Chemotherapy Protocol

BREAST CANCER

Docetaxel-Pertuzumab/Trastuzumab SC

Regimen

- Breast Cancer – Docetaxel-Pertuzumab/Trastuzumab SC

Indication

- Treatment of metastatic breast cancer (MBC) in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.

- WHO Performance status 0, 1

Toxicity

Drug	Adverse Effect
Docetaxel	Hypersensitivity, fluid retention, neuropathy, joint pains, nail changes, fatigue
Pertuzumab/Trastuzumab SC	Injection related reactions, diarrhoea and other GI disturbances, left ventricular dysfunction, rash

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Diarrhoea can be severe in patients treated with the combination of pertuumab and trastuzumab . It is important to ensure patients are given appropriate therapy for the treatment of diarrhoea. This is not included in the regimen on Aria and must be added from the support folder.

Monitoring

Regimen

- HER2 status before initiating therapy

- LVEF to be assessed at baseline, prior to cycle four then every 4 cycles during maintenance monotherapy or as clinically indicated

- Blood pressure on day 1 of each cycle

- FBC, U&Es and LFTs prior to each cycle with docetaxel

Dose Modifications

Dose reductions are not recommended for pertuzumab / trastuzumab combination. If treatment with this combination is not tolerated it should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing if appropriate. The approach may be different depending on the clinical circumstances. The following is a general guide only.

Haematology

Patients may continue pertuzumab / trastuzumab combination treatment during periods of reversible chemotherapy-induced myelosuppression but they should be monitored carefully for complications of neutropenia during this time.

The following guidelines apply to docetaxel only**.**

Prior to prescribing cycle one the following treatment criteria must be met;

Criteria	Eligible Level (Docetaxel)
Neutrophil	Greater than or equal to $1.5x10^9$/L (unless due to bone marrow impairment)
Platelets	Greater than or equal to $100x10^9$/L (unless due to bone marrow impairment

Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL

Toxicity	Grade (NCI-CTC)	Docetaxel 75mg/m^2	Docetaxel 60mg/m^2
Neutropenia	1	75mg/m^2	60mg/m^2
	2	Delay until grade 1 then 75mg/m^2	Delay until grade 1 then 60mg/m^2
	3	Delay until grade 1 then 75mg/m^2	Delay until grade 1 then 60mg/m^2
	4	Delay until grade 1 then 60mg/m^2	Stop
Febrile Neutropenia	3	Delay until grade 1 then 60mg/m^2	Stop
	4	Delay until grade 1 then 60mg/m^2	Stop
Platelets	Greater than or equal to $100x10^9$/L	75mg/m^2	60mg/m^2
	Less than $100x10^9$/L	Delay until greater than or equal to $100x10^9$/L the 60mg/m^2	Stop

Hepatic Impairment

Drug	Recommendation					
Docetaxel	N/A		1.5xULN or greater	and	2.5xULN or greater	Give 75% dose
	Greater than ULN	and/ or	3.5xULN or greater	and	6xULN or greater	Not recommended
Pertuzumab/ Trastuzumab SC	No specific dose adjustments are recommended in hepatic impairment					

Renal Impairment

Drug	Recommendation
Docetaxel	No dose adjustment necessary
Pertuzumab/Trastuzumab SC	No dose adjustment necessary for mild or moderate renal impairment. No dose recommendations are available for severe renal impairment due to lack of data.

Other

Docetaxel

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

Peripheral neuropathy at NCI-CTC grade 3 should result in a dose reduction from 75mg/m^2 to 60mg/m^2 once the neuropathy has resolved to NCI-CTC grade 2 or below. If the NCI-CTC grade 3 neuropathy occurred at doses lower than 75mg/m^2 or a NCI-CTC grade 4 toxicity develops consider stopping treatment.

Excessive tearing / lacrimation are related to cumulative docetaxel doses and occur after a median of 400mg/m^2. Symptomatic treatment with hypromellose 0.3% eye drops four times a day may help. However, if the ocular irritation continues reduce the docetaxel dose to 80% of the original dose in the first instance.

Delay the docetaxel where a NCI-CTC grade 3 cutaneous toxicity is present on day one of the cycle until it resolves to NCI-CTC grade 1 or below. The subsequent doses of docetaxel should be reduced from 75mg/m^2 to 60mg/m^2. If it occurs with a dose of 60mg/m^2 or if there is no recovery after two weeks, docetaxel treatment should be stopped. Where a NCI-CTC grade 3 cutaneous toxicity occurs between cycles with recovery by day one then reduce the docetaxel dose as described. Docetaxel should be stopped in response to a NCI-CTC grade 4 cutaneous toxicity.

Left ventricular dysfunction

Pertuzumab/trastuzumab should be withheld for at least 3 weeks for any signs and symptoms suggestive of congestive heart failure. The combination should be discontinued if symptomatic heart failure is confirmed, the patient commenced on ACE inhibitor therapy and referred to a cardiologist. Further treatment should be discussed with the relevant oncology consultant.

Patients with metastatic breast cancer

Patients should have a pre-treatment left ventricular ejection fraction (LVEF) of equal to or greater than 50 %.

Pertuzumab/trastuzumab should be withheld for at least 3 weeks for:

- a drop in LVEF to less than 40 %
- a LVEF of 40 %-45 % associated with a fall of equal to or greater than 10 % points below pre-treatment value.

Pertuzumab-trastuzumab may be resumed if the LVEF has recovered to > 45%, or to 40-45% associated with a difference of less than 10% points below pre-treatment values.

Injection-related reactions

Pertuzumab/trastuzumab has been associated with injection-related reactions. The injection may be slowed or paused if the patient experiences injection-related symptoms Treatment including oxygen, beta agonists, antihistamines, rapid intravenous fluids and antipyretics may also help alleviate systemic symptoms. The injection should be discontinued immediately and permanently if the patient experiences a NCI-CTCAE grade 4 reaction (anaphylaxis), bronchospasm or acute respiratory distress syndrome.

Diarrhoea

Pertuzumab/trastuzumab may elicit severe diarrhoea. Diarrhoea is most frequent during concurrent administration with taxane therapy. Elderly patients (equal to or greater than 65 years) have a higher risk of diarrhoea compared with younger patients (less than 65 years). Early intervention with loperamide, fluids and electrolyte replacement should be considered, particularly in elderly patients, and in case of severe or prolonged diarrhoea. Interruption of treatment should be considered if no improvement in the patient's condition is achieved. When the diarrhoea is under control treatment may be reinstated.

Pulmonary events

Severe pulmonary events have been reported with the use of trastuzumab in the post-marketing setting. Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of pulmonary events. Therefore, these patients should not be treated with pertuzumab/trastuzumab. Caution should be exercised for pneumonitis, especially in patients being treated concomitantly with taxanes.

Regimen

21 day cycle for 6 cycles of docetaxel and pertuzumab/trastuzumab.

Pertuzumab-trastuzumab is then continued until disease progression or intolerance. This will be set up in ARIA with six cycles.

Cycle 1

Drug	Dose	Days	Administration
Docetaxel	75mg/m^2	1	Intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes
Pertuzumab/trastuzumab SC	1200mg/600mg (Loading)	1	Subcutaneous injection over 8 minutes

Cycle 2, 3, 4, 5, 6

Drug	Dose	Days	Administration
Docetaxel	75mg/m^2	1	Intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes
Pertuzumab/trastuzumab SC	600mg/600mg (Maintenance)	1	Subcutaneous injection over 5 minutes

Cycle 7 onwards

Drug	Dose	Days	Administration
Pertuzumab/trastuzumab SC	600mg/600mg (Maintenance)	1	Subcutaneous injection over 5 minutes

Dose Information

- The dose of docetaxel may be increased to 100mg/m^2 from cycle two onwards if well tolerated.
- Docetaxel induced fluid retention can lead to weight gain. This is not a reason to alter the doses
- Docetaxel will be dose banded according to national dose banding tables (20mg/ml)
- If the time between two sequential injections of pertuzumab/trastuzumab SC is less than 6 weeks, the maintenance dose of 600mg/600mg should be administered as soon as possible. Thereafter continue with the 3-weekly schedule.

- If the time between two sequential injections of pertuzumab/trastuzumab SC is 6 weeks or more, a loading dose of 1200mg/600mg should be re-administered followed by maintenance doses of 600mg/600mg every 3 weeks thereafter.

Administration Information

- Hypersensitivity reactions tend to occur with the first or second infusion of docetaxel. The docetaxel infusion should not be interrupted for minor symptoms such as flushing or localised rashes. Immediately discontinue the infusion for severe reactions which include profound hypotension, bronchospasm and generalised erythema.

- Docetaxel doses of more than 200mg should be diluted in 500ml sodium chloride 0.9% (maximum concentration 0.74mg/ml)

- Pertuzumab/trastuzumab SC has been associated with hypersensitivity and infusion related reactions. Patients should be observed for 30 minutes after the first injection and for 15 subsequent infusions.

- Pertuzumab/trastuzumab SC should be administered before any taxane, and the observation period must be completed before starting administration of the taxane.

- The pertuzumab/trastuzumab SC injection site should be alternated between the left and right thigh only. New injections should be given at least 2.5 cm from the previous site on healthy skin and never 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. During the treatment course, other medicinal products for subcutaneous administration should preferably be injected at different sites.

Extravasation

- Docetaxel – exfoliant

Additional Therapy

- Antiemetics (docetaxel cycles only)

  15-30 minutes before chemotherapy

  - metoclopramide 10mg oral or intravenous

  As take home medication

  - metoclopramide 10mg three times a day when required oral

- To prevent fluid retention and hypersensitivity reactions prescribe dexamethasone 8mg twice a day orally for three days starting 24 hours before the docetaxel administration. On the occasions where individuals attend for treatment and have forgotten to take the dexamethasone pre-medication administer dexamethasone 20mg once only dose intravenous

bolus.

- Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

- Diarrhoea is a common adverse effect, particularly on cycle one. Consider prescribing loperamide 4mg after the first loose motion then 2mg after each loose motion thereafter. This can be added from the support folder in Aria.

- For treatment of pertuzumab/trastuzumab SC injection reactions 'once only when required' doses of the following should be prescribed;

    - chlorphenamine 10mg intravenous
    - hydrocortisone 100mg intravenous
    - paracetamol 1000mg once oral

References

1. Baselga J, Cortes J, Sung-Bae K et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012; 366 (2): 109-119
2. Phesgo 600 mg/600 mg solution for injection / Phesgo 1200 mg/600 mg solution for injection SmPCs 01 January 2021

REGIMEN SUMMARY

Docetaxel-Pertuzumab/Trastuzumab SC

Cycle 1 Day One

1. Dexamethasone 8mg twice a day oral (from TTO)*
   Administration Instructions
   Ensure the patient has taken the dexamethasone pre-medication the day before and the day of docetaxel administration (and the day after). On the occasions where individuals attend for treatment and have forgotten to take the dexamethasone pre-medication administer dexamethasone 20mg (or equivalent dose) IV stat 15-30 minutes before chemotherapy. If the patient has already taken a dose of dexamethasone do not administer this dose.

2. Pertuzumab/trastuzumab 1200mg/600mg (loading dose) subcutaneous injection over 8 minutes
   Administration Instructions
   Pertuzumab/trastuzumab 1200mg/600mg (pertuzumab 1200mg/trastuzumab 600mg) is a LOADING DOSE
   Administer as a single subcutaneous injection over 8 minutes (the whole dose should be given via a single syringe into a single administration site). The injection site should be alternated between the left and right thigh only. New injections should be given at least 2.5cm from the previous site on healthy skin and never into areas where the skin is red, bruised, tender or hard.
   Patients should be observed for 30 minutes after administration of the loading dose and for 15 minutes after each maintenance dose or according to local policy.
   Administer before any taxane, and the observation period must be completed before starting administration of the taxane.

   Pharmacy please state the brand dispensed by either adding the brand from “favourites” or writing below

   Brand: ……

3. Metoclopramide 10mg oral or intravenous

4. Docetaxel 75mg/m² intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes
   Administration Instructions
   Ensure the patient has taken the dexamethasone pre-medication the day before and the day of docetaxel administration (and the day after). On the occasions where individuals attend for treatment and have forgotten to take the dexamethasone pre-medication administer dexamethasone 20mg IV stat, or equivalent dose, 15-30 minutes before chemotherapy.

5. Chlorphenamine 10mg intravenous when required for infusion related reactions

6. Hydrocortisone 100mg intravenous when required for infusion related reactions

7. Paracetamol 1000mg oral when required for infusion related reactions

Take Home Medicines

8. Dexamethasone 8mg twice a day oral for 3 days starting the day before the docetaxel infusion

9. Metoclopramide 10mg three times a day when required oral

Cycle 2, 3, 4, 5 Day One

10. Pertuzumab/trastuzumab 600mg/600mg (maintenance) subcutaneous injection over 5 minutes
    Administration Instructions
    Pertuzumab/trastuzumab 600mg/600mg (pertuzumab 600mg/trastuzumab 600mg) is a maintenance dose Administer as a single subcutaneous injection over 5 minutes (the whole dose should be given via a single syringe into a single administration site). The injection site should be alternated between the left and right thigh only. New injections should be given at least 2.5cm from the previous site on healthy skin and never into areas where the skin is red, bruised, tender or hard. Patients should be monitored for 15 minutes after each injection or according to local policy

    Administer before any taxane, and the observation period must be completed before starting administration of the taxane.

    Pharmacy please state the brand dispensed by either adding the brand from "favourites" or writing below

    Brand: ……

11. Metoclopramide 10mg oral or intravenous

    Docetaxel 75mg/m² intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes
    Administration Instructions
    Ensure the patient has taken the dexamethasone pre-medication the day before and the day of docetaxel administration (and the day after). On the occasions where individuals attend for treatment and have forgotten to take the dexamethasone pre-medication administer dexamethasone 20mg IV stat, or equivalent dose, 15-30 minutes before chemotherapy.

12. Chlorphenamine 10mg intravenous when required for infusion related reactions

13. Hydrocortisone 100mg intravenous when required for infusion related reactions

14. Paracetamol 1000mg oral when required for infusion related reactions

Take Home Medicines

15. Dexamethasone 8mg twice a day oral for 3 days starting the day before the docetaxel infusion

16. Metoclopramide 10mg three times a day when required oral

Cycle 6 Day one

17. Pertuzumab/trastuzumab 600mg/600mg (maintenance) subcutaneous injection over 5 minutes
    Administration Instructions
    Pertuzumab/trastuzumab 600mg/600mg (pertuzumab 600mg/trastuzumab 600mg) is a maintenance dose Administer as a single subcutaneous injection over 5 minutes (the whole dose should be given via a single syringe into a single administration site). The injection site should be alternated between the left and right thigh only. New injections should be given at least 2.5cm from the previous site on healthy skin and never into areas where the skin is red, bruised, tender or hard. Patients should be monitored for 15 minutes after each injection or according to local policy

    Administer before any taxane, and the observation period must be completed before starting administration of the taxane.

    Pharmacy please state the brand dispensed by either adding the brand from "favourites" or writing below

Brand: .....

18. Metoclopramide 10mg oral or intravenous

19. Docetaxel 75mg/m² intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes
    Administration Instructions
    Ensure the patient has taken the dexamethasone pre-medication the day before and the day of docetaxel administration (and the day after). On the occasions where individuals attend for treatment and have forgotten to take the dexamethasone pre-medication administer dexamethasone 20mg IV stat, or equivalent dose, 15-30 minutes before chemotherapy.

20. Chlorphenamine 10mg intravenous when required for infusion related reactions

21. Hydrocortisone 100mg intravenous when required for infusion related reactions

22. Paracetamol 1000mg oral when required for infusion related reactions

Take Home Medicines

23. Metoclopramide 10mg three times a day when required oral

Cycle 7, 8, 9, 10, 11 onwards

Pertuzumab/trastuzumab 600mg/600mg (Maintenance) subcutaneous injection over 5 minutes
Administration Instructions
Pertuzumab/trastuzumab 600mg/600mg (pertuzumab 600mg/trastuzumab 600mg) is a maintenance dose Administer as a single subcutaneous injection over 5 minutes (the whole dose should be given via a single syringe into a single administration site). The injection site should be alternated between the left and right thigh only. New injections should be given at least 2.5cm from the previous site on healthy skin and never into areas where the skin is red, bruised, tender or hard. Patients should be monitored for 15 minutes after each injection or according to local policy

Administer before any taxane, and the observation period must be completed before starting administration of the taxane.

Pharmacy please state the brand dispensed by either adding the brand from “favourites” or writing below

Brand: .....

24. Chlorphenamine 10mg intravenous when required for infusion related reactions

25. Hydrocortisone 100mg intravenous when required for infusion related reactions

26. Paracetamol 1000mg oral when required for infusion related reactions

Cycle 12

27. Warning – Check further cycles required

28. Pertuzumab/trastuzumab 600mg/600mg (Maintenance) subcutaneous injection over 5 minutes
    Administration Instructions
    Pertuzumab/trastuzumab 600mg/600mg (pertuzumab 600mg/trastuzumab 600mg) is a maintenance dose

Administer as a single subcutaneous injection over 5 minutes (the whole dose should be given via a single syringe into a single administration site). The injection site should be alternated between the left and right thigh only. New injections should be given at least 2.5cm from the previous site on healthy skin and never into areas where the skin is red, bruised, tender or hard. Patients should be monitored for 15 minutes after each injection or according to local policy

Administer before any taxane, and the observation period must be completed before starting administration of the taxane.

29. Pharmacy please state the brand dispensed by either adding the brand from "favourites" or writing below

30. Brand: .....

31. Chlorphenamine 10mg intravenous when required for infusion related reactions

32. Hydrocortisone 100mg intravenous when required for infusion related reactions

33. Paracetamol 1000mg oral when required for infusion related reactions

*Cycle one dexamethasone must be prescribed in advance of the chemotherapy. In ARIA Planner the dexamethasone 8mg twice daily will appear on days 1, 2, 3 of treatment. This is the supply for the next cycle. The administration instructions reflect this. On the last cycle no dexamethasone will appear for prescribing.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	March 2021	None	Rebecca Wills Pharmacist	Dr Sanjay Raj Consultant Clinical Oncologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.