Tucatinib, Capecitabine & Trastuzumab

Indication

Locally advanced or metastatic breast cancer after 2 or more anti-HER2 regimens.
Patients with brain metastases are eligible with new, previously treated or progressive brain disease as long as local brain directed treatment not required urgently

Regimen details

Tucatinib 300mg PO twice daily continually (with or without food)
Capecitabine 1000mg/m2 PO twice daily on days 1-14 (within 30mins of food)
Trastuzumab 600mg SC on day 1

Cycle frequency

Repeat every 21 days

Number of cycles

Treatment to continue until disease progression or unacceptable toxicity

Administration

The 600 mg Trastuzumab dose should be administered as a subcutaneous injection only over 2-5 minutes. The injection site should be alternated between the left and right thigh. New injections should be given at least 2.5 cm from the old site and never into areas where the skin is red, bruised, tender, or hard. During the treatment course with Herceptin subcutaneous formulation other medicinal products for subcutaneous administration should preferably be injected at different sites.
Patients should be observed for two hours after the first injection and for 30 minutes after subsequent injections for signs or symptoms of administration-related reactions. The observation time in subsequent doses may be reduced at local clinician's discretion

Oral Tucatinib to be taken with or without food
Oral Capecitabine to be taken within 30 minutes of food

Emetogenicity

Low risk

Additional supportive medication

Oral paracetamol 30 mins pre-trastuzumab
Loperamide prn
Cyclizine prn

Extravasation

No risk

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFT (including AST)	14 days
Bone profile	14 days

Glucose	14 days
HbA1C	14 days
Hepatitis B serology	14 days
DPYD screen	n/a
Cardiac assessment with MUGA or ECG	28 days

Investigations –pre subsequent cycles

FBC, U&Es, LFTs, Bone profile, Glucose

Cardiac assessment with MUGA or echocardiogram every 4 months

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	**Limit**
Neutrophil count	≥ 1.5 x 10^9/L (Discuss with consultant if 1.0 to 1.5)
Platelet count	≥ 100 x 10^9/L
Creatinine clearance (NB. Serum creatinine increase may be observed during treatment due to inhibition of renal tubular transport of creatinine without affecting glomerular function.)	≥ 50 mL/min Creatinine clearance. If CrCl 30-50 then reduce capecitabine to 75%. (Contraindicated if CrCl <30)
Bilirubin	≤ 1.5 x ULN (if Gilberts syndrome then conjugated Bilirubin <1.5 x ULN)
ALT/AST	< 2.5 x ULN (or <5 x ULN if liver metastases) – for 1st cycle but see toxicity table for action with deranged LFTs whilst on treatment

Dose modifications

Tucatinib

First dose reduction – 250mg twice daily
Second dose reduction – 200mg twice daily
Third dose reduction – 150mg twice daily
If not tolerated at 150mg twice daily then permanently discontinue

Diarrhoea
Grade 1 or 2 – Treat with loperamide. No dose modification required
Grade 3 without anti-diarrhoeal treatment – initiate or intensify appropriate medical therapy. Hold tucatinib until recovery to grade 1, then resume at same dose level
Grade 3 with anti-diarrhoeal treatment – Initiate or intensify appropriate medical therapy. Hold tucatinib until recovery to grade 1, then resume at lower dose level
Grade 4 – Permanently discontinue Tucatinib

Increased ALT, AST or Bilirubin
Grade 1 Bilirubin (>ULN to 1.5 ULN) – No dose modification required
Grade 2 Bilirubin (>1.5 ULN to 3 x ULN) – Hold tucatinib until recovery to Grade 1 then resume at the same dose level
Grade 3 ALT/AST (>5 ULN to 20 x ULN) **OR** Grade 3 bilirubin (>3 ULN to 10 x ULN) – Hold tucatinib until recovery to grade 1, then resume at the next lower dose
Grade 4 ALT/AST (>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

Bilirubin >3 x ULN or ALT/AST >2.5 x ULN omit Capecitabine until liver function recovers

Other adverse reactions
Grade 1 and 2 – No dose modification required
Grade 3 – Hold Tucatinib until recover to grade 1 and then resume at 1 reduced dose level
Grade 4 – Permanently discontinue Tucatinib

Toxicity due to capecitabine can be managed symptomatically and or modification of dose / dose delay

Adverse effects –

for full details consult product literature/ reference texts

Lethargy
Diarrhoea
Nausea / vomiting
PPE
Stomatitis
Elevated AST/ALT
Elevated creatinine
Cardiac toxicity
Myelosuppression
Infusion reactions

Significant drug interactions

– for full details consult product literature/ reference texts

Tucatinib is a strong CYP3A inhibitor and may increase plasma concentrations of drugs metabolised via CYP3A (e.g. simvastatin)
Tucatinib is a substrate of P-gp and may increase plasma concentrations of other P-gp substrates (e.g. digoxin)
Co-administration of tucatinib with strong CYP3A or moderate CYP2C8 inducers should be avoided as these may result in decreased activity of tucatinib
Co-administration of tucatinib with strong CYP2C8 inhibitors (e.g. gemfibrozil) should be avoided as it may result in increased toxicity of tucatinib
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.

THIS PROTOCOL HAS BEEN DIRECTED BY DR MOON, DESIGNATED LEAD CLINICIAN FOR BREAST CANCER

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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