PIK3CA-mutated breast cancer clinical guidance document

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Contents

Objective and scope

The aim of this document is to provide clinical staff with guidance on phosphatidylinositol 3-kinase (PI3K) testing pathway in hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer in adults.

The guidance is relevant to all staff involved with the management of adults who are eligible to have their tumour tested for this genetic biomarker.

For those patients whose tumour is subsequently identified to have a *PIK3CA* (phosphatidylinositol 3-kinase catalytic subunit alpha) variant and are eligible to receive alpelisib, this guideline summarises the prescribing information and recommended baseline investigations and on-treatment monitoring requirements for this therapy.

Section 1: *PIK3CA* testing guidance

Background

The phosphatidylinositol 3-kinase (PI3K) signaling pathway regulates diverse cellular functions, including cell proliferation, survival, protein synthesis, glucose metabolism, cell migration, and angiogenesis (1).

Activating somatic missense mutations of the *PIK3CA* (phosphatidylinositol 3-kinase catalytic subunit alpha) gene that increase the kinase activity of the PI3Kα protein have been identified in approximately 40% of patients with HR-positive, HER2-negative breast cancer. The majority of gain-of function mutations identified in the *PIK3CA* gene were reported to occur in mutational hotspots in exons 8, 10 and 21 (2).

Alpelisib is an orally bioavailable, small-molecule, *PIK3CA* inhibitor. Alpelisib plus fulvestrant is recommended by NICE as an option for treating hormone receptor-positive, HER2-negative, *PIK3CA*-mutated, locally advanced or metastatic breast cancer in adults, if their cancer has progressed after a CDK4/6 inhibitor plus an aromatase inhibitor. This a narrower indication than the marketing authorization. NICE guidance suggests that alpelisib is used second line after disease progression on a CDK4/6 inhibitor plus an aromatase inhibitor (3).

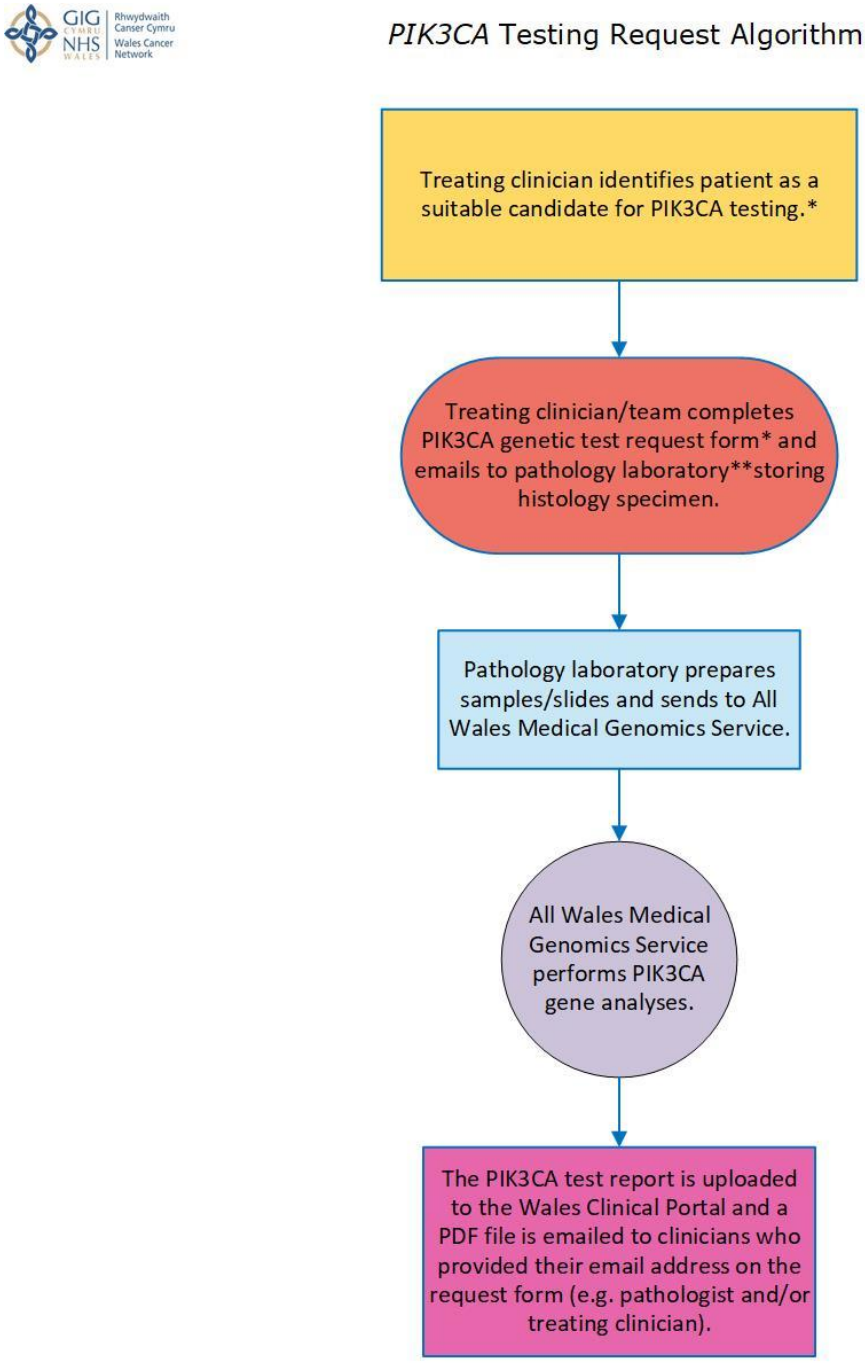
Alpelisib with fulvestrant was investigated in two studies, BYLieve (4) and SOLAR-1 (5). NICE only considered BYLieve as generalisable to UK clinical practice as it studied alpelisib plus fulvestrant in advanced breast cancer that had progressed on or after a CDK4/6 inhibitor with an aromatase inhibitor, which is standard care. Further information on these two trials is included in appendix 1.

Current treatment for hormone receptor-positive, HER2-negative, *PIK3CA*-mutated, locally advanced or metastatic breast cancer after endocrine-based therapy with a CDK4/6 inhibitor plus an aromatase inhibitor is usually everolimus with exemestane. Alpelisib with fulvestrant is a new treatment for this condition. NICE guidance states that clinical evidence from indirect comparisons suggests that alpelisib plus fulvestrant is more effective than everolimus plus exemestane, but the analyses are uncertain.

Alpelisib plus fulvestrant meets NICE criteria to be a life-extending treatment at the end of life. The most likely cost-effectiveness estimates are uncertain but within the range that NICE considers an acceptable use of NHS resources. Therefore alpelisib plus fulvestrant is recommended by NICE.

Testing for *PIK3CA* variants in breast cancer

PIK3CA Testing Request Algorithm



*Available on the All Wales Medical Genomics Service webpage.

*Individual pathology laboratory email addresses are available in this PIK3CA-mutated breast cancer clinical guidance document.

Who to test?

Male and female HR+, HER2- advanced breast cancer patients for whom there is no perceived contraindication to alpelisib plus fulvestrant.

When to test?

To allow upfront treatment planning, test at first confirmation of locally advanced or metastatic HR+, HER2- breast cancer. NICE recommend re-biopsy at first presentation of metastatic disease to confirm hormone receptor status, which also provides an opportunity to test for *PIK3CA* variants.

Alternatively, consider *PIK3CA* variant testing during first–line (1L) endocrine-based therapy (ahead of anticipated progression) for patients who would be suitable for alpelisib plus fulvestrant treatment. Waiting to test following progression on first line endocrine-based therapy for metastatic disease is not recommended due to potential impact on treatment planning by laboratory turnaround times.

What sample to test?

Ideally, test metastatic tissue from the first relapse biopsy or most recent biopsy. If this is not available, archival tissue from the primary tumour can be used.

Formalin-fixed paraffin-embedded (FFPE) samples are acceptable.

The tumour must be confirmed as HR+, HER- prior to requesting *PIK3CA* genetic testing.

Testing of ctDNA in plasma samples using a validated test is an equally valid approach, although not currently routinely available within the NHS. A negative test (no *PIK3CA* variants detected) by ctDNA should be confirmed using tissue.

Which *PIK3CA* mutations confer sensitivity to alpelisib?

The clinical trial assays for SOLAR-1 (5) and BYLieve (4) included 11 frequently observed variants in the *PIK3CA* gene (C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R, H1047Y) providing evidence that these variants can predict sensitivity to alpelisib. These variants are located in exons 8, 10 and 21 according to the gene reference sequence used by AWMGS [NM_006218.4 (LRG_310t1)]; however, it should be noted that these exons are widely referred to in the literature as exons 7, 9 and 20. The difference is because the first exon of *PIK3CA* is non-coding and historically exon numbering was based on coding exons only. The difference in the numbering of the exons does not affect variant numbering which is the same regardless of the exon numbering.

Patients may benefit from adding alpelisib to fulvestrant when harboring *PIK3CA* mutations outside of these 11 hotspots. Data on the use of alpelisib in breast cancer with *PIK3CA* variants beyond the eleven hotspot mutations comes from retrospective and exploratory analyses. With the lack of prospective, randomized

data for alpelisib in these less common variants, the clinical judgement of the treating physician is required when selecting therapy.

Further information on the clinical evidence for *PIK3CA* variants predictive ability is given in appendix 2.

What *PIK3CA* gene regions are tested?

There are several techniques available to detect *PIK3CA* variants in advanced breast cancer tumour samples; the service provided by the All Wales Medical Genomics Service (AWMGS) will utilise Next Generation Sequencing (NGS) of DNA. This breast service is an expansion of CYSGODI (Cymru Service for Genomic Oncology Diagnoses), which is an NGS-based service launched in August 2021 to deliver a high-quality precision medicine service for cancer patients (solid tumour and haematological malignancy). The advantage of implementing an NGS-based testing service is the ability to simultaneously interrogate all clinically relevant *PIK3CA* variants, which minimises tissue requirements and time taken to issue a report. The use of NGS will also allow additional genetic markers to be investigated in the future should the needs of the service change; this is an important consideration given that the number of genetic markers required to guide treatment decisions for many tumour types is increasing.

At AWMGS, the NGS analysis of the *PIK3CA* gene in advanced breast cancer patients will target the three exons (8, 10 and 21) where the eleven *PIK3CA* variants included in the BYLieve (4) and SOLAR-1 (5) studies are located, namely:

- Exon 8 variant: C420R (p.Cys420Arg)
- Exon 10 variants: E542K (p.Glu542Lys), E545A (p.Glu545Ala), E545D (p.Glu545Asp), E545G (p.Glu545Gly), E545K (p.Glu545Lys), Q546E (p.Gln546Glu), Q546R (p.Gln546Arg)
- Exon 21 variants: H1047L (p.His1047Leu), H1047R (His1047Arg), H1047Y (p.His1047Tyr)

The NGS analysis will therefore allow the identification of these eleven variants as well as the identification of other less well characterized variants within exons 8, 10 and 21. The eleven *PIK3CA* variants investigated within the BYLieve (4) and SOLAR-1 (5) studies account for ~85% of the *PIK3CA* variants in breast cancer according to COSMIC (Catalogue of Somatic Mutations in Cancer) database (http://cancer.sanger.ac.uk/cosmic/), with an additional 4% of COSMIC variants being found in other regions of exons 8, 10 and 21. Any other *PIK3CA* variants in exons 8, 10 and 21, outside of the eleven clinically relevant variants, will be investigated and reported appropriately as described in the 'Interpreting a *PIK3CA* test result' below.

Interpreting a *PIK3CA* test result

When a *PIK3CA* test is reported, the following outcomes are possible (the exact wording may differ on a case-by-case basis if clinically appropriate):

1. Clinically relevant *PIK3CA* variant detected

This relates to the detection of one of the eleven *PIK3CA* variants interrogated within the BYLieve (4) and SOLAR-1 (5) studies. This report template will also be used for the detection of the c.1635G>C p.(Glu545Asp) variant, which was not investigated in the BYLieve (4) and SOLAR-1 (5) studies, but tumours with this protein change [p.(Glu545Asp)] were assessed in these studies and have been shown to be sensitive to PI3K inhibitors.

The AWMGS report will describe the variant identified using HGVS (Human Genome Variation Society) nomenclature, e.g. *c.3140A>G p.(His1047Arg).*

The AWMGS report will include a therapeutic comment: *Based on the presence of a clinically relevant PIK3CA variant, this patient has an increased likelihood of response to PI3K inhibitors.*

2. No *PIK3CA* variants detected

The AWMGS report will report the results: *No currently actionable variants detected in PIK3CA.*

The AWMGS report will include a therapeutic comment: *Based on the absence of a clinically relevant PIK3CA variant, this patient has a reduced likelihood of response to PI3K inhibitors.*

3. Poorly characterised *PIK3CA* variant detected

This relates to the detection of a variant in exon 8, 10 and 21 outside one of the eleven *PIK3CA* variants interrogated within the BYLieve (4) and SOLAR-1 (5) studies.

The AWMGS report will describe the variant identified using HGVS (Human Genome Variation Society) nomenclature, e.g. *c.3145G>C p.(Gly1049Arg).*

The AWMGS report will include a therapeutic comment: *Tumours with sequence variations in exons 8, 10 and 21 have been shown to be sensitive to PI3K inhibitors. This variant was not investigated during the SOLAR-1 and BYLieve studies, and there is limited information available regarding whether this variant confers a response to PI3K inhibitors. Therefore, this patient's response to PI3K inhibitors is uncertain.*

PIK3CA test requesting process

All requests should be made using the appropriate All Wales Medical Genomics Service (AWMGS) request form which is available at*:* *http://www.medicalgenomicswales.co.uk*. The oncologist should complete the patient demographic information and enter their own name and email address in the appropriate sections. Requests should not be made directly to the AWMGS laboratory as samples are not stored here and histopathology services are unavailable in this laboratory.

In order to reduce turnaround times, it is recommended that the form is then emailed to the local pathology laboratory storing the diagnostic specimen which is to be tested. The majority of laboratories now have generic emails addresses, the accounts for which are checked on a daily basis (see table 1). If a generic address is not available, the request should be sent to a named individual at the local pathology laboratory who knows to expect the request and initiate the required sample preparation thus avoiding unnecessary delays.

- Referring clinician to contact histopathology laboratory where the tissue is stored and send a completed AWMGS request form indicating the requirement for *PIK3CA* testing (see appendix).
- The histopathology laboratory will retrieve the histological specimen and perform slide cutting and tumour assessment.
- The pathology laboratory should complete the remaining fields on the request form and send a paper copy of the form with the prepared slides directly to the AWMGS laboratory within a 5 working day turnaround time.

University Health Board	Generic email address(es)
Aneurin Bevan	Hist.ReferralRGWOLD.ABB@wales.nhs.uk
Betsi Cadwaladr	BCU.CellPathMolecular@wales.nhs.uk
Cwm Taf Morgannwg	CTM.CellularPathologyMolecularRequests@wales.nhs.uk
Cardiff and Vale	Mg.Cellpath@wales.nhs.uk
Hywel Dda	WWGH.Histology@wales.nhs.uk (laboratory) HDD.Secretaries@wales.nhs.uk (secretaries)
Swansea Bay	Generic email address not yet available. Please contact the appropriate laboratory directly to request an email address to which the request can be sent.

Table 1: Generic email address details for health boards

Histopathological sample preparation requirements for *PIK3CA* testing

The local pathology laboratory housing the specimen should prepare the sample as follows before sending the FFPE slides to AWMGS with an appropriately completed request form (see appendix):

1 H&E stained slide with area of highest neoplastic cell content CLEARLY circled.

60µM (preferably 6x 10µM) air dried unstained sections mounted on slides.

AWMGS contact details

All Wales Genetics Laboratory
Institute of Medical Genetics
University Hospital of Wales
Heath Park
Cardiff
CF14 4XW

Telephone: 02921845347

Email address: Admin.Genetics.cav@wales.nhs.uk

Website: *http://www.medicalgenomicswales.co.uk*
Opening hours: Monday – Friday 8.30am – 5:00pm

Section 2: Prescribing information for alpelisib

Eligibility guidance for treatment with alpelisib

Identification of a *PIK3CA* gene mutation (within tumour or plasma specimens) can indicate that a patient may be commenced on alpelisib treatment if the following criteria are met: (as per NICE Technology appraisal guidance [TA816](6) and NHS England Cancer Drugs fund (7).

- Diagnosed with hormone receptor-positive, HER2-negative, locally advanced/metastatic breast cancer.
- Cancer progression after a CDK4/6 inhibitor plus an aromatase inhibitor.
- No previous treatment with alpelisib or another *PIK3CA* inhibitor.
- The patient has had no prior treatment with fulvestrant.
- Alpelisib and fulvestrant will be otherwise used as set out in their respective Summaries of Product Characteristics (SPCs).

The NHS England Cancer Drugs fund criteria requires a performance status 0-1.

Males and females are eligible. If female, is either post-menopausal or if pre- or peri-menopausal has undergone ovarian ablation or suppression with LHRH agonist treatment.

Prior to cycle one of treatment patient consent must be obtained in order to commence alpelisib treatment.

The decision to commence treatment with alpelisib should be made by the treating clinician on a case-by-case basis, taking into account patient specific factors (e.g. comorbidities, acceptability of potential toxicities) and clinical experience.

Once commenced, treatment with alpelisib should continue until disease progression, or unacceptable toxicity, or if the patient chooses to stop treatment.

Exclusions/Contraindications

- History of severe cutaneous reactions eg: 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 (ONJ)

Cautions

- Alpelisib has not been trialed in patients with advanced, symptomatic, visceral spread who are at risk of life-threatening complications in the short term including patients with massive uncontrolled effusions (pleural, pericardial, peritoneal), pulmonary lymphangitis, and liver involvement resulting in markedly raised bilirubin or transaminases. The activity and safety in such populations are thus unknown.

- Prior to initiating treatment, it is paramount for the patient to have optimised blood sugars. The SOLAR-1 and BYLieve trials studied patients with stable Type 2 Diabetes (T2DM) only. The safety of alpelisib in uncontrolled T2DM and Type 1 Diabetes has not been established and considered higher risk thus endocrinology input must be sort before initiation.
- Conditions pre-disposing to diarrhea
- Patients undergoing radiotherapy. The treating consultant should use their clinical judgment to make the treatment decision on the concomitant use of radiation. No literature has been identified on the use of alpelisib and radiation in breast cancer.

Alpelisib is associated with an increased risk of hyperglycaemia. In some cases, severe hyperglycaemia, in some cases associated with hyperglycaemic hyperosmolar non-ketotic syndrome (HHNKS) or ketoacidosis, has been observed in patients treated with alpelisib. Some cases of ketoacidosis with fatal outcome have been reported to Novartis. Consider consultation with a healthcare professional experienced in the treatment of hyperglycaemia if appropriate prior to prescribing alpelisib.

For patients at higher risk (diabetic, prediabetic, FG >13.9 mmol/L, BMI ≥30, or age ≥75 years)

- Patients at higher risk need consultation with a healthcare professional or diabetologist experienced in the treatment of hyperglycaemia.
- The patient's current antidiabetic treatment might be affected by the treatment with alpelisib through interaction with oral antidiabetics metabolised by CYP2C9 and CYP2C8 (including, but not limited to, repaglinide, rosiglitazone, glipizide, and tolbutamide).

Baseline investigations and on-treatment monitoring for alpelisib

Table 2 summarises the required baseline investigations and on-treatment monitoring for patients receiving alpelisib treatment.

Investigation		**Baseline**	**On-treatment**
Bloods	FBC U&E LFTs	Yes	Prior to every 28 day cycle.
	Fasting blood glucose	Yes	See table 3 below for

			monitoring/self-monitoring recommended by the manufacturer.
	HbA1C	Yes	Cycle 2 D1 and every 3 months thereafter.
Imaging	Radiological imaging of disease (including CT TAP scan)	Yes	Repeat restaging imaging at 12 weeks to assess response; then every three months or as clinically indicated.

Table 2: Baseline and on-treatment monitoring requirements when prescribing alpelisib

	Recommended schedule for the monitoring of fasting glucose and HbA1c levels in all patients treated with alpelisib	**Recommended schedule of monitoring of fasting glucose and HbA1c levels in patients with diabetes, pre-diabetes, BMI ≥30 or age ≥75 years treated with alpelisib**
At screening, before initiating treatment with alpelisib	Test for fasting plasma glucose (FPG), HbA1c, and optimise the patient's level of blood glucose.	
After initiating treatment with alpelisib	Monitor fasting glucose at weeks 1, 2, 4, 6 and 8 after treatment start and monthly thereafter.	
	Monitor/self-monitor fasting glucose regularly, more frequently in the first 4 weeks and especially within the first 2 weeks of treatment, according to the instructions of a healthcare professional*.	Monitor/self-monitor fasting glucose daily for the first 2 weeks of treatment. Then continue to monitor fasting glucose as frequently as needed to manage hyperglycaemia according to the instructions of a healthcare professional*.
	HbA1c should be monitored after 4 weeks of treatment and every 3 months thereafter.	
If hyperglycaemia develops after	Monitor fasting glucose regularly, as per local standard of care and at least until fasting glucose decreases to normal levels.	

initiating treatment with alpelisib	During treatment with antidiabetic medication, continue monitoring fasting glucose at least once a week for 8 weeks, followed by once every 2 weeks, and monitor fasting glucose according to the instructions of a healthcare professional with expertise in the treatment of hyperglycaemia.
* All glucose monitoring should be performed at the clinicians discretion, as clinically indicated.	

Table 3: Schedule of fasting glucose monitoring recommended by manufacturer

Clinical review requirements: alpelisib

- Prior to each cycle of alpelisib treatment, a clinical review is required in line with the investigations requirements above.
- The fasting blood glucose should also be checked at frequent intervals (see Table 2 and 3 above) within the first two cycles and an appropriate mechanism for this monitoring review could be undertaken through modes of delivery such as telephone clinics and GP blood testing.

Dosages

Treatment Regimen: alpelisib in combination with fulvestrant				
Drug	Dose	Route	Frequency	Length of cycle
Alpelisib*	300mg once daily (2x150mg)	Oral	Continuous dosing (Days 1-28)	28 days
Fulvestrant	500mg (2x250mg)	Intramuscularly	Cycle 1 – D1&15 then Cycle 2 onwards D1 only	28 days
Take Home Meds				
Loperamide	4mg (2x2mg capsules initially followed by 1x 2mg capsule with each loose stool when needed (max 16mg daily)	Oral	When needed	28 days
Metoclopramide	10mg three times a day when needed	Oral	5 days when needed	28 days
Cetirizine**	10mg once daily	Oral	28 days	28 days
*Alpelisib is available as 200mg, 150mg or 50 mg tablets.				

**SOLAR-1 trial showed reduction in rash occurrence when antihistamines were prescribed prophylactically throughout treatment with alpelisib.

Alpelisib administration information

- ****lpelisib should only be prescribed in combination with fulvestrant IM****
- No pre-medications are required prior to taking alpelisib
- Take alpelisib orally with a glass of water with/immediately after food
- Take at approximately the same time each day
- If patient vomits after taking alpelisib dose – avoid taking an additional dose on that day and resume the usual dosing schedule on the next day at the usual time.
- Missed doses
- If **less than** 9 hours since usual administration time – take alpelisib immediately
- If **more than** 9 hours after usual time of dose administration – skip alpelisib dose for that day and on the next day, take alpelisib at the usual time.

Patient counselling prior to prescribing alpelisib

- Advise patient how to manage missed doses or doses after potentially vomiting (see above)
- Advise patients to promptly report signs and symptoms of possible serious AEs associated with alpelisib including:
  - *Hypersensitivity* - dyspnoea, flushing, rash, fever, tachycardia
  - *Severe Cutaneous Adverse Reactions (SCARs)* -a prodrome of fever, flu-like symptoms, mucosal lesions, progressive skin rash
  - *Hyperglycaemia* - excessive thirst, urinating more often than usual or higher amount of urine than usual, increased appetite with weight loss
  - *Pneumonitis* - new or worsening respiratory symptoms
  - *Osteonecrosis of the jaw (ONJ)* e.g. signs are pain, swelling or numbness of the jaw, feeling of heaviness in the jaw, loosening of a tooth, non-healing of mouth sores or discharge.
- If moderate to severe side effects are experienced patients need to interrupt treatment immediately and seek medical advice.
- Diarrhoea management: start loperamide treatment, increase oral fluids, and call the cancer centre if > 4 stools per day or if diarrhoea does not respond to loperamide treatment within 24 hours.
- Nausea and vomiting management: take metoclopramide for nausea and/or vomiting and call the cancer centre hotline if vomiting does not respond to metoclopramide treatment within 24 hours.
- Rash: in clinical trials rash was reduced by patients who took regular antihistamines, therefore advise regular cetirizine as above.

Alpelisib dose modification guidance

Dose modifications at cycle 1 for pre-existing blood parameter impairment or toxicity must be discussed with the treating consultant.

Fulvestrant may continue in the absence of alpelisib if deferred or discontinued due to tolerability or toxicity in the absence of disease

progression. However, if fulvestrant is permanently withheld due to tolerability or toxicity then alpelisib must also be discontinued and an alternative treatment option discussed.

Dose modification levels advised by manufacturer

Dose Levels	**Dose**
Recommended starting dose	300mg daily
First dose reduction	250mg daily
Second dose reduction	200mg daily
Third dose reduction	Discontinue treatment and/or discuss with treating consultant
N.B. If patient has pancreatitis - one dose reduction only is permitted before discontinuation of treatment.	

Renal Impairment	
Creatinine Clearance	*Dose*
≥ 30ml/min	100%
< 30ml/min*	Insufficient data are available to provide any dose adjustment recommendation

*<30ml/min is classified as severe renal impairment within clinical practice

Hepatic impairment
There is no dose modification documented as a requirement by the manufacturer for patients with mild, moderate or severe hepatic impairment. However, consider whether deranged liver function is indicative of progressive disease.

Within the manufacturer SPC for Alpelisib, there is no documented requirement for haematological parameters and respective dose modifications as neutropenia and thrombocytopenia is unexpected. Although AWGOG is aware that haematological parameters are needed within clinical practice.

Other cancer centres within the UK are using the following haematological parameters. Therefore, these haematological parameters have been included within this document for guidance only and local practice guidance should be agreed when developing SACT protocols and with the clinical use of Alpelisib.

Haematological			
These recommendations maybe superseded by Consultant decision regarding acceptable blood parameters.			
Neutrophils		*Platelet*	*Action*
≥1.0	*and*	≥75	Proceed with treatment
<1.0	*and*	≥75	**Neutropenia is not expected** with alpelisib treatment. Discuss with consultant.

≥1.0	*and*	<75	Defer treatment until platelets ≥75 and resume alpelisib at 1 lower dose level.

Anaemia
Dose adjustments not documented within manufacturers SPC for Alpelisib as anaemia is not expected with the use of Alpelisib. If occurs, please treat as per local guidance for anaemia regarding blood transfusion requirements and monitoring parameters for haemoglobin.

- Christie NHS Foundation Trust. 2022. Clinical Guideline for ALPELISIB in Advanced Breast Cancer. (assessed via email exchange with Advanced Breast Cancer Pharmacist at Christie NHS Foundation Trust)

Interactions documented with alpelisib

Drug class	**Examples of drugs within class**	**Details of drug interaction**	**Action advised**
BCRP inhibitors	Eltrombopag, lapatinib, pantoprazole	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.	**Caution and monitoring for toxicity advised**
Acid-reducing agents	Proton pump inhibitors, H2 receptor antagonists and antacids	The co-administration of the H2 receptor antagonist in combination with a single 300 mg oral dose of PIQRAY® slightly reduced the bioavailability of aleplisib and decreased overall exposure of alpelisib. Population pharmacokinetic analysis showed no significant effect of co-administration of acid-reducing agents, including proton pump inhibitors, H2 receptor antagonists and antacids, on the pharmacokinetics of PIQRAY®.	Alpelisib can be co-administered with acid-reducing agents, provided alpelisib is taken **immediately after food.**
CYP3A4 substrates	Rifampicin, ribociclib, encorafenib	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.	**Caution recommended**
CYP2C9 substrates with narrow	Warfarin	*In vitro* evaluations indicated that the pharmacological activity of CYP2C9 substrates with a narrow therapeutic index such as warfarin	**Caution is recommended in** (the absence

therapeutic index		may be reduced by the CYP2C9 induction effects of alpelisib.	of clinical data on CYP2C9.)
CYP2B6 substrates	Bupropion	Alpelisib may reduce the clinical activity of sensitive CYP2B6 substrates or CYP2B6 substrates with a narrow therapeutic window.	**Caution recommended**
Substances that are substrates of transporters	None listed; check interaction references checker (link below table)	Alpelisib (and/or its metabolite BZG791) has a potential to inhibit the activities of drug transporters OAT3 and intestinal BCRP and P-gp. Use alpelisib with caution in combination with sensitive substrates of these transporters which exhibit a narrow therapeutic index because PIQRAY® may increase the systemic exposure of these substrates.	**Caution recommended**
Anti-diabetic medication	Repaglinide, rosiglitazone, glipizide and tolbutamide	A patient's current antidiabetic treatment may be affected by treatment with alpelisib through interaction with oral antidiabetics metabolised by CYP2C9 and CYP2C8.	**Caution and close monitoring needed.**

For a complete list of potential interactions see The Electronic Medicines Compendium or use a reputable interaction checker e.g. www.cancer-druginteractions.org, Stockley or www.drugs.com.

Main toxicities

(see SPC: Alpelisib https://www.medicines.org.uk/emc/product/11683/smpc)

Main toxicities	**Listed as Very common/common**
Haematological	Anaemia, thrombocytopenia, lymphocytopenia, electrolyte disturbances (hypokalaemia, hypocalcaemia, hypomagnesemia), increased transaminases, creatinine increase, aPTT prolonged, lipase increased, albumin decreased.
Gastrointestinal	Diarrhoea, nausea, vomiting, decreased appetite, taste disturbances, dry mouth, abdominal pain, dyspepsia, mucosal inflammation, mucosal dryness
Urinary	Urinary tract infection
Glycaemia control	Hyperglycaemia
Cutaneous	Rash, alopecia, dry skin, pruritus, severe cutaneous reactions (rare)
Respiratory	Pneumonitis
Miscellaneous	Headache, fatigue, peripheral oedema, pyrexia, weight decreased, ONJ.

Management of common toxicities

Hyperglycaemia		
If hyperglycaemia of any grade occurs refer to Diabetes Nurse Specialists who will contact the patient for follow up within 3/7		
Fasting plasma glucose (mmol/L)	*Initial recommendation*	*Follow up & monitoring*
>ULN-8.1 mmol/L **or** >ULN-160mg/dl (grade 1)	Treat hyperglycaemia (see guidance below) No dose adjustment needed	Monitor fasting glucose regularly, as per local standard of care and at least until fasting glucose decreases to normal levels then continue monitoring fasting glucose at least once a week for 8 weeks, followed by once every 2 weeks or as recommended by healthcare professional with expertise in the treatment of hyperglycaemia.
>8.1 to 13.9 mmol/L **or** >160-250 mg/dl (grade 2)	Treat hyperglycaemia (see guidance below) No dose adjustment needed unless 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.	Monitor fasting glucose regularly, as per local standard of care and at least until fasting glucose decreases to normal levels then continue monitoring fasting glucose at least once a week for 8 weeks, followed by once every 2 weeks or as recommended by healthcare professional with expertise in the treatment of hyperglycaemia.
>13.9 to 27.8 mmol/L **or** >250-500mg/dl (grade 3)	Hold treatment Consider admission for hydration / appropriate interventions. Initiate or intensify oral antidiabetic treatment and consider additional antidiabetic medications (such as insulin) for 1–2 days until hyperglycaemia resolves, as clinically	Monitor fasting glucose regularly, as per local standard of care and at least until fasting glucose decreases to normal levels. If fasting glucose does not decrease to ≤8.9 mmol/L within 3 to 5 days under appropriate antidiabetic treatment, consultation with a physician with expertise in the treatment of hyperglycaemia is recommended. If alpelisib is resumed continue monitoring fasting glucose at least once a week for 8 weeks, followed by once every 2 weeks or as recommended by healthcare professional with expertise in the treatment of hyperglycaemia.

> 27.8 mmol/L **or** >500mg/dl (grade 4)	Permanently discontinue alpelisib treatment. Admit patient for hydration / appropriate interventions	

Further guidance for the management of hyperglycaemia

Applicable antidiabetic medicinal products, such as metformin, SGLT2 inhibitors, or insulin

sensitisers (such as thiazolidinediones or dipeptidyl peptidase-4 [DPP-4] inhibitors), should be initiated and the respective prescribing information should be reviewed for dosing and dose titration recommendations, including local diabetic treatment guidelines.

Patient status	**Management recommendations within SOLAR-1 study**
Patients with no prior diagnosis of diabetes or diet controlled diabetes	• Initiate metformin (if no contraindications) Initial dose: 500 mg once daily. • Based on tolerability, metformin dose may be increased to: • 500 mg twice daily, followed by • 500 mg with breakfast, and 1000 mg with dinner, followed by • further increase to 1000 mg twice daily if needed. • Monitor fasting glucose regularly at least once weekly for 8 weeks, followed by once every 2 weeks or as per local standard of care and at least until fasting glucose decreases to normal levels. • Refer the patient urgently to the diabetes team. • The patient's GP should also receive an urgent notification about the hyperglycaemia.
For patients already receiving anti-hyperglycaemic therapy:	
For patients on anti-hyperglycaemic therapy	• Manage as per local hyperglycaemia guidelines • Refer the patient urgently to the diabetes team. • Continue other diabetes treatments. • The patient's GP should also receive an urgent notification about the hyperglycaemia.

****Insulin may be used for alpelisib-induced hyperglycaemia for 1-2 days until hyperglycaemia resolves if required. However, this may not be necessary in the majority of cases of alpelisib-induced hyperglycaemia,**

given the short half-life of alpelisib and the expectation that glucose levels will normalise following interruption of alpelisib.**

Diarrhoea	
Grade 1	• No dose adjustment required. • Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 2	• Defer treatment until recovery to ≤ grade 1 • Initiate or intensify appropriate medical therapy and monitor as clinically indicated. • When recovered to grade 1 or less resume alpelisib at same dose level.
Grade 3 and 4	• Defer treatment until recovery to ≤ grade 1 • Initiate or intensify appropriate medical therapy and monitor as clinically indicated. • When recovered to ≤ grade 1 resume alpelisib at the next lower dose level.

Skin Toxicity	
Grade 1: <10% BSA (body surface area) with active skin toxicity	• No dose adjustment required. • Initiate topical corticosteroid treatment and consider adding regular oral antihistamine to manage symptoms if not already taking • If aetiology is SCAR – permanently discontinue alpelisib
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. • Consider referral to a dermatologist. • If aetiology is SCAR – permanently discontinue alpelisib
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. • Refer to a dermatologist. • If aetiology is SCAR* – permanently discontinue alpelisib • If aetiology is **not** a SCAR, interrupt dose until recovery to grade ≤ 1, then resume alpelisib 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	• Permanently discontinue alpelisib. • Refer to a dermatologist.

indicated, life threatening	

*SCAR: Severe Cutaneous Adverse Reactions e.g. Stevens–Johnson syndrome (SJS), erythema multiforme (EM), drug reaction with eosinophilia and systemic symptoms (DRESS) or toxic epidermal necrolysis (TEN).

Pneumonitis	
Patients who have new or worsening respiratory symptoms or are suspected to have developed pneumonitis	Interrupt alpelisib immediately and evaluate the patient for pneumonitis
Patients with confirmed pneumonitis	Permanently discontinue alpelisib

Management of other toxicities not listed	
Grade 1 or 2	Proceed with treatment, initiate appropriate medical therapy and monitor as clinically indicated
Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures	Interrupt treatment until symptoms improve to ≤ grade 1 or baseline (or, at the clinician's discretion, Grade ≤2 if not considered a safety risk for the patient) Reduce alpelisib by one dose level
Grade 3	Interrupt treatment until symptoms improve to ≤ grade 1 or baseline (or, at the clinician's discretion, Grade 2 if not considered a safety risk for the patient) Reduce alpelisib by one dose level
Grade 4	Consider discontinuing treatment

Appendices

Appendix 1: Clinical trial data

BYL719X2402 (BYLieve) (4)

Apelisib was evaluated in a phase 2, multicentre, open-label, non-comparative, three-cohort trial, patients in combination with endocrine therapy (either fulvesterant or letrozole) in women and men aged 18 years or older with HR-positive, HER2-negative locally advanced or metastatic breast cancer harbouring *PIK3CA* mutation(s), and whose disease has progressed on or after prior treatments.

In cohort A, the cohort on which the NICE recommendation is based, patients received a CDK4/6 inhibitor plus an aromatase inhibitor as immediate previous therapy. Patients could have had no more than two previous anticancer therapies and no more than one previous chemotherapy regimen in the advanced or metastatic setting.

Patients received oral alpelisib 300 mg/day (continuously) plus fulvestrant 500 mg intramuscularly on day 1 of each 28-day cycle and on day 15 of cycle 1.

The primary outcome of BYLieve is progression-free survival. BYLieve included 121 people who had treatment with alpelisib plus fulvestrant after a CDK4/6 inhibitor plus an aromatase inhibitor. The median duration of follow up was 11.7 months. BYLieve met its primary end point, with 50.4% of people alive without disease progression at 6 months (95% confidence interval [CI] 41.2 to 59.6; lower bound of the 95% CI exceeding 30%, which was the protocol-defined clinically meaningful threshold).

Adverse events of any grade were reported for 126 (99%) of 127 patients; all 126 had at least one adverse event considered to be treatment-related. The most frequent (≥5%) adverse events of grade 3 or more were hyperglycaemia (36 [28%]), rash (12 [9%]), rash maculopapular (12 [9%]), and diarrhoea (seven [6%]). Serious adverse events occurred in 33 (26%) patients; 20 (16%) patients had events that were treatment related. Hyperglycaemia was the most frequent treatment related serious adverse event, and was experienced by seven (6%) patients.

Study CBYL719C2301 (SOLAR-1) (5)

Apelisib was evaluated in a phase III, randomised, double-blind, placebo-controlled study of alpelisib in combination with fulvestrant in postmenopausal women, and men, with HR+, HER2- advanced (locoregionally recurrent or metastatic) breast cancer whose disease had progressed or recurred on or after an aromatase-inhibitor-based treatment (with or without CDK4/6 inhibitor combination). Patients were excluded if they had received chemotherapy previously for advanced disease

A total of 572 patients were enrolled into two cohorts, one cohort with *PIK3CA* mutation and one cohort without *PIK3CA* mutation breast cancer. Patients were randomised to receive either alpelisib 300 mg plus fulvestrant or placebo plus fulvestrant. A total of 20 patients (5.9%) had received CDK4/6 inhibitor.

In the cohort with *PIK3CA*-mutated cancer the median progression-free survival was 11.0 months (95% confidence interval [CI], 7.5 to 14.5) in the alpelisib–fulvestrant group, as compared with 5.7 months (95% CI, 3.7 to 7.4) in the placebo–fulvestrant group (hazard ratio for progression or death, 0.65; 95% CI, 0.50 to 0.85; P<0.001).

In the cohort of patients without *PIK3CA*-mutated cancer the median progression-free survival was 7.4 months (95% CI, 5.4 to 9.3) in the alpelisib–fulvestrant group and 5.6 months (95% CI, 3.9 to 9.1) in the placebo– fulvestrant group (hazard ratio for progression or death, 0.85; 95% CI, 0.58 to 1.25).

The adverse events of any grade that occurred in at least 35% of the patients in either group were hyperglycemia (in 63.7% of the patients who received alpelisib–fulvestrant and 9.8% of those who received placebo– fulvestrant), diarrhea (in 57.7% and 15.7%, respectively), nausea (in 44.7% and 22.3%), decreased appetite (in 35.6% and 10.5%), and rash (in 35.6% and 5.9%) or maculopapular rash (in 14.1% and 1.7%). The most common adverse events of grade 3 or 4, occurring in at least 5% of patients in either group, were hyperglycemia (in 36.6% of the patients who received alpelisib– fulvestrant and 0.7% of those who received placebo–fulvestrant), rash (in 9.9% and 0.3%, respectively), maculopapular rash (in 8.8% and 0.3%), and diarrhea (in 6.7% and 0.3%).

Appendix 2: Further clinical evidence for the predictive ability of *PIK3CA* variants

Juric D, et al. (8) reported exploratory biomarker results from a NGS retrospective analysis of samples containing additional *PIK3CA* mutations that were not detected by the PCR assay used for screening in the SOLAR-1 trial. A pre-planned analysis using NGS testing of cancer markers, including those of the PI3K pathway, was performed on the *PIK3CA*-mutant and *PIK3CA* non-mutant cohorts. The samples were retrospectively tested with the FoundationOne® CDx® 324-gene panel NGS-based in vitro diagnostic device. Valid NGS results were available for 404 patients (70.6%) of those enrolled in the SOLAR-1 trial. There were 31 patient samples with *PIK3CA* mutations that were not initially detected by PCR-based methods. Within this small group of patients, no benefit was demonstrated with the addition of alpelisib (8.5 months vs 13.0 months, HR=0.75, 95% CI, 0.21-2.73) however the results should be interpreted with caution due to the small number of patients (n=31) in this group.

Rugo HS et al. (9) reported results of a real-world analysis looking at the prevalence of the *PIK3CA* mutations that were the basis of the SOLAR-1 trial (*PIK3CA* exons 7, 9 and 20 defined as SOLAR1m) as well as other predicted activating mutations elsewhere in the *PIK3CA* gene (defined as OTHERm) in patients with breast cancer. Using comprehensive genomic profiling (CGP), results were assessed from 31,765 tissue and 1,346 liquid biopsies from patients with breast cancer. Clinical characteristics and treatment history were available for 1,579 patients with *PIK3CA* mutations in a de-identified Flatiron Health-Foundation Medicine clinico-genomic database. Three cohorts of patients were identified:

Cohort A, including patients with HR+/HER2- breast cancer with any type of *PIK3CA* mutation (SOLAR1m and OTHERm) receiving fulvestrant alone (n=124) or alpelisib/fulvestrant (n=111) as ≥2L treatment.
Cohort B, patients with HR+/HER2- breast cancer with any type of *PIK3CA* mutation who received alpelisib (n=627).
Cohort C, patients with *PIK3CA* mutations other than those identified in the SOLAR-1 trial (OTHERm) and received alpelisib (n=36).

The other *PIK3CA* mutations (OTHERm) and the percentage in tissue and liquid biopsies is outlined in Table 1.9

Table 1. Other *PIK3CA* Mutations

Mutation	% in Tissue	% in Liquid Biopsies
N345K	1.9	1.7
E726K	1.1	1.2
p85 BD indel	1.0	1.2
C2 indel	0.5	0.7
G1049R	0.4	0.5
Q546K	0.4	0.2
E453K	0.4	0.8
G118D	0.2	0.1
M1043I	0.2	0.4
N1044K	0.2	0.1
E81K	0.2	0.3
E365K	0.2	0.4
E418K	0.2	0.3
E545Q	0.2	0.0
R88Q	0.2	0.1
exon 20 fs	0.2	0.3
K111E	0.2	0.1
Others	3.6	4.2

Within Cohort A, a benefit in the real world PFS (rwPFS) was demonstrated with the addition of alpelisib vs fulvestrant alone (6.5 months vs 4.1 months, respectively; P=0.027) demonstrating that alpelisib provides a benefit in patients with other PIK3CA mutations in addition to those mutations considered the SOLAR-1 mutations [SOLAR1m]. Within Cohort C, five patients with mutations in N345K, Q75E, R38C, G106_108del, and N345K/N1044K had a rwPFS of > 6 months. Additionally, of the 36 patients in Cohort C, only 15 progressed on alpelisib, most of whom received prior chemotherapy and CDK4/6 inhibitor therapy. The results suggests that patients may benefit from adding alpelisib to fulvestrant when harboring *PIK3CA* mutations outside of the 11 hotspot mutations that were considered the SOLAR-1 mutations.9

Appendix 3: AWMGS referral form for *PIK3CA* analysis in breast cancer

An example of the referral form is shown below. The referral form is available at http://www.medicalgenomicswales.co.uk and should be downloaded completed via this link.

Please note: this referral form can also be used for NTRK fusion testing on breast samples.

Fill in patient details below – or affix addressograph (top left)			
Patient Forename:			Clinician (address report to):
Patient Surname:			Requested by:
DoB:		NHS number:	Hospital Name (*essential for report*):
Sex:		Hospital Number:	**Email Addresses (*for reports*):** *(NHS Wales or NHS.net)* oncologists/pathologists/MDT coordinators
Address:		Alternative Hospital no:	
		Date requested:	

Please note: Gene analysis relies on sampling tumour tissue.
Tissues blocks for genomic analysis can no longer be accepted.

This section is for completion by Pathology Laboratory.		
Pathologist:	Pathology Hospital:	Block Number:
Sampling method, biopsy type and fixation method.	Date sample sent to AWMGS	**Tumour sample has now been exhausted** *Yes* ☐ *No* ☐

Sample details:
Archived tissue ☐ New biopsy ☐ Date of biopsy _____

For ALL requests please provide:
1 H&E stained slide with area of highest neoplastic cell content CLEARLY circled.
Please state the approx. % neoplastic cell content present in the H&E circled tumour area: _____%

Relevant Clinical Summary (e.g. tumour histology) *Please also attach appropriate pathology report*

Test		***Test directory***	***Technology***	***Sample requirements***
Multi-target DNA NGS panel: small variant – PIK3CA	☐	**n/a**	**DNA NGS Panel**	**DNA**: 60µM (preferably **6x 10µM**) air dried unstained sections mounted on slides.
Multi-target RNA NGS panel: structural variant - NTRK1, NTRK2, NTRK3	☐	**M3.5**	**RNA NGS Panel**	**RNA**: 50µM (preferably **5x 10µM**) air dried unstained sections mounted on slides. *Note: slides for RNA - ideally prepared in an RNase-free environment.* **For salvage FISH** testing for NTRK1, NTRK2 and NTRK3 (in the event that RNA-based NGS cannot be performed or is unsuccessful): **2x 3-4µM** sections (singly mounted) on charged/adhesion slides **PER GENE**

For all RNA-based NGS panel testing requests, we ask that additional slides for FISH analysis are provided upfront at point of test request to allow activation (with minimal delay) of the salvage FISH pathway for clinically relevant gene rearrangements in the event that insufficient RNA is obtained for NGS testing/NGS testing is unsuccessful.

In the event of insufficient tissue/low cellularity/low neoplastic cell content samples, please discuss with AWMGS appropriate alternate routes of testing before sending samples

Samples should be dispatched as soon as possible as the patient's treatment is dependent upon the molecular analysis
For further information on testing, please refer to the AWMGL website:
https://www.medicalgenomicswales.co.uk/

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