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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 approved on 14 September 2026

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
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BC	Breast cancer
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DCO	Data cut off
DDI	Drug-drug interaction
DFS	Disease free survival
DOR	Duration of response
EBC	Early breast cancer
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
HR	Hazard ratio
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
IDFS	Invasive disease-free survival
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NACT	Neoadjuvant chemotherapy
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
pCR	Pathological complete response
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics

PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
T-DM1	Trastuzumab emtansine
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.

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

Enertu is indicated for the treatment of adult patients with HER2-positive (IHC3+ or ISH+) breast cancer who have residual invasive disease after neoadjuvant HER2-targeted treatment.

2.2.2 Approved indication

HER2-positive early breast cancer (Early Breast Cancer, EBC)
Enhertu as a monotherapy is indicated for the adjuvant treatment of adult patients with HER2-positive (IHC3+ or ISH+) early breast cancer, who have residual invasive disease in breast and/or lymph nodes after neoadjuvant chemotherapy containing taxan in combination with at least trastuzumab as HER2 targeted treatment.

2.2.3 Requested dosage

Summary of the requested standard dosage:
5.4 mg / kg body weight as i.v. infusion given every 3 weeks (21-day cycle) for up to 14 cycles unless disease recurrence or unacceptable toxicity.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	05 February 2026
Formal control completed	06 February 2026
Preliminary decision	03 June 2026
Response to preliminary decision	02 July 2026
Labelling corrections and/or other aspects	23 July 2026
Response to labelling corrections and/or other aspects	23 August 2026
Final decision	14 September 2026
Decision	approval

3 Medical context

Breast cancer (BC) is the most common cancer in women and the leading cause of cancer death in women. Approximately 15-20% of invasive BCs overexpress HER2 due to gene amplification and are therefore classified as HER2-positive. These cancers show a more aggressive behaviour than HER2-negative BC (Chia et al. 2008, Gonzalez-Angulo et al. 2009, Slamon et al.1987). HER2-positive breast cancers carry a higher risk of recurrence and poorer survival outcomes compared to HER2-negative breast cancers without adequate treatment.

Adjuvant trastuzumab emtansine (T-DM1) is the standard treatment for HER2-positive early breast cancer (EBC) patients who do not achieve a pathological complete response (pCR) at surgery after neoadjuvant chemotherapy (NACT).

References:

Chia S, Norris B, Speers C, Cheang M, Gilks B, Gown AM, Huntsman D, Olivotto IA, Nielsen TO, Gelmon K. Human epidermal growth factor receptor 2 overexpression as a prognostic factor in a large tissue microarray series of node-negative breast cancers. J Clin Oncol. 2008 Nov 10;26(35):5697-704.

Gonzalez-Angulo AM, Litton JK, Broglio KR, Meric-Bernstam F, Rakkhit R, Cardoso F, Peintinger F, Hanrahan EO, Sahin A, Guray M, Larsimont D, Feoli F, Stranzl H, Buchholz TA, Valero V, Theriault R, Piccart-Gebhart M, Ravdin PM, Berry DA, Hortobagyi GH. High risk of recurrence for patients with breast cancer who have human epidermal growth factor receptor 2-positive, node-negative tumors 1 cm or smaller. J Clin Oncol. 2009 Nov 2;27(34):5700-6.

Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science. 1987 Jan 9;235(4785):177-82.

4 Nonclinical aspects

The applicant did not submit new nonclinical studies to support the requested extension of the indication. This was considered acceptable. Based on the ERA, the extension of the indication will not be associated with a significant risk for the environment.

5 Clinical aspects

5.1 Clinical pharmacology

The exposure in DESTINY-Breast05 was in line with the previously described exposure for a trastuzumab deruxtecan (T-DXd) dose of 5.4 mg/kg.

Immunogenicity was low, as previously described for T-DXd.

5.2 Efficacy

The DB-05 study is an ongoing phase III, randomised open-label study to assess treatment with T-DXd as compared with T-DM1 in patients with HER2-positive breast cancer with residual invasive disease and node-positive disease at surgery or inoperable disease at diagnosis.

The control arm with T-DM1 is in line with recommendations of internationally accepted guidelines and approved in this setting in Switzerland.

Eligible patients had residual invasive disease in the breast or axillary lymph nodes after neoadjuvant therapy with high-risk characteristics defined as inoperable disease at presentation (tumour stage T4, nodal stage N0 to N3, and metastasis stage M0 or tumour stage T1 to T3, nodal stage N2 or N3, and metastasis stage M0 before neoadjuvant therapy) or operable disease (tumour stage T1 to T3, nodal stage N0 or N1, and metastasis stage M0) before neoadjuvant therapy with axillary node–positive disease (pathological stage of ypN1 to ypN3) after neoadjuvant therapy. All the patients completed neoadjuvant systemic therapy, including taxane-based chemotherapy and HER2-directed treatment (≥9 weeks of trastuzumab [with or without pertuzumab] and ≥9 weeks of taxane-based chemotherapy. For further details please refer to the Information for healthcare professionals.

The primary endpoint was invasive disease-free survival (IDFS) by investigator assessment.

The evidence in the literature presents a moderate correlation between IDFS and overall survival (OS) in metastatic breast cancer in a first-line or subsequent line treatment setting, particularly in HER2-positive patients and in patients treated with targeted therapy (Liu 2016; Michiels 2016; Petrelli 2014). Therefore, IDFS was evaluated in conjunction with OS.

The key secondary endpoint was disease-free survival (DFS). A further relevant secondary endpoint was OS, which was not controlled for multiplicity testing and was therefore descriptive.

At the data cutoff (DCO July 2, 2025), the median duration of follow-up was 29.9 months with T-DXd and 29.7 months with T-DM1. At this interim analysis, 153 invasive-disease events or deaths had been reported: 51 (6.2%) in the T-DXd group and 102 (12.5%) in the T-DM1 group. The IDFS was statistically significant and clinically relevant with a hazard ratio of 0.47 (CI95%, 0.34 - 0.66; p<0.0001), and the 3-year IDFS was 92.4% with T-DXd and 83.7% with T-DM1.

A statistically significant difference was also observed in the key secondary endpoint DFS in favour of the T-DXd arm compared to T-DM1, with an HR of 0.47 (CI95% 0.34 – 0.66), p<0.0001.

Data for overall survival (OS) are immature (2.9% death rate), with 18 deaths (2.2%) in the T-DXd group and 29 (3.5%) in the T-DM1 group. The OS curves are overlapping during the whole observation period, and interpretation is limited by the high amount of censoring. However, no detriment was observed for T-DXd compared to T-DM1.

An additional OS analysis is planned when approximately 207 IDFS events have occurred, anticipated in Q4 2026. At this analysis, the median follow-up is expected to be approximately 4 years. The final OS analysis is planned in 2028 after a median follow-up of approximately 6 years.

5.3 Safety

The most common treatment-emergent adverse events (TEAEs) in the T-DXd arm (≥20%) in study DB-05 were nausea, fatigue, neutropenia, leukopenia, constipation, vomiting, transaminases increased, anaemia, radiation pneumonitis, thrombocytopenia, diarrhoea, musculoskeletal pain, and decreased appetite.

The most common TEAEs ≥Grade 3 in the T-DXd arm (≥5%) were neutropenia, leukopenia, lymphopenia, thrombocytopenia, and fatigue.

No new safety signals were observed, and the safety is in line with the already known safety profile of T-DXd. For details please refer to the Information for healthcare professionals.

5.4 Final clinical benefit risk assessment

The DB-05 study met its primary endpoint and showed a statistically and clinically meaningful improvement in terms of IDFS for T-DXd compared to T-DM1.
OS data were still immature at the time of DCO, and the OS Kaplan-Meier curves overlapped throughout the observation period. However, no detriment is visible for T-DXd in comparison to T-DM1.

The safety profile is consistent with the known safety profile of T-DXd. and no new safety signals were observed.

In summary the benefit-risk was evaluated as positive.

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-pro.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”).

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

Trastuzumab deruxtecan 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 early breast cancer (EBC)

Enhertu as monotherapy is indicated for adjuvant treatment of adult patients with HER2-positive (IHC3+ or ISH+) early breast cancer who have residual invasive disease in the breast and/or the lymph nodes after neoadjuvant taxane-based chemotherapy in combination with at least trastuzumab as HER2 targeted treatment.

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 and HER2-ultralow breast cancer

Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic

- hormone receptor (HR)-positive, HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining) breast cancer whose disease in the metastatic setting has progressed under one or more endocrine therapies and for whom a further endocrine therapy in the next line of therapy is not an option (see section “Properties/ Effects”).
- 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”).

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.

Indication with temporary authorisation

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.

HER2-positive breast cancer

Enhertu in combination with pertuzumab is indicated for the first-line treatment of adult patients with unresectable or metastatic HER2-positive (IHC3+ or ISH+) breast cancer.

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

Patient Selection for HER2-positive Metastatic Breast Cancer

Select patients for treatment of unresectable or metastatic HER2-positive breast cancer with Enhertu or Enhertu in combination with pertuzumab based on confirmed HER2-positive status (IHC 3+ or ISH+) as assessed by a validated test.

Patient selection for HER2-low or HER2-ultralow metastatic breast cancer

Select patients for treatment of unresectable or metastatic HER2-low breast cancer based on IHC 1+ or IHC 2+/ISH-, or HER2-ultralow breast cancer based on IHC 0 with membrane staining (IHC > 0 < 1 +) 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 tumor 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 highly emetogenic (see section “Undesirable Effects”), which includes delayed nausea and/or vomiting. Prior to each dose of Enhertu, patients should 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.

Table 1: Recommended Dosage:

Indication	**Recommended Enhertu Dosage**	**Duration of Treatment**
Monotherapy		
Early Breast Cancer - Post Neoadjuvant Treatment	5.4 mg/kg body weight given every 3 weeks (21-day cycle) as an intravenous infusion	14 cycles unless disease recurrence or unacceptable toxicity
Metastatic Breast Cancer and Other Metastatic Solid Tumors.	5.4 mg/kg body weight given every 3 weeks (21-day cycle) as an intravenous infusion	Until disease progression or unacceptable toxicity
Locally Advanced or Metastatic Gastric Cancer	6.4 mg/kg body weight given every 3 weeks (21-day cycle) as an intravenous infusion	Until disease progression or unacceptable toxicity
In Combination		
HER2-Positive Metastatic Breast Cancer in combination with pertuzumab	Cycle 1, Day 1: Enhertu 5.4 mg/kg, followed by pertuzumab 840 mg[a] Subsequent cycles, Day 1: Enhertu 5.4 mg/kg, followed by pertuzumab 420 mg every 3 weeks (21-day cycle)[a]	Until disease progression or unacceptable toxicity

[a] Administer pertuzumab 30 minutes after Enhertu.

Dose modifications

Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of Enhertu per guidelines provided in Tables 2 and 3.
Enhertu dose should not be re-escalated after a dose reduction is made.

Enhertu in Combination with Pertuzumab

When withholding, modifying, or discontinuing Enhertu refer to Table 3. Pertuzumab dose modifications should be managed according to the pertuzumab prescribing information. Pertuzumab is not to be administered as a single agent.

Table 2: 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 3: Dose modifications for adverse reactions

Adverse reaction	Severity	Treatment modification
Interstitial lung disease (ILD)/pneumonitis *(for radiotherapy-related pneumonitis see below)*	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 2). • consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (see section “Warnings and precautions”).
	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 2).

Adverse reaction	Severity		Treatment modification
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 2).
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.
	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).

Dose modifications for radiotherapy-related pneumonitis in the post neoadjuvant early breast cancer setting

If patients develop radiotherapy-related pneumonitis following sequential or concurrent adjuvant radiation therapy, the Enhertu dose should be adjusted as follows:

- Grade 1 (asymptomatic): Continue treatment with Enhertu
- Grade 2 (symptomatic): Interrupt Enhertu until recovered to baseline or Grade ≤ 1. Manage per standard of care.
- Grade 3 or 4 (symptomatic, severe or life threatening): Permanently discontinue Enhertu. Manage per standard of care.

The relationship to radiotherapy should be confirmed. If drug-related ILD/pneumonitis is suspected, see Interstitial Lung Disease (ILD)/Pneumonitis section above.

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 to 10 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 or Enhertu in combination with pertuzumab (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 3 (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”).

In the post neoadjuvant early breast cancer setting, radiotherapy related pneumonitis can occur among those treated with radiotherapy (see section “Dosage/Administration” and “Undesirable effects”).

Neutropenia

Cases of neutropenia, including febrile neutropenia with a fatal outcome, were reported in clinical studies of Enhertu or Enhertu in combination with pertuzumab. 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 dysfunction

Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies. LVEF should be assessed prior to initiation of Enhertu or Enhertu in combination with pertuzumab 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

Enhertu in combination with pertuzumab

The effect of the concomitant use of trastuzumab deruxtecan on pertuzumab has been investigated. No pharmacokinetic interactions were observed between the two medicinal products.

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.
In vitro metabolism studies in human liver microsomes indicate that DXd is metabolised mainly by CYP3A4 via oxidative pathways and does not undergo significant metabolism by UGT or other CYP enzymes. In clinical studies, 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

Enhertu as Monotherapy

The pooled safety population has been evaluated for patients who received at least one dose of Enhertu 5.4 mg/kg and above (n = 5306) across multiple tumor types in clinical studies. The median duration of treatment in this pool was 8.5 months (range: 0.1 to 76.0 months).

- The most common adverse reactions were nausea (69.1%), fatigue (56.0%), neutropenia (39.1%), anaemia (36.2%), vomiting (35.1%), constipation (32.0%), decreased appetite (31.0%), alopecia (30.9%), diarrhoea (29.5%), transaminases increased (27.6%), musculoskeletal pain (25.4%), leukopenia (25.2%) and thrombocytopenia (25.0%).
- The most common serious adverse reactions were ILD/pneumonitis (3.4%), pneumonia (1.9%), anaemia (1.5%), vomiting (1.3%), thrombocytopenia (1.1%), nausea (1.1%), fatigue (0.9%) and decreased appetite (0.7%)..

- 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 (20.9%), anaemia (11.3%), fatigue (7.8%), leukopenia (7.8%), thrombocytopenia (6.6%), lymphopenia (5.1%), nausea (4.8%), hypokalaemia (3.7%), transaminases increased (3.4%), decreased appetite (2.2%), vomiting (2.1%), diarrhoea (2.1%), pneumonia (1.6%), febrile neutropenia (1.1%), ejection fraction decreased (0.9%), abdominal pain (0.9%), ILD/pneumonitis (0.8%), musculoskeletal pain (0.8%), weight decreased (0.8%) and blood bilirubin increased (0.7%). Grade 5 adverse reactions occurred in 1.2% of patients, including ILD (1.0%).
- Dose interruptions due to adverse reactions occurred in 34.9% of patients treated with Enhertu. The most frequent adverse reactions associated with dose interruption were neutropenia (13.2%), anaemia (4.9%), fatigue (4.6%), leukopenia (3.7%), upper respiratory tract infection (3.5%), ILD (3.0%), thrombocytopenia (3.0%), and pneumonia (2.4%).
- Dose reductions occurred in 22.7% of patients treated with Enhertu. The most frequent adverse reactions associated with dose reduction were fatigue (6.2%), nausea (5.1%), neutropenia (4.0%), thrombocytopenia (2.6%), and decreased appetite (1.7%).
- Discontinuation of therapy due to an adverse reaction occurred in 11.2% of patients treated with Enhertu. The most frequent adverse reactions associated with permanent discontinuation was ILD/pneumonitis (8.3%).

Enhertu in Combination with Pertuzumab

The pooled safety population has been evaluated for patients who received at least one dose of Enhertu 5.4 mg/kg in combination with pertuzumab in a pooled analysis of 431 patients with unresectable or metastatic breast cancer in DESTINY-Breast07 (n=50) and DESTINY-Breast09 (n=381). The median duration of treatment was 21.95 months (range: 0.3 to 44.5 months).

- The most common adverse reactions were nausea (74.2%), diarrhoea (64.0%), fatigue (53.4%), neutropenia (49.0%), alopecia (47.8%), vomiting (45.7%), anaemia (40.4%), transaminases increased (38.7%), upper respiratory tract infection (32.0%), constipation (31.3%), decreased appetite (31.3%), leukopenia (29.7%), decreased weight (28.1%), hypokalaemia (26.7%), thrombocytopenia (25.8%) ejection fraction decreased (25.3%), musculoskeletal pain (23.0%), abdominal pain (22.3%).
- The most common serious adverse reactions were ILD/pneumonitis (2.3%) diarrhoea (2.1%), hypokalaemia (1.9%), febrile neutropenia (1.6%), vomiting (1.2%), upper respiratory tract infection (1.2%), neutropenia (0.9%) and thrombocytopenia (0.9%).
- The most common NCI-CTCAE v.5.0 Grade 3 or 4 adverse reactions were neutropenia (24.8%), hypokalaemia (13.2%), anaemia (10.7%), diarrhoea (7.4%), fatigue (7.2%), thrombocytopenia (7.0%), transaminases increased (5.3%), leukopenia (5.1%), nausea (4.9%), lymphopenia (3.9%), ejection fraction decreased (3.2%), decreased weight (2.8%), febrile neutropenia (2.3%) decreased appetite (2.1%), vomiting (2.1%), upper respiratory tract infection (1.6%), and stomatitis

(1.2%). Grade 5 adverse reactions occurred in 0.9% of patients, including ILD/pneumonitis (0.5%), febrile neutropenia (0.2%) and dyspnoea (0.2%).

- Dose interruptions due to adverse reactions occurred in 53.4% of patients treated with Enhertu 5.4 mg/kg in combination with pertuzumab. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia (15.5%), upper respiratory tract infection (12.3%), anaemia (7.2%), fatigue (7.2%), ILD (6.5%), hypokalaemia (6.3%), diarrhoea (5.8%), thrombocytopenia (5.3%), leukopenia (3.9%), increased transaminases (3.7%), cough (2.6%), increased blood bilirubin (2.3%), decreased appetite (2.1%), pyrexia (2.1%) and vomiting (2.1%).
- Dose reductions occurred in 38.3% of patients treated with Enhertu 5.4 mg/kg in combination with pertuzumab. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue (11.6%), neutropenia (7.4%), nausea (6.5%), diarrhoea (6.0%), ILD (3.2%), thrombocytopenia (3.2%), vomiting (3.0%), increased transaminases (2.8%), decreased weight (2.3%) and febrile neutropenia (2.1%).
- The permanent discontinuation of any drug due to an adverse reaction occurred in 15.3% of patients treated with Enhertu 5.4 mg/kg in combination with pertuzumab. The most frequent adverse reaction (>2%) associated with permanent discontinuation was ILD (6.0%).

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 4. 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 4: Adverse reactions in patients treated with trastuzumab deruxtecan 5.4 mg/kg and above in multiple tumor types

System organ class/preferred term or grouped term	**Any Grade (%)***		**Grade 3-4 (%)***
Infections and infestations			
Upper respiratory tract infection[a]	Very common	17.3	0.3
Pneumonia	Common	-	-
Blood and lymphatic system disorders			
Neutropenia[b]	Very common	39.1	20.9
Anaemia[c]	Very common	36.2	11.3

System organ class/preferred term or grouped term	Any Grade (%)*		Grade 3-4 (%)*
Leukopenia[d]	Very common	25.2	7.8
Thrombocytopenia[e]	Very common	25.0	6.6
Lymphopenia[f]	Very common	11.0	5.1
Febrile neutropenia	Common	-	-
Metabolism and nutrition disorders			
Decreased appetite	Very common	31.0	2.2
Hypokalaemia[g]	Very common	11.5	3.7
Dehydration	Common	-	-
Nervous system disorders			
Headache[h]	Very common	15.0	0.3
Peripheral neuropathy[i]	Common	-	-
Dizziness	Common	-	-
Dysgeusia	Common	-	-
Eye disorders			
Dry eye	Common	-	-
Vision blurred[j]	Common	-	-
Cardiac disorders			
Ejection fraction decreased[k]	Very common	13.5	0.9
Respiratory, thoracic and mediastinal disorders			
Cough	Very common	14.5	0.1
Interstitial lung disease[l]	Very common	12.4	0.8
Dyspnoea	Common	-	-
Epistaxis	Common	-	-
Gastrointestinal disorders			
Nausea	Very common	69.1	4.8
Vomiting	Very common	35.1	2.1

System organ class/preferred term or grouped term	Any Grade (%)*		Grade 3-4 (%)*
Constipation	Very common	32.0	0.4
Diarrhoea	Very common	29.5	2.1
Abdominal pain[m]	Very common	17.6	0.9
Stomatitis[n]	Very common	13.0	0.5
Dyspepsia	Common	-	-
Abdominal distension	Common	-	-
Flatulence	Common	-	-
Gastritis	Common	-	-
Hepatobiliary disorders			
Transaminases increased[o]	Very common	27.7	3.4
Blood alkaline phosphatase increased	Common	-	-
Blood bilirubin increased[p]	Common	-	-
Skin and subcutaneous tissue disorders			
Alopecia	Very common	30.9	0.1
Rash[q]	Common	-	-
Pruritus	Common	-	-
Skin hyperpigmentation[r]	Common	-	-
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain[s]	Very Common	25.4	0.8
Renal and urinary disorders			
Blood creatinine increased	Common	-	-
General disorders and administration site conditions			
Fatigue[t]	Very common	56.0	7.8
Pyrexia	Very common	13.5	0.3
Weight decreased	Very common	13.4	0.8

System organ class/preferred term or grouped term	Any Grade (%)*		Grade 3-4 (%)*
Oedema peripheral	Common	-	-
Injury, poisoning and procedural complications			
Radiation pneumonitis[u]	Very common**	31.4	0
Infusion-related reactions[v]	Uncommon	-	-

*% grade values for common and uncommon frequencies are not applicable.

** radiation pneumonitis was observed with the use of adjuvant radiotherapy in the post neoadjuvant early breast cancer setting (N=757).

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

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

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

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

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

[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 and PTs of Cardiac failure, Cardiac failure acute, Cardiac failure chronic, Cardiac failure congestive, Ejection fraction decreased, Left ventricular dysfunction.

[l] Interstitial lung disease (grouped term) includes PTs of Acute respiratory failure, Alveolitis, Atypical pneumonia, Bronchiectasis, Bronchitis, Bronchitis chronic, COVID-19 pneumonia, Hypersensitivity pneumonitis, Idiopathic interstitial pneumonia, Interstitial lung disease, Lower respiratory tract infection, Lung disorder, Lung infiltration, Lung opacity, Lymphangitis, Organising pneumonia, Pneumocystis jirovecii pneumonia, Pneumonia, Pneumonia bacterial, Pneumonia fungal, Pneumonitis, Pulmonary fibrosis, Pulmonary mass, Pulmonary toxicity, Radiation fibrosis – lung, Radiation pneumonitis, Respiratory failure. These events were adjudicated as drug-related ILD for T-DXd. Some studies did not have adjudication and were excluded for ILD grouped term. The number of patients in the All Tumor Types Pool T-DXd >=5.4 mg/kg for ILD Grouped Term were 3713.

[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 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, Hypertransaminasaemia, 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 Arthralgia, 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] In post neoadjuvant early breast cancer setting with T-DXd 5.4 mg/kg and adjuvant radiotherapy, Radiation pneumonitis (grouped term) includes PTs of Pulmonary radiation injury, Radiation fibrosis-lung, Radiation pneumonitis.

[v] Infusion related reaction (grouped term) includes PTs of Hypersensitivity, Infusion related reaction.

Table 5: Adverse reactions in patients treated with trastuzumab deruxtecan in combination with Pertuzumab

System organ class/preferred term or grouped term	Any Grade (%)*		Grade 3-4 (%)*
Infections and infestation			
Upper respiratory tract infection[a]	Very common	32.0	1.6
Blood and lymphatic system disorders			
Neutropenia[b]	Very common	49.0	24.8
Anaemia[c]	Very common	40.4	10.7
Leukopenenia[d]	Very common	29.7	5.1
Thrombocytopenia[e]	Very common	25.8	7.0
Lymphopenia[f]	Very common	12.8	3.9
Febrile neutropenia	Common	-	-
Metabolism and nutrition disorders			
Decreased appetite	Very common	31.3	2.1
Hypokalaemia[g]	Very common	26.7	13.2

System organ class/preferred term or grouped term	Any Grade (%)*		Grade 3-4 (%)*
Dehydration	Common	-	-
Nervous system disorders			
Headache[h]	Very common	19.0	0.2
Peripheral neuropathy[i]	Very common	14.8	0
Dizziness	Very common	12.5	0.2
Dysgeusia	Very common	11.8	0
Eye disorders			
Dry eye	Very common	10.4	0
Vision blurred[j]	Common	-	-
Cardiac disorders			
Ejection fraction decreased[k]	Very common	25.3	3.2
Respiratory, thoracic and mediastinal disorders			
Cough	Very common	16.0	0.2
Interstitial lung disease[l]	Very common	12.3	0.2
Dyspnoea	Common	-	-
Epistaxis	Common	-	-
Gastrointestinal disorders			
Nausea	Very common	74.2	4.9
Diarrhoea	Very common	64.0	7.4
Vomiting	Very common	45.7	2.1
Constipation	Very common	31.3	0.2
Abdominal pain[m]	Very common	22.3	0.2
Stomatitis[n]	Very common	17.4	1.2
Dyspepsia	Very common	11.8	0
Abdominal distension	Common	-	-
Flatulence	Common	-	-

System organ class/preferred term or grouped term	Any Grade (%)*		Grade 3-4 (%)*
Gastritis	Common	-	-
Hepatobiliary disorders			
Transaminases increased[o]	Very common	38.7	5.3
Blood alkaline phosphatase increased	Very common	11.1	0.2
Blood bilirubin increased[p]	Common	-	-
Skin and subcutaneous tissue disorders			
Alopecia	Very common	47.8	0
Rash[q]	Very common	16.5	0.5
Pruritus	Very common	10.7	0.2
Skin hyperpigmentation[r]	Common	-	-
Dry skin	Common	-	-
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain[s]	Very Common	23.0	0.9
Renal and urinary disorders			
Blood creatinine increased	Common	-	-
General disorders and administration site conditions			
Fatigue[t]	Very common	53.4	7.2
Weight decreased	Very common	28.1	2.8
Pyrexia	Very common	15.1	0
Mucosal inflammation	Common	-	-
Injury, poisoning and procedural complications			
Infusion-related reactions[u]	Common	-	-

*% grade values for common frequency are not applicable

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

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

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

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

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

[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.

[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 and PTs of Cardiac failure, Cardiac failure chronic Ejection fraction decreased, Left ventricular dysfunction.

[l] Interstitial lung disease (grouped term) includes PTs of Chronic obstructive pulmonary disease, Interstitial lung disease, Organising pneumonia, Pneumonia, Pneumonitis. These events were adjudicated as ILD and related to use of 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 mucosal eruption.

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

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

[u] Infusion related reaction (grouped term) includes PTs of Infusion related reaction.

Description of selected undesirable effects

Interstitial lung disease/pneumonitis

Enhertu as Monotherapy

In clinical studies across multiple tumor types (n = 4802), ILD occurred in 12.4% of patients treated with Enhertu 5.4 mg/kg and above. Median time to first onset was 4.2 months (range: -0.5 to 40.2).

Most ILD cases were Grade 1 (2.9%) and Grade 2 (7.7%). Grade 3 cases occurred in 0.8% of patients. One Grade 4 case and 46 Grade 5 events occurred (1.0%).
In clinical studies with patients treated with Enhertu 5.4 mg/kg and above across multiple tumor types, the incidence of ILD with moderate renal impairment (18.6%) was higher compared to patients with normal renal function (11.3%).

Radiotherapy-Related Pneumonitis and skin injury in the Post Neoadjuvant Early Breast Cancer Setting

Patients receiving adjuvant radiotherapy also underwent regular chest CT screening at specified intervals (see Section “Clinical Efficacy DESTINY-Breast05”). Among Patients receiving sequential or concurrent adjuvant radiotherapy (ART) in DESTINY-Breast05, radiation pneumonitis occurred in 31.4% of patients receiving Enhertu 5.4 mg/kg (N=757). All cases of patients receiving Enhertu and adjuvant radiotherapy were either Grade 1 (26.6%) or Grade 2 (4.9%).
The incidence of radiotherapy-related pneumonitis with Enhertu 5.4 mg/kg was higher in patients who received sequential ART compared with those who received concurrent ART (34% vs. 29%). The median time to first occurrence was 4.1 months (range: 1.3 – 11.6 months).
Among patients receiving ART and Enhertu, radiation skin injury occurred in 20.1% of all patients, of which 1.6% were Grade 3 and none were Grade 4.

Enhertu in combination with Pertuzumab

In patients treated with Enhertu 5.4 mg/kg in combination with pertuzumab (n=431), ILD occurred in 12.3% of patients. Median time to first onset was 8.0 months (range: 0.6 to 33.8). ILD cases were Grade 1 (3.9%), Grade 2 (7.7%) and Grade 3 (0.2%). No Grade 4 cases occurred. Grade 5 events occurred in 0.5% of patients.

Neutropenia

Enhertu as Monotherapy

In clinical studies (n= 5306) across multiple tumor types in patients treated with Enhertu 5.4 mg/kg and above, neutropenia was reported in 39.1% of patients and 20.9% 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 1.2% of patients and 0.04% were Grade 5 (see section “Warnings and precautions”).

Enhertu in combination with Pertuzumab

In patients treated with Enhertu 5.4 mg/kg in combination with pertuzumab (n=431), Neutropenia occurred in 49% of patients. Median time to first onset was 42 days (range: 1 day to 36.8 months) and median duration of the first event was 20 days (range: 1 day to 27.6 months). Neutropenia cases were Grade 1 (6.3%) and Grade 2 (17.9%). Grade 3 cases occurred in (19.3%) and Grade 4 cases occurred in (5.6%). Febrile neutropenia was reported in 2.6% of patients and 0.2 % were Grade 5

(see section “dosage/administration”). There were two Grade 5 cases of sepsis, one of which was associated with neutropenia.

Left ventricular dysfunction

Enhertu as Monotherapy

In 5306 patients, across multiple tumor types in clinical studies who received Enhertu 5.4 mg/kg and above, LVEF decreased was reported in 234 patients (4.4%), of which 19 (0.4%) were Grade 1, 189 (3.6%) were Grade 2, 25 (0.5 %) were Grade 3, and 1 case was Grade 4. The observed frequency of LVEF decreased based on laboratory parameters (echocardiogram or multigated acquisition [MUGA] scanning) was 656/4734 (13.9%) for Grade 2, and 38/4734 (0.8%) for Grade 3. Treatment with Enhertu has not been studied in patients with LVEF less than 50 % prior to initiation of treatment.
In study DESTINY-Breast06, adverse reactions of LVEF decreased were reported in 9.0 % of all Enhertu-treated patients (n = 434) with 1 patient (0.2 %) showing grade 1, 34 (7.8 %) grade 2 and 4 (0.9 %) grade 3. However, the observed incidence of LVEF decreased as determined by echocardiogram or MUGA scan was 63/396 (15.9%) for grade 2 and 3/396 (0.8%) for grade 3.

Enhertu in combination with Pertuzumab

In patients treated with Enhertu 5.4 mg/kg in combination with pertuzumab (n=431), LVEF decrease was reported in 46 patients (10.7%), of which 14 (0.9%) were Grade 1, 33 (7.7%) were Grade 2, 8 (1.9%) were Grade 3, 1 (0.2%) Grade 4.

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

Enhertu as Monotherapy

Of the 5306 patients across multiple tumor types in clinical studies treated with Enhertu 5.4 mg/kg and above, 26.5% were 65 years or older and 5.2% were 75 years or older. The incidence of Grade 3-4 adverse reactions was 51.3% in patients 65 years or older and 46.3% in younger patients.

Enhertu in Combination with Pertuzumab

In patients treated with Enhertu 5.4 mg/kg in combination with pertuzumab (n=431), 17.4% were 65 years or older and 3.0% were 75 years or older. The incidence of Grade 3-4 adverse reactions observed in patients aged 65 years or older was 52% and in younger patients was 55.6%.

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 tumor 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-Breast05

The efficacy and safety of Enhertu were evaluated in DESTINY-Breast05, a Phase III, randomized, multicenter, open-label study that enrolled 1635 adult patients with HER2-positive breast cancer with

residual invasive disease following neoadjuvant therapy. HER2-positivity (IHC3+ or ISH+) was determined by the PATHWAY/VENTANA anti-HER2/neu (4B5) and the VENTANA HER2 Dual ISH DNA Probe Cocktail at a central laboratory.
Patients were eligible if they had HER2-positive breast cancer with residual invasive disease following neoadjuvant therapy and at least one high risk criteria: inoperable at disease presentation (clinical stages T4, N0-3, M0 or T1-3, N2-3, M0) with residual invasive disease in the breast or axillary lymph nodes or operable at disease presentation (clinical stages T1-3, N0-1, M0) with positive pathological node status (ypN1-3) after neoadjuvant therapy. The completed prior neoadjuvant systemic therapy included a treatment with trastuzumab (with or without pertuzumab) and taxane-based chemotherapy over at least 9 weeks each. The time interval between the date of the last surgical procedure and randomization was no more than 12 weeks.

The study excluded patients who have had history of ILD/pneumonitis requiring treatment with steroids or ILD/pneumonitis at screening or ECOG performance status >1.

Patients received concurrent or sequential adjuvant radiotherapy as per investigator discretion and hormonal therapy as per local guidelines. In addition to all patients receiving computed tomography (CT) scans of the chest at screening, patients receiving radiotherapy also received regular CT scans of the chest during treatment period, and after end of treatment.

Patients were randomized 1:1 to receive either 14 cycles of Enhertu 5.4 mg/kg (N=818) by intravenous infusion every three weeks or 14 cycles of trastuzumab emtansine (T-DM1) (N=817) 3.6 mg/kg by intravenous infusion every three weeks. Patients were stratified by operative status at disease presentation (operable, inoperable), Post neoadjuvant pathological nodal status (*positive, negative*), tumor hormone receptor status (*positive, negative*), and HER2-targeted neoadjuvant therapy (*single, dual*). Treatment with Enhertu was administered for a maximum of 14 cycles or until disease recurrence, death, or unacceptable toxicity.

The primary efficacy outcome measure was invasive disease-free survival (IDFS), defined as the time from randomization to first occurrence of ipsilateral local or regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, or death from any cause. Key secondary efficacy endpoints measure were disease-free survival (DFS) and overall survival (OS).

The study population characteristics for patients were median age of 50.5 years (range: 21 to 83), 10.0% age 65 or older; 99.6% female; 38.8% White, 48.0% Asian, and 2.1% Black. Tumour characteristics were: 71.2% had HR+ status and 28.8% had HR- status; 52.3% had inoperable tumours at disease presentation (T4, N0-3, M0 or T1-3, N2-3, M0); 80.6% had post neoadjuvant

pathological nodal status (ypN1-3). Neoadjuvant treatment characteristics were: 21.2% of patients received singe HER2-targeted neoadjuvant therapy; 78.8% received dual HER2-targeted neoadjuvant therapy; 50.3% of patients received anthracyclines and 100% received taxanes as part of neoadjuvant regimen. Characteristics of adjuvant radiotherapy were: 37.0% of patients received sequential adjuvant radiotherapy, 56.1% of patients received concurrent adjuvant RT.

Efficacy results are summarised in Table 6.

Table 6. Efficacy Results in DESTINY-Breast05

Efficacy Parameter	**Enhertu (5.4 mg/kg) N=818**	**Trastuzumab emtansine (3.6 mg/kg) N=817**
Invasive Disease-Free Survival (IDFS)		
Number of events (%)	51 (6.2)	102 (12.5)
3-year event free rate, % (95% CI)	92.4 (89.7, 94.4)	83.7 (80.2, 86.7)
Hazard ratio (95% CI)	0.47 (0.34, 0.66)	
p-value[a]	p<0.0001	
Disease-Free Survival (DFS)		
Number of events (%)	52 (6.4)	103 (12.6)
3-year event free rate, % (95% CI)	92.3 (89.5, 94.3)	83.5 (79.9, 86.4)
Hazard ratio (95% CI)	0.47 (0.34, 0.66)	
p-value[b]	p<0.0001	
Overall Survival (OS)		
Number of events (%)	18 (2.2)	29 (3.5)
Hazard ratio (95% CI)	0.61 (0.34, 1.10)	

[a] Two-sided p-value is based on a stratified log-rank test; crossed the efficacy boundary of 0.0183.

[b] Two-sided p-value is based on a stratified log-rank test; crossed the efficacy boundary of 0.0144.

Metastatic Breast Cancer

DESTINY-Breast09

The efficacy and safety of Enhertu in combination with pertuzumab were evaluated in DESTINY-Breast09, a Phase III, randomized, three-arm, multicenter, global study that enrolled 1157 adult patients with HER2-positive (IHC 3+ or ISH+) advanced, or metastatic breast cancer (as determined at a central laboratory using PATHWAY/VENTANA anti-HER-2/neu (4B5) and VENTANA HER2 Dual ISH DNA Probe Cocktail).

The study included adult patients with unresectable or metastatic HER2-positive breast cancer who had not received prior chemotherapy or HER2-targeted therapy for advanced or metastatic breast cancer. Patients were eligible if they (a) had *de novo* metastatic breast cancer disease or (b) had received neoadjuvant or adjuvant chemotherapy and/or HER2-targeted therapy which was completed more than 6 months before the diagnosis of advanced or metastatic disease. A single line of prior endocrine therapy was permitted for advanced or metastatic breast cancer. The study excluded patients with a history of ILD/pneumonitis requiring treatment with steroids or ILD/pneumonitis at screening, patients with symptomatic brain metastases, or ECOG performance status >1, and patients with a history of clinically significant cardiac disease.

Patients were randomized 1:1:1 to receive either Enhertu 5.4 mg/kg monotherapy (n=387), Enhertu 5.4 mg/kg plus pertuzumab (n=383) or THP (taxane [docetaxel or paclitaxel], trastuzumab, and pertuzumab) (n=387) by intravenous infusion every three weeks. Patients who received Enhertu plus pertuzumab or THP and who had HR positive tumors (n=416) were allowed to receive concurrent endocrine therapy after 6 cycles of Enhertu or after discontinuation of the taxane in the THP arm. This occurred in 13.5% (n=28) of patients with HR positive tumors in the Enhertu plus pertuzumab arm and 38.3% (n=80) of patients in the THP arm, respectively.

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 the key secondary efficacy outcome measure. PFS based on investigator assessment, confirmed objective response rate (ORR), and duration of response (DOR) were secondary endpoints.

In overall population, demographic and baseline disease characteristics were balanced between treatment arms. Of the 1157 patients randomized, the median age was 54 years (range: 20-88); 82% were <65 years; 100% were female; 50% of the patients were Asian, 37.2% were White, and 2.6% were black or African American; the remainder were of another race or race unknown. The percentage of patients who had *de novo* disease was 52.2% and recurrent disease was 47.8%. The percentage of patients who had HR positive tumors was 53.2%, HR negative was 46.8%, and 30.9% of patients had a PIK3CA mutation.

At the prespecified interim analysis for PFS, the study demonstrated a statistically significant and clinically meaningful improvement in PFS per BICR in patients randomized to Enhertu in combination with pertuzumab compared to THP.

Efficacy results for Enhertu in combination with pertuzumab compared to THP are summarized in Table 7.

Table 7: Efficacy Results in DESTINY-Breast09

Efficacy Parameter	Enhertu 5.4 mg/kg + Pertuzumab*	THP[§]
Progression-Free Survival (PFS) per BICR		
N	383	387
Number of events (%)	118 (30.8)	172 (44.4)
Median, months (95% CI)	40.7 (36.5, NE)	26.9 (21.8, NE)
At 6 months, % (95% CI)	93.0 (89.9, 95.2)	87.8 (84.0, 90.7)
At 12 months, % (95% CI)	85.9 (81.9, 89.1)	72.4 (67.4, 76.8)
At 24 months, % (95% CI)	70.1 (64.8, 74.8)	52.1 (46.4, 57.5)
Hazard ratio (95% CI)	0.56 (0.44, 0.71)	
p-value[† ¶]	< 0.0001	
Overall Survival (OS)		
N	383	387
Number of events (%)	58 (15.1)	68 (17.6)
Median, months (95% CI)	NE	NE
At 12 months, % (95% CI)	94.7 (91.9, 96.6)	95.8 (93.2, 97.4)
At 24 months, % (95% CI)	87.9 (84.1, 90.9)	87.1 (83.1, 90.1)
Hazard ratio (95% CI)	0.84 (0.59, 1.19)	

CI = confidence interval; NE = not estimable

[§] THP = taxane [docetaxel or paclitaxel], trastuzumab,and pertuzumab.

*Patients who discontinued Enhertu due to toxicity prior to disease progression could continue study treatment with trastuzumab, and this occurred in 13.5% of patients in the Enhertu in combination with pertuzumab arm.

¶At this DCO (26 February 2025), interim analysis criterion for superiority (P-value <0.00043) already met for Enhertu in combination with pertuzumab vs THP. Enhertu plus placebo remains blinded until final PFS analysis, which is planned after a predefined number of PFS events across all arms.

[†] The p-value was calculated using a stratified log-rank test.

Similar improvement in PFS was observed across prespecified subgroups including PIK3CA mutated vs non-mutated patients, *de novo* vs recurrent metastatic disease and hormone receptor positive vs negative HER2+ metastatic breast cancer patients.

DESTINY-Breast03

The efficacy and safety of Enhertu were studied in DESTINY-Breast03, a multicentre, open-label, active controlled, randomised, two-arm phase III 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 tumor 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.

Table 8: Efficacy results in DESTINY Breast03

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 III, 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 9.

Table 9: 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[†]	
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

In 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 II 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 tumor 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 10.

Table 10: 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 Kaplan-Meier estimation

	DESTINY-Breast01 N = 184

NR = not reached

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

DESTINY-Breast06

The efficacy and safety of Enhertu were evaluated in study DESTINY-Breast06, a randomized, multicenter, open-label, phase III study that randomized 866 adult patients with advanced or metastatic HR+ breast cancer with HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow expression as determined by the PATHWAY/VENTANA anti-HER2/neu (4B5) evaluated at a central laboratory. HER2-ultralow (IHC 0 with membrane staining, described as IHC >0< 1 + in the study) is defined as faint and incomplete membrane HER2 staining that is seen in 10% or fewer tumor cells. Patients were eligible if they had disease progression on (a) at least 2 lines of endocrine therapy in the metastatic setting or (b) one line of endocrine therapy in the metastatic setting and demonstrated progression within 24 months from the start of adjuvant endocrine therapy, or within 6 months of starting first line endocrine therapy in combination with a CDK 4/6 inhibitor in the metastatic setting. Patients with prior chemotherapy in the neo-adjuvant or adjuvant setting were eligible if they had a disease-free interval greater than 12 months. The study excluded patients with prior chemotherapy for advanced or metastatic disease, patients with a history of ILD/pneumonitis requiring treatment with steroids or ILD/pneumonitis at screening, uncontrolled or significant cardiovascular disease, untreated and symptomatic brain metastases, or ECOG performance status >1.

Patients were randomized 1:1 to receive either Enhertu 5.4 mg/kg (n = 436) by intravenous infusion every three weeks or physician's choice of single agent chemotherapy (n = 430, capecitabine 60%, nab-paclitaxel 24%, or paclitaxel 16%). Randomization was stratified by prior CDK 4/6 inhibitor use (yes or no), prior taxane use in the non-metastatic setting (yes or no), and HER2 IHC status of tumor samples (IHC 2+/ISH- vs. IHC 1+ vs. IHC >0 <1+). Treatment with Enhertu was administered until disease progression, death, withdrawal of consent, or unacceptable toxicity.

The primary efficacy outcome measure was PFS in patients with HER2-low 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 (HER2-low and HER2-ultralow), OS in HER2-low patients, and OS in the overall population. ORR, DOR, and patient-reported outcomes (PROs) were secondary endpoints.

In the overall population, demographics and baseline tumor characteristics were similar between treatment arms. Of the 866 patients randomized, the median age was 57 years (range: 28 to 87); 31% were age 65 or older; 99.9% were female; 53% were White, 35% were Asian, and 1% were Black or African American. Patients had an ECOG performance status of 0 (59%) or 1 (39%) at baseline; 18%

were IHC >0<1+, 55% were IHC 1+, 27% were IHC 2+/ISH-; 67% had liver metastases, 32% had lung metastases, 8% had brain metastases, and 3% had bone-only metastases. Patients had a median of 2 prior lines of endocrine therapy in the metastatic setting (range: 1 to 5) with 17% having 1 and 68% having 2. Eighty-nine percent of patients had prior endocrine therapy in combination with CDK4/6i treatment in the metastatic setting, 41% had prior taxane use in the non-metastatic setting. The study demonstrated a statistically significant and clinically meaningful improvement in PFS in the patients randomized to Enhertu compared to chemotherapy in both the HER2-low cohort and the overall population. Overall survival (OS) data was immature (39 %) at the time of analysis. Efficacy results are summarized in Table 11.

Table 11: Efficacy Results in DESTINY-Breast06

Efficacy Parameter	HER2-low		Overall Population (HER2-low and HER2-ultralow)	
	Enhertu (N=359)	Chemotherapy (N=354)	Enhertu (N=436)	Chemotherapy (N=430)
Progression Free Survival per BICR				
Number of events (%)	225 (62.7)	232 (65.5)	269 (61.7)	271 (63.0)
Median, months (95% CI)	13.2 (11.4, 15.2)	8.1 (7.0, 9.0)	13.2 (12.0, 15.2)	8.1 (7.0, 9.0)
Hazard ratio (95% CI)	0.62 (0.52, 0.75)		0.64 (0.54, 0.76)	
p-value	< 0.0001		< 0.0001	
Overall Survival				
Number of events (%)	136 (37.9)	146 (41.2)	161 (36.9)	174 (40.5)
Median, months (95% CI)	28.9 (25.7, 33.7)	27.1 (23.5, 29.9)	28.9 (26.4, 32.7)	27.4 (23.9, 29.9)
Hazard ratio (95% CI)	0.83 (0.66, 1.05)		0.81 (0.66, 1.01)	
p-value	0.1299		Not tested*	
Survival at 12 months (95% CI)†	87.6% (83.7, 90.6)	81.7% (77.1, 85.4)	87.0% (83.5, 89.9)	81.1% (77.0, 84.6)
Survival at 18 months (95% CI)†	74.0% (68.9, 78.3)	69.6% (64.3, 74.3)	74.8% (70.3, 78.8)	68.7% (63.8, 73.1)

CI = confidence interval

*Since the OS p-value in the HER2-low population did not cross the prespecified efficacy boundary, OS in the ITT population was not tested.

†Based on Kaplan-Meier estimates

Consistent PFS benefit was observed across multiple prespecified subgroups, including HER2 expression (IHC >0 < 1+, IHC 1+, IHC 2+/ISH-), prior CDK 4/6 inhibitor use (yes or no), prior taxane use in the non-metastatic setting (yes or no), and number of prior lines of endocrine therapy in the metastatic setting.

In the exploratory analysis of PFS in the HER2-ultralow subgroup, median PFS was 13.2 months (95% CI: 9.8, 17.3) in patients randomized to Enhertu and 8.3 months (95% CI: 5.8, 15.2) in patients randomized to chemotherapy with a hazard ratio of 0.78 (95% CI: 0.50, 1.21).

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-HER2/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 tumor 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 tumor 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 CDK 4/6 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 12.

Table 12: 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)
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 1 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.

Locally advanced or metastatic gastric cancer

DESTINY-Gastric04

The efficacy and safety of Enhertu were evaluated in DESTINY-Gastric04, a Phase III, randomized, multicenter, open-label, active-controlled study. The study included adult patients with HER2-positive locally advanced, unresectable, or metastatic gastric or GEJ adenocarcinoma who had progressed on or after a trastuzumab-containing regimen. Patients were randomized 1:1 to receive either Enhertu (N=246) or ramucirumab plus paclitaxel (N=248). Randomization was stratified by HER2 status (IHC 3+ or IHC 2+/ISH-positive), geographical region (Asia [excluding mainland China] versus Western Europe versus mainland China/rest of the world), and time to progression on first-line therapy (<6 months or ≥6 months). Enhertu was administered by intravenous infusion at 6.4 mg/kg every three weeks. Ramucirumab was administered by intravenous infusion on days 1 and 15 of a 28-day cycle at 8 mg/kg. Paclitaxel was administered by intravenous infusion days 1, 8, and 15 of a 28-day cycle at 80 mg/m^2. Tumor samples were required to have locally or 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, or unacceptable toxicity. The primary efficacy outcome measure was overall survival (OS). PFS, confirmed ORR, and DOR were secondary outcome measures.
Demographic and baseline disease characteristics were similar between treatment arms. Of the 494 patients enrolled in DESTINY-Gastric04, the median age was 63.7 years (range 21.1 to 87.0); 79.4% were male; 49.8% were White, 40.1% were Asian, and 0.4% were Black or African American. Patients had an ECOG performance status of either 0 (37.4%) or 1 (61.9%); 61.1% had gastric adenocarcinoma and 38.9% had GEJ adenocarcinoma; 84% were IHC 3+ and 16% were IHC 2+/ISH-positive; 70% of patients had two or more metastatic sites, 61.7% had liver metastases, 6.9% had brain metastases; 15.6% of patients previously received immunotherapy.

The study demonstrated a statistically significant and clinically meaningful improvement in OS in patients randomized to Enhertu compared with ramucirumab plus paclitaxel. Efficacy results are summarized in Table 13.

Table 13: Efficacy Results in DESTINY-Gastric04

Efficacy Parameter	Enhertu N=246	Ramucirumab plus paclitaxel N=248
Overall Survival (OS)		
Number of events (%)	124 (50.4)	142 (57.3)
Median, months (95% CI)	14.7 (12.1, 16.6)	11.4 (9.9, 15.5)
Hazard ratio (95% CI)*	0.70 (0.55, 0.90)	
p-value†	p=0.0044	
Progression-free Survival (PFS) per Investigator Assessment		
Number of events (%)	166 (67.5)	156 (62.9)
Median, months (95% CI)	6.7 (5.6, 7.1)	5.6 (4.9, 5.8)
Hazard ratio (95% CI)*	0.74 (0.59, 0.92)	
p-value†	p=0.0074	
Confirmed Objective Response Rate (ORR) per Investigator Assessment††		
n (%)	104 (44.3)	69 (29.1)
95% CI	(37.8, 50.9)	(23.4, 35.3)
p-value§	p=0.0006	

CI=confidence interval

*Two-sided p-value from stratified log-rank test and stratified Cox proportional hazards model adjusted for IRT stratification factors: HER2 status (IHC 3+ or IHC 2+/ISH+).

†Based on log rank test stratified by HER2 status (IHC3+ or IHC2+/ISH+)

††ORR-eligible subjects are those who were randomized at least 77 days (ie, 2 × 6 weeks - 1 week) before DCO date of interim analysis. Confirmed ORR and BOR are calculated using the eligible subjects as the denominator: Enhertu = 235, ramucirumab plus paclitaxel = 237

§p-value is based on the Cochran-Mantel-Haenszel test adjusted for HER2 status (IHC 3+ or IHC 2+/ISH+).

DESTINY-Gastric02

The efficacy and safety of Enhertu were studied in DESTINY-Gastric02, a Phase II, 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 14.

Table 14: 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 cut-off 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).

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 II, 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 II, multicenter, open-label study that enrolled and treated 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 II, 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 II, 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 15 and Table 16.

Table 15: 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 (%)	4 (3.6)	1 (5.9)	0 (0)
Partial Response, n (%)	53 (47.7)	8 (47.1)	30 (46.9)
Duration of Response			
Median§, months (95% CI*)	19.4 (10.0, 29.9)	6.9 (4.0, 9.8)	5.5 (4.2, 8.1)

CI = Confidence interval

†Assessed by independent central review
‡CI is derived based on the Clopper-Pearson method
§Calculated using the Kaplan-Meier technique.
*CI is derived based on the Brookmeyer-Crowley method.

Table 16: 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)	29.9 (5.8, NE)
Ovarian cancer	15	66.7 (38.4, 88.2)	19.6 (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, NE)
Pancreatic cancer	5	0.0 (0.0. 52.2)	NE
Oropharyngeal neoplasm	1	100.0 (2.5, 100.0)	21.1 (NE, NE)
Vulvar cancer	1	100.0 (2.5, 100.0)	2.6 (NE, NE)
Extramammary Paget's Disease	1	100.0 (2.5, 100.0)	19.4 (NE, NE)
Lacrimal Gland Cancer	1	100.0 (2.5, 100.0)	NE
Lip and/or Oral Cavity Cancer	1	0.0 (0, 97.5)	NE
Esophageal Adenocarcinoma	1	100.0 (2.5, 100.0)	2.8 (NE, NE)
Esophageal Squamous Cell Carcinoma	1	0.0 (0, 97.5)	NE

CI = Confidence interval, NE = Not estimable

†Assessed by independent central review

‡CI is derived based on the Clopper-Pearson method

§Calculated using the Kaplan-Meier technique

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 (V_c) 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.
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 approximately 20% higher than in patients with metastatic HER2-positive breast cancer.
In cycle 3, the apparent elimination half-life ($t_{1/2}$) 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. Chemical and physical in-use stability has been demonstrated for up to 48 hours at 2 ºC to 8 ºC.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8 ºC, unless reconstitution has taken place in controlled and validated aseptic conditions.

Diluted solution

It is recommended that the diluted solution be used immediately. If not used immediately, the reconstituted solution diluted in infusion bags containing 5% glucose may be stored at room temperature for up to 4 hours including preparation and infusion or in a refrigerator at 2-8 ºC for up to 24 hours, protected from light.

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.
- From a microbiological point of view, the product should be used immediately. If not used immediately, chemical and physical in-use stability has been demonstrated for up to 48 hours at 2 ºC to 8 ºC. Store the reconstituted Enhertu vials in a refrigerator at 2-8 ºC, protected from light. Do not freeze.
- The product does not contain a preservative. Discard unused Enhertu after 24 hours refrigerated.

Dilution

- The maximum time from reconstitution of the vial through the end of administration should not exceed 24 hours. Discard if storage time exceeds these limits.
- 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 2-8 ºC 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 (2-8 ºC), 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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