Enhertu® (Trastuzumab DERUXTECAN)

Indication

Unresectable locally advanced or metastatic HER-2 positive breast cancer after 2 or more lines of anti-HER-2 containing therapies which must have included trastuzumab and Kadcyla (trastuzumab emtansine).
(NICE TA704)

Unresectable locally advanced or metastatic HER-2 positive breast cancer after 1 or more lines of anti-HER-2 containing therapies in patients who have received trastuzumab but have NOT received Kadcyla for advanced/metastatic breast cancer.
(NICE TA862)

ICD-10 codes

Codes prefixed with C50

Regimen details

Day	Drug	Dose	Route
1	Enhertu®	5.4mg/kg	IV infusion

To reduce the risk of medication errors it is recommended that all trastuzumab containing products are referred to by brand name i.e. Enhertu® (trastuzumab deruxtecan).

Cycle frequency

21 days

Number of cycles

Until disease progression or unacceptable toxicity.

Administration

Enhertu is administered in 100mL glucose 5% with a 0.22 micron in-line filter. It is recommended that the solution be equilibrated to room temperature prior to commencing infusion. The first dose is administered over 90 minutes. If the first infusion was well tolerated, subsequent doses may be administered over 30 minutes.

In the event of infusion related reactions, the infusion rate should be slowed or interrupted. Enhertu should be discontinued following severe infusion reactions.

Pre-medication

Nil

Emetogenicity

This regimen has moderate emetic potential.

Additional supportive medication

Antiemetics as per local policy.
H_2 antagonist or PPI, if required, as per local policy.
Mouthwashes as per local policy.
Loperamide if required

Extravasation

Enhertu is irritant (Group 3)

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)[#]	14 days
LFTs	14 days
Blood pressure*	14 days
Echocardiogram	Baseline

[#]Low potassium should be corrected prior to commencing treatment.

*If BP consistently ≥ 140/90 mmHg, this should be controlled and managed by the GP prior to commencing treatment.

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days
Blood pressure	Baseline then 3 monthly or as clinically indicated
Echocardiogram	Every 3-6 months, or as per local policy.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	**Limit**
Neutrophils	≥ 1 x 10^9/L
Platelets	≥ 50 x 10^9/L
Haemoglobin	≥ 80g/L
Creatinine clearance (CrCl)	≥ 30mL/min
Bilirubin	≤ 1.5 x ULN
ALT/AST	≤ 3 x ULN
LVEF	> LLN or <10% absolute drop from baseline

Dose modifications

Dose reduction level	**Enhertu Dose**
Full dose	5.4mg/kg
1st dose reduction	4.4mg/kg
2nd dose reduction	3.2mg/kg

If more than 2 dose reductions are required treatment should be discontinued.

Doses should **not** be re-escalated following a dose reduction.

- **Haematological toxicity**

Neutropenia

Neutrophil count (x 10^9/L)	**Action**
0.5-0.99	Withhold Enhertu until ≥ 1 x 10^9/L Continue at current dose
<0.5	Withhold Enhertu until ≥ 1 x 10^9/L Reduce dose by 1 dose level
Febrile neutropenia (neutrophils < 1.0 and temperature >38.3°C or >38°C for more than 1 hour)	Withold Enhertu until resolved Reduce dose by 1 dose level

Thrombocytopenia

Platelet count (x 10^9/L)	**Action**
25-49	Withhold Enhertu until platelets recover to ≥ 75 x 10^9/L If resolved in ≤ 7 days, maintain dose If resolved in > 7 days, reduce dose 1 level
<25	Withhold Enhertu until ≥ 75 x 10^9/L Reduce dose by 1 dose level

Anaemia

Haemoglobin (g/L)	**Action**
<80	Transfuse and withhold Enhertu until haemoglobin recovers to ≥ 80g/L
<80 and life threatening consequences	Transfuse and withhold Enhertu until haemoglobin recovers to ≥ 80g/L Reduce dose by 1 dose level

- **Renal impairment**

Creatinine Clearance	**Action**
30-60mL/min	No dose adjustment required. Note increased incidence of interstitial lung disease observed in those with CrCl 30-60ml/min so close monitoring is required.
<30mL/min	Lack of data available so no recommendations on dose adjustment can be made. Consultant decision to proceed and close monitoring required.

- **Hepatic impairment**

Bilirubin

Bilirubin	**Action**
<1.5 x ULN	No dose reduction indicated
>1.5 – 3 x ULN	Withhold Enhertu until ≤ Grade 1 - If resolved in ≤ 7 days, restart treatment at same dose - If resolved in > 7 days, reduce treatment by 1 dose level
>3 – 10 x ULN	Withhold Enhertu until ≤ Grade 1 - If resolved in ≤ 7 days, reduce treatment by 1 dose level - If resolved in > 7 days, discontinue Enhertu
>10 x ULN	Discontinue Enhertu

Transaminases

ALT/AST	Action
>3 – 5 x ULN	If bilirubin < 1.5 x ULN – no dose reduction indication If bilirubin ≥ 1.5 x ULN - Withhold Enhertu and repeat LFTs in 7 days. - If recovered to ≤ baseline values within 7 days restart Enhertu at same dose. - If results remain deranged beyond 7 days but recover within 21 days restart at next level dose reduction - If results remain deranged beyond 21 days or suspected drug-related hepatotoxicity discontinue Enhertu
>5 – 20 x ULN	Withhold Enhertu until ≤ Grade 1 - If resolved in ≤ 7 days, restart treatment at same dose If resolved in > 7 days, reduce treatment by 1 dose level
>20 x ULN	Discontinue Enhertu

- **Other toxicities**

Left ventricular dysfunction

LVEF	Action
>45% and absolute decrease from baseline 10-20%	Continue treatment with Enhertu
40-45% and absolute decrease from baseline <10%	Continue treatment with Enhertu Repeat LVEF assessment within 3 weeks
40-45% and absolute decrease from baseline is 10-20%	Interrupt Enhertu Repeat LVEF assessment within 3 weeks If LVEF has not recovered to within 10% of baseline, discontinue Enhertu. If LVEF recovers to within 10% of baseline restart Enhertu at 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 less than 40% or absolute decrease from baseline of 20% is confirmed, permanently discontinue Enhertu.
Symptomatic congestive heart failure (CHF)	Permanently discontinue Enhertu

Pulmonary toxicity

Cases of interstitial lung disease (ILD), including pneumonitis, some leading to acute respiratory distress syndrome or a fatal outcome, have been reported. Signs and symptoms include dyspnoea, cough, fatigue, and pulmonary infiltrates. If ILD is suspected, withhold treatment until excluded. If ILD diagnosed Enhertu should be discontinued.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Interstitial lung disease
Febrile neutropenia

- **Frequently occurring side effects**

Myelosuppression
Nausea, vomiting
Fatigue
Alopecia

Constipation
Diarrhoea
Decreased appetite
Stomatitis
Cough
Headache

- **Other side effects**

Hypokalaemia
Increased transaminases
Infusion related reactions
Rash

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.

Additional comments

Women of childbearing potential should use effective contraception during treatment and for at least 7 months after the last dose of Enhertu. Male patients with female partners of childbearing potential should use effective contraception during treatment and for at least 4 months after the last dose of Enhertu.

Anthracyclines must not be given in combination with Enhertu and, preferably, should not be give within 6 months of last dose of, Enhertu.

References

- Modi et al. Trastuzumab Deruxtecan in previously treated HER2-positive Breast Cancer. NEJM 2020; 382:610-621
- Summary of Product Characteristics – Enhertu (Daiichi Sankyo) accessed 19 May 2021 via www.medicines.org.uk
- National Institute for Health and Care Excellence (NICE TA706) accessed 26 May 2021 via www.nice.org.uk
- National Institute for Health and Care Excellence (NICE TA862) accessed 2 March 2023 via www.nice.org.uk

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