Systemic Anti Cancer Therapy Protocol

ABEMACICLIB and FULVESTRANT
Locally Advanced and Metastatic Breast Cancer

PROTOCOL REF: MPHAABFUBR
(Version: 1.1)

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 registration required: see blueteq for full eligibility criteria

Dosage:

Drug	Dosage	Route	Frequency
Abemaciclib tablets	150mg	Oral	Twice daily continuously
Fulvestrant injection	500mg	IM	Cycle 1, Day 1 and 15 **ONLY** Then on day 1 for subsequent cycles

Frequency of each cycle is 28 days, treatment continues until disease progression or unacceptable toxicity

Administration and Counselling Points:

- Abemaciclib is available as 50mg, 100mg an 150mg tablet.
- Abemaciclib tablets should be taken at approximately the same time each day, ideally 12 hours apart.
- The tablets can be taken with or without food and swallowed whole.

- Please note the tablets contain lactose.
- Fulvestrant is administered as two consecutive 5mL injections by slow intramuscular injection (1-2 minutes per inuection), one into each buttock.
- If relevant, ensure appropriate contraceptive measures are discussed.

Emetogenic risk:

Mildly emetogenic

Supportive treatments:

Loperamide 2mg – TWO capsules to be taken initially followed by each loose stool (maximum daily dose 12mg) – to be taken when required

Extravasation risk:

Not applicable

Dosing in renal and hepatic impairment:

Renal	Abemaciclib and fulvestrant: No dose adjustments are required for mild to moderate impairment (CrCl ≥ 30mL/min) Insufficient data for patients with severe impairment or receiving dialysis.
Hepatic	**Abemeciclib:** No dose adjustments are necessary in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. In patients with severe (Child Pugh C) hepatic impairment, a decrease in dosing frequency to ONCE daily is recommended. **Fulvestrant:** No dose adjustments are recommended for patients with mild to moderate hepatic impairment. However, as fulvestrant exposure may be increased, Faslodex should be used with caution in these patients. There is no data in patients with severe hepatic impairment.

Drug Interactions:

Abemaciclib is metabolized by the cytochrome CYP3A4 pathway

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

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

Abemaciclib may also interact with medicines via the P-glycoprotein mechanism, in particular those medicines with narrow therapeutic index such as digoxin or dabigatran.

Fulvestrant: There are no known drug interactions with fulvestrant.

Main Toxicities:

Abemaciclib: Neutropenia, anaemia, thrombocytopenia, diarrhea, infection, fatigue, nausea, stomatitis, alopecia, thrombosis and raised transaminases.

Fulvestrant: injection site reactions, hot flushes, nausea, rash, joint pains

Investigations and Treatment plan:

	Pre	Cycle 1	Cycle 1, D14	Cycle 2	Cycle 2, D14	Cycle 3	Ongoing
Informed Consent	X						
Clinical Assessment	X					X	Every 3 months
SACT Assessment		X	X	X	X	X	Every cycle
FBC	X		X	X	X	X	Every cycle
U&Es, LFTs (AST and ALT)	X			X		X	Every cycle
CT Scan	X					X	As clinically indicated
PS recorded	X	X	X	X	X	X	Every cycle
Toxicities documented	X	X	X	X	X	X	Every cycle
Weight recorded	X	X	X	X	X	X	Every cyce

Dose Modifications and Toxicity Management:

Fulvestrant: There are no recommended dose modifications with fulvestrant.

Abemeciclib:

Dose Level	Dose
Recommended dose	150mg TWICE daily
First dose reduction	100mg ONCE daily
Second dose reduction	50mg TWICE daily

If 50mg twice daily is not tolerated then treatment should be discontinued.

Haematological toxicity

Administer Abemeciclib on day 1 of each cycle if:-

ANC ≥ 1.0 x 10^9/L	Platelets ≥ 100 x 10^9/L

FBC should be monitored on day 14 of cycle 1 and cycle 2 – see table above

CTC grade	Dose modifications - abemaciclib
Grade 1 or 2 (ANC ≥ 1.0 x 10^9/L)	No dose adjustment is required
Uncomplicated Grade 3 (ANC 0.5 to 0.9 x 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 ≥ 38.5^{o}C. Or recurrent grade 3 neutropenia.	Withhold abemaciclib until recovery to grade ≤2 Reduce by one dose level
All grade 4 haematological toxicities (ANC < 0.5 x 10^9/L) except lymphopenia (unless associated with clinical events, e.g., opportunistic infections).	Withhold abemaciclib until recovery to grade ≤2 Reduce by one dose level

Non-haematological toxicities

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CTC grade	Dose modifications - abemaciclib
Grade 1	No dose adjustment is required
Grade 2	If does not resolve within 24 hours to grade 1, suspend treatment until improved, then can resume on current dose.
Grade 2 persistent or recurring Grade ≥ 3	Withhold until symptoms resolved to grade 1 Resume at the next lower dose.

Other non-haematological toxicities

CTC grade	Dose modifications - abemaciclib
Grade 1 or 2	No dose adjustment is required
Grade ≥ 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.

Hepatic impairment – ALT and AST

CTC grade	Dose modifications – abemaciclib and fulvestrant
Grade 1 (less than 3 x ULN) Grade 2 (between 3 and 5 x ULN)	No dose adjustment is required
Grade 2 persistent or recurring Grade 3 (between 5 and 20 x ULN)	Stop abemaciclib until returned to grade 1 Resume at next lower dose For grade 3 also withhold fulvestrant until returned to grade 1
Grade 4 (above 20 x ULN)	Discontinue

References:

1. National Institute for Health and Care Excellence (May 2019). Abemeciclib with fulvestrant for treating hormone receptor-positve, HER2 – negative advanced breast cancer after endocrine therapy [TA 579].
2. Summary of Product Characteristics, Verzenios®, Abemeciclib, Eli Lilly, last updated November 2018, http://www.medicines.org.uk [accessed 17th May 2019]
3. Sledge G., Toi M, et al. MONARCH 2. Abemaciclib in combination with Fulvestratn in women with HR+/HER2- advanced breast cancer who had progressed while receiving endocrine therapy. *J. Clin Oncol* 35: 2875-2884