NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Alpelisib with fulvestrant for treating hormone receptor-positive, HER2-negative, PIK3CA-mutated advanced breast cancer

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using alpelisib in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

Has all of the relevant evidence been taken into account?
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
Are the recommendations sound and a suitable basis for guidance to the NHS?
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

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Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
At that meeting, the committee will also consider comments made by people who are not consultees.
After considering these comments, the committee will prepare the final appraisal document.

- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using alpelisib in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 21 April 2022

Second appraisal committee meeting: 10 May 2022

Details of membership of the appraisal committee are given in section 5

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1 Recommendations

1.1 Alpelisib plus fulvestrant is not recommended, within its marketing authorisation, for treating hormone receptor-positive, HER2-negative, PIK3CA-mutated, locally advanced or metastatic breast cancer in women after menopause, and men, who have disease progression after endocrine-based therapy.

1.2 This recommendation is not intended to affect treatment with alpelisib plus fulvestrant that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Current treatment for hormone receptor-positive, HER2-negative, PIK3CA-mutated, locally advanced or metastatic breast cancer is usually only everolimus with exemestane. Alpelisib with fulvestrant is a new treatment for this condition.

There is no direct evidence comparing alpelisib plus fulvestrant with everolimus plus exemestane. The clinical trial evidence presented either did not compare alpelisib plus fulvestrant with other treatments, or it only included a small number of people who would be eligible for alpelisib with fulvestrant in clinical practice. Indirect comparisons suggest that alpelisib plus fulvestrant may be more effective than everolimus plus exemestane, but these analyses are highly uncertain.

The results of the economic model show that alpelisib plus fulvestrant is not a cost-effective use of NHS resources. Also, the limitations in the clinical evidence mean that the results are very uncertain. So, alpelisib plus fulvestrant cannot be recommended for routine use.

Issues with the clinical evidence would not be resolved by ongoing studies. So, alpelisib plus fulvestrant cannot be recommended for use in the Cancer Drugs Fund.

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2 Information about alpelisib

Marketing authorisation indication

2.1 Alpelisib (Piqray, Novartis Pharmaceuticals UK) has a marketing authorisation for use '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'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for alpelisib.

Price

2.3 The company's list price is £4082.14 per 56-pack of 150 mg film-coated tablets (BNF online, accessed March 2022). The average cost of a course of combination treatment at list price is £6,170.70 for the loading dose and £5,126.42 for the following cycles.

The company has a commercial arrangement, which would have applied if the technology had been recommended.

3 Committee discussion

The appraisal committee considered evidence submitted by Novartis, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

Clinical need and treatment pathway

There is a population who could benefit from alpelisib plus fulvestrant

3.1 Advanced breast cancer is incurable and the aim of treatment is to delay progression and extend survival. Patient experts explained that being

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diagnosed with advanced breast cancer is extremely difficult for people and their family and friends. It can cause considerable anxiety and fear. These feelings can negatively affect mental health. Women who have been through the menopause, and men, who do not need urgent chemotherapy treatment are offered 1 of 3 CDK4/6 inhibitor treatments (abemaciclib, ribociclib or palbociclib), each with an aromatase inhibitor, as initial treatment. This is in line with NICE's guideline on advanced breast cancer. See NICE's technology appraisal guidance on abemaciclib, ribociclib or palbociclib. Clinical experts noted that women with hormone receptor-positive, HER2-negative advanced breast cancer who have not been through menopause, or who are going through perimenopause, will be offered ovarian suppression. This is to mimic a natural menopause, so they are also eligible for a CDK4/6 inhibitor plus an aromatase inhibitor. After initial treatment with a CDK4/6 inhibitor plus an aromatase inhibitor, current treatment options are limited. People can have exemestane plus everolimus (see NICE's technology appraisal guidance on everolimus with exemestane for treating advanced breast cancer after endocrine therapy), but clinical experts noted that adverse events associated with everolimus limit its use. Because of this, chemotherapy is sometimes used instead. However, clinical experts noted overall that people and clinicians are looking for options to delay the need for cytotoxic chemotherapy. The committee concluded that an additional treatment option for this population would be welcome.

Targeted treatment options are valued by people with advanced breast cancer and clinicians

3.2 Mutations of PIK3CA are found in around 30% to 40% of oestrogen receptor-positive, HER2-negative breast cancers. The company noted that PIK3CA-mutated breast cancer may be more resistant to endocrine therapy. Clinical experts explained that they are keen to offer targeted treatments for people with advanced breast cancer, but these options have been limited except for drugs acting on hormone receptors. They noted that alpelisib, which is used with fulvestrant, is the first targeted

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treatment option for advanced breast cancer that has a PIK3CA mutation. Clinical experts stated that the toxicity profile of alpelisib plus fulvestrant is notably worse than that seen with a CDK4/6 inhibitor. However, for people who can tolerate it, alpelisib plus fulvestrant is another step in delaying cytotoxic chemotherapy, which has worse adverse events. They explained that this allows people to stay well for longer, for themselves and as carers for others. Patient experts noted that for people with PIK3CA-mutated advanced breast cancer, knowing a drug was targeted to their mutation was very powerful and had a positive emotional impact. Patient experts commented that PIK3CA mutations are not routinely tested for in the NHS. However, the Cancer Drugs Fund clinical lead stated that, from April 2022, genomic testing for PIK3CA mutation should be included in the National Genomic Test Directory and so would be funded in the NHS shortly, as long as there are no implementation issues. The clinical experts noted that PIK3CA testing can be done at any point in the treatment pathway for breast cancer, so if it is not done or available at diagnosis it could be done later when exploring treatment options. The committee noted that, while PIK3CA mutation testing had not been routinely available, this situation is changing and PIK3CA mutation status will soon be routinely identified in clinical practice. It concluded that targeted treatment options for identifiable mutations are valued by people with advanced breast cancer and clinicians.

The relevant place in the treatment pathway is second line after disease progression on a CDK4/6 inhibitor plus an aromatase inhibitor

3.3 The company positions alpelisib plus fulvestrant 'after disease progression following a CDK4/6 inhibitor' in its base case. This is narrower than the marketing authorisation for alpelisib plus fulvestrant, which is 'after disease progression following endocrine-based therapy'. Clinical experts stated that a CDK4/6 inhibitor plus an aromatase inhibitor, with or without chemotherapy, is standard practice for the first-line treatment of hormone receptor-positive, HER2-negative advanced breast cancer, with or without a PIK3CA mutation (section 3.1). They noted that this would be

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offered to most people except those who are unable to tolerate treatment with a CDK4/6 inhibitor. It is more appropriate for these people to have endocrine monotherapy, with or without chemotherapy. Therefore, the clinical experts considered that the company's positioning of alpelisib plus fulvestrant was in line with expected clinical use. The committee concluded that the company's positioning of alpelisib with fulvestrant as second line after disease progression on a CDK4/6 inhibitor plus an aromatase inhibitor was appropriate.

The relevant comparator is everolimus plus exemestane

3.4 The company used everolimus plus exemestane as its base-case comparator. Clinical experts noted that because of tolerability issues with exemestane plus everolimus, some people have oral, single-agent chemotherapy with capecitabine instead. This has a lower toxicity burden than other chemotherapies. Some people with advanced breast cancer may have oral capecitabine or more cytotoxic chemotherapy, instead of everolimus plus exemestane, as second-line treatment after a CDK4/6 inhibitor and an aromatase inhibitor. The Cancer Drugs Fund clinical lead noted that most people have everolimus plus exemestane in NHS practice. The committee concluded that everolimus plus exemestane is the most relevant comparator for this appraisal.

Clinical evidence

Alpelisib with fulvestrant was investigated in 2 studies, BYLieve and SOLAR-1, but only BYLieve is generalisable to UK clinical practice

3.5 Alpelisib with fulvestrant was studied in 1 phase 2 non-randomised, open label, non-comparative study (BYLieve) and 1 phase 3 randomised controlled trial (SOLAR-1). The evidence from these studies submitted by the company is in hormone receptor-positive, HER2-negative advanced breast cancer that has a confirmed PIK3CA mutation. The clinical experts noted that almost everyone had stage 4 breast cancer on entry to the studies. BYLieve included 121 people with breast cancer progression on

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or after a CDK4/6 inhibitor with an aromatase inhibitor. People had treatment with alpelisib plus fulvestrant as first-, second-, third- or later-line treatment for advanced disease. Clinical experts noted that BYLieve is relevant to UK clinical practice because 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. The committee concluded that the population of BYLieve was generalisable to the NHS.

Clinical evidence for alpelisib plus fulvestrant after a CDK4/6 inhibitor plus an aromatase inhibitor is uncertain because it is based on 1 single-arm study

3.6 The primary outcome of BYLieve is progression-free survival. Secondary outcomes include overall survival, objective response rate, clinical benefit rate and duration of response. BYLieve included 121 people who had treatment with alpelisib plus fulvestrant after a CDK4/6 inhibitor plus an aromatase inhibitor. Some of these people had alpelisib plus fulvestrant second line (section 3.5). The median duration of follow up was 11.7 months. SOLAR-1 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) for all lines of treatment (n=121). In people who had alpelisib plus fulvestrant second line, the results suggest it could be clinically effective. The company considers that the data is confidential so it cannot be reported here. However, the relative effectiveness is uncertain because of the lack of comparative data to assess alpelisib plus fulvestrant effectiveness with other treatment options. The committee concluded that evidence from BYLieve suggests that alpelisib plus fulvestrant may be clinically effective, but this evidence was highly uncertain because of the lack of comparative data.

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SOLAR-1 was limited because it only included a small number of people relevant to this appraisal

3.7 SOLAR-1 included 341 people with PIK3CA-mutated breast cancer that recurred or progressed on or after treatment with an aromatase inhibitor. It compared alpelisib plus fulvestrant with placebo plus fulvestrant. But clinical experts noted that fulvestrant monotherapy is not used in NHS practice and does not reflect standard care for second-line treatment of hormone receptor-positive, HER2-negative, advanced breast cancer (see section 3.1). Most people had treatment with alpelisib plus fulvestrant as first- or second-line treatment for advanced disease. People who had alpelisib plus fulvestrant or placebo plus fulvestrant as second-line treatment after an aromatase inhibitor from now are called the second-line proxy population. Clinical experts noted that for most people in SOLAR-1, overall and in the second-line proxy population, the data was not relevant to UK clinical practice. This is because very few people had an aromatase inhibitor with a CDK4/6 inhibitor before treatment with alpelisib plus fulvestrant or placebo plus fulvestrant. The committee noted that only 20 people had a CDK4/6 inhibitor with an aromatase inhibitor, and so only these 20 people are relevant to this appraisal. In SOLAR-1, median duration of follow up was 42.4 months for the final data-cut point. The results suggested that alpelisib plus fulvestrant may be more effective than placebo plus fulvestrant when given as second-line treatment. Data is considered confidential by the company and cannot be reported here. The committee concluded that this study was limited because it only included 20 people relevant to this appraisal.

Adverse effects

Alpelisib plus fulvestrant is associated with grade 3 or higher adverse events that need additional monitoring

3.8 Not everyone will be able to tolerate treatment with alpelisib plus fulvestrant (section 3.2). In BYLieve and SOLAR-1, more than 60% of

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people who had alpelisib plus fulvestrant had a treatment-emergent adverse event of grade 3 or higher. Clinical experts noted that a grade 3 or 4 rash is a rash that covers more than half the body, seen in 9% to 10% of people who had alpelisib plus fulvestrant. They also noted that grade 3 or 4 diarrhoea, seen in 6% to 7% of people who had alpelisib plus fulvestrant, is difficult for people to tolerate. Clinical experts explained that grade 3 or higher hyperglycaemia means that older people or those with a high body mass index or obesity might need weekly testing and follow up during initial treatment. This was seen in around 30% of people who had alpelisib plus fulvestrant. The experts noted that these adverse events and the need for additional monitoring is a burden to both patients and clinicians. The patient expert noted that they were aware that someone who had treatment with alpelisib plus fulvestrant had reported struggling with diarrhoea and having blood sugars monitored weekly. However, this person felt that the benefits of treatment outweighed any discomfort they were experiencing. The ERG noted that 14% of people in BYLieve stopped treatment because of adverse events (based on full analysis set [n=127]). Also, 23% of the alpelisib plus fulvestrant group and 4% of the placebo plus fulvestrant group stopped treatment in SOLAR-1 because of treatment-related adverse events (based on safety set [n=571]). Clinical experts stated that alpelisib with fulvestrant could be difficult for some people to tolerate. However, over time clinicians are developing ways to mitigate toxic effects and are limiting who has treatment or stopping treatment if adverse events are not manageable. The committee concluded that alpelisib plus fulvestrant is associated with grade 3 or higher adverse events that may need additional monitoring.

Indirect treatment comparison

The company did an indirect treatment comparison using the Bucher method

3.9 There were no trials directly comparing alpelisib plus fulvestrant with exemestane plus everolimus. So, the company presented indirect

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analyses, including an indirect treatment comparison using the Bucher method (used in the company base case) and a population adjusted indirect comparison (used in exploratory analyses), for outcomes including overall survival and progression-free survival. The Bucher analysis included publicly available data from 4 trials. It took known hazard ratios for alpelisib plus fulvestrant compared with placebo plus fulvestrant from SOLAR-1. It then linked these to the BOLERO-2 study of everolimus plus exemestane compared with exemestane monotherapy via 2 other trials, CONFIRM and SoFEA. The ERG explained that this approach is a 'reverse' Bucher method when known hazard ratios for the treatment being studied are used to calculate hazard ratios for the comparator group. It is more usual to know the comparator hazard ratios and use these to calculate hazard ratios for the treatment being studied. The ERG noted that the company restricted the dataset of BOLERO-2 to the second-line population with a PIK3CA mutation based on tumour tissue sample. This led to 92% of patients being excluded from the analysis. The committee noted that if PIK3CA mutation based on plasma sampling was included it may be possible to increase the number of people included in the analysis. The company stated that the Bucher analysis showed that alpelisib plus fulvestrant was associated with better efficacy in terms of both progression-free survival and overall survival compared with everolimus plus exemestane. The results of the analysis are confidential and cannot be reported here. The ERG and committee noted that the confidence intervals of the hazard ratios presented for these comparisons were very wide, which makes them unreliable. The committee questioned the internal validity of the Bucher results because when comparing placebo plus fulvestrant with everolimus plus exemestane, 1 treatment group was favoured for progression-free survival and the other group was favoured for overall survival. Clinical experts noted that there is a lack of robust data for treatments used after first line. Some of the comparisons that would help validate the analysis have not been done in trials.

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The results of the Bucher analysis are highly uncertain for several reasons

3.10 The ERG noted that across the 4 trials of hormone receptor-positive advanced breast cancer included in the Bucher indirect treatment comparison, the patient populations had differences including line of treatment and HER2 status. Almost no one had previously had a CDK4/6 inhibitor with an aromatase inhibitor and only SOLAR-1 included PIK3CA-mutated breast cancer. The ERG's clinical expert commented that HER2 status may be an important effect modifier for alpelisib plus fulvestrant compared with everolimus plus exemestane. At the request of the ERG, the company did the same Bucher analysis but used a subpopulation of SoFEA that included people with known HER2-negative status. The committee noted that in this subset analysis a treatment effect in favour of alpelisib plus fulvestrant was seen but this was reduced compared with the overall analysis and was uncertain (section 3.9). The company explained that it preferred not to restrict the population from SoFEA in this way so as not to reduce the patient numbers. It also noted that it is not known whether HER2 status is an effect modifier for alpelisib plus fulvestrant compared with everolimus plus exemestane. The company noted that technology appraisals of a CDK4/6 inhibitor plus an aromatase inhibitor did not restrict analyses to a HER2-negative population. The committee concluded that the results of the Bucher analysis are highly uncertain for several reasons:

- A reverse Bucher was done, deriving comparator hazard ratios from those known for alpelisib plus fulvestrant.
- Hazard ratios for the indirect comparison of alpelisib plus fulvestrant with everolimus plus exemestane had very wide confidence intervals, which means they are unreliable.
- Hazard ratios for the indirect comparison of placebo plus fulvestrant with everolimus plus exemestane may lack face validity.

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- There is a lack of generalisability of the 4 trials (patient populations differed including in terms of PIK3CA-mutation status, and there was a lack of previous treatment with a CDK4/6 inhibitor plus an aromatase inhibitor).
- There is a potential for HER2 status to be an effect modifier.

Alpelisib plus fulvestrant may be more effective than everolimus plus exemestane, but the results of the indirect analyses are highly uncertain

3.11 As noted in section 3.10, the indirect treatment comparison was highly uncertain. The company stated that favourable results for alpelisib plus fulvestrant were support by real-world evidence. It noted that data from the Flatiron database supports progression-free survival with alpelisib plus fulvestrant in BYLieve being better than that with standard care after a CDK4/6 inhibitor. To support this, the company presented a matching/weighting analysis of BYLieve compared with standard care. The ERG noted that the Flatiron database is a real-world dataset from the US where standard care may differ from that in England. The company also presented an unanchored patient-adjusted indirect comparison of the progression-free survival and overall survival results for alpelisib plus fulvestrant from SOLAR-1 and everolimus plus exemestane from BOLERO-2. The results of the analysis are confidential and cannot be reported here. The company and ERG noted that the results of the patient-adjusted indirect comparison should be interpreted with caution because of the small sample sizes. The committee concluded that alpelisib plus fulvestrant may be more effective than everolimus plus exemestane, but the results of the indirect analyses are highly uncertain.

The company's economic model

The company's economic model is suitable for decision making

3.12 The company submitted a partitioned survival model to estimate the cost effectiveness of alpelisib plus fulvestrant compared with everolimus plus exemestane. It had 3 health states: progression-free, progressed, and

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dead. The model had a lifetime time horizon (40 years). The committee considered that the partitioned survival model is a standard approach to estimate the cost effectiveness of cancer drugs and is suitable for decision making.

The modelling of overall survival and progression-free survival is highly uncertain

3.13 The company's model linked progression-free survival distributions to overall survival by using an indirect treatment comparison. The company selected a log-logistic function to extrapolate overall survival and a log-normal function to extrapolate progression-free survival for alpelisib plus fulvestrant from the second-line population in BYLieve. For everolimus plus exemestane, the hazard ratio for overall survival and progression-free survival from the Bucher analysis was applied to the alpelisib plus fulvestrant model. The company explained that it selected log-logistic for the overall survival curve based on goodness-of-fit statistics, visual inspection of fitted distributions, to be consistent with the assumption that projected overall survival is equal to or higher than projected progression-free survival, and after examination of hazard plots and validation by clinical experts. It explained that it selected log-normal for progression-free survival based on goodness-of-fit statistics, visual inspection of fitted distributions, hazard functions, time-dependent hazard ratios, diagnostic plots for treatment effects, and clinical plausibility. Clinical experts thought that the projections for overall survival and progression-free survival in the model were reasonable. They noted that a long tail to the modelled overall survival is as might be expected in breast cancer. The ERG was generally satisfied with the survival functions used, although it noted that the Gompertz and Weibull provided slightly better model fit than log-logistic for overall survival. The ERG also explained that the log-logistic model appears to overestimate overall survival for alpelisib plus fulvestrant group after around 1.5 years, although very few events occur beyond this. The ERG explored the impact of alternative extrapolations for overall survival and progression-free survival, which showed that the incremental cost-

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effective ratio (ICER) was very sensitive to these alternative extrapolations. The committee noted that there were a number of issues with the data underpinning the survival extrapolations. For the alpelisib plus fulvestrant arm, the clinical data underpinning this was either non-comparative (section 3.6) or for very few patients (section 3.7). For the everolimus plus exemestane arm, data was taken from the Bucher indirect analysis, which was highly uncertain. The committee concluded that the overall survival and progression-free survival estimates were highly uncertain.

Modelled relative treatment effects are highly uncertain

3.14 Relative treatment effects of alpelisib plus fulvestrant and everolimus plus exemestane were derived from a Bucher indirect treatment comparison (section 3.9). The ERG's clinical experts considered that the relative treatment effects of alpelisib plus fulvestrant compared with everolimus plus exemestane were plausible. The committee and the ERG recalled that alpelisib plus fulvestrant may be more effective than everolimus plus exemestane. However, given the uncertainty in the underpinning data, quantifying the treatment effect and quality-adjusted life year (QALY) estimates would be highly uncertain (section 3.9 to 3.11). The ERG noted that the Bucher model was similar to a fixed effects model in that it assumes no between-study variation, which might not be reasonable. It noted that in a fixed effect model, confidence intervals can underestimate the true uncertainty. However, if the assumption for no between-study variation was relaxed, confidence intervals would be even wider. The ERG also explained that because the network of the Bucher analysis involves a single chain of evidence (with no closed loops), and each comparison is informed by only 1 trial, it is not possible to assess the consistency of the evidence. The committee concluded that the relative treatment effect of alpelisib plus fulvestrant compared with everolimus plus exemestane was highly uncertain.

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The model assumes an indefinite treatment effect which is optimistic

3.15 The model has a lifetime time horizon (section 3.12). It assumes that the treatment effects of alpelisib plus fulvestrant compared with everolimus plus exemestane are indefinite with no loss of treatment effect over time. The clinical experts stated that it was not reasonable to say there is indefinite treatment effect. The ERG and its own clinical experts considered an indefinite duration of treatment effect to be optimistic. The ERG noted that the company did not present evidence to support the assumption of no treatment waning effect. The ERG did additional sensitivity analyses to explore the possibility that the treatment effect of alpelisib plus fulvestrant for progression-free survival and overall survival wanes and switches to that of everolimus plus exemestane at 3 or 5 years. These analyses led to large increases in the ICER. The company stated that it is more consistent with the model, where hazard ratios for everolimus plus exemestane are derived from those for alpelisib plus fulvestrant, to apply the waning assumption to everolimus plus exemestane. The company therefore preferred to switch the treatment effect for everolimus plus exemestane to that of alpelisib plus fulvestrant at 3 and 5 years. The committee noted that this reduced the increases in the ICER that are seen when taking account of waning. The committee noted that it is more usual to switch the treatment effect of the drug being studied, in this case alpelisib plus fulvestrant, to that of the comparator when taking account of waning. It also noted that switching the treatment effect for everolimus plus exemestane to that of alpelisib plus fulvestrant is clinically implausible because it means the treatment effect of everolimus plus exemestane will increase over time. The committee concluded that the assumption of an indefinite treatment effect is optimistic.

It is reasonable to assume equal utilities for both treatments

3.16 Across the different health states in the model, the company assumed equal utilities for alpelisib plus fulvestrant and everolimus plus

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exemestane (the utility values are confidential). The ERG and clinical experts agreed that this assumption is reasonable. The ERG noted that the company does not include utility decrement for grade 3 or 4 adverse events. Alpelisib plus fulvestrant is associated with grade 3 or higher adverse events and these events and the need for additional monitoring is a burden to patients (section 3.8). However, the clinical experts advised that everolimus with exemestane is associated with some toxicity. The committee concluded that it is reasonable to assume equal utilities for both treatments.

The appropriate utility value after disease progression is uncertain and may be overestimated by the company

3.17 The company used SOLAR-1 to derive utility values in the pre-progression and death health states. However, SOLAR-1 had limited health-related quality-of-life data after disease progression. Therefore, in its base case, the company used a utility value for the modelled health state after disease progression from a publication by Mitra et al. (2016). The ERG explained that the value used from Mitra is likely to overestimate utility after disease progression because it is based on people with hormone receptor-positive, HER2-negative advanced and metastatic breast cancer having treatment at third line or later. The ERG preferred to use a 0.51 post-progression utility value from Lloyd et al. (2006) that has been used in previous technology appraisals. The company noted that Lloyd is outdated and does not reflect the treatment landscape and people having treatment today. It noted that Mitra was used and preferred to Lloyd in the recent NICE technology appraisal guidance on abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy. It also stated that before the committee meeting it did interviews with healthcare professionals. In these interviews Mitra et al. was considered the utility value that most reflected NHS practice. The ERG's clinical experts noted that in SOLAR-1, which had a post-progression utility value close to that of Mitra, the value was consistent with people who have radiological progression

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on 1 to 3 lines of treatment without a significant change in health-related quality of life. The Cancer Drugs Fund clinical lead noted that the post-progression utility value is assumed constant for the duration of the post-progression health state and does not take account of whether people have additional treatments. As such, the Mitra value is optimistic and may overestimate utility for most of the post-progression state. The committee noted that it may support a high utility value after disease progression because people may have several further lines of treatment and asymptomatic progression is common. However, the true value is uncertain. The ERG did exploratory analyses to consider a utility value around midway between those of Lloyd and Mitra, which led to a large increase in the company base-case ICER. The committee concluded that the appropriate utility value for the modelled health state after disease progression is uncertain and may be overestimated by company.

Treatment costs after disease progression are reasonable but uncertain

3.18 The company assumed a fixed cost of £1,500 per month for 'all future treatment-related costs' for people after disease progression, excluding end of life care. It noted that this is based on NICE's technology appraisal guidance on ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy. The ERG noted that it is unclear whether the company assumption is reasonable. It noted that lower estimated post-progression treatment costs (£1,140 to £1,200) were preferred by the committee in NICE's technology appraisal guidance on ribociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer. The ERG suggested that it may be more appropriate to apply subsequent-line treatment costs based on observed post-progression treatments in the alpelisib plus fulvestrant clinical studies. Clinical experts noted that it is reasonable to base treatment costs after disease progression on those assumed for ribociclib plus fulvestrant. The ERG had explored alternative costs assumptions (increasing and decreasing costs by £750), which led to minor changes to

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the ICER. The committee concluded that treatment costs after disease progression are uncertain, but are not unreasonable and not a major driver of cost-effectiveness results.

End of life

Whether alpelisib plus fulvestrant meets end of life criteria has not been robustly shown by the evidence presented

3.19 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. The clinical experts considered that people with hormone receptor-positive, HER2-negative, PIK3CA mutated advanced breast cancer whose disease had progressed on a CDK4/6 inhibitor with an aromatase inhibitor are unlikely to live longer than 24 months. However, they considered that it was less certain whether alpelisib plus fulvestrant extended life by 3 months or more. Alpelisib plus fulvestrant had not been directly compared with everolimus plus exemestane and the treatment effect estimates for alpelisib plus fulvestrant from the indirect analyses are highly uncertain (section 3.14). The committee noted that to meet end of life criteria, it needed to be satisfied that estimates are robust and it was not satisfied that they were. The ERG noted that end of life criteria are met for the company's base case and the ERG's preferred analysis using the deterministic model. However, the criteria were not met using the company's probabilistic base-case model or if only people with HER2-negative cancer from the SoFEA study were included in the Bucher analysis (deterministic or probabilistic model). The committee preferred to use the probabilistic model but noted that it would take both ICERs into account in its decision making (section 3.20). It concluded that it was possible that alpelisib plus fulvestrant met end of life criteria, but this was not shown robustly enough by the evidence so far presented.

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Cost-effectiveness results

The committee preferred to use the probabilistic model because this took account of uncertainty in the modelling

3.20 The committee noted that probabilistic methods are generally considered most appropriate for decision making because they allow for full expression of the uncertainty in model parameters. In contrast, a deterministic model excludes this uncertainty. However, the ERG noted that the company's probabilistic estimate of the ICER is substantially higher (around £10,000 per QALY gained) than its deterministic estimate, which was highly unusual. The ERG and company explained that the larger ICER taken from the probabilistic analysis was likely to be because of the variation associated with the treatment effect. This includes when the sampled treatment effect sometimes suggests a considerable and clinically implausible lower effectiveness of alpelisib plus fulvestrant compared with everolimus plus exemestane. The company noted that a constraint could have been added to ensure that all sampled hazard ratios favoured alpelisib plus fulvestrant, but this was not included for sake of transparency. The ERG agreed that a constraint should not have been added but noted that the extent of survival loss for alpelisib plus fulvestrant was implausible in several samples. It noted that the main driver of the discrepancy between the deterministic and probabilistic modelled cost effectiveness was the wide confidence intervals associated with the hazard ratio for overall survival. A wide confidence interval means that the hazard ratio for overall survival is unreliable. Because the Bucher model was similar to a fixed effects model, confidence intervals can underestimate the true uncertainty (section 3.14). The committee noted that the deterministic model was not behaving linearly as it should and should therefore be considered with caution. It stated that using alpelisib plus fulvestrant for the baseline of the overall survival model and the skewness of this baseline (section 3.13) also contributed to the discrepancy between the deterministic and probabilistic estimates. It

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noted that some sampling in the probabilistic model was implausible. The committee concluded that on balance it preferred to use the probabilistic model. Although it was skewed by some unrealistic values, it overall better accounted for uncertainty than the deterministic ICER. However, it would take both ICERs into account in its decision making.

The cost-effectiveness estimates are higher than what NICE considers a cost-effective use of NHS resources so alpelisib with fulvestrant is not recommended

3.21 Given the uncertainty noted in the data presented by the company, the committee preferred the following more conservative assumptions for decision making: assuming some waning of treatment effect, and using the midpoint utility value between Lloyd and Mitra and the probabilistic ICER. The committee also noted that, if available, additional data to support survival extrapolations and end of life criteria would help reduce uncertainty in these areas. Because of confidential commercial arrangements for alpelisib, fulvestrant, everolimus and exemestane, the ICERs cannot be reported here. Taking into account all confidential discounts, the company's base-case ICER was above £50,000 per QALY gained, and end of life criteria was not robustly shown to be met. When the committee's preferred assumptions were taken into account, the ICER would likely be even higher. The committee concluded that the cost-effectiveness estimates for alpelisib plus fulvestrant compared with everolimus plus exemestane were higher than what NICE considers a cost-effective use of NHS resources. Therefore, the committee could not recommend alpelisib plus fulvestrant for routine use in the NHS.

Cancer Drugs Fund

Alpelisib plus fulvestrant cannot be recommended through the Cancer Drugs Fund

3.22 Having concluded that alpelisib plus fulvestrant could not be recommended for routine use, the committee considered if it could be

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recommended within the Cancer Drugs Fund. It discussed whether the clinical uncertainties identified in the company's modelling could be addressed by collecting more data in the Cancer Drugs Fund. The committee was aware that the ongoing randomised, controlled EPIK-B5 trial would provide further data on progression-free and overall survival for alpelisib plus fulvestrant compared with placebo fulvestrant in people with hormone receptor-positive, HER2-negative, PIK3CA-mutated advanced breast who had previous treatment with a CDK4/6 inhibitor plus an aromatase inhibitor. But the company said that it did not consider this appraisal to be appropriate for the Cancer Drugs Fund, because the EPIK-B5 trial would not address any of the substantial uncertainty about the clinical effectiveness of alpelisib plus fulvestrant compared with the relevant comparator everolimus plus exemestane. The committee also noted that the company's base case was not plausibly cost effective, and the committee's preferred assumptions would likely further increase the ICER. The committee concluded that alpelisib plus fulvestrant could not be recommended for the Cancer Drugs Fund.

Innovation

Alpelisib plus fulvestrant is not innovative

3.23 The company noted that alpelisib is the first licensed alpha-selective PI3K inhibitor. When used with fulvestrant it is the first targeted treatment option for hormone receptor-positive, HER2-negative, PIK3CA-mutated, advanced breast cancer that has progressed on a CDK4/6 inhibitor plus an aromatase inhibitor. Targeted treatment options are valued by people with advanced breast cancer and clinicians (section 3.2). However, the committee noted that it is highly uncertain whether alpelisib plus fulvestrant is more effective than everolimus plus exemestane. The clinical expert also advised that although alpelisib is effective, it was associated with tolerability issues. The committee concluded that alpelisib plus fulvestrant was not innovative.

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4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review 3 years after publication of the guidance. NICE welcomes comment on this proposed date. NICE will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Jane Adam
Chair, appraisal committee A
March 2022

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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Technical lead

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Carl Prescott

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