Chemotherapy Protocol

Breast Cancer

Fulvestrant-Palbociclib

Regimen

- Breast Cancer – Fulvestrant-Palbociclib

Indication

Palbociclib with fulvestrant is recommended for use within the Cancer Drugs Fund as an option for treating 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;

- the patient 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
- the patient has received previous endocrine therapy according to one of the three populations as set out below;
  - has progressive disease whilst still receiving adjuvant or neoadjuvant endocrine therapy for early breast cancer with no subsequent endocrine therapy received following disease progression or,
  - 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 or,
  - has progressive disease on 1st line endocrine therapy for advanced/metastatic breast cancer with no subsequent endocrine therapy received following disease progression.
- has had no prior treatment with a CDK 4/6 inhibitor unless either abemaciclib (in combination with fulvestrant) or ribociclib (in combination with fulvestrant) has been stopped within 6 months of its start solely as a consequence of dose-limiting toxicity and in the clear absence of disease progression or palbociclib has been received as part of an early access scheme for the combination of palbociclib plus fulvestrant.
- no prior treatment with fulvestrant
- no prior treatment with everolimus
- palbociclib will only be given in combination with a fulvestrant
- an ECOG performance status of 0 or 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
Palbociclib	Infection, myelosuppression, GI disturbances, blurred vision, increased lacrimation, dry eye, rash, alopecia, dry skin, fatigue, asthenia, pyrexia, raised ALT/AST, epistaxis, interstitial lung disease/ pneumonitis.

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
- Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis (e.g. hypoxia, cough, dyspnoea).

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.

Palbociclib Dose Reduction levels

Dose Level	Palbociclib Dose (mg/day)
0	125
-1	100
-2	75

Palbociclib should be discontinued if the 75mg 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	Palbociclib dose adjustment
1 or 2 (ANC 1 or above)	No dose adjustment is required
3 (ANC 0.5 – 0.9)	Day 1 of cycle: Withhold, until recovery to grade 2 or below, and repeat complete blood count monitoring within 1 week. When recovered to grade 2 or below, start the next cycle at the same dose. Day 15 of first 2 cycles: If grade 3 on Day 15, continue palbociclib at the current dose to complete cycle and repeat complete blood count on Day 22. If grade 4 on Day 22, see grade 4 dose modification guidelines below. Consider dose reduction in cases of prolonged (greater than 1 week) recovery from grade 3 neutropenia or recurrent grade 3 neutropenia on Day 1 of subsequent cycles.
3 with fever and/or infection	At any time: Withhold palbociclib until recovery to grade 2 or below Resume at next lower dose.
4 (ANC less than 0.5)	At any time: Withhold palbociclib until recovery to grade 2 or below Resume at next lower dose.

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 of palbociclib is required for patients with mild, moderate or severe renal impairment (creatinine clearance greater than or equal to 15 mL/min).

Insufficient data are available in patients requiring haemodialysis to provide any dose adjustment recommendation in this patient population.

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 palbociclib is required for patients with mild or moderate hepatic impairment (Child-Pugh classes A and B).
A starting dose of palbociclib 75mg once a day (21 days on/ 7 days off) is recommended for patients with severe hepatic impairment (Child-Pugh class C).

Other

Lung

Permanently discontinue palbociclib in patients with severe interstitial lung disease (ILD)/pneumonitis.

Other toxicities

NCI-CTC Grade	Palbociclib dose adjustment
1 or 2	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated
3 or above (if persisting despite medical treatment)	Withhold until symptoms resolve to grade 1 or below (grade 2 or below if not considered a safety risk for the patient) the resume at the next lower dose

Infections were reported more frequently with palbociclib 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 palbociclib 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
Palbociclib	125mg per day	1-21 (inclusive)	Oral

Cycle Two onwards

Drug	Dose	Days	Route
Fulvestrant	500mg	1	Intramuscular
Palbociclib	125mg 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.
- Palbociclib is available as 75mg, 100mg and 125mg capsules

Administration Information

- Palbociclib should be swallowed whole and should be taken with food, preferably a meal to ensure consistent palbociclib exposure.
- Palbociclib should not be taken with grapefruit or grapefruit juice.
- If the patient vomits or misses a dose of palbociclib, 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 palbociclib.
- It must be made clear to all staff, including those in the community, that palbociclib should only be prescribed under the supervision of a consultant oncologist.
- Palbociclib interacts with many other agents. Always check for drug interactions. If coadministration with a strong CYP3A inhibitor is unavoidable, reduce the palbociclib dose to 75 mg once a day.
- Ovarian ablation or suppression with a LHRH agonist is mandatory for patients receiving palbociclib with fulvestrant who are pre or peri menopausal.

References

1. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. M. Cristofanilli, N. Turner, I. Bondarenko et al. The Lancet 17;4;425-439, April 01, 2016
2. Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer NICE [TA619] 15 January 2020

REGIMEN SUMMARY

Fulvestrant-Palbociclib

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. Palbociclib 125mg once a day for 21 days oral
   Administration Instructions
   Oral SACT
   Palbociclib is taken from day one to day 21 of a 28 day cycle.
   To be swallowed whole with food, preferably a meal.

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. Palbociclib 125mg once a day for 21 days oral
   Administration Instructions
   Oral SACT
   Palbociclib is taken from day one to day 21 of a 28 day cycle.
   To be swallowed whole with food, preferably a meal.

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.