Chemotherapy Protocol

Breast Cancer

Fulvestrant-Ribociclib

Regimen

- Breast Cancer – Fulvestrant-Ribociclib

Indication

- Fulvestrant and ribociclib is indicated for oestrogen receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer which is not amenable to curative treatment and;

- is male or is female and if female is either post-menopausal or if pre- or peri-menopausal has undergone ovarian ablation or suppression with LHRH agonist treatment
- has received previous endocrine therapy according to one of the three populations below;
  - patient has progressive disease whilst still receiving adjuvant or neoadjuvant endocrine therapy for early breast cancer with no subsequent endocrine therapy received following disease progression
  - has progressive disease within 12 or less months of completing adjuvant endocrine therapy for early breast cancer with no subsequent endocrine therapy received following disease progression
  - has progressive disease on 1st line endocrine therapy for advanced/metastatic breast cancer with no subsequent endocrine therapy received following disease progression.
- patient has had no prior treatment with a CDK 4/6 inhibitor unless either abemaciclib (in combination with fulvestrant) or palbociclib (in combination with fulvestrant) 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 abemaciclib has been received as part of an early access scheme for the combination of abemaciclib plus fulvestrant and the patient meets all other criteria.
- patient has had no prior treatment with fulvestrant
- patient has had no prior treatment with everolimus
- ribociclib will only be given in combination with a fulvestrant
- patient has an ECOG performance status of 0, 1 or 2

Toxicity

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

Drug	Adverse Effect
Fulvestrant	Osteoporosis, headache, hot flushes, alopecia, arthralgia, rash, vaginal dryness, asthenia, liver abnormalities, injection site reactions, nausea
Ribociclib	Infection, myelosuppression, peripheral neuropathy, fatigue, mucositis, anorexia, eye disorders, venous thromboembolism, cardiac abnormalities

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

Monitoring

Drugs

- FBC and LFTs at baseline (prior to the start of treatment) then every 2 weeks for the first 2 cycles then every 4 weeks (prior to day 1) for subsequent cycles until clinically stable when bloods tests may be less frequent.
- U&Es (including potassium, calcium, phosphorus and magnesium) at baseline and then on day one of each cycle
- QTcF should be less than 450msec 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.

Ribociclib Dose Reduction Levels

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

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

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 $1x10^9$/L
Platelets	Equal to or more than $50x10^9$/L

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

Dose adjustments for neutropenia

NCI-CTC Grade	Ribociclib dose adjustment
1 or 2 (ANC 1 or above)	No dose adjustment is required
3 (ANC 0.5 – 0.9)	Dose interruption until recovery to grade 2 or below. Resume ribociclib at the same dose level. If toxicity recurs at grade 3: dose interruption until recovery to grade 2 or below, then resume ribociclib and reduce by 1 dose level.
3 with fever	Dose interruption until recovery to grade 2 or below. Resume ribociclib and reduce by 1 dose level
4 (ANC less than 0.5)	Dose interruption until recovery to grade 2 or below. Resume ribociclib and reduce by 1 dose level.

Neutropenia was the most frequently reported adverse effect of ribociclib combination treatment with a median onset of 16 days for grade 2, 3 or 4 neutropenia. The median time to resolution of grade 3 or below is 12 days following treatment interruption and/or reduction and/or discontinuation.

No dose reductions are required for fulvestrant due to myelosuppression.

Renal Impairment

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

No dose adjustment for ribociclib is necessary in patients with mild or moderate renal impairment. A starting dose of 400 mg once a day is recommended in patients with severe renal impairment (creatinine clearance less than 30ml/min). Caution should

be used in patients with severe renal impairment with close monitoring for signs of toxicity.

Hepatic Impairment

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

No dose adjustment for ribociclib is required for patients with mild hepatic impairment (Child-Pugh class A).

A starting dose of ribociclib 400mg once a day (21 days on/ 7 days off) is recommended for patients with moderate (Child-Pugh class B) and severe hepatic impairment (Child-Pugh class C).

AST/ALT (units/L)		**Bilirubin (µmol/L)**	**Ribociclib dose adjustment**
Grade 1	and	Less than or equal to 2xULN	No dose adjustment is required
Grade 2	and	Less than or equal to 2xULN	If baseline ALT/AST is less than grade 2; dose interrupt until recovery to baseline grade or below, then resume ribociclib at same dose level. If grade 2 recurs dose interrupt until recovery to baseline grade or below, then resume ribociclib at next lower dose level. If baseline AST/ALT is grade 2; no dose interruption is required.
Grade 3	and	Less than or equal to 2xULN	Dose interrupt ribociclib until recovery to baseline grade or below, then resume at next lower dose level. If grade 3 recurs, discontinue ribociclib.
Grade 4	and	Less than or equal to 2xULN	Discontinue ribociclib
Greater than 3xULN	and	Greater than 2xULN in the absence of cholestasis	Discontinue ribociclib irrespective of baseline grade

Other

Cardiac – QT prolongation

QTcF Value	Ribociclib dose adjustment
ECGs with QTcF greater than 480msec	The dose should be interrupted. If QTcF prolongation resolves to less than 481msec, resume treatment at the same dose level. 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, 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

Other toxicities

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

Infections were reported more frequently with ribociclib combination treatment 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.

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 for patients receiving ribociclib with fulvestrant who are pre or peri menopausal. This is not included in the regimen on ARIA.

Cycle One

Drug	Dose	Days	Route
Fulvestrant	500mg	1 and 15	Intramuscular
Ribociclib	600mg per day	1-21 (inclusive)	Oral

Cycle Two onwards

Drug	Dose	Days	Route
Fulvestrant	500mg	1	Intramuscular
Ribociclib	600mg per day	1-21 (inclusive)	Oral

Fulvestrant will be set up to be administered in the hospital setting (internal). If it is to be dispensed by the hospital and administered elsewhere please change this to a pickup internal in ARIA.

Dose Information

- Fulvestrant is available as pre-filled syringes containing 250mg in 5ml for intramuscular injection.
- Ribociclib is available as 200mg tablets

Administration Information

- Ribociclib should be swallowed whole and may be taken with or without food. Patients should be encouraged to take their dose at approximately the same time each day, preferably in the morning.
- If the patient vomits or misses a dose of ribociclib, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time.
- Fulvestrant should be administered as two consecutive 5 ml injections by slow intramuscular injection (1-2 minutes/injection); one in each buttock (gluteal area).Caution should be taken if injecting fulvestrant at the dorsogluteal site due to the proximity of the underlying sciatic nerve.

Additional Information

- The National Patient Safety Alert on oral chemotherapy (NPSA/2008/RRR001) must be 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 for patients receiving ribociclib with fulvestrant who are pre or peri menopausal.

References

1. Slamon DJ, Neven P, Chia S et al. Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: MONALEESA-3. J Clin Oncol. 2018 Aug 20;36(24):2465-2472
2. Ribociclib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer [TA593] 14 August 2019.

REGIMEN SUMMARY

Fulvestrant-Ribociclib

Cycle 1 Day One

1. Fulvestrant 500mg intramuscular
   Administration Instructions
   Fulvestrant should be administered as two consecutive 5 ml injections by slow intramuscular injection (1-2 minutes/injection), one in each buttock (gluteal area).Caution should be taken if injecting fulvestrant at the dorsogluteal site due to the proximity of the underlying sciatic nerve. Please refer to the package insert for instructions on administering the injection.

2. Ribociclib 600mg once a day for 21 days oral
   Administration Instructions
   Oral SACT
   Ribociclib is taken from day one to day 21 of a 28 day cycle. Swallow this medicine whole. Do not chew or crush.

Cycle 1 Day Fifteen

3. Fulvestrant 500mg intramuscular
   Administration Instructions
   Fulvestrant should be administered as two consecutive 5 ml injections by slow intramuscular injection (1-2 minutes/injection), one in each buttock (gluteal area).Caution should be taken if injecting fulvestrant at the dorsogluteal site due to the proximity of the underlying sciatic nerve. Please refer to the package insert for instructions on administering the injection.

Cycle 2 onwards Day One

4. Fulvestrant 500mg intramuscular
   Administration Instructions
   Fulvestrant should be administered as two consecutive 5 ml injections by slow intramuscular injection (1-2 minutes/injection), one in each buttock (gluteal area).Caution should be taken if injecting fulvestrant at the dorsogluteal site due to the proximity of the underlying sciatic nerve. Please refer to the package insert for instructions on administering the injection.

5. Ribociclib 600mg once a day for 21 days oral
   Administration Instructions
   Oral SACT
   Ribociclib is taken from day one to day 21 of a 28 day cycle. Swallow this medicine whole. Do not chew or crush.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	Sept 2020	None	Rebecca Wills 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 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.