Tucatinib, Capecitabine & Trastuzumab (Breast)

Indication

HER2-positive unresectable locally advanced or metastatic breast cancer after 2 or more anti-HER2 treatment regimens and not previously treated with capecitabine in the locally advanced/metastatic disease setting.

(NICE TA786)

ICD-10 codes

C50

Regimen details

Day	Drug	Dose	Route
1	Trastuzumab	600mg	SC*
1-21 (continuous)	Tucatinib	300mg BD	Oral
1-14	Capecitabine	1000mg/m^2 BD	Oral

* NHSE recommends patients are treated with subcutaneous trastuzumab within this regimen due to the benefits for patients and service capacity advantages. The intravenous formulation and dosing (8mg/kg loading and 6mg/kg maintenance) may be used if the subcutaneous formulation is unsuitable.

All patients must have documented DPYD status and capecitabine doses adjusted accordingly prior to commencing treatment as per local practice.

Cycle frequency

21 days

Number of cycles

Until disease progression or unacceptable toxicity

Administration

Trastuzumab is administered as a flat dose of 600mg in a volume of 5mL by subcutaneous injection over 2-5 minutes. The injection site should be alternated between left and right thigh, with new injections at least 2.5cm from the old site. Avoid administration into sites that are bruised, inflamed, tender or hard. Other medicinal products for subcutaneous administration should preferably be injected at different sites.

Patients should be observed for 6 hours after the first dose and up to 2 hours after subsequent doses for administration related reactions (or according to local policy).

It is important to check the product labels to ensure that the correct formulation of trastuzumab (intravenous or subcutaneous) is being administered to the patient. The two formulations are NOT interchangeable.

Capecitabine is available as 150mg and 500mg tablets.
Tablets should be taken after food, within 30 minutes of a meal, and swallowed whole with a glass of water.

Tucatinib is available as 150mg and 50mg tablets.
Tablets should be swallowed whole approximately 12 hours apart with or without a meal. It can be taken at the same time as capecitabine. If a dose is missed the patient should take their next dose at the regularly scheduled time.

Pre-medication
Nil

Emetogenicity
This regimen has low emetic potential – refer to local policy

Additional supportive medication
Loperamide with the first cycle then as required
Topical emollients to prevent palmar plantar erythema
Proton pump inhibitor if required
Mouthwash as per local policy

Extravasation
N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U&E	14 days
LFTs	14 days
Echocardiogram	Baseline

DPYD status must be available prior to starting capecitabine treatment as per local practice.

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	96 hours
U&E	7 days
LFTs	7 days
Echocardiogram	3-4 monthly increasing to every 6 months if stable (more frequently if patient developing asymptomatic cardiac dysfunction)

Standard limits for administration to go ahead
If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 100 x 10^9/L
Creatinine Clearance (CrCl)	> 50ml/min
Bilirubin	≤ 1.5 x ULN
AST/ALT	≤ 2.5 x ULN

Dose modifications

Dose level	Tucatinib Dose
Starting dose	300mg BD
First dose reduction	250mg BD
Second dose reduction	200mg BD
Third dose reduction	150mg BD

Tucatinib should be permanently discontinued in patients unable to tolerate 150mg BD

- **Haematological toxicity**

Trastuzumab – no dose modification is required. Patient may continue on trastuzumab during periods of myelosuppression

Tucatinib – no dose modification is required. Patients may continue on tucatinib during periods of myelosuppression

Capecitabine – if neutrophils <1.0 x 10^9/L and/or platelets <100 x 10^9/L delay 1 week or until recovery. Consider reducing to 75% dose for future cycles.

- **Renal impairment**

Trastuzumab – no dose modification is required.

Tucatinib – no dose adjustment is required in mild, moderate or severe impairment. NB. Serum creatinine increase may be observed during treatment due to inhibition of renal tubular transport of creatinine without affecting glomerular function.

Capecitabine:

CrCl (mL/min)	**Capecitabine dose**
>50	100%
30-50	75% (with close monitoring)
<30	Contra-indicated

- **Hepatic impairment**

Trastuzumab – no dose modification is required

Tucatinib – no dose adjustment is required in patients with mild or moderate impairment. For patients with severe hepatic impairment (Child-Pugh C), a reduced starting dose of 200mg BD is recommended. See toxicity section for elevations in liver enzymes during treatment.

Capecitabine:

AST +/or ALT (x ULN)		**Bilirubin (x ULN)**	**Capecitabine dose**
≤ 2.5	and	≤ 3	100%
> 2.5	or	> 3	Consultant decision*

- **Other toxicities**

Trastuzumab

Cardiac toxicity: LVEF must be above LLN for trastuzumab treatment to go ahead. If LVEF percentage drops ≥10 points from baseline AND to below 50% (cardiotoxicity), treatment should be withheld, patients should be started on a beta-blocker (eg, Bisoprolol 1.25mg od) and an angiotensin-converting enzyme (ACE) inhibitor (eg, Ramipril 1.25mg od), referred to a cardiologist and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or declined further, or symptomatic cardiac failure has developed, trastuzumab should be discontinued, unless the benefits for the individual patient are deemed to outweigh the risks.

Other indications to refer to cardiology include LVEF percentage drop of <10% to below 50% (Possible subclinical cardiotoxicity) and if LVEF percentage drops ≥10 points from baseline but remains above 50% AND an accompanying relative decline in global longitudinal strain (GLS) >15% (probable subclinical cardiotoxicity).

Tucatinib

Toxicity	Definition	Tucatinib dose modification
Diarrhoea	Grade 1 or 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	Grade 1 bilirubin (>ULN - 1.5 x ULN)	No dose modification is required
	Grade 2 bilirubin (1.5 - 3 x ULN)	Hold tucatinib until recovery to ≤ Grade 1, then resume tucatinib at the same dose level
	Grade 3 AST/ALT (5 - 20 x ULN) Or Grade 3 bilirubin (3 - 10 x ULN)	Hold tucatinib until recovery to ≤ Grade 1, then resume tucatinib at the next lower dose level
	Grade 4 AST/ALT (>20 x ULN) Or Grade 4 Bilirubin (>10 x ULN)	Permanently discontinue tucatinib
	ALT/AST > 3 x ULN ***And*** Bilirubin > 2 x ULN	Permanently discontinue tucatinib
Other adverse reactions	Grade 1 or 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

Capecitabine

Other toxicities should be managed by symptomatic treatment and/or dose modification (i.e. by treatment interruption or undertaking a dose reduction).
Once the dose has been reduced, it should not be increased at a later time.

For those toxicities considered unlikely to become serious or life-threatening (e.g. alopecia, altered taste or nail changes) treatment can be continued at the same dose without reduction or interruption.

Patients should be informed of the need to interrupt treatment immediately if they develop moderate or severe side effects particularly diarrhoea – not controlled by loperamide, palmar-plantar erythrodyaesthesia or infection.

Dose modifications should be made as per the following table:

Toxicity grade	1st occurrence	2nd occurrence	3rd occurrence	4th occurrence
0-1	100%	100%	100%	100%
2	Delay then 100%	Delay then 75%	Delay then 50%	Discontinue
3	Delay then 75%	Delay then 50%	Discontinue	
4	Delay then 50%	Discontinue		

Any delays should be until the toxicity has resolved to grade 0-1.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Hypersensitivity reactions, including bronchospasm, tachycardia, angioedema, anaphylaxis
Hepatotoxicity
Left ventricular cardiac dysfunction
ARDS, pneumonitis, pleural effusion, dyspnoea
Cardiotoxicity
Myelosuppression
Diarrhoea
Thrombus/embolism

- **Frequently occurring side effects**

Nausea and vomiting
Diarrhoea
Headache
Hypertension
Conjunctivitis
Nausea and vomiting
Stomatitis/Mucositis
PPE
Fatigue
Skin reactions
Nail changes
Taste disturbance
Myalgia, arthralgia
Rash
Epistaxis
Deranged liver function

- **Other side effects**

Asthenia
Fluid retention
Alopecia

Significant drug interactions – for full details consult product literature/ reference texts

Trastuzumab
No documented significant interactions

Tucatinib:
CYP3A substrates e.g. midazolam, alfentanil, simvastatin – Tucatinib is a strong CYP3A inhibitor so plasma concentrations of CYP3A substrates may be increased
P-gp substrates e.g. digoxin – increased plasma concentrations of P-gp substrate, consider dose reduction of substrate
Strong CYP3A/moderate CYP2C8 inducers e.g. rifampicin, St John's wort, carbamazepine – reduced plasma concentrations of tucatinib, avoid.
Strong/moderate CYP2C8 inhibitors e.g. gemfibrozil – strong inhibitors increased plasma concentrations of tucatinib, increased risk of tucatinib toxicity. No data for moderate inhibitors but consider additional monitoring for tucatinib toxicity

Capecitabine:
Folinates - Avoid concomitant use of folinic and folic acid – enhanced toxicity of capecitabine.
Co-trimoxazole/trimethoprim - Avoid if possible – enhances antifolate effect. If essential, monitor FBC regularly.
Phenytoin and fosphenytoin – toxicity has occurred during concomitant capecitabine therapy – monitor levels regularly.
Sorivudine and its analogues – co-administration causes increased toxicity which may be fatal.
Allopurinol – A decrease in capecitabine activity has been shown when taken in combination of allopurinol. Avoid if possible.
Warfarin/coumarin anticoagulants - Avoid use due to elevations in INR. Switch to low molecular weight heparin or DOAC during treatment.
Antacids – the use of antacids with capecitabine can decrease absorption – avoid.

Additional comments

Because the half-life of trastuzumab is approximately 4-5 weeks, it may persist in the circulation for up to 20-25 weeks after stopping trastuzumab treatment.

References

- National Institute for Health and Care Excellence (TA786) accessed 29 June 2022 via www.nice.org.uk
- Summary of Product Characteristics – Trastuzumab (Roche) accessed 29 June 2022 via www.medicines.org.uk
- Summary of Product Characteristics – Tucatinib (Seagen) accessed 29 June 2022 via www.medicines.org.uk
- Summary of Product Characteristics – Capecitabine (Accord) accessed 29 June 2022 via www.medicines.org.uk
- Murthy, RK et al. Tucatinib, trastuzumab and capecitabine for HER2-positive metastatic breast cancer. N Engl J Med 2020;382:597-609

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