Systemic Anti Cancer Treatment Protocol

EC-D with HP
Epirubicin, Cyclophosphamide, Followed by Docetaxel or Paclitaxel, Trastuzumab, Pertuzumab
Neoadjuvant and Adjuvant Protocol

PROTOCOL REF: MPHAECDHPBR
(Version No: 2.1)

During COVID19 there are contingency options for pertuzumab/trastuzumab combination to be administered without chemotherapy, please see blueteq for full criteria and register patient at time of consent to ensure compliance with rapidly changing criteria.

Approved for use in:

Neoadjuvant treatment: first line treatment of HER2 positive T2 to T4b and/or histologically or cytologically proven node positive early breast cancer.

Baseline LVEF ≥ 55%

Adjuvant treatment: following neoadjuvant treatment (as detailed) and ONLY if fulfills one of the following criteria:

- Axillary lymph node (LN) involvement pathologically confirmed prior to the start of neoadjuvant chemotherapy.
- Node negative prior to neoadjuvant treatment:
  - Confirmed residual carcinoma in the axillary node(s) following surgery.
  - In the absence of invasive carcinoma in the axillary LNs post-surgery, confirmed histological changes (e.g. fibrosis) indicative of previous axillary nodal involvement.

No disease progression following neoadjuvant treatment.

Prior to starting adjuvant treatment- LVEF ≥ 50%.

PS 0-1

Separate Blueteq registration **forms** required for neoadjuvant and adjuvant use.

Preparation of Phesgo:

Loading Dose (Pertuzumab/Trastzumab S/C 1200mg/600mg)

Withdrawn the contents of the vial into a 15mL syringe using a transfer needle and then change the needle to a subcutaneous 25-27 Gauge needle prior to administering the dose

Maintenance Dose (Pertuzumab/Trastzumab S/C 600mg/600mg)

Withdrawn the contents of the vial into a 10mL syringe using a transfer needle and then change the needle to a subcutaneous 25-27 Gauge needle prior to administering the dose

Considerations

- The injection site should be alternated between the left and right thigh.
- Ensure both nursing staff and patient are in comfortable position before beginning
- New injections should be given at least 2.5 cm from the old site and never into areas where the skin is red, bruised, tender, or hard.
- Medication should be warmed/come to room temperature before injection. This is easily done by asking patient to hold vial of Phesgo while nurse performs assessment/documentation. Never injection cold medication into the patient
- The dose should not be split between two syringes or between two sites of administration

Dosage:

Neoadjuvant treatment:

Drug	Dosage	Route	Frequency
Epirubicin	90mg/m²	IV Bolus	Cycles 1 to 3 Day 1 only of a 21 day cycle*
Cyclophosphamide	600mg/m²	IV Bolus	
Followed by			
Docetaxel	Initially 75mg/m² Can increase to 100mg/m² at cycle 2 at consultants' discretion.	IV infusion	Cycles 1 to 4 Day 1 only of a 21 day cycle
OR			
Paclitaxel	80mg/m²	IV infusion	Cycles 1 to 4 Days 1, 8 and 15 of a 21 day cycle
Phesgo	Pertuzumab 1200mg/ Trastuzumab 600mg	Subcutaneous injection	Cycle 1 loading dose
Phesgo	Pertuzumab 600mg/ Trastuzumab 600mg	Subcutaneous injection	Cycles 2 to 4

***For patients PS0 and able to tolerate, EC can be given as dose dense option, same doses given every 2 weeks for 3 cycles. Docetaxel/paclitaxel part of regimen commences 2 weeks after cycle 3 EC**

Alternative intravenous option

Trastuzumab	8mg/kg loading dose cycle 1. Then 6mg/kg cycle 2, 3 and 4.	IV infusion	Cycles 1 to 4 Day 1 only of a 21 day cycle
Pertuzumab	840mg loading dose cycle 4. Then 420mg cycles 2, 3 and 4.	IV infusion	Cycles 1 to 4 Day 1 only of a 21 day cycle

Adjuvant treatment: As 18 cycles of HER2 agents will given, ensure that cycle numbers are correct when starting adjuvant treatment to avoid stopping sooner than planned.

Eligible for adjuvant treatment with Pertuzumab

Drug	Dosage	Route	Frequency
Phesgo	Pertuzumab 1200mg/ Trastuzumab 600mg	Subcutaneous injection	Loading dose required if 6 weeks from previous dose
Phesgo	Pertuzumab 600mg/ Trastuzumab 600mg	Subcutaneous injection	Cycles 5 to 18 Day 1 only of a 21 day cycle

Intravenous alternative

Drug	Dosage	Route	Frequency
Trastuzumab	8mg/kg loading dose (≥ 6 weeks from last dose) cycle 8. Then 6mg/kg to continue thereafter for a total of 18 doses	IV infusion	Cycles 5 to 18 Day 1 only of a 21 day cycle
Pertuzumab	840mg loading dose (≥ 6 weeks from last dose) cycle 8. Then 420mg thereafter for a total of 18 doses	IV infusion	

Not eligible for adjuvant treatment with Pertuzumab:

Drug	Dose	Route	Frequency
Trastuzumab	600mg To continue for 18 doses in total	SC	Cycles 5 to 18 Day 1 only of a 21 day cycle

Supportive Treatments- cycles 1-7

Ondansetron 8mg orally twice a day for three days.

Domperidone 10mg tablets, three times a day as required.

Filgrastim subcutaneous injection daily for 7 days starting on day 3, dose as follows:

- Weight < 70kg- Filgrastim 300 micrograms daily SC.
- Weight ≥ 70kg- Filgrastim 480 micrograms daily SC.

Additional item with EC combination treatment – cycles 1-3

Dexamethasone 4mg orally twice a day for three days (anti-emetic).

Additional item Docetaxel – cycles 4-7

Premedication of dexamethasone 8 mg oral twice daily for 3 days starting 1 day prior to docetaxel administration to prevent hypersensitivity reactions.

Docetaxel can be administered as the first part of the regimen i.e. cycles 1 to 4, followed by EC as cycles 5 to 7 if surgery can be scheduled following cycle 4 (as NEOSPHERE trial protocol). Treatment with trastuzumab and pertuzumab should start with the Docetaxel component but should be withheld during the EC component.

Extravasation risk

Refer to the network guidance for the prevention and management of extravasation.

Epirubicin is a vesicant. Erythematous streaking along the vein proximal to the site of injection has been reported, and must be differentiated from an extravasation event. This reaction usually subsides within 30 minutes.

Cyclophosphamide- neutral

Pertuzumab- neutral

Trastuzumab- neutral

Docetaxel – exfoliant

Paclitaxel- vesicant

Phesgo- No extravasation risk as subcutaneous route of injection

Administration

Cycles 1 to 3

Day	Drug	Dose	Route	Diluent and rate
1	Ondansetron	24mg	PO	30mins before chemotherapy
	Dexamethasone	12mg	PO	30mins before chemotherapy
	Epirubicin	90mg/m^2	IV Bolus	IV bolus over 10 to 15 minutes Concurrent administration; epirubicin at 400mL/hr and sodium chloride 0.9% at 100mL/hr
	Cyclophosphamide	600mg/m^2	IV Bolus	IV bolus over 30 minutes

Repeat every 21 days

For patients PS0 and able to tolerate, EC can be given as dose dense option, same doses given every 2 weeks for 3 cycles. Docetaxel/paclitaxel part of regimen commences 2 weeks after cycle 3 EC

If cycle 3 is followed by docetaxel treatment then ensure patient has dexamethasone pre-medication to start prior to the first cycle of docetaxel.

Nasal stuffiness can occur immediately with administration of cyclophosphamide, if uncomfortable for the patient the drug can be slowed down.

Encourage an oral fluid intake of 2 litres per day to promote urinary output & prevent chemical cystitis with cyclophosphamide.

Cycle 1

Docetaxel and subcutaneous Trastuzumab/Pertuzumab

Day	Drug	Dose	Route	Diluent and rate
Premedication: Dexamethasone 8 mg twice daily for 3 days starting 1 day prior to docetaxel administration				
1	Ondansetron	8mg	Oral	30mins before chemotherapy
	Phesgo	Pertuzumab 1200mg/ trastuzumab 600mg	S/C injection	Over 8 minutes
	Docetaxel	75mg/m^2	IV infusion	250mL sodium chloride 0.9% over 60 minutes

Docetaxel, Trastuzumab, Pertuzumab intravenous

Day	Drug	Dose	Route	Diluent and rate
Premedication: Dexamethasone 8 mg twice daily for 3 days starting 1 day prior to docetaxel administration				
1	Ondansetron	8mg	Oral	30mins before chemotherapy
	Pertuzumab	840mg Loading dose	IV infusion	250mL sodium chloride 0.9% over 60 minutes
	Trastuzumab	8mg/kg Loading dose	IV infusion	250mL sodium chloride 0.9% over 90 minutes
	Docetaxel	75mg/m^2	IV infusion	250mL sodium chloride 0.9% over 60 minutes

OR

Paclitaxel and subcutaneous Trastuzumab/Pertuzumab

Day	Drug	Dose	Route	Diluent and rate
1	Phesgo	Pertuzumab 1200mg/ trastuzumab 600mg	S/C injection	Over 8 minutes

	Dexamethasone	6.6mg	IV Bolus	30 minutes before chemotherapy Reduce to 3.3mg from week 2
	Famotidine	20mg	Orally	At least 1 hour before chemotherapy
	Chlorphenamine	10mg	IV Bolus	30 minutes before chemotherapy
	Paclitaxel	80mg/m^2	IV infusion	250 to 500mL sodium chloride 0.9% over 60 minutes using a non-PVC giving set with a 0.22 micron filter

Paclitaxel, Trastuzumab, Pertuzumab intravenous

Day	Drug	Dose	Route	Diluent and rate
1	Pertuzumab	840mg Loading dose	IV infusion	250mL sodium chloride 0.9% over 60 minutes
	Trastuzumab	8mg/kg Loading dose	IV infusion	250mL sodium chloride 0.9% over 90 minutes
	Dexamethasone	6.6mg	IV Bolus	30 minutes before chemotherapy Reduce to 3.3mg from week 2
	Famotidine	20mg	orally	At least 1 hour before chemotherapy
	Chlorphenamine	10mg	IV Bolus	30 minutes before chemotherapy
	Paclitaxel	80mg/m^2	IV infusion	250 to 500mL sodium chloride 0.9% over 60 minutes using a non-PVC giving set with a 0.22 micron filter

Cycles 2 to 4

Docetaxel and subcutaneous Trastuzumab/Pertuzumab

Day	Drug	Dose	Route	Diluent and rate
Dexamethasone* 8 mg twice daily for 3 days starting 1 day prior to docetaxel				
1	Ondansetron	8mg	Oral	30mins before chemotherapy
	Phesgo	Pertuzumab 600mg/ trastuzumab 600mg	S/C injection	Over 5 minutes
	Docetaxel	75mg/m^2 Can increase to100mg/m^2 from cycle 2 at consultants' discretion.	IV infusion	250mL sodium chloride 0.9% over 60 minutes

Docetaxel, Trastuzumab, Pertuzumab intravenous

Day	Drug	Dose	Route	Diluent and rate
Dexamethasone* 8 mg twice daily for 3 days starting 1 day prior to docetaxel				
1	Ondansetron	8mg	Oral	30mins before chemotherapy
	Pertuzumab	420mg Maintenance dose	IV infusion	250mL sodium chloride 0.9% over 30 minutes
	Trastuzumab	6mg/kg Maintenance dose	IV infusion	250mL sodium chloride 0.9%. If cycle 4 well tolerated give subsequent cycles over 30 minutes
	Docetaxel	75mg/m^2 Can increase to100mg/m^2 from cycle 2 at consultants' discretion.	IV infusion	250mL sodium chloride 0.9% over 60 minutes

OR

Day	Drug	Dose	Route	Diluent and rate
1	Phesgo	Pertuzumab 600mg / trastuzumab 600mg	S/C injection	Over 5 minutes

1,8 And 15	Dexamethasone	6.6mg	IV Bolus	30 minutes before chemotherapy Reduce to 3.3mg from week 2
	Famotidine	20mg	orally	At least 1 hour before chemotherapy for first 3 doses
	Chlorphenamine	10mg	IV Bolus	30 minutes before chemotherapy
	Paclitaxel	80mg/m^2	IV infusion	250 to 500mL sodium chloride 0.9% over 60 minutes using a non-PVC giving set with a 0.22 micron filter

Paclitaxel, Trastuzumab, Pertuzumab intravenous

Day	Drug	Dose	Route	Diluent and rate
1	Pertuzumab	420mg Maintenance dose	IV infusion	250mL sodium chloride 0.9% over 30 minutes
	Trastuzumab	6mg/kg Maintenance dose	IV infusion	250mL sodium chloride 0.9%. If cycle 4 well tolerated give subsequent cycles over 30 minutes
1, 8 and 15	Dexamethasone	6.6mg	IV Bolus	30 minutes before chemotherapy Reduce to 3.3mg from week 2
	Famotidine	20mg	Orally	At least 1 hour before chemotherapy for first 3 doses
	Chlorphenamine	10mg	IV Bolus	30 minutes before chemotherapy
	Paclitaxel	80mg/m^2	IV infusion	250 to 500mL sodium chloride 0.9% over 60 minutes using a non-PVC giving set with a 0.22 micron filter

Cycles repeated every 21 days

*If oral dexamethasone has not been taken then an intravenous dose of 8mg can be administered on the day of treatment, in addition to the oral dose of 8mg.

Cycles 5 to 18 for HER2 therapy (Adjuvant Treatment)

To commence 3 weeks after final cycle of chemotherapy (cycle 5 may be before surgery has taken place).

Adjuvant pertuzumab treatment

Subcutaneous

Drug	Dosage	Route	Frequency
Phesgo	Pertuzumab 1200mg/ Trastuzumab 600mg	Subcutaneous injection	Over 8 minutes **Loading dose required ONLY if 6 weeks from previous dose**
Phesgo	Pertuzumab 600mg/ Trastuzumab 600mg	Subcutaneous injection	Over 5 minutes

Intravenous alternative

Day	Drug	Dose	Route	Diluent and rate
1	Pertuzumab	8mg/kg loading dose (≥ 6 weeks from last dose) cycle5. Then 6mg/kg to continue thereafter for a total of 18 doses	IV infusion	250mL sodium chloride 0.9% over 60 minutes. If well tolerated then reduce to 30 minutes on subsequent infusions.
	Trastuzumab	840mg loading dose (≥ 6 weeks from last dose) cycle 5 Then 420mg thereafter for a total of 18 doses	IV infusion	250mL sodium chloride 0.9% over 90 minutes. If well tolerated then reduce to 30 minutes on subsequent infusions.

OR

Adjuvant trastuzumab treatment ONLY

Day	Drug	Dose	Route	Diluent and rate
1	Trastuzumab	600mg	SC	Over 5 minutes

Cycles repeated every 21 days

Main Toxicities

Haematological	Neutropenia, thrombocytopenia and anaemia.
Gastrointestinal	Nausea, vomiting, stomatitis, diarrhoea. Pertuzumab can cause severe diarrhea, especially when given in combination with taxane therapy.
Cardiotoxicity	Epirubicin - sinus tachycardia and/or electrocardiogram (ECG) abnormalities such as non-specific ST-T wave changes. Other cardiac events have been reported, included delayed toxicity. Pertuzumab and Trastuzumab - decreases in LVEF have been reported with medicinal products that block HER2 activity, including Pertuzumab and Trastuzumab; see cardiotoxicity dose modification section below for details.
Respiratory	Acute respiratory distress syndrome, pneumonitis
Dermatological	Alopecia, small risk of permanent alopecia following docetaxel Docetaxel: Brittle, chipped and ridged nails.
Urological	Red colouration of urine for 1 to 2 days after administration following epribucin Urotoxicity can occur with short-term and long-term use of cyclophosphamide. Hemorrhagic cystitis, pyelitis, ureteritis, and haematuria. Mesna can be given if required.
Ocular	Watery eyes, gritty and irritated
Hypersensitivity reactions	Reactions may occur within a few minutes following the initiation of treatment with taxanes, facilities for the treatment of hypotension and bronchospasm should be available. Patients should be monitored for hypersensitivity and infusion reactions with pertuzumab for 60 minutes after the first dose, and for 30 minutes after subsequent doses. Trastuzumab: injection-related symptoms (mild to moderate in severity): fever, chills, headache, nausea, rash, arthralgia/myalgia (occur mainly with 1st intravenous dose) and anaphylaxis. The

	majority of these events occur during or within 2.5 hours of the start of the first infusion.
Nervous system	Taxanes: peripheral neuropathy is very common
Musculoskeletal	Arthralgia, myalgia common with Taxanes.
Infertility	Amenorrhea, risk of premature menopause However ensure appropriate contraceptive advice is given

Investigations and Treatment Plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Comments
Medical Assessment	X		X		X		X		Alternate cycles then every 3 months whilst on pertuzumab and/or trastuzumab.
Nursing Assessment	X	X	X	X	X	X	X	X	Every cycle
ECHO	X			X				X	ECHO must be performed before pertuzumab and/or trastuzumab commences. Then every 4 months thereafter.
FBC	X		X	X	X	X	X	X	Every cycle
U&E & LFT	X		X	X	X	X	X	X	Every cycle
Informed Consent	X								
PS recorded	X	X	X	X	X	X	X	X	Every cycle
Toxicities documented			X	X	X	X	X	X	Every cycle
Weight recorded	X	X	X	X	X	X	X	X	Every cycle
Height recorded	X	X							

Dose Modifications and Toxicity Management:

Haematological Toxicity

Proceed rules on chemotherapy cycles:

ANC ≥ 1.0 x 10^9/L	Platelets ≥ 100 x 10^9/L

Defer by 7 days or until blood counts recovered if Neutrophils ≤ 1.0 **or** platelets ≤ 100 x 10^9/L

Second episode or severe neutropenic sepsis: Defer by 7 days or until blood counts recovered if Neutrophils ≤ 1.0 **or** platelets ≤ 100 x 10^9/L **and reduce** to 80% dose

For pertuzumab/trastuzumab only cycles – no blood tests required

Hepatic impairment:

	Epirubicin	**Cyclophosphamide**
LFTs	**Dose**	**Dose**
Bil 21 to 51 µmol/L Or AST 2-4 x ULN	50%	100%
Bil 52 to 85 µmol/L Or AST > 4 x ULN	25%	75%
Bil > 85 µmol/L Or Child-Pugh C	Omit	Omit

Docetaxel	
AST and/or ALT > 1.5- 5 x ULN concomitant with ALP > 2.5 –5.0 x ULN and normal bilirubin	Consider 75% of the original dose
AST or ALT >1.5-5 x ULN concomitant with ALP ≤ 2.5-6 x ULN and/or bilirubin ≤ 1-1.5 x ULN	consider 50% of the original dose

Bilirubin > 1.5 x ULN or AST/ALT > 10 x ULN or ALP > 6 x ULN	Not recommended

Paclitaxel	
Bilirubin less than 1.25 times ULN and AST < 10 x ULN	Give 100% dose
Bilirubin greater than 1.25 times ULN	Consider dose reduction
ALP more than 3 times ULN	Consider dose reduction
ALT and/or AST ≥10 x ULN or bilirubin > 5 x ULN:	Contra-.indicated

Trastuzumab and Pertuzumab
No need for dose adjustment is required.

Renal impairment:

Cyclophospamide

CrCl	**Dose (%)**
≥ 30	100
10-29	75
< 10 Or Haemodialysis (HDx)	Not recommended. If unavoidable consider 50% of the original dose

Epirubicin, Trastuzumab, Pertuzumab Paclitaxel and Docetaxel

All grades including patients on HDx - no dose adjustment required.
For patients on epirubicin requiring HDx- consider weekly dosing.

Peripheral Neuropathy

NCI-CTC grade 2 peripheral neuropathy: withhold taxane until neuropathy recovers to grade 1 then dose reduce by 20%

If NCI-CTC grade 3 (or persistent grade 2) peripheral neuropathy occurs, discontinue taxane.

Pulmonary Impairment:

Trastuzumab-Pulmonary events have been reported with the use of trastuzumab.
These events have occasionally been fatal.
Caution should be exercised for pneumonitis.

Dose Modifications

Dose reductions for trastuzumab and pertuzumab are not recommended. If trastuzumab treatment is discontinued, treatment with Pertuzumab should be discontinued.

Recommendations regarding delayed or missed doses of trastuzumab and pertuzumab

Time between two sequential infusions	**Intravenous pertuzumab and trastuzumab**	**subcutaneous**	
		Phesgo	**trastuzumab single agent**
< 6 weeks	The 420 mg dose of intravenous pertuzumab should be administered as soon as possible. Do not wait until the next planned dose. Thereafter, revert to the original planned schedule.	The 600mg/600mg fixed dose should be administered as soon as possible	The fixed dose of 600mg trastuzumab SC should be administered as soon as possible. Do not wait until the next planned dose.
≥ 6 weeks	The 840 mg loading dose of intravenous pertuzumab should be re-administered as a 60 minute infusion, followed by a maintenance dose of 420 mg IV administered every 3 weeks thereafter.	The loading dose of 1200mg/600mg should be administered over 8 minutes and then back to 600mg/600mg maintenance dose every 3 weeks thereafter.	

Toxicities

Hypersensitivity

Taxanes- If hypersensitivity reactions occur; minor symptoms such as flushing or localised rash with or without pruritus do not require interruption of therapy. However, severe reactions, such as severe hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of taxane and appropriate treatment. Patients who have developed severe hypersensitivity reactions should not be re-challenged.

Should an infusion reaction occur the infusion should be discontinued. The symptoms should be managed using paracetamol, with addition of chlorphenamine and hydrocortisone if anaphylaxis suspected. Please refer to the trusts Hypersensitivity-Management Prevention Policy for full details.

Patient should be monitored until resolution of all observed symptoms. Patients experiencing dyspnoea at rest may be at increased risk of a fatal infusion reaction; these patients should not be treated with trastuzumab.

Cardiotoxicity

Management of Trastuzumab and Pertuzumab-Induced Cardiotoxicity (refer to NCRI recommendations 2009 outlined below)

- Sharp falls in LVEF (10 points or to <50%) during cytotoxic chemotherapy may indicate increased susceptibility to cardiac dysfunction on trastuzumab/pertuzumab. Prophylactic ACE inhibitor therapy may be considered for such patients.
- Assessment at the end of treatment is recommended for patients requiring cardiovascular intervention during treatment.
- Additional testing is required in patients who have LV systolic dysfunction.
- Patients developing signs and symptoms of heart failure should have their trastuzumab/pertuzumab treatment interrupted, receive an ACE inhibitor and be referred to a cardiologist.

- If the LVEF falls to ≤ 40%, (representing biologically important LV systolic dysfunction) trastuzumab/pertuzumab should be interrupted the patient should receive an ACE inhibitor and be referred to a cardiologist for treatment.
- After trastuzumab interruption and appropriate medical therapy, LVEF should be re-checked after 6–8 weeks. Trastuzumab may be re-initiated if the LVEF is restored to a level above the LLN.
- If the LVEF falls to below the LLN but > 40%, trastuzumab may be continued, but an ACE inhibitor should be initiated.
- If the patient is already on an ACE inhibitor, they should be referred to a cardiologist.
- LVEF assessment should be repeated after 6–8 weeks.
- If the LVEF falls by 10 points or more but remains above the LLN, trastuzumab may be continued. Intervention with an ACE inhibitor is recommended in an attempt to reduce the risk of further LVEF decline of symptomatic CHF.
- LVEF Monitoring should be repeated after 6–8 weeks.

NCRI recommendations for cardiac monitoring
Ref: British Journal of Cancer 2009 100:684-692

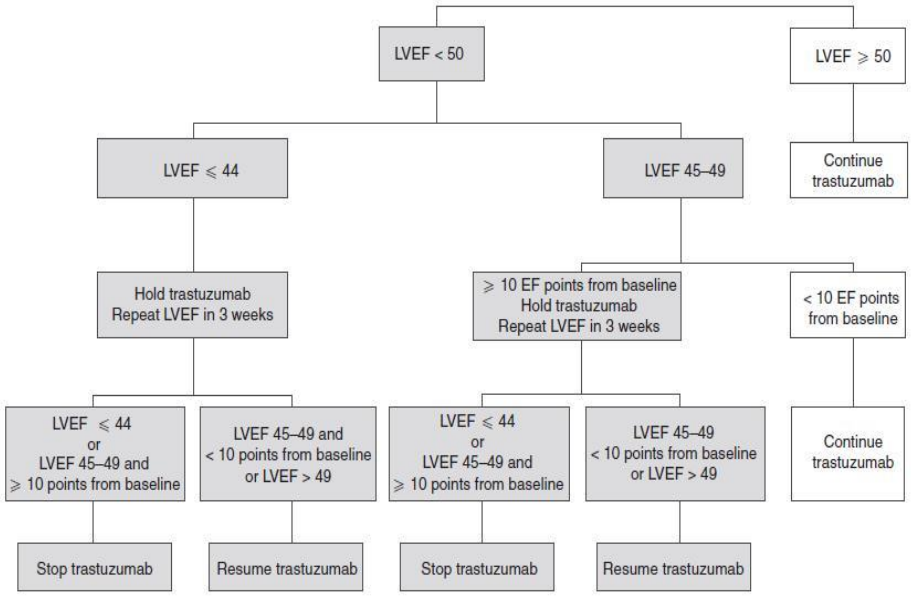

Figure 1 Current recommendations for cardiac monitoring in trastuzumab-treated patients (reproduced from Suter *et al*, 2007; online Appendix only). Reproduced with permission of the American Society of Clinical Oncology, from Suter *et al*, 2007.

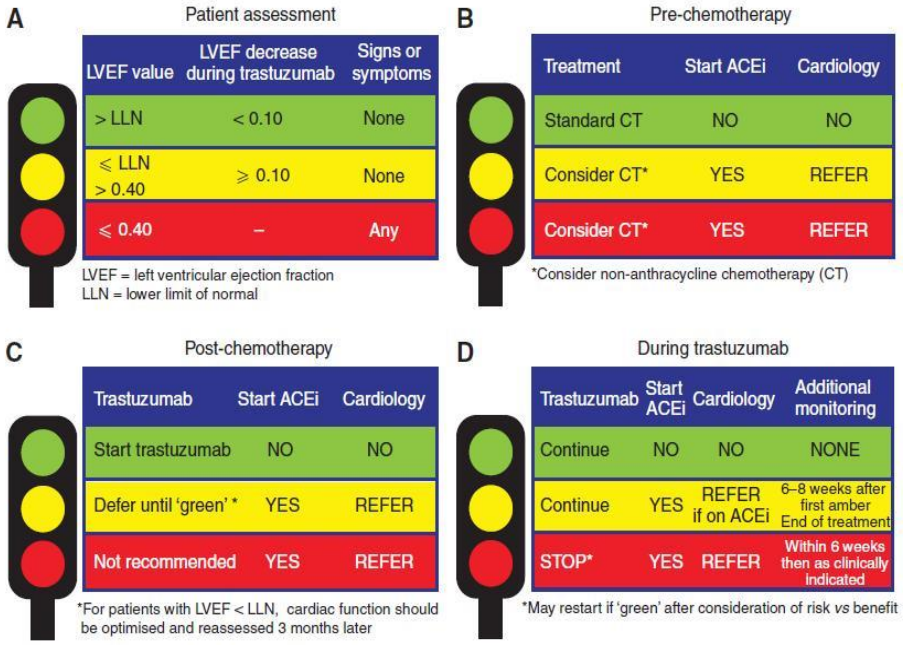

Figure 2 Traffic light system to prevent, monitor, and manage cardiac events in patients undergoing cytotoxic chemotherapy. (**A**) Patient assessment during trastuzumab therapy; (**B**–**D**) indications for ACEi therapy and referral to a cardiologist before (**B**) and after (**C**) chemotherapy, and (**D**) during trastuzumab therapy, when additional cardiac assessments may also be required. ACEi = angiotensin-converting enzyme inhibitor.

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