Chemotherapy Protocol

BREAST CANCER

ENHERTU

(trastuzumab deruxtecan)

ENHERTU is NOT the same drug as Kadcyla (trastuzumab emtansine) or generic trastuzumab). There is considerable risk of confusion between the products during the prescription, preparation, and administration processes.

Confusion can lead to overdose, undertreating and / or toxicity.

Healthcare professions should use the full INN name, trastuzumab deruxtecan and invented name Enhertu when prescribing, preparing, and administering Enhertu (trastuzumab deruxtecan)

Regimen

- Breast Cancer – Enhertu (trastuzumab deruxtecan)

Indication

- Enhertu (trastuzumab deruxtecan) is indicated for patients who have;

- unresectable locally advanced or metastatic breast cancer.
- histologically documented breast cancer which is HER2 3+ by immunohistochemistry and/or has a HER2 amplification ratio of greater than or equal to 2.0 by in situ hybridisation.
- previously been treated with trastuzumab emtansine and is now either resistant or refractory to trastuzumab emtansine or had to discontinue trastuzumab emtansine due to intolerance.
- received two or more anti-HER2 therapies which must have included trastuzumab and trastuzumab emtansine.

  This includes all clinical settings (neoadjuvant, adjuvant and locally advanced/metastatic indications; eg a treatment pathway of neoadjuvant pertuzumab plus trastuzumab regimen followed by adjuvant trastuzumab and then a 1st relapse treated with a pertuzumab plus trastuzumab regimen and a 2nd relapse treated with trastuzumab emtansine counts as 4 anti-HER2 therapies)

- has a baseline left ventricular ejection fraction (LVEF) of at least 50%.
- do not have untreated or symptomatic brain metastases
- had no prior treatment with trastuzumab deruxtecan unless it has been received as part of the Daiichi Sankyo early access scheme and the patient meets all the other criteria set out here.
- trastuzumab deruxtecan will be used as monotherapy and commencing at a dose of 5.4 mg/Kg administered every 3 weeks
- trastuzumab deruxtecan will be given until disease progression or unacceptable toxicity or patient choice to stop treatment.

Note: trastuzumab deruxtecan is not to be used beyond first disease progression outside the CNS. It is advised that trastuzumab deruxtecan is not (at least initially) discontinued if disease progression is within the CNS alone.

Toxicity

Drug	Adverse Effect
Enhertu (trastuzumab deruxtecan)	Gastrointestinal disorders, headache, interstitial lung disease, left ventricular dysfunction, neutropenia, thrombocytopenia, hypersensitivity

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

- Prior to the first cycle

  - HER2 test
  - Cardiac assessment (history, physical examination, ECG, echocardiogram with or without MUGA

- Prior to all cycles

  - FBC, U&Es and creatinine, LFTs

- Monitor LVEF every three months

- Respiratory assessment for symptoms of interstitial lung disease

Dose Modifications

The dose modifications listed are for a limited number of toxicities. Dose adjustments may be necessary for other toxicities as well.

The Enhertu (trastuzumab deruxtecan) dose should not be re-escalated after a dose reduction is made.

Please discuss all dose reductions / delays with the relevant consultant before prescribing if appropriate. The approach may be different depending on the clinical circumstances. The following applies:

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

Haematology

Prior to prescribing on day one of each cycle the following criteria must be met:

Neutrophils (x10^9/L)	Action
1 or more	100% dose
Grade 3 (less than 1.0-0.5)	Interrupt treatment until resolved to NCI-CTC grade 2 or less, then maintain dose.
Grade 4 (less than 0.5)	Interrupt treatment until resolved to NCI-CTC grade 2 or less. Reduce dose by one level (see table above).
Febrile neutropenia	Interrupt treatment until resolved. Reduce dose by one level (see table above).
Platelets (x10^9/L)	**Action**
50 or more	100% dose
Grade 3 (less than 50 – 25)	Dose delay until resolved to NCI-CTC grade 1 or below. If resolved in 7 days or less, maintain the dose If resolution takes more than 7 days, reduce dose by one level (see table above)
Grade 4 (less than 25)	Delay dose until resolved to NCI-CTC grade 1 or below, then reduce dose by one level (see table above)

Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (NCI-CTCAE v.4.03).

Consider blood transfusion if patient symptomatic of anaemia or haemoglobin of less than 8g/dL

Hepatic Impairment

Drug	Dose (% of original dose)
Enhertu (trastuzumab deruxtecan)	No dose adjustment needed in patients with total bilirubin less than or equal to 1.5 times upper limit of normal (ULN), irrespective of AST value. Insufficient data in patients with total bilirubin more than 1.5 time ULN hence monitored patient carefully and considered dose adjustment.

Renal Impairment

Drug	Dose (% of original dose)
Enhertu (trastuzumab deruxtecan)	No dose adjustment needed in patients with mild or moderate renal impairment. Insufficient data in patients with severe renal impairment hence monitored patient carefully.

Others

Interstitial lung disease (ILD)/pneumonitis

Cases of interstitial lung disease/pneumonitis, have been reported with trastuzumab deruxtecan and fatal outcomes have been observed. All patients need to be aware of the need to immediately report cough, dyspnoea, fever, and/or any new or worsening respiratory symptoms and if a diagnosis is made of interstitial ling disease/pneumonitis, management will include dose interruptions and modifications of trastuzumab deruxtecan

Severity	Action
Asymptomatic ILD/pneumonitis (Grade 1)	Interrupt treatment 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 above). • consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (see below).
Symptomatic ILD/pneumonitis (Grade 2 or greater)	• Permanently discontinue treatment. • Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected (see below).

For asymptomatic (Grade 1) ILD/pneumonitis, consider corticosteroid treatment (e.g. 0.5 mg/kg prednisolone or equivalent). Treatment should be withheld until recovery to NCI-CTC grade 0.

For symptomatic ILD/pneumonitis (Grade 2 or greater), promptly initiate corticosteroid treatment (e.g. 1 mg/kg prednisolone or equivalent) and continue for at least 14 days or until complete resolution of clinical and chest CT findings. Then gradually taper for at least 4 weeks. Treatment should be permanently discontinued.

Patients with a history of ILD/pneumonitis may be at increased risk of developing ILD/pneumonitis.

Cardiac

Severity		Action
LVEF greater than 45% and absolute decrease from baseline is 10% to 20%		• Continue with treatment.
LVEF 40% to 45%	And absolute decrease from baseline is less than 10%	• Continue with treatment • Repeat LVEF assessment within 3 weeks.
	And absolute decrease from baseline is 10% to 20%	• Interrupt treatment. • Repeat LVEF assessment within 3 weeks. • If LVEF has not recovered to within 10% from baseline, permanently discontinue treatment. • 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 treatment. • 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 treatment.
Symptomatic congestive heart failure (CHF)		• Permanently discontinue treatment.

Regimen

21 day cycle until disease progression or toxicity occurs (twelve cycles will be set in Aria)

Drug	Dose	Days	Administration
Enhertu (trastuzumab deruxtecan)	5.4mg/kg	1	Glucose 5% 100ml over 90 minutes for the first infusion, if this is well tolerated subsequent infusions may be given over 30 minutes

Dose Information

- Enhertu (trastuzumab deruxtecan) will be dose banded in accordance with the national dose bands

Administration Information

Extravasation

- Irritant

Others

- The reconstituted solution should be diluted in polyvinyl chloride (PVC) or latex-free PVC-free polyolefin infusion bags.
- The use of 0.20 or 0.22 micron in-line polyethersulfone (PES) or polysulfone (PS) filter is required for the infusion.
- The infusion should be slowed for mild infusion related reactions. It should be stopped for those that are life threatening or severe.
- Administer the first infusion over 90 minutes. For subsequent infusions administer over 30 minutes, if the prior infusions were well tolerated.

Additional Therapy

- For treatment of infusion related reactions 'once only when required' doses of the following should be prescribed:

  - chlorphenamine 10mg intravenous
  - hydrocortisone 100mg intravenous
  - paracetamol 1000mg oral

- Antiemetics

  As take home medication;

  - metoclopramide 10mg three times a day oral when required

- Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed

References

1. Modi S, Saura C, Yamashita T, Park YH, Kim SB, Tamura K et al. DESTINY-Breast01 Investigators. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. N Engl J Med. 2020; 13;382(7):610-621.

REGIMEN SUMMARY

Enhertu (trastuzumab deruxtecan)

Day One

1. Enhertu (trastuzumab deruxtecan) 5.4mg/kg in 100ml glucose 5% over 90 minutes.
   Administration Instructions
   Administer the first infusion over 90 minutes. For subsequent infusions administer over 30 minutes, if the prior infusions were well tolerated.
   Administer the treatment with a 0.20 or 0.22 micron in-line polyethersulfone (PES) or polysulfone (PS) filter.

2. Chlorphenamine 10mg intravenous when required for infusion related reactions.

3. Hydrocortisone 100mg intravenous when required for infusion related reactions

4. Paracetamol 1000mg oral when required for infusion related reactions

Take Home Medicines

5. Metoclopramide 10mg three times a day when required oral
   Administration Instructions
   Please supply 28 tablets or nearest original pack size

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	June 2021	None	Ms Siow Chin Phua Pharmacist	Dr Ellen Copson Consultant Medical Oncologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury Hospital NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.