Systemic Anti Cancer Treatment Protocol

Docetaxel, Trastuzumab, Pertuzumab with Paclitaxel Alternative Advanced Breast Cancer

PROTOCOL REF: MPHADTPBR
(Version No: 1.1)

Approved for use in:

First line treatment of HER2 positive locally advanced or metastatic breast cancer

PS 0 or 1

Adjuvant trastuzumab should have completed more than 12 months prior to metastatic diagnosis

Blueteq registration required

Switch to paclitaxel is **only** permitted if the patient has an allergic reaction to docetaxel and is unsuccessfully re-challenged.

COVID contingency plans also allow switch to paclitaxel.

Dosage:

Drug	Dosage	Route	Frequency
Docetaxel	75mg/m^2	IV	Day 1 only of a 21 day cycle for 6 cycles
Or Paclitaxel	80mg/m^2	IV	Days 1, 8 and 15 of a 21 day cycle for 6 cycles
Phesgo	Pertuzumab 1200mg Trastuzumab 600mg	SC	Cycle 1 loading dose
Phesgo	Pertuzumab 600mg Trastuzumab 600mg	SC	Cycle 2 onwards, every 21 days

Alternative intravenous option

Drug	Dosage	Route	Frequency
Docetaxel	75mg/m^2	IV	Day 1 only of a 21 day cycle for 6 cycles
Or Paclitaxel	80mg/m^2	IV	Days 1, 8 and 15 of a 21 day cycle for 6 cycles
Trastuzumab	8mg/kg loading dose cycle 1. Then 6mg/kg from cycle 2.	IV	Day 1 only of a 21 day cycle
Pertuzumab	840mg loading dose cycle 1. Then 420mg from cycle 2.	IV	Day 1 only of a 21 day cycle

Cycle is repeated every 21 days

If docetaxel is well tolerated, up to 8 cycles can be administered if clinically indicated. The same applies for paclitaxel 8 cycles of day 1, 8 and 15 dosing (21 day cycle).

Once docetaxel/paclitaxel is discontinued, the pertuzumab and trastuzumab continue until disease progression (outside CNS) or unacceptable toxicity

Supportive Treatments:

Ondansetron 8mg orally twice a day for three days

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

Famotidine 20mg orally at least one hour prior to treatment with paclitaxel for first 3 cycles.

Premedication of dexamethasone 8 mg twice daily for 3 days starting 1 day prior to docetaxel administration

Extravasation risk:

Pertuzumab: non-vesicant

Trastuzumab: non-vesicant

Docetaxel: exfoliant

Phesgo- No extravasation risk as subcutaneous route of injection

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Withdrawn the contents of the vial into a 15mL syringe using a transfer needle and then change the needle to a subcutaneous 25-27 Gauge needle prior to administering the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Withdrawn the contents of the vial into a 10mL syringe using a transfer needle and then change the needle to a subcutaneous 25-27 Gauge needle prior to administering the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 inject cold medication into the patient
- The dose should not be split between two syringes or between two sites of administration

Administration:

Cycle 1

Subcutaneous

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
1	**Phesgo**	**Pertuzumab 1200mg/ trastuzumab 600mg**	**SC**	Over 8 minutes
1	**Docetaxel**	**75mg/m^2**	**IV**	250mL sodium chloride 0.9% over 60 minutes

Or intravenous option

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
1	**Paracetamol**	**1000mg**	**Oral**	30mins before chemotherapy
1	**Trastuzumab**	**8mg/kg**	**IV**	250mL sodium chloride 0.9% over 90 minutes
1	**Pertuzumab**	**840mg**	**IV**	250mL sodium chloride 0.9% over 60 minutes
1	**Docetaxel**	**75mg/m^2**	**IV**	250mL sodium chloride 0.9% over 60 minutes

Cycle 2 to 6

Subcutaneous

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
1	**Phesgo**	**Pertuzumab 600mg/ trastuzumab 600mg**	**SC**	Over 5 minutes
1	**Docetaxel**	**75mg/m^2**	**IV**	250mL sodium chloride 0.9% over 60 minutes

Or intravenous option

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
1	**Paracetamol**	**1000mg**	**Oral**	30mins before chemotherapy
1	**Trastuzumab**	**6mg/kg**	**IV**	250mL sodium chloride 0.9% over 60 minutes at cycle 2 and then 30 minutes if well tolerated
1	**Pertuzumab**	**420mg**	**IV**	250mL sodium chloride 0.9% over 30 minutes
1	**Docetaxel**	**75mg/m^2**	**IV**	250mL sodium chloride 0.9% over 60 minutes

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

Paclitaxel (where patient has NOT received Docetaxel and Phesgo in past 6 weeks)

Loading dose cycle 1

Day	Drug	Dose	Route	Diluent and rate
1	Phesgo	Pertuzumab 1200mg / trastuzumab 600mg	S/C injection	Over 8 minutes
1, 8 and 15	Dexamethasone	6.6mg	IV Bolus	30 minutes before chemotherapy Reduce to 4mg 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

Maintenance dose Phesgo cycle 2 onwards

Day	Drug	Dose	Route	Diluent and rate
1	Phesgo	Pertuzumab 600mg / trastuzumab 600mg	S/C injection	Over 5 minutes
1, 8 and 15	Dexamethasone	3.3mg	IV Bolus	30 minutes before chemotherapy
	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

Cycle 7 onwards subcutaneous

Day	Drug	Dose	Route	Diluent and rate
1	**Phesgo**	**Pertuzumab 600mg / trastuzumab 600mg**	**SC**	Over 5 minutes

Or intravenous option

Day	Drug	Dose	Route	Diluent and rate
1	**Trastuzumab**	**6mg/kg**	**IV**	250mL sodium chloride 0.9% over 30 minutes
1	**Pertuzumab**	**420mg**	**IV**	250mL sodium chloride 0.9% over 30 minutes

Paclitaxel switch from Docetaxel (where patient received Docetaxel and Phesgo in last 6 weeks)

Maintenance dose Phesgo cycle 2 onwards

Day	Drug	Dose	Route	Diluent and rate
1	Phesgo	Pertuzumab 600mg / trastuzumab 600mg	S/C injection	Over 5 minutes
1, 8 and 15	Dexamethasone	3.3mg	IV Bolus	30 minutes before chemotherapy
	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

Cycle 7 onwards subcutaneous

Day	Drug	Dose	Route	Diluent and rate
1	**Phesgo**	**Pertuzumab 600mg / trastuzumab 600mg**	**SC**	Over 5 minutes

Or intravenous option

Day	Drug	Dose	Route	Diluent and rate
1	**Trastuzumab**	**6mg/kg**	**IV**	250mL sodium chloride 0.9% over 30 minutes
1	**Pertuzumab**	**420mg**	**IV**	250mL sodium chloride 0.9% over 30 minutes

Main Toxicities

Haematological	Neutropenia, thrombocytopenia and anaemia.
Gastrointestinal	Nausea, vomiting, stomatitis, diarrhoea
Cardiotoxicity	Pertuzumab and trastuzumab - decreases in LVEF have been reported with medicinal products that block HER2 activity, including 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.
Ocular	Watery eyes, gritty and irritated
Hypersensitivity reactions	Reactions may occur within a few minutes following the initiation of treatment with docetaxel, facilities for the treatment of hypotension and bronchospasm should be available. 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 docetaxel and appropriate treatment. Patients who have developed severe hypersensitivity reactions should not be re-challenged with docetaxel.

	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: Infusion reactions, allergic-like reactions and hypersensitivity can occur. The majority of these events occur during or within 2.5 hours of the start of the first infusion. Should an infusion reaction occur the infusion should be discontinued or the rate of infusion slowed and the 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.
Nervous system	Docetaxel: peripheral neuropathy is very common
Musculoskeletal	Arthralgia, myalgia common with docetaxel
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	Comments
Clinical Assessment	X		X		X		Alternate cycles. Then every 3 months whilst on pertuz/trastuz
SACT Assessment (includes PS and toxicities)	X	X	X	X	X	X	Every cycle
ECHO	X			X			ECHO must be performed before pertuz/trastuz commences. Then every 4 months whilst on trastuzumab
FBC	X		X	X	X	X	Every cycle of docetaxel or every administration of Paclitaxel
U&E & LFT	X		X	X	X	X	Every cycle of docetaxel or every administration of Paclitaxel
Informed Consent	X						
CT scan	X						Every 8 to 12 weeks as clinically indicated
Weight recorded	X	X	X	X	X	X	Every cycle
Height	X						

ECHO – frequency can be reduced if stable results for 12 months

Dose Modifications and Toxicity Management:

Haematological Toxicity:

Proceed with chemotherapy treatment if;

Neutrophils $\geq$ 1.0 **and** platelets $\geq$ 100 x 10^9/L

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

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

For pertuzumab/trastuzumab only cycles – no blood tests required

Hepatic impairment:

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:	contraindicated

Renal impairment:

Trastuzumab, Pertuzumab Paclitaxel and Docetaxel
All grades including patients on HDx - no dose adjustment required.

Peripheral Neuropathy

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

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

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.

Trastuzumab Dose Modifications and Toxicities;

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.	

Hypersensitivity

Injection-related symptoms (mild to moderate in severity): fever, chills, headache, nausea, rash, arthralgia/myalgia (occur mainly with 1st intravenous dose) and anaphylaxis. These symptoms should be managed using paracetamol, with addition of chlorphenamine and hydrocortisone if anaphylaxis suspected.

Dose reductions are not indicated to manage toxicity

- 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.

Cardiotoxicity: Pertuzumab and Trastuzumab;

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

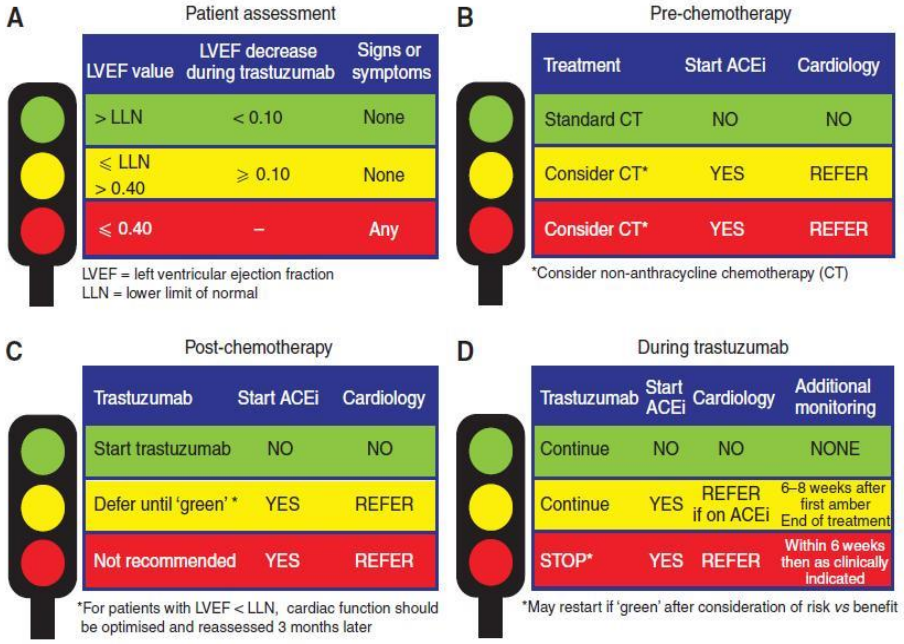

Figure 2 Traffic light system to prevent, monitor, and manage cardiac events in patients undergoing cytotoxic chemotherapy. (**A**) Patient assessment during trastuzumab therapy; (**B**–**D**) indications for ACEi therapy and referral to a cardiologist before (**B**) and after (**C**) chemotherapy, and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

References:

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