Chemotherapy Protocol

BREAST CANCER

Capecitabine– Trastuzumab (SC)-Tucatinib

Regimen

- Breast Cancer – Capecitabine–Trastuzumab (SC)-Tucatinib

Indication

- Treatment of over-expressed HER2 positive unresectable locally advanced or metastatic breast cancer after 2 or more anti-HER2 treatment regimens where;
  - the patient has unresectable locally advanced or metastatic breast cancer.
  - the patient has histologically documented breast cancer which is HER2 3+ by immunohistochemistry and/or has a HER2 amplification ratio of greater than or equal to 2 by in situ hybridisation.
  - the patient has received two or more anti-HER2 treatment regimens which must have included a trastuzumab-containing regimen and a trastuzumab emtansine treatment regimen.
  - the patient has not received Tucatinib treatment before unless the patient has received tucatinib via a company early access scheme and the patient meets all the criteria on blueteq.
  - the patient has not previously been treated with capecitabine in the locally advanced/metastatic disease setting.
  - the patient has an ECOG performance status of 0 or 1.
  - treatment will be continued until disease progression or unacceptable toxicity or the patient choices to stop treatment.

Toxicity

Drug	Adverse Effect
Trastuzumab	Injection related reactions, diarrhoea and other GI disturbances, left ventricular dysfunction, rash, haematotoxicity, infections, pulmonary adverse reactions, anorexia,
Tucatinib	Diarrhoea, increased transaminases, nausea, vomiting, stomatitis, rash, arthralgia, increased bilirubin, weight loss, epistaxis
Capecitabine	Diarrhoea, nausea, vomiting, abdominal pain, stomatitis, palmer-planter erythrodysesthesia, fatigue, cardiotoxicity, anorexia

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

Monitoring

Regimen

- HER2 status before initiating therapy
- Cardiac function must be assessed prior to starting trastuzumab. Thereafter it should be assessed every 12 weeks for 24 weeks, then every 24 weeks thereafter (unless clinical evidence of cardiac failure).
- FBC, U&Es and LFTs prior to each cycle
- Patients with complete or partial dihydropyrimidine dehydrogenase (DPD) deficiency are at increased risk of severe and fatal toxicity during treatment with capecitabine. All patients should be tested for DPD deficiency before initiation (cycle 1) to minimise the risk of these reactions (unless they have previously had capecitabine or fluorouracil).

Dose Modifications

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 trastuzumab and tucatinib treatment during periods of reversible chemotherapy-induced myelosuppression but they should be monitored carefully for complications of neutropenia during this time.

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

Prior to starting a cycle of capecitabine the following treatment criteria should be met:

Criteria	Eligible level
Neutrophil	$1.5x10^9$/L
Platelets	$100x10^9$/L

If counts on day 1 are below these criteria for neutrophil and/or platelets delay treatment by seven days. Treatment should only be resumed when these levels are reached. If the delay is seven days or less, then resume at the same dose. If a delay of longer than 7 days is required to achieve these levels, or it has occurred for a second time reduce dose to 80%. If despite dose reduction these levels are not achieved, consider stopping treatment.

If unscheduled laboratory assessments during treatment show that the neutrophil count is less than $1x10^9$/L or platelet count less than $75x10^9$/L treatment with capecitabine should be interrupted.

Hepatic Impairment

Capecitabine and Trastuzumab (SC)

Drug	Recommendation
Capecitabine	There is a lack of information available. In patients, with mild to moderate hepatic dysfunction due to liver metastases, 100% of the dose is probably acceptable. Capecitabine should be held if there are treatment related elevations in bilirubin greater than 3xULN or AST/ALT greater than 2.5xULN. Treatment with capecitabine can be restarted when the bilirubin less than or equal to 3xULN or AST/ALTless than or equal to 2.5xULN.
Trastuzumab SC	No specific dose adjustments are recommended in hepatic impairment

Tucatinib

No initial dose reductions are required for patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. Patients with severe hepatic impairment (Child Pugh C) should be initiated on a reduced dose of 200mg twice a day.

If elevations in bilirubin or transaminases occur after starting treatment with tucatinib the following recommendations are made:

Grade of increase	Recommendation
Grade 1 bilirubin (greater than ULN to 1.5xULN)	No dose modification required
Grade 2 bilirubin (graeter than 1.5 to 3xULN)	Hold tucatinib until recovery to less than or equal to grade 1, then resume tucatinib at the same dose level.
Grade 3 AST or ALT (greater than 5xULN to 20xULN) OR Grade 3 bilirubin (greater than 3xULN to 10xULN)	Hold tucatinib until recovery to less than or equal to grade 1, then resume tucatinib at the next lower dose level.

Grade 4 ALT or AST (greater than 20xULN) OR Grade 4 bilirubin (greater than 10xULN)	permanently discontinue tucatinib
ALT or AST greater than 3xULN AND Bilirubin greater than 2xULN	Permanently discontinue tucatinib

Renal Impairment

Drug	Recommendation	
Capecitabine	Creatinine Clearance (ml/min)	Dose (% of original dose)
	Greater than 50	100%
	30-50	75%
	Less than 30	contraindicated
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.	
Tucatinib	No dose adjustment is required in patients with mild, moderate or severe renal impairment.	

Tucatinib adverse effects

Recommended tucatinib dose reductions for adverse reactions

Dose level	Tucatinib dose
Recommended starting dose	300mg twice daily
First dose reduction	250mg twice daily
Second dose reduction	200mg twice daily
Third dose reduction	150mg twice daily

If patients are unable to tolerate 150mg twice daily tucatinib should be permanently discontinued.

Diarrhoea

Severity	Tucatinib dose modification
Grade 1 or 2	No dose modification is required.
Grade 3 without anti-diarrheal treatment	Initiate or intensify appropriate medical therapy. Hold tucatinib until recovery to less than or equal to grade 1, then resume tucatinib at the same dose level.
Grade 3 with anti-diarrheal treatment	Initiate or intensify appropriate medical therapy. Hold tucatinib until recovery to less than or equal to grade 1, then resume tucatinib at one dose level lower.
Grade 4	Permanently discontinue tucatinib

Other adverse effects

Grade of adverse effect	Recommendation
Grade 1 or 2	No dose modification is required
Grade 3	Hold tucatinib until recovery to less than or equal to grade 1, then resume tucatinib at one dose level lower.
Grade 4	Permanently discontinue tucatinib.

Capecitabine other adverse effects

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. Dose limiting toxicities include diarrhoea, abdominal pain, emesis, stomatitis and palmer-planter erythrodysesthesia among others. If chest pain occurs, consider stopping capecitabine.

NCI-CTC grade 2

Interrupt treatment until the toxicity resolves to NCI-CTC grade 1 or below then continue at the same dose. If the toxicity recurs for a second time again interrupt the treatment until it resolves to NCI-CTC grade 1 or below, then resume therapy at 75% of the original dose. If the same adverse effect develops on a third occasion once more interrupt treatment until it resolves to NCI-CTC grade 1 or below, then continue at 50% of the original dose. Stop treatment if the toxicity re-appears on a fourth instance.

NCI-CTC Grade 3

Interrupt treatment until the toxicity resolves to NCI-CTC grade 1 or below then continue treatment using 75% of the original dose with prophylaxis if appropriate. If the toxicity recurs for a second time, again interrupt treatment until it resolves to NCI-CTC grade 1 or below and then resume therapy at 50% of the original dose. If the same adverse effect develops on a third occasion discontinue capecitabine.

NCI-CTC Grade 4

Discontinue treatment unless the responsible consultant considers it to be in the best interest of the patient to continue at 50% of the original dose once the toxicity has resolved to NCI-CTC grade 1 or below.

When capecitabine is stopped for toxicity, the doses are omitted and not delayed.

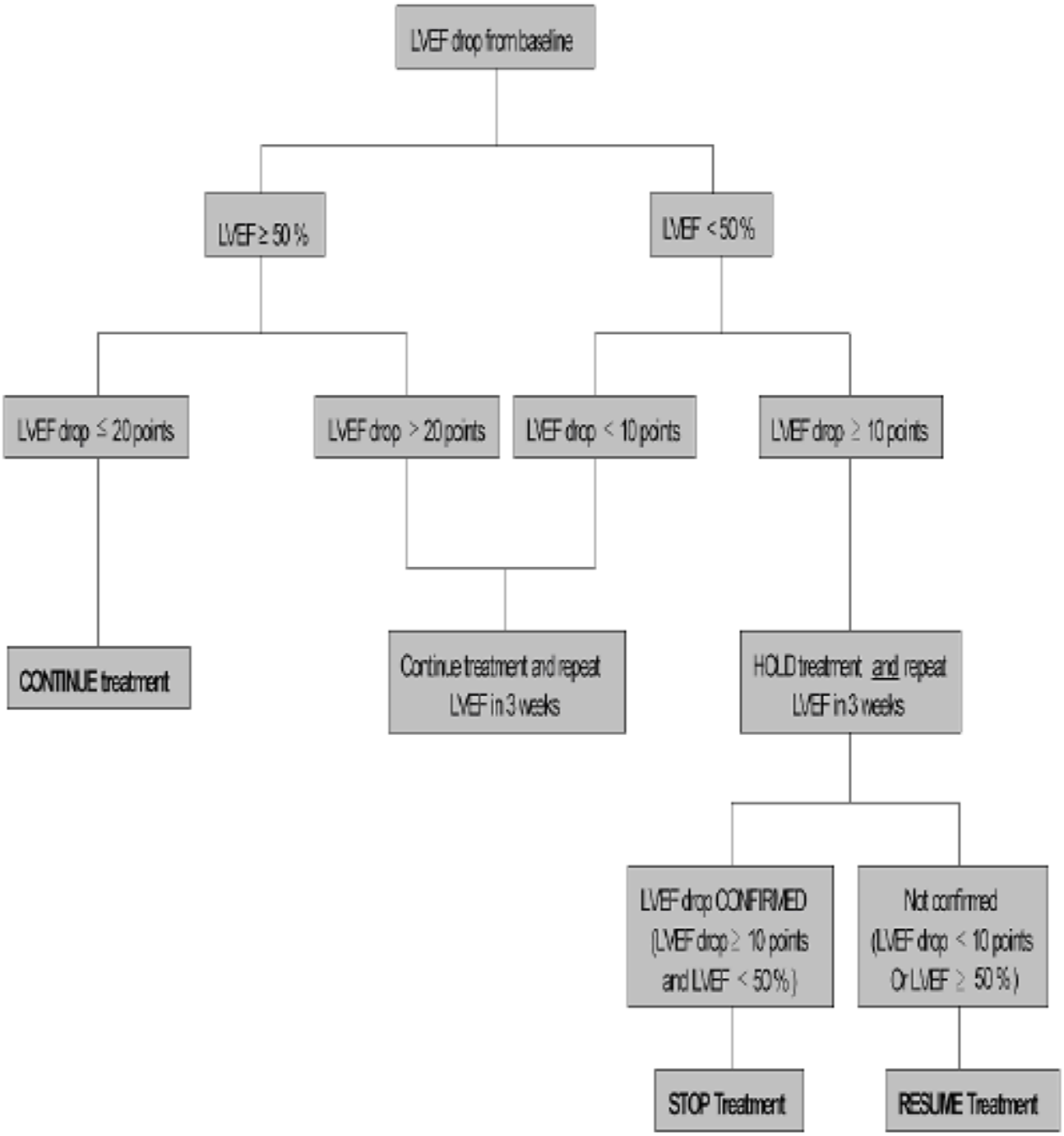
Trastuzumab

Cardiac

The LVEF should be fifty or above before starting cycle one of trastuzumab.

Subsequent Echocardiograms

The flow chart below describes the process to be followed if there is an **asymptomatic** decline in LVEF during trastuzumab treatment.



In general patients who develop **symptomatic** cardiac dysfunction should have trastuzumab discontinued, be commenced on ACE inhibitor therapy and be referred to a cardiologist. Further treatment should be discussed with the relevant oncology consultant.

Administration-related reactions

Administration-related reactions are known to occur with subcutaneous trastuzumab. Although serious administration-related reactions including dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress, were not reported in the clinical trial with the subcutaneous trastuzumab formulation, caution should be exercised as these have been associated with the intravenous formulation. Patients should be observed for administration-related reactions for 30 minutes after the first injection and 15 minutes after subsequent injections. Patients should be counselled about the possibility of delayed symptoms and instructed to contact the hospital in the event of these occurring.

Regimen

21 day cycle until disease progression or unacceptable toxicity (8 cycles will be set on aria).

Drug	Dose	Days	Administration
Capecitabine	1000mg/m^2 Twice a day	1-14 followed by 7 day break	Oral
Trastuzumab (SC)	600mg	1	Subcutaneous injection over 2-5 minutes.
Tucatinib	300mg twice a day	1-21 (continuous)	Oral

Dose Information

- Capecitabine will be dose banded in accordance with the national dose bands.
- Capecitabine is available as 500mg and 150mg tablets.
- Tucatinib is available as 150mg and 50mg film coated tablets.
- If the patient misses a dose of subcutaneous trastuzumab it is recommended to administer the 600mg dose as soon as possible. The interval between consecutive subcutaneous administrations should not be less than three weeks.

Administration Information

- Trastuzumab is associated with hypersensitivity reactions. The SPC recommends that patients should be observed for 30 minutes following the first administration of subcutaneous trastuzumab, and for 15 minutes following subsequent administrations.
- The trastuzumab injection site should be alternated between the left and right thigh. New injections should be given at least 2.5cm from the old site and

never into areas where the skin is red, bruised, tender or hard.

- If a dose of tucatinib is missed, the patient should take their next dose at the regularly scheduled time.
- Tucatinib tablets should be swallowed whole and should not be chewed, crushed or split prior to swallowing.
- Tucatinib doses should be taken approximately 12 hours apart, at the same time every day with or without food.
- Tucatinib may be taken at the same time as capecitabine.
- Capecitabine should be taken with or after food.

Additional Therapy

- For treatment of trastuzumab injection reactions 'once only when required' doses of the following should be prescribed;
  - chlorphenamine 10mg intravenous
  - hydrocortisone 100mg intravenous
  - paracetamol 1000mg once oral
- Antiemetics

  As take home medication on cycle one only. This can be added from "favourites" if required on future cycles.
  - Metoclopramide 10mg three times a day when required
- Oral loperamide 4mg after the first stool, then 2-4mg four times a day when required for the relief of diarrhoea (maximum 16mg/24hours). This will be added to cycle one only. It can be added from "favourites" if required on future cycles.
- Mouthwashes according to local or national policy on the treatment of mucositis.
- Gastric protection with a proton pump inhibitor or H^2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

Additional Information

- The National Patient Safety Agency alert NPSA/2008/RRR001 must be followed when prescribing, dispensing or administering oral chemotherapy.
- Ensure the total daily dose of capecitabine is divided into two doses given twelve hours apart (the first should be administered the evening of day 1 of the cycle). Serious toxicity has occurred where the total daily dose has been given twice a day.

- Patients should be assessed for suitability for oral chemotherapy prior to starting treatment.

References
1. Glenmark Pharmaceuticals Europe Ltd (2021). Capecitabine 150mg film-coated tablets summary of product characteristics. Available from www.medicines.org.uk. Accessed 11/07/2022.
2. Seagen U.K Ltd (2021). Tukysa 150mg film-coated tablets summary of product characteristics. Available from www.medicines.org.uk. Accessed 11/07/2022.
3. Roche products limited (2021). Herceptin 600mg solution for injection in vial summary of product characteristics. Available from www.medicines.org.uk. Accessed 11/07/2022.
4. Murthy RK et al. Tucatinib, Trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. N Engl J Med (2020); 382: 597-609.

REGIMEN SUMMARY

Capecitabine–Trastuzumab (SC)-Tucatinib

Cycle 1 Day One

1. Trastuzumab 600mg subcutaneous injection over 2 to 5 minutes
   Administration instructions:
   The injection site should be alternated between the left and right thigh. New injections should be given at least 2.5cm from the old site and never into areas where the skin is red, bruised, tender or hard.

   Chlorphenamine 10mg intravenous when required for infusion related reactions
   Administration instructions
   For the treatment of infusion related reactions

2. Hydrocortisone 100mg intravenous when required for infusion related reactions
   Administration instructions
   For the treatment of infusion related reactions

3. Paracetamol 1000mg oral when required for infusion related reactions
   Administration Instructions
   Please check if the patient has taken paracetamol in the last four hours. The maximum dose is 4000mg/24 hours. For the treatment of infusion related reactions

Take Home Medicines

4. Capecitabine 1000mg/m^2 twice a day for 14 days oral
   Administration instructions
   To start the evening of day 1 of the cycle.
   Take with or after food.
   Oral SACT

5. Tucatinib 300mg twice a day for 21 days oral
   Administration Instructions
   To start the evening of day 1 of the cycle.
   Swallow whole
   Oral SACT

6. Metoclopramide 10mg three times a day when required oral
   Administration instructions
   Please dispense 28X10mg tablets or nearest equivalent pack size.

7. Loperamide 4mg after the first loose stool and 2mg after each loose stool thereafter. Maximum dose is 16mg/24 hours.
   Administration Instructions
   Please supply 28x2mg capsules or nearest equivalent original pack size.

Cycle Two Day 1 Onwards

8. Trastuzumab 600mg subcutaneous injection over 2 to 5 minutes
   Administration instructions:
   The injection site should be alternated between the left and right thigh. New injections should be given at least 2.5cm from the old site and never into areas where the skin is red, bruised, tender or hard.

9. Chlorphenamine 10mg intravenous when required for infusion related reactions
   Administration instructions
   For the treatment of infusion related reactions

10. Hydrocortisone 100mg intravenous when required for infusion related reactions
    Administration instructions
    For the treatment of infusion related reactions

11. Paracetamol 1000mg oral when required for infusion related reactions
    Administration Instructions
    Please check if the patient has taken paracetamol in the last four hours. The maximum dose is 4000mg/24 hours. For the treatment of infusion related reactions

Take Home Medicines

12. Capecitabine 1000mg/m^2 twice a day for 14 days oral
    Administration instructions
    To start the evening of day 1 of the cycle.
    Take with or after food.
    Oral SACT

13. Tucatinib 300mg twice a day for 21 days oral
    Administration Instructions
    To start the evening of day 1 of the cycle.
    Swallow whole
    Oral SACT

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	July 2022	None	Alexandra Pritchard Pharmacist	Dr Marcus Remer Consultant

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 Hospital 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.