

Systemic Anti Cancer Therapy Protocol

PALBOCICLIB and FULVESTRANT **Locally advanced or metastatic breast cancer**

PROTOCOL REF: MPHAPAFUBR
(Version No. 1.2)

Approved for use in:

Locally advanced or metastatic breast cancer, ER positive (HER2 negative):

- Following disease progression on adjuvant/neoadjuvant endocrine therapy for early breast cancer or within 12 months of completing adjuvant endocrine therapy
- Following disease progression on 1st line endocrine therapy for metastatic/locally advanced breast cancer with no subsequent endocrine therapy (i.e. second line treatment), with no previous CDK4/6 inhibitor treatment

In pre or peri menopausal women, goserelin administration will also be required.

Blueteq required - see criteria for full details on eligibility

Dosage:

Drug	Dose	Route	Frequency	
Palbociclib	125mg	Oral	Once daily for 21 days, repeated every 28 days	Until disease progression or unacceptable toxicity
Fulvestrant	500mg	IM	Every 28 days, with an additional dose on day 15 of cycle 1	

Administration + Counselling Points:

Palbociclib

Capsules should be taken at approximately the same time each day.

It can be taken with or without food (but not be taken with grapefruit or grapefruit juice), and swallowed whole. No capsule should be ingested if broken, cracked or not intact.

If relevant, ensure appropriate contraceptive measures are discussed.

Note: the capsules contain lactose.

Fulvestrant

Administered as two consecutive 5mL injections by slow intramuscular injection (1 to 2 minutes per injection), one into each buttock.

Emetogenic risk:

Low emetogenicity.

Supportive treatments:

Loperamide 4mg orally after initial diarrhoea, followed by 2mg after each episode up to maximum of 16mg in 24 hours

Extravasation risk:

Not applicable

Dosing in renal and hepatic impairment:

Renal	Palbociclib	No dose adjustments needed if CrCl \geq 15ml/min. There is insufficient data for patients receiving dialysis
	Fulvestrant	No safety data in severe renal impairment (CrCl < 30mL/min)

Hepatic	Palbociclib	No dose adjustments necessary for mild – moderate impairment. Reduction to 75mg daily is recommended for patients with severe hepatic impairment (Child-Pugh class C).																												
	Fulvestrant	No data on fulvestrant in patients with severe hepatic impairment.																												
		<p><u>*Assessing a Child-Pugh score (for an adult patient)</u></p> <table border="1"> <thead> <tr> <th>Parameters</th> <th>1 point</th> <th>2 points</th> <th>3 points</th> </tr> </thead> <tbody> <tr> <td>Total bilirubin (µmol/L)</td> <td>< 34</td> <td>34–50</td> <td>> 50</td> </tr> <tr> <td>Serum albumin (g/L)</td> <td>> 35</td> <td>28–35</td> <td>< 28</td> </tr> <tr> <td>Prothrombin time, prolongation (s) Or INR</td> <td>< 4 < 1.7</td> <td>4–6 1.7-2.3</td> <td>> 6 >2.3</td> </tr> <tr> <td>Ascites</td> <td>None</td> <td>Mild to Moderate (diuretic responsive)</td> <td>Severe (diuretic refractory)</td> </tr> <tr> <td>Hepatic encephalopathy</td> <td>None</td> <td>Grade I–II (or suppressed with medication)</td> <td>Grade III–IV (or refractory to medication)</td> </tr> </tbody> </table> <table border="1"> <thead> <tr> <th>Child-Pugh Class</th> </tr> </thead> <tbody> <tr> <td>A (5-6 points)</td> </tr> <tr> <td>B (7-9 points)</td> </tr> <tr> <td>C (10 or more points)</td> </tr> </tbody> </table> <p>INR: International Normalised Ratio. Please note: assessment of Child-Pugh Class is to help guide clinical teams when prescribing and pharmacists when screening.</p>	Parameters	1 point	2 points	3 points	Total bilirubin (µmol/L)	< 34	34–50	> 50	Serum albumin (g/L)	> 35	28–35	< 28	Prothrombin time, prolongation (s) Or INR	< 4 < 1.7	4–6 1.7-2.3	> 6 >2.3	Ascites	None	Mild to Moderate (diuretic responsive)	Severe (diuretic refractory)	Hepatic encephalopathy	None	Grade I–II (or suppressed with medication)	Grade III–IV (or refractory to medication)	Child-Pugh Class	A (5-6 points)	B (7-9 points)	C (10 or more points)
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Interactions:

Please refer to the SPC for a detailed list of interactions:

<https://www.medicines.org.uk/emc/product/11962>

Palbociclib is metabolized by the cytochrome CYP3A4 pathway

INDUCERS (lowers palbociclib levels): Carbamazepine, phenobarbital, phenytoin, dexamethasone, rifabutin, rifampicin, St John's Wort, troglitazone, pioglitazone

INHIBITORS (increases palbociclib levels): Indinavir, nelfinavir, ritonavir, clarithromycin, erythromycin, itraconazole, ketoconazole, nefazodone, grapefruit juice, verapamil, diltiazem, cimetidine, amiodarone, fluvoxamine, mibefradil

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	Palbociclib	125mg	PO	Once daily for 21 days of 28 day cycle
	Fulvestrant	500mg	IM	Every 28 days
15 CYCLE 1 ONLY	Fulvestrant	500mg	IM	Extra dose on CYCLE 1 ONLY

Main toxicities:

Please refer to the SPC for a detailed list: <https://www.medicines.org.uk/emc/product/11962>

and fulvestrant: <https://www.medicines.org.uk/emc/product/12022/smpc>

Palbociclib	
Blood and lymphatic system	Neutropenia, leukopenia, anaemia, thrombocytopenia, febrile neutropenia

Metabolism and nutrition disorders	Decreased appetite
Eye disorders	Blurred vision, lacrimation increased, dry eye
Respiratory	Epistaxis, ILD/pneumonitis
Gastrointestinal disorders	Stomatitis, nausea, vomiting, diarrhea
Skin disorders	Rash, alopecia, dry skin
General disorders	Fatigue, pyrexia, taste disorders
Fulvestrant	
Infections	Urinary tract infection
Bloods and lymphatic system disorders	Reduced platelet count
Metabolism disorders	Anorexia
Gastrointestinal disorders	Nausea, vomiting, diarrhea
Musculoskeletal and connective tissue disorders	Joint and musculoskeletal pain, back pain
General disorders	Headache, hot flushes, rash, vaginal hemorrhage, injection site reactions, asthenia, sciatica, peripheral neuropathy

SACT PROTOCOL



The Clatterbridge
Cancer Centre
NHS Foundation Trust

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Investigations and treatment plan:

	Pre	Cycle 1	Cycle 1 D14	Cycle 2	Cycle 3	Cycle 4	Ongoing
Informed Consent	X						
Clinical Assessment	X				X		As clinically indicated
SACT Assessment (to include PS and toxicities)		X	X	X	X	X	Every cycle
FBC	X		X	X	X	X	Every cycle
U&E & LFTs & Magnesium	X			X	X	X	Every Cycle
CrCl (Cockcroft and Gault)	X	X		X	X		Every cycle
CT scan	X				X		Every 3 months for the first 12 months then as clinically indicated, cycle 4 can continue irrespective of date of CT
Weight Recorded	X	X		X	X	X	Every cycle
Height Recorded	X						

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Dose Modifications and Toxicity Management:

Dose Level	Dose
Recommended dose	125mg once daily
First dose reduction	100mg once daily
Second dose reduction	75mg once daily

If 75mg once daily is not tolerated then treatment should be discontinued.

Haematological toxicity:

Proceed on day 1 if-

ANC $\geq 1.0 \times 10^9/L$	Plt $\geq 50 \times 10^9/L$
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FBC should be monitored on day 14 of cycle 1 and cycle 2

CTC grade	Dose modifications
Grade 1 or 2 (ANC $\geq 1.0 \times 10^9/L$)	No dose adjustment is required
Uncomplicated Grade 3 (ANC 0.5 to $0.9 \times 10^9/L$) All other grade 3 haematological toxicities except lymphopenia (unless associated with clinical events, e.g., opportunistic infections).	Day 1 of cycle: Withhold, repeat complete blood count monitoring within 1 week. When recovered to Grade ≤ 2 , start the next cycle at the same dose. Day 14 of first 2 cycles: Continue at current dose to complete cycle. Repeat complete blood count on Day 21. Consider dose reduction in cases of prolonged (>1 week) recovery from Grade 3 neutropenia or recurrent Grade 3 neutropenia in subsequent cycles
Grade 3 neutropenia associated with a documented infection and/or fever $\geq 38.5^\circ C$	Withhold palbociclib until recovery to grade ≤ 2 Reduce by one dose level
All grade 4 haematological toxicities except lymphopenia (unless associated with clinical events, e.g., opportunistic infections).	Withhold palbociclib until recovery to grade ≤ 2 Reduce by one dose level

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non- Haematological toxicity:

CTC grade	Dose modifications
Grade 1 or 2	No dose adjustment is required
Grade \geq 3	Withhold until symptoms resolved to grade 1 or grade 2 (if not considered a safety risk for the patient) Resume at the next lower dose.
ILD/Pneumonitis suspected e.g shortness of breath or dry cough	Hold treatment and contact consultant for advice

References:

1. SmPC for Palbociclib, last updated April 2023
<https://www.medicines.org.uk/emc/product/11962>
2. Fulvestrant: <https://www.medicines.org.uk/emc/product/12022/smpc>
3. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20: e201–08.
4. BNF available via: <https://bnf.nice.org.uk/>
5. Overall survival with palbociclib and fulvestrant in advanced breast cancer. NEJM 2018 379:1926-1936. Turner et al

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Circulation/Dissemination

Date added into Q-Pulse	13 th October 2023
Date document posted on the Intranet	N/A

Version History

Date	Version	Author name and designation	Summary of main changes
	1.2	Gabriella Langton	Updated to new protocol format, updated renal and hepatic information from SPC