administration, protected from light.
- Administer Enhertu as an intravenous infusion only with a 0.20 or 0.22 micron in-line polyethersulfone (PES) or polysulfone (PS) filter. Do not administer as an intravenous push or bolus.

- Cover the infusion bag to protect from light.
- Do not mix Enhertu with other medicinal products or administer other medicinal products through the same intravenous line.

Disposal

The reconstituted product contains no preservative and is intended for single use only. Discard any unused portion left in the vial.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Authorisation number

67967 (Swissmedic)

Packs

Enhertu is provided in 10 mL Type 1 amber borosilicate glass vial sealed with a fluoro-resin laminated butyl rubber stopper, and a polypropylene/aluminium yellow flip-off crimp cap.

Pack containing 1 vial with 100 mg of trastuzumab deruxtecan (A)

Marketing authorisation holder

DAIICHI SANKYO (Schweiz) AG, Zürich

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