Indication	For unresectable locally advanced or metastatic HER2-positive breast cancer in patients: who have received **2 or more anti-HER2 therapies** and who have received trastuzumab emtansine (Kadcyla®) in the advanced/metastatic disease setting. OR have been treated with **1 or more anti-HER2 therapies** and who are treatment-naïve for trastuzumab emtansine in the advanced/metastatic disease setting and have been treated with a prior regimen which contained at least trastuzumab and a taxane or trastuzumab and capecitabine for advanced /metastatic breast cancer or developed disease recurrence during or within 6 months of completing an adjuvant or neoadjuvant treatment regimen which contained at least trastuzumab and a taxane or adjuvant treatment with trastuzumab emtansine. NB The patient must have had no prior treatment with trastuzumab deruxtecan unless it has been received as part of the Daiichi Sankyo early access scheme.
Treatment Intent	Palliative
Frequency and number of cycles	Repeat every 21 days. Continue until disease progression or unacceptable toxicity or patient choice to stop treatment. NB May be continued if disease progression is within the CNS alone.
Monitoring Parameters pre-treatment	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • **The use of trastuzumab deruxtecan is restricted to patients whose tumours have documented HER2 positive at the 3+ level by IHC or a ratio of >/= 2.0 by FISH/ISH positive disease.** • FBC, U&Es and LFTs should be monitored at baseline and prior to each cycle. Proceed with treatment if neuts >/= 1.0 and PLT >/= 100. • Cardiac function should be monitored prior to treatment (ECHO/MUGA and ECG) and baseline left ventricular ejection fraction (LVEF) must be >/=50%. Thereafter, ECHO / MUGA every 3 months or as clinically indicated. See table 1 for management of decreased LVEF. • High resolution chest CT every 6 weeks, await results and consultant review before proceeding with next cycle. • The patient should not have untreated or symptomatic brain metastases prior to starting treatment. • **Hepatic impairment:** No adjustment to the starting dose is required for patients with total bilirubin </= 1.5 times upper limit of normal (ULN), irrespective of aspartate transaminase (AST) value. Limited data of use in patients with total bilirubin > 1.5 times ULN, irrespective of AST value, these patients should be closely monitored.

	• **Renal impairment:** No adjustment to the starting dose is needed in patients with mild or moderate renal impairment (CrCl 30 - 89ml/min). Limited data of use in patients with severe renal impairment (CrC l<30ml/min). A higher incidence of Grade 1 and 2 ILD has been observed in patients with moderate renal impairment. Patients with CrCl <60ml/min should be closely monitored. • **Dose Modification:** If a dose reduction is required the first reduction should be to 4.4mg/kg and the second to 3.2mg/kg. No further dose reduction is permitted. Do not re-escalate a previously reduced dose. See table 1 for dose modification guidelines. • **Infusion-related reactions:** • The infusion rate of should be slowed or interrupted if the patient develops infusion-related symptoms. Treatment should be permanently discontinued in case of severe infusion reactions. • **Management of adverse reactions and dose adjustments:** • **Interstitial lung disease (ILD)**, including pneumonitis, has been reported in patients treated with trastuzumab deruxtecan, see table 1 for recommended dose adjustments in ILD. At each nurse assessment assess for dyspnoea, cough & fatigue and patients should be advised to immediately report cough, dyspnoea, fever, and/or any new or worsening respiratory symptoms. Evidence of ILD/pneumonitis should be promptly investigated. Patients with suspected ILD/pneumonitis should be evaluated by radiographic imaging, preferably a computed tomography (CT) scan. Consultation with a pulmonologist should be considered. Patients with a history of ILD/pneumonitis or patients with moderate or severe renal impairment may be at increased risk of developing ILD/pneumonitis and should be monitored carefully. • **<u>Common drug interactions (for comprehensive list refer to BNF/SPC)</u>:** No significant interactions. • Females of reproductive potential should be advised to use effective contraception during treatment and for at least 7 months following the last dose. Male patients with female partners of reproductive potential should be advised to use effective contraception during treatment and for at least 4 months after the last dose. • **Missed dose:** If a dose is missed, it should be administered as soon as possible and the schedule adjusted to maintain a 3-weekly interval between doses. • **Driving:** Patients should be advised to use caution when driving or operating machinery in case they experience fatigue, headache or dizziness during treatment. • Patients should be advised to carry the Enhertu® patient card.
References	KMCC protocol BRE-084 V2 CDF list V1.321

NB For funding information, refer to CDF and NICE Drugs Funding List

Table 1: Dose modifications for adverse reactions

Adverse reaction	Severity		Treatment modification
Interstitial lung disease (ILD)/pneumonitis	Asymptomatic ILD/pneumonitis (Grade 1)		Interrupt 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.
	Symptomatic ILD/pneumonitis (Grade 2 or greater)		• Permanently discontinue. • 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.
Neutropenia	Grade 3 (less than 1.0-0.5 × 10^9/L)		• Interrupt until resolved to Grade 2 (>/=1.0 x 10^9/L), or less, then maintain dose.
	Grade 4 (less than 0.5 × 10^9/L)		• Interrupt until resolved to Grade 2 (>/=1.0 x 10^9/L), or less. • Reduce dose by one level.
Febrile neutropenia	Absolute neutrophil count of less than 1.0 × 10^9/L and temperature greater than 38.3 °C or a sustained temperature of 38 °C or greater for more than one hour.		• Interrupt until resolved. • Reduce dose by one level.
Left ventricular ejection fraction (LVEF) decreased	LVEF greater than 45% and absolute decrease from baseline is 10% to 20%		• Continue treatment.
	LVEF 40% to 45%	And absolute decrease from baseline is less than 10%	• Continue 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. • If LVEF recovers to within 10% from baseline, resume treatment 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.
	Symptomatic congestive heart failure (CHF)		• Permanently discontinue.

Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v.5.0).

Repeat every 21 days.

Day	Drug	Dose	Route	Infusion Duration	Administration
Day 1	Ondansetron	<75yrs 16mg >/=75yrs 8mg	IV	15 min	In 50ml Sodium chloride 0.9%
	Dexamethasone	8mg	PO		
	TRASTUZUMAB DERUXTECAN (Enhertu®)	**5.4mg/kg**	IV	1st infusion over 90mins. If the first dose is well tolerated then give subsequent doses over 30 minutes.	In 100ml **5% glucose** with 0.22micron in-line PES filter.
TTO	Drug	Dose	Route	Directions	
Day 1	Dexamethasone	6mg	PO	OM for 3 days. Take with or just after food, or a meal.	
	Metoclopramide	10mg	PO	10mg 3 times a day for 3 days then 10mg up to 3 times a day as required. Do not take for more than 5 days continuously. (dispense 28 tablets on cycle 1, then only when required)	
	Loperamide	2mg-4mg	PO	Take 4mg initially then 2mg after each loose stool when required (max 16mg a day) (dispense 1x op on cycle 1, then only when required)	