Alpelisib & Fulvestrant (Breast)

Indication

Hormone receptor-positive, HER2-negative, PIK3CA-mutated, locally advanced inoperable or metastatic breast cancer in combination with fulvestrant in patients with disease progression after a CDK4/6 inhibitor plus an aromatase inhibitor.

(NICE TA816)

ICD-10 codes

C50

Regimen details

Cycle 1

Day	Drug	Dose	Route
1-28	Alpelisib	300mg OD	Oral
1 & 15	Fulvestrant	500mg	Intramuscular injection

Cycle 2 onwards

Day	Drug	Dose	Route
1-28	Alpelisib	300mg OD	Oral
1	Fulvestrant	500mg	Intramuscular injection

Cycle frequency

28 days

Number of cycles

Until disease progression or unacceptable toxicity.

Administration

Alpelisib is available as 200mg, 150mg and 50mg film-coated tablets. Tablets should be swallowed whole immediately after food at approximately the same time each day.

If a dose of alpelisib is missed, it can be taken immediately following food and within 9 hours after the time it is usually administered. After more than 9 hours, the dose should be skipped for that day. On the next day, alpelisib should be taken at the usual time. If the patient vomits after taking an alpelisib dose, the patient should not take and additional dose on that day and should resume the usual dosing schedule the next day at the usual time.

Fulvestrant should be administered as two consecutive 5ml (250mg) injections by slow intramuscular injection (1-2 minutes/injection), one in each buttock (gluteal area).

Pre-medication

Prophylactic oral antihistamines can be considered

Emetogenicity

This regimen has low emetic potential – refer to local policy

Additional supportive medication

Loperamide as required
Topical corticosteroids and antihistamines as required for skin rash

Extravasation

N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Fasting glucose	14 days
HbA1c	14 days
Potassium	14 days
Calcium	14 days
Magnesium	14 days
Blood pressure	14 days

Note: The safety of alpelisib in patients with Type 1 and uncontrolled Type 2 diabetes has not been established as these patients were excluded from clinical studies

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	Monthly
U+E (including creatinine)	Monthly
LFTs	Monthly
Fasting glucose	Weeks 1, 2, 4, 6 and 8 and monthly thereafter
HbA1c	After 4 weeks then 3 monthly thereafter
Potassium	Monthly
Calcium	Monthly
Magnesium	Monthly
Blood pressure	Monthly

Standard limits for administration to go ahead

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

Investigation	Limit
Neutrophils	≥ 1 x 10^9/L
Platelets	≥ 50 x 10^9/L
Creatinine Clearance (CrCL)	≥ 30 mL/min
Bilirubin	<1.5 x ULN (or <1.5 x baseline, if baseline was abnormal)
ALT/AST	<5 x ULN (or <5 x baseline, if baseline was abnormal)
Fasting glucose	≤ 13.9 mmol/L

Dose modifications

Dose level	Dose
Starting dose	300mg OD
First dose reduction	250mg OD
Second dose reduction	200mg OD

- **Haematological toxicity**

Neutrophils (x 10^9/L)	Dose modification
≥1.0	Maintain dose level
<1.0	Omit dose until neutrophils ≥ 1.5 x 10^9/L then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then reduce by one dose level
Febrile neutropenia (neutrophils < 1.0 and a single temperature of ≥ 38.5°C or sustained temperature of > 38°C for more than 1 hour)	Omit dose until resolved, then reduce by one dose level

Platelets (x 10^9/L)	Dose modification
≥50	Maintain dose level
25-50	Omit dose until neutrophils ≥ 1.5 x 10^9/L then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then reduce by one dose level
<25	Omit dose until resolved, then reduce by one dose level

- **Renal impairment**

No dose adjustment is necessary in patient with mild or moderate renal impairment. Caution should be used in patients with severe renal impairment (CrCl<30mL/min) as there is no experience of Alpelisib in this population. See toxicity section for management of creatinine rises during treatment.

- **Hepatic impairment**

No dose adjustment is necessary in mild, moderate or severe (Child Pugh class A, B or C) hepatic impairment. See toxicity section for management of LFT derangement during treatment.

- **Other toxicities**

Hyperglycaemia

Consultation with endocrinologist should be considered for all patients and is recommended for patients who are pre-diabetic or those with a fasting glucose >13.9 mmol/L, body mass index (BMI) ≥30 or age 75 years.

Fasting glucose	Recommended actions
>ULN-8.9mmol/L	No dose adjustment required. Initiate or intensify oral antidiabetic treatment*
8.9-13.9mmol/L	No dose adjustment required. Initiate or intensify oral antidiabetic treatment* If fasting glucose does not decrease to ≤8.9mmol/L within 21 days of appropriate antidiabetic treatment, reduce alpelisib by one dose level
13.9-27.8mmol/L	Hold alpelisib Initiate or intensify oral antidiabetic treatment and consider additional antidiabetic medicinal products such as insulin for 1-2 days** until hyperglycaemia resolves as clinically indicated. Administer intravenous hydration and consider appropriate treatment (e.g. intervention for electrolyte/ketoacidosis/hyperosmolar disturbances) If fasting glucose decreases to ≤8.9mmol/L within 3 to 5 days under appropriate antidiabetic treatment, resume alpelisib at next lower dose level If fasting glucose does not decrease to ≤8.9mmol/L within 3 to 5 days under appropriate antidiabetic treatment, consultation with an endocrinologist is recommended. If fasting glucose does not decrease to ≤8.9mmol/L within 21 days of appropriate antidiabetic treatment, permanently discontinue alpelisib.

≥27.8mmol/L	Hold alpelisib Initiate or intensify antidiabetic treatment (administer intravenous hydration and consider appropriate treatment (e.g. intervention for electrolyte/ketoacidosis/hyperosmolar disturbances)), recheck within 24 hours and as clinically indicated. If fasting glucose decreases to ≤27.8mmol/L then follow the recommendations for the fasting glucose level above. If fasting glucose is confirmed as ≥27.8mmol/L after 24 hours , permanently discontinue alpelisib.

*SOLAR-1 trial recommendations: initiate metformin at 500mg once daily then based on tolerability, the metformin dose should be increased to 500mg twice daily, followed by 500mg with breakfast and 1000mg with the evening meal followed by a further increase to 1000mg twice daily if needed. SGLT2 inhibitors or insulin sensitizers e.g. thiazolidinediones or dipeptidyl peptidase-4 inhibitors could also be considered.
**recommended in SOLAR-1 trial but may not be necessary in majority of cases of alpelisib-induced hyperglycaemia given short half-life of alpelisib.

Rash

Severe cutaneous reactions have been reported with alpelisib including Stevens-Johnson syndrome, erythema multiforme and drug reaction with eosinophilia and systemic symptoms (DRESS). Patients should be advised of the signs and symptoms of severe cutaneous reactions (e.g. prodrome of fever, flu-like symptoms, mucosal lesions or progressive skin rash) and alpelisib should be withheld. If severe cutaneous reaction is confirmed, alpelisib should be permanently discontinued.

Topical corticosteroids should be initiated at the first signs of rash and systemic corticosteroids should be considered for moderate to severe rashes. Consultation with a dermatologist should always be considered. Criteria for dose interruption, reduction or discontinuation are below.

Grade	**Recommendation**
Grade 1 (<10% body surface area (BSA) with active skin toxicity)	No dose adjustment is required Initiate topical corticosteroid treatment Consider adding oral antihistamine to manager symptoms If active rash is not improved within 28 days of appropriate treatment, add a low dose systemic corticosteroid
Grade 2 (10-30% BSA with active skin toxicity)	No dose adjustment is required Initiate or intensify topical corticosteroid and oral antihistamine treatment Consider low dose systemic corticosteroid treatment If rash improves to ≤ grade 1 within 10 days, systemic corticosteroid may be discontinued.
Grade 3 (e.g. severe rash not responsive to medical management) (>30% BSA with active skin toxicity)	Hold alpelisib until rash improves to ≤ grade 1 Initiate or intensify topical/systemic corticosteroid and oral antihistamine treatment Once rash improves to ≤ grade 1, resume alpelisib at next lower dose level
Grade 4 (e.g. severe bullous, blistering or exfoliating skin conditions) (any % BSA associated with extensive superinfection, with intravenous antibiotics indicated; life-threatening consequences)	Permanently discontinue alpelisib

Diarrhoea

Grade	Recommendation
Grade 1 (Increase of <4 stools per day over baseline)	No dose adjustment is required Initiate appropriate medical therapy and monitor.
Grade 2 (Increase of 4-6 stools per day over baseline)	Hold alpelisib Initiate or intensify appropriate medical therapy and monitor If diarrhoea improves to ≤ grade 1 then resume alpelisib at same dose level If diarrhoea recurs as ≥ grade 2, hold alpelisib until improvement to ≤ grade 1 then resume alpelisib at the next lower dose level
Grade 3 (Increase of >=7 stools per day over baseline)	Hold alpelisib Initiate or intensify appropriate medical therapy and monitor If diarrhoea improves to ≤ grade 1 then resume alpelisib at the next lower dose level.
Grade 4 (Life threatening, urgent intervention indicated)	Permanently discontinue alpelisib

Bilirubin elevation

Grade	Recommendation
Grade 1 (>ULN-1.5 x ULN)	No dose adjustment is required
Grade 2 (1.5 - 3 x ULN)	Hold alpelisib until recovery to ≤ grade 1. If resolved in: • ≤ 14 days – restart at same dose level • > 14 days – restart at next lower dose level
Grade 3 (3 – 10 x ULN)	Hold alpelisib until recovery to ≤ grade 1. Resume alpelisib at next lower dose level
Grade 4 (> 10 x ULN)	Permanently discontinue alpelisib

Creatinine increases

Serum creatinine	Recommendation
< 2 x ULN	No dose adjustment is required
2 – 3 x ULN	Hold alpelisib until recovery to ≤ grade 1. If resolved in: • ≤ 7 days – restart at same dose level • > 7 days – restart at next lower dose level
Grade 3 or 4 > 3 x ULN	Permanently discontinue alpelisib

Pancreatitis

For grade 2 or 3 pancreatitis, hold alpelisib until improvement to ≤ grade 1 and resume at next lower dose level. Only one dose reduction is permitted. If toxicity recurs, permanently discontinue alpelisib.

Pneumonitis

In patients with new or worsening respiratory symptoms or a suspected diagnosis of pneumonitis, alpelisib should be withheld. If pneumonitis diagnosis is confirmed, then alpelisib should be permanently discontinued.

Hypersensitivity reactions
Serious hypersensitivity reactions (including anaphylaxis and anaphylactic shock) manifested by symptoms including, but not limited to dyspnoea, flushing, rash, fever or tachycardia have been reported in patients treated with alpelisib. Alpelisib should be permanently discontinued in patients with serious hypersensitivity reactions.

Any other toxicity

CTCAE Grade	Recommendation
Grade 1 or 2	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated
Grade 3	Hold alpelisib until recovery to ≤ grade 1. Resume alpelisib at next lower dose level
Grade 4	Permanently discontinue alpelisib

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Hyperglycaemia
Severe cutaneous reactions
Pneumonitis
Pancreatitis
Hypersensitivity reactions including anaphylaxis

- **Frequently occurring side effects**

Rash
Hyperglycaemia
Creatinine increased
Diarrhoea
LFT derangement
Nausea, vomiting
Lymphopenia
Thrombocytopenia
Fatigue
Anaemia
Decreased appetite
Hypocalcaemia
Alopecia
Activated partial thromboplatin time (aPPT) prolonged
Increased lipase
Stomatitis
Hypokalaemia
Hypomagenesaemia
Headache
Taste disturbance
Decreased albumin
Pyrexia

- **Other side effects**

Hypertension
Palmar-plantar erythrodysaesthesia
Myalgia

Osteonecrosis of the jaw
Oedema

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible and consider switching patient to low molecular weight heparin or DOAC during treatment. If the patient continues on treatment monitor the INR at least once a week and adjust dose accordingly.
BCRP inhibitors e.g. eltrombopag, lapatinib, pantoprazole: potential for increased exposure to alpelisib, use with caution and monitor for toxicity
Specific CYP3A4 substrates that themselves cause a time dependent inhibition or induction of CYP3A4 affecting their own metabolism e.g. rifampicin, encorafenib: use with caution as alpelisib may interfere with the suctrates effects on CYP3A4.
CYP2C9 substrates with a narrow therapeutic index e.g. warfarin: use with caution, alpelisib may reduce activity of substrate through CYP3A4 induction.
Sensitive CYP2B6 substrates with a narrow therapeutic index e.g. bupropion: use with caution, alpelisib may reduce activity of substrate through CYP2B6 induction.
Substrates of OAT3, intestinal BCRP and P-gp transporters: alpelisib may inhibit these transporters potentially increasing systemic exposure of these substrates.

Additional comments

The safety of alpelisib in patients with Type 1 and uncontrolled Type 2 diabetes has not been established as these patients were excluded from clinical studies. Patients with a history of diabetes mellitus may require intensified diabetic treatment and should be closely monitored.

Caution should be exercised when alpelisib is administered, simultaneously or sequentially, alongside bisphosphonates or denosumab due to a potential increased risk of osteonecrosis of the jaw. Alpelisib should not be initiated in patients with ongoing osteonecrosis of the jaw from current or previous bisphosphonate/denosumab treatment.

References

- Summary of Product Characteristics – Alpelisib (Novartis) accessed 11th August 2022 via www.medicines.org.uk
- National Institute for Health and Care Excellence (TA816) accessed 11th August 2022 via www.nice.org.uk
- Andre, F. *et al*. Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. N Engl J Med 2019;380:1929-1940

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