TUCATINIB (Tukysa) CAPECITABINE TRASTUZUMAB (Herceptin subcutaneous)

INDICATION (ICD10) C50

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/) (TUC1)

1. For treating over-expressed HER2 positive (HER2 3+ and/or HER2 amplification ratio ≥2.0) unresectable locally advanced or metastatic breast cancer after 2 or more anti-HER2 treatment regimens, no previous capecitabine.PS 0 or 1. (TA786)

REGIMEN

Day 1	*TRASTUZUMAB	600mg SC over 5 minutes
Days 1 to 14	CAPECITABINE	1000mg/m^{2*} twice daily (2000mg/m^2/day) oral followed by a 7 day rest
Days 1 to 21	TUCATINIB	300mg oral twice daily

*For patients unable to receive SC trastuzumab on cycle 1, and therefore the treatment intent is to use IV trastuzumab for the entire treatment period with tucatinib in combination with trastuzumab and capecitabine, see the trastuzumab monotherapy regimen for IV trastuzumab doses, observation times etc.

Trastuzumab - observation time post injection 30 minutes after the first injection and for 15 minutes after subsequent injections.

CYCLE FREQUENCY AND NUMBER OF CYCLES

Every 21 days until progression or unacceptable toxicity.
Trastuzumab may continue every 21 days even if capecitabine and tucatinib are delayed.

ADMINISTRATION

Capecitabine
Tablets should be taken 12 hours apart.
Swallow with water within 30 minutes after a meal, or dissolve in 200ml luke warm water, stir thoroughly (squash may be added if unpalatable).

Tucatinib
Tablets should be taken 12 hours apart.
Swallow whole with water.

ANTI-EMETICS

Low risk days 1 to 14

CONCURRENT MEDICATION REQUIRED

Capecitabine	Mouth and bowel support eg Loperamide, benzydamine mouthwash
Trastuzumab	Infusion related chills and/or fevers – treat with paracetamol and chlorphenamine.
Tucatinib	Mouth and bowel support eg Loperamide, benzydamine mouthwash

EXTRAVASATION AND TYPE OF LINE / FILTERS

Trastuzumab SC – neutral

INVESTIGATIONS

Blood results required before tucatinib and capecitabine administration
FBC, U&E and LFTs every cycle
Neutrophils x 10^9/L ≥1.0
Platelets x 10^9/L ≥100
Serum creatinine - GFR each cycle ≥50ml/min
DPYD test
Blood pressure – base line and every cycle
Monitor cardiac function according to network guidelines
Baseline weight and every cycle

MAIN TOXICITES AND ADVERSE REACTIONS

Capecitabine	Palmar plantar (handfoot syndrome) causing red palms and soles – treat with pyridoxine 50mg tds Diarrhoea – treat with loperamide or codeine Cardiotoxicity – monitor cardiac function. To minimise risk of anthracycline induced cardiac failure signs of cardiotoxicity e.g. cardiac arrhythmias, pericardial effusion, tachycardia with fatigue. All patients should be told to report any cardiac symptoms immediately and should be told to stop the medication immediately if any suspicion of cardiac problems. Stomatitis
Trastuzumab	Cardiotoxicity - monitor cardiac function. Trastuzumab infusion related chills and/or fevers are commonly observed during the first infusion (but infrequently with subsequent infusions). Other symptoms may include nausea, hypertension, vomiting, pain, rigors, headache, cough, dizziness, rash, and asthenia. Some adverse reactions to trastuzumab infusion including dyspnoea, hypotension, wheezing, bronchospasm, supraventricular tachyarrhythmia, reduced oxygen saturation and respiratory distress can be serious and potentially fatal. If symptoms of back ache, nausea or vomiting, do a set of obs. Give hydrocortisone 100mg IV, chlorphenamine 10mg IV.
Tucatinib	Diarrhoea. Increased ALT, AST, and bilirubin. Increased creatinine without impaired renal function.

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS
(not exhaustive list check SPC/BNF/Stockleys)

Capecitabine	Brivudine and analogues should be avoided Warfarin and caution with all oral anticoagulants Phenytoin Allopurinol
Tucatinib	Many interactions check carefully, including CYP3A/CYP2C8 inducers, CYP2C8 inhibitors, CYP3A substrates and P-gp substrates.

DOSE MODIFICATIONS

Any drugs should be discontinued if a delay of that drug greater than 6 weeks is required due to treatment-related toxicity.

Haematological

Capecitabine

Neutrophils <1.0x10^9/l or platelets <100x10^9/l delay capecitabine treatment for 1 week. Repeat FBC. If recovered, restart capecitabine, using dose adjustment guidelines below, according to worst grade of haematological toxicity recorded.

Toxicity Grades	Dose changes within a treatment cycle	Dose adjustment for next cycle/dose (% of starting dose)
Grade 2 (neutrophils 1.0-1.5x10^9/l and / or platelets 50-75x10^9/l) - 1st appearance	Interrupt until resolved to grade 0-1	100%
Grade 2 - 2nd appearance	Interrupt until resolved to grade 0-1	75%
Grade 2 - 3rd appearance	Interrupt until resolved to grade 0-1	50%
Grade 2 - 4th appearance	Discontinue treatment permanently	Not applicable
Grade 3 (neutrophils 0.5-1.0x10^9/l and / or platelets 25-50x10^9/l) - 1st appearance	Interrupt until resolved to grade 0-1	75%
Grade 3 - 2nd appearance	Interrupt until resolved to grade 0-1	50%
Grade 3 - 3rd appearance	Discontinue treatment permanently	Not applicable
Grade 4 (neutrophils <0.5x10^9/l and / or platelets <25x10^9/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%
Grade 4 - 2nd appearance	Discontinue treatment permanently	Not applicable

Trastuzumab

No dose reduction or cessation of trastuzumab is required if patient has acute reversible neutropenia.

Non-haematological

Capecitabine

Dose limiting toxicities include diarrhoea, abdominal pain, nausea, stomatitis and handfoot syndrome.

Toxicity can be managed by symptomatic treatment and/or modification of the dose (treatment interruption or dose reduction).

Once the dose has been reduced it should not be increased at a later time.

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

Toxicity Grades	Dose changes within a treatment cycle	Dose adjustment for next cycle/dose (% of starting dose)
Grade 2 - 1st appearance	Interrupt until resolved to grade 0-1	100%
Grade 2 - 2nd appearance	Interrupt until resolved to grade 0-1	75%
Grade 2 - 3rd appearance	Interrupt until resolved to grade 0-1	50%
Grade 2 – 4th appearance	Discontinue treatment permanently	Not applicable
Grade 3 – 1st appearance	Interrupt until resolved to grade 0-1	75%
Grade 3 - 2nd appearance	Interrupt until resolved to grade 0-1	50%
Grade 3 - 3rd appearance	Discontinue treatment permanently	Not applicable
Grade 4 - 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%
Grade 4 - 2nd appearance	Discontinue treatment permanently	Not applicable

Tucatinib

Recommended dose	300mg twice daily
First dose reduction	250mg twice daily
Second dose reduction	200mg twice daily
Third dose reduction	150mg twice daily

If both capecitabine and trastuzumab are discontinued, patients should also discontinue tucatinib.

Diarrhoea

Grade 1 and 2	No dose modification is required.
Grade 3 without anti-diarrhoeal treatment	Initiate or intensify appropriate medical therapy. Hold tucatinib until recovery to ≤grade 1, then resume tucatinib at the same dose level.
Grade 3 with anti-diarrhoeal treatment	Initiate or intensify appropriate medical therapy. Hold tucatinib until recovery to ≤grade 1, then resume tucatinib at the next lower dose level.
Grade 4	Permanently discontinue tucatinib.

Increased ALT, AST or bilirubin on treatment

Grade 1 bilirubin (>ULN to 1.5xULN)	No dose modification is required.
Grade 2 bilirubin (>1.5 to 3×ULN)	Hold tucatinib until recovery to ≤grade 1, then resume tucatinib at the same dose level.
Grade 3 ALT or AST (>5 to 20×ULN) or grade 3 bilirubin (>3 to 10×ULN)	Hold tucatinib until recovery to ≤grade 1, then resume tucatinib at the next lower dose level.
Grade 4 ALT or AST (>20×ULN) or grade 4 bilirubin (>10×ULN)	Permanently discontinue tucatinib.
ALT or AST >3×ULN and bilirubin >2×ULN	Permanently discontinue tucatinib.

Other adverse reactions

Grade 1 and 2	No dose modification is required.
Grade 3	Hold tucatinib until recovery to ≤grade 1, then resume tucatinib at the next lower dose level.
Grade 4	Permanently discontinue tucatinib

Trastuzumab
Continuation and discontinuation of trastuzumab based on interval LVEF assessment as per network guidelines

Hepatic impairment
Capecitabine

Bilirubin of >3xULN or ALT/AST >2.5xULN	Interrupt capecitabine Treatment may be resumed when bilirubin decreases to <3xULN or hepatic aminotransferases decrease to <2.5xULN.

Tucatinib
No dose adjustment is required in patients with mild or moderate hepatic impairment.
Severe hepatic impairment (Child-Pugh C), a reduced starting dose of 200mg orally twice daily is recommended.

Renal impairment
Capecitabine

CrCl >50ml/min	give 100% dose
CrCl 30-50ml/min	give 75% dose
CrCl <30ml/min	contraindicated

Tucatinib
No dose adjustment is required in patients with mild, moderate, or severe renal impairment.

REFERENCES
1. SPC Tucatinib October 2021