Single Technology Appraisal

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after endocrine treatment [ID6225]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after endocrine treatment [ID6225]

Contents:

The following documents are made available to stakeholders:

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

NICE National Institute for Health and Care Excellence

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 22 October 2024. 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):	Menarini Stemline

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 22 October 2024. Please submit via NICE Docs.

Disclosure Please disclose any funding received from the Company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the Company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Not applicable
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Menarini Stemline

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.
Overview	Menarini Stemline extends is thanks and gratitude to the NICE Committee for the opportunity to respond to draft guidance for the appraisal of elacestrant for the treatment of patients with ER positive, HER2-negative advanced breast cancer with an *ESR1* mutation after at least 1 endocrine treatment. We are committed to engaging with NICE and NHS England to ensure that eligible patients with *ESR1* mutations who currently have no tailored treatment options available to them, can access elacestrant. Our responses below address the clinical and economic issues stated in the draft guidance, as follows: • For issues 1, 2, 3, 5, 6 and 9, we have provided a structured reply utilising information already presented to try and provide further clarification/explanation. For issues 4,7 and 8 further analyses have been performed as was suggested in the NICE draft guidance. To reflect our commitment and based on the discussions at ACM1, the Company has submitted a revised PAS, to reflect the change in base case assumptions for: • Inclusion of everolimus generic price • New OS extrapolation for elacestrant in the population who received prior treatment for ≥12 months with CDK4/6i + ET (see issue 4) • Inclusion of TTD: PFS hazard ratio (HR) for both everolimus + exemestane and alpelisib + fulvestrant (see issue 5)
1 Target population: people with ESR1-mut who received CDK4/6i +	*Section 3.18* *"The Committee decided there were many areas of uncertainty (see section 3.17). It would like clarification and further analyses on the:* • *Company's target population"* *Section 3.5*

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 22 October 2024. Please submit via NICE Docs.

ET for ≥12 months	*"The Committee noted that the target population was based on post-hoc subgroup analyses from EMERALD. It acknowledged that the 12-month threshold for previous treatment with endocrine therapy and a CDK 4 and 6 inhibitor was arbitrary but concluded it has biological plausibility."* The Company submission focuses on the sub-group of patients who have disease progression following ≥12 months prior treatment with ET + CDK4/6i, as there was widespread agreement from the clinical community that this was where elacestrant would provide the most value in UK clinical practice.[1] The Company maintains that this is appropriate, and that there is a clear rationale for selecting the 12-month cut-off point. Elacestrant should be positioned for patients deemed endocrine sensitive, and thus could benefit from further endocrine treatment. Prior treatment for ≥12 months with ET + CDK4/6i helps to identify patients with *ESR1*-mutated tumours that remain endocrine-sensitive to elacestrant, enabling ET sequencing before other targeted therapies and drug combinations, and may delay chemotherapy-based regimens, including antibody–drug conjugates.[2] Current definitions of 'endocrine resistance' were developed before CDK4/6i became a standard frontline treatment,[3,4] however, the addition of CDK4/6i to ET has led to prolonged treatment duration and an improvement in survival for patients with mBC.[5–11] This prolonged PFS is reflected in the ESMO Breast cancer living guidelines when choosing subsequent treatments, where additional endocrine-based treatments are recommended for patients who experience a long PFS on previous CDK4/6i + ET (if there is no BRCA/PALB2 mutation).[12] As the ESMO guidelines do not specify what qualifies as 'long PFS', the Company engaged extensively with UK clinical experts to better understand appropriate cut-offs for ET in determining subsequent treatment decisions.[1] According to UK clinical feedback, in the post-CDK4/6i era, while patients who progress within 6 months of CDK4/6i + ET are considered to have primary endocrine resistance and are unlikely to benefit from further endocrine treatment, there is still uncertainty for patients who progress between 6 and 12 months. Other factors must be considered in these patients when deciding further treatment, including presentation and disease biology. Patients who progress after at least 12 months of CDK4/6i are deemed endocrine sensitive (as long as ESR1-mediated, acquired resistance is overcome) and would benefit from further endocrine treatment.[1] Menarini Stemline understands, and takes on board, the comment from the NHS England Cancer Drugs Lead that the CDF criteria will reflect this restriction, and that patients receiving 11 months of CDK4/6i + ET will not be eligible for elacestrant. UK clinical feedback is that the majority of these patients do not suddenly progress, and it is routine practice to scan patients every 3 months for signs of progression. This was taken into consideration, so it was important to align to standard screening intervals. Considering both the feedback from UK clinicians on where they see elacestrant providing most value and the current routine for follow-up and monitoring of these patients, the Company maintain that this is not an arbitrary cut off point but is the most appropriate use of NHS resources when considering elacestrant in clinical practice.
2 Presence of dual mutated patients	*Section 3.7* *"The Committee noted that breast cancer with dual mutation would typically be treated with alpelisib plus fulvestrant (see section 3.4). It noted that the activating ESR1-mutation subgroup included 39%*

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 22 October 2024. Please submit via NICE Docs.

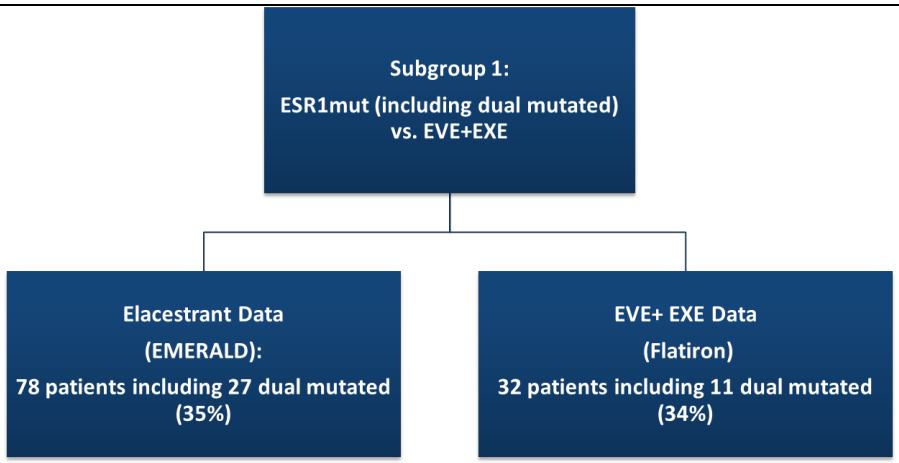
within the EMERALD data	*(62/159) of dual mutated breast cancer. It decided that the comparator of everolimus plus exemestane only in the activating ESR1-mutation subgroup did not reflect NHS clinical practice. It decided that the activating ESR1-mutation subgroup comparing elacestrant with everolimus plus exemestane should only include people with breast cancer that had the ESR1 mutation and not the PIK3CA mutation (97/159). It considered that for the Company's target population, separate analyses of the 2 distinct subgroups, an activating ESR1-mutation without PIK3CA mutation (n=97) and the dual-mutated subgroup (n=62) should have been done using the appropriate comparators. The Committee concluded that the analyses from the Company's ESR1-mutation subgroup were not appropriate for decision making because 39% of this subgroup consisted of people that had breast cancer with a dual mutation that had not been compared with alpelisib plus fulvestrant."* *Section 3.11* *"using everolimus plus exemestane as a comparator for the activating ESR1-mutation subgroup was not appropriate because the subgroup included people with dual mutated breast cancer, who would have had alpelisib plus fulvestrant (see section 3.7) "* The Committee expressed concerns that the data from EMERALD and Flatiron used to inform the comparison in the *ESR1-mut* and ≥12 months of prior ET + CDK4/6i subgroup were representative of different populations, owing to the presence of dual mutated patients within the EMERALD data. The Company clarifies that the Flatiron data used in this comparison also contained dual mutated patients, which aligns with how everolimus + exemestane is used in clinical practice. It should also be noted that the 39% (62/159) stated in the Draft Guidance is the overall *ESR1-mut* population that have received at least 12 months of CDK4/6i + ET, including the comparator arm. 78 *ESR1*-mut patients were treated with elacestrant of which 27 were dual mutated (35%). Clinical expert advice to the Company indicated that everolimus + exemestane will be considered for all eligible patients within the population in the submission as its indication does not restrict the combination to a specific biomarker. In clinical practice, everolimus + exemestane will be used in dual mutated patients in those for whom alpelisib + fulvestrant would not be preferred due to specific comorbidities such as diabetes and the preference for an oral regimen. This clinical expert advice is reinforced by the comparator Flatiron dataset that was used to inform the MAIC (patients who had received prior treatment for ≥12 months with ET + CDK4/6i and subsequent treatment with everolimus + exemestane), where there was a similar percentage of patients who were dual mutated (34%) as that documented in the equivalent EMERALD post-hoc subgroup (35%). The populations presented in the initial submission are therefore appropriate and reflect clinical practice in the UK based on clinical advice: • EMERALD patients who had received prior treatment for ≥12 months with ET + CDK4/6i and had an *ESR1-mutation*: 35% were dual mutated • Flatiron patients who had received prior treatment for ≥12 months with ET + CDK4/6i, subsequent treatment with everolimus + exemestane and had an *ESR1-mutation*: 34% were dual mutated. The proportion of dual mutated patients in each population is also in line with what would be expected in clinical practice.[13]

NICE National Institute for Health and Care Excellence

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 22 October 2024. Please submit via NICE Docs.

	 Based on clinical expert opinion, conducting an analysis using *ESR1-mut* without a *PIK3CA-mut* from EMERALD vs everolimus + exemestane is inappropriate, as this would not reflect clinical practice in the UK. In addition, reducing the patient populations further and with no way of identifying which of the EMERALD dual mutated patients would have received everolimus + exemestane, and which patients would have received alpelisib + fulvestrant in clinical practice would not resolve any of the uncertainties highlighted.
3 Tamoxifen and chemotherapy as a comparator	*Section 3.7* *"The Committee noted the clinical experts' advice that a very small proportion of people may have tamoxifen, but also noted the large discrepancy in the numbers of people starting a CDK 4 and 6 inhibitor and those progressing onto second-line therapy (see section 3.4). The Committee would have liked to have seen scenario analyses that included varying proportions of people having tamoxifen."* *Section 3.10* *"The Committee noted that standard care in EMERALD was not representative of NHS clinical practice."* *Section 3.17* *"For both the activating ESR1-mutation subgroup and the dual-mutated subgroup, the Committee decided there was a high level of uncertainty particularly about the:* • *composition of the comparator arms, specifically whether tamoxifen and chemotherapy (oral capecitabine) should be included (see section 3.4 and 3.7)"* Based on UK clinical expert opinion, chemotherapy in the UK is reserved for patients with imminent risk of organ failure, for patients who have exhausted other endocrine based treatment or for patients who are deemed primary endocrine resistant.[1] As such chemotherapy is not considered a relevant comparator for elacestrant in the patient population in this submission. This submission addresses a population that will still benefit from further endocrine treatment. In the UK, tamoxifen is indicated for the treatment of pre- and perimenopausal patients with ER+ advanced breast cancer where a CDK4/6i would not be used.[14–17] By contrast, elacestrant is indicated for the treatment of postmenopausal women, and men, with ER+/HER2-, locally

Please return to: **NICE DOCS**

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 22 October 2024. Please submit via NICE Docs.

	advanced/mBC with an *ESR1* mutation who have disease progression following at least one line of ET including a CDK4/6i.[18] This indication is consistent with the NICE clinical guideline 'Advanced breast cancer: diagnosis and treatment [CG81] where 'tamoxifen and ovarian suppression can be offered as 1L treatment to premenopausal and perimenopausal women with ER-positive advanced breast cancer not previously treated with tamoxifen' and as 'first-line treatment to men with ER-positive advanced breast cancer'.[14] Clinical feedback received by the Company is that tamoxifen is not an appropriate comparator in the target patient population for elacestrant, and that it is not widely used in UK clinical practice.[1] At the initial Committee meeting, the clinical experts agreed that tamoxifen is used in a small proportion of patients, but that this is not where elacestrant would be considered. The Company acknowledge that tamoxifen is used in a minority of patients but are not asking NICE to consider these patients for elacestrant. Exclusion of tamoxifen and chemotherapy as a relevant comparator is consistent with the appraisal for alpelisib + fulvestrant for treating advanced hormone receptor positive, HER2-negative, *PIK3CA*-mutated breast cancer [TA816], in which neither were considered appropriate comparators by the Committee in the post CDK4/6i setting, and where the Committee determined everolimus + exemestane was the most appropriate comparator.[19]
4 *ESR1-mut* and ≥12 months of prior ET + CDK4/6i subgroup: elacestrant OS extrapolation	*Section 3.13* *"It decided the EAG's gamma distribution provided the better fit but would have preferred that overall survival was capped such that the treatment effect of everolimus plus exemestane was not higher than elacestrant at and beyond the point of convergence at about 5 years."* To address the Committee's concerns around the modelled overall survival (OS) of elacestrant in the *ESR1-mut* and ≥12 months of prior ET + CDK4/6i subgroup, the Company implemented three additional scenarios to produce survival estimates that lie between the Company-preferred log-logistic and EAG-preferred gamma extrapolations. The scenarios are as follows: • **Average S(t):** The log-logistic and gamma survival curves are averaged at each point in time. • **Average h(t):** The underlying hazard functions of the log-logistic and gamma extrapolations are averaged at each point in time. • **Gamma + capped h(t):** Gamma extrapolation used to inform OS, with the underlying hazard of death capped by the underlying hazard of the everolimus + exemestane gamma OS extrapolation. o This scenario allows the use of the gamma curve (per the EAG's preference) but ensures the hazard of death cannot be greater for patients treated with elacestrant. All three scenarios ensure the treatment effect of everolimus + exemestane is not higher than elacestrant at any point in time, aligned with the Committee preference and as was previously highlighted in clinical opinion provided to the Company. Figure 1 presents the elacestrant OS extrapolations for the three scenarios, alongside the log-logistic, gamma and KM estimates for the *ESR1-mut* and ≥12 months of prior ET + CDK4/6i subgroup.

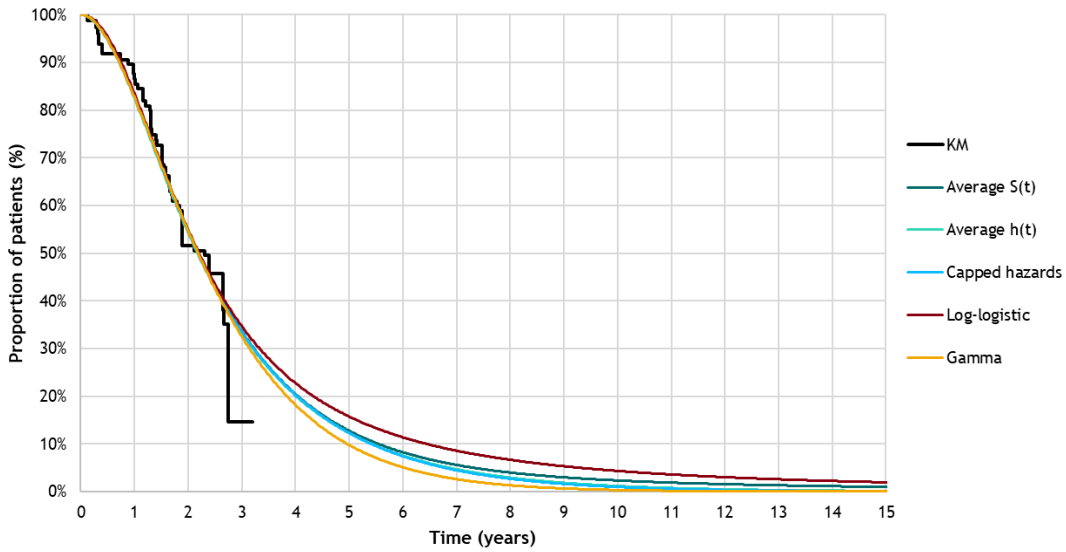
NICE National Institute for Health and Care Excellence

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 22 October 2024. Please submit via NICE Docs.

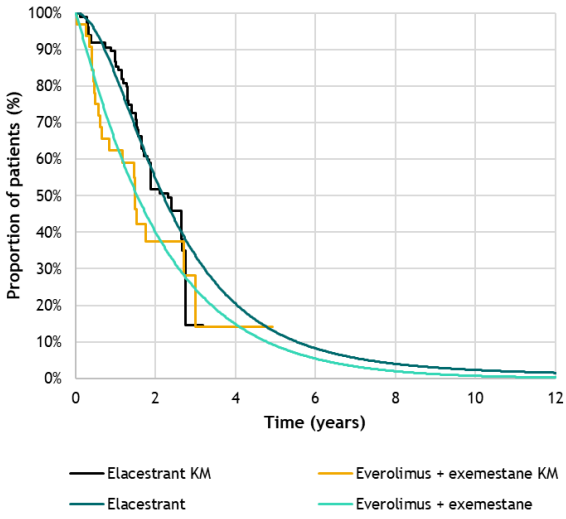
Figure 1: *ESR1-mut* and ≥12 months of prior ET + CDK4/6i elacestrant OS extrapolation scenarios



Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; KM, Kaplan-Meier; OS, overall survival.

Figure 2 to Figure 4 present the OS extrapolations for the scenarios in the *ESR1-mut* and ≥12 months of prior ET + CDK4/6i subgroup. The 'Average S(t)" scenario provides the most optimistic elacestrant OS curve, with the 'Gamma + capped h(t)' scenario providing the most pessimistic projections of elacestrant survival.

Figure 2: *ESR1-mut* and ≥12 months of prior ET + CDK4/6i OS - Average S(t) scenario



Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; KM, Kaplan-Meier; OS, overall survival.

Please return to: **NICE DOCS**

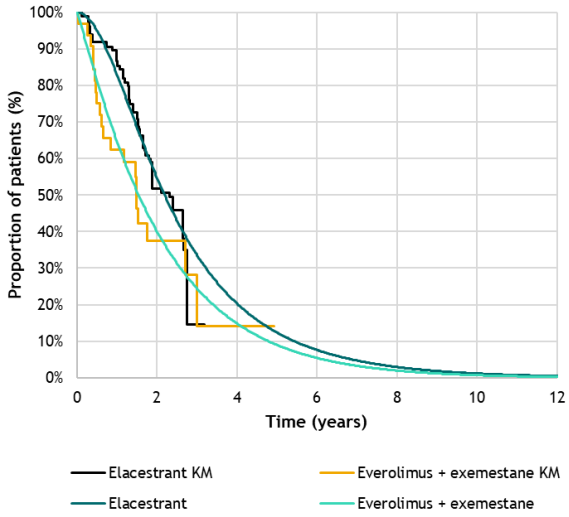
NICE National Institute for Health and Care Excellence

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Draft guidance comments form

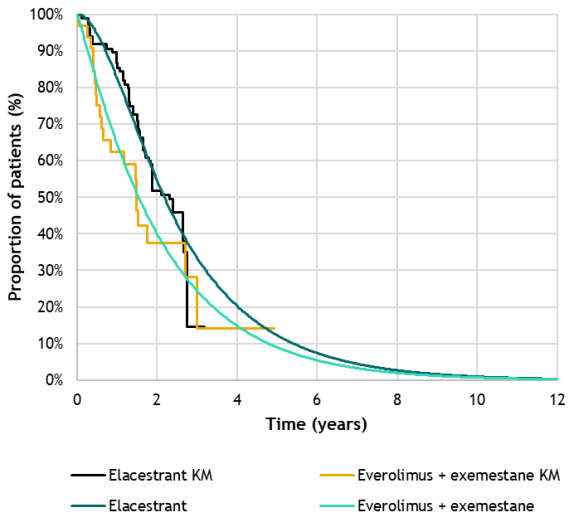
Consultation on the draft guidance document – deadline for comments end of day on 22 October 2024. Please submit via NICE Docs.

Figure 3: *ESR1-mut* and ≥12 months of prior ET + CDK4/6i OS - Average h(t) scenario



Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; KM, Kaplan-Meier; OS, overall survival.

Figure 4: *ESR1-mut* and ≥12 months of prior ET + CDK4/6i OS - Gamma + capped h(t) scenario



Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; KM, Kaplan-Meier; OS, overall survival.

Table 1 presents the landmark estimates of the log-logistic (Company original base case), gamma (EAG base case) and post appraisal consultation document (ACD) scenarios for elacestrant OS. The three scenarios project long-term estimates of survival between that of the log-logistic and gamma.

Please return to: **NICE DOCS**

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 22 October 2024. Please submit via NICE Docs.

<table>
<tr><td></td><td>

Table 1: Landmark survival estimates | Elacestrant OS (weighted to everolimus + exemestane) and post-ACD scenarios | ESR1-mut and ≥12 months of prior ET + CDK4/6i population

Model	Landmarks (years)				
	1	2	3	4	5
Log-logistic	83.5%	54.6%	34.5%	15.7%	4.3%
Average S(t)	83.1%	54.5%	33.4%	12.7%	2.3%
Average h(t)	83.1%	54.5%	33.4%	12.4%	1.2%
Gamma + capped h(t)	82.8%	54.4%	33.3%	12.3%	1.0%
Gamma	82.8%	54.4%	32.4%	9.8%	0.3%

Abbreviations: ACD, appraisal consultation document; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; OS, overall survival.

The Company considers the selection of the gamma curve with no adjustment to inform elacestrant OS (per the EAG base case) to project unrealistic estimates of long-term survival when considered alongside the selected OS extrapolation for everolimus + exemestane. When the unadjusted gamma curve is selected, the OS curves for elacestrant and everolimus + exemestane cross at approximately 5.6 years, and the underlying hazard of death is greater for elacestrant from 2.15 years, which implies that people treated with elacestrant have a greater risk of death from 2.15 years. The ACD states *"The clinical experts at the Committee meeting advised that it would be unlikely for everolimus plus exemestane to have better overall survival at 5 years than elacestrant.".* Therefore, the gamma curve produces a clinically implausible comparative OS estimate for elacestrant.

The additional three scenarios provide OS options in the model that ensure the curves and underlying hazards do not cross, and that elacestrant does not result in worse OS than everolimus + exemestane, which is aligned with clinical opinion. Clinical feedback was that whilst all 3 scenarios looked reasonable, the average h(t) was the preferred scenario based on the 10-year landmark analysis.

While the Company considers the log-logistic, 'Average S(t)' and 'Average h(t)' selections each provide reasonable estimates of elacestrant OS in the *ESR1-mut* and ≥12 months of prior ET + CDK4/6i subgroup, the updated Company base case implements the most pessimistic and more pessimistic than based on clinical feedback 'Gamma + capped h(t)' scenario to align with the Committee's preference for accounting for uncertainty in long-term estimates. Cost-effectiveness results implementing the log-logistic, gamma, 'Average S(t)' and 'Average h(t)' options are presented in the scenario analyses in Appendix 1.

</td></tr>
<tr><td>5 Comparator treatment duration</td><td>

Section 3.14
"So, the Committee decided it was inappropriate to assume that time to treatment discontinuation for the comparators is equal to progression-free survival. It would have preferred to have seen analyses based on evidence of treatment discontinuation for the comparators."

The Company base case assumption regarding comparator time to treatment discontinuation (TTD) has been updated to allow a difference between TTD and progression-free survival (PFS), to align with the Committee preference.

In the updated base case, comparator TTD is informed via a hazard ratio (HR) applied to the comparator PFS curve. In the absence of direct evidence, the Company aligned with the EAG-

</td></tr>
</table>

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 22 October 2024. Please submit via NICE Docs.

	suggested HRs of 0.8 for everolimus + exemestane in the *ESR1-mut* and ≥12 months of prior ET + CDK4/6i subgroup and 0.5 for alpelisib + fulvestrant in the *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i subgroup. The Committee recognised that the TTD to PFS HRs applied by the EAG were not based on any published data and asked the Company to look into potential data sources to support the TTD to PFS HR. No data were available from the literature specific to the populations considered in this appraisal. However, as the Committee preferred for the TTD HRs to be informed by evidence, the Company sought information from previous relevant appraisals to inform the HRs explored, with cost-effectiveness results produced from alternative values presented in scenario analysis (please see Appendix 1). The findings were as follows: • A HR of 1.27 for PFS vs. TTD was reported in TA816 for everolimus + exemestane, which equates to a HR of 0.79 for TTD when applied to PFS (per the direct applied in the economic model).[19] While these data are in the front-line metastatic breast cancer setting, the population in TA816 is relevant to this appraisal given it is in a post-CDK4/6i setting and also used a TTD to PFS ratio to inform everolimus + exemestane TTD when compared to alpelisib + fulvestrant . The HR reported in TA816 is aligned to the EAG's assumption of a HR of 0.8 between TTD and PFS for everolimus + exemestane and therefore this is used in the base case presented. • The alpelisib + fulvestrant TTD data were redacted in TA816 and could therefore not be used. However, data from the SOLAR-1 trial publication, which includes both front-line and post CDK4/6i metastatic breast cancer patients, report a median PFS of 11 months and median treatment durations of 5.5 and 8.3 months for alpelisib and fulvestrant, respectively.[20] This equates to HRs of 0.5 for alpelisib and 0.75 for fulvestrant. Therefore, the EAG base case of 0.5 was included in the revised base case presented
6 ESR1-mut testing	*Section 3.15* *"The Cancer Drugs Fund clinical lead explained that the NHS GMS has advised that for this evaluation the cost of ESR1-mutation testing should be included at a value of £850 for each test. So, the cost of each case identified for treatment should be £1,700 using a 50% prevalence rate for a positive test. The Committee concluded that the cost of ESR1-mutation testing of £1,700 for each case identified should be implemented in the base-case analyses for the 2 subgroups."* The Company would like to thank the CDF clinical lead for highlighting the need for liquid biopsy on ctDNA on the basis of the Summary of Product Characteristics for elacestrant. We also understand the desire for the NHS to introduce an NGS panel which will allow for testing of all current and future mutations for treatments tailored to specific mutations in breast cancer. The Company is aware of at least 3 future treatments in breast cancer that will require specific mutation testing: • Capivasertib + fulvestrant - PIK3CA/AKT1/PTEN-altered subgroup (ID6370) *Truqap is indicated in combination with fulvestrant for the treatment of adult patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative (defined as IHC 0 or 1+, or IHC 2+/ISH-) locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following recurrence or progression on or after an endocrine based regimen.*[21] • Camizestrant

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 22 October 2024. Please submit via NICE Docs.

<table>
<tr><td></td><td>

- Inavolisib

The Company maintain that the cost of introducing NGS panel for testing all current and future mutations should not be included in the cost-effectiveness model for elacestrant and the cost of £850 is far higher than the actual cost of introducing ESR1mut testing alone into clinical practice. This could be done on droplet PCR at a lower cost per test.
</td></tr>
<tr><td>7
Severity</td><td>

Section 3.16
"It decided that the absolute and proportional shortfalls generated by the Company and the EAG could not be used to inform its decision making on severity for the activating ESR1-mutation subgroup. So, it was unable to conclude if a severity modifier should be applied for the activating ESR1-mutation subgroup."

The Company has applied the severity modifier as stated in the NICE methods guide and has therefore aligned with NICE methodology while conducting this submission.

The populations in the data sources used to inform the comparison between elacestrant and everolimus + exemestane in the *ESR1-mut* and ≥12 months of prior ET + CDK4/6i subgroup are demonstrated to be aligned in Comment 2.

As the Company base case has been updated to use the MAIC-adjusted baseline age (please see Comment 8), the QALY shortfall was recalculated using the R-Shiny QALY shortfall calculator tool developed by Schneider et al. (2021).[22] The input data are presented in Table 2.

Table 2: Summary features of QALY shortfall analysis

Factor	Value		Reference to section in submission
	***ESR1-mut* and ≥12 months of prior ET + CDK4/6i population**	***ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i population**	
Sex distribution (% female)	[redacted]%	[redacted]%	Table 26 & Table 28 (Document B.2.9.2)
Starting age (years)	[redacted]	[redacted]	

Abbreviations**:** QALY, quality adjusted life years.

The total remaining discounted QALYs for patients treated with everolimus + exemestane or alpelisib + fulvestrant were taken from the cost-effectiveness model 'results' sheet and inputted into the QALY shortfall tool to 2 decimal places.

Results of the QALY shortfall calculator are presented in Table 3.

The Company noted that alpelisib + fulvestrant in TA816 in a mutated advanced breast cancer population, post-CDK4/6i met the previous end of life criteria with an ICER threshold of £50,000 as stated in the final guidance. The Company has, however, followed the severity modifier methods as are applicable today and as currently described in the NICE methods guide.

In this appraisal, the criteria for applying a x1.2 severity modifier/QALY weight are met for the *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population considered by the model. No severity modifier is applicable for the *ESR1-mut*, *PIK3CA*-mut and ≥12 months of prior ET + CDK4/6i population.
</td></tr>
</table>

NICE National Institute for Health and Care Excellence

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 22 October 2024. Please submit via NICE Docs.

<table>
<tr><td></td><td>

Table 3: Summary of QALY shortfall analysis

<table>
<tr><th>Expected total QALYs for the general population</th><th>Total QALYs that people living with a condition would be expected to have with current treatment</th><th>QALY shortfall</th></tr>
<tr><td>[redacted]</td><td>Everolimus + exemestane</td><td>Absolute: [redacted]
Proportional: [redacted]%
QALY weight: x1.2</td></tr>
<tr><td>[redacted]</td><td>Alpelisib + fulvestrant</td><td>Absolute: [redacted]
Proportional: [redacted]%
QALY weight: x1</td></tr>
</table>

Abbreviations: QALY, quality adjusted life years.
Note: QALY shortfall for everolimus + exemestane was conducted in the *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population; QALY shortfall for alpelisib + fulvestrant was conducted in the *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i population.
</td></tr>
<tr><td>8
Cost-effectiveness estimates</td><td>

Section 3.17
"The Committee noted that for the activating ESR1-mutation subgroup none of the Company's or EAG's ICERs were relevant, including those from the base case and scenario analyses."
"So, the Committee concluded that it did not have a preferred ICER for the dual-mutated subgroup. This was mostly because of uncertainty about the relative clinical effectiveness of elacestrant (see section 3.9) and modelling of treatment duration of alpelisib plus fulvestrant (see section 3.14)."

The economic model has been updated to address the Committee's concerns, resulting in an updated ICER of £27,897 associated with elacestrant in the *ESR1-mut* and ≥12 months of prior ET + CDK4/6 population versus everolimus + exemestane, and with elacestrant demonstrating dominance over alpelisib + fulvestrant in the *ESR1-mut*, *PIK3CA*-mut and ≥12 months of prior ET + CDK4/6i population.

The Company has addressed committee concerns noted in Section 3.17 of the ACD, around the survival extrapolation in the *ESR1-mut* and ≥12 months of prior ET + CDK4/6 subgroup and treatment durations of everolimus + exemestane and alpelisib + fulvestrant.

In summary:

- Alternative scenarios to inform elacestrant OS in the *ESR1-mut* and ≥12 months of prior ET + CDK4/6 subgroup to allow long-term survival estimates between the log-logistic (Company-preferred) and gamma (EAG-preferred) extrapolations (please see Comment 4)
- Comparator TTD informed by the application of a HR to comparator PFS to address Committee concerns of treatment duration overestimation (please see Comment 5)

Other updates to the economic model include:

- A revised patient access scheme (PAS) for elacestrant has been submitted to PASLU. The model and all results have been updated to reflect this new PAS.

The Company acknowledge the concerns regarding the relative clinical effectiveness of elacestrant (detailed ACD Section 3.9). However, these concerns were unable to be addressed owing to the limited availability of comparative data, as noted by the Committee: *"The Committee acknowledged that the Company had done as much as possible to provide comparative evidence for elacestrant with treatments used in the NHS."*.
</td></tr>
</table>

Please return to: **NICE DOCS**

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 22 October 2024. Please submit via NICE Docs.

The updates and additional scenarios have been incorporated into the economic model to assess the cost-effectiveness of elacestrant to the comparator in both the *ESR1-mut* and ≥12 months of prior ET + CDK4/6i and *ESR1-mut*, *PIK3CA*-mut and ≥12 months of prior ET + CDK4/6i populations.

Changes to the Company base case

The updated Company base case incorporates the following changes:

- Use of MAIC-adjusted baseline age (aligned with EAG preferred assumptions)
- Use of eMIT everolimus price (aligned with EAG preferred assumptions)
- Exclusion of *ESR1-mut* testing costs (based on the expectation that ESR1 mutations would be identified via an NGS panel, the cost of which falls outside the scope of the economic model)
- *ESR1-mut* and ≥12 months of prior ET + CDK4/6i elacestrant OS extrapolation: Gamma + capped h(t)
    - Note: No change is made to elacestrant OS in the *ESR1-mut*, PIK3CA-mut and ≥12 months of prior ET + CDK4/6i population
- Comparator TTD approach (aligned with EAG preferred assumptions):
    - TTD vs. PFS HR, set to 0.8 and 0.5 for everolimus + exemestane and alpelisib + fulvestrant, respectively
- Elacestrant PAS price updated to £[redacted] (345mg) and £[redacted] (86mg) per 28-tablet pack (equivalent to a [redacted]% discount)

Base case results

Updated base case deterministic results including the fixed PAS price are presented in Table 4. Full cost-effectiveness results including sensitivity and scenario analyses are presented in Appendix 1.

In the *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population, the results demonstrate that elacestrant is associated with a deterministic ICER of £27,897 and a probabilistic ICER of £26,975 versus everolimus + exemestane (including a x1.2 severity modifier).

Considering the *ESR1-mut*, PIK3CA-mut and ≥12 months of prior ET + CDK4/6i population, the base case results demonstrate that elacestrant is associated with deterministic incremental costs and QALYs of -£11,516 and 0.277 and probabilistic incremental costs and QALYs of -£11,608 and 0.276 versus alpelisib + fulvestrant.

Table 4: Base-case results (deterministic) - Fixed PAS price

Technologies	Total			Incremental			ICER versus baseline (£/QALY)	Incremental NMB (£, £30,000/ QALY)
	Costs (£)	LYG	QALYs	costs (£)	LYG	QALYs*		
***ESR1-mut* and ≥12 months of prior ET + CDK4/6i**								
Everolimus + exemestane	[redacted]	[redacted]	[redacted]					
Elacestrant	[redacted]	[redacted]	[redacted]	13,177	0.581	0.472	27,897	993

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 22 October 2024. Please submit via NICE Docs.

<table>
<tr><td></td><td>
<table>
<tr><th colspan="9">ESR1-mut, PIK3CA-mut and ≥12 months of prior ET + CDK4/6i</th></tr>
<tr><td>Alpelisib + fulvestrant</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Elacestrant</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>-11,516</td><td>0.430</td><td>0.277</td><td>Dominant</td><td>19,817</td></tr>
</table>
Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ESR1, oestrogen receptor 1 gene; ET, endocrine therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; PAS, patient access scheme; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; QALYs, quality-adjusted life years. Note: *A severity modifier of 1.2 is applied to the discounted incremental QALYs.
</td></tr>
<tr><td>9
Cost-minimisation analyses</td><td>
Section 3.18
“The Committee decided that given the high uncertainty about the post-hoc subgroups from EMERALD and the clinical effectiveness of elacestrant relative to the comparators, it would like to see exploratory cost-minimisation analyses that assume equivalent clinical effectiveness on all outcomes such as progression-free and overall survival, time to treatment discontinuation and adverse events.“

Although the Company takes on board the Committee’s concern regarding uncertainty, the Company does not believe it is appropriate to present a cost-minimisation analysis.

In addition, the clinical community does not believe elacestrant to be equally effective to everolimus + exemestane in ESR1-mut and ≥12 months of prior ET + CDK4/6i patients. In the UKBCG submission presented at ACM1 it was stated that elacestrant is a ‘step-change’ in treatment, which was later confirmed with further clinical feedback provided to the Company post-ACM1.

Clinical feedback is that it is not appropriate to perform a cost-minimisation that assumes elacestrant and everolimus + exemestane are clinically equivalent. If this were the case, there would be no value in subjecting people to additional testing for ESR1-mut and potentially delaying treatment if clinical belief was that treatment with elacestrant has no benefit in terms of efficacy compared to everolimus + exemestane.

The Company would also like to highlight that the absence of a statistically significant difference in clinical outcomes should not be considered to be evidence of similar clinical effectiveness. Much of the uncertainty associated with the clinical effectiveness of elacestrant relative to the comparators is due to the necessity to carry out an (unanchored) indirect treatment comparison and the relatively small sample size of people receiving the relevant treatments in populations specific to the scope of this appraisal.

The Company acknowledges the limitations of the analyses performed and appreciates the Committees’ recognition that “…the Company had done as much as possible to provide comparative evidence for elacestrant with treatments used in the NHS.”. However, based on this rationale, the Company has not conducted an exploratory cost-minimisation analyses as the weight of evidence supports the expectation that elacestrant provides improved clinical outcomes for patients, warranting its use in the NHS.
</td></tr>
<tr><td>References</td><td>

1. Menarini Stemline. UK Clinical Expert Opinion, Data on File. 2024.

2. Bardia A, Cortés J, Bidard FC, Neven P, Garcia-Sáenz J, Aftimos P, et al. Elacestrant in ER+, HER2- Metastatic Breast Cancer with ESR1-Mutated Tumors: Subgroup Analyses from the Phase III EMERALD Trial by Prior Duration of Endocrine Therapy plus CDK4/6 Inhibitor and in Clinical Subgroups. Clin Cancer Res. 2024 Oct 1;30(19):4299–309.

</td></tr>
</table>

Please return to: **NICE DOCS**

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 22 October 2024. Please submit via NICE Docs.

	3. Cardoso F, Paluch-Shimon S, Senkus E, Curigliano G, Aapro MS, André F, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Annals of Oncology. 2020 Dec 1;31(12):1623–49. 4. Cardoso F, Senkus E, Costa A, Papadopoulos E, Aapro M, André F, et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)†. Ann Oncol. 2018 Aug 1;29(8):1634–57. 5. Han Y, Wang J, Wang Z, Xu B. Comparative efficacy and safety of CDK4/6 and PI3K/AKT/mTOR inhibitors in women with hormone receptor-positive, HER2-negative metastatic breast cancer: a systematic review and network meta-analysis. Current Problems in Cancer. 2020 Dec 1;44(6):100606. 6. MHRA. Summary of Product Characteristics: IBRANCE 125 mg hard capsules [Internet]. [cited 2024 May 25] p. 29. Available from: https://mhraproducts4853.blob.core.windows.net/docs/a0e37fe1624c9cc0b8a503c7fffb8cf7fdae51c6 7. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. Annals of Oncology. 2018 Jul;29(7):1541–7. 8. Tripathy D, Im SA, Colleoni M, Franke F, Bardia A, Harbeck N, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. The Lancet Oncology. 2018 Jul 1;19(7):904–15. 9. Im SA, Lu YS, Bardia A, Harbeck N, Colleoni M, Franke F, et al. Overall Survival with Ribociclib plus Endocrine Therapy in Breast Cancer. N Engl J Med. 2019 Jul 25;381(4):307–16. 10. Johnston S, Martin M, Di Leo A, Im SA, Awada A, Forrester T, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. NPJ Breast Cancer. 2019 Jan 17;5:5. 11. Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, et al. Palbociclib and Letrozole in Advanced Breast Cancer. N Engl J Med. 2016 Nov 17;375(20):1925–36. 12. Curigliano G, Castelo-Branco L, Gennari A, Harbeck N, Criscitiello C. ESMO Metastatic Breast Cancer Living Guideline > ER-positive HER2-negative Breast Cancer. 2023 May [cited 2023 Aug 11]; Available from: https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline/er-positive-her2-negative-breast-cancer 13. Bhave MA, Quintanilha JCF, Tukachinsky H, Li G, Scott T, Ross JS, et al. Comprehensive genomic profiling of ESR1, PIK3CA, AKT1, and PTEN in HR(+)HER2(-) metastatic breast cancer: prevalence along treatment course and predictive value for endocrine therapy resistance in real-world practice. Breast Cancer Res Treat. 2024 Oct;207(3):599–609. 14. NICE. Advanced breast cancer: diagnosis and treatment CG81 [Internet]. National Institute for Health and Care Excellence; 2017 Aug [cited 2023 Aug 10]. Available from:

NICE National Institute for Health and Care Excellence

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 22 October 2024. Please submit via NICE Docs.

	https://www.nice.org.uk/guidance/cg81/resources/advanced-breast-cancer-diagnosis-and-treatment-pdf-975683850181 15. NICE. Abemaciclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer: TA563 [Internet]. National Institute for Health and Care Excellence; 2019 Feb [cited 2023 Aug 11]. Available from: https://www.nice.org.uk/guidance/ta563 16. NICE. Ribociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer: TA496 [Internet]. National Institute for Health and Care Excellence; 2017 Dec [cited 2023 Aug 11]. Available from: https://www.nice.org.uk/guidance/ta496 17. NICE. Palbociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer: TA495. National Institute for Health and Care Excellence; 2017 Dec. 18. MHRA. Summary of Product Characteristics (KORSERDU) [Internet]. Medicines and Healthcare products Regulatory Agency; 2023 Dec [cited 2024 Jan 22]. Available from: https://mhraproducts4853.blob.core.windows.net/docs/95258a8afaced7089a5b5cbdc45108ce15ac7bf2 19. NICE. Alpelisib with fulvestrant for treating hormone receptor-positive, HER2-negative, *PIK3CA*-mutated advanced breast cancer: TA816 [Internet]. National Institute for Health and Care Excellence; 2022 Aug [cited 2023 Aug 11]. Available from: https://www.nice.org.uk/guidance/ta816 20. André F, Ciruelos E, Rubovszky G, Campone M, Loibl S, Rugo HS, et al. Alpelisib for *PIK3CA*-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2019 May 16;380(20):1929–40. 21. EMA. Truqap - Summary of Product Characteristics (SmPC). 22. Schneider P, McNamara S, Love-Koh J, Doran T, Gutacker N. QALY Shortfall Calculator [Internet]. [cited 2024 Mar 21]. Available from: https://shiny.york.ac.uk/shortfall

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 funding from the Company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist

NICE National Institute for Health and Care Excellence

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 22 October 2024. Please submit via NICE Docs.

of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.

- Do not include medical information about yourself or another person from which you or 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 draft guidance 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.

Appendix 1

Base-case results

Base case deterministic results including the fixed PAS price are presented in Table 1 with net-health benefit (NHB) results provided in Table 3 (at willingness-to-pay [WTP] thresholds of £20,000 and £30,000 per QALY gained). Results are provided for both populations: *ESR1-mut* + ≥12 months of prior ET + CDK4/6i, and *ESR1-mut, PIK3CA-mut* + ≥12 months of prior ET + CDK4/6i.

The NICE manual states cost-effectiveness estimates should be derived from a probabilistic analysis, when possible. Therefore, results are presented using probabilistic results Table 2 and Table 4.

When considering a x1.2 QALY weight gain for the *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population (Document B.3.6), the base case results demonstrate that elacestrant is associated with a deterministic ICER of £27,897 and a probabilistic ICER of £26,969 versus everolimus + exemestane.

Considering no severity modifier for the *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i population (Document B.3.6), the base case results demonstrate that elacestrant is associated with deterministic incremental costs and QALYs of -£11,516 and 0.277 and probabilistic incremental costs and QALYs of -£11,608 and 0.276 versus alpelisib + fulvestrant.

Table 1: Base-case results (deterministic) – Fixed PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs*	ICER versus baseline (£/QALY)	Incremental NMB (£, £30,000/QALY)
***ESR1-mut* and ≥12 months of prior ET + CDK4/6i**								
Everolimus + exemestane	[redacted]	[redacted]	[redacted]					
Elacestrant	[redacted]	[redacted]	[redacted]	13,177	0.581	0.472	27,897	993
***ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i**								
Alpelisib + fulvestrant	[redacted]	[redacted]	[redacted]					
Elacestrant	[redacted]	[redacted]	[redacted]	-11,516	0.430	0.277	Dominant	19,817

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; PAS, patient access scheme; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; QALYs, quality-adjusted life years. Note: *A severity modifier of 1.2 is applied to the discounted incremental QALYs.

Table 2: Base-case results (probabilistic) – Fixed PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs*	ICER versus baseline (£/QALY)	Incremental NMB (£, £30,000/QALY)
***ESR1-mut* and ≥12 months of prior ET + CDK4/6i**								
Everolimus + exemestane	[redacted]	[redacted]	[redacted]					
Elacestrant	[redacted]	[redacted]	[redacted]	12,730	0.581	0.472	26,969	1,431
***ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i**								
Alpelisib + fulvestrant	[redacted]	[redacted]	[redacted]					
Elacestrant	[redacted]	[redacted]	[redacted]	-£11,608	0.429	0.276	Dominant	£19,895

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; PAS, patient access scheme; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; QALYs, quality-adjusted life years.

Note: *A severity modifier of 1.2 is applied to the discounted incremental QALYs.

Table 3: Net health benefit (deterministic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
***ESR1-mut and* ≥12 months of prior ET + CDK4/6i**						
Everolimus + exemestane	[redacted]	[redacted]				
Elacestrant	[redacted]	[redacted]	13,177	0.472	-0.187	0.033
***ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i**						
Alpelisib + fulvestrant	[redacted]	[redacted]				
Elacestrant	[redacted]	[redacted]	-£11,516	0.277	0.853	0.661

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; NHB, net health benefit; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; QALYs, quality-adjusted life years.
Note: *A severity modifier of 1.2 is applied to the discounted incremental QALYs.

Table 4: Net health benefit (probabilistic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
***ESR1-mut and* ≥12 months of prior ET + CDK4/6i**						
Everolimus + exemestane	[redacted]	[redacted]				
Elacestrant	[redacted]	[redacted]	12,730	0.472	-0.164	0.048
***ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i**						
Alpelisib + fulvestrant	[redacted]	[redacted]				
Elacestrant	[redacted]	[redacted]	-£11,608	0.276	0.857	0.663

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; NHB, net health benefit; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; QALYs, quality-adjusted life years.
Note: *A severity modifier of 1.2 is applied to the discounted incremental QALYs.

B.1.1 Exploring uncertainty

B.1.1.1 Probabilistic sensitivity analysis

Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA). In PSA, all parameters are simultaneously varied from an assigned probability distribution (see Document B.3.8.1). PSA inputs were randomly drawn, and results recorded across 5,000 iterations, by which point costs and outcomes had stabilised and were considered reliable for capturing uncertainty (assessed by visual inspection of convergence plots in the submitted cost-effectiveness model).

Mean probabilistic results are presented in Table 2 and Table 4. Figure 1 and Figure 2 presents the cost-effectiveness acceptability curves for elacestrant versus everolimus + exemestane and alpelisib + fulvestrant, respectively. At a WTP threshold of £30,000 per QALY gained, elacestrant has the highest probability of being the most cost-effective option for both populations (when considering the x1.2 severity modifier for the *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population).

Figure 3 and Figure 4 present an incremental cost-effectiveness plane for elacestrant versus everolimus + exemestane and alpelisib + fulvestrant, respectively. Of 5,000 PSA iterations, [redacted]% and [redacted]% indicate that elacestrant provides more QALYs at an increased cost per patient compared to everolimus + exemestane and alpelisib + fulvestrant, respectively, at a willingness-to-pay threshold of £30,000.

Figure 1: Cost-effectiveness acceptability curve | *ESR1-mut* and ≥12 months of prior ET + CDK4/6i

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ELA, elacestrant; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; EVE, everolimus; EXE, exemestane; NMB, net monetary benefit.
Note: A severity modifier of 1.2 is applied to the discounted incremental QALYs.

Figure 2: Cost-effectiveness acceptability curve | *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i

Abbreviations: ALP, alpelisib; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ELA, elacestrant; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; FUL, fulvestrant; NMB, net monetary benefit; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

Figure 3: Incremental cost-effectiveness plane | *ESR1-mut* and ≥12 months of prior ET + CDK4/6i

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; ELA, elacestrant; EVE, everolimus; EXE, exemestane; QALY, quality-adjusted life year; WTP, willingness-to-pay.
Note: A severity modifier of 1.2 is applied to the discounted incremental QALYs.

Figure 4: Incremental cost-effectiveness plane | *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i

Abbreviations: ALP, alpelisib; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ELA, elacestrant; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; FUL, fulvestrant; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; QALY, quality-adjusted life year; WTP, willingness-to-pay.

B.1.1.2 Deterministic sensitivity analysis

One-way sensitivity analysis (OWSA) was conducted to test the impact of individual parameter uncertainty on cost-effectiveness results, holding all else constant. In turn, inputs were set to their respective lower and upper limits (presented in Document B.3.8.1), while all other parameters were maintained at their base case setting. If the variance of a parameter was not available, a simplifying assumption was made assuming that the standard error was 10% of the mean values. Correlated inputs with joint uncertainty, such as parametric survival model coefficients which are varied in PSA using a multivariate normal distribution, were not included in the OWSA.

Figure 5 and Figure 6 present the tornado plots showing the 10 parameters with the largest impact on the incremental net-monetary benefit (INMB) for elacestrant versus everolimus + exemestane and alpelisib + fulvestrant, respectively, at a willingness-to-pay threshold of £30,000.

For the *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population, the OWSA demonstrates that model findings are robust to reasonable variation in parameters, with the

RDI, comparator TTD HR and the cost of everolimus having the largest impact on the results.

Figure 5: Tornado plot of OWSA results (INMB) | *ESR1-mut* and ≥12 months of prior ET + CDK4/6i

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; HSUV, health state utility value; INMB, incremental net-monetary benefit; OWSA, one-way sensitivity analysis; PD, progressed disease; PF, progression free; QALY, quality-adjusted life year; RDI, relative dose intensity; tx, treatment; WTP, willingness-to-pay.
Note: INMB calculated using a WTP threshold of £30,000 per QALY gained. A severity modifier of 1.2 is applied to the discounted incremental QALYs. Correlated inputs with joint uncertainty (such as parametric survival model coefficients) are not included in the OWSA.

For the *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i population, the parameters with the largest impact on the INMB were the TTD HR for alpelisib + fulvestrant and RDI for alpelisib and elacestrant. As seen with the comparison to everolimus + exemestane, the OWSA versus alpelisib + fulvestrant demonstrates the model findings are robust to reasonable variation in parameters.

Figure 6: Tornado plot of OWSA results (INMB) | *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i

Abbreviations: ALP, alpelisib; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; FUL, fulvestrant; HSUV, health state utility value; INMB, incremental net-monetary benefit; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PD, progressed disease; PF, progression free; OWSA, one-way sensitivity analysis; QALY, quality-adjusted life year RDI, relative dose intensity; tx, treatment; WTP, willingness-to-pay.
Note: INMB calculated using a WTP threshold of £30,000 per QALY gained. Correlated inputs with joint uncertainty (such as parametric survival model coefficients) are not included in the OWSA.

B.1.1.3 Scenario analysis

Scenario analyses were performed to test key structural and methodological assumptions within the model. As the base case probabilistic results and deterministic results were close, scenario analyses were conducted deterministically. Results of the scenario analyses are presented in Table 5 and Table 6 compared to everolimus + exemestane and alpelisib + fulvestrant, respectively. All scenarios presented for the *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population met the x1.2 severity modifier criteria.

Table 5: Scenario analysis results | *ESR1-mut* and ≥12 months of prior ET + CDK4/6i – elacestrant versus everolimus + exemestane

Parameter/setting	Base case	Scenario	ICER	NMB
Time horizon	37 years	10 years	£28,009	£935
		20 years	£27,897	£993
Discount rates for costs and QALYs	3.5%	1.5%	£27,235	£1,369
		6.0%	£28,706	£578
MAIC approach	Independent PSM extrapolation	HR	Dominated	-£1,204
Elacestrant OS		Log-logistic	£19,646	£7,832

	Gamma + capped hazards	Gamma	£33,275	-£1,248
		Average S(t): log-log, gamma	£24,116	£3,350
		Average h(t): log-log, gamma	£27,143	£1,397
Everolimus + exemestane TTD HR	0.8	0.9	£27,327	£1,263
		0.7	£28,453	£731
RDI	Include	Exclude	£28,148	£875
ESR1-mut testing costs	Exclude	Include	£29,167	£393
Subsequent treatment costs	Include	Exclude	£27,901	£992
Progressed utility source	EMERALD EQ-5D analysis ([redacted])	Lloyd *et al*. (2006), absolute approach (0.601)	£27,721	£1,083
Age-adjusted utilities	Enabled	Disabled	£27,488	£1,204
AE disutilities	Exclude	Include	£27,822	£1,031

Abbreviations: AE, adverse event; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; EQ-XD, Euro-QoL X-dimension; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; INMB, incremental net-monetary benefit; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; PSM, parametric survival model; NMB, net-monetary benefit; QALY, quality-adjusted life year; RDI, relative dose intensity; TTD, time to treatment discontinuation; WTP, willingness-to-pay.
Note: INMB calculated using a WTP threshold of £30,000 per QALY gained. A severity modifier of 1.2 is applied to the discounted incremental QALYs.

Table 6: Scenario analysis results | *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i – elacestrant versus alpelisib + fulvestrant

Parameter/setting	Base case	Scenario	ICER	NMB
Time horizon	37 years	10 years	Dominant	£19,828
		20 years	Dominant	£19,817
Discount rates for costs and QALYs	3.5%	1.5%	Dominant	£20,087
		6.0%	Dominant	£19,500
MAIC approach	Independent PSM extrapolation	HR	Dominant	£13,260
Elacestrant OS	Weibull	Gamma	Dominant	£24,769
		Log-normal	Dominant	£37,616
Alpelisib + fulvestrant OS	Gamma	Weibull	Dominant	£21,204
		Log-normal	Dominant	£14,684
		Log-logistic	Dominant	£26,025
RDI	Include	Exclude	Dominant	£21,257
ESR1-mut testing costs	Exclude	Include	Dominant	£19,217
Subsequent treatment costs	Include	Exclude	Dominant	£19,817

Progressed utility source	EMERALD EQ-5D analysis ([redacted])	Lloyd *et al*. (2006), absolute approach (0.601)	Dominant	£18,915
Age-adjusted utilities	Enabled	Disabled	Dominant	£19,949
AE disutilities	Exclude	Include	Dominant	£19,847

Abbreviations: AE, adverse event; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; EQ-XD, Euro-QoL X-dimension; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; INMB, incremental net-monetary benefit; MAIC, matching-adjusted indirect comparison; NMB, net-monetary benefit; OS, overall survival; PFS, progression-free survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PSM, parametric survival model; QALY, quality-adjusted life year; RDI, relative dose intensity; TTD, time to treatment discontinuation; WTP, willingness-to-pay.
Note: INMB calculated using a WTP threshold of £30,000 per QALY gained.

NICE National Institute for Health and Care Excellence

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 22 October 2024. 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

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 22 October 2024. Please submit via NICE Docs.

Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Breast Cancer Now has received funding from a number of drug companies towards our support services. However, we do not receive any pharmaceutical funding for our Policy, Evidence and Influencing work, which includes our work on access to drugs. Over the last 12 months (October 2023-October 2024) we have received funding from the following companies listed in the stakeholder list for this appraisal: • Menarini Stemline: £10,500 to support our nursing conference • Novartis: £15k to support our nursing conference and £50k to partly fund a research project at UCL led by Prof Horne looking at Inequalities for Black women with breast cancer in the UK. Breast Cancer Now hosts the UK Interdisciplinary Breast Cancer Symposium (UKIBCS) alongside a number of partners including professional bodies and charities. The meeting is held every 2 years and the UKIBCS provides a space to bring together those with an interest in breast cancer research and treatment to advance understanding of the disease. The event is managed by a third party who receive and process sponsorship on behalf of the host and partners. Sponsors have no control over the running of the event and editorial control has been retained by the UKIBCS executive board. In the past 12 months (since October 2023), this has included the following listed on this appraisal matrix: • AstraZeneca: £3k for an additional stand at UKIBCS (December 2023) • Novartis: £50k for advertising space at UKIBCS (December 2023). • Pfizer: £6k for an exhibitors package at UKBICS (November 2023) • Pierre Fabre: £3k for an exhibitors package at UKBICS (October 2023).
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	none

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 22 October 2024. Please submit via NICE Docs.

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.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are disappointed that NICE has provisionally rejected elacestrant (Korserdu) for use on the NHS in England. For patients with ER-positive, HER2-negative secondary breast cancer with an ESR1 mutation this decision takes away hope of a new targeted treatment being made available to them. This new treatment could have offered them precious additional time with loved ones and doing what matters most to them before their disease progresses.
2	We note the concerns of the committee, as outlined in the draft guidance, around uncertainties in the data on the clinical and cost-effectiveness of elacestrant and have called for NICE and Menarini Stemline to work closely together to resolve these issues.
3	We note the committee's specific concerns about lack of comparator data, the use of Flatiron data and the reliance on unanchored matching-adjusted indirect comparisons. We have been informed by the company that the data submitted was the only applicable set that they could identify that would provide the committee with the necessary information. We would urge the committee to take a pragmatic approach to the data limitations in this case.
4	
5	
6	

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 funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 22 October 2024. Please submit via NICE Docs.

- Do not include medical information about yourself or another person from which you or 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 draft guidance 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.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 22 October 2024. 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):	METUPUK

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 22 October 2024. Please submit via NICE Docs.

Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	None
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
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.
Example 1	We are concerned that this recommendation may imply that ……..
1	Has all of the relevant evidence been taken into account?

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 22 October 2024. Please submit via NICE Docs.

	Patients with ESR1 mutations would value access to elacestrant because current NHS standard of care (SOC) which includes fulvestrant combinations or EE does not meet every individual's needs. Some patients/oncologists elect not to use everolimus and exemestane (EE) or alpelisib with fulvestrant (if testing positive for a PIK3CA mutation) at second line because of toxicity, or comorbidities. For example, if a patient has diabetes, they may be recommended to avoid alpelisib with fulvestrant. Alternative choices may include EE, but could also include capecitabine (or possibly tamoxifen). We are unsure how many patients select this option. Is there data to resolve the uncertainty about how often capecitabine/tamoxifen is used in the NHS (albeit in the untested ESR1 population)? The EMERALD trial admitted patients with no more than one line of chemo in the metastatic setting, so although chemo was not a comparator, patients were not required to be chemo naive. We believe it is reasonable for the committee consider capecitabine as a comparator.
2	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? There is an unmet need for patients with an ESR1 mutation. ESR1 mutations are associated with faster progression and worse survival (Brett *et al*, 2021). Testing for ESR1 mutations will be carried out using a ctDNA blood biopsy. This non-invasive testing has the potential to be a step change in NHS cancer care. Rolling out capability for ctDNA testing across the NHS will not just benefit breast cancer patients but has further potential across all oncology services. Elacestrant delays the need for chemotherapy and has fewer toxic side effects than the comparators – exemestane with everolimus or alpelisib with fulvestrant. ESR1 mutation subgroup – We understand that the committee has asked for the data from this subgroup to be separated into ESR1 mutation plus mutated PIK3CA and ESR1 mutation plus wildtype PIK3CA because of the assumption that patients with a PIK3CA mutation will have alpelisib plus fulvestrant and so should be considered separately. We would like the committee to consider that a proportion of patients with PIK3CA mutations (we hope there is NHS data to determine what this proportion is) do not go onto have alpelisib plus fulvestrant because their oncologist has suggested they are unsuitable or they are concerned about toxicity. We can see an argument for a third group containing both wildtype and mutated PIK3CA mutations– but do agree that separate analyses on mutated and wildtype PIK3CA mutations should also be done as suggested by the committee. Brett, J.O. *et al.* (2021) 'ESR1 mutation as an emerging clinical biomarker in metastatic hormone receptor-positive breast cancer', *Breast Cancer Research*, 23(1) available at https://breast-cancer-research.biomedcentral.com/articles/10.1186/s13058-021-01462-3 accessed 20 October 2024.
3	Are the recommendations sound and a suitable basis for guidance to the NHS? No the recommendations are not a sound and suitable guidance to the NHS. Elacestrant is the first oral selective estrogen receptor degrader (SERD) shown in trials to demonstrate improvement in PFS compared to SOC in patients with ER-positive HER2-negative MBC with ESR1 mutations. Improved PFS translates to reduced tumour load and improved quality of life for patients. Fulvestrant is the only SERD currently available on the NHS and was approved in 2004. Fulvestrant is delivered by intramuscular treatment into the buttocks. More painful for

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 22 October 2024. Please submit via NICE Docs.

	patients, and more time spent in hospital waiting rooms for patients. The MBC patient community would value elacestrant as an option. For patients with ESR1 mutations, elacestrant is standard of care in the USA and in Europe has been adopted into the ESMO Living Guidelines for Metastatic Breast cancer (https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline/er-positive-her2-negative-breast-cancer - accessed 20 October 2024). Our engagement with the MBC community has found that patients believe NHS access to medicines should be comparable to similar income countries within Europe. Patients particularly value treatments targeted to their disease. The introduction of ESR1 testing within the NHS is seen as a step towards personalised care. Many patients are concerned about being channelled through fixed treatment lines and would prefer their tumour biology to be considered when treatments are selected. Elacestrant delays the need for chemotherapy and has fewer toxic side effects than the comparators – exemestane with everolimus or alpelisib with fulvestrant. Elacestrant reduces the time patients spend in hospitals thereby freeing up time for people follow their own interests. Elacestrant is also a less workforce intensive treatment than fulvestrant, and workforce issues are a limiting factor in providing NHS cancer care.
4	Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people? None noted
5	
6	

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 funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 22 October 2024. Please submit via NICE Docs.

- 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 draft guidance 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.

Please return to: **NICE DOCS**

It was disappointing that Elacestrant was not recommended in the published draft guidelines for patients with metastatic breast cancer with an ESR1 mutation after progression on CDK4/6 inhibitor therapy. Elacestrant is an oral drug targeting the ESR 1 mutation, a common mutation for developing endocrine resistance. As it is an acquired mutation, patients need ESR 1 testing at the time of progression on a CDK4/6 inhibitor.

Our current approved treatments for these patients include

a. Exemestane & Everolimus
b. Faslodex & Alpelesib (for PIK3CA mutation)
c. Chemotherapy

In clinical experience, the duration of response on Exemestane & Everolimus is short post CDK4/6 inhibitor therapy. Both Faslodex & Alpelesib and Exemestane & Everolimus therapy carry significant side effects for patients and many clinicians/patients are reluctant to use or continue these treatments. Both patients and clinicians also want to delay the use of chemotherapy if possible. Elacestrant as an oral agent is well tolerated with favourable safety profile. Results from the EMERALD study showed PFS of 8.6 months for patients with ESR 1 mutation who respond to CDK4/6 inhibitor for ≥ 12 months.

Regarding the NICE appraisal documents, please consider the following:

a. Tamoxifen is not a suitable alternative for patients who will be offered Elacestrant in the NHS. Its use is limited to <5% patients who are not suitable for other therapies due to poor performance status. Use of Tamoxifen for a minority should not impact on the NICE decision on Elacestrant.

b. In the absence of real-world data, the extrapolation of OS data curves is difficult. However, the use of gamma distribution for Elacestrant would suggest that at 5 and 10 years, patients receiving Elacestrant would have worse outcome than Everolimus & Exemestane. This is not clinically plausible so a different statistical fitting model should be considered.

c. Use of Exemestane and Everolimus based on the Bolero 2 study included all patients as the routine testing of ESR1 and PIK3CA was not available at that time. In clinical practice, not all patients with PIK3CA mutation will receive Faslodex & Alpelesib due to prior Faslodex exposure, unavailability of PIK3CA results and patient factors like pre-existing diabetes.

Both the clinical and patient community are keen for Elacestrant to be made available for suitable group of patients in the NHS. We will urge that both NICE and Menarini Stemline work together to make Elacestrant available within the NHS.

External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Elacestrant for treating oestrogen receptor-positive, HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

EAG critique of the company's response to draft guidance

Produced by	**Southampton Health Technology Assessments Centre (SHTAC)**
Authors	Emma Maund, Marcia Takahashi, Joanne Lord, Jonathan Shepherd
Correspondence to	Dr Jonathan Shepherd Southampton Health Technology Assessments Centre (SHTAC) School of Healthcare Enterprise and Innovation University of Southampton Alpha House, Enterprise Road, University of Southampton Science Park, Southampton SO16 7NS www.southampton.ac.uk/shtac
Date completed	30 October 2024

Source of Funding	This report was commissioned by the National Institute for Health and Care Research (NIHR) Evidence Synthesis Programme as project number 136220.

Confidential (CON) information is highlighted in blue and underlined

Introduction

This document is the External Assessment Group (EAG) critique of the response made by Menarini Stemline UK Ltd as part of a consultation on draft guidance issued by NICE in September 2024 for the health technology evaluation of 'Elacestrant for treating oestrogen receptor positive HER2-negative advanced breast cancer with an ESR1 mutation after endocrine treatment'. The draft guidance states that:

"Elacestrant is not recommended, within its marketing authorisation, for treating oestrogen receptor (ER)-positive HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation that has progressed after at least 1 line of endocrine therapy including a cyclin-dependent kinase (CDK) 4 and 6 inhibitor". This is applicable to women, trans men and non-binary people after menopause, and to men.

In this document we summarise each of the main issues flagged by the company and provide a critique of the company response to each issue (Table 1). We present updated cost effectiveness results from the company and the EAG's analyses. These results include a confidential patient access scheme (PAS) discount for elacestrant, but other drugs are costed at non-confidential NHS prices. We report results, including all confidential discounts for comparators and subsequent treatments in a confidential 'cPAS' addendum to this report.

Table 1 Summary of the company's response to the draft NICE guidance

Number	Company comment	New data / new analyses
1	Target population ≥12 months prior ET + CDK4/6i	No
2	Presence of dual mutated patients within the EMERALD data	No
3	Tamoxifen and chemotherapy as a comparator	No
4	ESR1-mut subgroup: elacestrant OS extrapolation	Yes
5	Comparator treatment duration	Yes
6	ESR1-mut testing	Yes
7	Severity	Yes
8	Cost-effectiveness estimates	Yes
9	Cost-minimisation analysis	No

Comment 1. Target population ≥12 months prior ET + CDK4/6i

(No new data or new analyses of existing data have been provided in relation to this issue)

The company quotes draft guidance sections 3.18 and 3.5, specifically the NICE evaluation committee's description of the 12-month prior treatment threshold as being "arbitrary". In their response, the company reiterate the points made in their submission and responses to EAG clarification question A7a and b.

- They discuss the need to redefine endocrine resistance in the CDK4/6i treatment era. Acquired resistance has become more common due to patients surviving without progression for longer with the advent of CDK4/6i + ET therapy.
- They mention the results of the post hoc subgroup analysis of the EMERALD trial, in which elacestrant treatment response was assessed in patients who had progressed after **<6 months**, **6-12 months**, **12-18 months**, and **≥18 months** of CDK4/6i + ET therapy, respectively. PFS increased in patients treated with elacestrant, and this increase was more pronounced in patients with at least 12 months of prior CDK4/6i treatment duration.
- The selection of the above thresholds appears to have been informed by UK clinicians consulted by the company who advised on appropriate intervals used in practice to assess progression and whether to proceed to subsequent treatment lines. It is not clear if, in the first instance, the thresholds were proposed by the company and then presented to the clinicians for discussion and agreement, or, whether the thresholds were proposed by clinicians independently and then applied by the company as post hoc subgroups of the EMERALD trial.
- The EAG notes the company's assertion that when differentiating between primary endocrine resistance and treatment-acquired resistance, there is greatest uncertainty for patients who progress between 6 and 12 months. Given this, an interim threshold at 9 months may have been informative for a sub-group analysis, particularly as NHS England anticipates it will not fund elacestrant in people who progress after 11 months treatment.

EAG comment

The company reiterate their justification for elacestrant targeted at a population with ≥12 months prior ET + CDK4/6i, based on consultation with expert clinicians. As we have previously commented (EAG report, section 2.2.3.1), the EAG's clinical advisor agreed that 12 months is a suitable length of time to discern between primary resistance and resistance acquired from ET + CDK4/6i therapy. In the EAG's opinion the company's

choice of the ≥12-month threshold appears to be more “data-driven” than arbitrary, given the post hoc status of the subgroup analyses.

Comment 2. Presence of dual mutated patients within the EMERALD data

(No new data or new analyses of existing data have been provided in relation to this issue)

The company quotes draft guidance sections 3.7 and 3.11, specifically the committee’s concern that the activating ESR1-mutation subgroup included 39% (62/159) of patients with dual mutated breast cancer. The evaluation committee’s view is that that the activating ESR1-mutation subgroup comparing elacestrant with everolimus plus exemestane should only include people with breast cancer that had the ESR1 mutation and not the PIK3CA mutation. Patients with dual ESR1 and PIK3CA mutations should be analysed in a separate group distinct from the ESR1 without dual mutation. For the dual mutation subgroup, the appropriate comparator would be alpelisib plus fulvestrant, and not everolimus plus exemestane.

In their response, the company state that the marketing authorisation for everolimus plus exemestane does not restrict its use to a specific biomarker, and it would be considered for all eligible patients in the scope of this appraisal. The company also contend that everolimus plus exemestane is used in practice in dual mutated patients who are unable to take alpelisib + fulvestrant due to comorbidities (e.g. diabetes), as well as those preferring an oral regimen.

A further point made by the company is that the proportion of ESR1- mutation patients with prior treatment for ≥12 months in the EMERALD trial who have both mutations is similar to that seen in the Flatiron database (to recap, Flatiron was the source of comparator data in the company’s MAIC). Again, based on expert clinical advice the company considers that the EMERALD trial and the Flatiron database are representative of the type of patients seen in clinical practice.

EAG comment

The EAG acknowledges the points made by the company, but it appears that the company has misinterpreted the draft guidance in their response. The main issue is that for people with both the ESR1-mut and PIK3CA-mut (i.e. dual mutation) the economic analysis should include both comparators (i.e. alpelisib plus fulvestrant and everolimus plus exemestane). However, the company’s economic model doesn’t allow for this. In

contrast, people with ESR1-mut but not PIK3CA-mut are only eligible for everolimus plus exemestane.

Comment 3. Tamoxifen and chemotherapy as a comparator

(No new data or new analyses of existing data have been provided in relation to this issue)

The company quotes draft guidance sections 3.7, 3.10 and 3.17 which discuss the committee's preference for the inclusion of tamoxifen and chemotherapy as comparator treatments. Specifically, the evaluation committee would have liked to see scenario analyses that included varying proportions of people having tamoxifen. In their response, the company reiterate the points made in their submission, including:

- Chemotherapy in the UK is reserved for patients with imminent risk of organ failure, for patients who have exhausted other endocrine based treatment or for patients who are deemed primary endocrine resistant.
- Tamoxifen is not widely used in UK clinical practice; It is indicated for the treatment of pre- and perimenopausal patients with ER+ advanced breast cancer where a CDK4/6i would not be used. It would therefore not be considered as a treatment for patients eligible for elacestrant.
- The company cites expert clinical opinion, NICE clinical guideline CG81 ('Advanced breast cancer: diagnosis and treatment'), and NICE TA816 ('Alpelisib + fulvestrant for treating advanced hormone receptor positive, HER2-negative, PIK3CA-mutated breast cancer') as supporting their position.

EAG comment

As we have stated previously (EAG report section 2.2.3) expert clinical advice to the EAG agrees that chemotherapy is reserved for patients at imminent risk of organ failure, and therefore it is not widely used.

The EAG's expert clinical advisor also noted that patients previously treated in the adjuvant setting who progress after first line treatment for advanced/metastatic breast cancer would need to switch to a different endocrine therapy (e.g. from a non-steroidal to steroidal aromatase inhibitor) with or without everolimus. Tamoxifen is one of the treatment options for patients at this line, if the patient has not already received it earlier (e.g. in the adjuvant setting). This suggests that in some cases, tamoxifen may be used where elacestrant would be considered as a treatment option.

Comment 4. ESR1-mut subgroup: elacestrant OS extrapolation

(New company analyses submitted)

The NICE committee stated a preference for a gamma distribution for elacestrant OS in the activating ESR1-mutation subgroup but capped to prevent the treatment effect of the comparator (everolimus plus exemestane) becoming higher than that of elacestrant at and beyond the point of convergence at about 5 years (draft guidance paragraph 3.13).

In their response, the company has added three options for modelling elacestrant OS in the ESR1-mutation subgroup 1:

1. **Average S(t)**: mean of log-logistic and gamma survival at each timepoint
2. **Average h(t)**: mean of log-logistic and gamma hazard of death at each timepoint
3. **Gamma + capped h(t)**: elacestrant hazard set to the minimum of the gamma hazard for elacestrant and the hazard for everolimus plus exemestane at each timepoint

Figure 1 in the company's response shows the effect of the above scenarios on survival estimates for elacestrant, alongside previously preferred options (log-logistic in the company's base case; and gamma for the EAG). Figures 2 to 4 show survival estimates for elacestrant and for everolimus plus exemestane, as well as KM data. The company also report survival estimates in Table 1 of their response document. We note that the landmark timepoints in this table are incorrectly labelled (year 5 is labelled as year 4, and year 10 as year 5). Table 2 below shows the results with the correct landmark labels, and with the addition of OS estimates for everolimus plus exemestane.

Table 2 Landmark survival estimates: ESR1-mut and ≥12 months prior ET + CDK4/6i

Model	Landmarks (years)				
	1	2	3	5	10
Elacestrant					
Log-logistic	83.5%	54.6%	34.5%	15.7%	4.3%
Average S(t)	83.1%	54.5%	33.4%	12.7%	2.3%
Average h(t)	83.1%	54.5%	33.4%	12.4%	1.2%
Gamma + capped h(t)	82.8%	54.4%	33.3%	12.3%	1.0%
Gamma	82.8%	54.4%	32.4%	9.8%	0.3%
Everolimus plus exemestane					
Gamma	64.8%	39.8%	24.4%	9.0%	0.7%

Source: Adapted by EAG from Table 1 in the company's response to draft guidance, with correction to the labelling of timepoints and additional of estimates for everolimus plus exemestane

The company choose the ‘capped gamma’ extrapolation for their revised base case to align with the committee’s request, and report scenario analysis for the ‘average survival’ and ‘average hazard’ alternatives in their response appendix (Table 5). The company state that the log-logistic, average survival and average hazard options provide ‘reasonable estimates’, and note clinician feedback that the three new survival scenarios looked reasonable, but that average survival was their preferred option based on the 10-year landmark.

EAG comment

The EAG considers that the three additional options for modelling elacestrant OS have been correctly implemented in the company’s revised economic model. The Gamma + capped h(t) extrapolation that is used in the company’s revised base case reflects the committee’s preference for a gamma distribution capped ‘such that the treatment effect of everolimus plus exemestane is not higher than elacestrant at and beyond the point of convergence at about 5 years’ (Draft guidance paragraph 3.13).

Comment 5. Comparator treatment duration

(New company analyses submitted)

As requested by the committee (draft guidance 3.14), the company have changed their approach to modelling time to treatment discontinuation (TTD) for comparators. In their revised base case, the company apply the HRs used in EAG exploratory analysis: 0.8 for the *ESR1-mut* subgroup and 0.5 for the *dual mutation* subgroup. In the absence of evidence, we derived these estimates by ‘manual calibration’ to approximate the TTD curves in the subgroup elacestrant arms. Understandably, the committee stated would prefer HR estimates based on evidence.

However, the company have not identified any published evidence relevant to the scope for the current appraisal. They cite values from the NICE TA816 appraisal of alpelisib in combination with fulvestrant for people with advanced HR-positive, HER2-negative, PIK3CA-mutated breast cancer that has progressed after prior endocrine therapy in the neo/adjuvant or advanced setting, which included a everolimus plus exemestane as a comparator.

The company quote an HR of 1.27 for PFS versus TTD for everolimus plus exemestane from TA816, which would be equivalent to an HR of 0.79 (1/1.27) for TTD versus PFS. This appears to relate to an estimate derived from the BOLERO-2 trial data. We note that this value is referred to in different parts of the TA816 committee papers as an HR for TTD

versus PFS (Novartis submission, 2021 page 131), but also as an HR for PFS versus TTD (ScHARR Evidence Review group report, page 90).

TTD data for alpelisib plus fulvestrant were redacted in TA816, but the company found that a SOLAR-1 trial publication had reported a median PFS of 11 months and median treatment durations of 5.5 and 8.3 months for alpelisib and for fulvestrant respectively, from which the company approximate HR estimates for TTD versus PFS of 0.5 (5.5/11) and 0.75 (8.3/11).

EAG comment

The company report that there is no direct evidence for the relationship between TTD and PFS for the comparators in the population of interest. In the absence of evidence, they use HRs for TTD relative to PFS in their base case taken from values used in EAG exploratory analysis. The information that the company cite from TA816 is broadly supportive of these estimates. This evidence is very weak, but we agree that the company's approach is reasonable given the lack of any better information. We report scenario analysis to investigate sensitivity to changes in the HRs for TTD versus PFS (see Table 7 and Table 8 in 0 below).

Comment 6. ESR1-mutation testing

(New company analyses submitted)

The company do not follow the committee's request to include a cost of £1,700 for ESR1-mutation testing for each case identified in the base case analysis for the two subgroups (draft guidance 3.15). Instead, the company exclude the cost of ESR1-mutation testing from their revised base case analysis, on the basis of an understanding that there is a 'desire' for the NHS to introduce a next generation sequencing (NGS) panel for testing of all current and future mutations for treatments tailored to specific mutations in breast cancer. The company point to 3 treatments in development, one of which is currently in progress as a NICE Technology appraisal (ID6370). The company report scenario analysis results with a cost of £600 per positive case detected (£300 at 50% prevalence) for ESR1-mutation testing (company response Tables 5 and 6).

EAG comment

We consider it premature to assume that an NGS panel will be implemented in time for use with elacestrant (if recommended). We therefore include the cost of the ESR1-

mutation cost in EAG preferred analysis, as recommended by the CDF clinical lead (£850 per test; £1,700 per case identified in both subgroups).

Comment 7. Severity

(New company analyses submitted)

The company report updated QALY shortfall analysis for their revised base case (company response Tables 2 and 3). As the only change from the company's previous base case that affects the shortfall calculations is the baseline age for the ESR1-mutation subgroup, the QALY shortfall results are the same as the EAG's results (EAR Table 46). However, the committee was unable to conclude if a severity modifier should be applied for the ESR1-mutation subgroup, as both company and EAG calculations are based on data from a population that includes people with a dual mutation (draft guidance 3.16). See discussion in Comment 2 above.

EAG comment

The company's revised QALY shortfall calculations are consistent with calculations in the EAG report, but do not reflect the committee's view that the ESR1-mutation subgroup for whom everolimus and exemestane is the only relevant comparator should not include people with a dual mutation.

Comment 8. Cost-effectiveness estimates

(New company analyses submitted)

The company summarise changes to their previous base case in Comment 8 of their draft guidance response. In addition to the changes discussed above, the company include an updated confidential PAS price discount for elacestrant. Cost-effectiveness results for the company's revised base are reported in Table 4 of the draft guidance response, with additional sensitivity and scenario analysis in a separate appendix. Note that the company applied a QALY weight of 1.2 to incremental QALYs, ICERs and NMBs reported for all analyses that they present for the ESR1-mutation subgroup in these documents.

Results in the company's response to draft guidance and in this EAG critique document all include the updated PAS discount for elacestrant but all other drugs are costed at publicly available prices. We report results with all available CMU and PAS price discounts in a separate confidential addendum.

The EAG replicated all of the results in company's response document and appendix, with one exception: the scenario analysis with a log-logistic OS extrapolation for alpelisib with fulvestrant in the dual-mutated population (we obtained a NMB estimate at the £30,000 per QALY threshold of £14,407, not £26,025).

We report additional EAG analyses below. Table 3 and Table 4 show the cumulative impact of changes in the company's base case, produced by introducing changes to their assumptions one at a time. This demonstrates that results from the revised version of the company's model is consistent with the previous version.

EAG comment

We agree with the company's changes to their base case, with the exception of excluding the cost of the ESR1 test, which we consider to be premature. The EAG's preferred analysis follows the committee's conclusion that ESR1 test costs of £1,700 per positive case should be included for both subgroups. Deterministic and probabilistic for the EAG's preferred analysis are reported in Table 5 and Table 6 in Appendix 1 below, for the ESR1-mutation and dual mutation subgroups respectively.

We note that none of the revised cost-effectiveness results reported by the company or EAG additional analyses in this document incorporate the committee's requested changes to the population and relevant comparators as discussed in Comment 2 above.

Comment 9. Cost-minimisation analysis

(No new data or new analyses of existing data have been provided in relation to this issue)

The company quote draft guidance section 3.18 which calls for an exploratory cost minimisation analysis in which it is assumed that elacestrant is equivalent in clinical effectiveness to the comparator treatments. The justification for this request is due to the high uncertainty arising from the analysis of post-hoc subgroups from the EMERALD trial and the indirect comparison of elacestrant versus everolimus plus exemestane/alpelisib + fulvestrant in these subgroups by means of an unanchored MAIC.

The company acknowledge the committee's concerns about the high level of uncertainty, but state that they do not believe it is appropriate to report a cost-minimisation analysis for the following reasons:

- Expectation from the clinical community that elacestrant would be an advancement in the treatment of breast cancer (a “step-change”)
- Absence of a statistically significant difference in outcomes between elacestrant and comparator treatments should not necessarily imply clinical equivalence.
- Concern that testing for the ESR1 mutation would have no value if elacestrant is no more beneficial than existing treatments which don’t require testing.

We address the first two of these points below.

EAG comment

We acknowledge the clinical community support for an additional treatment in an area of unmet need, and the expectation that elacestrant will offer greater benefit over current standard therapy. Nonetheless, the EAG is of the opinion that the level of uncertainty is of such magnitude that an exploratory cost-minimisation analysis – assuming similar clinical effectiveness for elacestrant and comparators - would not be inappropriate.

We would like to emphasise that the guidance requests an ‘exploratory’ analysis. Exploratory analyses are commonly done in health economic modelling when there are limitations in the available evidence for certain model parameters. For example, exploratory scenario/sensitivity analyses might assume variations in clinical effectiveness estimates, including making the conservative assumption of no difference between experimental treatment and comparators. These analyses can help illuminate the degree to which changes in the ICER are driven by clinical effectiveness, and therefore the level of uncertainty in cost effectiveness estimates. We believe that the purpose of the request is to provide an alternative set of estimates to enable the appraisal committee to contextualise the results of the current cost-utility model.

In relation to the second bullet point above, the company is correct that lack of statistical significance does not necessarily imply clinical equivalence between two treatments (though it is a frequently made assumption in technology appraisals). Conversely, statistically significant differences between two treatments does not necessarily imply clinical difference. The results of subgroup analyses in clinical trials are compromised by lack of statistical power and risk of bias, and in scientific terms should be considered only as exploratory analyses whose findings require further testing and confirmation. The company’s reluctance to conduct an exploratory cost-minimisation analysis conflicts

with their chosen approach of a cost-utility analysis based on clinical effectiveness estimates which can only be considered as exploratory.

Appendix 1 Additional EAG analysis

2 Company's revised base: cumulative impact of changes

Table 3 Cumulative change in company base case: subgroup 1 (*ESR1-mut*)

Preferred assumption	Treatment	Total costs	Total QALYs	ICER £/QALY No QALY weight	ICER £/QALY With QALY weight (1.2)
Previous company base case	EVE + EXE	[redacted]	[redacted]	£29,872	£24,893
	Elacestrant	[redacted]	[redacted]		
+ MAIC-adjusted baseline age	EVE + EXE	[redacted]	[redacted]	£29,942	£24,952
	Elacestrant	[redacted]	[redacted]		
+ Exclude cost for ESR1-mut test	EVE + EXE	[redacted]	[redacted]	£28,990	£24,158
	Elacestrant	[redacted]	[redacted]		
+ Everolimus price from eMIT 2023	EVE + EXE	[redacted]	[redacted]	£46,771	£38,976
	Elacestrant	[redacted]	[redacted]		
+ OS: Gamma + capped h(t)	EVE + EXE	[redacted]	[redacted]	£70,620	£58,850
	Elacestrant	[redacted]	[redacted]		
+ Comparator TTD HR vs PFS 0.8	EVE + EXE	[redacted]	[redacted]	£71,943	£59,952
	Elacestrant	[redacted]	[redacted]		
+ Updated PAS discount ([redacted])	EVE + EXE	[redacted]	[redacted]	£33,476	£27,897
	Elacestrant	[redacted]	[redacted]		
Revised company base case	EVE + EXE	[redacted]	[redacted]	£33,476	£27,897
	Elacestrant	[redacted]	[redacted]		

Source: Produced by the EAG from the company's model

Table 4 Cumulative change in company base case: subgroup 2 (*Dual mutated*)

Preferred assumption	Treatment	Total costs	Total QALYs	ICER £/QALY	NMB (£)	
					WTP £20,000	WTP £30,000
Previous company base case	ALP+FUL	[redacted]	[redacted]	Dominant	£17,803	£20,570
	Elacestrant	[redacted]	[redacted]			
+ Exclude ESR1-mut test *cost*	ALP+FUL	[redacted]	[redacted]	Dominant	£18,403	£21,170
	Elacestrant	[redacted]	[redacted]			
+ Comparator TTD HR 0.5	ALP+FUL	[redacted]	[redacted]	£2,194	£4,927	£7,694
	Elacestrant	[redacted]	[redacted]			
+ Updated PAS discount ([redacted])	ALP+FUL	[redacted]	[redacted]	Dominant	£17,050	£19,817
	Elacestrant	[redacted]	[redacted]			
Revised company base case	ALP+FUL	[redacted]	[redacted]	Dominant	£17,050	£19,817
	Elacestrant	[redacted]	[redacted]			

Source: Produced by the EAG from the company's model

3 EAG's additional analyses

3.1 EAG preferred analysis

Table 5 EAG's preferred analysis: subgroup 1 (*ESR1-mut*)

Preferred assumption	Treatment	Total costs	Total QALYs	ICER £/QALY No QALY weight	ICER £/QALY With QALY weight (1.2)
EAG preferred (deterministic)	EVE + EXE	[redacted]	[redacted]	£37,795	£31,496
	Elacestrant	[redacted]	[redacted]		
EAG preferred (probabilistic)	EVE + EXE	[redacted]	[redacted]	£36,743	£30,619
	Elacestrant	[redacted]	[redacted]		

Source: Produced by the EAG from the company's model

Table 6 EAG's preferred analysis: subgroup 2 (*Dual mutated*)

Preferred assumption	Treatment	Total costs	Total QALYs	ICER £/QALY	NMB (£) at £20,000 / QALY	NMB (£) at £30,000 / QALY
EAG preferred (deterministic)	ALP+FUL	[redacted]	[redacted]	Dominant	£15,350	£18,117
	Elacestrant	[redacted]	[redacted]			
EAG preferred (probabilistic)	ALP+FUL	[redacted]	[redacted]	Dominant	£15,481	£18,232
	Elacestrant	[redacted]	[redacted]			

Source: Produced by the EAG from the company's model

2.2 Deterministic sensitivity analysis

Figure 1 Tornado diagram for subgroup 1 (*ESR1-mut*) using EAG preferred assumptions

PSA: probabilistic sensitivity analysis, QALY Quality-adjusted life year, WTP: willingness to pay, ELA: elacestrant, EVE + EXE: everolimus with exemestane

Figure 2 Tornado diagram for subgroup 2 (*dual mutated*) using EAG preferred assumptions

PSA: probabilistic sensitivity analysis, QALY Quality-adjusted life year, WTP: willingness to pay, ELA: elacestrant, EVE + EXE: everolimus with exemestane

3.2 Probabilistic scatterplots

Figure 3 PSA scatterplot graph for subgroup 1 (*ESR1-mut*) using EAG preferred assumptions

Source: Produced by the EAG from the company's model
PSA: probabilistic sensitivity analysis, QALY Quality-adjusted life year, WTP: willingness to pay, ELA: elacestrant, EVE + EXE: everolimus with exemestane

Figure 4 PSA scatterplot graph for subgroup 2 (*dual mutated*) using EAG preferred assumptions

Source: Produced by the EAG from the company's model
PSA: probabilistic sensitivity analysis, QALY Quality-adjusted life year, WTP: willingness to pay, ELA: elacestrant, ALP + FUL: alpelisib with fulvestrant

2.4 Scenario analysis

Table 7 EAG preferred analysis: scenario analyses for subgroup 1 (*ESR1-mut*)

EAG preferred assumption	Scenario	Treatment	Total cost (£)	Total QALYs	ICER (£/QALY) No severity modifier	ICER (£/QALY) 1.2 severity modifier
EAG preferred analysis		EVE + EXE	[redacted]	[redacted]	£37,795	£31,496
		Elacestrant	[redacted]	[redacted]		
ESR1-mut testing cost: £850, prevalence based (50%) = £1,700	Exclude ESR1-mut testing cost	EVE + EXE	[redacted]	[redacted]	£33,476	£27,897
		Elacestrant	[redacted]	[redacted]		
MAIC approach: Independent PSM extrapolation	HR	EVE + EXE	[redacted]	[redacted]	Dominated	Dominated
		Elacestrant	[redacted]	[redacted]		
Elacestrant OS: Gamma + capped hazards	Log-logistic	EVE + EXE	[redacted]	[redacted]	£26,272	£21,893
		Elacestrant	[redacted]	[redacted]		
	Gamma	EVE + EXE	[redacted]	[redacted]	£45,284	£37,737
		Elacestrant	[redacted]	[redacted]		
	Average S(t): log-log, gamma	EVE + EXE	[redacted]	[redacted]	£32,523	£27,102
		Elacestrant	[redacted]	[redacted]		
	Average S(t): log-log, gamma	EVE + EXE	[redacted]	[redacted]	£36,744	£30,620
		Elacestrant	[redacted]	[redacted]		
EVE + EXE TTD HR: 0.8	0.7	EVE + EXE	[redacted]	[redacted]	£38,463	£32,052
		Elacestrant	[redacted]	[redacted]		

EAG preferred assumption	Scenario	Treatment	Total cost (£)	Total QALYs	ICER (£/QALY) No severity modifier	ICER (£/QALY) 1.2 severity modifier
	0.9	EVE + EXE	[redacted]	[redacted]	£37,111	£30,926
		Elacestrant	[redacted]	[redacted]		
NHS GMS, prevalence-based: £850/0.5= £1,700	Marsden360 assay cost, prevalence-based: £1,700/0.5 = £3,400	EVE + EXE	[redacted]	[redacted]	£42,114	£35,095
		Elacestrant	[redacted]	[redacted]		
	NHS GMS, non-prevalence base: £850	EVE + EXE	[redacted]	[redacted]	£35,636	£29,697
		Elacestrant	[redacted]	[redacted]		

Source: Produced by the EAG from the company's model

EAG scenario analyses for subgroup 2

Table 8 EAG preferred analysis: scenario analyses for subgroup 2 (*dual mutation*)

EAG preferred assumption	Scenario	Treatment	Total cost (£)	Total QALYs	NMB (£) for WTP £20,000	NMB (£) for WTP £30,000
EAG preferred analysis		ALP + FUL	[redacted]	[redacted]	£15,350	£18,117
		Elacestrant	[redacted]	[redacted]		
ESR1-mut testing cost: £850, prevalence based (50%) = £1,700	Exclude ESR1-mut testing cost	ALP + FUL	[redacted]	[redacted]	£17,050	£19,817
		Elacestrant	[redacted]	[redacted]		
MAIC approach: Independent PSM extrapolation	HR	ALP + FUL	[redacted]	[redacted]	£9,862	£11,560
		Elacestrant	[redacted]	[redacted]		
Elacestrant OS: Weibull	Gamma	ALP + FUL	[redacted]	[redacted]	£18,128	£23,069
		Elacestrant	[redacted]	[redacted]		
	Log-normal	ALP + FUL	[redacted]	[redacted]	£25,256	£35,916
		Elacestrant	[redacted]	[redacted]		
Alpelisib + fulvestrant OS: Gamma	Weibull	ALP + FUL	[redacted]	[redacted]	£16,125	£19,504
		Elacestrant	[redacted]	[redacted]		
	Log-normal	ALP + FUL	[redacted]	[redacted]	£12,493	£12,984
		Elacestrant	[redacted]	[redacted]		
	Log-logistic	ALP + FUL	[redacted]	[redacted]	£12,347	£12,707
		Elacestrant	[redacted]	[redacted]		
Alpelisib + fulvestrant TTD versus PFS: HR = 0.5	0.4	ALP + FUL	[redacted]	[redacted]	£12,632	£15,399
		Elacestrant	[redacted]	[redacted]		

EAG preferred assumption	Scenario	Treatment	Total cost (£)	Total QALYs	NMB (£) for WTP £20,000	NMB (£) for WTP £30,000
	0.6	ALP + FUL	[redacted]	[redacted]	£18,029	£20,796
		Elacestrant	[redacted]	[redacted]		
ESR1-mut testing cost: £850, prevalence-based (50%) = £1,700	NHS GMS, non-prevalence base: £850	ALP + FUL	[redacted]	[redacted]	£16,200	£18,967
		Elacestrant	[redacted]	[redacted]		
	NHS GMS, prevalence-based: £850/0.2= £4,250	ALP + FUL	[redacted]	[redacted]	£12,800	£15,567
		Elacestrant	[redacted]	[redacted]		

Source: Produced by the EAG from the company's model