Indication	Monotherapy treatment for patients with HER2-positive early breast cancer who have residual invasive disease following the combination of taxane-based and HER2-targeted neoadjuvant systemic therapy and surgery.
Treatment Intent	Adjuvant
Frequency and number of cycles	Repeat every 21 days for a maximum of 14 cycles. NB If trastuzumab emtansine has to be discontinued early, without disease progression, when prescribed for early breast cancer, completion of the intended adjuvant treatment duration up to 14 cycles of adjuvant HER2-directed therapy can be done with trastuzumab (if lymph node negative) or trastuzumab with pertuzumab (if lymph node positive). NB: A maximum of 18 cycles of HER2-directed therapy (neoadjuvant plus adjuvant) are funded provided all other criteria are met.
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 emtansine is restricted to patients whose tumours significantly overexpress HER2 at the 3+ level or greater, or a ratio of >/= 2.0 by ISH • FBC, U&Es and LFTs should be monitored at baseline and prior to each cycle. • At the start of each cycle ensure PLT >/= 100 and neuts >/= 1.0. • Patients with thrombocytopenia (≤ 100 x 10^9/l) and patients on anti-coagulant treatment should be monitored closely while on trastuzumab emtansine, cases of haemorrhage have been reported. • Blood pressure before every cycle. • Cardiac function should be monitored at baseline (ECHO/MUGA and ECG) and then every 3 months (ECHO or MUGA) during treatment or as clinically indicated. • Record on KOMs Cardiac Monitoring Record. • It is the prescribers' responsibility to check that the ECHO/MUGA result is satisfactory before starting and continuing treatment. LVEF should be >/=50% at baseline. **See Table 1** for dose modifications. • **Hepatic Impairment:** No adjustment to the starting dose is required for patients with mild or moderate hepatic impairment. Trastuzumab emtansine has not been studied in patients with severe hepatic impairment. Treatment of patients with hepatic impairment should be undertaken with caution due to known hepatotoxicity observed with trastuzumab emtansine. • **Renal Impairment:** No adjustment to the starting dose is needed in patients with mild or moderate renal impairment (CrCl >/=30ml/min and <90ml/min). Use with caution in patients with severe renal impairment (CrCl<30ml/min). • **Dose modification:** • If a dose reduction is required the first should be to 3mg/kg and the second to 2.4mg/kg. No further dose reduction is permitted. Do not re-escalate a previously reduced dose. Treatment should be discontinued if symptoms persist. See **table 1** for dose modification guidelines. ○ Trastuzumab emtansine should be temporarily discontinued in patients experiencing Grade 3 or 4 peripheral neuropathy until resolution to ≤ Grade 2. At retreatment a dose reduction may be considered.

	• **Infusion rates and infusion related reaction:**
	  ○ Patients must be observed closely for infusion related adverse effects during the infusion and for at least 90 minutes following the first infusion and (if tolerated) for subsequent doses, during the infusion and for at least 30 minutes after the end of the infusion.
	  ○ If the first dose is well tolerated (no infusion related reactions), then the second and subsequent doses may be administered over 30 minutes (no pre-medication required).
	• **Interstitial lung disease (ILD),** including pneumonitis, has been reported in patients treated with trastuzumab emtansine. At each nurse assessment assess for dyspnoea, cough & fatigue. It is recommended that treatment be permanently discontinued in patients who are diagnosed with ILD or pneumonitis, except for radiation pneumonitis in EBC (see table 1 for guidance on radiation pneumonitis).
	• **Common drug interactions: (for comprehensive list refer to BNF/SPC)**
	• Concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, and voriconazole) should be avoided if possible.
	• **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.

References	KMCC protocol BRE-075 V1 BlueTeq form accessed online 10.10.2023 SPC accessed online 10.10.23

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

Table 1

Dose Modifications for Patients with EBC		
Adverse reaction	**Severity**	**Treatment modification**
Increased Alanine Transaminase (ALT)	Grade 2-3 (> 3.0 to ≤ 20× ULN on day of scheduled treatment)	Do not administer trastuzumab emtansine until ALT recovers to Grade ≤ 1 (≤ 3 x ULN), and then reduce one dose level
	Grade 4 (> 20 × ULN at any time)	Discontinue trastuzumab emtansine
Increased Aspartate Transaminase (AST)	Grade 2 (> 3.0 to ≤ 5× ULN on day of scheduled treatment)	Do not administer trastuzumab emtansine until AST recovers to Grade ≤ 1 (≤ 3 x ULN), and then treat at the same dose level
	Grade 3 (> 5 to ≤ 20× ULN on day of scheduled treatment)	Do not administer trastuzumab emtansine until AST recovers to Grade ≤ 1 (< 3 x ULN), and then reduce one dose level
	Grade 4 (> 20 × ULN at any time)	Discontinue trastuzumab emtansine
Hyperbilirubinemia	TBILI > 1.0 to ≤ 2.0× the ULN on day of scheduled treatment	Do not administer trastuzumab emtansine until total bilirubin recovers to ≤ 1.0× ULN, and then reduce one dose level
	TBILI > 2× ULN at any time	Discontinue trastuzumab emtansine
Drug Induced Liver Injury (DILI)	Serum transaminases > 3 x ULN and concomitant total bilirubin > 2× ULN	Permanently discontinue trastuzumab emtansine in the absence of another likely cause for the elevation of liver enzymes and bilirubin, e.g. liver metastasis or concomitant medication
Nodular Regenerative Hyperplasia (NRH)	All Grades	Permanently discontinue trastuzumab emtansine
Peripheral Neuropathy	Grade 3-4	Do not administer trastuzumab emtansine until resolution ≤ Grade 2
Left Ventricular Dysfunction	LVEF < 45%	Do not administer trastuzumab emtansine. Repeat LVEF assessment within 3 weeks. If LVEF < 45% is confirmed, discontinue trastuzumab emtansine.
	LVEF 45% to < 50% and decrease is ≥ 10% points from baseline*	Do not administer trastuzumab emtansine. Repeat LVEF assessment within 3 weeks. If the LVEF remains < 50% and has not recovered to < 10% points from baseline, discontinue trastuzumab emtansine.
	LVEF 45% to < 50% and decrease is < 10% points from baseline*	Continue treatment with trastuzumab emtansine. Repeat LVEF assessment within 3 weeks.
	LVEF ≥ 50%	Continue treatment with trastuzumab emtansine
Heart Failure	Symptomatic CHF, Grade 3-4 LVSD or Grade 3-4 heart failure, or Grade 2 heart failure accompanied by LVEF <45%	Discontinue trastuzumab emtansine
Pulmonary Toxicity	Interstitial lung disease (ILD) or pneumonitis	Permanently discontinue trastuzumab emtansine
Radiotherapy-Related Pneumonitis	Grade 2	Discontinue trastuzumab emtansine if not resolving with standard treatment
	Grade 3-4	Discontinue trastuzumab emtansine

ALT = alanine transaminase; AST = aspartate transaminase, CHF = congestive heart failure, LVEF = left ventricular ejection fraction, LVSD = left ventricular systolic dysfunction, TBILI = Total Bilirubin, ULN = upper limit of normal

* Prior to starting trastuzumab emtansine treatment.

Repeat every 21 days.

Day	Drug	Dose	Route	Infusion Duration	Administration
Day 1	**TRASTUZUMAB EMTANSINE (Kadcyla®)**	**3.6mg/kg**	IV	90 min for first infusion. See notes for subsequent infusions	In 250ml sodium chloride 0.9% with 0.22micron in-line PES filter