Indication	For the treatment of node negative HER2 positive early breast cancer
Treatment Intent	Adjuvant
Frequency and number of cycles	4 cycles of EC every 21 days followed by 4 cycles of paclitaxel (weekly on days 1, 8 and 15) and trastuzumab SC every 21 days followed by 14 cycles of trastuzumab SC every 21 days or until disease recurrence, or unmanageable toxicity, or patient's decision whichever occurs first. NB patients can be switched between trastuzumab SC therapy 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 cycle 1 to 4.** • **ECG** should be checked prior to cycle 1 and undertake ECHO/MUGA as clinically indicated (see on-going cardiac monitoring below during 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 Trastuzumab SC cycles 5-22.** ○ The use of trastuzumab is restricted to patients whose tumours significantly over express HER2 (3+) level or greater. ○ Trastuzumab must not be given within 3 weeks of an anthracycline, if applicable it must be started a minimum of 3 weeks after administration of the final dose of anthracycline therapy. ○ Monitor FBC, U&E and LFT on days 1,8 and 15 of cycles 5-8 then from cycle 9 FBC, U&Es and LFTs every 3 months or as clinically indicated. ○ **Cycles 5 to 8,** If neuts <1.0 and or PLT<100 delay one week, if neuts> /= 1 and PLT >/=100 continue with treatment. • **Hepatic impairment:** ○ Paclitaxel: If bilirubin </= 1.25 x ULN and transaminase < 10 x ULN, dose at full dose. Otherwise consider dose reduction see table 1, not recommended in severe hepatic impairment. ○ Trastuzumab: There are no recommendations for dose adjustments of trastuzumab in hepatic impairment. • **Renal impairment:** ○ Paclitaxel: no dose reduction necessary. ○ Trastuzumab: There are no recommendations for dose adjustments of trastuzumab in renal impairment. • **Cardiac Monitoring:** ○ 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/

	○ **It is the prescribers' responsibility to check that the ECHO/MUGA result is satisfactory before continuing treatment.** ○ At each nurse assessment patients should be assessed for signs of dyspnoea. • **Infusion / injection related reactions and trastuzumab SC administration:** • **Paclitaxel:** • Patients developing hypersensitivity reactions to Paclitaxel may be re-challenged 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. • **Trastuzumab SC:** ○ Inject into the subcutaneous tissue of the thigh, 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 into areas where the skin is red, bruised, tender, or hard. ○ During treatment with trastuzumab solution for subcutaneous injection, do not administer other medicinal products for subcutaneous use at the same site. ○ Patients should be observed for 30 minutes after the first trastuzumab injection and for 15 minutes after subsequent injections. • **Management of adverse reactions and dose adjustments:** • **Dose Modification:** ○ Dose reduce Paclitaxel by 20% in the event of >/= grade 2 neuropathy and consider a delay until recovery to </= grade 1. ○ 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 required for trastuzumab SC. • **Common drug interactions (for comprehensive list refer to BNF/SPC):** ○ **Trastuzumab SC:** No formal drug interaction studies have been performed. Caution with other cardiotoxic drugs. ○ **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. ○ **Epirubicin:** Caution, ciclosporin increases concentration of epirubicin. • **Missed dose:** If the patient misses a dose of trastuzumab, administer the dose as soon as possible. The interval between the consecutive dose should not be less than 3 weeks. • **Driving:** Patients should be advised their ability to drive or operate machinery may be impaired.
References	ARIA regimen BRE-064 KMCC protocol BRE-052 V0.2

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	

Cycles 5 to 8: repeat every 21 days.

Day	Drug	Dose	Route	Infusion/ injection Duration	Administration
1	**TRASTUZUMAB (Herceptin®)**	**600mg**	SC	2-5min	Alternate injection site between the right and left thigh at least 2.5cm away from previous injection site
	Patients should be observed for 30 minutes after the first trastuzumab injection and for 15 minutes after subsequent injections. Observation should be completed prior to any subsequent administration of chemotherapy.				
	Give pre-meds 30 minutes prior to paclitaxel				
	Dexamethasone	8mg (may be reduced to 4mg from cycle 1 day 8)	IV	bolus	
	Chlorphenamine	10mg	IV	bolus	Over 3 min through a fast running Sodium chloride 0.9% intravenous infusion
	Metoclopramide	20mg	IV	bolus	
	PACLITAXEL	**80mg/m²**	IV	Over 1 hour	Diluted in 250ml sodium chloride 0.9% (non-PVC bag and non PVC giving set) via in-line 0.22micron filter Flush with sodium chloride 0.9%
8	**Give pre-meds 30 minutes prior to paclitaxel**				
	Dexamethasone	8mg (may be reduced to 4mg from cycle 1 day 8)	IV	bolus	
	Chlorphenamine	10mg	IV	bolus	Over 3 min through a fast running Sodium chloride 0.9% intravenous infusion
	Metoclopramide	20mg	IV	bolus	
	PACLITAXEL	**80mg/m²**	IV	Over 1 hour	Diluted in 250ml sodium chloride 0.9% (non-PVC bag and non PVC giving set) via in-line 0.22micron filter. Flush with sodium chloride 0.9%
15	**Give pre-meds 30 minutes prior to paclitaxel**				
	Dexamethasone	8mg (may be reduced to 4mg from cycle 1 day 8)	IV	bolus	
	Chlorphenamine	10mg	IV	bolus	Over 3 min through a fast running Sodium chloride 0.9% intravenous infusion
	Metoclopramide	20mg	IV	bolus	
	PACLITAXEL	**80mg/m²**	IV	Over 1 hour	Diluted in 250ml sodium chloride 0.9% (non-PVC bag and non PVC giving set) via in-line 0.22micron filter. Flush with sodium chloride 0.9%

TTO	Drug	Dose	Route	Directions
Day 1, 8 and 15	Metoclopramide	10mg	PO	3 times a day for 3 days after paclitaxel, 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. Take with or just after food, or a meal.

Cycle 9 to 22: repeat every 21 days

Day	Drug	Dose	Route	Infusion/ injection Duration	Administration Details
1	**TRASTUZUMAB (Herceptin®)**	600mg	Sub Cut	2 to 5 min	Alternate injection site between the right and left thigh at least 2.5cm away from the previous injection site.
	Patients should be observed for 15minutes after the trastuzumab injection				