Systemic Anti Cancer Therapy Protocol

ALPELISIB (Piqray®) and FULVESTRANT

Locally Advanced and Metastatic Breast Cancer

PROTOCOL REF: MPHAALFUBR
Version No.: 2.0

Approved for use in:

Alpelisib is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men with ER positive, HER2 negative, locally advanced or metastatic breast cancer with a *PIK3CA* mutation after disease progression, only if their cancer has progressed after a CDK4/6 inhibitor plus an aromatase inhibitor

****BLUETEQ REQUIRED****

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.

Dosage:

Drug	Dose	Route	Frequency
Alpelisib Tablets	**300mg**	Oral	Once daily continuously
Fulvestrant Injection	**500mg**	IM	Cycle 1, Day 1 and 15 ONLY Then on day 1 for subsequent cycles

Repeated every 28 days until disease progression or unacceptable toxicity.

Contraindications:

- History of Stevens–Johnson syndrome (SJS), erythema multiforme (EM), drug reaction with eosinophilia and systemic symptoms (DRESS) or toxic epidermal necrolysis (TEN)
- Active osteonecrosis of the jaw

Administration:

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

Advise patients to promptly report signs and symptoms of possible serious adverse reactions as below:

Symptoms	May indicate:
• Dyspnoea • Flushing • Rash • Fever • Tachycardia	Severe hypersensitivity
• Prodrome of fever • Flu-like symptoms • Mucosal lesions • Progressive skin rash	Severe cutaneous reaction
• Excessive thirst • Urinating more often than usual or higher amount of urine than usual • Increased appetite with weight loss • Difficulty in breathing • Nausea and vomiting	Hyperglycaemia
• New or worsening respiratory symptoms • Cough • Dyspnoea	Pneumonitis
• Pain • Swelling or numbness of jaw • Loosening of a tooth • Non-healing of mouth sores or discharge	Osteonecrosis of the jaw
• Advise patients to start anti-diarrhoeal treatment (loperamide), increase oral fluids and notify healthcare professional if diarrhoea occurs while taking alpelisib	In the event of diarrhoea

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

Supportive treatments:

Loperamide 2mg – TWO capsules to be taken initially followed by ONE capsule with each loose stool as required (maximum daily dose 16mg)

Non-sedating antihistamine (e.g cetirizine or equivalent) – the SOLAR-1 trial showed reduction in rash occurrence when antihistamines were used prophylactically.

Dosing in renal and hepatic impairment:

Renal	**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	**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.

Interactions:

Fulvestrant: There are no known drug interactions with fulvestrant

Alpelisib:

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).

Main toxicities:

Please consult summary of product characteristics (SmPC) for full list of adverse effects for each agent.

Fulvestrant	
	Injection site reactions, hot flushes, nausea, rash, joint pain
Alpelisib	
	Listed as very common- 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.

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 1 Day 7	Cycle 1 D15	Cycle 2	Cycle 3	Ongoing
PIK3CA Testing	X						
Informed Consent	X						
Clinical Assessment	X						As clinically indicated or at the end of treatment
SACT Assessment; PS, toxicities and full observations (including BP)*		X		X	X	X	Every cycle
HbA1c	X				X		After 4 weeks and then every 3 months thereafter
Fasting Blood Glucose	X	X	X	X	X	X	At least once weekly for the first 2 weeks and then once every 4 weeks or as clinically indicated**
FBC	X	X			X	X	Every cycle
U&E (including magnesium) & LFTs	X	X			X	X	Every cycle
Bone Profile	X	X			X	X	Every cycle
CrCl (Cockcroft and Gault)	X	X			X	X	Every cycle
CT scan	X					X	At 8 weeks and then 12 weekly
Weight recorded	X	X			X	X	Every Cycle

*Due to risk of pneumonitis and hypertension – check full observations each cycle

**If patient has own blood glucose machine they can monitor at home with a telephone review to check results. Patients must be reminded that this is a fasting test. If patient is already diabetic, pre-diabetic, BMI ≥ 30 or ≥ 75 years then continue to monitor as frequently as needed to manage hyperglycemia according to healthcare professional / specialist

Dose Modifications and Toxicity Management:

Fulvestrant: There are no recommended dose modifications with 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)

- Only one dose reduction is permitted for pancreatitis.
- If further dose reduction below 200mg once daily is required, discontinue alpelisib.

Haematological toxicity:

Thrombocytopenia	
Grade 1 (PLT < lower limit of normal range to 75 x10^9/L) Grade 2 (PLT 75 to 50 x10^9/L)	Maintain dose level
Grade 3 (PLT 50 to25 x10^9/L)	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 4 (PLT below 25 x10^9/L)	Hold treatment until resolved to ≤ Grade 1 then to reduce by one dose level. For less than 10 x 10^9/L consider transfusion

Non- Haematological toxicity– ALPELISIB ONLY:

Hyperglycemia

Dose modification and management should only be based on **fasting glucose values.**

If hyperglycaemia occurs, further expert advice should be sort. The medical team can contact Endocrinologist Dr Sid McNulty from St Helens and Knowsley (Whiston) through switchboard. Patients should always be referred to a diabetic specialist to monitor and counsel patient on lifestyle changes.

See Appendix 1 for **Protocol Guidance for Treatment of Hyperglycemia in SOLAR-1 trial**

CTC Grade	Recommendation
Grade 1 **Fasting glucose >8.9 mmol/L**	No dose adjustment needed - Initiate or intensify anti-diabetic treatment (see Appendix 1)
Grade 2 **Fasting glucose >8.9 to 13.9 mmol/L**	No dose adjustment needed - Initiate or intensify anti-diabetic treatment (see Appendix 1) - 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

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 and 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, **referral to dermatologist should occur. The medical team can contact dermatologist Dr Elaine Hindle from St Helens and Knowsley (St Helens) who runs a weekly urgent review clinic and is contactable via secretary or via referral letter.**

See *Appendix 2* for Protocol Guidance for Treatment of Skin and Subcutaneous Disorders in SOLAR-1 trial

CTC Grade	Recommendation
Grade 1 <10% BSA (body surface area) 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 (see Appendix 2) If etiology 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 etiology 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 etiology is SCAR – permanently discontinue If etiology 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 (Excluding Hyperglycaemia, Rash and Diarrhoea)

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 (see Appendix 3), 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 (see Appendix 3), 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.

References:

1. Piqray 200mg film-coated tablets, summary of product characteristics. Available at: https://www.medicines.org.uk/emc/product/11684/smpc#gref
2. British National Formulary (BNF). Alpelisib. Available at: https://bnf.nice.org.uk/medicinal-forms/alpelisib.html
3. https://www.health.novartis.co.uk/medicines/oncology/piqray-alpelisib
4. Supplementary Appendix to: 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

Appendix 1

Protocol Guidance for Treatment of Hyperglycemia in SOLAR-1

Grade 1

Maintain dose level and remind patient of lifestyle changes.

- If fasting plasma glucose (FPG) <7.8 mmol/L, consider adding metformin*
- If FPG 7.8–8.9 mmol/L, start or intensify metformin*
    - Initiate metformin 500 mg once daily with dinner.
- If no GI intolerance after several days, increase to 500 mg twice daily with breakfast and dinner
- If tolerated, 1 g twice daily with breakfast and dinner
- If not tolerated, reduce to prior tolerated dose
    - Monitor FPG as clinically indicated and at least weekly for 8 weeks, then every 2 weeks until FPG is within baseline values.

Grade 2

Maintain dose level and remind patient of lifestyle changes.

- Metformin 500 mg twice daily with breakfast and dinner
- If no GI intolerance, increase to 500 mg with breakfast, 1000 mg with dinner
- If tolerated, 1000 mg bd with breakfast and dinner
- If not tolerated, reduce to prior tolerated dose
- Titrate to the maximum tolerated dose over a period of 3 weeks
    - Exclude confounding factors such as UTI and consider consultation with a diabetologist.
    - If FPG continues to rise, or is persistently >8.9 mmol/L, on MTD of metformin, add an insulin-sensitizer, e.g. pioglitazone 30 mg.
    - Monitor FPG as clinically indicated, and at least weekly, until FPG resolves to ≤Grade 1.
- If FPG does not resolve to ≤Grade 1 within 21 days after initiation of appropriate antidiabetic treatment, reduce alpelisib by one dose level.
- Continue with antidiabetic treatment and check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks.
- Alert treating physician if FPG >13.9mmol/L

Grade 3

Interrupt treatment with alpelisib and confirm fasting status of the assessment. If non-fasting, re-check within 24 hours.

- Exclude confounding factors such as UTI and consider consultation with a diabetologist.
- Administer IV hydration and intervention for electrolyte/ketoacidosis/hyperosmolar disturbances as clinically appropriate.
- Start metformin and titrate as outlined for Grade 2, add pioglitazone as outlined for Grade 2.
- Insulin may be used for 1–2 days until hyperglycemia resolves; however this may not be necessary in the majority of cases of alpelisib-induced hyperglycemia, given the short half-life of alpelisib.
    - Monitor FPG as clinically indicated and at least twice weekly until FPG resolves to ≤ Grade 1.
- If FPG resolves to ≤Grade 1 within 3–5 days, while off treatment and on metformin, re-start alpelisib and reduce one dose level, continue with antidiabetic treatment and check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks, alert treating physician if FPG >13.9mmol/L.
- If FPG does not resolve to Grade 1 within 3–5 days while off treatment and on metformin, consultation with a diabetologist for management of diabetes is strongly recommended.
- If FPG does not resolve to ≤Grade 1 within 21 days after initiation of appropriate antidiabetic treatment in cooperation with a diabetologist, and exclusion of confounding factors e.g. urinary tract infection, permanently discontinue patient from alpelisib treatment.

Grade 4

Interrupt treatment with alpelisib, confirm fasting status of the assessment. If non-fasting, re-check within 24 hours.

- Exclude confounding factors such as UTI and consider consultation with a diabetologist.
- Initiate or intensify medication with appropriate antidiabetic treatment (see Grade 3), re-check within 24 hours.
- If grade improves then follow specific grade recommendations.
- If FPG is confirmed at Grade 4 and confounding factors can be excluded, permanently discontinue patient from alpelisib.

Always consider consultation with a diabetologist and reinforce advice on lifestyle changes, i.e. exercise and dietary advice.
*The preferred option for treating alpelisib-induced hyperglycemia is metformin, given its wide availability and well-characterized safety profile. However, in case of intolerance or unavailability of metformin, treating clinician's judgement should be exercised and other insulin sensitizers such as thiazolidinediones or DPP4 inhibitors can be used.

Appendix 2

Protocol Guidance for Treatment of Skin and Subcutaneous Disorders in SOLAR-1

Refer to dermatologist

Grade 1
(<10% BSA with active skin toxicity)

Maintain dose level.

- Initiate topical corticosteroids 3–4 times daily.
- Preferred compounds to use are triamcinolone, betamethasone while skin toxicity is active, during maximum 28 days.
    - For patients with symptoms like burning and/or pruritus add non-sedating antihistamine, consider adding a sedating antihistamine at night.
    - If active rash is not resolved within 28 days of appropriate treatment, consider adding low-dose systemic corticosteroid (20–40 mg daily).

Grade 2
(10–30% BSA with active skin toxicity)

Maintain dose level.

• Initiate topical corticosteroids 3–4 times daily.
o Preferred compounds to use are triamcinolone or betamethasone while skin toxicity is active, for up to 28 days.
• Consider adding systemic corticosteroids 20–40 mg daily.
• If rash resolves to ≤Grade 1 within 10 days systemic corticosteroid may be discontinued.
• For patients with symptoms like burning, stinging and/or pruritus, add non-sedating antihistamine, consider adding a sedating antihistamine at night.

Grade 3
(>30% BSA with active skin toxicity)
Interrupt treatment with alpelisib until rash/skin toxicity is no longer active but fading to Grade 1, consider exploratory skin biopsy for central assessment.
• Initiate topical corticosteroids 3–4 times daily, preferred compounds to use are triamcinolone or betamethasone for at least 28 days.
• Add systemic corticosteroids 20–40 mg daily.
• If rash resolves to ≤Grade 1 within 10 days, systemic corticosteroid may be discontinued.
• For patients with symptoms like burning, stinging and/or pruritus, add non-sedating antihistamine during the day, consider adding a sedating antihistamine at night.
• When re-starting alpelisib dose:
o At same dose in case of first occurrence, at reduced dose level in case of second occurrence.
o If rash/skin toxicity still active in up to 10% BSA after more than 14 days, continue oral corticosteroid for at least 48 hours upon re-initiation of alpelisib
o If rash and/or pruritus do not reoccur within 48 hours after rechallenge with alpelisib, systemic corticosteroid may be discontinued.
• For patients with symptoms like burning, stinging and/or pruritus, antihistamine regimen should be continued for a minimum of 28 days after re-initiation of alpelisib.

Grade 4
(skin toxicity associated with extensive superinfection, with IV antibiotics indicated; life-threatening

consequences) **Permanently discontinue alpelisib** and consider consultation with a dermatologist. • Treatment of rash should follow guidelines for Grade 3 above, except that alpelisib must not be re-initiated. • Consider exploratory skin biopsy for central assessment.

Consultation with a dermatologist is highly recommended for better assessment and management of alpelisib induced skin toxicity.

Appendix 3

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Pancreatitis	-	Enzyme elevation (amylase and lipase); radiologic findings only	Severe pain; vomiting; medical intervention indicated (e.g., analgesia, nutritional support)	Life-threatening consequences; urgent intervention indicated	Death
Blood Bilirubin Increased	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal	Death

Circulation/Dissemination

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Version History

		Author name and designation	Summary of main changes
		Gabriella Langton **Advanced Pharmacist- NMP** **Breast SRG Pharmacist**	New document
Version 2.0		**Gabriella Langton** **Advanced Pharmacist- NMP** **Breast SRG Pharmacist**	**Updated protocol due to NICE approval, criteria change**