Systemic Anti Cancer Therapy Protocol

Tucatinib with Trastuzumab and Capecitabine Advanced Breast Cancer

PROTOCOL REF: MPHATTCABC
(Version No. 1.0)

Approved for use in:

Tucatinib (Tukysa®) is a kinase inhibitor indicated in combination with trastuzumab and capecitabine for treating over-expressed HER2 positive unresectable locally advanced or metastatic breast cancer after 2 or more anti-HER2 treatment regimens

DPYD bloods need to be taken before commencing treatment

***********Blueteq form Required**********

Dosage:

Drug	Dose	Route	Frequency
Tucatinib	**300mg**	Oral	Twice a day (morning and evening) for 21 days
Capecitabine	**1000mg/m^2**	Oral	Twice a day (morning and evening) for 14 days
Trastuzumab	**600mg**	SC	Day 1 Given slowly over 2-5 minutes

Repeat every 21 days until disease progression or unacceptable toxicity

Administration Points

- Swallow tucatinib and capecitabine whole – do not chew, crush or split prior to swallowing. Do not ingest tablet if it is broke, cracked or not otherwise intact
- Tucatinib and capecitabine can be taken at the same time morning and evening. Doses for both are to be taken 12 hours apart at roughly the same time each day. Capecitabine should be taken within 30 minutes of a meal.
- If vomiting occurs or a dose is missed, take the next dose at its usual scheduled time. Do not double up missed doses
- Do not add doses missed due to toxicity onto the end of the cycle. Continue according to the treatment plan and stop taking on the originally scheduled day.

- Regularly moisturise hands and feet
- Capecitabine - Caution in patients with pre-existing coronary heart disease, angina pectoris, arrhythmias or those on high dose aspirin or anticoagulants

Trastuzumab

- Withdraw the contents of the vial into a 10mL syringe using a 16 gauge needle. Prior to administering the dose change the needle to a subcutaneous 24 gauge needle.
- The injection site should be alternated between the left and right thigh. Each injection should be given at least 2.5 cm from the old site while ensuring the area of skin is not red, bruised, tender or hard.
- Following administration of the first dose, monitor the patient for 2 hours for signs of hypersensitivity, refer to 'Hypersensitivity: Management and Prevention' policy for guidance.
- Medication should be warmed to room temperature before administration. This is easily achieved by asking the patient to warm the vial of trastuzumab in their hands while the nurse performs assessment/documentation. Never inject cold medication into the patient

Emetogenic risk:

Mildly emetogenic.

Supportive treatments:

Domperidone 10mg oral tablets, up to 3 times a day or as required

Loperamide Initially 4mg, followed by 2mg after each loose stool. Maximum 16mg in 24 hours

Extravasation risk:

N/A

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

Dosing in renal and hepatic impairment:

<table>
<tr><td>Hepatic</td><td>Tucatinib
If Child-Pugh C reduce the recommended starting dosage to 200mg twice daily
<table>
<tr><th>Parameters</th><th>1 point</th><th>2 points</th><th>3 points</th></tr>
<tr><td>Total bilirubin (µmol/L)</td><td>< 34</td><td>34–50</td><td>> 50</td></tr>
<tr><td>Serum albumin (g/L)</td><td>> 35</td><td>28–35</td><td>< 28</td></tr>
</table></td></tr>
</table>

	Prothrombin time, prolongation (s) *Or* INR	< 4 < 1.7	4–6 1.7-2.3	> 6 >2.3
	Ascites	None	Mild to Moderate (diuretic responsive)	Severe (diuretic refractory)
	Hepatic encephalopathy	None	Grade I–II (or suppressed with medication)	Grade III–IV (or refractory to medication)

INR: International Normalised Ratio.
Child-Pugh Class A = 5-6 points
Child-Pugh Class B = 7-9 points
Child-Pugh Class C = 10 or more points
Please note: assessment of Child-Pugh Class is to help guide clinical teams when prescribing and pharmacists when screening.

Capecitabine	No dose adjustments required
Trastuzumab	No dose adjustments required

Renal	**Tucatinib**	No dose adjustments required. Crcl <30ml/min not recommended	
	Trastuzumab	No dose adjustments required	
	Capecitabine	Calculate creatinine clearance using Cockroft and Gault at baseline and before each cycle and adjust dose accordingly	
		Creatinine Clearance	***Dose***
		>50ml/min	100%
		30-50ml/min	75%
		<30ml/min	Not recommended

Interactions:

Tucatinib - Avoid concomitant use of strong CYP2C8 inhibitors with tucatinib. If concomitant use with a strong CYP2C8 inhibitor cannot be avoided, reduce the recommended dosage to 100 mg orally twice daily. After discontinuation of the strong CYP2C8 inhibitor for 3 elimination half-lives, resume the tucatinib dose that was taken prior to initiating the inhibitor

Capecitabine

- Phenytoin – potentially toxic levels of phenytoin have been reported- monitor carefully
- Warfarin and other coumarin anticoagulants – increased bleeding risk, monitor INR carefully, consider switch to LMWH.

- Sorivudine and analogues – Potentially fatal interaction – avoid completely
- Allopurinol – reduced efficacy of capecitabine – avoid.

For more detailed interactions please refer to the specific drug SPC

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**Trastuzumab**	**600mg**	**SC**	Given slowly over 2-5 minutes
	Capecitabine	**1000mg/m^2**	Oral	Twice a day (morning and evening) for 14 days
	Tucatinib	**300mg**	Oral	Twice (morning and evening) a day for 21 days

Main toxicities:

Tucatinib	
Haematological	Anaemia
Skin	Rash, Palmar Plantar Erythema (PPE or hand- foot syndrome)
Hepatobiliary	Increased liver function blood tests
Gastrointestinal	Diarrhoea, nausea, vomiting, stomach pain, decreased appetite, stomatitis
General disorders	Headache, fatigue, fertility issues, epistaxis, electrolyte disturbances, increased creatinine due to inhibition of renal tubular transport of creatinine without affecting glomerular function.
Capecitabine	
Haematological	Neutropenia, anaemia, thrombocytopenia,
Cardiac and Vascular disorders	Angina
Gastrointestinal	Nausea, vomiting, diarrhoea, constipation, mucositis
Hepatobiliary	Elevation of liver transaminases, alkaline phosphatase and bilirubin.
Skin and subcutaneous tissue disorders	Palmar Plantar Erythema (PPE or hand- foot syndrome),

General disorders and administration site conditions	Fatigue, taste changes Infertility, early menopause
DPD deficiency – leads to severe early fluoropyrimidine toxicity, it affects approximately 3-6% of population, may be life threatening in up to 1% of cases.	
Trastuzumab	
Cardiotoxicity	Congestive heart failure is a common adverse effect associated with trastuzumab. See separate cardiac toxicity below for further details.
Hypersensitivity reactions	Subcutaneous preparation is less likely to cause administration reactions than intravenous. Monitor for dyspnoea, hypotension. See below for further information
General disorders and administration site conditions	Fatigue Injection site reactions Pulmonary events – less common with subcutaneous preparation. See below for further information

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Ongoing
Informed Consent	x				
Clinical Assessment	x			x	As clinically indicated
Dihydropyrimidine dehydrogenase (DPD) deficiency test	x				This test is normally only required if a patient has not had capecitabine, or fluorouracil in the past. However a consultant may still request this test if capecitabine or fluorouracil was not tolerated previously. The result must be available before administration of chemotherapy unless clear documentation from the consultant is available to the contrary. Treatment with capecitabine and fluorouracil is contraindicated in patients with known complete DPD deficiency.
SACT Assessment (to include PS and toxicities)	x	x	x	x	Every cycle
FBC	x	x	x	x	Every cycle
U&E & LFTs & Magnesium	x	x	x	x	Every Cycle
CrCl (Cockcroft and Gault)	x	x	x	x	Every cycle
CT scan	x				Baseline and 3 monthly

ECHO	x				Baseline, then at 3 to 4 months for first 12 months, as clinically indicated thereafter
Full Observations (*RR, HR and O2 sats)*	x				Repeat if clinically indicated
Weight recorded	x	x	x	x	Every cycle

Dose Modifications and Toxicity Management:

- No dose adjustments needed for trastuzumab

Recommended dose reductions for Tucatinib	
First Dose Reduction	250 mg orally twice daily
Second Dose Reduction	200 mg orally twice daily
Third Dose Reduction	150 mg orally twice daily
Permanently discontinue in patients unable to tolerate 150 mg orally twice daily	

Recommended dose reductions for capecitabine

Toxicity grades / Haematological parameter	**Dose changes within a treatment cycle**	**Dose adjustment for next cycle/dose (% of starting dose)**
• *Grade 1* *Neutrophils ≥ 1.5 x 10^9/L but less than lower limit of normal.* *AND/OR* *Platelets ≥ 75 x 10^9/L but less that lower limit of normal*	Maintain dose level	Maintain dose level
• *Grade 2* *Neutrophils 1.0 x 10^9/L to less than 1.5 x 10^9/L* AND/OR *Platelets 50 x 10^9/L to less than 75 x 10^9/L*		
-1st appearance	Interrupt until resolved to grade 0-1	100%
-2nd appearance		75%
-3rd appearance		50%
-4th appearance	Discontinue treatment permanently	Not applicable
• *Grade 3*		

Neutrophils 0.5 x 10^9/L to less than 1.0 to x 10^9/L *AND/OR* *Platelets 25 x 10^9/L to less than 50 x 10^9/L*		
-1st appearance	Interrupt until resolved to grade 0-1	75%
-2nd appearance		50%
-3rd appearance	Discontinue treatment permanently	Not applicable
• *Grade 4* *Neutrophils less than 0.5 x 10^9/L* *AND/OR* *Platelets less than 25 x 10^9/L*		
-1st appearance	Discontinue permanently *Or* If physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1	50%
-2nd appearance	Discontinue permanently	Not applicable

Haematological toxicity:

Proceed on day 1 if-

ANC ≥ 1.0 x 10^9/L	Plt ≥ 100 x 10^9/L

Delay 1 week on day 1 if-

ANC ≤ 0.9 x 10^9/L	Plt ≤ 99 x 10^9/L

Non- Haematological toxicity:

Tucatinib

Diarrhoea	Grade 3 without anti-diarrheal treatment	Initiate or intensify appropriate medical therapy. Hold until recovery to ≤ Grade 1, then resume at the same dose level.
	Grade 3 with anti-diarrheal treatment Initiate or intensify appropriate medical therapy.	Hold until recovery to ≤ Grade 1, then resume at the next lower dose level.
	Grade 4	Permanently discontinue
Increased ALT, AST or bilirubin	Grade 2 bilirubin (>1.5 to 3 × ULN)	Hold until recovery to ≤ Grade 1, then resume at the same dose level.
	ALT or AST > 3 × ULN AND Bilirubin > 2 × ULN	Hold until recovery to ≤ Grade 1, then resume at the next lower dose level.
	Grade 3 ALT or AST (> 5 to 20 × ULN) OR Grade 3 bilirubin (> 3 to 10 × ULN)	Permanently discontinue.
	Grade 4 ALT or AST (> 20 × ULN) OR Grade 4 bilirubin (> 10 × ULN)	Permanently discontinue.
Other adverse reactions	Grade 3	Hold until recovery to ≤ Grade 1, then resume at the next lower dose level.
	Grade 4	Permanently discontinue

Capecitabine

Diarrhoea	Loperamide at standard doses, codeine may be added – see table for dose reductions
Stomatitis	Regular mouthwashes (water, saline), brush gently with a soft brush, adequate pain relief, nutritional support in severe cases – see below for dose reductions.
Palmar plantar erythema or hand foot syndrome	Withhold treatment until resolved to grade 1, dose reductions as per table above.
Sore eyes / Conjunctivitis	Eye drops for symptomatic treatment
Chest Pain / coronary artery spasm	Stop capecitabine, standard angina investigations, refer to consultant, if symptoms persist stop capecitabine permanently

Renal impairment	Calculate creatinine clearance using Cockroft and Gault before each cycle and adjust dose accordingly	
	Creatinine Clearance	***Dose***
	>50ml/min	100%
	30-50ml/min	75%
	<30ml/min	Not recommended

Trastuzumab

Pulmonary Impairment:

Pulmonary events have been reported with the use of Trastuzumab. These events have occasionally been fatal.

<u>Caution should be exercised for pneumonitis.</u>

Hypersensitivity

Injection-related symptoms (mild to moderate in severity and less likely to occur with subcutaneous injection): fever, chills, headache, nausea, rash, arthralgia/myalgia (occur mainly with 1st intravenous dose) and anaphylaxis. These symptoms should be

managed using paracetamol and chlorphenamine or adrenaline if suspected anaphylaxis.

Cardiotoxicity

- Sharp falls in LVEF (10 points or to <50%) during cytotoxic chemotherapy may indicate increased susceptibility to cardiac dysfunction on trastuzumab. 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 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 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.
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Cardiac toxicity should be managed used the NCRI recommendations reproduced below:

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

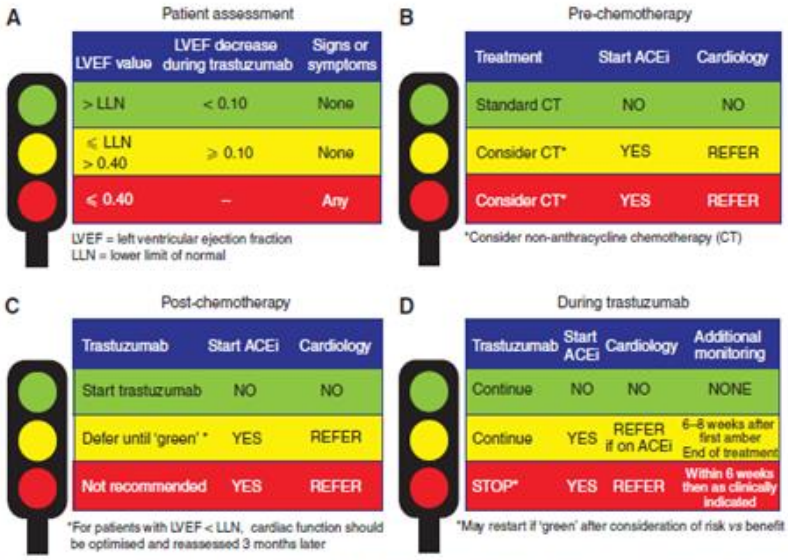

Figure 2 Traffic light system to prevent, monitor, and manage cardiac events in patients undergoing cytotoxic chemotherapy. (**A**) Patient assessment during trastuzumab therapy; (**B**–**D**) indications for ACEi therapy and referral to a cardiologist before (**B**) and after (**C**) chemotherapy, and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

References:

1. Capecitabine Accord 150mg film-coated tablets, SmPC, Accord Healthcare Limited. Available from www.medicines.org.uk/emc/medicine. (Last updated 17th May 2021). Herceptin 600 mg solution for injection in vial SmPC, Roche Products Limited accessed via the electronic medicines compendium at https://www.medicines.org.uk/emc (Last updated 28th September 2021.

2. Krens, S. D., et al. (2019). Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *The Lancet Oncology*, 20(4), e200-e207.
3. Murthy, R. K., et al. (2020). Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. *New England Journal of Medicine*, 382(7), 597-609.
4. NICE TA786: Tucatinib with trastuzumab and capecitabine for treating HER2-positive advanced breast cancer after 2 or more anti-HER2 therapies. Published: 27 April 2022.
5. Tucatinib 150mg film-coated tablets, SmPC, Seagen U.K. Ltd. Available from www.medicines.org.uk/emc/medicine. (Last updated 8th October 2021).

Circulation/Dissemination

Date added into Q-Pulse	8th July 2022
Date document posted on the Intranet	N/A

Version History

		Author name and designation	Summary of main changes
		Gabriella Langton **Breast SRG Pharmacist**	New Regimen Protocol V1.0
