Alpelisib and fulvestrant

Indication
ER positive, Her2 negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression, following endocrine therapy

Regimen details
Alpelisib tablets 300mg orally once daily, continuously
Fulvestrant injection 500mg intramuscularly monthly (with additional dose given on day 15 of cycle 1 only)

Cycle frequency
Every 28 days

Number of cycles
Until disease progression or unacceptable toxicity

Administration
Fulvestrant is administered as two consecutive 5mL injections by slow intramuscular injection (1-2 minutes per injection), one into each buttock

Alpelisib is available as 200mg, 250mg and 300mg tablet packs.

Alpelisib should be swallowed whole with food and taken at the same time each day
If dose is missed it can be taken immediately following food if within 9 hours of usual time, if over 9 hours then skip dose and take next dose at usual time

Pre-medication
None

Emetogenicity
Minimal

Additional supportive medication
Supply loperamide to be used if required and non-sedating antihistamine (e.g. cetirizine) to be used prophylactically

Extravasation
N/A

Investigations – pre first cycle
Prior to initiating treatment, it is paramount for the patient to have optimised blood sugars. The SOLAR-1 trial studied stable T2DM patients only. The safety of alpelisib in uncontrolled T2DM and T1DM has not been established and considered higher risk thus endocrinology input must be sort before initiation

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFT (including AST)	14 days
HbA1c	14 days
Fasting blood glucose	14 days
Bone profile	14 days

Investigations –pre subsequent cycles

Fasting blood glucose every week for the first 2 weeks then once every 4 weeks or as clinically indicated
Repeat HbA1c after 4 weeks and then every 3 months thereafter
FBC, U&Es, LFTs and bone profile before every cycle

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	**Limit**
Neutrophil count	≥ 1.0 x 10^9/L
Platelet count	≥ 50 x 10^9/L
Creatinine clearance	≥ 30 mL/min (see under "Dose modifications")
Bilirubin	≤ 2.5 x ULN (see under "Dose modifications")

Dose modifications

No dose modifications for fulvestrant

Alpelisib:

Dose level	**Dose**
Recommended starting dose	300mg once daily (2 x 150mg)
First dose reduction	250mg once daily (1 x 200mg & 1 x 50mg)
Second dose reduction	200mg once daily (1 x 200mg)

Renal impairment:

Alpelisib 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 impairment:

Alpelisib: no dose adjustment is necessary in patients with mild, moderate or severe hepatic impairment
Fulvestrant: No dose adjustments are recommended for patients with mild to moderate hepatic impairment. However, as fulvestrant exposure may be increased, it should be used with caution in these patients. There is no data in patients with severe hepatic impairment.

Haematological toxicity:

Thrombocytopenia

Grade 1 (platelets < LLN - 75 x 10^9/L) Grade 2 (platelets < 75 - 50 x 10^9/L)	Maintain dose level
Grade 3 (platelets < 50-25 x 10^9/L)	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then reduce 1 dose level
Grade 4 (platelets < 25 x 10^9/L)	Omit dose until resolved to ≤ Grade 1, then reduce 1 dose level

Neutropenia

Grade 1 (neutrophils < LLN - 1.5 x 10^9/L) Grade 2 (neutrophils < 1.5 - 1.0 x 10^9/L)	Maintain dose level
Grade 3 (neutrophils < 1.0 - 0.5 x 10^9/L) Grade 4 (neutrophils < 0.5 x 10^9/L)	Omit dose until resolved to ≤ Grade 1, then reduce 1 dose level

Non haematological toxicity:

Hyperglycaemia

Dose modification and management should only be based on fasting glucose values. If hyperglycaemia occurs, further expert advice should be sought. Patients should always be referred to a diabetic specialist to monitor and counsel patient on lifestyle changes.

CTC Grade	Recommendation
Grade 1 Fasting glucose <8.9 mmol/L	No dose adjustment needed - Initiate or intensify anti-diabetic treatment
Grade 2 Fasting glucose >8.9 to 13.9 mmol/L	No dose adjustment needed - Initiate or intensify anti-diabetic treatment - If fasting glucose does not decrease to below 8.9mmol/L within 21 days under appropriate anti-diabetic treatment then reduce alpelisib by 1 dose level
Grade 3 Fasting glucose 13.9 to 27.8 mmol/L	Hold treatment Consider admission for hydration / appropriate interventions If fasting glucose does not decrease to below 8.9 mmol/L within 21 days following appropriate treatment – permanently discontinue treatment
Grade 4 Fasting glucose above 27.8 mmol/L	Discontinue treatment

(For more detailed advice see Table 6-3 of the SOLAR-1 trial protocol – click here)

Diarrhoea

CTC Grade	Recommendation
Grade 1	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated
Grade 2	Initiate or intensify appropriate medical therapy and monitor as clinically indicated. Interrupt treatment until recovery to ≤ grade 1 – resume at same dose level
Grade 3 & 4	Initiate or intensify appropriate medical therapy and monitor as clinically indicated. Interrupt treatment until recovery to ≤ grade 1 – then resume at the next lower dose level

Rash and Severe Cutaneous Adverse Reactions (SCARs)

For all grades of rash, refer to a dermatologist

CTC Grade	Recommendation
Grade 1 < 10% body surface area (BSA) with active skin toxicity	No dose adjustment is required. Initiate topical corticosteroid treatment and consider adding regular oral antihistamine to manage symptoms if not already taking If aetiology is SCAR – permanently discontinue
Grade 2 10% to 30% BSA with active skin toxicity	No dose adjustment is required. Initiate or intensify topical corticosteroid treatment and oral antihistamine treatment. Consider low dose systemic corticosteroid treatment. If aetiology is SCAR – permanently discontinue
Grade 3 (e.g. severe rash not responsive to medical management) More than 30% BSA with active skin toxicity	Interrupt treatment Initiate or intensify topical/systemic corticosteroid treatment and oral antihistamine treatment. If aetiology is SCAR – permanently discontinue If aetiology is not a SCAR, interrupt dose until recovery to grade ≤ 1, then resume at the same dose lever for first occurrence of rash or next lower dose if second reoccurrence.
Grade 4 (e.g. severe bullous, blistering or exfoliating skin conditions) Any % BSA associated extensive superinfection, with IV antibiotics indicated, life threatening	Permanently discontinue

Other toxicities

Renal

Creatinine	**Recommendation**
Less than 2 times upper limit of normal range	Maintain dose level
2 to 3 x ULN	Hold treatment until resolved to ≤ Grade 1 then: • If resolved in ≤ 7 days, maintain dose level • If resolved > 7 days, then reduce by one dose level
Grade 3 (3.0–6.0 x ULN) or Grade 4 (more than 6.0 x ULN)	Permanently discontinue treatment

Other

CTC Grade	**Recommendation**
Grade 1 or 2	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated
Grade 3	Interrupt treatment until recovery to ≤ grade 1 – then resume at next lower dose level.
Grade 4	Permanently discontinue

For grade 2 and 3 pancreatitis interrupt treatment until recovery to grade < 2 and resume at next lower dose level. Only one dose reduction is permitted. If toxicity reoccurs, permanently discontinue treatment

For Grade 2 total bilirubin elevation, interrupt treatment until recovery to Grade ≤ 1 and resume at same dose if resolved in ≤ 14 days or resume at next lower dose if resolved in > 14 days.

Adverse effects –

for full details consult product literature/ reference texts

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

Alpelisib: Urinary tract infection, anaemia, thrombocytopenia, lymphocytopenia, hyperglycaemia, decreased appetite, electrolyte disturbances (hypokalaemia, hypocalcaemia, hypomagnesemia), headache, taste disturbances, diarrhoea, nausea, vomiting, dry mouth, abdominal pain, dyspepsia, rash, alopecia, dry skin, alopecia, pruritus, fatigue, peripheral oedema, pyrexia, mucosal inflammation, mucosal dryness, weight decreased, increased transaminases, creatinine increase, aPTT prolonged, lipase increased, albumin decreased

Significant drug interactions

– for full details consult product literature/ reference texts

BCRP inhibitors

Alpelisib is a substrate for BCRP in vitro. BCRP is involved in the hepatobiliary export and intestinal secretion of alpelisib, therefore inhibition of BCRP in the liver and in the intestine during elimination may lead to an increase in systemic exposure of alpelisib. Therefore, caution and monitoring for toxicity are advised during concomitant treatment with inhibitors of BCRP (e.g. eltrombopag, lapatinib, pantoprazole).

Acid-reducing agents

Alpelisib can be co-administered with acid-reducing agents, provided alpelisib is taken immediately after food.

CYP3A4 substrates

Caution is recommended when alpelisib is used in combination with CYP3A4 substrates that also possess an additional time-dependent inhibition and induction potential on CYP3A4 that affects their own metabolism (e.g. rifampicin, ribociclib, encorafenib).

CYP2C9 substrates with narrow therapeutic index

In the absence of clinical data on CYP2C9, caution is recommended. In vitro evaluations indicated that the pharmacological activity of CYP2C9 substrates with a narrow therapeutic index such as warfarin may be reduced by the CYP2C9 induction effects of alpelisib.

Anti-diabetic medication

A patient's current antidiabetic treatment may be affected by treatment with alpelisib + fulvestrant through interaction with oral antidiabetics metabolised by CYP2C9 and CYP2C8 (including, but not limited to, repaglinide, rosiglitazone, glipizide and tolbutamide).

Additional comments

Patients and carers should also be cautioned on the effects on driving and performance of skilled tasks due to the increased risk of fatigue or blurred vision.

References

André F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-mutated, hormone receptor–positive advanced breast cancer. N Engl J Med 2019;380:1929-40. DOI: 10.1056/NEJMoa1813904

THIS PROTOCOL HAS BEEN DIRECTED BY DR YOUNG, CONSULTANT CLINICAL ONCOLOGIST

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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