NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee Papers

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Alpelisib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative, PIK3CA-mutated breast cancer [ID3929]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Patient organisation	METUP UK	*Has all of the relevant evidence been taken into account?* As lay people, the different models produced by the company and the ERG are too technical to be accessible. Although, we did note that models used the same evidence modelled in different ways to come up with different conclusions. To help make sense of this, we looked at a third source of evidence for more information, the ESMO guidelines. We understand the ESMO guidelines do not take into account value for healthcare systems, only clinical outcomes, and so are not identical in purpose. The ESMO guidelines state alpelisib–fulvestrant is a treatment option for patients with PIK3CA-mutant tumours, noting the need to carefully select candidates for this treatment, considering comorbidities, especially pre-existing diabetes.	Thanks for your comment. The committee took these comments into consideration along with the company's updated model and the updated discount. The recommendation has changed and alpelisib combination is recommended for treating hormone receptor-positive, HER2-negative, PIK3CA-mutated advanced breast cancer that has progressed after a CDK4/6 inhibitor plus an aromatase inhibitor.
2	Patient organisation	METUP UK	*Are the recommendations sound and a suitable basis for guidance to the NHS?* No, the recommendations are not a sound guidance for the NHS. Successive health secretaries have lauded genomics as the future for cancer care. In 2020 the government published Genome UK: the future of healthcare which hailed the use of personalised medicine and pharmacogenomics in the NHS. As noted in the supporting documents, genomic testing is being rolled out for patients with MBC across the NHS from April 2022. For patients who have had genomic testing, the knowledge that they have a targetable mutation for which there is a treatment but that the treatment is not funded is a blow. Alpelisib is the first treatment available which targets the PIK3CA mutation in ER-positive HER2-negative MBC, so we believe it is innovative. Patient advocate [redacted] writes: "I had genetic testing via the Foundation One test which identified I have a PIK3CA mutation and recommended the drug combination of alpelisib and fulvestrant as a good option for me. NICE, with their decision to not recommend alpelisib and fulvestrant for use in the NHS have taken this opportunity and thus my hope for the future away - unless we are able to fund these drugs ourselves which is extremely unlikely. I fail to understand why this has been rejected when it targets a very specific mutation for which there is little else available. What is the point in telling patients they have this mutation and then not allowing us to access the drugs? All I want is the opportunity to try and this decision will deny me that." We believe there is an unmet need for a treatment which targets the PIK3CA mutation. The recommendation for use of alpelisib–fulvestrant by ESMO indicates that this treatment is being used in many European countries. We understand alpelisib–fulvestrant has a toxicity profile which means it is not suitable for all patients with a PIK3CA mutation, and would expect patient selection to be a decision for oncologists alongside their patients to make.	Thanks for your comments. The committee took these comments into consideration (see FAD section 3.2) along with the company's updated model and the updated discount. The recommendation has changed and alpelisib combination is recommended for treating hormone receptor-positive, HER2-negative, PIK3CA-mutated advanced breast cancer that has progressed after a CDK4/6 inhibitor plus an aromatase inhibitor.

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3	Patient organisation	Breast Cancer Now	It is disappointing that NICE has provisionally been unable to recommend alpelisib with fulvestrant as it would have improved the options available for this group of patients and would provide the first targeted treatment for patients with a PIK3CA mutation. We urge the company, Novartis and NICE to work together during this consultation period to consider every possible solution. In particular, it is difficult to understand why the Cancer Drugs Fund (CDF) is not being considered a potential option in this case. Whilst there may not be a suitable clinical trial ongoing that will resolve the uncertainties that exist, we understand that types of data collection for drugs on the CDF will vary from drug to drug and can include SACT and population-based datasets. We would therefore welcome clarity on the reasons why the CDF is not being explored as this could be an important route to enabling access to patients whilst further data is collected.	Thanks for your comments. The recommendation has changed and alpelisib combination is recommended for routine use 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.
4	Patient organisation	Breast Cancer Now	We would reiterate as per our original submission that following progression on a CDK 4/6 plus aromatase inhibitor there are limited effective treatment options – with everolimus and exemestane generally having poor uptake due to the side effect profile and therefore in some instances single agent capecitabine being preferred. Alpelisib with fulvestrant could provide an important new treatment option, especially as PIK3CA mutations can be associated with a poorer prognosis and increased resistance to treatments.	Thanks for your comment. The committee took these comments into consideration along with the company's updated model and the updated discount. The recommendation has changed and alpelisib combination is recommended for treating hormone receptor-positive, HER2-negative, PIK3CA-mutated advanced breast cancer that has progressed after a CDK4/6 inhibitor plus an aromatase inhibitor.
5	Patient organisation	Breast Cancer Now	We urge flexibility regarding the end of life criteria given the uncertainties that have been highlighted and given that it is possible that alpelisib with fulvestrant does in need meet end of life criteria. We would welcome the company and NICE working together to identify the further data and modelling that would be required to ensure the evidence is as robust as it can be.	Thanks for your comment. The committee took these comments into consideration along with the company's updated model (deterministic). As noted in FAD section 3.20, the committee now consider end of life criteria are met.
6	Patient organisation	Breast Cancer Now	We are surprised that alpelisib has not been recognised as an innovative treatment, given the role PIK3CA may play in progression and that the treatment specifically targets this and could provide an important additional treatment option. As a patient explains: "it is important to me as patient that I can access a drug which targets a mutation I know that I have." The patient goes on to explain: "A tailored approach to our treatment as patients clearly will optimise our chances of a treatment response and mean that money is well spent on a treatment we know works more effectively in the population it is being used in."	NICE considers "the innovative nature of a technology… [when it] adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case QALY measure" (section 6.3.3 of NICE guide to the methods of a technology appraisal 2013). The committee considered all benefits associated with alpelisib plus fulvestrant are captured in the modelling. However, alpelisib combination has now been recommended for treating hormone receptor-positive, HER2-negative, PIK3CA-mutated advanced breast

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				cancer that has progressed after a CDK4/6 inhibitor plus an aromatase inhibitor.
7	Patient organisation	Breast Cancer Now	[Please see comment 8, also submitted directly by the patient]	[See comment 8]
8	Patient	Current patient and NHS physician	I was first diagnosed with ER+ breast cancer and unfortunately in 2021 it recurred despite full compliance with both Letrozole and also a trial of Abemaciclib (CDK 4/6 inhibitor) as part of Monarch E. The tumour recurred in visceral lymph nodes which were not resectable. It expresses PIK3CA and this was also found in my blood. My conclusion is that the tumour acquired a PIK3CA mutation and that this directly contributed to endocrine resistance, resulting in my recurrence and my current prognosis. Current treatments available on the NHS for this type of breast cancer (e.g. normally after a CDK 4/6 inhibitor with an aromatase inhibitor treatment include everolimus with exemestane or capecitabine). Unfortunately, there is a significant toxicity profile and this combination and although there seem to be few studies making a direct comparison, it is important to me as patient that I can access a drug which targets a mutation I know that I have. Alpelisib is the first drug which can do this in the area of advanced breast cancer for patients with this mutation. There is therefore a significant likely impact that alpelisib with fulvestrant could make if it was recommended for use on the NHS. There is a major unmet need for therapies that specifically address the effects of this mutation as there are currently no recommended therapies that specifically target the PIK3CA mutation for UK patients who have it with endocrine resistant HR+, HER2– advanced breast cancer (ABC). This is what I have as I also now have bone mets which are growing as they are ER+. My risk of developing more visceral disease without targeted treatment for PIK3CA is very high and it's very important to have more than one option, especially when there are associated toxicities. Options are crucially important for patients in my position. I understand that UK clinicians report that improvements in PFS alone with Alpelisib and Fulvestrant and therefore this would give me more options that the toxicity I will get from prolonged chemotherapy or combination treatment with everolimus and exmestene/capecitabine. Patients can get side effects from a range of medications and it is crucial to have choices in situations such as mine. It is imperative that new treatments that improve survival and provide personalised options for clinicians are made available. There is clearly a high unmet need as I am one of the 40% of women who develop this mutation as a cause for their recurrence and I now have incurable breast cancer. Without this treatment my options for survival to look after my children (aged 12 and 16) are significantly reduced. I have served my patients all my working life and now find myself in this catastrophic position of perhaps having very few months to live unless I can access targeted treatments which may help me. This summary doesn't even cover the devastation I have had to deal with through losing my left breast / all my hair twice / my eyebrows / my livelihood. I am at least fortunate that I know I have the mutation so that I can keep searching for potential treatments but I am deeply concerned that there is currently a lack of treatment options with the associated genomic test for this mutation. This should be standard practice so that it can be used to predict which patients are likely to	Thanks for your comments. The committee took these comments into consideration (see FAD section 3.2 of the final guidance) along with the company's updated model and the updated discount. The recommendation has changed and alpelisib combination is recommended for treating hormone receptor-positive, HER2-negative, PIK3CA-mutated advanced breast cancer that has progressed after a CDK4/6 inhibitor plus an aromatase inhibitor.

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			benefit from treatment. A tailored approach to our treatment as patients clearly will optimise our chances of a treatment response and mean that money is well spent on a treatment we know works more effectively in the population it is being used in. This is not the case for many drugs we prescribe as doctors and therefore this drug represents not only better value for money because it can be targeted but also it is the future for patients like me as improvements in survival from metastatic cancer will be afforded by personalised (genomic) medicine. As a doctor and a patient I know that trial data has shown alpelisib in combination with fulvestrant to be effective in prolonging progression free survival in advanced hormone receptor-positive, HER2-negative, PIK3CA-positive breast cancer. Progression free survival means the world to me as it means I can spend more vital time with my family. I would urge you to progress this as quickly as possible in order to help all those on my position whose very lives depend on it.	
9	Clinical expert	N/a	Recommendation, section 1: *'Current treatment for hormone receptor-positive, HER2-negative, PIK3CA-mutated, locally advanced or metastatic breast cancer is usually only everolimus with exemestane.'* This is not a fair statement as usually only is a contradiction in terms and in fact chemotherapy may be used in this situation rather than everolimus exemestane	Thanks for your comment, which the committee took into consideration. The final guidance notes (section 3.1) that 'people without symptomatic visceral disease can have exemestane plus everolimus'. And that 'capecitabine chemotherapy is sometimes used instead'. The final recommendations (FAD section 1) notes that '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'. The recommendation has changed and alpelisib combination is recommended for treating hormone receptor-positive, HER2-negative, PIK3CA-mutated advanced breast cancer that has progressed after a CDK4/6 inhibitor plus an aromatase inhibitor.
10	Clinical expert	N/a	Recommendation, section 1: '*There is no direct evidence comparing alpelisib plus fulvestrant with everolimus plus exemestane*.' There is also no clinical trial evidence for the use of everolimus exemestane compared to chemotherapy. Being a legacy regimen means that an expensive treatment option with no evidence is allowed but a new targeted treatment for a smaller population cannot . This is inconsistent.	Thanks for your comment. Please see response to comment 9.
11	Clinical expert	N/a	Section 3.4: '*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.'* How has this figure been arrived at, as although can pick up from CDF those applying for everolimus exemestane that requires funding approval , will not see number receiving single agent chemo as not using CDF??	Thanks for your comment. Please see response to comment 9.

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12	Company	Novartis	Novartis is disappointed by the draft recommendation from NICE to not recommend alpelisib plus fulvestrant for the treatment of hormone receptor positive (HR+), human epidermal growth factor 2 negative (HER2–), locally advanced or metastatic breast cancer with a phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) mutation after disease progression following a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i). The Committee regards alpelisib plus fulvestrant as providing "another step in delaying cytotoxic chemotherapy", with clinical experts favouring to offering targeted treatment options for patients with advanced breast cancer (ABC). The Committee also heard that, for those patients with a PIK3CA mutation, "knowing a drug was targeted to their mutation was very powerful and had a positive emotional impact."1 This is particularly important given the fact that patients in this population have a substantial unmet need due to there being limited treatment options after CDK4/6is, and where the mainstay of treatment offers limited survival benefit. If the initial decision remains unchanged, patients will be denied access to the first targeted treatment option for ABC that has a PIK3CA mutation. Novartis is grateful for the opportunity to respond to the Appraisal Consultation Document (ACD) to address the outstanding questions and would like to provide further comment and clarification on the remaining uncertainties in the appraisal. The following topics are addressed within this response: • End-of-life (EoL) criteria • Probabilistic sensitivity analyses (PSA) • HER2– subgroup in the indirect treatment comparison (ITC) • 'Reverse' Bucher method for the ITC • Method of PIK3CA identification in the ITC • Post-progression utility values • Treatment waning assumptions • Point of factual inaccuracy In addition to the comments provided within this document, a revised economic model and appendix at the end of this response have been provided with a revised base case that includes a treatment waning assumption applied at 5 years. Novartis has also submitted an adjustment to the existing Patient Access Scheme (PAS) price for alpelisib to PASLU. The cost-effectiveness analyses in the appendix are based on this revised PAS price.	Thanks for your comments. The committee took these comments into consideration along with the company's updated model and the updated discount. The recommendation has changed and alpelisib combination is recommended for treating hormone receptor-positive, HER2-negative, PIK3CA-mutated advanced breast cancer that has progressed after a CDK4/6 inhibitor plus an aromatase inhibitor.
13	Company	Novartis	Alpelisib plus fulvestrant meets the EoL criteria set out by NICE when considering the totality of the evidence available and their basis in NICE's Social Value Judgements, as set out in the appeal decision for avelumab Section 3.19 of the ACD states that the Committee "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." As set out in the recent appeal for the appraisal of avelumab for the maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy (and acknowledged by the Committee in 3.21 of the avelumab FAD; ID3735), due consideration must be applied to the totality of evidence available, and the social value judgments underpinning the decision modifier, when assessing whether a drug meets the short life expectancy criterion:2-4 • Patients with HR+, HER2– ABC with a PIK3CA mutation have a poor prognosis, with a shorter overall survival (OS) and progression-free survival (PFS), and reduced sensitivity to chemotherapy compared with wild-type PIK3CA disease.5-16	Thanks for your comments. The committee took these comments into consideration along with the company's updated model (deterministic). As noted in section 3.20 of the final guidance, the committee now consider end of life criteria are met.

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			• The poor prognosis (less than 24 months) for this group of patients is supported by the model predictions. The mean undiscounted life years marginally exceed 24 months only in a limited set of scenarios. Further, the likelihood of those scenarios is low, due to outliers in the PSA (evidenced by the number of clinically implausible sample estimates, as noted by the Committee and stated in the ACD [described in response 3]), and the lack of evidence of HER-2 status as a treatment effect modifier and clinically inconsistent results observed in SoFEA for the HER2– subgroup (as described in response 4). • The short life expectancy (less than 24 months) of this group of patients was also reiterated by both clinical experts during the Committee Meeting. As highlighted in the ACD, clinical experts stated that patients "are unlikely to live longer than 24 months." Evidence further suggests that alpelisib plus fulvestrant is able to extend life expectancy by >3 months: • While there are some uncertainties in the treatment effect due to the single arm nature of BYLieve, the model predictions demonstrate that alpelisib plus fulvestrant increases life expectancy compared with everolimus plus exemestane by greater than three months. Again, this criterion is not met only in an extreme and unrealistic scenario due to outliers in the PSA. • Further supportive evidence that alpelisib is able to extend life expectancy by >3 months is provided by the SOLAR-1 trial, where alpelisib plus fulvestrant had a median OS of 39.3 versus 31.4 months for fulvestrant (difference of 7.9 months). Clinical experts during the Committee Meeting suggested that it was not unreasonable to assume fulvestrant to be as efficacious as everolimus plus exemestane, and therefore data from SOLAR-1 support the conclusion that alpelisib is able to extend life expectancy by >3 months compared with everolimus plus exemestane. Following the Committee Meeting, Novartis have engaged with four external clinical experts about their experiences of PIK3CA-mutated cancer in the context of the end-of-life criteria for this appraisal. Three of the experts considered that patients with PIK3CA-mutated ABC following CDK4/6i treatment would not be expected to live beyond 24 months, whilst the other one was unable to comment. For the extension to life criterion, the clinical experts found it challenging to comment on this in the absence of head-to-head data, and in the absence of long-term experience using alpelisib plus fulvestrant in clinical practice, however the data presented above support that alpelisib plus fulvestrant extends life expectancy by >3 months. In conclusion, considering the totality of the evidence available and the social value judgements underpinning the modifier, alpelisib plus fulvestrant meets the EoL criteria.	
14	Company	Novartis	The probabilistic analysis in its current form is not suitable for decision-making and a constraint is required to ensure results are clinically plausible, as suggested in the updated method guide Novartis recognise and agree with the standard approach that results from the PSA should typically be considered to account for the combined effects of uncertainty. However, in the context of this appraisal, there are significant concerns in using PSA results for decision-making, as acknowledged by the ERG (Section 5.3.4, page 114 of the ERG report) and Committee (Section 3.20, page 20 of the ACD). In its current form, the PSA generates results which clinical experts described as clinically implausible during the Committee Meeting, and as acknowledged in the ACD ("sampled treatment effect sometimes suggests a considerable and clinically implausible lower effectiveness of alpelisib plus fulvestrant compared with everolimus plus exemestane"). As such, these results should not be considered in decision-making as justified	Thanks for your comments. The committee took these comments and the company's updated model into consideration. As noted in section 3.19 of the final guidance, the committee agreed that the probabilistic model is not suitable for decision making, but it was not satisfied with the company's approach of constraining the outputs of the probabilistic sensitivity analysis. The final guidance notes (FAD section 3.22)

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			below. The probabilistic sampling of OS suggests that alpelisib plus fulvestrant is associated with reduced survival (undiscounted) as compared with everolimus plus exemestane in ~20% of samples. Whilst Novartis recognise that it may be possible for some of the probabilistic iterations to favour everolimus plus exemestane, the extent of increase in life years for everolimus plus exemestane predicted in the model is clinically implausible in a large number of iterations. As highlighted in the ERG report (Section 5.3.4, page 114 of the ERG report), "in several samples, the incremental loss in survival for Alp/Fulv is substantial; this is unlikely to be plausible" with estimates of a difference in life years gained of up to 8 years in favour of everolimus plus exemestane. When considering the 20.4% of PSA iterations where everolimus plus exemestane was more effective compared with alpelisib plus fulvestrant, the mean (median) relative increase in life years for everolimus plus exemestane is large and clinically unlikely at 44.2% (26.3%) as shown in Figure 1 (graph generated using the original submitted base case version of the model). Although implicit in the NICE method guide (2013) that is applicable to this appraisal, clarity on how to handle uncertainty when analyses are clinically implausible is provided in the updated NICE method guide (2022).17, 18 Whilst this appraisal is subject to the earlier methods guide, the spirit of the following clarifications has broad application and are equally justifiable in this appraisal: • Section 4.6.27: "In general, all model parameter values used in base-case, sensitivity, scenario and subgroup analyses should be both clinically plausible and should use methods that are consistent with the data. Results from analyses that do not meet these criteria will not usually be suitable for decision making." • Section 4.6.28: "Sometimes it may be difficult to define what is plausible and what is not, for example, in very rare conditions or for innovative medical technologies, when the evidence base may be less robust. In such situations, consider expert elicitation to identify a plausible distribution of values" Consequently, Novartis consider that results from the PSA are not suitable in their current form, given the scope to introduce biases into the interpretation of the results informing decision making. Novartis continue to consider the deterministic results to be more appropriate to inform the cost-effectiveness of alpelisib plus fulvestrant. As we recognise the Committee's preference to use probabilistic results to account for the combined uncertainty, Novartis have, therefore, sought clinical expert opinion to identify a plausible distribution of values for OS efficacy, in line with the NICE method guide (Section 4.6.28). Clinical experts were asked to specify the extent of increase in life years for everolimus plus exemestane compared with alpelisib plus fulvestrant that would be deemed to be clinically implausible. Two of the four clinical experts consulted considered that an increase in life years for everolimus plus exemestane greater than 10% would be clinically implausible. The third clinical expert considered between 5–10% would be the limit of clinical plausibility whilst the fourth was not able to provide an estimate. Consequently, in line with the NICE method guide and to ensure results are clinically plausible and suitable for decision-making, the PSA has been amended to remove iterations where everolimus plus exemestane was associated with an increase in life year greater than 10% as elicited by clinical experts. The updated PSA results, incorporating this constraint, are presented	'that while the deterministic model did not take account of the high uncertainty in the modelling…, [the committee] would use it in its decision making'.

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			in the Appendix to this response.	
15	Company	Novartis	Use of the full population from SoFEA is appropriate in the Bucher analysis, and consistent with prior appraisals in previously treated, advanced breast cancer Section 3.10 of the ACD states that "the committee concluded that the results of the Bucher analysis are highly uncertain for several reasons", including that "there is the potential for HER2 status to be an effect modifier." As described in the Company Submission, two relevant trials were identified to connect SOLAR-1 and BOLERO-2: SoFEA and CONFIRM. Both trials included patients with HER2+ and HER2– ABC, and only SoFEA reported results separated by HER2 status. Whilst there is an observed difference between the populations with HER2+ and HER2– tumours in the SoFEA trial, with the effect of fulvestrant 250 mg versus exemestane being favourable in patients with HER2+ tumours and unfavourable in those with HER2– tumours, it is uncertain if this difference is a result of a treatment modifying effect or external, limiting factors. Approximately 35% of patients in SoFEA had unknown HER2 status (n=166), and as such the estimated HRs for patients with known HER2 status may be affected by information bias. Similarly, the numbers of patients with known HER2+ status were small (6%; n=31) and so estimates for this subgroup may be unreliable. Use of the full population of SoFEA is also in line with the use of the full population of CONFIRM (where results by HER2 status were not available). Further to this, the hazard ratios (HRs) for PFS and OS in the HER2– subgroup in SoFEA for fulvestrant 150 mg versus exemestane were 1.06 (95% CI: 0.83, 1.34) and 1.26 (95% CI: 0.95, 1.66), respectively, leading to a prediction that exemestane is more effective than fulvestrant, which we believe lacks face validity and further highlights the uncertainty in the results of the subgroup analysis.19 Based on these results, Novartis do not consider the data from the SoFEA trial to provide any evidence that HER2 status is a treatment effect modifier as it is unclear if the observed difference is in fact an artifact of the bias arising from the small sample size. To date, all of the NICE appraisals for CDK4/6is in combination with fulvestrant that use CONFIRM and SoFEA in their networks to connect to everolimus plus exemestane use the overall population and the Committee have found this a reasonable basis for decision making on each occasion.20-22 These prior appraisals were all also for drugs indicated for patients with HER2– disease only. Therefore, if the HER2– subgroup of SoFEA were to be used in this appraisal, this would represent the first time this approach had been taken in an appraisal for ABC and would contradict the aforementioned precedent. Overall, the use of the full population from SoFEA is considered the most appropriate approach for the Bucher analysis; there are insufficient data to support a conclusion that HER2 status is a treatment effect modifier and use of the HER2– subgroup in the Bucher analysis would be inconsistent with prior appraisals within ABC.	Thanks for your comments. The committee took these comments into consideration. As noted in section 3.11 of the final guidance, the committee heard that committee papers of previous appraisals stated that not restricting the dataset of SoFEA to HER2-negative patients is a source of heterogeneity and/or may impact outcomes. They noted that people with HER2-positive breast cancer should not be included where possible as they have a different treatment regimen. They also heard that the HER2-negative subgroup was a reasonably sized group, and the influence on the Bucher analysis of not restricting the population is unclear, which leads to uncertainty. The final guidance notes 'the results of the Bucher analysis are highly uncertain for several reasons… there is a potential for HER2 status to be an effect modifier'.
16	Company	Novartis	Use of a 'reverse' Bucher method was required to allow comparison, and did not lead to an increase in uncertainty Further to points 3 and 4 above, Section 3.10 of the ACD states that "the committee concluded that the results of the Bucher analysis are highly uncertain for several reasons", including because "a reverse Bucher was done, deriving comparator hazard ratios from those known for alpelisib plus fulvestrant." This approach was used because the evaluation was based on survival data for alpelisib plus fulvestrant from the BYLieve trial. As stated on page 7 of the ACD, patients in BYLieve were	Thanks for your comments. This issue was resolved during consultation. In the final guidance, this section (3.11) has been updated to remove the statement that the 'reverse' method was a reason for uncertainty in the Bucher analysis.

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			generalisable to UK clinical practice because they had previously progressed on a CDK4/6 inhibitor. However, since BYLieve was a single-arm trial, it was necessary to estimate PFS and OS curves for everolimus plus exemestane by applying estimates of the HRs for PFS and OS for everolimus plus exemestane versus alpelisib plus fulvestrant to the estimated PFS and OS curves for alpelisib plus fulvestrant. It is unclear to the company why the method employed would introduce any more uncertainty than the approach considered by the ERG to be the more standard approach. There is no rationale outlined in the ACD in this regard and this was not discussed in the ERG report in any context. As such, the conclusion that this approach introduces uncertainty is overstated, and rather the approach taken is simply an alternative approach based on the available data.	
17	Company	Novartis	Utilising PIK3CA mutation data based on tumour sampling is an appropriate approach for the Bucher ITC Section 3.9 of the ACD states that "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." This approach was taken by the company because the study populations in SOLAR-1 and BYLieve trials assessed PIK3CA mutation based on tumour samples. Patients with PIK3CA-mutated disease in BOLERO-2 using tumour samples were therefore utilised for consistency, as use of different sampling methods across trials may introduce potential bias. For example, in the study by Moynahan et al. (2017) among patients with PIK3CA-mutated disease identified by circulating tumour DNA (ctDNA), the HR for PFS for everolimus plus exemestane versus exemestane was 0.37 (95% CI: 0.27, 0.51); in the study by Hortobagyi et al. (2016) among patients with PIK3CA-mutated disease identified by plasma samples, the HR for PFS for everolimus plus exemestane versus exemestane was 0.51 (95% CI: 0.34, 0.77). Neither study looked at OS, but this suggests the sampling method used yields different HRs for PFS. Whilst information on PIK3CA mutations based on ctDNA was also collected in SOLAR-1, basing the analysis on such data would have broken randomisation (subjects in SOLAR-1 were randomised within the PIK3CA-mutated cohort with the mutation identified based on tumour samples).	Thanks for your comments. The committee took these comments into consideration. As noted in 3.10 of the final guidance, 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 noted it understood the company's rationale for restricting the population of BOLERO-2, but this increases uncertainty in the Bucher analysis and contributes to the wide confidence intervals seen for the hazard ratios. The final guidance notes (section 3.11) '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'.
18	Company	Novartis	The post-progression utility value of 0.69 from the literature source, Mitra et al., is the most appropriate estimate to use in the cost-effectiveness model Section 3.17 of the ACD states that "the committee concluded that the appropriate utility value for the modelled health state after disease progression is uncertain and may be overestimated by company." Novartis maintains that applying the utility value from Mitra et al (2019) is the most appropriate value to use. As highlighted at technical engagement and acknowledged by the ERG (reflected their preferred analysis), the value from Lloyd et al (2006) is not appropriate. Changes to the treatment landscape in ABC over the last 15 years mean that the vignette description from Lloyd et al. (2006) no longer reflects the experiences of patients in the modelled post-progression health state.23 As highlighted in our technical engagement response, the utility value derived	Thanks for your comments. The committee took these comments into consideration. As noted in 3.17 of the final guidance, 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. Also, that while the company conducted interviews with clinical experts who considered Mitra reflective

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			from Mitra et al. is also methodologically preferable to the value from Lloyd et al. because the study used EQ-5D to measure health-related quality of life in people with breast cancer. To validate the most appropriate value to inform the cost-effectiveness model, Novartis conducted a series of interviews with four additional clinical experts (the ACD states that these meetings were conducted prior to the Committee Meeting; however, these were conducted for the technical engagement response). All four of the clinical experts interviewed by Novartis considered that patients seen in their practice at a third-line setting (i.e. equivalent to the post-progression survival (PPS) state in the cost-effectiveness model) would have a utility that is reflective of the Mitra et al. (2016) publication, noting that this value is very similar to the PPS value of [redacted] measured in the SOLAR-1 trial. Clinical experts during the Committee Meeting provided further validation that the value from Mitra et al (2019) was deemed to be clinically plausible. In addition, the most recently appraised technology in ABC (TA725; abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy) proposed a utility value for the PPS state from Mitra et al. (2016), with a value for the PPS health state of 0.69.* 20, 24 In TA725, this value was considered to be methodologically preferable as compared to that derived from Lloyd et al. (2006) due to the use of EQ-5D to measure health-related quality of life in people with breast cancer.20, 23, 24 This value was used as part of the base case on which the NICE Committee based their decision to recommend the technology. During the 15 March meeting, the Committee members heard that the validity of using the value from Mitra was also discussed in TA725. Specifically, it was raised that a value of 0.69 may be too high, when considering this value represents the experience of patients during all subsequent treatments, including chemotherapy. It was nonetheless accepted as a basis for decision making. The rationale for why an inconsistent decision has been made – by the same Committee, in the face of the same information, within a 12-month period – has not been provided. Following technical engagement, the ERG preferred-base-case uses an arbitrary value of [redacted]. In the ERG's commentary on the company's technical engagement response, they highlighted input from one clinical expert they had consulted which suggested that a value of [redacted] would be consistent with the patient population in question. A second clinical expert suggested that a value between [redacted] and [redacted] would be reasonable in the third-line setting (i.e. a mid-point between Mitra et al. [2016] and Lloyd et al. [2006]).23, 24 Despite this, an arbitrary value of [redacted] was used by the ERG which is inconsistent with estimates from their own clinical experts, and uses the most pessimistic estimate. Overall, Novartis strongly believe that the post-progression utility value of 0.69 from the literature source, Mitra et al., is the most appropriate estimate from an evidence-based, methodological standpoint, and is also in line with previous Committee discussion and agreement in TA725. Novartis further note that a utility value of [redacted] and above is more closely aligned with that elicited from the ERG clinical experts: a value of [redacted] is arbitrary and reflects the most pessimistic estimate. * Please note: this is reported as 0.670 in TA725, however, the source publication states that the utility value for third-line or later patients with ABC is 0.69.20, 24	of patients receiving third-line treatment, the utility value needs to reflect the entire 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 noted this value may have greater face validity than available empirical estimates. The final guidance notes 'the appropriate utility value for the modelled health state after disease progression is uncertain and may be overestimated by the company'. Please also note: section 3.17 of the final guidance has been corrected to reflect that company conducted interviews with clinical experts at technical engagement.
19	Company	Novartis	Assuming treatment waning at a three-year timepoint is overly pessimistic given a lack of data to support waning assumptions; a five-year timepoint is a more reasonable assumption and has	Thanks for your comments. The committee took these comments and the

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			been adopted in the updated company base case Section 3.15 of the ACD states that the model "assumes that the treatment effects of alpelisib plus fulvestrant compared with everolimus plus exemestane are indefinite with no loss of treatment effect over time", and that "the committee concluded that the assumption of an indefinite treatment effect is optimistic." Whilst there is uncertainty in the longevity of the treatment effect associated with alpelisib plus fulvestrant, given an absence of long-term data equivalent to the lifetime horizon of the economic model, it is pessimistic to assume that the hazards for the alpelisib plus fulvestrant group would switch to the hazards for the everolimus plus exemestane group after three years. Overall, there is a lack of evidence to support an assumption of treatment waning and when this would occur; alpelisib plus fulvestrant is a treatment that is received continuously rather than for a set duration, and relatively long-term data are available from SOLAR-1 (follow-up from data beyond the three-year timepoint are available from SOLAR-1 (42.4 months [range: 33.1–55.7] for the final OS analysis). At the final OS analysis for SOLAR-1 (23rd April 2020), alpelisib plus fulvestrant showed longer-term benefit and a [redacted] risk reduction in disease progression or death over placebo plus fulvestrant ([redacted]). There was an approximate 14% reduction in the risk of death in the alpelisib plus fulvestrant arm compared with the placebo plus fulvestrant arm (HR: 0.86; 95% CI: 0.64, 1.15; p=0.15), albeit these results did not cross the pre-specified O-Brien Fleming stopping boundary (one-sided p≤0.0161).25, 26 We further believe that assuming a waning of treatment beyond 5 years is more realistic when considering the data that inform the NMA. Patients were followed up to 48 months in BOLERO-2, 36 months in SoFEA and 80 months in CONFIRM.19, 27, 28 Whilst there are long-term data available from SOLAR-1, the company does acknowledge the uncertainty in assuming an indefinite treatment effect for alpelisib plus fulvestrant versus everolimus plus exemestane. Thus, as part of an updated base case for this response, a waning of the treatment effect at five years has been implemented. This timepoint was chosen as three years is assumed to be overly pessimistic, whilst acknowledging the uncertainty associated with assuming an indefinite treatment effect. Updated base case results are presented in the Appendix below.	company's updated model that assumes a 5-year duration of treatment effect into consideration. The committee noted in section 3.16 of the final guidance that the company's assumed duration of treatment effect is not based on evidence, but it heard from a clinical expert that assuming a 5 year treatment effect is reasonable. The final guidance notes 'the assumption of a 5-year duration of treatment effect is uncertain'.
20	Company	Novartis	Novartis note a factual inaccuracy on page 17 of the ACD: "it also stated that before the committee meeting it did interviews with healthcare professionals." These meetings however were conducted for the technical engagement response and as such, Novartis would be grateful if the wording were updated as follows in the ACD: "it also stated that for the technical engagement response it did interviews with healthcare professionals."	Thanks for your comment. Section 3.17 of the final guidance has been corrected to reflect that company conducted interviews with clinical experts at technical engagement.
N/a	Company	Novartis	References: National Institute for Health and Care Excellence (NICE). Alpelisib with fulvestrant for treating hormone receptor-positive, HER2-negative, PIK3CA-mutated advanced breast cancer: Appraisal consultation document [ID3929]. Available at: https://www.nice.org.uk/guidance/gid-ta10825/documents/129 [Last accessed: 11 April 2022]. 2. National Institute for Health and Care Excellence (NICE). Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]: Appeal decision. Available at: https://www.nice.org.uk/guidance/gid-ta10624/documents/appeal-decision-2 [Last accessed: 11 April 2022]. 3. National Institute for Health and Care Excellence (NICE). Our Principles. Available at:	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			https://www.nice.org.uk/about/who-we-are/our-principles. [Last accessed: 14 April 2022]. 4. National Institute for Health and Care Excellence (NICE). Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]: Final Appraisal Document 2. Available at: https://www.nice.org.uk/guidance/gid-ta10624/documents/final-appraisal-determination-document-2 [Last accessed: 20 April 2022]. 5. Mosele F, Verret B, Lusque A, et al. Abstract 4895: Natural history and outcome of patients presenting a metastatic breast cancer with PIK3CA mutation. AACR. 2019;79. 6. Lai Y-L, Mau B-L, Cheng W-H, et al. PIK3CA exon 20 mutation is independently associated with a poor prognosis in breast cancer patients. Annals Surg Oncol 2008;15:1064-1069. 7. Sobhani N, Roviello G, Corona SP, et al. The prognostic value of PI3K mutational status in breast cancer: A meta-analysis. J Cell Biochem 2018;119:4287-4292. 8. Li SY, Rong M, Grieu F, et al. PIK3CA mutations in breast cancer are associated with poor outcome. Br Cancer Res Treat 2006;96:91-95. 9. Aleskandarany MA, Rakha EA, Ahmed MA, et al. PIK3CA expression in invasive breast cancer: a biomarker of poor prognosis. Breast Cancer Res Treat 2010;122:45-53. 10. Di Leo A, Johnston S, Lee KS, et al. Buparlisib plus fulvestrant in postmenopausal women with hormone-receptor-positive, HER2-negative, advanced breast cancer progressing on or after mTOR inhibition (BELLE-3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2018;19:87-100. 11. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med 2012;366:520-9. 12. Slamon DJ, Neven P, Chia S, et al. Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: MONALEESA-3. J Clin Oncol 2018;36:2465-2472. 13. Sledge GW, Jr., Toi M, Neven P, et al. MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. J Clin Oncol 2017;35:2875-2884. 14. Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol 2016;17:425-439. 15. Mosele F, Stefanovska B, Lusque A, et al. Outcome and molecular landscape of patients with PIK3CA-mutated metastatic breast cancer. Ann Oncol 2020;31:377-386. 16. Signorovitch J, Andre F, Wang I, et al. PIK3CA mutation status and progression-free survival in advanced hormone receptor positive (HR+)/ human endocrine receptor negative (HER2–) metastatic breast cancer (mBC): a meta-analysis of published clinical trials. Journal of Clinical Oncology 2020;38:1069. 17. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. Available at: https://www.nice.org.uk/process/pmg9/chapter/foreword [Last accessed: 20 April 2022]. 18. National Institute for Health and Care Excellence (NICE). NICE health technology evaluations: the manual. Available at: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation	

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			[Last accessed: 20 April 2022]. 19. Johnston SR, Kilburn LS, Ellis P, et al. Fulvestrant plus anastrozole or placebo versus exemestane alone after progression on non-steroidal aromatase inhibitors in postmenopausal patients with hormone-receptor-positive locally advanced or metastatic breast cancer (SoFEA): a composite, multicentre, phase 3 randomised trial. Lancet Oncol 2013;14:989-98. 20. National Institute for Health and Care Excellence (NICE): TA725. Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy. Available at: https://www.nice.org.uk/guidance/ta725 [Last accessed: 11 April 2022]. 21. National Institute for Health and Care Excellence (NICE): TA687. Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer. Available at: https://www.nice.org.uk/guidance/TA687 [Last accessed: 11 April 2022]. 22. National Institute for Health and Care Excellence (NICE): TA619. Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer. Available at: https://www.nice.org.uk/guidance/TA619 [Last accessed: 11 April 2022]. 23. Lloyd A, Nafees B, Narewska J, et al. Health state utilities for metastatic breast cancer. British journal of cancer 2006;95:683-690. 24. Mitra D, Wood R, De Courcy J, et al. Patient reported health utility in HR+/HER2- advanced/metastatic breast cancer. Value in Health 2016;19 (7):A749. 25. Novartis. Clinical Overview of Alpelisib in Combination with Fulvestrant in Subjects with HR-positive, HER2-negative, Advanced Breast Cancer with PIK3CA Mutation. Data on File. 2021. 26. André F, Ciruelos EM, Juric D, et al. Alpelisib Plus Fulvestrant for PIK3CA-Mutated, Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor-2-Negative Advanced Breast Cancer: Final Overall Survival Results From SOLAR-1. Ann Oncol 2021;32:208-217. 27. Piccart M, Hortobagyi, G. N., Campone, M., Pritchard, K. I., et al. Everolimus plus exemestane for hormonereceptor- positive, human epidermal growth factor receptor-2-negative advanced breast cancer: Overall survival results from BOLERO-2. Ann Onc 2014;25:2357-2362. 28. Di Leo A, Jerusalem G, Petruzelka L, et al. Results of the CONFIRM phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer. J Clin Oncol 2010;28:4594-600.	

Document processed	Organisation name – Stakeholder or respondent	Disclosure on tobacco funding / links	Number of comments extracted	Comments
Alpelisib response draft_METUPUK_26.4.22	Patient organisation – METUP UK	[None]	2	**Number 1 and 2 in table above**
Breast Cancer Now_ ACD stakeholder comments form_ alpelisib RZ 210422	Patient organisation – Breast Cancer Now	N/A	5	**Number 3–7 in table above**
[ID3929] alpelisib - ACD web comments - 050522 [noACIC]	Patient – Current patient and NHS physician	[None]	1	**Number 8 in table above**
ID3929 alpelisib advanced breast cancer PIK3Ca mutation_ACD v0.10_final to PM_240322_ [no ACIC] response RZ 290322	Clinical expert – Dr Catherine Harper-Wynne	[None]	3	**Number 9–11 in table above**
ID3929 Novartis_Alpelisib_ACD Response_210422 RZ [ACIC]	Company – Novartis	Since April 2005 Novartis has exclusively licensed glycopyrronium bromide and certain intellectual property relating to its use and formulation from Vectura and its co-development partner, Sosei Heptares. The following inhaled medications are comprised of, or contain glycopyrronium bromide: • Seebri® Breezhaler® (glycopyrronium bromide) (used as a maintenance treatment for Chronic Obstructive Pulmonary Disease [COPD]) • Ultibro® Breezhaler® (indacaterol/glycopyrronium bromide) is used as a maintenance treatment for COPD • Enerzair® Breezhaler® (indacaterol/glycopyrronium bromide/mometasone furoate) is used as a maintenance treatment for asthma uncontrolled with LABA/ICS. Phillip Morris International (a tobacco company) is currently in the process of acquiring Vectura Group plc.	9	**Number 12–20 in table above**

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Alpelisib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative, PIK3CA-mutated breast cancer [ID3929]

Consultation on the appraisal consultation document – deadline for comments 5pm on 21 April 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. 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 provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Novartis Pharmaceuticals UK Ltd

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Since April 2005 Novartis has exclusively licensed glycopyrronium bromide and certain intellectual property relating to its use and formulation from Vectura and its co-development partner, Sosei Heptares. The following inhaled medications are comprised of, or contain glycopyrronium bromide: • Seebri® Breezhaler® (glycopyrronium bromide) (used as a maintenance treatment for Chronic Obstructive Pulmonary Disease [COPD]) • Ultibro® Breezhaler® (indacaterol/glycopyrronium bromide) is used as a maintenance treatment for COPD • Enerzair® Breezhaler® (indacaterol/glycopyrronium bromide/mometasone furoate) is used as a maintenance treatment for asthma uncontrolled with LABA/ICS. Phillip Morris International (a tobacco company) is currently in the process of acquiring Vectura Group plc.
Name of commentator person completing form:	[redacted]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Novartis is disappointed by the draft recommendation from NICE to not recommend alpelisib plus fulvestrant for the treatment of hormone receptor positive (HR+), human epidermal growth factor 2 negative (HER2–), locally advanced or metastatic breast cancer with a phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA)* mutation after disease progression following a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i). The Committee regards alpelisib plus fulvestrant as providing *"another step in delaying cytotoxic chemotherapy*", with clinical experts favouring to offering targeted treatment options for patients with advanced breast cancer (ABC). The Committee also heard that, for those patients with a *PIK3CA* mutation, "*knowing a drug was targeted to their mutation was very powerful and had a positive emotional impact*."[1] This is particularly important given the fact that patients in this population have a substantial unmet need due to there being limited treatment

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	options after CDK4/6is, and where the mainstay of treatment offers limited survival benefit. If the initial decision remains unchanged, patients will be denied access to the first targeted treatment option for ABC that has a *PIK3CA* mutation. Novartis is grateful for the opportunity to respond to the Appraisal Consultation Document (ACD) to address the outstanding questions and would like to provide further comment and clarification on the remaining uncertainties in the appraisal. The following topics are addressed within this response: • End-of-life (EoL) criteria • Probabilistic sensitivity analyses (PSA) • HER2– subgroup in the indirect treatment comparison (ITC) • 'Reverse' Bucher method for the ITC • Method of *PIK3CA* identification in the ITC • Post-progression utility values • Treatment waning assumptions • Point of factual inaccuracy In addition to the comments provided within this document, a revised economic model and appendix at the end of this response have been provided with a revised base case that includes a treatment waning assumption applied at 5 years. Novartis has also submitted an adjustment to the existing Patient Access Scheme (PAS) price for alpelisib to PASLU. The cost-effectiveness analyses in the appendix are based on this revised PAS price.
2	**Alpelisib plus fulvestrant meets the EoL criteria set out by NICE when considering the totality of the evidence available and their basis in NICE's Social Value Judgements, as set out in the appeal decision for avelumab**

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	Section 3.19 of the ACD states that the Committee *"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."* As set out in the recent appeal for the appraisal of avelumab for the maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy (and acknowledged by the Committee in 3.21 of the avelumab FAD; ID3735), due consideration must be applied to the totality of evidence available, and the social value judgments underpinning the decision modifier, when assessing whether a drug meets the short life expectancy criterion:[2-4] • Patients with HR+, HER2– ABC with a *PIK3CA* mutation have a poor prognosis, with a shorter overall survival (OS) and progression-free survival (PFS), and reduced sensitivity to chemotherapy compared with wild-type *PIK3CA* disease.[5-16] • The poor prognosis (less than 24 months) for this group of patients is supported by the model predictions. The mean undiscounted life years marginally exceed 24 months only in a limited set of scenarios. Further, the likelihood of those scenarios is low, due to outliers in the PSA (evidenced by the number of clinically implausible sample estimates, as noted by the Committee and stated in the ACD [described in response 3]), and the lack of evidence of HER-2 status as a treatment effect modifier and clinically inconsistent results observed in SoFEA for the HER2– subgroup (as described in response 4). • The short life expectancy (less than 24 months) of this group of patients was also reiterated by both clinical experts during the Committee Meeting. As highlighted in the ACD, clinical experts stated that patients *"are unlikely to live longer than 24 months."* Evidence further suggests that alpelisib plus fulvestrant is able to extend life expectancy by >3 months: • While there are some uncertainties in the treatment effect due to the single arm nature of BYLieve, the model predictions demonstrate that alpelisib plus fulvestrant increases life expectancy compared with everolimus plus exemestane by greater than three months. Again, this criterion is not met only in an extreme and unrealistic scenario due to outliers in the PSA.

Alpelisib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative, PIK3CA-mutated breast cancer [ID3929]

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	• Further supportive evidence that alpelisib is able to extend life expectancy by >3 months is provided by the SOLAR-1 trial, where alpelisib plus fulvestrant had a median OS of 39.3 versus 31.4 months for fulvestrant (difference of 7.9 months). Clinical experts during the Committee Meeting suggested that it was not unreasonable to assume fulvestrant to be as efficacious as everolimus plus exemestane, and therefore data from SOLAR-1 support the conclusion that alpelisib is able to extend life expectancy by >3 months compared with everolimus plus exemestane. Following the Committee Meeting, Novartis have engaged with four external clinical experts about their experiences of *PIK3CA*-mutated cancer in the context of the end-of-life criteria for this appraisal. Three of the experts considered that patients with *PIK3CA*-mutated ABC following CDK4/6i treatment would not be expected to live beyond 24 months, whilst the other one was unable to comment. For the extension to life criterion, the clinical experts found it challenging to comment on this in the absence of head-to-head data, and in the absence of long-term experience using alpelisib plus fulvestrant in clinical practice, however the data presented above support that alpelisib plus fulvestrant extends life expectancy by >3 months. In conclusion, considering the totality of the evidence available and the social value judgements underpinning the modifier, alpelisib plus fulvestrant meets the EoL criteria.
3	**The probabilistic analysis in its current form is not suitable for decision-making and a constraint is required to ensure results are clinically plausible, as suggested in the updated method guide** Novartis recognise and agree with the standard approach that results from the PSA should typically be considered to account for the combined effects of uncertainty. However, in the context of this appraisal, there are significant concerns in using PSA results for decision-making, as acknowledged by the ERG (Section 5.3.4, page 114 of the ERG report) and Committee (Section 3.20, page 20 of the ACD). In its current form, the PSA generates results which clinical experts described as clinically implausible during the Committee Meeting, and as acknowledged in the ACD ("*sampled treatment effect sometimes suggests a considerable and clinically implausible lower effectiveness of alpelisib plus fulvestrant compared with everolimus plus exemestane*"). As such, these results should not be considered in decision-making as justified below. The probabilistic sampling of OS suggests that alpelisib plus fulvestrant is associated with reduced survival (undiscounted) as compared with everolimus plus exemestane in ~20% of samples. Whilst Novartis recognise that it may be possible for some of

	the probabilistic iterations to favour everolimus plus exemestane, the extent of increase in life years for everolimus plus exemestane predicted in the model is clinically implausible in a large number of iterations. As highlighted in the ERG report (Section 5.3.4, page 114 of the ERG report), "*in several samples, the incremental loss in survival for Alp/Fulv is substantial; this is unlikely to be plausible*" with estimates of a difference in life years gained of up to 8 years in favour of everolimus plus exemestane. When considering the 20.4% of PSA iterations where everolimus plus exemestane was more effective compared with alpelisib plus fulvestrant, the mean (median) relative increase in life years for everolimus plus exemestane is large and clinically unlikely at 44.2% (26.3%) as shown in Figure 1 (graph generated using the original submitted base case version of the model).

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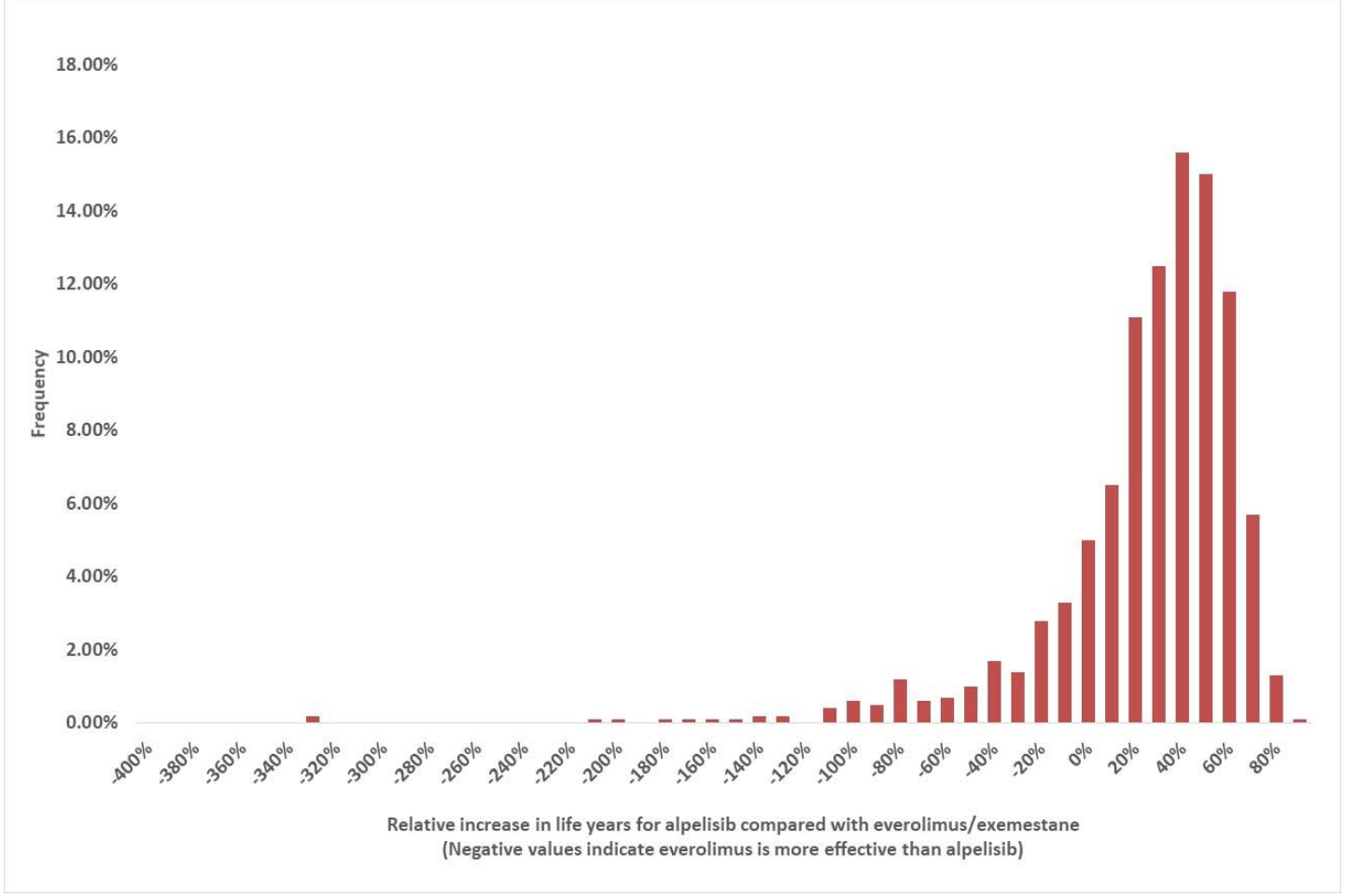
Figure 1: Relative increase in life years for everolimus plus exemestane compared with alpelisib



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	Although implicit in the NICE method guide (2013) that is applicable to this appraisal, clarity on how to handle uncertainty when analyses are clinically implausible is provided in the updated NICE method guide (2022).[17, 18] Whilst this appraisal is subject to the earlier methods guide, the spirit of the following clarifications has broad application and are equally justifiable in this appraisal: • Section 4.6.27: *"In general, all model parameter values used in base-case, sensitivity, scenario and subgroup analyses should be both clinically plausible and should use methods that are consistent with the data. Results from analyses that do not meet these criteria will not usually be suitable for decision making."* • Section 4.6.28: *"Sometimes it may be difficult to define what is plausible and what is not, for example, in very rare conditions or for innovative medical technologies, when the evidence base may be less robust. In such situations, consider expert elicitation to identify a plausible distribution of values"* Consequently, Novartis consider that results from the PSA are not suitable in their current form, given the scope to introduce biases into the interpretation of the results informing decision making. Novartis continue to consider the deterministic results to be more appropriate to inform the cost-effectiveness of alpelisib plus fulvestrant. As we recognise the Committee's preference to use probabilistic results to account for the combined uncertainty, Novartis have, therefore, sought clinical expert opinion to identify a plausible distribution of values for OS efficacy, in line with the NICE method guide (Section 4.6.28). Clinical experts were asked to specify the extent of increase in life years for everolimus plus exemestane compared with alpelisib plus fulvestrant that would be deemed to be clinically implausible. Two of the four clinical experts consulted considered that an increase in life years for everolimus plus exemestane greater than 10% would be clinically implausible. The third clinical expert considered between 5–10% would be the limit of clinical plausibility whilst the fourth was not able to provide an estimate. Consequently, in line with the NICE method guide and to ensure results are clinically plausible and suitable for decision-making, the PSA has been amended to remove iterations where everolimus plus exemestane was associated with an increase in life year greater than 10% as elicited by clinical experts. The updated PSA results, incorporating this constraint, are presented in the Appendix to this response.

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4	**Use of the full population from SoFEA is appropriate in the Bucher analysis, and consistent with prior appraisals in previously treated, advanced breast cancer** Section 3.10 of the ACD states that "*the committee concluded that the results of the Bucher analysis are highly uncertain for several reasons*", including that "*there is the potential for HER2 status to be an effect modifier.*" As described in the Company Submission, two relevant trials were identified to connect SOLAR-1 and BOLERO-2: SoFEA and CONFIRM. Both trials included patients with HER2+ and HER2– ABC, and only SoFEA reported results separated by HER2 status. Whilst there is an observed difference between the populations with HER2+ and HER2– tumours in the SoFEA trial, with the effect of fulvestrant 250 mg versus exemestane being favourable in patients with HER2+ tumours and unfavourable in those with HER2– tumours, it is uncertain if this difference is a result of a treatment modifying effect or external, limiting factors. Approximately 35% of patients in SoFEA had unknown HER2 status (n=166), and as such the estimated HRs for patients with known HER2 status may be affected by information bias. Similarly, the numbers of patients with known HER2+ status were small (6%; n=31) and so estimates for this subgroup may be unreliable. Use of the full population of SoFEA is also in line with the use of the full population of CONFIRM (where results by HER2 status were not available). Further to this, the hazard ratios (HRs) for PFS and OS in the HER2– subgroup in SoFEA for fulvestrant 150 mg versus exemestane were 1.06 (95% CI: 0.83, 1.34) and 1.26 (95% CI: 0.95, 1.66), respectively, leading to a prediction that exemestane is more effective than fulvestrant, which we believe lacks face validity and further highlights the uncertainty in the results of the subgroup analysis.[19] Based on these results, Novartis do not consider the data from the SoFEA trial to provide any evidence that HER2 status is a treatment effect modifier as it is unclear if the observed difference is in fact an artifact of the bias arising from the small sample size. To date, all of the NICE appraisals for CDK4/6is in combination with fulvestrant that use CONFIRM and SoFEA in their networks to connect to everolimus plus exemestane use the overall population and the Committee have found this a reasonable basis for decision making on each occasion.[20-22] These prior appraisals were all also for drugs indicated for patients with HER2– disease only. Therefore, if the HER2– subgroup of SoFEA were to be used in this appraisal, this would represent the first time this approach had been taken in an appraisal for ABC and would contradict the aforementioned precedent.

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	Overall, the use of the full population from SoFEA is considered the most appropriate approach for the Bucher analysis; there are insufficient data to support a conclusion that HER2 status is a treatment effect modifier and use of the HER2– subgroup in the Bucher analysis would be inconsistent with prior appraisals within ABC.
5	**Use of a 'reverse' Bucher method was required to allow comparison, and did not lead to an increase in uncertainty** Further to points 3 and 4 above, Section 3.10 of the ACD states that "*the committee concluded that the results of the Bucher analysis are highly uncertain for several reasons*", including because "*a reverse Bucher was done, deriving comparator hazard ratios from those known for alpelisib plus fulvestrant."* This approach was used because the evaluation was based on survival data for alpelisib plus fulvestrant from the BYLieve trial. As stated on page 7 of the ACD, patients in BYLieve were generalisable to UK clinical practice because they had previously progressed on a CDK4/6 inhibitor. However, since BYLieve was a single-arm trial, it was necessary to estimate PFS and OS curves for everolimus plus exemestane by applying estimates of the HRs for PFS and OS for everolimus plus exemestane versus alpelisib plus fulvestrant to the estimated PFS and OS curves for alpelisib plus fulvestrant. It is unclear to the company why the method employed would introduce any more uncertainty than the approach considered by the ERG to be the more standard approach. There is no rationale outlined in the ACD in this regard and this was not discussed in the ERG report in any context. As such, the conclusion that this approach introduces uncertainty is overstated, and rather the approach taken is simply an alternative approach based on the available data.
6	**Utilising *PIK3CA* mutation data based on tumour sampling is an appropriate approach for the Bucher ITC** Section 3.9 of the ACD states that *"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."* This approach was taken by the company because the study populations in SOLAR-1 and BYLieve trials assessed *PIK3CA* mutation based on tumour samples. Patients with *PIK3CA*-mutated disease in BOLERO-2 using tumour samples were therefore

	utilised for consistency, as use of different sampling methods across trials may introduce potential bias. For example, in the study by Moynahan *et al.* (2017) among patients with *PIK3CA*-mutated disease identified by circulating tumour DNA (ctDNA), the HR for PFS for everolimus plus exemestane versus exemestane was 0.37 (95% CI: 0.27, 0.51); in the study by Hortobagyi *et al.* (2016) among patients with *PIK3CA*-mutated disease identified by plasma samples, the HR for PFS for everolimus plus exemestane versus exemestane was 0.51 (95% CI: 0.34, 0.77). Neither study looked at OS, but this suggests the sampling method used yields different HRs for PFS. Whilst information on *PIK3CA* mutations based on ctDNA was also collected in SOLAR-1, basing the analysis on such data would have broken randomisation (subjects in SOLAR-1 were randomised within the *PIK3CA*-mutated cohort with the mutation identified based on tumour samples).
7	**The post-progression utility value of 0.69 from the literature source, Mitra *et al.*, is the most appropriate estimate to use in the cost-effectiveness model** Section 3.17 of the ACD states that *"the committee concluded that the appropriate utility value for the modelled health state after disease progression is uncertain and may be overestimated by company."* Novartis maintains that applying the utility value from Mitra et al (2019) is the most appropriate value to use. As highlighted at technical engagement and acknowledged by the ERG (reflected their preferred analysis), the value from Lloyd et al (2006) is not appropriate. Changes to the treatment landscape in ABC over the last 15 years mean that the vignette description from Lloyd *et al.* (2006) no longer reflects the experiences of patients in the modelled post-progression health state.[23] As highlighted in our technical engagement response, the utility value derived from Mitra et al. is also methodologically preferable to the value from Lloyd et al. because the study used EQ-5D to measure health-related quality of life in people with breast cancer. To validate the most appropriate value to inform the cost-effectiveness model, Novartis conducted a series of interviews with four additional clinical experts (the ACD states that these meetings were conducted prior to the Committee Meeting; however, these were conducted for the technical engagement response). All four of the clinical experts interviewed by Novartis considered that patients seen in their practice at a third-line setting (i.e. equivalent to the post-progression survival (PPS) state in the cost-

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	effectiveness model) would have a utility that is reflective of the Mitra *et al.* (2016) publication, noting that this value is very similar to the PPS value of [redacted] measured in the SOLAR-1 trial. Clinical experts during the Committee Meeting provided further validation that the value from Mitra et al (2019) was deemed to be clinically plausible. In addition, the most recently appraised technology in ABC (TA725; abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy) proposed a utility value for the PPS state from Mitra *et al.* (2016), with a value for the PPS health state of 0.69.* [20, 24] In TA725, this value was considered to be methodologically preferable as compared to that derived from Lloyd *et al.* (2006) due to the use of EQ-5D to measure health-related quality of life in people with breast cancer.[20, 23, 24] This value was used as part of the base case on which the NICE Committee based their decision to recommend the technology. During the 15 March meeting, the Committee members heard that the validity of using the value from Mitra was also discussed in TA725. Specifically, it was raised that a value of 0.69 may be too high, when considering this value represents the experience of patients during all subsequent treatments, including chemotherapy. It was nonetheless accepted as a basis for decision making. The rationale for why an inconsistent decision has been made – by the same Committee, in the face of the same information, within a 12-month period – has not been provided. Following technical engagement, the ERG preferred-base-case uses an arbitrary value of 0.6. In the ERG's commentary on the company's technical engagement response, they highlighted input from one clinical expert they had consulted which suggested that a value of [redacted] would be consistent with the patient population in question. A second clinical expert suggested that a value between [redacted] would be reasonable in the third-line setting (i.e. a mid-point between Mitra *et al.* [2016] and Lloyd *et al.* [2006]).[23, 24] Despite this, an arbitrary value of 0.6 was used by the ERG which is inconsistent with estimates from their own clinical experts, and uses the most pessimistic estimate.

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	Overall, Novartis strongly believe that the post-progression utility value of 0.69 from the literature source, Mitra *et al.*, is the most appropriate estimate from an evidence-based, methodological standpoint, and is also in line with previous Committee discussion and agreement in TA725. Novartis further note that a utility value of 0.65 and above is more closely aligned with that elicited from the ERG clinical experts: a value of 0.6 is arbitrary and reflects the most pessimistic estimate. * Please note: this is reported as 0.670 in TA725, however, the source publication states that the utility value for third-line or later patients with ABC is 0.69.[20, 24]
8	**Assuming treatment waning at a three-year timepoint is overly pessimistic given a lack of data to support waning assumptions; a five-year timepoint is a more reasonable assumption and has been adopted in the updated company base case** Section 3.15 of the ACD states that the model "*assumes that the treatment effects of alpelisib plus fulvestrant compared with everolimus plus exemestane are indefinite with no loss of treatment effect over time*", and that "*the committee concluded that the assumption of an indefinite treatment effect is optimistic."* Whilst there is uncertainty in the longevity of the treatment effect associated with alpelisib plus fulvestrant, given an absence of long-term data equivalent to the lifetime horizon of the economic model, it is pessimistic to assume that the hazards for the alpelisib plus fulvestrant group would switch to the hazards for the everolimus plus exemestane group after three years. Overall, there is a lack of evidence to support an assumption of treatment waning and when this would occur; alpelisib plus fulvestrant is a treatment that is received continuously rather than for a set duration, and relatively long-term data are available from SOLAR-1 (follow-up from data beyond the three-year timepoint are available from SOLAR-1 (42.4 months [range: 33.1–55.7] for the final OS analysis). At the final OS analysis for SOLAR-1 (23rd April 2020), alpelisib plus fulvestrant showed longer-term benefit and a [redacted] risk reduction in disease progression or death over placebo plus fulvestrant ([redacted]). There was an approximate 14% reduction in the risk of death in the alpelisib plus fulvestrant arm compared with the placebo plus fulvestrant arm (HR: 0.86; 95% CI: 0.64, 1.15; p=0.15), albeit these results did not cross the pre-specified O-Brien Fleming stopping boundary (one-sided p≤0.0161).[25, 26] We further believe that assuming a waning of treatment beyond 5 years is more realistic

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	when considering the data that inform the NMA. Patients were followed up to 48 months in BOLERO-2, 36 months in SoFEA and 80 months in CONFIRM.[19, 27, 28] Whilst there are long-term data available from SOLAR-1, the company does acknowledge the uncertainty in assuming an indefinite treatment effect for alpelisib plus fulvestrant versus everolimus plus exemestane. Thus, as part of an updated base case for this response, a waning of the treatment effect at five years has been implemented. This timepoint was chosen as three years is assumed to be overly pessimistic, whilst acknowledging the uncertainty associated with assuming an indefinite treatment effect. Updated base case results are presented in the Appendix below.
9	Novartis note a factual inaccuracy on page 17 of the ACD: "*it also stated that before the committee meeting it did interviews with healthcare professionals*." These meetings however were conducted for the technical engagement response and as such, Novartis would be grateful if the wording were updated as follows in the ACD: "*it also stated that for the technical engagement response it did interviews with healthcare professionals.*"

Insert extra rows as needed

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under [redacted] and all information submitted under [redacted]. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
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Appendix: Revised company base case

The revised company base case for this appraisal, compared with that submitted at technical engagement, includes a revised PAS ([redacted]) and the following settings, taking into account the Committee's preferences:

- Treatment waning applied from 5 years
- Constraint added to PSA to remove iterations where everolimus plus exemestane was associated with an increase in life years of greater than 10% as elicited by clinical experts

Deterministic base case

Table 1: Base case results – WITH PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Company base case at Technical Engagement							
Alpelisib plus fulvestrant	[redacted]	2.36	[redacted]	[redacted]	0.62	[redacted]	49,881
Everolimus plus exemestane	[redacted]	1.73	1.21	-	-	-	-
Company base case at Technical Engagement + treatment effect duration = 5 years							
Alpelisib plus fulvestrant	[redacted]	2.25	[redacted]	[redacted]	0.52	[redacted]	37,410
Everolimus plus exemestane	[redacted]	1.73	1.21	-	-	-	-
Company base case at Technical Engagement + updated PAS							
Alpelisib plus fulvestrant	[redacted]	2.36	[redacted]	[redacted]	0.62	[redacted]	37,873
Everolimus plus exemestane	[redacted]	1.73	1.21	-	-	-	-
Updated company base case (combining both treatment waning assumption and updated PAS)							
Alpelisib plus fulvestrant	[redacted]	2.25	[redacted]	[redacted]	0.52	[redacted]	38,787
Everolimus plus exemestane	[redacted]	1.73	1.21	-	-	-	-

Abbreviations: AI: aromatase inhibitor; CDK: cyclin-dependent kinase; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life years.

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Probabilistic base case

Table 2: PSA results – WITH PAS

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Company base case at Technical Engagement					
Alpelisib plus fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	55,171
Everolimus plus exemestane	[redacted]	1.37	-	-	-
Updated company base case (combining both treatment waning assumption and updated PAS)					
Alpelisib plus fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	41,664
Everolimus plus exemestane	[redacted]	1.37	-	-	-
Updated company base case (combining both treatment waning assumption and updated PAS), applying constraint to remove clinically implausible iterations					
Alpelisib plus fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	37,541
Everolimus plus exemestane	[redacted]	1.16	-	-	-

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life years.

Figure 2: Cost-effectiveness plane – Company base case at Technical Engagement

Abbreviations: PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years.

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Figure 3: Cost-effectiveness acceptability curve – Company base case at Technical Engagement

Abbreviations: WTP: willingness to pay.

Figure 4: Cost-effectiveness plane – Updated company base case (combining both treatment waning assumption and updated PAS)

Abbreviations: PAS: patient access scheme; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years.

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Figure 5: Cost-effectiveness acceptability curve – Updated company base case (combining both treatment waning assumption and updated PAS)

Abbreviations: PAS: patient access scheme; WTP: willingness to pay.

Figure 6: Cost-effectiveness plane – Updated company base case (combining both treatment waning assumption and updated PAS), applying constraint to remove clinically implausible iterations

Abbreviations: PAS: patient access scheme; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years.

Alpelisib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative, PIK3CA-mutated breast cancer [ID3929]

Consultation on the appraisal consultation document – deadline for comments 5pm on 21 April 2022. Please submit via NICE Docs.

Figure 7: Cost-effectiveness acceptability curve – Updated company base case (combining both treatment waning assumption and updated PAS), applying constraint to remove clinically implausible iterations

Abbreviations: PAS: patient access scheme; WTP: willingness to pay.

NICE National Institute for Health and Care Excellence

Alpelisib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative, PIK3CA-mutated breast cancer [ID3929]

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Table 1: PSA results – WITH PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Company base case at Technical Engagement							
Alpelisib plus fulvestrant	[redacted]	2.71	[redacted]	[redacted]	0.54	[redacted]	55,171
Everolimus plus exemestane	[redacted]	2.17	1.37	-	-	-	-
Updated company base case (combining both treatment waning assumption and updated PAS)							
Alpelisib plus fulvestrant	[redacted]	2.33	[redacted]	[redacted]	0.37	[redacted]	41,664
Everolimus plus exemestane	[redacted]	1.96	1.37	-	-	-	-
Updated company base case (combining both treatment waning assumption and updated PAS), applying constraint to remove clinically implausible iterations							
Alpelisib plus fulvestrant	[redacted]	2.26	[redacted]	[redacted]	0.62	[redacted]	37,541
Everolimus plus exemestane	[redacted]	1.64	1.16	-	-	-	-

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life years.

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Alpelisib with fulvestrant ID3929

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 21 April 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. 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 provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Breast Cancer Now
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	It is disappointing that NICE has provisionally been unable to recommend alpelisib with fulvestrant as it would have improved the options available for this group of patients and would provide the first

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	targeted treatment for patients with a PIK3CA mutation. We urge the company, Novartis and NICE to work together during this consultation period to consider every possible solution. In particular, it is difficult to understand why the Cancer Drugs Fund (CDF) is not being considered a potential option in this case. Whilst there may not be a suitable clinical trial ongoing that will resolve the uncertainties that exist, we understand that types of data collection for drugs on the CDF will vary from drug to drug and can include SACT and population-based datasets. We would therefore welcome clarity on the reasons why the CDF is not being explored as this could be an important route to enabling access to patients whilst further data is collected.
2	We would reiterate as per our original submission that following progression on a CDK 4/6 plus aromatase inhibitor there are limited effective treatment options – with everolimus and exemestane generally having poor uptake due to the side effect profile and therefore in some instances single agent capecitabine being preferred. Alpelisib with fulvestrant could provide an important new treatment option, especially as PIK3CA mutations can be associated with a poorer prognosis and increased resistance to treatments.
3	We urge flexibility regarding the end of life criteria given the uncertainties that have been highlighted and given that it is possible that alpelisib with fulvestrant does in need meet end of life criteria. We would welcome the company and NICE working together to identify the further data and modelling that would be required to ensure the evidence is as robust as it can be.
4	We are surprised that alpelisib has not been recognised as an innovative treatment, given the role PIK3CA may play in progression and that the treatment specifically targets this and could provide an important additional treatment option. As a patient explains: “it is important to me as patient that I can access a drug which targets a mutation I know that I have.” The patient goes on to explain: “A tailored approach to our treatment as patients clearly will optimise our chances of a treatment response and mean that money is well spent on a treatment we know works more effectively in the population it is being used in.”
5	A patient with this type of breast cancer who knows they have the PIK3CA mutation explains: “I am 53 years old and have worked as a neurologist in the NHS for nearly 30 years. Aged 48 I was first diagnosed with ER+ breast cancer and unfortunately in 2021 it recurred despite full compliance with both Letrozole and also a trial of abemaciclib (CDK 4/6 inhibitor) as part of MonarchE. The tumour recurred in both my retrocrural and retroperitoneal lymph nodes so it was not resectable. It expresses PIK3CA and this was also found in my blood. My conclusion is that the tumour acquired a PIK3CA mutation and that this directly contributed to endocrine resistance, resulting in my recurrence and my current prognosis. Current treatments available on the NHS for this type of breast cancer (e.g. normally after a CDK 4/6 inhibitor with an aromatase inhibitor treatment include everolimus with exemestane or capecitabine). Unfortunately there is a significant toxicity profile with this combination and although there seem to be few studies making a direct comparison, it is important to me as patient that I can access a drug which targets a mutation I know that I have. Alpelisib is the first drug which can do this in the area of advanced breast cancer for patients with this mutation. There is therefore a significant likely impact that alpelisib with fulvestrant could make if it was recommended for use on the NHS. There is a major unmet need for therapies that specifically address the effects of this mutation as there are currently no recommended therapies that specifically target the PIK3CA mutation for UK patients who have it with endocrine resistant HR+, HER2– advanced breast cancer (ABC). This is

Alpelisib with fulvestrant ID3929

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 21 April 2022. Please submit via NICE Docs.

	what I have as I also now have bone metastases which are growing as they are ER+. My risk of developing more visceral disease without targeted treatment for PIK3CA is very high and it's very important to have more than one option, especially when there are associated toxicities. Options are crucially important for patients in my position. I understand that UK clinicians report that improvements in progression free survival alone with alpelisib and fulvestrant and therefore this would give me more options that the toxicity I will get from prolonged chemotherapy or combination treatment with everolimus and exmestene/capecitabine. Patients can get side effects from a range of medications and it is crucial to have choices in situations such as mine. It is imperative that new treatments that improve survival and provide personalised options for clinicians are made available. There is clearly a high unmet need as I am one of the 40% of women who develop this mutation as a cause for their recurrence and I now have incurable breast cancer. Without this treatment my options for survival to look after my children (aged 12 and 16) are significantly reduced. I have served my patients all my working life and now find myself in this catastrophic position of perhaps having very few months to live unless I can access targeted treatments which may help me. I am at least fortunate that I know I have the mutation so that I can keep searching for potential treatments but I am deeply concerned that there is currently a lack of treatment options with the associated genomic test for this mutation. This should be standard practice so that it can be used to predict which patients are likely to benefit from treatment. A tailored approach to our treatment as patients clearly will optimise our chances of a treatment response and mean that money is well spent on a treatment we know works more effectively in the population it is being used in. This is not the case for many drugs we prescribe as doctors and therefore this drug represents not only better value for money because it can be targeted but also it is the future for patients like me as improvements in survival from metastatic cancer will be afforded by personalised (genomic) medicine As a doctor and a patient I know that trial data has shown alpelisib in combination with fulvestrant to be effective in prolonging progression free survival in advanced hormone receptor-positive, HER2-negative, PIK3CA-positive breast cancer. Progression free survival means the world to me as it means I can spend more vital time with my family. I would urge you to progress this as quickly as possible in order to help all those on my position whose very lives depend on it."

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or

Alpelisib with fulvestrant ID3929

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 21 April 2022. Please submit via NICE Docs.

the person could be identified.

- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Alpelisib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative, PIK3CA-mutated breast cancer [ID3929]

Consultation response from patient group METUPUK

Contact details: [redacted]

- Has all of the relevant evidence been taken into account?

As lay people, the different models produced by the company and the ERG are too technical to be accessible. Although, we did note that models used the same evidence modelled in different ways to come up with different conclusions.

To help make sense of this, we looked at a third source of evidence for more information, the ESMO guidelines. We understand the ESMO guidelines do not take into account value for healthcare systems, only clinical outcomes, and so are not identical in purpose. The ESMO guidelines state alpelisib–fulvestrant is a treatment option for patients with PIK3CA-mutant tumours, noting the need to carefully select candidates for this treatment, considering comorbidities, especially pre-existing diabetes.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No comments due to redactions in both the trial evidence and the cost of the treatment and comparators.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No, the recommendations are not a sound guidance for the NHS. Successive health secretaries have lauded genomics as the future for cancer care. In 2020 the government published Genome UK: the future of healthcare which hailed the use of personalised medicine and pharmacogenomics in the NHS. As noted in the supporting documents, genomic testing is being rolled out for patients with MBC across the NHS from April 2022. For patients who have had genomic testing, the knowledge that they have a targetable mutation for which there is a treatment but that the treatment is not funded is a blow. Alpelisib is the first treatment available which targets the PIK3CA mutation in ER-positive HER2-negative MBC, so we believe it is innovative. Patient advocate Emma writes:

"I had genetic testing via the Foundation One test which identified I have a PIK3CA mutation and recommended the drug combination of alpelisib and fulvestrant as a good option for me. NICE, with their decision to not recommend alpelisib and fulvestrant for use in the NHS have taken this opportunity and thus my hope for the future away - unless we are able to fund these drugs ourselves which is extremely unlikely. I fail to understand why this has been rejected when it targets a very specific mutation for which there is little else available. What is the point in telling patients they have this mutation and then not allowing us to access the drugs? All I want is the opportunity to try and this decision will deny me that."

We believe there is an unmet need for a treatment which targets the PIK3CA mutation. The recommendation for use of alpelisib–fulvestrant by ESMO indicates that this treatment is being used in many European countries. We understand alpelisib–fulvestrant has a toxicity profile which means it is not suitable for all patients with a PIK3CA mutation, and would expect patient selection to be a decision for oncologists alongside their patients to make.

- 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?

None noted.

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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?

Issue date: March 2022

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

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.

Commented [public1]: This is not a fair staement as usually only is a contradiction in terms and infact chemotherapy may be used in this situation rather than everolimus exemestane

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.

Commented [public2]: There is also no clinical trial evidence for the use of everolimus eexemestane compared to chemotherapy. Being a legacy regimen means that an expensive treatment option with no evidence is allowed but a new targeted treatment for a smaller population cannot . This is inconsistent.

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.

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

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

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

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.

Commented [public3]: How has this figure been arrived at, as although can pick up from CDF those applying for everolimus exemestane that requires funding approval , will not see number receiving single agent chemo as not using CDF??

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

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~~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.

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 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

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.

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 3.93.10). 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.

- 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

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-

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.

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

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

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

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.

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

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

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.

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.

Catherine Spanswick
Technical lead

CONFIDENTIAL UNTIL PUBLISHED

Carl Prescott
Technical adviser

Jeremy Powell
Project manager

ISBN: [to be added at publication]

Issue date: March 2022

Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	No
Notes	
Comments on the ACD:	

I am an NHS physician and now a patient. Aged 48 I was first diagnosed with ER+ breast cancer and unfortunately in 2021 it recurred despite full compliance with both Letrozole and also a trial of Abemaciclib (CDK 4/6 inhibitor) as part of Monarch E.

The tumour recurred in visceral lymph nodes which were not resectable. It expresses PIK3CA and this was also found in my blood.

My conclusion is that the tumour acquired a PIK3CA mutation and that this directly contributed to endocrine resistance, resulting in my recurrence and my current prognosis.

Current treatments available on the NHS for this type of breast cancer (e.g. normally after a CDK 4/6 inhibitor with an aromatase inhibitor treatment include everolimus with exemestane or capecitabine).

Unfortunately there is a significant toxicity profile and this combination and although there seem to be few studies making a direct comparison, it is important to me as patient that I can access a drug which targets a mutation I know that I have. Alpelisib is the first drug which can do this in the area of advanced breast cancer for patients with this mutation. There is therefore a significant likely impact that alpelisib with fulvestrant could make if it was recommended for use on the NHS.

There is a major unmet need for therapies that specifically address the effects of this mutation as there are currently no recommended therapies that specifically target the PIK3CA mutation for UK patients who have it with endocrine resistant HR+, HER2– advanced breast cancer (ABC). This is what I have as I also now have bone mets which are growing as they are ER+.

My risk of developing more visceral disease without targeted treatment for PIK3CA is very high and it's very important to have more than one option, especially when there are associated toxicities. Options are crucially important for patients in my position.

I understand that UK clinicians report that improvements in PFS alone with Alpelisib and Fulvestrant and therefore this would give me more options that the toxicity I will get from prolonged chemotherapy or combination treatment with everolimus and exmestene/capecitabine. Patients can get side effects from a range of medications and it is crucial to have choices in situations such as mine.

It is imperative that new treatments that improve survival and provide personalised options for clinicians are made available.

There is clearly a high unmet need as I am one of the 40% of women who develop this mutation as a cause for their recurrence and I now have incurable breast cancer. Without this treatment my options for survival to look after my children (aged 12 and 16) are significantly reduced. I have served my patients all my working life and now find myself in this catastrophic position of perhaps having very few months to live unless I can access targeted treatments which may help me.

This summary doesn't even cover the devastation I have had to deal with through losing my left breast / all my hair twice / my eyebrows / my livelihood.

I am at least fortunate that I know I have the mutation so that I can keep searching for potential treatments but I am deeply concerned that there is currently a lack of treatment options with the associated genomic test for this mutation. This should be standard practice so that it can be used to predict which patients are likely to benefit from treatment. A tailored approach to our treatment as patients clearly will optimise our chances of a treatment response and mean that money is well spent on a treatment we know works more effectively in the population it is being used in. This is not the case for many drugs we prescribe as doctors and therefore this drug represents not only better value for money because it can be targeted but also it is the future for patients like me as improvements in survival from metastatic cancer will be afforded by personalised (genomic) medicine

As a doctor and a patient I know that trial data has shown alpelisib in combination with fulvestrant to be effective in prolonging progression free survival in advanced hormone receptor-positive, HER2-negative, PIK3CA-positive breast cancer. Progression free survival means the world to me as it means I can spend more vital time with my family. I would urge you to progress this as quickly as possible in order to help all those on my position whose very lives depend on it.

Alpelisib in combination with fulvestrant for treating advanced hormone receptor positive, HER2-negative, *PIK3CA*-mutated breast cancer [ID3929]

ERG commentary on the company's response to the ACD

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1. Introduction

In March 2022, the National Institute for Health and Care Excellence (NICE) issued the following recommendation within its Appraisal Consultation Document (ACD) for alpelisib: "*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.*" (NICE ACD,[1] Section 1.1).

The ACD raises concerns regarding the uncertainty surrounding the company's indirect treatment comparison (ITC) and states that the results of the company's model "*show that alpelisib plus fulvestrant is not a cost-effective use of NHS resources.*"

In April 2022, the company submitted a response to the ACD.[2] The company's ACD response includes a written response document and an updated version of the company's economic model. The company's ACD response document discusses the following eight points:

1. End-of-life criteria
2. Probabilistic sensitivity analyses (PSA)
3. The HER2-negative subgroup in the ITC
4. The "Reverse Bucher" method for the ITC
5. The method of *PIK3CA* identification in the ITC
6. Post-progression utility values
7. Treatment effect waning assumptions
8. One point of factual inaccuracy.

Since the NICE ACD[1] was issued, the company has increased the Patient Access Scheme (PAS) discount for alpelisib to [redacted] (discounted cost per pack = £[redacted]). The company's ACD response[2] includes additional analyses including this updated PAS discount as well as an assumed discount for fulvestrant (Fulv).

This ERG addendum provides a commentary on the points raised in the company's ACD response[2] and provides additional economic analyses using the company's updated model. Section 2 summarises the critiques the points raised in the company's ACD response. Section 3 summarises the company's updated analyses, including the new PAS for alpelisib. Section 4 presents additional analyses undertaken by the ERG, including the new PAS.

2. ERG commentary on points raised in the company's ACD response

Point 1 - End-of-life criteria

The NICE ACD[1] (Section 3.19) states that the Appraisal Committee 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.*"

The company's ACD response[2] cites the recent appeal for the appraisal of avelumab for locally advanced or metastatic urothelial cancer[3] and argues that "*considering the totality of the evidence available and the social value judgements underpinning the modifier, alpelisib plus fulvestrant meets the EoL criteria.*" The company notes that patients with HR+, HER2–negative advanced breast cancer (ABC) with a *PIK3CA* mutation have a poor prognosis of less than 2 years, which is supported by the model predictions (except in some extreme probabilistic samples) and by clinical opinion, and these points are acknowledged in the NICE ACD.[1] The company's ACD response also argues that HER2 status is not a treatment effect modifier and that the results of the ITC including the HER2-negative subgroup of SoFEA[4] produce clinically inconsistent results. The company also argues that whilst there is uncertainty around the relative effectiveness of alpelisib plus fulvestrant (Alp/Fulv), the deterministic version of the company's model predicts an incremental overall survival (OS) gain which is greater than 3 months. The company also argues that the SOLAR-1 randomised controlled trial (RCT)[5] provides randomised evidence that alpelisib extends survival by more than 3 months compared with Fulv, and that clinical experts believe that it is reasonable to assume that everolimus plus exemestane (Eve/Exe) is as efficacious as Fulv.

As noted in the ERG report[6] (Section 5.3.4, critical appraisal point [9]), the deterministic versions of the company's base case model and the ERG's preferred analysis each suggest that Alp/Fulv meets both of NICE's EoL criteria. However, if the company's revised Bucher ITC including only HER2-negative patients in SoFEA[4] is used, mean OS in the Eve/Exe group is greater than 2 years. The probabilistic version of the company's model suggested that neither EoL criteria are met, irrespective of which Bucher ITC is used. The ERG believes that judgements about whether alpelisib meets the EoL criteria therefore firstly require judgements about whether the HER2-negative subgroup in SoFEA should be included in the ITC and whether the probabilistic or deterministic model should be used for decision-making. These points are discussed separately in Points [2] and [3] below. The ERG notes an additional related point – the ERG's clinical advisors believed that the model predicted OS and PFS were plausible (see ERG report, Section 5.2.4, Figures 11 and 14); these judgements were made based on examination of the model predictions obtained from the deterministic version of the model.

Point 2 - Use of probabilistic model

The ACD[1] (Section 3.20) discusses the issues relating to the probabilistic version of the company's model. The ACD states that the Appraisal 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."*

The company's ACD response[2] repeats arguments previously made during the earlier stages of the appraisal and states that the deterministic results are *"more appropriate to inform the cost-effectiveness of alpelisib plus fulvestrant."* The company's ACD response includes a re-analysis of the probabilistic version of the model including a constraint which excludes probabilistic samples in which the OS for Eve/Exe is ≥10% greater than that for Alp/Fulv, based on additional input obtained from clinical experts consulted by the company.

The ERG believes that, in general, decisions should be made on the basis of the expectation of the mean, generated from a faithful representation of uncertainty surrounding all model parameters. The ERG report[6] highlighted the discrepancies between the company's deterministic and probabilistic incremental cost-effectiveness ratios (ICERs), and noted that the interpretation of the ICERs obtained from the deterministic model are problematic because of the use of median hazard ratios (HRs), whilst the interpretation of the probabilistic ICERs are problematic due to a large proportion of implausible samples and the non-linear response of the model to extreme HRs. As discussed in the original ERG report (see Section 5.3.4, critical appraisal point [9]), the ERG does not believe that the inclusion of a constraint to truncate the probabilistic samples is appropriate, as the resulting distribution of expected incremental quality-adjusted life years (QALYs) no longer reflects the intervals estimated from the ITCs. This, in turn, arbitrarily impacts on the mean incremental QALYs and costs. Overall, the ERG's view is unchanged and it remains unclear whether it is more appropriate to rely on the results of the deterministic or probabilistic model. The ERG notes that there does not appear to be a simple solution to this problem, and the ERG agrees with the Appraisal Committee that both the deterministic and probabilistic should be taken into account.

The ERG's additional exploratory analyses are reported using both the deterministic and probabilistic versions of the company's updated model, excluding the company's sampling constraint (see Section 4).

Point 3 - Use of HER2-negative subgroup from SoFEA

The ACD[1] (Section 3.10) states that *"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".

The company's ACD response[2] states that *"use of the full population from SoFEA is considered the most appropriate approach"*. This is based on the following points:

a) The company considers that there are insufficient data to conclude that HER2 status is a treatment effect modifier;
b) Approximately 35% (n=166) patients in SoFEA[4] had unknown HER2 status, so restricting to those with known HER2 status may lead to information bias;
c) Use of the full population of SoFEA is consistent with use of the full population of CONFIRM[7] (where results by HER2 status were not available);
d) The HRs for PFS and OS in the HER2-negative subgroup of SoFEA favoured Exe over Fulv, which the company believes lacks face validity;
e) Previous NICE appraisals for CDK4/6is plus Fulv, which use CONFIRM and SoFEA in their networks, use the overall trial populations, despite the appraisal populations being focussed on HER2-negative disease.

The ERG response to each of these points is as follows:

a) CS Appendix D[8] noted that HER2 status may be an important treatment effect modifier based on the subgroup analyses of SoFEA. Clinical advisors to the ERG also stated that HER2 status may be an important treatment effect modifier. The HRs for PFS and OS differ substantially in magnitude between the HER2-negative and HER2-positive subgroups in SoFEA[4] (Table 1). This may be due to the small numbers in the HER2-positive subgroup or may reflect a true difference in treatment effect. The ERG considers that the most relevant data, i.e., those for the HER2-negative subgroup, should be used where available.
b) In the SoFEA trial population, 60% (n=283) were HER2-negative, which the ERG considers a reasonably sized subgroup. The ERG considers that information bias is unlikely to be a problem, unless the HER2-negative patients with unknown HER2 status were expected to have different outcomes to the HER2-negative patients with known HER2 status.
c) Although CONFIRM[7] did not report results by HER2 status, the other trials in the network (SOLAR-1 and BOLERO-2) were restricted to HER2-negative populations. Ideally, the data from CONFIRM would also be restricted to HER2-negative patients, but this is not possible. The extent to which this might influence the ITC results is unclear.
d) The ERG is unclear why the company considers that the results for the HER2-negative subgroup lack face validity. The HRs for the HER2-negative subgroup appear numerically similar to the overall HRs for PFS and OS, with neither showing a statistically significant

treatment effect (see Table 1). For OS, both the overall and HER2-negative HRs numerically favour Exe over Fulv.

e) The ERG has checked the NICE appraisals for CDK4/6is plus Fulv (TA725, TA619 and TA687[9-11]). In all three appraisals, the committee papers (either within the ERG report or information from the manufacturers) note that SoFEA is not restricted to HER2-negative patients and that this is a source of heterogeneity and/or may impact on outcomes.

Table 1: SoFEA results by HER2 subgroup

Subgroup	N (%)	PFS HR for Fulv vs Exe (95% CI)	OS HR for Fulv vs Exe (95% CI)
All patients	480 (100%)	0.95 (0.79 to 1.14)	1.05 (0.84 to 1.29)
HER2-negative	283 (60%)	1.06 (0·83 to 1·34)	1.26 (0.95 to 1.66)
HER2 unknown	166 (35%)	0.93 (0·68 to 1·27)	0.99 (0.69 to 1.41)
HER2-positive	31 (6%)	0.20 (0·08 to 0·51)	0.30 (0.10 to 0.84)

CI, confidence interval; Exe, exemestane; Fulv, fulvestrant; HR, hazard ratio; OS, overall survival; N, number of patients; PFS, progression-free survival
Ref: Johnston et al., 2013[4]

In summary, both the company's base case and the ERG preferred analysis use the ITC results based on the overall population of SoFEA.[4] However, the ERG considers that it is reasonable to consider the impact of using only the HER2-negative subgroup of SoFEA in the ITC and the economic model. Therefore, a sensitivity analysis using the ITC results based on this subgroup is also provided (see Section 4).

Point 4 - Use of "reverse" Bucher method

The ACD[1] (Section 3.10) discusses the issues contributing to the uncertainties around the relative treatment effect estimates for Alp/Fulv versus Eve/Exe. The first bullet-point in the list states *"A reverse Bucher was done, deriving comparator hazard ratios from those known for alpelisib plus fulvestrant."*

The company's ACD response[2] states that the use of inverse HRs was necessary given the use of data from BYLIEVE.[12]

The ERG agrees with the company that the inversion of the HRs is necessary within the economic model given the inclusion of data from BYLIEVE[12] as a baseline. The ERG believes that the use of inverse HRs, together with the very wide 95% confidence intervals (CIs) generated from the Bucher ITCs, contributes to the problems regarding implausible samples in the PSA (see Point [2]). The ERG agrees that this is not a standalone issue and that the bullet-point can be removed from subsequent NICE guidance documents.

Point 5 - Use of *PIK3CA* mutation data based on tumour sampling in BOLERO-2

The ACD[1] (Section 3.9) states that, within the Bucher ITC, *"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's ACD response[2] states that *"This approach was taken by the company because the study populations in SOLAR-1 and BYLieve trials assessed PIK3CA mutation based on tumour samples. Patients with PIK3CA-mutated disease in BOLERO-2 using tumour samples were therefore utilised for consistency, as use of different sampling methods across trials may introduce potential bias."* The company also states that *PIK3CA* mutation data based on plasma sampling were also collected in SOLAR-1,[5] but that use of these data would have broken randomisation.

The ERG notes that, as stated in the ERG report,[6] the PFS HR for the BOLERO-2 subgroup included in the ITC is less favourable to Eve/Exe than the HRs reported in publications for the wider population (see Table 2).[13] The ERG understands the company's justification for restricting BOLERO-2 data for the ITC to the second-line tumour tissue subgroup. However, the ERG considers that the restriction to n=57 out of 724 patients (8% of the overall trial population) increases the uncertainty in the ITC results.

Table 2: BOLERO-2 results by subgroup

Source	Subgroup	N	PFS HR for Eve/Exe vs Exe (95% CI)
CS[14] - used in Bucher ITC	- Second-line - Used tumour tissue for mutation status	57	0.61 (0.33 to 1.14)
Hortobagyi 2016[15]	- Used tumour tissue for mutation status	143	0.51 (0.34 to 0.77)
Moynahan 2017[16]	- Used plasma-derived cell-free DNA for mutation status	238	0.37 (0.27 to 0.51)

CI, confidence interval; Eve, everolimus; Exe, exemestane; Fulv, fulvestrant; HR, hazard ratio; N, number of patients; PFS, progression-free survival

Point 6 - Post-progression utility values

The NICE ACD[1] (Section 3.17) states that *"The committee concluded that the appropriate utility value for the modelled health state after disease progression is uncertain and may be overestimated by company."*

The company's ACD response[2] maintains that the utility value of 0.69 obtained from Mitra *et al.*[17] is the most appropriate estimate to use in the model. The company argues that this study is appropriate because it uses the EQ-5D and that the study reported by Lloyd *et al.*[18] is outdated. The company's

ACD response refers to interviews conducted by the company with clinical experts at the technical engagement (TE) stage in which the experts *"considered that patients seen in their practice at a third-line setting (i.e. equivalent to the post-progression survival (PPS) state in the cost-effectiveness model) would have a utility that is reflective of the Mitra et al. (2016) publication, noting that this value is very similar to the PPS value of* [redacted] *measured in the SOLAR-1 trial."* The company's ACD response also argues that the value from Mitra *et al.* was used in the recent appraisal of abemaciclib for ABC (TA725)[9] and that using a different value in the alpelisib appraisal would lead to inconsistent decision-making. Finally, the company argues that the utility value of [redacted] applied in the ERG's TE response,[19] which was based on input from the ERG's clinical advisors, is both arbitrary and pessimistic.

The ERG notes the following observations:

- No new evidence has been presented in the company's ACD response.[2] As such, the ERG remains concerned that the utility values obtained from Mitra *et al.*[17] and SOLAR-1 may be implausibly high.
- As discussed in the ERG's TE response,[19] all three sources of post-progression utility considered are subject to limitations:
  - SOLAR-1[5] included the use of the EQ-5D-5L, which was mapped to the 3L version by the company. The CS[14] states that EQ-5D-5L data in SOLAR-1 *"were largely missing after progression."* The ERG has concerns that the estimates obtained from SOLAR-1 may not be representative of the broader group of patients with disease progression.
  - Lloyd *et al.*[18] used a time trade-off (TTO) vignette approach rather than the EQ-5D and is relatively old. This source has however been used in the majority of NICE appraisals in ABC (see ERG report,[6] Table 39).
  - Mitra *et al.*[17] reports EQ-5D-3L estimates for patients with HR+/HER2-negative advanced/metastatic breast cancer in five major EU countries and the US, and reports a utility value specifically for patients at third-line or later. However, this study is only published as an abstract and it is unclear which EQ-5D tariffs have been used to generate the utility estimates. It is unlikely that these reflect the UK tariff. Very limited methodological details are provided.
- At the technical engagement stage, one of the ERG's clinical advisors suggested that the mid-point of the estimates from Lloyd *et al.*[18] and Mitra et al.[17] might be more appropriate for patients with progressed disease state (i.e., utility = [redacted]). The ERG's second clinical advisor to the ERG commented that a value of [redacted] may be reasonable in the third-line setting.[19] The ERG presented additional exploratory analyses using a post-progression utility value of [redacted], as this may have greater face validity than the available empirical estimates.

- The company's ACD response[2] indicates that the company asked clinical experts about the plausibility of utility values in the third-line setting. As discussed by the ERG during the first Appraisal Committee meeting, the modelled health state relates to the entire duration of survival following disease progression on second-line therapy, including all subsequent lines of therapy and additional time spent receiving supportive care.

Owing to the uncertainties detailed above, the ERG's additional analyses presented in this document include the utility values from Mitra *et al.*,[17] Lloyd *et al.*[18] and the ERG's clinical advisor[19] (values of 0.69, 0.51 and [redacted], respectively – see Section 4).

Point 7: Treatment effect waning assumptions

The NICE ACD[1] (Section 3.15) states that *"The committee concluded that the assumption of an indefinite treatment effect is optimistic."*

The company's ACD response[2] acknowledges that there is the uncertainty in assuming an indefinite treatment effect for Alp/Fulv versus Eve/Exe. Updated economic analyses are presented using a 5-year treatment effect duration. The company's ACD response argues that assuming a 3-year treatment effect duration is overly pessimistic.

The NICE ACD[1] does not present a conclusion regarding the Appraisal Committee's preferred assumption about the duration of relative treatment effect for Alp/Fulv. As such, the ERG has presented updated scenario analyses in which the modelled hazards of PFS and OS for the Alp/Fulv group switch to those for the Eve/Exe group at 3 years and 5 years (see Section 4).

Point 8: Factual inaccuracy

The company's ACD response[2] highlights an inaccuracy in the ACD relating to the time point at which the company held additional interviews with clinical experts. The ERG notes that this issue is minor but agrees that it would be reasonable to amend the text in subsequent guidance documents.

3. Company's updated economic analyses

Table 3 summarises the results of the updated economic analyses presented in the company's ACD response.[2] The company's updated analyses include:

- The updated PAS discount for alpelisib ([redacted])
- The post-progression utility value from Mitra *et al.*[17] (utility = 0.69)
- An assumption of treatment effect waning at 5-years (included in all analyses except Scenario C1)

- A constraint which removes implausible probabilistic samples (Scenario C2c only)
- The company's ACD response includes a discount for Fulv of [redacted]. This has been excluded from the results presented in Table 3. Results including all confidential prices are included in a separate appendix to this addendum.

The company's updated base case model suggests that the deterministic ICER for Alp/Fulv versus Eve/Exe is £50,459 per QALY gained. Assuming an indefinite treatment effect reduces the deterministic ICER to £47,726 per QALY gained. The probabilistic version of the company's updated base case model suggests that the ICER is £47,610 per QALY gained when the PSA sampling constraint is applied and £57,951 per QALY gained when the constraint is excluded.

Table 3: Company's updated economic results presented in ACD response, including alpelisib PAS and Fulv list price

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Analysis C1: Company base case at technical engagement, no treatment effect waning, updated PAS, deterministic†							
Alp/Fulv	2.58	1.64	[redacted]	0.76	[redacted]	[redacted]	**£47,726**
Eve/Exe	1.81	1.21	[redacted]	-	-	-	-
Analysis C2a: Updated company base case, 5-year treatment effect waning, updated PAS, deterministic							
Alp/Fulv	2.40	1.57	[redacted]	0.59	[redacted]	[redacted]	**£50,459**
Eve/Exe	1.81	1.21	[redacted]	-	-	-	-
Analysis C2b: Updated company base case, 5-year treatment effect waning, updated PAS, probabilistic (no constraint in PSA sampling)							
Alp/Fulv	2.54	1.62	[redacted]	0.38	[redacted]	[redacted]	**£57,951**
Eve/Exe	2.17	1.35	[redacted]	-	-	-	-
Analysis C2c: Updated company base case, 5-year treatment effect waning, updated PAS, probabilistic (implausible PSA samples removed)							
Alp/Fulv	2.44	1.58	[redacted]	0.70	[redacted]	[redacted]	**£47,610**
Eve/Exe	1.73	1.14	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; Alp/Fulv - alpelisib plus fulvestrant; Eve/Exe - everolimus plus exemestane; PAS - Patient Access Scheme
** Undiscounted*
† This analysis is equivalent to the second analysis presented in Table 2 of the ERG's TE response[19]

4. Additional exploratory analyses undertaken by the ERG

The ERG undertook seven sets of additional exploratory analyses using the company's updated base case model. These include scenarios using the post-progression utility values from Mitra *et al.*,[17] Lloyd *et al.*,[18] and the ERG's clinical advisor[19] and assumptions of treatment effect waning at 3- and 5-years. A further analysis was undertaken using the HRs for PFS and OS from the ITC including the HER2-negative subgroup of SoFEA; this was only applied to the company's base case scenario. Each analysis was undertaken using both the deterministic and the probabilistic versions of the company's model (excluding the PSA constraint).

Across the range of analyses using the deterministic version of the model, the ICER for Alp/Fulv versus Eve/Exe is estimated to range from £50,459 to £73,642 per QALY gained. The probabilistic ICERs are consistently higher, ranging from £57,951 to £199,847 per QALY gained. These results do not include all relevant confidential prices; the results of the analyses including confidential prices for all drugs are presented in a separate confidential appendix to this report.

Table 4: Additional exploratory analyses undertaken by the ERG

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Analysis ERG1a: Company's updated base case, post-progression utility from Mitra *et al.* (utility=0.69) 3-year treatment effect waning, updated PAS, deterministic							
Alp/Fulv	2.27	[redacted]	[redacted]	0.46	[redacted]	[redacted]	**£55,150**
Eve/Exe	1.81	[redacted]	[redacted]	-	-	-	-
Analysis ERG2a: Company's updated base case, post-progression utility from Mitra *et al.* (utility=0.69), 5-year treatment effect waning, updated PAS, deterministic							
Alp/Fulv	2.40	[redacted]	[redacted]	0.59	[redacted]	[redacted]	**£50,459**
Eve/Exe	1.81	[redacted]	[redacted]	-	-	-	-
Analysis ERG3a: Company's updated base case, post-progression utility from Lloyd *et al.*, (utility=0.51), 3-year treatment effect waning, updated PAS, deterministic							
Alp/Fulv	2.27	[redacted]	[redacted]	0.46	[redacted]	[redacted]	**£64,516**
Eve/Exe	1.81	[redacted]	[redacted]	-	-	-	-
Analysis ERG4a: Company's updated base case, post-progression utility from Lloyd *et al.*, (utility=0.51), 5-year treatment effect waning, updated PAS, deterministic							
Alp/Fulv	2.40	[redacted]	[redacted]	0.59	[redacted]	[redacted]	**£60,508**
Eve/Exe	1.81	[redacted]	[redacted]	-	-	-	-
Analysis ERG5a: Company's updated base case, post-progression utility from clinical advisor (utility= [redacted]), 3-year treatment effect waning, updated PAS, deterministic							
Alp/Fulv	2.27	[redacted]	[redacted]	0.46	[redacted]	[redacted]	**£59,341**
Eve/Exe	1.81	[redacted]	[redacted]	-	-	-	-
Analysis ERG6a: Company's updated base case, post-progression utility from clinical advisor (utility= [redacted]), 5-year treatment effect waning, updated PAS, deterministic							
Alp/Fulv	2.40	[redacted]	[redacted]	0.59	[redacted]	[redacted]	**£54,894**
Eve/Exe	1.81	[redacted]	[redacted]	-	-	-	-
Analysis ERG7a: Company's updated base case (Analysis 2a) using ITC including HER2-negative subgroup in SoFEA, deterministic							
Alp/Fulv	2.49	[redacted]	[redacted]	0.30	[redacted]	[redacted]	**£73,642**
Eve/Exe	2.19	[redacted]	[redacted]	-	-	-	-
Analysis ERG1b: Company's updated base case, post-progression utility from Mitra *et al.* (utility=0.69) 3-year treatment effect waning, updated PAS, probabilistic							
Alp/Fulv	2.46	[redacted]	[redacted]	0.29	[redacted]	[redacted]	**£64,600**
Eve/Exe	2.17	[redacted]	[redacted]	-	-	-	-
Analysis ERG2b: Company's updated base case, post-progression utility from Mitra *et al.* (utility=0.69) 5-year treatment effect waning, updated PAS, probabilistic							
Alp/Fulv	2.54	[redacted]	[redacted]	0.38	[redacted]	[redacted]	**£57,951**
Eve/Exe	2.17	[redacted]	[redacted]	-	-	-	-
Analysis ERG3b: Company's updated base case, post-progression utility from Lloyd *et al.*, (utility=0.51), 3-year treatment effect waning, updated PAS, probabilistic							
Alp/Fulv	2.46	[redacted]	[redacted]	0.29	[redacted]	[redacted]	**£74,218**
Eve/Exe	2.17	[redacted]	[redacted]	-	-	-	-

Analysis ERG4b: Company's updated base case, post-progression utility from Lloyd *et al.*, (utility=0.51), 5-year treatment effect waning, updated PAS, probabilistic							
Alp/Fulv	2.54	[redacted]	[redacted]	0.38	[redacted]	[redacted]	**£68,343**
Eve/Exe	2.17	[redacted]	[redacted]	-	-	-	**-**
Analysis ERG5b: Company's updated base case, post-progression utility from clinical advisor (utility= [redacted]), 3-year treatment effect waning, updated PAS, probabilistic							
Alp/Fulv	2.46	[redacted]	[redacted]	0.29	[redacted]	[redacted]	**£68,947**
Eve/Exe	2.17	[redacted]	[redacted]	-	-	-	**-**
Analysis ERG6b: Company's updated base case, post-progression utility from clinical advisor (utility= [redacted]), 5-year treatment effect waning, updated PAS, probabilistic							
Alp/Fulv	2.54	[redacted]	[redacted]	0.38	[redacted]	[redacted]	**£62,580**
Eve/Exe	2.17	[redacted]	[redacted]	-	-	-	**-**
Analysis ERG7b: Company's updated base case (Analysis 2a) using ITC including HER2-negative subgroup in SoFEA, probabilistic							
Alp/Fulv	2.66	[redacted]	[redacted]	-0.03	[redacted]	[redacted]	**£199,847**
Eve/Exe	2.68	[redacted]	[redacted]	-	-	-	**-**

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; Alp/Fulv - alpelisib plus fulvestrant; Eve/Exe - everolimus plus exemestane; PAS - Patient Access Scheme
** Undiscounted*

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