National Institute for Health and Care Excellence

Single Technology Appraisal (STA)
Alpelisib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative, PIK3CA-mutated breast cancer
Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Breast Cancer Now	Yes, the topic is appropriate for a NICE appraisal.	Thank you for your comment. No action needed.
	Novartis Pharmaceuticals UK Limited	Yes. Novartis believes that it is important to highlight the unmet need in this patient population, particularly with regards to the specific nature of alpelisib in targeting the *PIK3CA* mutation, which is associated with a poorer prognosis and worse survival outcomes.[1-5] PI3K pathway hyperactivation due to a *PIK3CA* mutation can contribute to endocrine resistance, resulting in a major unmet need for therapies that specifically address the effects of this mutation.[6-8] Despite this, there are currently no recommended therapies that specifically inhibit *PIK3CA* for UK patients with endocrine resistant HR+, HER2– advanced breast cancer (ABC).	Thank you for your comments. No action needed.

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		UK clinicians report that improvements in PFS alone and therefore, delaying the initiation of cytotoxic chemotherapy (via increased time remaining progression-free), is a positive outcome in the ABC treatment landscape.[9, 10] Therefore, novel treatments that improve PFS and provide sequencing options for clinicians are of immense benefit for patients and their caregivers in meeting a high unmet need.[11] Moreover, there is currently a lack of treatment options with an associated genomic test that can be used to predict which patients are likely to benefit from treatment. Such a treatment would allow for a tailored approach to patients' treatment to optimise their chances of a treatment response.	
Wording	Breast Cancer Now	Yes, the wording is appropriate.	Thank you for your comment. No action needed.
	Novartis Pharmaceuticals UK Limited	Yes	Thank you for your comment. No action needed.
Timing Issues	Breast Cancer Now	Clinical 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 is highly valued by patients with incurable breast cancer and we therefore believe this appraisal should be progressed quickly.	Thank you for your comments. NICE aims to provide draft guidance to the NHS within 6 months from the date when marketing authorisation for a technology is granted. NICE has scheduled this topic into

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			its work programme. No action needed.
	Novartis Pharmaceuticals UK Limited	There is an urgency for this appraisal as there are currently no licenced treatment options for HR+ve, HER2-ve, *PIK3CA*-mutated Advanced Breast Cancer patients. Alpelisib in combination with fulvestrant is expected to gain a UK Marketing Authorisation in [redacted], therefore Novartis believes a timely appraisal should occur in order to provide the NHS with guidance for these patients.	Thank you for your comments. NICE aims to provide draft guidance to the NHS within 6 months from the date when marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action needed.

Comment 2: the draft scope

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Background information	Breast Cancer Now	The information is accurate	Thank you for your comment. No action needed.
	Novartis Pharmaceuticals UK Limited	Please note that alpelisib in combination with fulvestrant is also being trialled in patients who received a prior CDK4/6 inhibitor plus an aromatase inhibitor or CDK4/6 inhibitor plus fulvestrant (BYLieve trial – Cohorts A and B [NCT03056755]) and this should be mentioned in the background section of the scope.	Thank you for your comment. The background section was updated.

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The technology/ intervention	Breast Cancer Now	Yes	Thank you for your comment. No action needed.
	Novartis Pharmaceuticals UK Limited	No. “Alpelisib (brand name unknown, Novartis)” should be changed to “Alpelisib (Piqray®, Novartis)”	Thank you, the brand name was updated.
Population	Breast Cancer Now	It should be clarified whether both pre- and postmenopausal women are included in the population. As far as we are aware, only postmenopausal women and men have been included in clinical trials of the treatment.	Thank you for your comment. Alpelisib will be appraised within its marketing authorisation. No action needed.
	Novartis Pharmaceuticals UK Limited	Yes, but Novartis would propose changing the current draft scope wording to: *People with advanced hormone-receptor positive, HER2-negative, PIK3CA-mutated breast cancer that has progressed after prior endocrine-based therapy (in the neo/adjuvant or advanced setting)*	Thank you for your comment, ‘PK3CA-positive’ was changed to ‘PK3CA-mutated’.
Comparators	Breast Cancer Now	Yes, these are the standard treatments currently used. Fulvestrant is not recommended by NICE, but we’re aware it is offered in some areas. Whilst drugs recommended for use within the Cancer Drugs Fund cannot be considered comparators during an appraisal, it should be noted that in	Thank you for your comments. Fulvestrant was removed as it is not nationally available to all patients. Chemotherapy was removed as it is only offered to patients if symptoms are severe or

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		practice CDK4/6 inhibitors in combination with fulvestrant are likely to be an important treatment option for this population.	the disease is rapidly progressive. CDK4/6 inhibitors have been added.
	Novartis Pharmaceuticals UK Limited	Based on clinical experts' feedback, exemestane monotherapy, fulvestrant monotherapy and tamoxifen are not relevant comparators as they are not widely used in UK clinical practice in this setting and, therefore, should not be considered standard of care. Therefore, everolimus plus exemestane represents the most relevant comparator to alpelisib in combination with fulvestrant for this submission which is consistent with that taken in other appraisals in a similar setting.[12-14] Fulvestrant monotherapy is not recommended within its licensed indication, as an alternative to aromatase inhibitors for the treatment of ER+, locally advanced or metastatic breast cancer in postmenopausal women whose cancer has relapsed on or after adjuvant anti-oestrogen therapy (i.e. ET), or who have disease progression on anti-oestrogen therapy (i.e. ET) (TA239).[15] It should also be noted that abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy (TA579), palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer (TA619) and ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer (TA593) are currently recommended for use within the Cancer Drugs Fund (CDF) as an option for treating hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer in people who have had previous endocrine	Thank you for your comments. Fulvestrant was removed as it is not nationally available to all patients. Chemotherapy was removed as it is only offered to patients if symptoms are severe or the disease is rapidly progressive. CDK4/6 inhibitors have been added.

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		therapy and would be relevant comparators when they transition from the CDF to routine baseline commissioning.[12-14]	
Outcomes	Breast Cancer Now	Yes	Thank you for your comment. No action needed.
	Novartis Pharmaceuticals UK Limited	It should be noted that for the purposes of this appraisal only outcomes specific to the mutated *PIK3CA* cohort from SOLAR-1 will be considered in line with the proposed license wording for alpelisib in combination with fulvestrant. This is due to the fact that in SOLAR-1, 231 wild-type *PIK3CA* patients underwent randomisation for a proof of concept (PoC) analysis. However, no treatment benefit was obtained in this biomarker-negative control cohort and, consequently, this appraisal should focus on patients with HR+, HER2− ABC with a *PIK3CA* mutation only. In addition to SOLAR-1, outcomes from BYLieve (Cohort A) are also anticipated to be presented within the submission.	Thank you for your comments. No action needed.
Economic analysis	Breast Cancer Now	No comment	-
	Novartis Pharmaceuticals UK Limited	The economic analysis will be in accordance with the NICE reference case.	Thank you for your comment. No action needed.
Equality and Diversity	Breast Cancer Now	The scope does not appear to promote discrimination	Thank you for your comment. No action needed.

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	Novartis Pharmaceuticals UK Limited	Novartis has not identified any issues related to equality that should be covered in the remit or scope of this appraisal.	Thank you for your comment. No action needed.
Other considerations	Novartis Pharmaceuticals UK Limited	The clinical efficacy and safety of alpelisib in combination with fulvestrant in the patient population of interest for this appraisal will come from two sources: SOLAR-1 (NCT02437318) and BYLieve (NCT03056755).	Thank you for your comments. No action needed.
Innovation	Breast Cancer Now	We consider alpelisib to be an innovative technology. It is the first breast cancer treatment targeted at tumours with PIK3CA mutations, which are common in hormone receptor-positive disease. Alpelisib in combination with fulvestrant has the potential to make a significant impact by expanding the options available to many patients with incurable hormone receptor-positive breast cancer.	Thank you for your comments. The extent to which the technology may be innovative will be considered in any appraisal of the technology. No action needed.
	Novartis Pharmaceuticals UK Limited	The addition of alpelisib (in combination with fulvestrant) to the treatment landscape for Advanced Breast Cancer (ABC) in the UK would represent a paradigm shift in the management of this condition, moving towards a system where patients can be tested for specific mutations (such as *PIK3CA*) and then treated accordingly. This aligns with the aims of the NHS to be world-leading in its use of cutting-edge genomic technologies to predict and diagnose disease, and to subsequently treat in a personalised manner, as genomic testing for *PIK3CA* within the NHS would enable the prediction of patients most likely to benefit from treatment with alpelisib in combination with fulvestrant.	Thank you for your comments. The extent to which the technology may be innovative will be considered in any appraisal of the technology. We encourage companies to submit all relevant and available evidence for consideration.

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		Breast cancer, and ABC in particular, is also associated with a substantial economic burden, both via direct treatment and drug development costs and indirect costs such as absenteeism and reduced productivity for both patients and their caregivers.	
Questions for consultation	Breast Cancer Now	Diagnostic testing for PIK3CA mutations in people with advanced hormone receptor-positive, HER2-negative breast cancer will also need to be made available for full adoption of alpelisib. This type of diagnostic testing is not routinely available on the NHS.	Thank you for your comment. No action needed.
	Novartis Pharmaceuticals UK Limited	**Which treatments are considered to be established clinical practice in the NHS for advanced hormone-receptor positive, HER2-negative, *PIK3CA* positive breast cancer?** Novartis: Everolimus plus exemestane is considered to be the most relevant comparator to alpelisib in combination with fulvestrant in UK clinical practice according to clinical experts' feedback. Everolimus plus exemestane is recommended by NICE for treating advanced breast cancer after endocrine therapy (TA421) and was consistently accepted as a comparator in the CDK4/6 plus fulvestrant appraisals.[16] **Have all relevant comparators for alpelisib been included in the scope?** Novartis: Please see 'comparators' section above. **Is diagnostic testing for *PIK3CA* mutation in people with advanced hormone-receptor positive, HER2-negative breast cancer now routinely used in the NHS?**	Thank you for your comments. Fulvestrant and chemotherapy were removed from the list of comparators. CDK4/6 inhibitors have been added. The company is encouraged to expand on its rationale of using everolimus plus exemestane as the key comparator in its submission.

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		Novartis is aware that the test directory is being updated in April 2020. **Are the outcomes listed appropriate?** Novartis: Please see 'outcomes' section above. **Are there any subgroups of people in whom alpelisib is expected to be more clinically effective and cost effective or other groups that should be examined separately?** • **Should people,** ○ **whose disease relapsed within 12 months of completion of neo/adjuvant endocrine therapy;** ○ **people whose disease relapsed more than 12 months from completion of neo/adjuvant endocrine therapy and then subsequently progressed on or after one line of endocrine therapy in the advanced setting; and** ○ **people with newly diagnosed advanced breast cancer, that progressed on or after one line of endocrine therapy in the advanced setting;** **be considered separately?** Novartis: These populations are not anticipated to be treated differently in clinical practice, or benefit differentially following treatment with alpelisib in combination with fulvestrant. These populations were not appraised separately in other appraisals in a similar setting:	

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		• abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy (TA579), • palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer (TA619) and • ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer (TA593), and the same should apply for alpelisib in combination with fulvestrant for consistency. **Where do you consider alpelisib will fit into the existing NICE pathway, advanced breast cancer?** Novartis: Alpelisib in combination with fulvestrant should be considered as a treatment option within its expected marketing authorisation, i.e., for patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced breast cancer with a *PIK3CA* mutation after disease progression following an endocrine-based regimen. **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** Novartis: No barriers identified at present. **NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process.**	

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		(Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction). **Novartis agrees that the appraisal of alpelisib in combination with fulvestrant for the treatment of HR+, HER2– ABC with a *PIK3CA* mutation is suitable for assessment via the STA process.**	
Additional comments on the draft scope	Novartis Pharmaceuticals UK Limited	None	Thank you for your comment. No action needed.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

None.