Trastuzumab Deruxtecan (ENHERTU)

Single agent treatment for patients with HER2+ve unresectable or metastatic breast cancer in adults after 1 or more anti-HER2 therapies.

Drugs/Dosage:	Enhertu (Trastuzumab DERUXTECAN)	5.4mg/kg	IV	Day 1
Administration:	• To be administered in 100ml of glucose 5% and infused via a giving set with a 0.2 micron in-line filter. • **Infuse the first dose over 90 minutes.** • If prior infusions were well tolerated, infuse subsequent doses over 30 minutes. • The infusion rate should be slowed or interrupted in the event of any infusion-related symptoms, and permanently discontinued in patients with severe infusion reactions.			
Frequency:	Every 3 weeks - administer until disease progression or unacceptable toxicity			
Main Toxicities:	• Myelosuppression • Infection • Nausea and vomiting • Headache • Increased transaminases • Fatigue	• Alopecia • Diarrhoea or constipation • Decreased appetite • Musculoskeletal pain	• Interstitial lung disease / pneumonitis • Cardiotoxicity (LV Function decrease)	
Anti-emetics:	• Highly emetogenic, including delayed nausea and/or vomiting.			
Extravasation:	Non-vesicant			
Regular Investigations:	**FBC** **U&Es and LFTs** **CA 15-3** **Echo/MUGA** **ECG & Blood Pressure**	Day 1 Day 1 Day 1, only if elevated prior to treatment Baseline (must be ≥ 50%); every 3 - 4 months for 12 months, then every 6 months if stable patient Baseline and as indicated.		
	• If blood pressure ≥ 140/90 mmHg, a diagnosis of hypertension should be considered. Consider asking patient to visit GP for ambulatory or home blood pressure monitoring. • Patients with a confirmed diagnosis of hypertension should be treated with an ACE inhibitor which is also licensed for the treatment of heart failure e.g. Ramipril.			
Missed/ delayed doses	• 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.			
HER2 Testing:	Patients treated with trastuzumab deruxtecan must have documented HER2-positive tumour status by IHC or by FISH/ DDISH.			

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Review Clinic:	Consultant/ Nurse/ Registrar/ NMP led clinic each cycle.
End of treatment review:	Treatment should be continued as long as the patient is having a clinical benefit from therapy or until unacceptable toxicity occurs.

DOSE MODIFICATIONS		
Dose reduction schedule	1st dose reduction	4.4 mg/kg
	2nd dose reduction	3.2 mg/kg
	Requirement for further dose reduction	Discontinue treatment
Haematological toxicity	**Grade 3**: Neutrophils ≤ 0.5-0.9 x 10^9 /L	Withhold until recovery to Grade 2 or less: neutrophils ≥ 1.0 x 10^9 /L, then restart at same dose
	Grade 4: Neutrophils < 0.5 x 10^9 /L	Withhold until Grade 2 or less: neutrophils ≥ 1.0 x 10^9 /L, then dose **reduce by one level**
	Febrile neutropenia	Withhold until resolved, then dose reduce by one level.
Interstitial lung disease (ILD)/pneumonitis	• Cases of interstitial lung disease (ILD), and/or pneumonitis, have been reported with Enhertu. Fatal outcomes have been observed. • Monitor patients for signs and symptoms of ILD/pneumonitis. • Advise patients to immediately report cough, dyspnoea, fever, and/or any new or worsening respiratory symptoms. • Patients with suspected ILD/pneumonitis should be promptly investigated, including urgent CT thorax. • Initiate steroid treatment as below, as soon as pneumonitis is suspected; and no further Enhertu should be administered until pulmonary toxicity is excluded. • Consider referral to a respiratory consultant.	

	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.*
		• consider corticosteroid treatment (e.g. ≥ 0.5 mg/kg/day prednisolone or equivalent) as soon as ILD/pneumonitis is suspected.

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	Symptomatic ILD/pneumonitis (**Grade 2 or greater**)	• Permanently discontinue Enhertu. • Promptly initiate corticosteroid treatment (e.g. ≥ 1 mg/kg/day prednisolone or equivalent) as soon as ILD/pneumonitis is suspected and continue for at least 14 days followed by gradual taper for at least 4 weeks.
Renal Impairment	**Mild** (CrCl: 60 to 90mL/min) or **Moderate** (CrCl: 30 to 60mL/min).	No dose adjustment is required
	Severe (CrCl:<30mL/min)	The potential need for dose adjustment in patients with severe renal impairment cannot be determined due to insufficient data.
	A higher incidence of Grade 1 and 2 ILD has been observed in patients with moderate renal impairment. **Patients with moderate or severe renal impairment should be monitored carefully**	
Hepatic Impairment	**Total bilirubin** <1.5 times ULN	No dose adjustment is required
	Total bilirubin >1.5 times ULN	The potential need for dose adjustment cannot be determined due to insufficient data; therefore, these patients should be monitored carefully
Cardiotoxicity	- Patients treated with anti-HER2 therapy are at increased risk for developing Congestive Heart Failure (CHF) or asymptomatic cardiac dysfunction. - Treatment with these agents has not been studied in patients with a prior history of CHF or conditions that could impair left ventricular function such as; uncontrolled hypertension, recent myocardial infarction, serious cardiac arrhythmia requiring treatment or a cumulative prior anthracycline exposure to > 360 mg/m^2 of doxorubicin or its equivalent. Caution should be exercised in treating patients with increased cardiac risk, e.g. uncontrolled hypertension, documented coronary artery disease, CHF, LVEF of <55%, older age. Patients who have received prior anthracycline or prior radiotherapy to the chest area may be at higher risk of LVEF declines. - Cardiac risk should be carefully considered and balanced against the medical need of the individual patient before use of anti-HER2 therapy with an anthracycline. Based on the pharmacological actions of HER2-targeted agents and anthracyclines, the risk of cardiac toxicity might be expected to be higher with concomitant	

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use, than with sequential use. Anti-HER2 therapy should not be given concurrently with anthracyclines in the adjuvant / metastatic treatment setting.

- As per **local agreement**, cardiac monitoring (via ECHO/ MUGA) should be performed at baseline, then at a minimum interval of 3 to 4 monthly during the first year of treatment. This interval can be increased to 6 monthly in the advanced setting if clinically appropriate/ stable cardiac function present. Post-treatment cardiac monitoring is recommended at a minimum interval of every 12 months for 2 years.

- If symptomatic cardiac failure develops during therapy, it should be treated with standard medicinal products for CHF. Most patients who developed CHF or asymptomatic cardiac dysfunction in trials improved with standard CHF treatment consisting of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and a beta-blocker. The majority of patients with cardiac symptoms and evidence of a clinical benefit of treatment continued on therapy without additional clinical cardiac events.

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

Parameters below have been agreed locally following review of anti-HER2 therapy product literature & European Cardiology Society guidelines. ***See local policy on Cardiotoxicity & Anti-HER2 Therapies***

LVEF		Treatment Modifications
LVEF greater than 45% and absolute decrease from baseline is 10% to 20%		Continue treatment with Enhertu.
LVEF 40% to 45%	And absolute decrease from baseline is less than 10%	• Continue treatment with Enhertu. • Repeat LVEF assessment within 3 weeks.
	And absolute decrease from baseline is 10% to 20%	– **Withhold & repeat LVEF assessment within 3 weeks.** – If LVEF recovers to within 10% from baseline, resume treatment with Enhertu at the same dose. – If LVEF has not recovered to within 10% from baseline, permanently discontinue Enhertu. – Consider cardiology referral.

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	LVEF less than 40% or absolute decrease from baseline is greater than 20%	• **Withhold & 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. • Cardiology referral is recommended.
	Symptomatic congestive heart failure (CHF)	- Permanently discontinue Enhertu - Refer to Cardiology.

References:

- SPC Enhertu: https://www.medicines.org.uk/emc/product/12135/smpc
- https://www.royalsurrey.nhs.uk/download.cfm?doc=docm93jijm4n19604.pdf&ver=48363
- Local Cardiotoxicity Protocol: Cardiotoxicity & Anti-HER2 Therapies (sharepoint.com)
- NICE TA 862: https://www.nice.org.uk/guidance/ta862
- Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer | NEJM
- Study of DS-8201a in Subjects With Advanced Solid Malignant Tumors - Full Text View - ClinicalTrials.gov
- https://www.clatterbridgecc.nhs.uk/application/files/7716/2375/2367/Enhertu_Trastuzumab_Deruxtecan_HER2_Positive_Advanced_Breast_Cancer_Protocol.pdf
- 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS): Developed by the task force on cardio-oncology of the European Society of Cardiology (ESC): https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehac244/6673995

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