NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

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

1 Recommendations

1.1 Alpelisib plus fulvestrant is recommended as an option for treating hormone receptor-positive, HER2-negative, PIK3CA-mutated, locally advanced or metastatic breast cancer in adults, only if:

- their cancer has progressed after a CDK4/6 inhibitor plus an aromatase inhibitor and
- the company provides alpelisib according to the commercial arrangement (see section 2).

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 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. The company has positioned alpelisib with fulvestrant after a CDK4/6 inhibitor plus an aromatase inhibitor, which is narrower than its marketing authorisation (licence).

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Clinical evidence from indirect comparisons suggests that alpelisib plus fulvestrant is more effective than everolimus plus exemestane, but the analyses are uncertain. The clinical trial evidence presented only included a small number of people who would be eligible for alpelisib with fulvestrant in clinical practice.

Alpelisib plus fulvestrant meets NICE's 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. So, alpelisib plus fulvestrant is recommended.

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 £4,082.14 per 56-pack of 150 mg film-coated tablets (BNF online, accessed May 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.

2.4 The company has a commercial arrangement (simple discount patient access scheme). This makes alpelisib available to the NHS with a discount. The size of the discount is commercial in confidence. It is the

company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by Novartis, a review of this submission by the evidence review group (ERG), responses from stakeholders and comments on the appraisal consultation document. 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 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 without symptomatic visceral disease 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,

capecitabine chemotherapy is sometimes used instead. However, clinical experts noted that people and clinicians are looking for options to delay the need for cytotoxic chemotherapy. They noted that people who have had previous treatment with a CDK4/6 inhibitor plus fulvestrant would not be eligible for alpelisib. 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 The PIK3CA gene is involved in protein production. It is an important part of the phosphatidylinositol-3-kinase (PI3K) enzyme pathway that drives cancer cell growth. 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 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 important and had a positive emotional impact. The Cancer Drugs Fund clinical lead stated that genomic testing for PIK3CA mutation is now included in the National Genomic Test Directory and so should be funded in the NHS, as long as there are no implementation issues. Patient experts noted in their consultation response for this appraisal that telling people they have this mutation but not allowing access to the drug does not make sense. They

described a patient's experience where PIK3CA mutation may have directly contributed to their endocrine resistance, resulting in recurrence and a prognosis of incurable breast cancer. 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 positioned 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 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 (see section 3.1) as its base-case comparator. Clinical experts noted that because of tolerability issues with everolimus plus exemestane, some people have oral, single-agent chemotherapy with capecitabine instead. This has a lower toxicity burden than other chemotherapies. The committee noted that 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 people with 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 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. 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) 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.

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 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 the 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 everolimus plus exemestane. So, the company presented an indirect treatment comparison using the Bucher method (used in the company base case) 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 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.

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

3.10 The ERG noted that, of the 4 trials of hormone receptor-positive advanced breast cancer included in the Bucher indirect treatment comparison, only SOLAR-1 prospectively enrolled people with PIK3CA-mutated breast cancer. It noted that the company restricted the dataset of BOLERO-2 used in the analysis to the second-line population with a PIK3CA mutation based on tumour tissue samples. This led to 92% of people 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. In its consultation response, the company noted that it restricted the dataset of BOLERO-2 for consistency with the sampling method used in BYLieve and SOLAR-1. It stated that this was to avoid introducing potential bias. It noted that plasma testing was also done in SOLAR-1, but this data was not used because it would have broken the randomisation of the study. The clinical expert noted that they would prefer that the population of BOLERO-2 was

not restricted. They advised that using plasma to test for PIK3CA mutation is helpful because it means it is more likely that the test is being done for a metastatic tumour sample. The ERG understood the company's rationale for restricting the population of BOLERO-2. But it noted that this increases uncertainty in the Bucher analysis and contributes to the wide confidence intervals seen for the hazard ratios.

3.11 The ERG noted that the patient populations of the trials included in the Bucher analysis also had other differences including line of treatment and HER2 status. Almost no one had previously had a CDK4/6 inhibitor with an aromatase inhibitor. 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 there is insufficient data to know whether HER2 status is an effect modifier for alpelisib plus fulvestrant compared with everolimus plus exemestane. In its consultation response, 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 ERG noted that committee papers of these previous appraisals state that not restricting the dataset of SoFEA to people with HER2-negative breast cancer is a source of heterogeneity and may impact outcomes. The clinical expert noted that people with HER2-positive breast cancer should not be included when possible, because they have a completely different treatment regimen. The ERG noted that the HER2-negative subgroup of SoFEA was a reasonably sized group (n=283), 60% of the total study population. It noted that the influence on the Bucher analysis of not restricting the population of

SoFEA is unclear, which leads to uncertainty. The committee concluded that the results of the Bucher analysis are highly uncertain for several reasons:

- Hazard ratios for the indirect comparison of alpelisib plus fulvestrant with everolimus plus exemestane had very wide confidence intervals (section 3.9).
- Hazard ratios for the indirect comparison of placebo plus fulvestrant with everolimus plus exemestane may lack face validity (section 3.9).
- There is heterogeneity between the 4 trials and some have a lack of generalisability. Patient populations differed, including in terms of PIK3CA-mutation status and HER2 status, and there was a lack of previous treatment with a CDK4/6 inhibitor plus an aromatase inhibitor (section 3.10 to 3.11).
- There is a potential for HER2 status to be an effect modifier (section 3.11).

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

3.12 As noted in section 3.11, the indirect treatment comparison was highly uncertain. The company stated that favourable results for alpelisib plus fulvestrant were supported 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 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

3.13 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 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 plausible but highly uncertain

3.14 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 and ERG noted that their clinical experts thought that the projections for overall survival and progression-free survival in the model were plausible. The experts noted that a long tail to the modelled overall survival might be expected in breast cancer. The ERG noted that the projections were based on the company's deterministic model (see section 3.19), including data on PIK3CA mutation from tumour samples in BOLERO-2 (see section 3.10) and the overall population of SoFEA (see section 3.11). It was generally satisfied with the survival functions used, but 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 the alpelisib plus fulvestrant group after around 1.5 years, although very few events happen after this. The ERG explored

the impact of alternative extrapolations for overall survival and progression-free survival, which showed that the incremental cost-effectiveness ratio (ICER) was very sensitive to these alternative extrapolations. The committee noted that there were several 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 people (section 3.7). For the everolimus plus exemestane arm, data was taken from the Bucher indirect analysis, which was highly uncertain (see section 3.11). The committee concluded that the overall survival and progression-free survival estimates were plausible but highly uncertain.

Modelled relative treatment effects are highly uncertain

3.15 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 3.12). 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.

The model assumes a 5-year duration of treatment effect which is uncertain

3.16 The model has a lifetime time horizon (section 3.13). In its original base case, the company assumed that the treatment effects of alpelisib plus fulvestrant compared with everolimus plus exemestane were 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 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. During consultation, the company presented an updated base case in which the treatment effect of alpelisib plus fulvestrant switches to that of everolimus plus exemestane at 5 years. It noted that to assume a 3-year duration of treatment effect is pessimistic, because in the SOLAR-1 study that was used in the Bucher analysis people had follow up for longer than this. The committee noted that the assumed duration of treatment effect of 5 years is not based on evidence. The clinical expert stated that assuming a 5-year treatment effect is reasonable. The committee concluded that the assumption of a 5-year duration of treatment effect is uncertain.

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

3.17 Across the different health states in the model, the company assumed equal utilities for alpelisib plus fulvestrant and everolimus plus exemestane, which the committee concluded was reasonable. The company used SOLAR-1 to derive utility values in the pre-progression health state and for terminal disease. 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 of 0.69 for the modelled health state after disease progression from a publication by Mitra et al.

(2016). The ERG noted that the Mitra study is only published as an abstract with very limited methodological details and the EQ-5D tariffs used to generate the utility estimates are unclear. It explained that the value used from Mitra is likely to overestimate utility after disease progression. This is because it is based on people with hormone receptor-positive, HER2-negative, advanced or metastatic breast cancer who are having treatment at third line or later. In its original critique, 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 when suitable data had not been collected in trials. 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 at technical engagement it did interviews with healthcare professionals. In these interviews Mitra et al. was considered to reflect the utility value of people having third-line treatment in the NHS. The ERG noted that the utility value needs to reflect the entre post-progression health state. The ERG's clinical experts suggested that a utility value around midway between Lloyd and Mitra might be more appropriate for people with a progressed disease state. The ERG did exploratory analyses to consider a value around the midpoint, which led to an increase in the company's base-case ICER. It noted that this value may have greater face validity than available empirical estimates. 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 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 there is no satisfactory utility value for after disease progression. The committee concluded that the appropriate utility value for the modelled health state after disease progression is uncertain and may be overestimated by the 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 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.

The probabilistic version of the model is not working as expected and is not suitable for decision making

3.19 During the first committee meeting, the ERG noted that the probabilistic estimate of the ICER was substantially higher (by around £10,000 per QALY gained) than its deterministic estimate, which was highly unusual.

The ERG and company noted that in the probabilistic analysis, the sampled treatment effect sometimes suggests a considerable and clinically implausible lower effectiveness of alpelisib plus fulvestrant compared with everolimus plus exemestane. The ERG noted that the main driver of the discrepancy between the deterministic and probabilistic modelled cost effectiveness was the wide confidence interval 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 is similar to a fixed effects model, confidence intervals can underestimate the true uncertainty (section 3.15). In its consultation response, the company updated its probabilistic base case using a constrained probabilistic analysis following input from clinical experts. It sought opinion from 4 experts to identify the extent of increase in life years for everolimus plus exemestane compared with alpelisib plus fulvestrant that would be deemed to be clinically implausible. As a result, the probabilistic analysis was amended to remove iterations where everolimus plus exemestane was associated with an increase in life years greater than 10%. The company noted that this approach shows the impact of the implausible samples on the probabilistic ICER, which was now aligned with that of the deterministic analysis. The ERG disagreed with the company's approach. It noted that removing samples that do not match expectations gives an arbitrary mean ICER. The committee noted that it is not satisfied with the company's probabilistic analysis where the outputs have been constrained. It noted that it would be more appropriate to constrain the inputs to the probabilistic analysis, such as the confidence intervals of the hazard ratio, based on expert elicitation. It recalled that the company's probabilistic analysis did not work as expected. It concluded that the probabilistic version of the model is not suitable for decision making.

End of life

End of life criteria are met

3.20 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. During the first meeting, 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 3.15). In the second meeting, the company and the ERG noted that end of life criteria are met for the company's updated deterministic base-case model. The committee noted that the model predicted that alpelisib with fulvestrant would prolong life by more than 3 months longer than everolimus plus exemestane. The ERG noted that the end of life criteria were not met using the 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 was unable to consider the results of the probabilistic model given the problems associated with it (see section 3.19). It concluded that end of life criteria were met.

Because of the uncertainty, an ICER comfortably under £50,000 per QALY gained would be necessary for this technology to be considered cost effective

3.21 NICE's guide to the methods of technology appraisals notes that the appraisal committee does not use a precise maximum acceptable ICER above which a technology would automatically be defined as not cost

effective, or below which it would. Also, consideration of the cost effectiveness of a technology is necessary, but is not the sole basis for decision making. Therefore, NICE considers that the influence of other factors on the decision to recommend a technology is greater when the ICER is closer to the top of the acceptable range. Judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee had concluded that end of life criteria applied (see section 3.20). However, the committee noted the high level of uncertainty (see section 3.23) and had considered different durations of treatment effect and post-progression utility values. It noted that the most plausible ICER range for decision making was deterministic. It was unable to consider the probabilistic ICER (see section 3.22). The committee agreed that, given the uncertainty, alpelisib plus fulvestrant would only represent a cost-effective use of NHS resources if the range of plausible ICERs was comfortably below £50,000 per QALY gained.

Cost-effectiveness results

The committee preferred to use the deterministic model for decision making

3.22 In the first meeting, 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. It stated that using alpelisib plus fulvestrant for the baseline of the overall survival model and the skewness of this baseline (section 3.14) contributed to the discrepancy between the deterministic and probabilistic estimates. In the second meeting, the committee noted that the probabilistic model was not suitable for decision making (see section 3.19). The ERG noted that interpretation of ICERs from the deterministic model is problematic because median, not mean, hazard ratios were used. The committee

concluded that while the deterministic model did not take account of the high uncertainty in the modelling (see sections 3.14 to 3.17), it preferred to use it for decision making.

The most likely cost-effectiveness estimates are highly uncertain

3.23 NICE's guide to the methods of technology appraisal notes that above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER and whether the technology meets the criteria for consideration as a 'life-extending treatment at the end of life'. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee noted the high level of uncertainty in the cost-effectiveness estimate caused by:

- an uncontrolled single-arm trial as the primary source of clinical evidence (see section 3.6)
- issues with the Bucher indirect treatment comparison (see section 3.11) including whether alpelisib with fulvestrant is more effective than everolimus plus exemestane (see section 3.12)
- modelled survival estimates (see section 3.14)
- modelled treatment effect of alpelisib plus fulvestrant compared with everolimus plus exemestane (see section 3.15)
- duration of treatment effect (see section 3.16)
- appropriate utility value after disease progression (see section 3.17)
- treatment costs after disease progression (see section 3.18)
- using the deterministic model because the probabilistic model is not suitable for use in decision making (see section 3.20).

The committee concluded that the most likely cost-effectiveness estimates are highly uncertain.

Alpelisib combination is recommended for routine use

3.24 Using the deterministic model and considering different durations of treatment effect and likely post-progression utility values, the plausible ICER range calculated by the ERG was, on balance, judged to be comfortably below £50,000 per QALY gained (see section 3.21). The committee concluded that alpelisib plus fulvestrant is a cost-effective use of NHS resources. Therefore, it can be recommended as an option for treating hormone receptor-positive, HER2-negative, PIK3CA-mutated, advanced breast cancer that has progressed after a CDK4/6 inhibitor plus an aromatase inhibitor.

Other factors

There are no equality issues

3.25 No equality or social value judgement issues were identified. The committee noted that a person can go through the menopause but not identify as a woman. Gender reassignment is a protected characteristic under the Equality Act 2010.

All benefits associated with alpelisib plus fulvestrant are captured in the modelling

3.26 NICE's guide to the methods of technology appraisal notes that a technology may be considered innovative in nature if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the modelling. The company noted that alpelisib is the first licensed PI3K inhibitor that is highly selective for the catalytic subunit alpha of PI3K. 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 while alpelisib plus fulvestrant may be more effective than everolimus plus exemestane,

the results of the indirect analyses are highly uncertain. The clinical expert also advised that although alpelisib is effective, it was associated with tolerability issues. The committee concluded that it did not think there were any additional benefits associated with alpelisib plus fulvestrant that had not been captured in the economic analysis.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources

for it within 2 months of the first publication of the final appraisal document.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has hormone receptor-positive, HER2-negative, PIK3CA-mutated advanced breast cancer that has progressed after a CDK4/6 inhibitor plus an aromatase inhibitor and the doctor responsible for their care thinks that alpelisib plus fulvestrant is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication. 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
July 2022

6 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.

Catherine Spanswick
Technical lead

Michelle Green, Carl Prescott
Technical advisers

Jeremy Powell
Project manager

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