Indication	First line endocrine therapy for oestrogen receptor-positive, HER2-negative, locally advanced or metastatic breast cancer. NB: Previous hormone therapy with anastrozole or letrozole whether as adjuvant therapy or as neoadjuvant treatment is allowed as long as the patient has had a disease-free interval of 12 months or more since completing treatment with anastrozole or letrozole. NB: No prior treatment with a CDK 4/6 inhibitor unless either palbociclib or abemaciclib has had to be stopped within 6 months of its start solely as a consequence of dose-limiting toxicity and in the clear absence of disease progression or ribociclib has been received as part of the compassionate use scheme and the patient meets all the other commissioning criteria
Treatment Intent	Palliative
Frequency and number of cycles	Every 28 days Until disease progression or excessive toxicity or patient choice to discontinue.
Monitoring parameters pre-treatment	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • Monitor FBC, U&E and LFT at baseline then at the beginning of each cycle. If grade >/=2 hepatic abnormalities are noted (see table 2 below), more frequent monitoring is recommended. • Correct abnormalities in potassium, calcium, phosphorus and magnesium prior to initiating treatment. • If neuts >/= 1 and PLT >/= 100 proceed with treatment. • If neuts <1 or PLT <100 withhold ribociclib and alert consultant. • **Cardiac monitoring and guidance:** • ECG before starting treatment and then on day ~14 of cycle 1 and before cycle 2, then as clinically indicated. • Treatment should only be initiated in patients with QTcF values less than 450 msec. • In case of QTcF prolongation during treatment, more frequent ECG monitoring is recommended. The use of ribociclib should be avoided in patients who already have or who are at significant risk of developing QTc prolongation including; patients with long QT syndrome, with uncontrolled or significant cardiac disease, including recent myocardial infarction, congestive heart failure, unstable angina and bradyarrhythmias, and patients with electrolyte abnormalities. • **Dose Modifications:** First dose reduction to 400mg/day, second dose reduction to 200mg/day. If further dose reduction required, discontinue treatment • **Haematological and non-haematological toxicities of ribociclib**, see tables below, for thrombocytopenia discuss with consultant.

	• **Hepatic impairment:** In patients with moderate and severe hepatic impairment (Child-Pugh B&C) ribociclib dose should be reduced to 400mg/day. • **Renal impairment:** In patients with severe renal impairment (CrCl <30 mL/min) a starting dose of 200mg/day is recommended, with close monitoring for signs of toxicitiy. • **Adverse drug reactions** include neutropenia, leukopenia, headache, back pain, nausea, fatigue, diarrhoea, vomiting, constipation, alopecia, abnormal liver function test, lymphopenia, hypophosphataemia. • **Interstitial lung disease/pneumonitis** • Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis (e.g. hypoxia, cough, dyspneoa). See table 5 below for dose modification and guidance in patients who have new or worsening respiratory symptoms and are suspected to have developed ILD/pneumonitis. • **Cases of toxic epidermal necrolysis** (TEN) have been reported with ribociclib treatment. If signs and symptoms suggestive of severe cutaneous reactions (e.g. progressive widespread skin rash often with blisters or mucosal lesions) appear, ribociclib should be discontinued immediately. • If patient is pre- or peri-menopausal they must have undergone ovarian ablation or suppression with LHRH agonist treatment • **Common drug interactions (for comprehensive list refer to BNF/SPC) & food interactions:** o Avoid concomitant use with strong CYP3A4 inhibitors (eg ketoconazole, itraconazole, clarithromycin) and consider an alternative medication with no or minimal CYP3A4 inhibition. If patients must be co-administered a strong CYP3A4 inhibitor, reduce ribociclib dose to 400mg/day (or where dose already reduced, to the next dose level). If the strong inhibitor is discontinued, the ribociclib dose should be changed to the dose used prior to the initiation of the strong CYP3A44 inhibitor after at least 5 half-lives of the strong CYP3A44 inhibitor. o Concomitant use with medicinal products known to prolong QTc interval should be avoided as this may lead to clinically meaningful prolongation of the QTcF interval. o Caution with CYP3A4 substrates with a narrow therapeutic index (e.g. cyclosporin, fentanyl, tacrolimus); the dose may need to be reduced as ribociclib may increase their exposure. Concomitant use of the following CYP3A44 substrates should be avoided: alfuzosin, amiodarone, cisapride, pimozide, quinidine, ergotamine, dihydroergotamine, quetiapine, lovastatin, simvastatin, sildenafil, midazolam, triazolam. o Concomitant use of ribociclib with strong CYP3A44 inducers (carbamazepine, phenytoin, rifampicin, St John's Wort) should be avoided as it may lead to reduced ribociclib exposure. o Contraindicated in patients with a peanut or soya allergy. o Do not take grapefruit juice / fruit. • **Driving:** Patients should be advised to be cautious when driving or using machines in case they experience fatigue, dizziness or vertigo during treatment.
Reference(s)	KMCC protocol BRE-063 V2 SPC accessed online 01.02.2024

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

Protocol No	BRE-063	Kent and Medway SACT Protocol Disclaimer: No responsibility will be accepted for the accuracy of this information when used elsewhere.	
Version	3	Written by	M.Archer
Supersedes version	2	Checked by	C.Waters V3 C.Wong V2 V3 (cardiac monitoring changes as requested by Dr J Glendenning)
Date	22.02.2024	Authorising consultant (usually NOG Chair)	C.Harper-Wynne V2

Table 1 Dose modification of ribociclib – Neutropenia

	Grade 1 or 2 Neuts 1 - ≤LLN	**Grade 3** Neuts 0.5 - <1	**Grade 3 febrile neutropenia** Neuts 0.5 - <1 and single fever >38.3°C (or above 38°C for more than one hour and/or concurrent infection)	**Grade 4** Neuts < 0.5
Neutropenia	No dose adjustment is required	Dose interruption until recovery to grade ≤2. Resume at the same dose level. If toxicity recurs at grade 3: dose interruption until recovery to grade ≤2, then resume and reduce by 1 dose level.	Dose interruption until recovery to grade ≤2. Resume and reduce by 1 dose level	Dose interruption until recovery to grade ≤2. Resume and reduce by 1 dose level.

Table 2 Dose modification of ribociclib – Hepatobiliary toxicity

	Grade 1 **(> ULN – 3 x ULN)**	**Grade 2** **(>3 to 5 x ULN)**	**Grade 3** **(>5 to 20 x ULN)**	**Grade 4** **(>20 x ULN)**
AST and/or ALT elevations from baseline, without increase in total bilirubin above 2 x ULN	No dose adjustment is required.	Baseline grade <2: Dose interruption until recovery to ≤ baseline grade, then resume at same dose level. If grade 2 recurs, resume at next lower dose level. Baseline grade = 2: No dose interruption.	Dose interruption until recovery to ≤ baseline grade, then resume at next lower dose level. If grade 3 recurs, discontinue.	Discontinue
Combined elevations in AST and/or ALT together with total bilirubin increase, in the absence of cholestasis	If patients develop ALT and/or AST >3 x ULN along with total bilirubin >2 x ULN irrespective of baseline grade, discontinue.			

Table 3 Dose modification of ribociclib – QT prolongation

ECGs with QTcF >480 msec	1. The dose should be interrupted. 2. If QTcF prolongation resolves to <481 msec, resume treatment at the same dose level. 3. If QTcF ≥481 msec recurs, interrupt dose until QTcF resolves to <481 msec and then resume at the next lower dose level.
ECGs with QTcF >500 msec	If QTcF is greater than 500 msec interrupt until QTcF is <481 msec then resume at next lower dose level. If QTcF interval prolongation to greater than 500 msec or greater than 60 msec change from baseline occurs in combination with torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia, permanently discontinue.

Table 4 Dose modification of ribociclib

Other toxicities excluding thrombocytopenia	**Grade 1 or 2**	**Grade 3**	**Grade 4**
	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.	Dose interruption until recovery to grade ≤1, then resume at the same dose level. If grade 3 recurs, resume at the next lower dose level.	Discontinue

Table 5 Dose modification of ribociclib and management – ILD/pneumonitis

	Grade 1 (asymptomatic)	**Grade 2** (symptomatic)	**Grade 3 or 4** (severe)
ILD/pneumonitis	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.	Dose interruption until recovery to grade <1, then resume at the next lower dose level	Discontinue

Repeat every 28 days

TTO	Drug	Dose	Route	Directions
Day 1	**RIBOCICLIB**	**600mg**	PO	OD for 21 days followed by a 7-day break Swallow whole, do not chew, crush or split tablets prior to swallowing. Take the dose at approximately the same time each day. If a dose is missed or vomiting occurs, an additional dose should not be taken that day. Do not take with grapefruit juice / fruit. Available as 200mg tablets
	LETROZOLE	**2.5mg**	PO	OD *An alternative aromatase inhibitor may be prescribed.*
	Metoclopramide	10mg	PO	10mg TDS PRN. Do not take for more than 5 days continuously. Dispense with cycle 1 only.