

Chemotherapy Protocol

Breast Cancer

Letrozole-Palbociclib

Regimen

- Breast Cancer – Letrozole-Palbociclib

Indication

- Palbociclib 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 ribociclib 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 palbociclib 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 anastrozole or letrozole.
 - WHO performance status of 0 – 2

Toxicity

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

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

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 should be assessed on day one and fourteen of the cycle (the full cycle of palbociclib may be dispensed on day 1)

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 $1.0 \times 10^9/L$
Platelets	Equal to or more than $100 \times 10^9/L$

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

Toxicity	Grade	Palbociclib 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 palbociclib 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 palbociclib dose reduced or held.

No dose reductions are required for letrozole due to myelosuppression.

Hepatic Impairment

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

No dose adjustments of palbociclib are required for patients with mild hepatic impairment (total bilirubin less than or equal to 1xULN and aspartate aminotransferase [AST] greater than 1xULN, or total bilirubin greater than 1 to 1.5xULN and any AST). Insufficient data are available in patients with moderate or severe hepatic impairment (total bilirubin greater than 1.5xULN and any AST) to provide any dose adjustment recommendation. Administer palbociclib to patients with moderate and severe hepatic impairment only after careful consideration of the potential benefits and risks and with close monitoring of signs of toxicity.

Renal Impairment

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

No dose adjustments of palbociclib 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 palbociclib 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	Palbociclib Dose (mg/day)	Letrozole dose (mg/day)
0	125	2.5
-1	100	2.5
-2	75	2.5

Toxicity	Grade	Palbociclib dose
Non-Haematological	1 or 2	No change
	3 or 4	Delay until recovery to NCI-CTC grade 2 or below. Restart at next lower dose level.

Infections were reported more frequently in the palbociclib 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.

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 in patients who are pre or peri menopausal due to the pharmacology of palbociclib and aromatase inhibitors in combination. This is not included in the regimen on ARIA.

Drug	Dose	Days	Route
Letrozole	2.5mg per day	Days 1-28 inclusive	Oral
Palbociclib	125mg per day	Days 1-21 inclusive	Oral

Dose Information

- Letrozole is available as 2.5mg tablets
- Palbociclib is available as 125mg, 100mg and 75mg capsules

Administration Information

- Palbociclib should be taken with 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
- Palbociclib capsules should be swallowed whole and not chewed.

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.
- Ovarian ablation or suppression with a LHRH agonist is mandatory in patients who are pre or peri menopausal due to the pharmacology of palbociclib and aromatase inhibitors in combination.
- Treatment breaks of up to 6 weeks are allowed but solely to allow toxicities to settle

Coding

- Procurement - X
- Delivery – X

References

1. Finn RS, Martin M, Rugo H et al. Palbociclib and letrozole in advanced breast cancer. N Engl J Med (2016); 375: 1925-1936.

REGIMEN SUMMARY

Letrozole-Palbociclib

Day One

1. Letrozole 2.5mg once a day for 28 days oral
2. Palbociclib 125mg once a day for 21 days oral
Administration Instructions
Oral chemotherapy
Palbociclib is taken from day 1 to day 21 of a 28 day cycle.
Swallow capsules whole do not chew.
Take with or after 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.