Indication	The neo-adjuvant, then adjuvant treatment of clinically defined axillary node negative HER2-positive early breast cancer.
Treatment Intent	Neo-adjuvant / adjuvant
Frequency and number of cycles	Every 3 weeks. Maximum of 6 cycles of TCPhesgo (if given neo-adjuvantly give these 6 cycles prior to surgery) followed by 12 cycles of trastuzumab (SC) or until disease recurrence, or unmanageable toxicity, or patient's decision whichever occurs first. For patients with residual invasive disease following neo-adjuvant therapy and surgery 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.
	• The use of Pertuzumab and trastuzumab SC is restricted to patients whose tumours significantly overexpress HER2 at the 3+ level by IHC or FISH/CISH positive disease.
	• **Ensure Dexamethasone pre-medication (8mg bd for 3 days starting day before docetaxel) is prescribed and given to the patient at new patient chat.**
	• At each nurse assessment, patients should be assessed for signs of dyspnoea.
	• FBC, U&Es and LFTs at each cycle of TCPhesgo and then every 3 months, i.e. pre the 1st, 5th and 9th dose of maintenance trastuzumab to correspond with pre-cycle 7, 11 and 15 of the regimen.
	• Prior to each cycle of TCPhesgo, if neuts <1.0 or PLT <100 delay 1 week. If neuts >/= 1 and PLT >/=100 continue with treatment.
	• Consider EDTA/DTPA otherwise C&G may be used to estimate CrCl.
	• GFR (C&G) or EDTA/DTPA must be >/= 30ml/min. If CrCl drops by >/=25% d/w consultant.
	• **Renal and Hepatic Impairment:**
	  ○ **Carboplatin:** Modify carboplatin if renal impairment (based on results from day 1 of each cycle). CrCl 31-49ml/min use AUC 5.
	  ○ **Docetaxel:** Consider dose reduction of docetaxel in hepatic impairment. Docetaxel is not recommended in severe hepatic impairment.
	  ○ **Pertuzumab and trastuzumab SC:** 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 or hepatic impairment.
	• **Cardiac function** must be monitored.
	  ○ An ECG should be carried out at the start of treatment.
	  ○ An ECHO/ MUGA should be carried out at baseline, then every 3 months throughout treatment and 3-4 weeks after treatment is completed.

- Record on KOMs Cardiac Monitoring Record
- Baseline LVEF must be >/= 55%
- **It is the prescribers' responsibility to check that the ECHO/MUGA result is satisfactory before continuing treatment.**
- Pertuzumab and trastuzumab SC should be withheld for at least 3 weeks in the event of signs and symptoms of CHF 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.
- For cardiac monitoring details please refer to Appendix B of the KMCC Oncological Treatment of breast cancer guideline on managing cardiac toxicity for patients receiving adjuvant Trastuzumab. https://www.kmcc.nhs.uk/medicines-and-prescribing-incorporating-sact-pathways/oncological-treatment-guidelines/

- **Dose Reduction:**
  - Dose reductions of docetaxel and/ or carboplatin 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. No dose reductions are recommended for pertuzumab and trastuzumab SC.
  - There should be no dose escalation of docetaxel.
- **Injection duration and monitoring:**
  Pertuzumab and trastuzumab SC: 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.
  Trastuzumab SC: Patients must be observed closely for injection related adverse effects for 30 mins after the 1st injection and for 15 minutes after subsequent injections.
  Docetaxel: Patients who have developed severe hypersensitivity reactions should not be re-challenged with docetaxel.
- **Administration of pertuzumab and trastuzumab (Phesgo®) and trastuzumab SC.**
  - Inject into the subcutaneous tissue of the thigh only. Injection sites should alternate between left and right thigh. Do not inject at other sites of the body.
  - New injections should be given at least 2.5 cm from the previous site.
  - Do not inject into areas where the skin is red, bruised, tender, or hard.
  - The dose should not be split between two syringes or between two sites of administration.
  - Do not administer other medicinal products for subcutaneous injection at the same site as pertuzumab and trastuzumab or trastuzumab.
- **Re-loading:**
- **Cycle 1-6** 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.

	• **Cycle 7** onwards. There is no loading dose required for SC trastuzumab. • **Common drug interactions (for comprehensive list refer to BNF/SPC):** o Pertuzumab and trastuzumab SC: No formal drug interaction studies have been performed. Caution with other cardiotoxic drugs. o Docetaxel: Concomitant use with medicines which induce, inhibit or are metabolised by cytochrome P450-3A (e.g. ciclosporin, ketoconazole and erythromycin) may affect levels of docetaxel use with caution. Avoid concomitant use with strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin and ritonavir), if treatment cannot be avoided consider dose reduction of docetaxel and monitor patient closely for signs of toxicity. o Carboplatin: Caution with other nephrotoxic drugs. • **Driving:** Pertuzumab and trastuzumab (Phesgo) has 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. Trastuzumab can cause dizziness and somnolence, patients should be aware when driving or operating machinery.
References	KMCC protocol BRE-079 V1 SPC accessed online 21.09.2023

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

Cycle 1: 21 day cycle

Day	Drug	Dose	Route	Infusion/ injection Duration	Administration Details
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 dexamethasone pre-med has been taken prior to administration of chemotherapy				
	Ondansetron	<75yrs 16mg ≥75yrs 8mg	IV	15 mins	In 50ml sodium chloride 0.9%
	DOCETAXEL	**75mg/m²**	IV	1 hr	Sodium Chloride 0.9% 250ml
	CARBOPLATIN	**AUC 6 Dose = 6 x (GFR + 25) (capped at 700mg)**	IV	30 min	Glucose 5% 500ml

TTO	Drug	Dose	Route	Directions
1	Dexamethasone	6mg	PO	OM for 2 days starting on day 3
	Metoclopramide	10mg	PO	Take TDS for 3 days then 10mg up to TDS PRN. Do not take for more than 5 days continuously.
	Ondansetron	8mg	PO	BD for 3 days
	Dexamethasone	8mg	PO	BD for 3 days starting the day before next cycle of docetaxel
	Filgrastim	300 micrograms or consider dose of 480 micrograms if patient > 80kg	SC	OD starting day 2 for 7 days
	Loperamide	2mg-4mg	PO	Take 4mg initially then 2mg after each loose stool when required (max. 16mg per day). Dispense original pack on cycle 1 then only if required.

Cycles 2-6: repeat every 21 days

Day	Drug	Dose	Route	Infusion/ 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®, observation should be completed prior to any subsequent administration of chemotherapy.				
	Please ensure dexamethasone pre-med has been taken prior to administration of chemotherapy				
	Ondansetron	<75yrs 16mg ≥75yrs 8mg	IV	15 mins	In 50ml sodium chloride 0.9%
	DOCETAXEL	**75mg/m²**	IV	1 hr	Sodium Chloride 0.9% 250ml
	CARBOPLATIN	**AUC 6 Dose = 6 x (GFR + 25) (capped at 700mg)**	IV	30 min	Glucose 5% 500ml

TTO	Drug	Dose	Route	Directions
Day 1 Cycles 2-6	Dexamethasone	6mg	PO	OM for 2 days starting on day 3
	Metoclopramide	10mg	PO	Take TDS for 3 days, then 10mg up to TDS PRN. Do not take for more than 5 days continuously.
	Ondansetron	8mg	PO	BD for 3 days
	Filgrastim	300 micrograms or consider dose of 480 micrograms if patient > 80kg	SC	OD starting on day 2 for 7 days
	Loperamide	2mg-4mg	PO	Take 4mg initially then 2mg after each loose stool when required (max. 16mg per day). Dispense original pack on cycle 1 then only if required.
Day 1 Cycles 2-5	Dexamethasone	8mg	PO	BD for 3 days starting the day before next cycle of docetaxel

Cycles 7-18 repeat every 21 days

Day	Drug	Dose	Route	Infusion Duration	Administration Details
1	**TRASTUZUMAB** Maintenance dose	**600mg**	Sub cut	**Over 2-5 mins**	Alternate injection site between the right and left thigh at least 2.5cm away from the previous injection site.