NEW ZEALAND DATA SHEET

1. PRODUCT NAME

ENHERTU 100 mg, powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of lyophilized powder for concentrate for solution for infusion delivers 100 mg of trastuzumab deruxtecan. After reconstitution, one vial of 5 mL solution delivers 20 mg/mL of trastuzumab deruxtecan (see Section 4.2 Dose and method of administration).

Trastuzumab deruxtecan is an antibody-drug conjugate (ADC) composed of three components: 1) a humanized anti-HER2 IgG1 monoclonal antibody (mAb) with the same amino acid sequence as trastuzumab, covalently linked to 2) a topoisomerase I inhibitor, an exatecan derivative, via 3) a tetrapeptide-based cleavable linker. Deruxtecan is composed of the linker and the topoisomerase I inhibitor.

The antibody is produced in Chinese hamster ovary cells by recombinant DNA technology and the topoisomerase I inhibitor and linker are produced by chemical synthesis. Approximately 8 molecules of deruxtecan are attached to each antibody molecule.

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Infusion, powder for concentrate

White to yellowish-white lyophilised powder.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Metastatic Breast Cancer

HER2-Positive

ENHERTU as monotherapy, is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who previously received:

- trastuzumab and a taxane for metastatic disease, or
- one prior anti-HER2-based regimen and developed disease recurrence during or within six months of completing neo-adjuvant or adjuvant therapy.

HER2-Low

ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-negative) 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 should additionally have received or be ineligible for endocrine therapy.

Unresectable or Metastatic Non-Small Cell Lung Cancer (NSCLC)

ENHERTU as monotherapy is indicated for the treatment of adult patients with advanced NSCLC whose tumours have an activating HER2 (ERBB2) mutation and who require systemic therapy following platinum-based chemotherapy with or without immunotherapy.

4.2 DOSE AND METHOD OF 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.

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

Patient Selection for HER2-low Metastatic Breast Cancer

Select patients for treatment of unresectable or metastatic HER2-low breast cancer based on IHC 1+ or IHC 2+/ISH- tumour status.

Patient Selection for Unresectable or Metastatic NSCLC

Select patients for the treatment of unresectable or metastatic NSCLC with ENHERTU based on the presence of activating HER2 (ERBB2) mutations detected by a validated test.

Premedication

ENHERTU is emetogenic [see Section 4.8 Adverse effects (undesirable effects)], which includes delayed nausea and/or vomiting. Prior to each dose of ENHERTU, patients should be premedicated with a combination regimen of two or three medicinal products (e.g., dexamethasone with either a 5-HT3 receptor antagonist and/or an NK1 receptor antagonist, as well as other medicinal products as indicated) for prevention of chemotherapy-induced nausea and vomiting.

Posology

The recommended dose of ENHERTU is 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.

The initial dose should be administered as a 90-minute intravenous infusion. If the initial infusion is 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.

Dose Modifications

Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of ENHERTU per guidelines provided in Table 1 and Table 2.

ENHERTU dose should not be re-escalated after a dose reduction is made.

Table 1: Dose Reduction Schedule

Dose Reduction Schedule (Starting dose is 5.4 mg/kg.)	Dose to Be Administered
First dose reduction	4.4 mg/kg
Second dose reduction	3.2 mg/kg
Requirement for further dose reduction	Discontinue treatment.

Table 2: Dose Modifications for Adverse Reactions

Adverse Reaction	Severity	Treatment Modification	
Interstitial Lung Disease (ILD)/Pneumonitis	Asymptomatic ILD/Pneumonitis (Grade 1)	Interrupt ENHERTU until resolved to Grade 0, then: • if resolved in 28 days or less from date of onset, maintain dose. • if resolved in greater than 28 days from date of onset, reduce dose one level (see Table 1). • consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (see Section 4.4 Special warnings and precautions for use/ *Interstitial lung disease/pneumonitis*).	
	Symptomatic ILD/Pneumonitis (Grade 2 or greater)	• Permanently discontinue ENHERTU. • Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected (see Section 4.4 Special warnings and precautions for use/ *Interstitial lung disease/pneumonitis*).	
Neutropenia	Grade 3 (less than 1.0-0.5 x 10^9/L)	• Interrupt ENHERTU until resolved to Grade 2 or less, then maintain dose.	
	Grade 4 (less than 0.5 x 10^9/L)	• Interrupt ENHERTU until resolved to Grade 2 or less. • Reduce dose by one level (see Table 1).	
Febrile Neutropenia	Absolute neutrophil count of less than 1 x 10^9/L and temperature greater than 38.3°C or a sustained temperature of 38°C or greater for more than one hour.	• Interrupt ENHERTU until resolved. • Reduce dose by one level (see Table 1).	
Left Ventricular Ejection Fraction (LVEF) Decreased	LVEF greater than 45% and absolute decrease from baseline is 10% to 20%	• Continue treatment with ENHERTU.	
	LVEF 40% to 45%	And absolute decrease from baseline is less than 10%	• Continue treatment with ENHERTU. • Repeat LVEF assessment within 3 weeks.
		And absolute decrease	• Interrupt ENHERTU. • Repeat LVEF assessment within 3 weeks.

Adverse Reaction	Severity	Treatment Modification	
		from baseline is 10% to 20%	• 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).

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 patient populations

Use in the elderly

No dose adjustment of ENHERTU is required in patients aged 65 years or older.

Paediatric use

The safety and efficacy of ENHERTU in children and adolescents below 18 years of age have not been established. No data are available.

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. Limited data are available in patients with severe renal impairment. A higher incidence of Grade 1 and 2 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 4.4 Special warnings and precautions for use/ *Interstitial lung disease/pneumonitis*).

Hepatic impairment

No dose adjustment is required in patients with mild (total bilirubin ≤ULN and any AST >ULN or total bilirubin >1 to 1.5 times ULN and any AST) hepatic impairment. There are insufficient 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. No data are available in patients with severe (total bilirubin >3 to 10 times ULN and any AST) hepatic impairment.

Method 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 ENHERTU before administration, see section 6.6.

Administration

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

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Interstitial Lung Disease/Pneumonitis

Cases of interstitial lung disease (ILD) and/or pneumonitis, have been reported with ENHERTU [see Section 4.8 Adverse effects (undesirable effects)].

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 radiographic imaging. Consultation with a pulmonologist should be considered. For asymptomatic (Grade 1) ILD/pneumonitis, consider corticosteroid treatment (e.g., ≥0.5 mg/kg/day prednisolone or equivalent). ENHERTU should be withheld until recovery to Grade 0 and may be resumed according to instructions in Table 2 (see section 4.2). 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 4.2 Dose and method of administration). Patients with a history of ILD/pneumonitis or with moderate or severe renal impairment may be at increased risk of developing ILD/pneumonitis and should be monitored carefully (see section 4.2 Dose and method of administration).

In patients treated with ENHERTU 5.4 mg/kg in clinical studies across multiple tumour types (N=1449), ILD occurred in 12.5% of patients as determined by independent review. Most ILD cases were Grade 1 (3.2%) and Grade 2 (7.4%). Grade 3 cases occurred in 0.8% and no grade 4 cases occurred. Grade 5 events occurred in 1.0% of patients. Median time to first onset was 5.5 months (range: 0.9 to 31.5).

Neutropenia

Cases of neutropenia, including febrile neutropenia, were reported in clinical studies of ENHERTU. Complete blood counts should be monitored prior to initiation of ENHERTU and prior to each dose, and as clinically indicated. Based on the severity of neutropenia, ENHERTU may require dose interruption or reduction (see Section 4.2 Dose and method of administration).

In patients treated with ENHERTU 5.4 mg/kg in clinical studies across multiple tumour types (N=1449), neutropenia was reported in 35.2% of patients and 17.0% had Grade 3 or 4 events. Median time of onset was 43 days (range: 1 day to 31.9 months), and median duration of the first event was 22 days (range: 1 day to 17.1 months). Febrile neutropenia was reported in 0.9% of patients (see section 4.2).

Left Ventricular Ejection Fraction Decrease

Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies. LVEF should be assessed prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. LVEF decrease should be managed through treatment interruption. ENHERTU should be permanently discontinued if LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed. ENHERTU should be permanently discontinued in patients with symptomatic congestive heart failure (CHF) (see Section 4.2 Dose and method of administration).

In patients treated with ENHERTU 5.4 mg/kg across multiple tumour types in clinical studies (N=1449), LVEF decrease was reported in 57 patients (3.9%), of which 10 (0.7%) were Grade 1, 40 (2.8%) were Grade 2, and 7 (0.5%) were Grade 3. The observed frequency of LVEF decreased based on laboratory parameters (echocardiogram or MUGA scanning) was 202/1341 (15.1%) for Grade 2, and 12/1341 (0.9%) for Grade 3. Treatment with ENHERTU has not been studied in patients with LVEF less than 50% prior to initiation of treatment.

Treatment with ENHERTU has not been studied in patients with LVEF less than 50% prior to initiation of treatment.

Embryo Foetal Toxicity

ENHERTU can cause foetal harm when administered to a pregnant woman. In post-marketing 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 can also cause embryo-foetal harm when administered to a pregnant woman (see Section 4.6 Fertility, pregnancy and 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 4.6 Fertility, pregnancy and lactation).

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Effects of Other Medicinal Products on the Pharmacokinetics of ENHERTU

In vitro studies indicate that the released topoisomerase I inhibitor is a substrate of the following transporters: P-glycoprotein (P-gp), OATP1B1, OATP1B3, MATE2K, MRP1, and BCRP. Inhibitors of these transporters could increase plasma concentrations of the released topoisomerase I inhibitor.

Coadministration of ritonavir (200 mg twice daily from day 17 of cycle 2 to day 21 of cycle 3), a dual inhibitor of OATP1B/CYP3A, increased exposure (AUC) of trastuzumab deruxtecan by 19% and the released topoisomerase I inhibitor by 22%.

Coadministration of itraconazole (200 mg twice daily from day 17 of cycle 2 to day 21 of cycle 3), a strong CYP3A inhibitor, increased exposure (AUC) of trastuzumab deruxtecan by 11% and the released topoisomerase I inhibitor by 18%.

Coadministration with ritonavir, a dual inhibitor of OATP1B/CYP3A, or with itraconazole, a strong CYP3A inhibitor, resulted in no clinically meaningful increase in exposures of trastuzumab deruxtecan or the released topoisomerase I inhibitor. No dose adjustment is required during coadministration of trastuzumab deruxtecan with drugs that are inhibitors of OATP1B or CYP3A.

No clinically meaningful interaction is expected with drugs that are inhibitors of P-gp, MATE2-K, MRP1, or BCRP transporters.

Effects of ENHERTU on the Pharmacokinetics of Other Medicinal Products

In vitro studies indicate that the topoisomerase I inhibitor does not inhibit or induce major CYP450 enzymes, including CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A. *In vitro* studies indicate that the topoisomerase I inhibitor does not inhibit OAT3, OCT1, OCT2, OATP1B3, MATE1, MATE2-K, P-gp, BCRP, or BSEP transporters, but has an inhibitory effect on OAT1 and OATP1B1 with IC_{50} values of 12.7 and 14.4 µmol/L, respectively, which are significantly higher than steady-state C_{max} (0.01 µmol/L) of topoisomerase I inhibitor at 5.4 mg/kg dose administered every 3 weeks. No clinically meaningful drug-drug interaction is expected with drugs that are substrates of OAT1 or OATP1B1 transporters.

4.6 FERTILITY, PREGNANCY AND LACTATION

Women of Childbearing Potential

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

Contraception in Males and Females

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

Trastuzumab deruxtecan can cause fetal harm when administered to a pregnant woman. There are no available data on the effects of trastuzumab deruxtecan in pregnant women. However, in post-marketing 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 trastuzumab deruxtecan can also cause embryo-fetal harm when administered to a pregnant woman.

Administration of ENHERTU to pregnant women is not recommended, and patients should be informed of the potential risks to the fetus before they become pregnant. Women who become pregnant must immediately contact their doctor. If a woman becomes pregnant during

treatment with ENHERTU or within 7 months following the last dose of ENHERTU, close monitoring is recommended.

Breast-feeding

It is not known if trastuzumab deruxtecan is excreted in human milk. Since many medicinal products are excreted in human milk and because of the potential for serious adverse reactions in breastfeeding infants, women should discontinue breastfeeding prior to initiating treatment with ENHERTU. Women may begin breastfeeding 7 months after concluding treatment.

Fertility

No dedicated fertility studies have been conducted with trastuzumab deruxtecan. Based on results from animal toxicity studies, ENHERTU may impair male reproductive function and fertility.

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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

ENHERTU is not expected to affect patients' ability to drive or use machines. Due to potential adverse reactions such as fatigue, headache and dizziness [see Section 4.8 Adverse effects (undesirable effects)], patients should be advised to use caution when driving or operating machinery.

4.8 UNDESIRABLE EFFECTS

Clinical trials experience

As clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Metastatic Breast Cancer

The safety of ENHERTU 5.4 mg/kg was evaluated in a pooled analysis of 1287 patients with unresectable or metastatic breast cancer in Study DS8201-A-J101 (Breast Cancer cohort, n=71), DESTINY-Breast01 (n=184), DESTINY-Breast02 (n=404), DESTINY-Breast03 (n=257), and DESTINY-Breast04 (n=371). The median duration of treatment was 10 months (range 0.2 to 45.1).

The pooled study population characteristics were as follows: the median age was 55.5 years (range 22 to 96); 99.5% were female; 49.2% were White, 40.8% were Asian, 2.6% were Black or African American; and 56.6% had an Eastern Cooperative Oncology Group (ECOG) performance status 0 and 43.3% had an ECOG performance status of 1. The studies excluded patients with a history of treated ILD or ILD at screening and patients with a history of clinically significant cardiac disease.

In the pooled studies, the most common adverse reactions (frequency ≥20%) were nausea (75.8%), fatigue (58.3%), vomiting (43.7%), alopecia (39.9%), neutropenia (35.7%), constipation (35.3%), anaemia (34.7%), decreased appetite (32%), diarrhoea (29.2%), transaminases increased (27.5%), musculoskeletal pain (27.2%), thrombocytopenia (24.7%), leukopenia (23.9%), and abdominal pain (20.6%). In the pooled studies, the most common

serious adverse reactions (frequency >1%) were interstitial lung disease (3.7%), vomiting (1.5%), anaemia (1.1%), and nausea (1.1%). There were 14 (1.1%) patients with adverse reactions leading to death, 13 attributed to ILD (1.0%) and 1 attributed to febrile neutropenia (0.1%).

Dose interruptions due to adverse reactions occurred in 32.7% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia (14%), fatigue (5.1%), anaemia (4.8%), leukopenia (4.1%), thrombocytopenia (3.2%), upper respiratory tract infection (2.8%), and interstitial lung disease (2.5%). Dose reductions occurred in 20.9% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were nausea (5.2%), fatigue (5.1%), neutropenia (3.6%), and thrombocytopenia (2.2%). Discontinuation of therapy due to an adverse reaction occurred in 12.4% of patients treated with ENHERTU. The most frequent adverse reaction (>2%) associated with permanent discontinuation was interstitial lung disease (9.5%).

Tabulated List of Adverse Reactions

The adverse reactions in patients with unresectable or metastatic breast cancer who received at least one dose of ENHERTU 5.4 mg/kg are presented in Table 3. The adverse reactions are listed by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and categories of frequency. Frequency categories are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3: Tabulated List of Adverse Reactions in Patients with Unresectable or Metastatic Breast Cancer Treated with Trastuzumab Deruxtecan 5.4 mg/kg

MedDRA System Organ Class/Preferred Term or Grouped Term	**ENHERTU Metastatic Breast Cancer Pooled N=1287**		
	Any Grade (%)		**Grade 3-4 (%)**
Blood and Lymphatic System Disorders			
Neutropenia[a]	Very Common	35.7	17.5
Anaemia[b]	Very Common	34.7	9.3
Thrombocytopenia[c]	Very Common	24.7	5.0
Leukopenia[d]	Very Common	23.9	6.8
Lymphopenia[e]	Very Common	11.3	5.1
Febrile neutropenia	Uncommon	0.9	0.9
Eye Disorders			
Dry eye	Common	5.8	0.2
Vision blurred[f]	Common	4.5	0
Gastrointestinal Disorders			
Nausea	Very Common	75.8	6.1

MedDRA System Organ Class/Preferred Term or Grouped Term	ENHERTU Metastatic Breast Cancer Pooled N=1287		
	Any Grade (%)		Grade 3-4 (%)
Vomiting	Very Common	43.7	2.7
Constipation	Very Common	35.3	0.4
Diarrhoea	Very Common	29.2	2.0
Abdominal pain[g]	Very Common	20.6	1.0
Stomatitis[h]	Very Common	15.2	0.8
Dyspepsia	Very Common	11.8	0
Abdominal distension	Common	4.0	0
Gastritis	Common	2.3	0.2
Flatulence	Common	1.9	0
General Disorders and Administration Site Conditions			
Fatigue[i]	Very Common	58.3	8.6
Pyrexia	Very Common	13.1	0.4
Hepatobiliary disorders			
Transaminases increased[j]	Very Common	27.5	3.8
Infections and Infestations			
Upper respiratory tract infection[k]	Very Common	19.9	0.2
Injury, poisoning and procedural complications			
Infusion related reaction[l]	Common	1.3	0
Investigations			
Weight decreased	Very Common	16.6	0.6
Blood alkaline phosphatase increased	Common	9.0	0.4
Blood bilirubin increased[m]	Common	8.6	0.9
Blood creatinine increased	Common	3.0	0.2
Metabolism and Nutrition Disorders			
Decreased appetite	Very Common	32.0	1.8
Hypokalaemia[n]	Very Common	11.5	3.3
Dehydration	Common	3.0	0.5
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain[o]	Very Common	27.2	0.9

MedDRA System Organ Class/Preferred Term or Grouped Term	ENHERTU Metastatic Breast Cancer Pooled N=1287		
	Any Grade (%)		Grade 3-4 (%)
Nervous System Disorders			
Headache[p]	Very Common	19.4	0.2
Dizziness	Very Common	10.3	0.3
Dysgeusia	Common	8.2	0
Respiratory, Thoracic and Mediastinal Disorders			
Cough	Very Common	14.8	0.1
Interstitial lung disease[q]	Very Common	12.8	0.9
Epistaxis	Very Common	11.1	0
Dyspnea	Very Common	10.7	0.9
Skin and Subcutaneous Tissue Disorders			
Alopecia	Very Common	39.9	0.2
Rash[r]	Very Common	10.3	0.1
Pruritus	Common	5.4	0.1
Skin hyperpigmentation[s]	Common	5.0	0

MedDRA = Medical Dictionary for Regulatory Activities
PT = preferred term

[a] Grouped term of neutropenia includes PTs of neutropenia and neutrophil count decreased.
[b] Grouped term of anaemia includes PTs of anaemia, haemoglobin decreased, haematocrit decreased, and red blood cell count decreased.
[c] Grouped term of thrombocytopenia includes PTs of thrombocytopenia and platelet count decreased.
[d] Grouped term of leukopenia includes PTs of leukopenia and white blood cell count decreased.
[e] Grouped term of lymphopenia includes PTs of lymphopenia and lymphocyte count decreased.
[f] Grouped term of vision blurred includes PTs of vision blurred and visual impairment.
[g] Grouped term of abdominal pain includes PTs of abdominal pain, abdominal discomfort, gastrointestinal pain, abdominal pain lower, abdominal pain upper.
[h] Grouped term of stomatitis includes PTs of stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosal eruption.
[i] Grouped term of fatigue includes PTs of fatigue, asthenia, malaise and lethargy.
[j] Grouped term of transaminases increased includes PTs of transaminases increased, alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, hepatic function abnormal, liver function test abnormal, liver function test increased, and hypertransaminasemia.
[k] Grouped term of upper respiratory tract infection includes PTs of upper respiratory tract infection, influenza, influenza like illness, nasopharyngitis, pharyngitis, sinusitis, rhinitis, and laryngitis.
[l] Grouped term of infusion related reactions includes PTs of hypersensitivity (n=2), and infusion related reaction (n=15).
[m] Grouped term of blood bilirubin increased includes PTs of blood bilirubin increased, hyperbilirubinemia, bilirubin conjugated increased, and blood bilirubin unconjugated increased.
[n] Grouped term of hypokalaemia includes PTs of hypokalaemia and blood potassium decreased.
[o] Grouped term of musculoskeletal pain includes PTs of back pain, myalgia, pain in extremity, musculoskeletal pain, muscle spasms, bone pain, neck pain, musculoskeletal chest pain, and limb discomfort.
[p] Grouped term of headache includes PTs of headache, migraine, and sinus headache.
[q] Interstitial lung disease includes events that were adjudicated as ILD for ENHERTU: pneumonitis, interstitial lung disease, idiopathic interstitial pneumonia, lung disorder, pulmonary toxicity, acute respiratory failure, alveolitis, hypersensitivity pneumonitis, lung infiltration, lung opacity, lymphangitis, organizing pneumonia, pneumonia, pneumonia fungal, pulmonary fibrosis, radiation pneumonitis, respiratory failure, and pulmonary mass. Grade 5 adjudicated drug-related ILD events were respiratory failure, acute respiratory failure, pulmonary fibrosis, lymphangitis, ILD, and pneumonitis.
[r] Grouped term of rash includes PTs of rash, rash pustular, rash maculo-papular, rash papular, rash macular, and rash pruritic.
[s] Grouped term of skin hyperpigmentation includes PTs of skin hyperpigmentation, skin discoloration, and pigmentation disorder.

Unresectable or Metastatic NSCLC

HER2-mutant at 5.4 mg/kg

The safety of ENHERTU was evaluated in 101 patients with HER2-mutant unresectable or metastatic lung cancer who received ENHERTU 5.4 mg/kg in DESTINY-Lung02 (see Section 5.1). The median duration of treatment was 7.7 months (range: 0.7 to 20.8).

In ENHERTU -treated patients (N=101), the median age was 59 years (range 30 to 83); 64.4% were female; 63.4% were Asian, 22.8% were White; and 29.7% had an ECOG performance status 0 and 70.3% had an ECOG performance status of 1. The studies excluded patients with a history of treated ILD or ILD at screening and patients with a history of clinically significant cardiac disease.

The most common adverse reactions (frequency ≥20%) were nausea (67.3%), fatigue (44.6%), neutropenia (42.6%), decreased appetite (39.6%), anaemia (36.6%), constipation (36.6%), vomiting (31.7%), leukopenia (28.7%), thrombocytopenia (27.7%), diarrhoea (22.8%), transaminases increased (21.8%), and alopecia (21.8%). The most common serious adverse reactions (frequency >1%) were ILD/pneumonitis (4.0%), thrombocytopenia (3.0%), nausea (2.0%), vomiting (2.0%) and dyspnoea (2.0%).

Dose interruptions due to adverse reactions occurred in 28.7% of patients. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia (11.9%) ILD/pneumonitis (5.0%), fatigue (5.0%), and anaemia (4.0%). Dose reductions occurred in 13.9% of patients. The most frequent adverse reactions (>2%) associated with dose reduction were neutropenia (4.0%), fatigue (3.0%) and decreased appetite (3.0%). Discontinuation of therapy due to an adverse reaction occurred in 10.9% of patients. The most frequent adverse reaction (>2%) associated with permanent discontinuation was ILD/pneumonitis (9.9%).

Tabulated List of Adverse Reactions

The adverse reactions in patients with unresectable or metastatic HER2-mutant NSCLC who received at least one dose of ENHERTU 5.4 mg/kg are presented in Table 4. The adverse reactions are listed by Medical Dictionary for Regulatory Activities (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. Tabulated List of Adverse Reactions in Patients with Unresectable or Metastatic NSCLC in DESTINY-Lung02 Treated with Trastuzumab Deruxtecan 5.4 mg/kg

MedDRA System Organ Class/Preferred Term or Grouped Term	ENHERTU N=101		
	Frequency	Any Grade (%)	Grades 3 or 4 (%)
Blood and Lymphatic System Disorders			
Neutropenia[a]	Very common	42.6	18.8
Anemia	Very common	36.6	10.9
Leukopenia[b]	Very common	28.7	5.0

MedDRA System Organ Class/Preferred Term or Grouped Term	ENHERTU N=101		
	Frequency	Any Grade (%)	Grades 3 or 4 (%)
Thrombocytopenia[c]	Very common	27.7	5.9
Lymphopenia[d]	Common	6.9	3.0
Gastrointestinal Disorders			
Nausea	Very common	67.3	4.0
Constipation	Very common	36.6	1.0
Vomiting	Very common	31.7	3.0
Diarrhea	Very common	22.8	1.0
Stomatitis[e]	Very common	15.8	0
Abdominal pain[f]	Common	9.9	0
General Disorders and Administration Site Conditions			
Fatigue[g]	Very common	44.6	7.9
Infections and Infestations			
Upper respiratory tract infection[h]	Common	8.9	0
Investigations			
Transaminases increased[i]	Very common	21.8	3.0
Metabolism and Nutrition Disorders			
Decreased appetite	Very common	39.6	2.0
Hypokalemia	Very common	12.9	6.9
Nervous System Disorders			
Headache[j]	Common	5.9	0
Respiratory, Thoracic and Mediastinal Disorders			
Interstitial lung disease[k]	Very common	12.9	1.0
Dyspnea	Common	5.0	2.0
Epistaxis	Common	4.0	0
Skin and Subcutaneous Tissue Disorders			
Alopecia	Very common	21.8	0
Rash[l]	Common	5.0	0

MedDRA = Medical Dictionary for Regulatory Activities
PT = preferred term

[a] Grouped term of neutropenia includes PTs of neutropenia and neutrophil count decreased.
[b] Grouped term of leukopenia includes PTs of leukopenia and white blood cell count decreased.
[c] Grouped term of thrombocytopenia includes PTs of thrombocytopenia and platelet count decreased.
[d] Grouped term of lymphopenia includes PTs of lymphopenia and lymphocyte count decreased.
[e] Grouped term of stomatitis includes PTs of stomatitis and mouth ulceration.
[f] Grouped term of abdominal pain includes PTs of abdominal discomfort, abdominal pain, and abdominal pain upper.
[g] Grouped term of fatigue includes PTs of fatigue, asthenia, and malaise.
[h] Grouped term of upper respiratory tract infection includes upper respiratory tract infection, rhinitis, nasopharyngitis, influenza, influenza-like illness, pharyngitis, and laryngitis.

[l] Grouped term of transaminases increased includes PTs of alanine aminotransferase increased aspartate aminotransferase increased, gamma-glutamyltransferase increased and hepatic function abnormal.
[j] Grouped term of headache includes PTs of headache and migraine.
[k] Interstitial lung disease includes events that were adjudicated as drug-related ILD: pneumonitis, interstitial lung disease, pulmonary toxicity, and respiratory failure. One Grade 5 adjudicated drug-related ILD event was reported.
[l] Grouped term of rash includes PTs of rash and rash maculo-papular.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Across all doses evaluated in clinical studies, 2.1% (47/2213) of evaluable patients developed antibodies against trastuzumab deruxtecan following treatment with ENHERTU. The incidence of treatment-emergent neutralizing antibodies against trastuzumab deruxtecan was 0.1% (2/2213). There was no association between development of antibodies and allergic-type reactions

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via https://pophealth.my.site.com/carmreportnz/s.

4.9 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antineoplastic agents, HER2 (Human Epidermal Growth Factor Receptor 2) inhibitors, ATC code: L01FD04

Mechanism of action

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 bound by a tetrapeptide-based cleavable linker. The ADC is stable in plasma under in vitro conditions. Following binding to HER2 on tumour cells, trastuzumab deruxtecan undergoes internalization and intracellular linker cleavage by lysosomal enzymes. Upon release, the membrane-permeable topoisomerase I inhibitor causes DNA damage and apoptotic cell death. The topoisomerase I inhibitor, an exatecan derivative, is approximately 10 times more potent than SN38, the active metabolite of irinotecan.

Pharmacodynamic Effects

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 in an open-label, single-arm study in 51 patients with HER2-expressing metastatic breast cancer.

Clinical Efficacy and Safety

Metastatic Breast Cancer

DESTINY-Breast03

The efficacy and safety of ENHERTU were demonstrated in a Phase 3, randomised, multicentre, open-label, active-controlled study: DESTINY-Breast03.

The study included adult patients with unresectable or metastatic HER2-positive breast cancer who received prior trastuzumab and taxane therapy for metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy. Archival breast tumour samples were required to show HER2 positivity defined as HER2 IHC 3+ or ISH-positive. The study excluded patients with a history of 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, and patients with prior treatment with an anti-HER2 antibody-drug conjugate in the metastatic setting. Patients were randomised 1:1 to receive either ENHERTU 5.4 mg/kg (N=261) or trastuzumab emtansine 3.6 mg/kg (N=263) by intravenous infusion every three weeks. Randomisation 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. PFS based on investigator assessment and confirmed objective response rate (ORR) were among some of the secondary endpoints.

Demographic and baseline disease characteristics were similar between treatment arms. Of the 524 patients randomised, the median age was 54 years (range 20 to 83); female (99.6%); Asian (59.9%), White (27.3%), Black or African American (3.6%); Eastern Cooperative Oncology Group (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% of patients received one line of prior systemic therapy in the metastatic setting. The percentage of patients who had not received prior treatment for metastatic disease was 9.5%.

At the prespecified interim analysis for PFS 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 randomised to ENHERTU compared to trastuzumab emtansine. At the overall survival (OS) analysis (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.

Efficacy results are summarised in Table 5 and Figure 1 and Figure 2.

Table 5: Efficacy Results in DESTINY-Breast03

Efficacy Parameter	**ENHERTU 5.4 mg/kg N=261**	**trastuzumab emtansine 3.6 mg/kg N=263**
PFS per 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< 0.000001[†]	

Table 5: Efficacy Results in DESTINY-Breast03

Efficacy Parameter	ENHERTU 5.4 mg/kg N=261	trastuzumab emtansine 3.6 mg/kg N=263
Overall Survival (OS)[b]		
Number of events (%)	72 (27.6)	97 (36.9)
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 per 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)	
PFS per Investigator Assessment[b]		
Number of events (%)	116 (44.4)	190 (72.2)
Median, months (95% CI)	29.1 (23.7, NE)	7.2 (6.8, 8.3)
Hazard ratio (95% CI)	0.30 (0.24, 0.38)	
Confirmed Objective Response Rate (ORR) per BICR[b]		
n (%)	205 (78.5)	92 (35.0)
95% CI	(73.1, 83.4)	(29.2, 41.1)
Complete Response n (%)	55 (21.1)	25 (9.5)
Partial Response n (%)	150 (57.5)	67 (25.5)

CI = confidence interval; NR= not reached, NE=not estimable, HR=hazard ratio
†presented as 6 decimal places
[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

Figure 1 Kaplan-Meier Plot of Overall Survival Data cutoff 25 July 2022

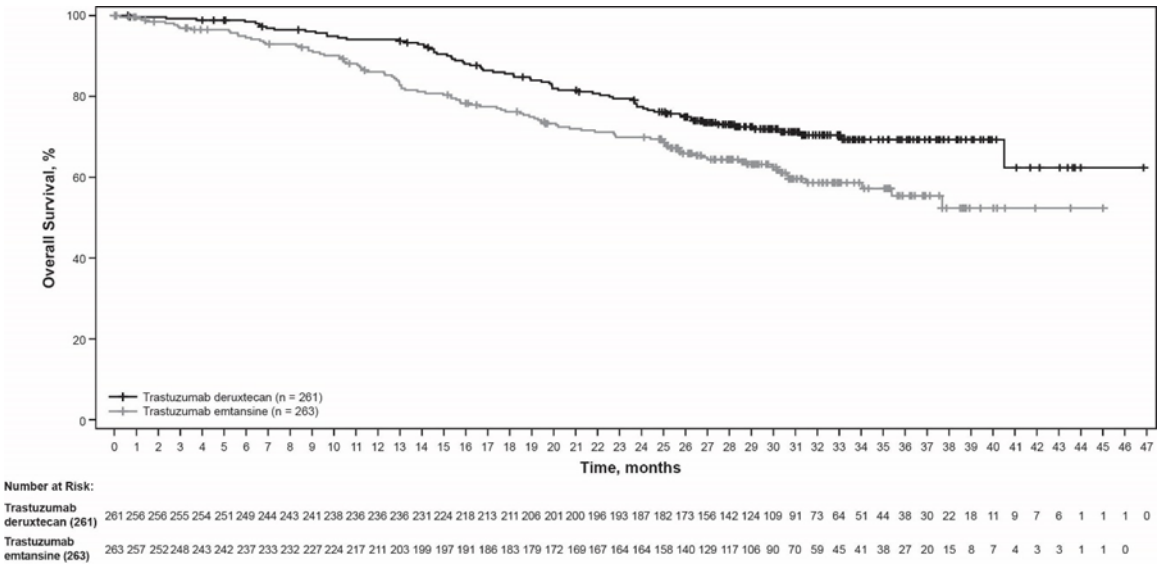
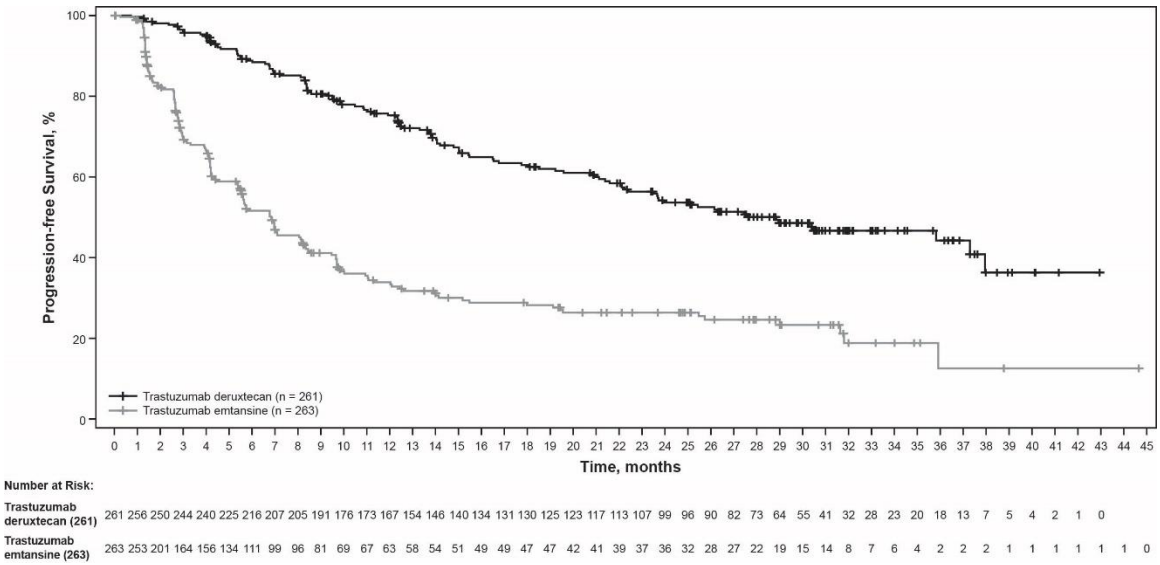


Figure 2 Kaplan-Meier Plot of Progression-free Survival per BICR Data cutoff 25 July 2022



Similar PFS results were observed across prespecified subgroups including prior pertuzumab therapy, hormone receptor status, presence of brain metastases, and presence of visceral disease.

DESTINY-Breast02

The efficacy and safety of ENHERTU were evaluated in study DESTINY-Breast02, a Phase 3, randomized, multicentre, 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 tumour 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. PFS based on investigator assessment, confirmed objective response rate (ORR), duration of response (DOR), Patient-Reported Outcomes (PRO), and time to hospitalization were secondary objectives.

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 6 and Figure 3 and Figure 4.

Table 6: 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)
PFS per Investigator Assessment		
Number of events (%)	206 (50.7)	152 (75.2)
Median, months (95% CI)	16.7 (14.3, 19.6)	5.5 (4.4, 7.0)
Hazard ratio (95% CI)	0.28 (0.23, 0.35)	
Confirmed Objective Response Rate (ORR) per BICR		
n (%)	283 (69.7)	59 (29.2)
95% CI	(65.0, 74.1)	(23.0, 36.0)
Complete Response n (%)	57 (14.0)	10 (5.0)
Partial Response n (%)	226 (55.7)	49 (24.3)
Duration of Response per BICR		
Median, months (95% CI)	19.6 (15.9, NE)	8.3 (5.8, 9.5)

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

Figure 3: Kaplan-Meier Plot of Progression-free Survival Per BICR

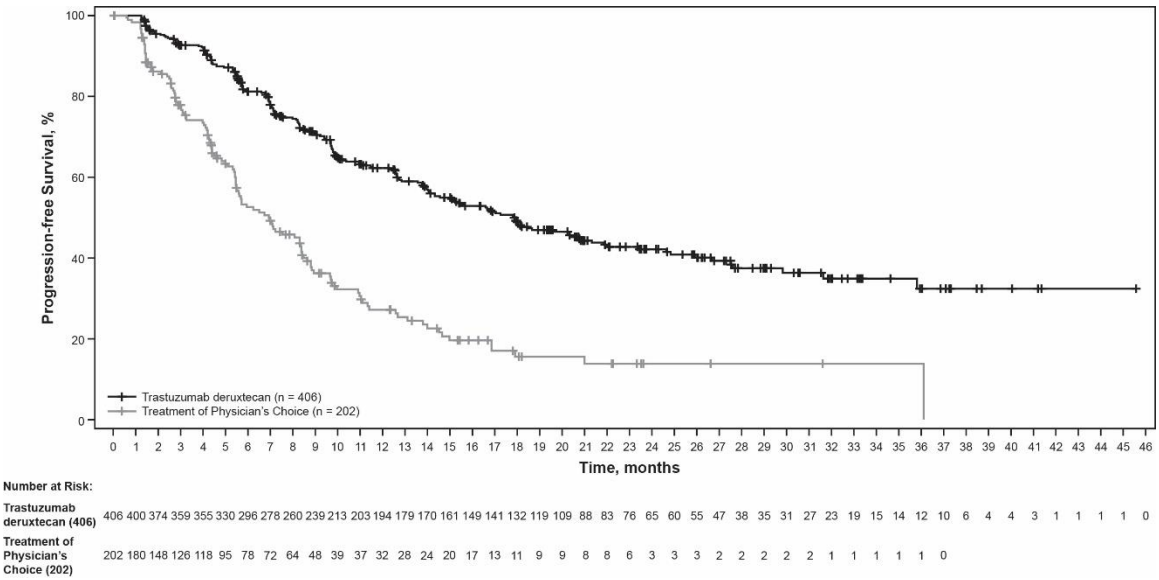
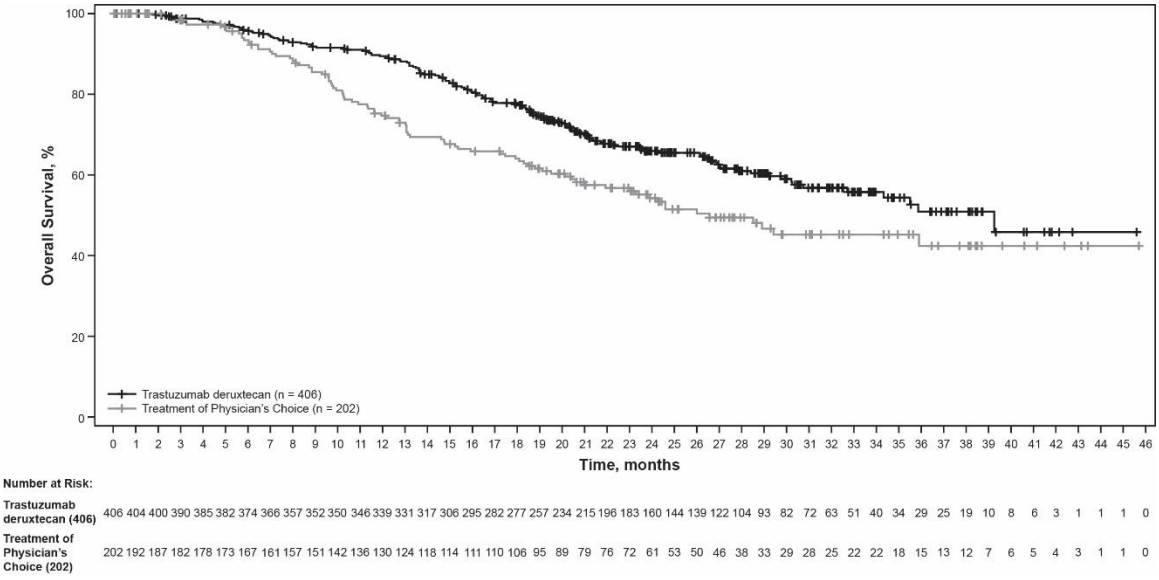


Figure 4: Kaplan-Meier Plot of Overall Survival



Similar PFS results were observed across prespecified subgroups including prior pertuzumab therapy, hormone receptor status, presence of visceral disease, and presence of brain metastases.

As secondary outcome measures, the PRO variables showed that the Quality of Life (QoL) of patients in the ENHERTU arm was either maintained or numerically improved on treatment compared with patients in the treatment of physician's choice arm. The mean changes from baseline in European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30 global health status (the primary PRO variable) demonstrated that overall health and QoL were maintained while patients were on treatment with ENHERTU.

For all prespecified subscales, the hazard ratio (HR) for time to definitive deterioration numerically favoured the ENHERTU arm over the treatment of physician's choice arm (HR ranging from 0.38 to 0.67). Median time to definitive deterioration for the global health status

from the EORTC QLQ-C30 was 14.1 months (95% CI: 10.4, 18.7) for the ENHERTU arm and 5.9 months (95% CI: 4.3, 7.9) for the treatment of physician's choice arm (HR 0.56 [95% CI: 0.44, 0.71]). The unadjusted p-values for the time to definitive deterioration HRs were less than 0.005 for EORTC QLQ-C30 emotional functioning (HR 0.67 [95% CI 0.51, 0.88]; p-value = 0.0041) and pain symptoms (HR 0.38 [95% CI: 0.29, 0.49]; p-value <0.0001) subscales, as well as for the visual analogue scale of the EuroQoL-5 dimensions-5 levels of severity (EQ-5D-5L) (HR 0.59 [95% CI: 0.46, 0.76]; p-value <0.001) and the arm symptoms subscale of the EORTC QLQ-BR23 (HR 0.57 [95% CI: 0.44, 0.75]; p-value <0.001). Since the EORTC QLQ-BR45 scoring algorithm has not been validated yet, all data captured with EORTC QLQ-BR45 were scored using the algorithm for EORTC QLQ-BR23.

Among the 92 (22.7%) patients in the ENHERTU arm and the 41 (20.3%) patients in the treatment of physician's choice arm who were hospitalized, time to first hospitalization was longer in the ENHERTU arm (median of 133 days and 83 days, respectively).

DESTINY-Breast01

The efficacy and safety of ENHERTU were demonstrated in a Phase 2, single-agent, open-label, multicentre study: DESTINY-Breast01.

The study included adult patients with unresectable or metastatic HER2-positive breast cancer who had received two or more prior anti-HER2 regimens, including trastuzumab emtansine (100%), trastuzumab (100%), and pertuzumab (65.8%). Archival breast tumour samples were required to show HER2 positivity defined as HER2 IHC 3+ or ISH-positive. The study excluded patients with a history of treated ILD or ILD at screening and patients with a history of clinically significant cardiac disease. ENHERTU was administered by intravenous infusion at 5.4 mg/kg once every three weeks until disease progression, death, withdrawal of consent, or unacceptable toxicity. The primary efficacy outcome measure was confirmed objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumours (RECIST v1.1) in the intent-to-treat (ITT) population as evaluated by independent central review. Duration of response (DOR) and progression-free survival (PFS) were additional outcome measures.

DESTINY-Breast01 (N = 184) 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 based on a data cut-off of 26 Mar 2021 with a median duration of follow-up of 26.5 months and median duration of treatment of 10.1 months are summarised in Table 7.

Table 7: Efficacy results in DESTINY-Breast01 (intent-to-treat analysis set)

	DESTINY-Breast01 N=184
Confirmed objective response rate (ORR) (95% CI)[#§]	62% (54.5, 69.0)
Complete response (CR)	7.1%
Partial response (PR)	54.9%
Duration of Response (DoR)*	

	DESTINY-Breast01 N=184
Median, months (95% CI)	18.2 (15.0, NR)
% with duration of response ≥6 months (95% CI)†	81.8% (72.5, 88.1)

ORR 95% CI calculated using Clopper-Pearson method
CI = confidence interval
95% CIs calculated using Brookmeyer-Crowley method
Confirmed responses (by blinded independent central review) were defined as a recorded response of either CR/PR, confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed.
§ Of the 184 patients, 35.3% had stable disease, 1.6% had progressive disease and 1.1% were not evaluable.
* Includes 69 patients with censored data
† Based on Kaplan-Meier estimates
Efficacy data based on DCO 21 March 2021, median duration of follow-up of 26.5 months

Consistent antitumour activity was observed with ENHERTU regardless of prior pertuzumab therapy and hormone receptor status. In DESTINY-Breast01, the subgroup of patients who received prior pertuzumab therapy had a confirmed ORR of 66% (95% CI: 57, 75), and those who did not receive prior pertuzumab therapy had a confirmed ORR of 57% (95% CI: 43, 69). The subgroup of patients who were hormone receptor positive at baseline had a confirmed ORR of 60% (95% CI: 49, 70), and those who were HR- at baseline had a confirmed ORR of 68% (95% CI: 56, 77).

DESTINY-Breast04

The efficacy and safety of ENHERTU were evaluated in study DESTINY-Breast04, a Phase 3, randomized, multicentre, open-label study that enrolled 557 adult patients with unresectable or metastatic HER2-low breast cancer. The study included 2 cohorts: 494 hormone receptor positive (HR+) patients and 63 hormone receptor negative (HR-) patients. HER2-low expression was defined as IHC 1+ or IHC 2+/ISH-, as determined by the PATHWAY/VENTANA anti-HER-2/neu (4B5) 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 randomized 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%). Randomization was stratified by HER2 IHC status of tumour samples (IHC 1+ or IHC 2+/ISH-), number of prior lines of chemotherapy in the metastatic setting (1 or 2), and HR status/prior CDK4/6i treatment (HR+ with prior CDK4/6 inhibitor treatment, HR+ without prior CDK4/6 inhibitor treatment, or HR-). Treatment was administered until disease progression, death, withdrawal of consent, or unacceptable toxicity. The study excluded patients with a history of ILD/pneumonitis requiring treatment with steroids or ILD/pneumonitis at screening and clinically significant cardiac disease. Patients were also excluded for untreated or symptomatic brain metastases or ECOG performance status >1.

The primary efficacy outcome measure was 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 randomized HR+ and HR- patients), OS in HR+ patients, and OS in the overall population. ORR, DOR, and PROs were secondary endpoints.

Demographics and baseline tumour characteristics were similar between treatment arms. Of the 557 patients randomized, the median age was 56.5 years (range: 28.4 to 80.5); 23.5% were age 65 or older; 99.6% were female and 0.4% were male; 47.9% were White, 40.0% were Asian, and 1.8% were Black or African American. Patients had an ECOG performance

status of 0 (54.8%) or 1 (45.2%) at baseline; 57.6% were IHC 1+, 42.4% were IHC 2+/ISH-; 69.8% had liver metastases, 32.9% had lung metastases, and 5.7% had brain metastases. In the metastatic setting, patients had a median of 3 prior lines of systemic therapy (range: 1 to 9) with 57.6% having 1 and 40.9% having 2 prior chemotherapy regimens; 3.9% were early progressors (progression in the neo/adjuvant setting). In HR+ patients, the median number of prior lines of endocrine therapy was 2 (range: 0 to 9) and 70% had prior CDK4/6i treatment.

The study demonstrated a statistically significant and clinically meaningful improvement in OS and PFS in patients randomized to ENHERTU compared to chemotherapy in both the HR+ cohort and the overall population.

Efficacy results are summarized in Table 8 and Figure 5 and Figure 6.

Table 8: Efficacy Results in DESTINY-Breast04

Efficacy Parameter	HR+ Cohort		Overall Population (HR+ and HR- Cohorts)	
	ENHERTU (N=331)	Chemotherapy (N=163)	ENHERTU (N=373)	Chemotherapy (N=184)
Overall Survival				
Number of events (%)	126 (38.1)	73 (44.8)	149 (39.9)	90 (48.9)
Median, months (95% CI)	23.9 (20.8, 24.8)	17.5 (15.2, 22.4)	23.4 (20.0, 24.8)	16.8 (14.5, 20.0)
Hazard ratio (95% CI)	0.64 (0.48, 0.86)		0.64 (0.49, 0.84)	
p-value	0.0028		0.001	
Progression-free Survival per BICR				
Number of events (%)	211 (63.7)	110 (67.5)	243 (65.1)	127 (69.0)
Median, months (95% CI)	10.1 (9.5, 11.5)	5.4 (4.4, 7.1)	9.9 (9.0, 11.3)	5.1 (4.2, 6.8)
Hazard ratio (95% CI)	0.51 (0.40, 0.64)		0.50 (0.40, 0.63)	
p-value	<0.0001		<0.0001	
Confirmed Objective Response Rate per BICR*				
n (%)	175 (52.6)	27 (16.3)	195 (52.3)	30 (16.3)
95% CI	47.0, 58.0	11.0, 22.8	47.1, 57.4	11.3, 22.5
Complete Response n (%)	12 (3.6)	1 (0.6)	13 (3.5)	2 (1.1)
Partial Response n (%)	164 (49.2)	26 (15.7)	183 (49.1)	28 (15.2)
Duration of Response per BICR*				
Median, months (95% CI)	10.7 (8.5, 13.7)	6.8 (6.5, 9.9)	10.7 (8.5, 13.2)	6.8 (6.0, 9.9)

CI = confidence interval

* Based on data from electronic case report form for the HR+ cohort: N=333 for ENHERTU arm and N=166 for chemotherapy arm.

Consistent OS and PFS benefit was observed across prespecified subgroups, including HR status, prior CDK4/6i treatment, number of prior chemotherapies, and IHC 1+ and IHC 2+/ISH- status. In the HR- subgroup, median OS was 18.2 months (95% CI: 13.6, not estimable) in patients randomized to ENHERTU compared to 8.3 months (95% CI: 5.6, 20.6) in patients randomized to chemotherapy with a hazard ratio of 0.48 (95% CI: 0.24, 0.95). Median PFS was 8.5 months (95% CI: 4.3, 11.7) in patients randomized to ENHERTU and 2.9 months (95% CI: 1.4, 5.1) in patients randomized to chemotherapy with a hazard ratio of 0.46 (95% CI: 0.24, 0.89).

Figure 5: Kaplan-Meier Plot of Overall Survival (Overall Population)

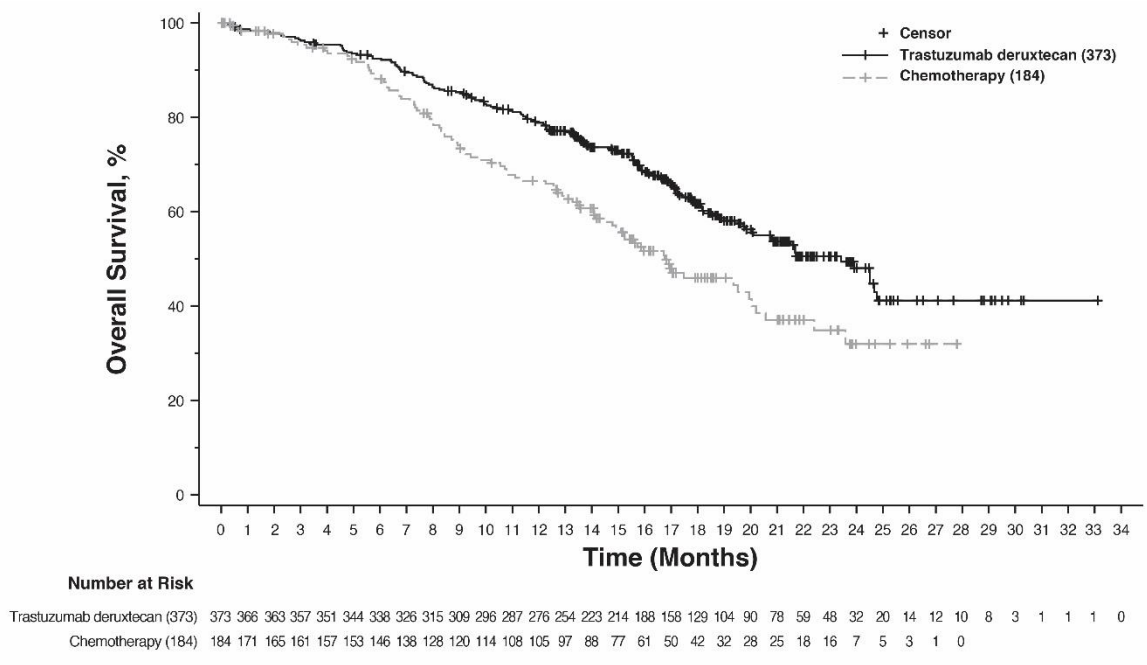
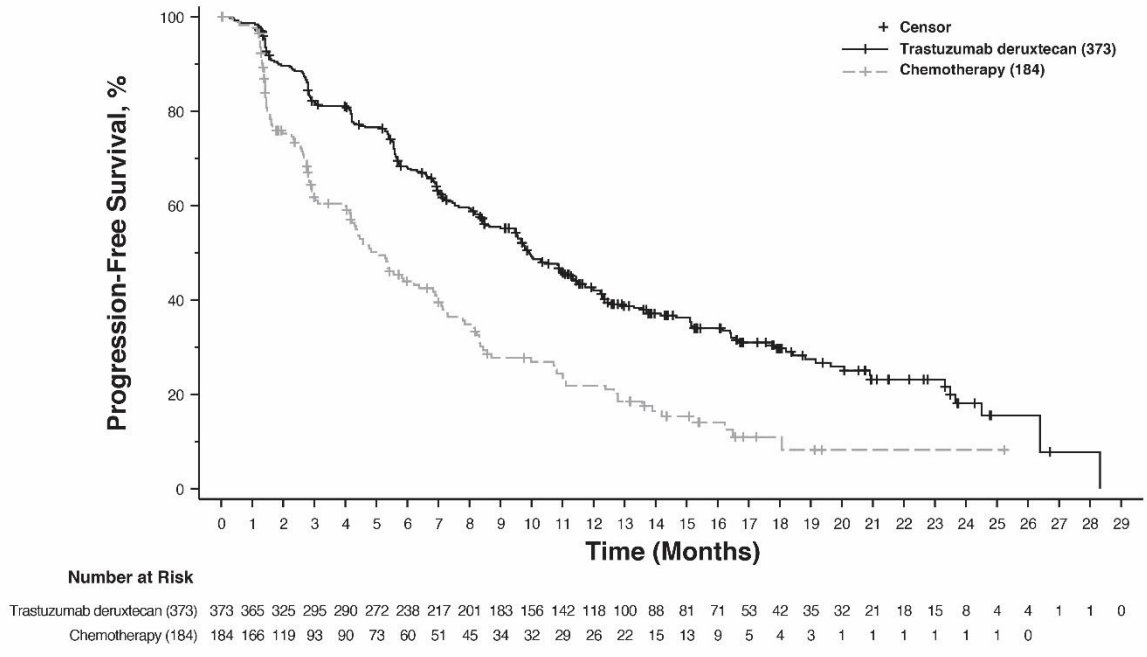


Figure 6: Kaplan-Meier Plot of Progression-free Survival per BICR (Overall Population)



For HR+ patients receiving ENHERTU, health-related quality-of-life was maintained throughout treatment, with the EORTC-QLQ-C30 Global Health status/QoL (primary PRO scale of interest) mean score remaining stable over time up to and including cycle 33.

In addition, the time to definitive deterioration (TTDD) in HR+ patients was longer in the ENHERTU arm compared to the chemotherapy arm for all prespecified scales of the EORTC-QLQ-C30 (global health status, pain symptoms, physical functioning, emotional functioning, and social functioning), suggesting that ENHERTU maintains quality of life longer than chemotherapy in patients with unresectable or metastatic HER2-low breast cancer. Of note, in the QLQ-C30 global health status scale, the median TTDD by at least 10 points in global health status/global QoL scale score was 7.6 months (95% CI: 5.8, 9.2) in the ENHERTU arm versus 5.1 months (95% CI: 3.1, 6.9) in the chemotherapy arm (stratified hazard ratio: 0.71 [95% CI: 0.56, 0.92]). In the QLQ C30 pain symptom subscale, the median TTDD by at least 10 points in pain symptoms was 9.7 months (95% CI: 8.5, 11.1) in the ENHERTU arm versus 4.4 months (95% CI: 2.8, 6.2) in the chemotherapy arm (stratified hazard ratio: 0.51 [95% CI: 0.39, 0.65]). These results are consistent with the primary result and confirm the QoL benefit of ENHERTU versus chemotherapy for patients with metastatic HER2-low breast cancer.

Unresectable or Metastatic NSCLC

ENHERTU was evaluated in DESTINY-Lung01 and at two dose levels in DESTINY-Lung02. The recommended dose of 5.4 mg/kg intravenously every 3 weeks in DESTINY-Lung02 is described below.

The efficacy and safety of ENHERTU were evaluated in DESTINY-Lung02, a Phase 2, randomized, 2-arm, multicentre study. The study included adult patients with HER2-mutated metastatic NSCLC who had received at least one regimen of prior anticancer therapy that must have contained a platinum-based chemotherapy drug. Patients were selected for treatment with ENHERTU based on the presence of activating HER2 (ERBB2) mutations in a tumour specimen. Patients were randomized 2:1 to receive ENHERTU 5.4 mg/kg or 6.4 mg/kg every 3 weeks, respectively. Randomization was stratified by prior anti-programmed cell death receptor-1 (PD-1) and/or anti-programmed cell death ligand 1 (PD-L1) treatment versus those who received neither. Treatment was administered until disease progression, death, withdrawal of consent, or unacceptable toxicity. The study excluded patients with a history of ILD/pneumonitis requiring treatment with steroids or ILD/pneumonitis at screening and clinically significant cardiac disease. Patients were also excluded for untreated and symptomatic brain metastases or ECOG performance status >1.

The major efficacy outcome was confirmed ORR as assessed by BICR using RECIST v1.1. DOR, PFS, and OS were secondary outcome measures.

Demographic and baseline disease characteristics were: median age 59.4 years (range 31 to 84); female (63.7%); Asian (63.7%), White (22.5%), or Other (13.7%); ECOG performance status 0 (28.4%) or 1 (71.6%); 97.1% had a mutation in the ERBB2 kinase domain, 2.9% in the extracellular domain; 34.3% had stable brain metastases; 46.1% were former smokers, none were current smokers; 21.6% had a prior lung resection. In the metastatic setting, 32.4% had greater than 2 prior systemic therapies, 100% had received platinum-based therapy, 73.5% had received anti-PD-1/PD-L1 therapy, and 50.0% had prior treatment with platinum therapy and anti-PD-1/PD-L1 therapy in combination.

Efficacy results are summarized in Table 9. The median time to initial response was 1.8 months (range 1.2 to 7.0 months).

Table 9: Efficacy Results in DESTINY-Lung02

Efficacy Parameter	**DESTINY-Lung02 5.4 mg/kg N=102**
Confirmed Objective Response Rate	
n (%)	50 (49.0)
(95% CI)*	39.0, 59.1
Complete Response n (%)	1 (1.0)
Partial Response	49 (48.0)
Duration of Response Median, months (95% CI)†	16.8 (6.4, NE)
Progression-free Survival (PFS) per BICR	
Number of events (%)	44 (43.1)
Median, months (95% CI)†	9.9 (7.4, NE)
Overall Survival	
Number of events (%)	37 (36.3)
Median, months (95% CI)†	19.5 (13.6, NE)
Survival at 12 months (95% CI)‡	67% (56.0, 76.0)

*ORR 95% CI calculated using Clopper-Pearson method
CI = confidence interval, NE = not estimable
†95% CI calculated using Brookmeyer-Crowley method
‡Based on Kaplan-Meier estimate.

5.2 PHARMACOKINETIC PROPERTIES

Distribution

Based on population pharmacokinetic analysis, the volume of distribution of the central compartment (Vc) of trastuzumab deruxtecan was estimated to be 2.69 L.

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

In vitro, the blood to plasma concentration ratio of the topoisomerase I inhibitor was approximately 0.6.

Biotransformation

Trastuzumab deruxtecan undergoes intracellular cleavage by lysosomal enzymes to release the active topoisomerase I inhibitor.

The humanised HER2 IgG1 monoclonal antibody is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

In vitro metabolism studies in human liver microsomes indicate that the topoisomerase I inhibitor is metabolized mainly by CYP3A4 via oxidative pathways.

Elimination

Based on population pharmacokinetic analysis, following intravenous administration of trastuzumab deruxtecan in patients across multiple tumour types, the clearance of trastuzumab deruxtecan was estimated to be 0.40 L/day and the clearance of the topoisomerase I inhibitor was 18.4 L/h. The median elimination half-life ($t_{1/2}$) of trastuzumab deruxtecan was 5.4-5.7 days and apparent median $t_{1/2}$ of released topoisomerase I inhibitor was approximately 5.4-6.1 days. Moderate accumulation (approximately 35% in cycle 3 compared to cycle 1) of trastuzumab deruxtecan was observed.

Following intravenous administration of the topoisomerase I inhibitor to rats, the major excretion pathway was faeces via the biliary route. The topoisomerase I inhibitor 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 topoisomerase I inhibitor was the most abundant component in urine and faeces.

Linearity/Nonlinearity

The exposure of trastuzumab deruxtecan and released topoisomerase I inhibitor 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

Age, race, ethnicity, sex and body weight

Based on population pharmacokinetic analysis, age (20-96 years), race, ethnicity, sex and body weight did not have a clinically meaningful effect on exposure of trastuzumab deruxtecan or released topoisomerase I inhibitor.

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 topoisomerase I inhibitor was not affected by mild to moderate renal impairment as compared to normal renal function (CLcr ≥90 mL/min).

Hepatic impairment

No dedicated hepatic impairment study was conducted. Based on population pharmacokinetic analysis, higher levels of AST and total bilirubin resulted in a lower clearance of topoisomerase I inhibitor. The impact of these changes is not expected to be clinically meaningful.

5.3 PRECLINICAL SAFETY DATA

Animal Toxicology and/or Pharmacology

In a six-week repeat-dose toxicity study, trastuzumab deruxtecan was administered to rats once every three weeks at doses up to 197 mg/kg (approximately 31 times the clinical dose of 5.4 mg/kg based on AUC). Toxicities were observed in intestines, lymphatic/hematopoietic organs (thymus, lymph nodes, bone marrow), kidneys, skin, testes, and incisor teeth. All changes observed, except for testicular and incisor teeth changes, were reversible following a nine-week recovery period.

In a three-month repeat-dose toxicity study, trastuzumab deruxtecan was administered to monkeys once every three weeks at doses up to 30 mg/kg (approximately 9 times the clinical dose of 5.4 mg/kg based on AUC). Toxicities were observed in intestines, testes, skin, bone marrow, kidneys, and lungs. Pulmonary toxicity was observed at the highest dose (30 mg/kg) and histopathologically characterized by aggregation of foamy alveolar macrophages and focal alveolus and/or interstitial inflammation which showed reversibility after a three-month recovery period. 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.

Mutagenesis/Carcinogenesis

The topoisomerase I inhibitor component of trastuzumab deruxtecan 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 studies have not been conducted with trastuzumab deruxtecan.

Impairment of Fertility and Teratogenicity

There were no animal reproductive or developmental toxicity studies conducted with trastuzumab deruxtecan. Based on results from general animal toxicity studies, trastuzumab deruxtecan and the topoisomerase I inhibitor component were toxic to rapidly dividing cells (lymphatic/hematopoietic organs, intestine, or testes), and the topoisomerase I inhibitor was genotoxic, suggesting the potential for embryotoxicity and teratogenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- L histidine
- L histidine hydrochloride monohydrate
- Sucrose
- Polysorbate 80

6.2 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.

6.3 SHELF LIFE

Unopened vial

36 months

Reconstituted Solution

It is recommended that the reconstituted solution be used immediately. If not used immediately, the reconstituted solution may be stored in a refrigerator at 2ºC to 8ºC for up to 24 hours from the time of reconstitution, protected from light.

Diluted Solution

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

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store vials in a refrigerator (2ºC to 8ºC) until time of reconstitution.

Do not freeze.

For storage conditions after reconstitution and dilution of the medicinal product, see Section 6.3 Shelf life.

6.5 NATURE AND CONTENTS OF CONTAINER

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.

Each carton contains 1 glass vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

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.
- Reconstitute each 100 mg vial using a sterile syringe to slowly inject 5 mL of sterile water for injection into each vial to obtain a final concentration of 20 mg/mL.
- Swirl the vial gently until completely dissolved. Do not shake.

- If not used immediately, store the reconstituted ENHERTU vials in a refrigerator at 2ºC to 8ºC for up to 24 hours from the time of reconstitution, protected from light. Do not freeze.
- The product does not contain a preservative. Discard unused ENHERTU after 24 hours refrigerated.

Dilution
Calculation to determine the volume of reconstituted ENHERTU (mL) to be further diluted:

$$\textbf{Reconstituted ENHERTU (mL)} = \frac{\text{ENHERTU dose (mg/kg) x Patient's Body Weight (kg)}}{20\ \text{mg/mL}}$$

- 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 colourless to light yellow. Do not use if visible particles are observed or if the solution is cloudy or discoloured.
- Dilute the calculated volume of reconstituted ENHERTU in an infusion bag containing 100 mL of 5% dextrose solution. Do not use sodium chloride solution (see Section 6.2 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 2ºC to 8ºC for up to 24 hours, protected from light. Do not freeze.
- Discard any unused portion left in the vial.

Disposal
The reconstituted product contains no preservative and is intended for single use only.

Discard any unused portion left in the vial.

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

AstraZeneca Limited
PO Box 87453
Meadowbank
Auckland 1742.
Telephone: 0800 684 432

9. DATE OF FIRST APPROVAL

7 December 2023

10. DATE OF REVISION OF THE TEXT

19 September 2024

ENHERTU® is a trademark of the Daiichi Sankyo Company limited, used under license by AstraZeneca.

VV-RIM-04950581 v4.0

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.1	Addition of unresectable or metastatic NSCLC indication
4.2	Addition of patient selection information for NSCLC
4.4	Updates to ILD, neutropenia and LVEF decrease sub-sections to include pooled lung cancer studies data.
4.8	NSCLC data added.
5.1	Addition of DESTINY-Lung01 and DESTINY-Lung02 study data.
5.2	Elimination data updated with evolving patient population in studies.