DRUG REGIMEN
Ribociclib

Indication for use
In combination with letrozole for the initial treatment of postmenopausal women with ER positive, HER2 negative advanced breast cancer

Regimen
Ribociclib 600mg once daily orally on days 1-21 every 28 days
(In combination with letrozole 2.5mg daily continuously)

Treatment is given until disease progression or unacceptable toxicity

Investigation prior to initiating treatment
FBC, U&E, LFT, ECG

Contraindications
Hypersensitivity to peanuts or soya

Cautions
Reduce starting dose to 400mg in patients with moderate or severe hepatic impairment
Reduce starting dose to 400mg in patients with severe renal impairment
Concomitant use of strong CYP3A4 inhibitors (see dose modifications)
Avoid concomitant use of strong CYP3A4 inducers
Concomitant use of drugs that prolong QT interval
Ribociclib is a moderate/strong CYP3A4 inhibitor and may interact with drugs metabolized by CYP3A4

Investigations and consultations prior to each cycle
FBC and LFTs at baseline and before each cycle
Also check on day 14 of the first 2 cycles
ECG at baseline, on day 14 of first cycle, at start of cycle 2 and then as clinically indicated
Clinical toxicity assessment for infection, bleeding, thromboembolism, fatigue, GI effects and neuropathy

Acceptable levels for treatment to proceed (if outside these levels defer one week or contact consultant)
See dose modification criteria

Side Effects
Neutropenia, liver toxicity, QT prolongation, infections, decreased appetite, headache, insomnia, dry eyes, dyspnoea, nausea, diarrhoea, vomiting, alopecia, rash, back pain, fatigue

Dose Modification Criteria

Dose Level	Ribociclib dose (mg/day) for 3 out of 4 weeks
Starting dose	600mg
First dose reduction	400mg
Second dose reduction	200mg

Haematological Toxicity

Grade 1 or 2 Neutrophils >1	**Grade 3** Neutrophils 0.5 - 1	**Grade 3 febrile neutropenia**	**Grade 4*** Neutrophils < 0.5
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.

Liver 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.	Dose interruption until recovery to ≤ baseline grade, then resume at next lower dose level If grade 3 recurs, discontinue	Discontinue
		Baseline grade = 2: No dose interruption.		
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			

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 500msec on at least 2 separate ECGs, interrupt until QTcF is <481msec then resume at next lower dose level. If QTcF interval prolongation to greater than 500msec or greater than 60msec change from baseline occurs in combination with torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia, permanently discontinue treatment.

Table 5 Dose modification and management – Other toxicities

Other toxicities	**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

Dose modifications with strong CYP3A4 inhibitors

Concomitant use of strong CYP3A4 inhibitors should be avoided and an alternative concomitant medicinal product with less potential to inhibit CYP3A4 inhibition should be considered. If patients must be given a strong CYP3A4 inhibitor concomitantly with ribociclib, the ribociclib dose should be reduced to 400mg once daily

In patients who have had their dose reduced to 400mg ribociclib daily and in whom initiation of co-administration of a strong CYP3A4 inhibitor cannot be avoided, the dose should be further reduced to 200mg

In patients who have had their dose reduced to 200mg ribociclib daily and in whom initiation of co-administration of a strong CYP3A4 inhibitor cannot be avoided, ribociclib treatment should be interrupted

Specific Information on Administration

If the patient vomits or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time

Tablets should be swallowed whole and not chewed

THIS PROTOCOL HAS BEEN DIRECTED BY DR BOARD, CLINICIAN FOR BREAST CANCER

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

DATE August 2019
REVIEW August 2021
VERSION 2