Chemotherapy Protocol

Breast Cancer

Exemestane-Ribociclib

Regimen

- Breast Cancer – Exemestane-Ribociclib

Indication

- Ribociclib in combination with an aromatase inhibitor is indicated for the treatment previously untreated, hormone receptor-positive, HER2- negative, locally advanced or metastatic breast cancer that is not amenable to curative treatment and where;

  - the patient has had no prior treatment with a CDK 4/6 inhibitor unless either palbociclib has had to be stopped within 3 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 criteria

  - the patient is male or is female and either post-menopausal or if pre- or peri-menopausal has undergone ovarian ablation or suppression with LHRH agonist treatment

  - the patient has had no previous hormone therapy for locally advanced or metastatic disease i.e. is hormone therapy naïve for locally advanced/metastatic breast cancer. 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 anastrazole or letrozole.

  - WHO performance status of 0 – 2

Toxicity

Treatment breaks of up to 6 weeks are allowed for ribociclib but solely to allow toxicities to settle.

Drug	Adverse Effect
Exemestane	Osteoporosis, headache, somnolence, hot flushes, alopecia, arthralgia, rash, vaginal dryness, asthenia, liver abnormalities, depression, insomnia
Ribociclib	Infection, myelosuppression, peripheral neuropathy, fatigue, mucositis, anorexia, eye disorders, venous thromboembolism, cadiac abnormalities

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

Drugs

- FBC, LFTs and U&Es at baseline and then on day one of each cycle (every twenty-eight days).
- For cycle one and two only the FBC and LFTs should be assessed on day one and fourteen of the cycle (the full cycle of ribociclib may be dispensed on day 1)
- ECG should be assessed before initiating treatment with ribociclib. After initiating treatment, ECG should be repeated at approximately day 14 of the first cycle and at the beginning of the second cycle, then as clinically indicated. In case of QTcF prolongation during treatment, more frequent ECG monitoring is recommended.

Dose Modifications

The dose modifications listed are for haematological, liver and renal function only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing if appropriate. The approach may be different depending on the clinical circumstances. The following is a general guide only.

Haematological

Dose modifications for haematological toxicity in the table below are for general guidance only. Always refer to the responsible consultant as any dose reductions or delays will be dependent on clinical circumstances and treatment intent.

Consider blood transfusion or the use of erythropoietin according to NICE TA323 if patient symptomatic of anaemia or has haemoglobin of less than 8g/dL (80g/L)

Prior to prescribing cycle 1 the following criteria must be met.

Criteria	**Eligible Level**
Neutrophils	Equal to or more than $1.0x10^9$/L
Platelets	Equal to or more than $100x10^9$/L

Thereafter dose adjustments for haematological toxicity are described in the table below;

Toxicity	Grade	Ribociclib dose
Haematological	1 or 2	No change
	3	Day 1: Delay one week. When recovered to NCI-CTC grade 2 or below restart at same dose Day 14 of first 2 cycles: continue current dose to complete the cycle. Repeat the FBC on day 21. Consider dose reduction if the recovery to eligible levels takes 7 days or longer or there is recurrent NCI-CTC grade 3 neutropenia in subsequent cycles
	3 with fever	Delay until recovery to NCI-CTC grade 2 or below. Restart at next lower dose level
	4	Delay until recovery to NCI-CTC grade 2 or below. Restart at next lower dose level

Neutropenia was the most frequently reported adverse effect of ribociclib with a median onset of 15 days for any grade and 28 days for NCI-CTC grade 3 or 4. Median duration of severe neutropenia was seven days and most patients had their ribociclib dose reduced or held.

No dose reductions are required for exemestane due to myelosuppression.

Hepatic Impairment

No dose change for exemestane is recommended in patients with mild hepatic disease. Caution is advised in patients with moderate to severe hepatic impairment

Ribcoclib in Hepatic Impairment	
NCI-CTC Grade 1	No dose adjustment
NCI-CTC Grade 2	No dose adjustment
NCI-CTC Grade 3	Delay treatment until recovery to NCI-CTC grade 2 or below, then resume at the same dose level.If a NCI-CTC grade 2 toxicity recurs resume traement at the lower dose level
NCI-CTC Grade 4	Interupt the dose until recovery to NCI-CTC grade 2 or below then resume at the next lowest dose level. Discontinue of NCI-CTC toxicity recurs.
Combination	If patients develop ALT and/or AST greater than 3xULN along with total bilirubin greater than 2xULN irrespective of baseline grade, discontinue ribociclib

Renal Impairment

No dose change is recommended for exemestane in patients with mild or moderate renal impairment. In patients with severe renal impairment, administration of exemestane should be performed with caution

No dose adjustments of ribociclib are required for patients with mild to moderate renal impairment (creatinine clearance [CrCl] more than or equal to 30ml/min). Insufficient data are available in patients with severe renal impairment (CrCl less than 30ml/min) or requiring haemodialysis to provide any dose adjustment recommendation. Administer ribociclib to patients with severe renal impairment only after careful consideration of the potential benefits and risks and with close monitoring of signs of toxicity.

Other

Doses for other toxicities should be adjusted according to the table below;

Dose Level	Ribociclib Dose (mg/day)	Letrozole dose (mg/day)
0	600	2.5
-1	400	2.5
-2	200	2.5

Ribociclib should be discontinued if the 200mg dose is not tolerated.

Ribociclib Dose Adjustments			
Other non-haematological or cardiac toxicities	**NCI-CTC Grade 1 or 2**	**NCI-CTC Grade 3**	**NCI-CTC Grade 4**
	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.	Dose interruption until recovery to NCI-CTC grade 1 or below, then resume ribociclib at the same dose level. If NCI-CTC grade 3 recurs, resume ribociclib at the next lower dose level.	Discontinue ribociclib

Infections were reported more frequently in the ribociclib combination treatment arm versus the single agent aromatase inhibitor alone arm and may be severe. Patients should be warned of the increased risk of infection and promptly report any occurrences of fever to their health care team.

Cardiac

ECGs with QTcF greater than 480msec	1. The dose should be interrupted. 2. If QTcF prolongation resolves to less than 481msec, resume treatment at the same dose level. 3. If QTcF greater than or equal to 481msec recurs, interrupt dose until QTcF resolves to less than 481msec and then resume ribociclib at the next lower dose level.
ECGs with QTcF greater than 500msec	If QTcF is greater than 500msec on at least 2 separate ECGs, interrupt ribociclib until QTcF is less than 481msec then resume ribociclib 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 ribociclib

Regimen

28 day cycle until disease progression or intolerance (twelve cycles will be set in ARIA)

Ovarian ablation or suppression with a LHRH agonist is mandatory is patients who are pre or peri menopausal due to the pharmacology of ribociclib and aromatase inhibitors in combination. This is not included in the regimen on ARIA.

Drug	Dose	Days	Route
Exemestane	25mg per day	Days 1-28 inclusive	Oral
Ribociclib	600mg per day	Days 1-21 inclusive	Oral

Dose Information

- Exemestane is available as 25mg tablets
- Ribociclib is available as 200mg tablets

Administration Information

- Ribociclib should be taken with or without food. 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.

Additional Information

- The National Patient Safety Alert on oral chemotherapy (NPSA/2008/RRR001) mustbe followed in relation to ribociclib
- It must be made clear to all staff, including those in the community, that ribociclib should only be prescribed under the supervision of a consultant oncologist
- Ribociclib interacts with many other agents. Always check for drug interactions.
- Ovarian ablation or suppression with a LHRH agonist is mandatory is patients who are pre or peri menopausal due to the pharmacology of ribociclib and aromatase inhibitors in combination.

Coding

- Procurement - X70.8
- Delivery – X73.1

References
1. Hortobagyi GN, Stemmer SN, Burris HA et al. Ribociclib as first line therapy for HR positive advanced breast cancer. N Engl J Med (2016); 375 (18): 1738-1748.

REGIMEN SUMMARY

Exemestane-Ribociclib

Day One

1. Exemestane 25mg once a day for 28 days oral

2. Ribociclib 600mg once a day for 21 days oral
   Administration Instructions
   Oral chemotherapy
   Ribociclib is taken from day one to day 21 of a 28 day cycle.
   Take with or without food

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	Feb 2018	None	Dr Deborah Wright Pharmacist	Dr Jenny Bradbury Consultant Medical Oncologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury Hospital NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.