Indication	Tucatinib in combination with trastuzumab and capecitabine for the treatment of over-expressed HER2 positive unresectable locally advanced or metastatic breast cancer after 2 or more anti-HER2 treatment regimens. Previous HER2 treatment **must have** included trastuzumab and trastuzumab emtansine, and the disease is now either resistant or refractory to trastuzumab emtansine or trastuzumab emtansine has been discontinued due to intolerance. Patients must **not have** been previously treated with capecitabine in the locally advanced setting or previously received tucatinib unless via an early access to medicines scheme.
Treatment Intent	Palliative
Frequency and number of cycles	Repeat every 21 days. Continue until disease progression, unacceptable toxicity or patient choice.
Monitoring Parameters pre-treatment	• ECG and ECHO/MUGA prior to cycle 1 then see cardiac monitoring below. • **DPD testing** must be undertaken in all patients before starting treatment; the result must be checked before treatment is started. • Monitor U&E, LFTs (ALT/AST and bilirubin) and FBC at each cycle or as clinically indicated. • Consider using alternative markers of renal function if serum creatinine is raised, increase in creatinine has been observed in patients receiving tucatinib due to inhibition of renal tubular transport of creatinine without affecting glomerular function. • PLT >/=100 and neuts >/=1.0 proceed with treatment, otherwise delay by 1 week. • **Renal impairment** Before starting treatment, GFR should be >/=50ml/min. o Capecitabine is contraindicated if CrCl <30ml/min. In patients with moderate renal impairment at baseline (ClCr 30-50ml/min), no dose reduction is required for a starting dose of 1000 mg/m^2 per dose. o Tucatinib no recommended dose adjustment required in mild, moderate or severe renal impairment. • **Hepatic impairment** o Capecitabine: No dose adjustments in hepatic impairment (insufficient data of capecitabine to make a dose recommendation). o Tucatinib: no dose adjustment required in mild or moderate hepatic impairment. A reduced starting dose of 200mg twice daily is recommended in severe impairment (Child-Pugh C). • **Cardiotoxicity** • Caution in patients with prior history of coronary heart disease, arrhythmias and angina pectoris. • Avoid anthracyclines for up to 7 months after stopping trastuzumab. If used, monitor cardiac function closely. • **Cardiac monitoring:** Cardiac function should be monitored at baseline (ECHO/MUGA and ECG) and then every 6 months (ECHO or MUGA) during treatment or as clinically indicated. It is the prescribers' responsibility to check that the ECHO/MUGA result is satisfactory before continuing treatment. • At each nurse assessment patients should be assessed for signs of dyspnoea. • **Injection related reactions:** Patients should be observed for 30 minutes after the first trastuzumab injection and for 15 minutes after subsequent injections. • **Dose interruption and reduction** o Capecitabine: Interrupt capecitabine in the event of >/= grade 2 non-haematological toxicity (with the exception of side effects such as alopecia, alteration in taste etc, considered to be not serious) until resolution of toxicity to grade 0-1.

	○ Dose reduction should be considered if grade 3 or 4 non-haematological toxicity or repeat appearance of grade 2 (except N&V and alopecia). Delay until resolution of toxicity to </= grade 1. ○ Tucatinib: First dose reduction, 250mg twice daily. Second dose reduction, 200mg twice daily. Third dose reduction 150mg twice daily. If a dose of 150mg twice daily cannot be tolerated, treatment should be permanently discontinued. For dose modification and reduction guidance see table 1. • **Drug interactions**: ○ **Capecitabine** must not be given with concurrent sorivudine or derivatives (e.g. brivudine), see SPC. Monitor PT and INR regularly in patients taking coumarin-derivative anticoagulants. Monitor phenytoin levels with concomitant use. Caution with folinic acid or folic acid – potential for increased toxicity. Avoid concomitant allopurinol. ○ Tucatinib has important drug interactions with the CYP2C8 and CYP3A systems, P-gp substrates and metformin. ○ Concomitant use of **tucatinib** with strong CYP2C8 inhibitors should be avoided. If coadministration with a strong CYP2C8 inhibitor cannot be avoided, the starting tucatinib dose should be reduced to 100 mg orally twice daily and the patient monitored closely for toxicity. After discontinuation of the strong CYP2C8 inhibitor for 3 elimination half-lives, the tucatinib dose that was taken prior to initiating the inhibitor should be resumed. Monitoring for tucatinib toxicity should be increased with moderate CYP2C8 inhibitors. ○ Tucatinib is a strong CYP3A inhibitor, co-administration of tucatinib with sensitive CYP3A substrates (e.g. tacrolimus, everolimus and midazolam) should be avoided due to increased risk of CYP3A substrate toxicity. Concomitant use with CYP3A substrates with narrow therapeutic index should be avoided e.g ciclosporin. If concomitant use is unavoidable, the CYP3A substrate dosage should be reduced in accordance with the concomitant medicinal product SmPC. ○ Co-administration of tucatinib with strong CYP3A inducers (e.g. rifampicin, carbamazepine, phenytoin) or moderate CYP2C8 inducers should be avoided. ○ Concomitant use of tucatinib with a P-gp substrate may increase the plasma concentrations of the P-gp substrate. Dose reduction of P-gp substrates (e.g. dabigatran) should be considered in accordance with the concomitant medicinal product SmPC. ○ Patients should not take St John's Wort. ○ Tucatinib may reduce renal clearance of metformin resulting in increased concentrations of metformin. • **Skin reactions:** Capecitabine can induce severe skin reactions such as Stevens-Johnson syndrome and Toxic Epidermal Necrolysis. Patients should be informed of the possibility of such reactions and informed to seek urgent medical advice should any symptoms of a severe skin reaction occur. Treatment should be permanently discontinued in affected patients. • **Missed dose**: ○ If the patient misses a dose of trastuzumab, administer the dose as soon as possible. The interval between the consecutive doses should not be less than 3 weeks. ○ If the patient misses a dose of capecitabine or tucatinib the patient should continue with the next dose at the regularly scheduled time. • **Excipients:** Tucatinib contains 55.3 mg sodium and 60.6 mg potassium per 300 mg dose. • Capecitabine may cause dizziness, fatigue and nausea. Patients should be aware this may affect their ability to drive or operate machinery. • For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet and Macmillan information sheet
References	BNF accessed online 01.03.2022 ARIA regimen BRE-039 V2 KMCC protocol BRE-002 V5 Blueteq form accessed online 01.03.2022. SPC accessed online tucatinib 01.03.2022.

NB For funding information, refer to CDF and NICE Drugs Funding List

Table 1 Dose modification of tucatinib for adverse reactions

Adverse Reaction	**Severity[1]**	**Tucatinib dosage modification**
Diarrhoea	Grade 1 and 2	No dose modification is required.
	Grade 3 without anti-diarrheal 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-diarrheal 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 to 1.5 x ULN)	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.

1. Grades based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03

Repeat every 21 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	**TRASTUZUMAB**	**600mg**	SC	2-5 min	Alternate injection site between the right and left thigh at least 2.5cm away from previous injection site
TTO	Drug	Dose	Route	Directions	
1	**CAPECITABINE**	**2000mg/m²/day** **In 2 divided doses**	PO	**BD for 14 days** (the 1st dose will be taken as the evening dose on day 1 and the last dose is taken the morning of day 15, followed by a 7-day rest period) Take within 30 minutes after food, and approximately every 12 hours Can be taken at the same time as tucatinib. **Available as 500mg and 150mg tablet**	
	TUCATINIB	**300mg***	PO	BD continuously (approximately 12 hours apart). Swallow whole, do not chew, crush or split the tablets. Can be taken at the same time as capecitabine. **Available as 150mg and 50mg tablets**	
	Metoclopramide	10mg	PO	10mg up to 3 times a day as required. Do not take for more than 5 days continuously.	
	Loperamide	2-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1 then only if required.	

*Note dose reduction required with concomitant use of strong CYP3A inhibitor