Indication	The neoadjuvant, then adjuvant or adjuvant treatment of clinically defined axillary node positive HER2-positive early breast cancer.
Treatment Intent	Neo-adjuvant / Adjuvant
Frequency and number of cycles	4 cycles of EC every 21 days followed by 4 cycles every 21 days of paclitaxel (weekly) and pertuzumab/trastuzumab SC followed by 14 cycles of pertuzumab/trastuzumab SC every 21 days or until disease recurrence, or unmanageable toxicity, or patient's decision whichever occurs first NB In the neo-adjuvant setting patients may receive 4 cycles of EC followed by 4 cycles of paclitaxel and pertuzumab /trastuzumab (SC) and then receive pertuzumab/trastuzumab (SC) adjuvantly. For patients with residual invasive disease following neo-adjuvant therapy offer trastuzumab emtansine (Kadcyla®), to a maximum of 14 cycles. Note: A maximum of 18 cycles of HER2-directed therapy (neo-adjuvant plus adjuvant) are funded provided all other criteria are met. NB patients can be switched between combination SC therapy (Phesgo®) or pertuzumab and trastuzumab IV therapy if the clinical need arises with the usual dosing interval.
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. • Consider using actual BSA. **EC** • ECG should be checked prior to cycle 1 and undertake ECHO/MUGA as clinically indicated (see on-going cardiac monitoring below during pertuzumab/trastuzumab treatment). • Maximum cumulative dose of epirubicin = 950mg/m^2. • Monitor FBC, LFT and U&E at each cycle. • If neuts >/= 1 and PLT >/=100 continue with treatment. If neuts <1 or PLT <100 delay 1 week. • **Hepatic and renal impairment:** d/w consultant or registrar if bilirubin elevated. • Epirubicin: if bilirubin is 24-51 µmol /L give 50%, if bilirubin is 52-85µmol/L give 25%, if bilirubin is >85µmol/L omit, see table 2. • Dose reduction should be considered if grade 3 or 4 non-haematological toxicity or repeat appearance of grade 2 (except N&V and alopecia). Delay until resolution of toxicity to </= grade 1 **Paclitaxel and Pertuzumab and Trastuzumab SC** • The use of trastuzumab and pertuzumab is restricted to patients whose tumours significantly overexpress HER2 at the 3+ level by IHC or FISH/CISH positive disease. • At each nurse assessment, patients should be assessed for signs of dyspnoea. • FBC, U&Es and LFTs on day 1,8 and 15 of each cycle of paclitaxel and pertuzumab and trastuzumab SC, and then FBC every 3 months of maintenance trastuzumab and pertuzumab SC to correspond with pre-cycle 9,13,17 and 21 of the regimen.

	• On days 1, 8 and 15 of each cycle of paclitaxel and pertuzumab and trastuzumab SC, if neuts <1.0 or PLT <100 delay 1 week. If neuts >/= 1 and PLT >/=100 continue with treatment. • **Renal and hepatic impairment:** Dose reductions of pertuzumab and trastuzumab SC are not required in mild to moderate renal impairment. There are no recommendations for dose reductions of pertuzumab and trastuzumab SC in severe renal impairment due to limited data. There are no recommendations for dose reductions of pertuzumab and trastuzumab SC in hepatic impairment. o Paclitaxel: If bilirubin < 1.25 x ULN and transaminase < 10 x ULN, dose at full dose. Otherwise consider dose reduction see table 1. • **<u>Pertuzumab and trastuzumab SC Injection duration and monitoring</u>:** • **Pertuzumab and trastuzumab**: The loading dose of pertuzumab and trastuzumab SC should be administered over 8 minutes, and the maintenance dose over 5 minutes. Patients must be observed closely for injection related adverse effects during administration and for 30 minutes after the completion of the loading dose of pertuzumab and trastuzumab SC and for 15 minutes after the completion of maintenance doses. If a significant injection-related reaction occurs, the injection should be slowed down or paused and appropriate medical therapies should be administered. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Discontinue pertuzumab and trastuzumab SC in the event of grade 4 hypersensitivity reaction. • **Paclitaxel hypersensitivity:** Patients developing hypersensitivity reactions to Paclitaxel may be rechallenged with full dose Paclitaxel following prophylactic medication (e.g. famotidine 40mg po given 4 hours prior to treatment plus hydrocortisone 100mg iv and chlorphenamine 10mg iv 30 minutes prior to treatment), then give paclitaxel over 3-6 hours (i.e. starting at over 6 hours and gradually increase rate if possible). If patients experience no hypersensitivity reactions after the first two doses of paclitaxel, remove pre-medication with dexamethasone, chlorphenamine and H2 antagonist from dose 3 onwards. • **Administration of pertuzumab and trastuzumab SC (Phesgo®):** o Inject into the subcutaneous tissue of the thigh only. Injection sites should alternate between left and right thigh. New injections should be given at least 2.5 cm from the previous site. Do not inject at other sites of the body. o Do not inject into areas where the skin is red, bruised, tender, or hard. o The dose should not be split between two syringes or between two sites of administration. o Do not administer other medicinal products for subcutaneous use at the same site as pertuzumab/trastuzumab SC. • **Re-loading:** The loading doses of pertuzumab and trastuzumab SC should be repeated if the interval between injections is 6 weeks or more (i.e. if the doses are missed by 3 weeks or more), thereafter the maintenance dose can be given. NB This applies regardless of whether prior treatment was pertuzumab iv and trastuzumab iv or pertuzumab and trastuzumab SC. • **Dose reductions:** o Dose reduce Paclitaxel by 20% in the event of >/= grade 2 neuropathy and consider a delay until recovery to </= grade 1. o Consider omitting paclitaxel in event of recurrent >/= grade 3 neuropathy or recurrent OR persistent >/=grade 2 neuropathy following a dose reduction.

	○ Dose reduction of paclitaxel should be considered if any other grade 3 or 4 non-haematological toxicity or repeat appearance of grade 2 (except N&V and alopecia). Delay until resolution of toxicity to </= grade 1. ○ No dose reductions are recommended for pertuzumab and trastuzumab SC. • **Cardiac function** must be monitored. ○ An ECHO/ MUGA should be carried out pre-cytotoxic chemotherapy (if indicated), pre-cycle 5 then every 3 months and 3-4 weeks after the end of treatment. ○ Record on KOMs Cardiac Monitoring Record ○ The pre-treatment left ventricular ejection fraction must be >/=55% and the LVEF must be >/=50% after completion of the anthracycline component of the adjuvant chemotherapy. ○ **It is the prescribers' responsibility to check that the ECHO/MUGA result is satisfactory before continuing treatment.** ○ Pertuzumab/trastuzumab SC should be withheld for at least 3 weeks in the event of signs and symptoms of congestive heart failure or drop in LVEF to less than 50% associated with a fall of >/=10% points below pre-treatment values. Pertuzumab and trastuzumab SC may be resumed if the LVEF has recovered to >/=50% or to a difference of < 10% points below pre-treatment values. • **Common drug interactions (for comprehensive list refer to BNF/SPC):** ○ Paclitaxel: Caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit either CYP2C8 or CYP3A4 (e.g. ketoconazole, erythromycin, fluoxetine, clopidogrel, cimetidine, ritonavir and nelfinavir); toxicity may be increased. CYP2C8 or CYP3A4 inducers (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) may reduce efficacy. ○ Pertuzumab and trastuzumab SC: No formal drug interaction studies have been performed. Caution with other cardiotoxic drugs. ○ Caution, ciclosporin increases concentration of epirubicin. • **Driving and operating machinery:** Pertuzumab/trastuzumab SC may have a minor influence on the ability to drive and use machines. Patients experiencing injection-related reactions or dizziness should be advised not to drive and use machines until symptoms resolve.
References	KMCC protocol BRE-081 V2 SPC accessed online 06.10.2023 Clatterbridge protocol accessed online 21.11.2023 for guidance for table 1 only SACT Protocol Template (clatterbridgecc.nhs.uk)

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

Table 1 Dose modification for paclitaxel in hepatic impairment

Bilirubin	Transaminase	Percentage dose
</= 1.25 x ULN **AND**	<10 x ULN	100%
>1.25 to <2 x ULN		80 %
2-5 x ULN		50%
>5 xULN **OR**	>/= 10 x ULN	contraindicated

Table 2 Dose modification for epirubicin in hepatic impairment

Bilirubin	Percentage Dose
<24 µmol /L	100%
24-51 µmol /L	50%
52-85µmol/L	25%
>85µmol/L	omit

Cycles 1-4 repeat every 21 days

Day	Drug	Dose	Route	Infusion Duration	Administration
Day 1	Dexamethasone	8mg	PO		stat
	Ondansetron	<75yrs 16mg >/=75yrs 8mg	IV	15 min	In 50ml Sodium chloride 0.9%
	EPIRUBICIN	**90mg/m²**	As a slow IV bolus		Through the side of a fast running 0.9% sodium chloride intravenous infusion
	CYCLOPHOSPHAMIDE	**600mg/m²**	As a slow IV bolus		Through the side of a fast running 0.9% sodium chloride intravenous infusion
TTO	Drug	Dose	Route	Directions	
Day 1	Dexamethasone	6mg	PO	OM for 3 days	
	Metoclopramide	10mg	PO	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.	
	Ondansetron	8mg	PO	BD for 3 days	
	Filgrastim	5mcg/kg	SC	Starting on day 5 for 5 days	

Cycle 5: cycle length 21 days

Day	Drug	Dose	Route	Infusion/ injection Duration	Administration Details
Day 1	**Phesgo® (pertuzumab/ trastuzumab)**	**1200mg pertuzumab /600mg trastuzumab**	SC	8 minutes	Inject 15 mL into the subcutaneous tissue of the left or right thigh over 8 minutes. Do not inject at other sites of the body. Injection sites should be rotated for successive injections.
	Patients should be observed for injection-related reactions and hypersensitivity reactions for 30 minutes following administration of Phesgo®, observation should be completed prior to any subsequent administration of chemotherapy.				
	Please ensure pre-meds are given 30 mins prior to paclitaxel				
	Chlorphenamine	10mg	IV	bolus	Over 3 min through a fast running Sodium chloride 0.9% intravenous infusion
	Metoclopramide	20mg	IV	bolus	
	Dexamethasone	8mg	IV	bolus	
	PACLITAXEL	**80mg/m²**	IV	1 hour	In 250ml Sodium Chloride 0.9% (non-PVC bag and non PVC administration set) via in-line 0.22 microns filter. Flush with sodium chloride 0.9%
Day 8 and 15	**Please ensure pre-meds are given 30 mins prior to paclitaxel**				
	Chlorphenamine	10mg	IV	bolus	Over 3 min through a fast running Sodium chloride 0.9% intravenous infusion
	Metoclopramide	20mg	IV	bolus	
	Dexamethasone	8mg (may be reduced to 4mg from cycle 5 day 8)	IV	bolus	
	PACLITAXEL	**80mg/m²**	IV	1 hour	In 250ml Sodium Chloride 0.9% (non-PVC bag and non PVC administration set) via in-line 0.22 microns filter. Flush with sodium chloride 0.9%

Cycle 6-8 repeat every 21 days

Day	Drug	Dose	Route	Infusion/ Injection duration	Administration
Day 1	**Phesgo® (pertuzumab/ trastuzumab)**	**600mg pertuzumab /600mg trastuzumab**	SC	5 minutes	Inject 10 mL into the subcutaneous tissue of the left or right thigh over 5 minutes. Do not inject at other sites of the body. Injection sites should be rotated for successive injections.
	Patients should be observed for injection-related reactions and hypersensitivity reactions for 15 minutes following administration of Phesgo®, observation should be completed prior to any subsequent administration of chemotherapy.				
	Please ensure pre-meds are given 30 mins prior to paclitaxel				
	Chlorphenamine	10mg	IV	bolus	Over 3 min through a fast running Sodium chloride 0.9% intravenous infusion
	Metoclopramide	20mg	IV	bolus	
	Dexamethasone	8mg (may be reduced to 4mg from cycle 5 day 8)	IV	bolus	
	PACLITAXEL	**80mg/m²**	IV	1 hour	In 250ml Sodium Chloride 0.9% (non-PVC bag and non PVC administration set) via in-line 0.22 microns filter. Flush with sodium chloride 0.9%
Day 8 and 15	**Please ensure pre-meds are given 30 mins prior to paclitaxel**				
	Chlorphenamine	10mg	IV	bolus	Over 3 min through a fast running Sodium chloride 0.9% intravenous infusion
	Metoclopramide	20mg	IV	bolus	
	Dexamethasone	8mg (may be reduced to 4mg from cycle 5 day 8)	IV	bolus	
	PACLITAXEL	**80mg/m²**	IV	1 hour	In 250ml Sodium Chloride 0.9% (non-PVC bag and non PVC administration set) via in-line 0.22 microns filter. Flush with sodium chloride 0.9%

TTO cycle 5-8

TTO Medication	Drug	Dose	Route	Directions
Day 1, 8 and 15	Metoclopramide	10mg	PO	3 times a day for 3 days, then 10mg up to 3 times a day as required (max. 30mg per day including 20mg pre-chemo dose). Do not take for more than 5 days continuously.
	Dexamethasone	4mg	PO	OM for 2 days starting the day after paclitaxel dose.

Cycles 9-22: repeat every 21 days

Day	Drug	Dose	Route	Injection Duration	Administration details
1	**Phesgo® (pertuzumab/ trastuzumab)**	**600mg pertuzumab/ 600mg trastuzumab**	SC	5 minutes	Inject 10 mL into the subcutaneous tissue of the left or right thigh over 5 minutes. Do not inject at other sites of the body. Injection sites should be rotated for successive injections.
	Patients should be observed for injection-related reactions and hypersensitivity reactions for 15 minutes following administration of Phesgo®				