



# alpelisib 50mg, 150mg, 200mg film-coated tablets (Piqray®)

Novartis

04 November 2022

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

**ADVICE:** following a full submission assessed under the end of life and orphan equivalent medicine process.

**alpelisib (Piqray®)** is not recommended for use within NHSScotland.

**Indication under review:** in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine-based therapy.

The addition of alpelisib to fulvestrant significantly increased progression-free survival in patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer with PIK3CA mutation.

The submitting company did not present a sufficiently robust clinical and economic analysis to gain acceptance by SMC.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

**Chairman  
Scottish Medicines Consortium**

## Indication

In combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine-based therapy.<sup>1</sup>

## Dosing Information

Alpelisib 300mg orally once daily on a continuous basis. Tablets should be swallowed whole immediately after food, at approximately the same time each day and should not be chewed, crushed or split prior to swallowing.

Alpelisib should be co-administered with fulvestrant. The recommended dose of fulvestrant is 500mg intramuscularly (IM) on days 1, 15 and 29, and once monthly thereafter.

Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs. Dose modifications to manage adverse events are detailed in the summary of product characteristics (SPC).

Treatment with alpelisib should be initiated by a physician experienced in the use of anticancer therapies.<sup>1</sup>

## Product availability date

22 December 2021

Alpelisib meets SMC end-of-life and orphan equivalent criteria.

## Summary of evidence on comparative efficacy

Alpelisib is an  $\alpha$ -specific class I phosphatidylinositol3kinase (PI3K $\alpha$ ) inhibitor. Mutations in the gene for the catalytic  $\alpha$ -subunit of PI3K (PIK3CA) can lead to activation of PI3K $\alpha$  and AKT-signalling, cellular transformation and the generation of tumours. PI3K inhibition by alpelisib can increase estrogen receptor (ER) transcription in breast cancer cells. The combination of alpelisib and the ER antagonist, fulvestrant, increases anti-tumour activity compared with either treatment alone in ER-positive, PIK3CA mutated breast cancer cell lines.<sup>1, 2</sup>

The submitting company has requested that SMC considers alpelisib when positioned for use in patients with disease progression following treatment with a cyclin dependent kinase 4/6 (CDK4/6) inhibitor plus an aromatase inhibitor.

An open-label, single arm phase II study (BYLieve) recruited adults with HR-positive, HER2-negative locally advanced or metastatic breast cancer with PIK3CA mutation not amenable to curative therapy. They had an Eastern Co-operative Oncology Group (ECOG) performance score of 2 or less and evidence of progression on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and were assigned to cohorts based on most recent previous therapy. Patients previously treated with a CDK4/6 inhibitor plus an aromatase inhibitor comprised cohort A, which is representative of

the proposed positioning within the submission, and results for this cohort are presented. All patients in cohort A received alpelisib 300mg orally once daily plus fulvestrant 500mg IM on day 1 of each 28-day cycle with an additional dose on day 15 of the first cycle. Treatment continued until disease progression or unacceptable toxicity. The primary outcome was the proportion of patients alive without disease progression (based on investigators' assessment via RECIST version 1.1) at 6 months. This was assessed in the modified full analysis set, which comprised patients with centrally-confirmed PIK3CA mutation who had at least one dose of study treatment. The primary outcome was pre-specified as clinically meaningful if the lower bound of the 95% confidence interval (CI) exceeded 30%.<sup>3</sup>

At the data cut-off 17 December 2019, median follow-up was 11.7 months. The primary outcome, proportion of patients alive without disease progression at 6 months, was 50% (61/121) and the lower limit of the 95% CI (41% to 60%) was greater than the 30% threshold for a clinically meaningful result.<sup>3</sup> In an updated analysis after 18 months follow-up, median progression-free survival (PFS) was 7.3 months, median overall survival was 26.4 months and overall response rate (defined as complete or partial response on RECIST version 1.1) was 19% (23/121), with one patient achieving a complete response.<sup>4</sup>

A double-blind, randomised, phase III study (SOLAR-1) recruited adults (postmenopausal where applicable) with HR-positive, HER2-negative advanced (locally recurrent not amenable to curative therapy or metastatic) breast cancer with ECOG performance status 0 or 1 and measurable disease on RECIST version 1.1 or at least one predominantly lytic bone lesion. They had previously had an aromatase inhibitor and had evidence of progression on or after one line of endocrine therapy in advanced disease or while on or within 12 months of (neo)adjuvant endocrine therapy (with no treatment in the advanced setting for the latter patients). Patients were assigned to cohorts based on PIK3CA mutation status: mutated versus not mutated. Within each cohort randomisation was stratified by presence of lung or liver metastases and previous CDK4/6 inhibitor, then patients were equally randomised to alpelisib 300mg orally once daily or placebo. All patients received fulvestrant 500mg IM on day 1 of 28-day cycles with an extra dose on day 15 of the first cycle. Treatment continued until disease progression or unacceptable toxicity. The primary outcome was investigator-assessed PFS, defined as the time from randomisation to disease progression as per RECIST version 1.1 criteria or death from any cause. This was primarily assessed in the PIK3CA-mutated cohort within the full analysis set, which comprised all randomised patients. The key secondary outcome, overall survival was tested in a hierarchy after PFS.<sup>2, 5</sup>

At the data cut-off 12 June 2018 (final analysis of PFS), within the PIK3CA-mutated cohort, median follow-up was 20 months. Alpelisib plus fulvestrant, compared with placebo plus fulvestrant, significantly increased PFS. At the data cut-off 23 April 2020 (final analysis of overall survival), within the PIK3CA-mutated cohort, median follow-up was 30.8 months. Alpelisib plus fulvestrant, compared with placebo plus fulvestrant, did not significantly change overall survival. These results are detailed in Table 1 along with data from the subgroup previously treated with CDK4/6 inhibitors who represent the positioning.<sup>2,5,6</sup>

**Table 1: Outcomes in selected cohorts of SOLAR-1 and BYLieve.<sup>2, 4, 5,6</sup>**

	SOLAR-1				BYLieve
	PIK3CA-mutated		PIK3CA-mutated Post CDK4/6 inhibitor		Post CDK4/6 inhibitor + AI
	Alpelisib- fulvestrant	Placebo- fulvestrant	Alpelisib- fulvestrant	Placebo- fulvestrant	Alpelisib- fulvestrant
	N=169	N=172	N=9	N=11	N=121
Progression free survival, investigator-assessed on RECIST version 1.1 <sup>a</sup>					
Events	103	129	7	10	91
Median (months)	11.0	5.7	5.5	1.8	7.3
HR (95% CI)	0.65 (0.50 to 0.85) p<0.001		0.48 (0.17 to 1.36)		-
KM estimated PFS at 12 months	46%	33%	-	-	-
Overall survival <sup>b</sup>					
Deaths	87	94	-	-	59
Median (months)	39.3	31.4	-	-	26.4
HR (95% CI)	0.86 (0.64 to 1.15), p=0.15		0.67 (0.21 to 2.18)		-
Overall response, investigator-assessed on RECIST version 1.1 <sup>a</sup>					
Events, n (%)	45 (27%)	22 (13%)	0	0	23 (19%)
- CR, %	0.6%	1.2%	0	0	0.8%
- PR, %	26%	12%	0	0	18%

CI = confidence interval; HR = hazard ratio; RECIST = Response Evaluation Criteria in Solid Tumors; CR = complete response; PR = partial response; PIK3CA = catalytic  $\alpha$ -subunit of phosphatidylinositol3kinase; CDK4/6 inhibitor = cyclin dependent kinase 4/6 (CDK4/6); AI = aromatase inhibitor; KM=Kaplan-Meier. (a) data cut-off for progression-free survival analysis in SOLAR-1 was 12 June 2018 and in BYLieve was 14 June 2021. (b) data cut-off for overall survival in SOLAR-1 was 23 April 2020 and in BYLieve was 14 June 2021.

In SOLAR-1, health related quality of life was assessed using European Organisation for Research and Treatment (EORTC) quality of life questionnaire core 30 (QLQ 30), EuroQol five dimension five level (EQ-5D-5L), and Brief Pain Inventory-Short Form (BPI-SF) questionnaires. There were no clinically relevant differences between the treatment groups during the study.<sup>2,7</sup>

Within the submission, there was a Bucher indirect treatment comparison of alpelisib plus fulvestrant versus everolimus plus exemestane using data from the SOLAR-1<sup>5-7</sup> and BOLERO-2<sup>8,9</sup> studies for the respective regimens via a linked network that also included the SoFEA<sup>10</sup> and CONFIRM<sup>11</sup> studies (which supported the base case economic analysis) and via an unanchored patient adjusted indirect comparison (which was applied to a scenario economic analysis). SOLAR-1 and BOLERO-2 data were from patients with HR-positive, HER-2 negative, PIK3CA mutated advanced breast cancer who had one prior line of therapy in the advanced setting. SoFEA and CONFIRM data were from patients with previously treated HR-positive advanced breast cancer, but results were not available for HER2-negative or PIK3CA mutated subgroups. The data were from mixed populations with HER2-positive and HER2-negative disease that may or may not have had PIK3CA mutations. In both indirect comparisons, hazard ratios (HR) for PFS and overall survival crossed one, suggesting no evidence of difference between treatments.

Other data were also assessed but remain confidential.\*

## Summary of evidence on comparative safety

A regulatory review concluded that alpelisib plus fulvestrant is more toxic than fulvestrant alone. In general terms, toxicity may be manageable, provided attention is paid to hyperglycaemia-related issues and gastrointestinal toxicity, both in the selection of patients and during treatment.<sup>2</sup>

In SOLAR-1, at data cut-off 30 September 2019, alpelisib plus fulvestrant and placebo plus fulvestrant had high rates of adverse events, 99% (282/284) and 93% (266/287) of patients, respectively, and these were treatment-related in 93% and 64%. Serious adverse events were reported by 37% and 19% of patients and were treatment related in 23% and 1.7%, respectively. Adverse events led to dose reduction or interruption in 79% and 23% of patients and to treatment discontinuation in 26% and 5.6%, respectively.<sup>2</sup>

In SOLAR-1, at data cut-off 30 September 2019, alpelisib plus fulvestrant compared with placebo plus fulvestrant was associated with higher rates of gastrointestinal adverse events, 77% versus 35%, including diarrhoea (60% versus 16%), nausea (47% versus 23%) and vomiting (28% versus 10%). It had higher rates of hyperglycaemia (67% versus 10%), rash (54% and 9.4%) and hypersensitivity reactions (16% versus 5.2%), alopecia (20% versus 2.4%) and headache (19% versus 13%). Adverse events of special interest included pancreatitis (8.1% and 6.3%), osteonecrosis of the jaw (5.6% and 1.7%), pneumonitis (1.8% and 0.3%) and severe cutaneous reactions (1.4% and 0).<sup>2</sup>

## Summary of clinical effectiveness issues

PIK3CA mutations occur in approximately 40% of patients with HR-positive, HER2-negative breast cancer. There are no currently available treatments that target this mutation, therefore patients receive standard therapy. For the majority of patients with HR-positive, HER2-negative advanced breast cancer the first-line standard of care is endocrine therapy in combination with a CDK4/6 inhibitor. After progression, selection of second-line therapy (chemotherapy versus further endocrine-based therapy) is based on disease aggressiveness, organ function and toxicity of potential therapies. Chemotherapy is usually preferred in cases of visceral involvement, when the disease is advancing at a fast pace or organ failure is imminent. The optimal sequence of endocrine-based therapy after progression on endocrine therapy plus CDK4/6 inhibitor is uncertain and depends on patient preference, previous therapy in the (neo)adjuvant or advanced settings, disease burden and duration of response to previous endocrine therapy. Treatment options include switching to another not previously used endocrine-based treatment or novel targeted therapy-based combinations. Endocrine therapies include selective ER modulators (tamoxifen), non-steroidal aromatase inhibitors (letrozole and anastrozole), steroidal aromatase inhibitors (exemestane), and ER antagonists (fulvestrant). These can be given in first, second, or later lines of therapy for advanced breast cancer. Guidelines recommend fulvestrant monotherapy as an option for second-line treatment of advanced HR-positive, HER2-negative breast cancer. Other options include targeted therapy based regimens, such as the mTOR inhibitor, everolimus, which is licensed for use in combination with exemestane for patients without symptomatic

visceral disease (or off-label everolimus-tamoxifen or everolimus-fulvestrant) and CDK4/6 inhibitors (palbociclib, ribociclib, and abemaciclib).<sup>2, 12</sup> It is unlikely that a CDK4/6 inhibitor would be used in patients who have already received this, for example within standard first-line therapy in advanced disease. Also, the positioning in patients post CDK4/6 inhibitor would limit this as a relevant comparator. Clinical experts consulted by SMC felt that alpelisib met an unmet need in this therapeutic area, namely as it is the first treatment to target the PIK3CA mutation in advanced breast cancer.<sup>1</sup>

The submitting company has requested that SMC considers alpelisib when positioned for use in patients with disease progression following treatment with a CDK4/6 inhibitor plus an aromatase inhibitor. Prior treatment with a CDK4/6 inhibitor may not be that restrictive in practice since most patients receive CDK4/6 inhibitors first-line.

In SOLAR-1, the addition of alpelisib to fulvestrant significantly increased PFS on average by 5.3 months in patients previously treated with an aromatase inhibitor who had PIK3CA mutations and it increased ORR by about 14%, but there was no significant change in overall survival. In the small subgroup (n=20) of patients who had previously received a CDK4/6 inhibitor (as per proposed positioning), PFS was increased by an average of 3.7 months, but no patients had complete or partial responses. A regulatory review considered the effects on PFS in SOLAR-1 to be clinically relevant.<sup>2,5,6</sup>

In BYLieve, at the data cut-off 17 December 2019 median follow-up was 11.7 months and 21% (25/121) of patients had died. After 18-months' follow-up, median PFS was 7.3 months and overall survival was 26.4 months.<sup>3,4</sup> Although the study population of BYLieve is more representative of the proposed positioning (prior CDK4/6 inhibitor plus aromatase inhibitor), the results are limited by the length of follow-up and uncontrolled study design. It is possible that overall survival estimates may change as data mature.

In SOLAR-1, the rate of adverse events was greater with alpelisib-fulvestrant versus fulvestrant monotherapy, including higher rates of gastrointestinal adverse events, hyperglycaemia, hypersensitivity reactions and alopecia. However, this did not translate into differences in health-related quality of life between the groups. A regulatory review noted that the safety profile was considered to have unblinded the investigators and this limited the quality of life data.<sup>2</sup>

The indirect comparisons of alpelisib-fulvestrant versus everolimus-exemestane had a number of limitations. Study selection was limited by including only everolimus-exemestane as a comparator; the company did not present any comparisons versus chemotherapy which was identified as a relevant comparator by clinical experts consulted by SMC. In the Bucher indirect comparison there was an extended network between the two relevant studies, which included studies in populations not representative of the indication or the positioning, that is, they were not solely in patients with HER2-negative disease and PIK3CA-mutated disease. HER2 status and PIK3CA mutations are potential treatment-effect modifiers. The unanchored patient adjusted indirect comparison had less population heterogeneity as it only included patients with HER2-negative disease and PIK3CA mutations. However, it had limitations characteristic of this type of analysis; due to very small sample size and effective sample size; and the matching did not fully account for baseline differences between the treatment groups. Both indirect comparisons had external validity issues as they were not conducted in populations that represent the positioning in patients

who have received a CDK4/6 inhibitor. The indirect comparisons did not assess safety or quality of life outcomes. The key limitation of both indirect comparisons related to the application of results to the economic analysis. Around the HR for PFS and overall survival there were wide CI, which crossed one and so the results do not demonstrate an advantage of alpelisib-fulvestrant. However, a HR indicative of a benefit with alpelisib-fulvestrant have been applied to the economic analyses. Overall, due to the limitations of the indirect comparisons, the results are highly uncertain.

A validated test for the presence of a PIK3CA mutation is necessary before initiating treatment with alpelisib. Molecular pathology laboratories in NHS Scotland have advised that testing for PIK3CA mutations is not current practice in patients with advanced breast cancer. The introduction of this testing may be associated with service implications.

Clinical experts consulted by SMC consider that alpelisib plus fulvestrant is a therapeutic advance due to improved outcomes relative to fulvestrant monotherapy and novel mechanism of action. They believe that it would be used in practice in place of current treatments, such as fulvestrant monotherapy, chemotherapies (capecitabine, taxanes) and everolimus-exemestane. It may be associated with service implications, in part due to the introduction of PIK3CA testing and in part due to the monitoring and management of adverse events.

### Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of alpelisib (Piqray), as an orphan-equivalent/end of life medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- HR-positive, HER2-negative locally advanced and metastatic breast cancer is incurable and reduces quality and duration of life. Patients with PIK3CA mutated disease have a poorer prognosis. They suffer physical symptoms, anxiety and emotional distress. Some may become unable to work, socialise and care for family. After progression on a CDK4/6 inhibitor in combination with an aromatase inhibitor, treatment options have limited efficacy and there is no treatment specifically targeting PIK3CA mutated disease.
- The addition of alpelisib to fulvestrant (a common therapy in this setting) improves progression-free survival and response rate. This could provide patients with a longer period when they are well and able to continue to work, care for family, socialise, plan and make memories. The psychological benefit of this for patients and their families is immeasurable. Patients are aware that alpelisib has a novel mechanism of action specifically targeting PIK3CA mutated disease and accessing this would provide reassurance that their treatment is optimal.
- Alpelisib is associated with adverse effects, such as hyperglycaemia, that may be an additional consideration for patients and the service. However, some patients are happy to manage these to obtain the benefits of improved progression-free survival. A discussion of adverse effects is necessary for informed choice of therapy.

- PACE participants noted that alpelisib would be used in a select group of patients. It was considered that alpelisib may not be suitable for all patients, in view of its toxicity profile. However, it could be particularly useful for a small group of patients who are able to manage adverse events and obtain substantial progression-free survival. It may be particularly useful for those who have adverse effects with or contraindications to other treatments.

### **Additional Patient and Carer Involvement**

We received patient group submissions from METUPUK and Breast Cancer Now. METUPUK is a charitable incorporated organisation and Breast Cancer Now is a registered charity. Breast Cancer Now has received 0.65% pharmaceutical company funding in the past two years, including from the submitting company. METUPUK has not received any pharmaceutical company funding in the past two years. Representatives from both organisations participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

### **Summary of comparative health economic evidence**

A cost-utility analysis was presented evaluating alpelisib plus fulvestrant within a restricted subpopulation of the alpelisib licensed indication, as described above. Comparison was provided against everolimus plus exemestane. No comparison with fulvestrant monotherapy was presented within the company's original submission but was received upon request and is presented below.

A standard three-state partitioned survival model was used to model the survival of patients on the two treatment regimens across a 40-year lifetime horizon. The model represented time spent in the progression-free health state (subdivided by whether patients were on or off treatment), followed by movement into a 'progressed disease' health state where patients remained until death.

Although a randomised controlled trial of alpelisib plus fulvestrant versus fulvestrant is available, the economic model utilised the single-arm BYLieve study to extrapolate PFS, overall survival and time to treatment discontinuation (TTD) for alpelisib and fulvestrant.<sup>3,4</sup> As described earlier, indirect comparisons were used to estimate the relative effectiveness of the alpelisib regimen versus everolimus plus exemestane. The company also conducted a Population-Adjusted Indirect Comparison (PAIC) and a matching/weighted analysis of the US Flatiron clinicogenomics database to provide supporting evidence. The PAIC analysis was presented as an economic scenario analysis, although the matching/weighted analysis using Flatiron was not.

Standard parametric distributions and 1-, 2- and 3-knot spline-based models were fitted to the alpelisib plus fulvestrant Kaplan Meier data. These were evaluated according to statistical goodness-of-fit, and inspection of hazard profiles and visual fit. Clinical plausibility was also considered, including via interviews with experts consulted by the submitting company. As a result, the company selected a lognormal distribution for extrapolation of PFS, a log-logistic distribution for overall survival and an exponential distribution for TTD. PFS and overall survival estimates were obtained for everolimus and exemestane by adjustment of the alpelisib extrapolated survival curve using the hazard ratio from the indirect comparison (on the

assumption that the proportional hazards assumption holds, despite the lognormal and log-logistic distributions both being accelerated failure time models). TTD for everolimus and exemestane was then derived by applying a hazard ratio to the PFS curves for the everolimus regimen, after deeming that the proportional hazards assumption holds and assuming that treatment duration is equal for everolimus and exemestane. A lifetime treatment effect was implicitly assumed in the base case.

Utility estimates for the PFS health state (both on and off-treatment) were derived from the SOLAR-1 study, which collected EQ-5D data and valued according to UK societal preferences.<sup>6</sup> Due to limited follow-up beyond progression, the submitting company relied upon a published source (Mitra et al. 2016) to estimate utility beyond progression (0.69).<sup>13</sup> A disutility of 0.11 was applied in the last three months of life. Age-specific declines in utility were also applied. Adverse event disutilities were assumed to be reflected in the source data from SOLAR-1.

Costs used in the analysis included those of medicines acquisition and administration, an assumed average monthly cost for subsequent lines of treatment of £1,500 and a range of healthcare resource costs including primary and secondary care consultations and procedures associated with disease monitoring and adverse event management. The cost to identify one patient with a PIK3CA mutation was adjusted for the estimated prevalence of PIK3CA mutations among breast cancer patients. Medicines costs were adjusted based upon relative dose intensities from the respective studies, and time on treatment estimated using the extrapolated TTD curves described above.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

A PAS discount is also in place for one or more preparations of everolimus. An estimate of the PAS discount for everolimus and the lowest priced available generic formulation of fulvestrant was included in the results for decision-making. SMC is unable to publish these results owing to commercial in confidence concerns. Base case and key scenario analysis results at list price for all medicines have therefore been presented in Table 2 below. The base case incremental cost-effectiveness ratio (ICER) at list prices for all medicines was £70,027 versus everolimus plus exemestane. The estimated life year gained was 0.76 years.

**Table 2: Base case results and key sensitivity analyses versus everolimus plus exemestane**

			<b>ICER (£ per QALY)</b>
	<b>Base case setting</b>	<b>Scenario</b>	<b>List price</b>
<b>0</b>	<b>Base case</b>	<b>Not applicable</b>	<b>70,027</b>
<b>1</b>	Alpelisib plus fulvestrant OS extrapolation: log-logistic	RCS 1 Weibull	132,997
<b>2</b>	Alpelisib TTD extrapolation: exponential	Lognormal	79,417

3	Post-progression survival (PPS)	Reduced by 25% (£1,125/month)	65,542
4	medicine costs: £1,500/month	Increased by 25% (£1,875/month)	74,512
5	PPS utility estimate: based on Mitra et al. 2016	PPS utility estimate: based on SOLAR-1 study	73,366

**Abbreviations:** PAS: patient access scheme; OS: overall survival; TTD: time to discontinuation;  
PPS: post-progression survival; QALY: quality-adjusted life year

As mentioned above, the company provided results using fulvestrant monotherapy as comparator upon request. The base case incremental cost-effectiveness ratio (ICER) at list prices for all medicines was £200,839. The estimated life year gained was 0.18 years.

There were a number of limitations with the analysis:

- Following the New Drugs Committee meeting, the submitting company provided revised base case results and sensitivity analysis to show the impact of using the updated data cut from the single arm ByLieve study. These updated results were considered by SMC and resulted in lower cost-effectiveness ratios given higher predicted health benefits (QALYs and life years gained). While the updated data and results were noted, significant concerns remained around the uncertainty with the estimated benefits given the nature of the comparative evidence base, as discussed above.
- There are some uncertainties regarding the relevant comparators in NHS Scotland. SMC clinical expert responses suggest that fulvestrant monotherapy is a relevant comparator within NHSScotland and thus it was helpful that this analysis was provided on request by the submitting company.
- SMC clinical experts also highlighted the use of chemotherapies (capecitabine, taxanes) in this patient population. No results were provided using chemotherapy as a comparator. The cost-effectiveness of alpelisib plus fulvestrant versus chemotherapies is therefore unknown.
- In common with the majority of oncology submissions, the extrapolation of overall survival is a key uncertainty and one which could result in a significant increase in the ICER. Although a systematic approach was taken to selecting the base case model, there are additional survival distributions which could be equally plausible and result in a lower estimate of long-term survival with alpelisib plus fulvestrant leading to an increased ICER.
- An ongoing treatment effect has been assumed across the time horizon. This may be optimistic in the absence of data; additional sensitivity analysis provided by the company on request showed an upwards influence on the ICER if the effect waned at 5 years.
- The approach to handling costs of subsequent treatment may ultimately overestimate the average monthly cost of treatment in the post-progression health state. Although conservative, it may be preferable to model the costs and duration of each treatment individually. This would likely counteract, to a degree, some of the increases in the ICER

introduced by any changes addressing the limitations highlighted above.

The Committee considered the benefits of alpelisib plus fulvestrant in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as alpelisib plus fulvestrant is an orphan equivalent and end-of-life medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee was unable to accept alpelisib plus fulvestrant for use in NHSScotland.

*Other data were also assessed but remain confidential.\**

### Additional information: guidelines and protocols

In 2021, the European Society of Medical Oncology (ESMO) published ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. For patients with HR-positive, HER2-negative disease the first-line standard of care is endocrine therapy in combination with a CDK4/6 inhibitor, since it is associated with substantial PFS and OS benefits and maintained or improved quality of life. Endocrine therapy alone in the first-line setting should be reserved for the small group of patients with comorbidities or performance status that precludes the use of CDK4/6 inhibitor combinations. After progression, selection of second-line therapy (chemotherapy versus further endocrine-based therapy) should be based on disease aggressiveness, extent and organ function, and consideration of associated toxicity profiles. Alpelisib-fulvestrant is a treatment option for patients with PIK3CA-mutant tumours (in exons 7, 9 or 20), prior exposure to an aromatase inhibitor ( $\pm$  CDK4/6 inhibitors) and appropriate HbA1c levels. Everolimus-exemestane is an option since it significantly prolongs PFS. Tamoxifen or fulvestrant can also be combined with everolimus. PARP inhibitor monotherapy (olaparib or talazoparib) should be considered for patients with germline pathogenic BRCA1/2 mutations and as an option for those with somatic pathogenic or likely pathogenic BRCA1/2 or germline PALB2 mutations. At least two lines of endocrine-based therapy are preferred before moving to chemotherapy. In patients with imminent organ failure, chemotherapy is a preferred option.<sup>12</sup>

In August 2017, the National Institute for Health and Care Excellence (NICE) updated clinical guideline number 81, Advanced Breast Cancer: diagnosis and treatment. This recommends endocrine therapy as first-line treatment for the majority of patients with ER-positive advanced breast cancer. On disease progression, offer systemic sequential therapy to the majority of patients with advanced breast cancer who have decided to be treated with chemotherapy.<sup>14</sup>

### Additional information: comparators

Fulvestrant monotherapy, everolimus-exemestane, (off label, everolimus-tamoxifen and everolimus-fulvestrant), chemotherapies (for example, capecitabine or paclitaxel).

### Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Alpelisib	300mg orally once daily	£56,202
Fulvestrant	500mg intramuscularly on days 1, 15 and 29, then once monthly thereafter	(£56,725, year 1)

*Costs from BNF online on 03 November 2022. Costs do not take patient access schemes into consideration.*

### Additional information: budget impact

The submitting company estimated there would be 71 patients eligible for treatment with alpelisib in year 1 and 73 patients in year 5 to which confidential estimates of treatment uptake were applied. The predicted budget impacts with and without the PAS remain confidential.

*Other data were also assessed but remain confidential.\**

## References

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This assessment is based on data submitted by the applicant company up to and including 16 September 2022.

*\*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*<https://www.scottishmedicines.org.uk/about-us/policies-publications/>

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

**Advice context:**

*No part of this advice may be used without the whole of the advice being quoted in full.*

*This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.*