Single Technology Appraisal

Capivasertib with fulvestrant for treating hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment [ID6370]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Capivasertib in combination with fulvestrant for second-line treatment in unresectable or metastatic HR-positive, HER2-negative breast cancer

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from AstraZeneca**
   a. **Draft Guidance erratum**

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Breast Cancer Now
   b. METUPUK

3. **Comments on the Draft Guidance from experts:**
   a. Kristen Spencer, nominated by METUPUK

4. **Comments on the Draft Guidance received through the NICE website**

5. **External Assessment Group critique of company comments on the Draft Guidance**
   a. Adjustments made to the company base-case economic model

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

Capivasertib with fulvestrant for treating hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment [ID6370]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 4 February 2025. 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):	AstraZeneca UK

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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.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	Rachel Evans (Health Economics Manager, AstraZeneca UK)

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Comments on the draft guidance

Comment number	Comments **Insert each comment in a new row.** **Do not paste other tables into this table, because your comments could get lost – type directly into this table.**
1	**Overall comments on the draft guidance** • We thank NICE for the comprehensive and clear summary of the evidence and views that were considered in the evaluation of capivasertib with fulvestrant for HR+/HER2- advanced breast cancer (aBC) and the recommendations and requests for follow-on analyses made by the committee. • We are however disappointed that the committee decided to *not* recommend capivasertib with fulvestrant for this indication in this instance. There was a clear consensus during the committee meeting that "… *people with HR+/HER2- aBC following initial endocrine treatment have a high unmet need*…" and that capivasertib with fulvestrant "…*addresses limitations with existing treatments and targets the AKT1 or PTEN gene mutation, for which no therapy options are currently available*". • Importantly, clinical experts stated that "… *capivasertib with fulvestrant is a highly effective and well-tolerated targeted treatment that represents a step change in managing breast cancer with PIK3CA, AKT1 or PTEN alterations*". The draft guidance document therefore clearly summarises the need for a targeted treatment for AKT-pathway altered HR+/HER2- aBC, the strength of the direct clinical evidence from CAPItello-291 and the advantages capivasertib with fulvestrant brings for patients compared to other currently available treatment options. • As outlined on page 4 of the draft guidance document, the reason for the negative recommendation seems to be primarily related to the uncertainties in the indirect comparisons and economic model rather than the clinical value of capivasertib with fulvestrant. As such, with our response to the draft guidance below, we aim to address some of these key uncertainties and demonstrate that the potential impact on the cost-effectiveness results is minimal. • To support the committee in their final decision-making, we are also providing all of the additional analyses requested, covering base-case changes and adaptations in key variables such as the modelling of long-term survival, health state utility values, testing costs and relative dose intensity (RDI), and including the updated PAS price for capivasertib ([redacted]). As per our original base-case, these further analyses continue to demonstrate that capivasertib with fulvestrant is a highly cost-effective option vs. everolimus plus exemestane and even strongly dominates alpelisib with fulvestrant across all plausible scenarios. • We hope that these scenarios support the committee in agreeing on the most appropriate decision-making ICERs during the next committee meeting and facilitate a positive recommendation for capivasertib with fulvestrant for use in clinical practice.
2	**Robustness of the indirect treatment comparison**

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	• A key point of critique in the draft guidance document is that the heterogeneity in certain baseline characteristics between the studies included in the network meta-analysis (NMA) may have biased the results, making the NMA hazard ratio (HR) and respective cost-effectiveness outputs uncertain. Although we understand the committee's concerns, we would like to take this opportunity to re-emphasise the evidence demonstrating that the magnitude of potential bias is minimal. • Firstly, a transparent, stepwise, and robust methodology was used to support the NMA. This included a full assessment of heterogeneity of the patient characteristics from the studies identified in the clinical systematic literature review (SLR), and 9 targeted literature searches on each identified factor of heterogeneity to identify evidence on the status and bias of potential treatment effect modifiers and/or prognostic factors. • Based on this research, there was no evidence to suggest that HER2 status, ECOG performance status or previous CDK4/6i treatment are treatment effect modifiers for any of the treatments included in the NMA. Particularly, regarding the prior use of CDK4/6i in 1L, there is no evidence from either CAPItello-291, or the other trials included in the NMA to suggest this is a treatment effect modifier, which implies that the relative effects used in the indirect comparison are applicable to a post-CDK4/6i 2L treatment setting. Indeed, one of the clinical experts during the committee meeting also mentioned that "… *although the absolute benefit is lower with fulvestrant after a CDK4/6i, there is no biological reason for there to be a difference in the relative benefit*". • This is an important point as the summary in the draft guidance conflates evidence on absolute vs. relative effects. Specifically, the committee notes that "… *previous CDK4/6i treatment appeared to have a substantial impact on overall survival in the fulvestrant arm of CAPItello-291 while the capivasertib arm appeared to be unaffected by previous CDK4/6i*". However, there is [redacted] in the relative outcomes (i.e., hazard ratio) between the subgroup of patients who received vs. who did not receive prior CDK4/6i in 1L in the CAPItello-291 trial. • Furthermore, simply naively comparing differences in outcomes, i.e., absolute differences in median PFS from single arms across studies as is done on page 10 of the draft guidance document, is not an appropriate method to determine whether a factor such as prior CDK4/6i status is an effect modifier. This is also inconsistent with the approach taken in the alpelisib appraisal (TA816), where the HRs from the overall population were adopted in analyses to support a recommendation in a post-CDK4/6i setting. Consequently, the treatment effects from the trials included in the NMA can be considered representative of the expected treatment effects in patients in a post-CDK4/6i setting. • In addition to the discussion on prior CDK4/6i status, the draft guidance document states that "… *ideally the indirect treatment comparisons would use subgroups with PI3K and AKT pathway alteration from all studies…*" and that "… *it was unknown how much variation in these alterations could bias the results*". However, we would like to clarify that, given there is no evidence to suggest that AKT-pathway alterations are an effect modifier for endocrine monotherapy or everolimus plus exemestane, there is no reason to believe that including the relative effects from the overall populations of the respective trials would have biased the results. The NMA already appropriately includes the HRs for those AKT-targeted treatments (i.e., capivasertib and alpelisib) for which AKT and PIK3CA-pathway alterations are evidenced effect modifiers respectively, and thus the level of bias by

	including non-biomarker specific HRs from the other therapy trials in the network (for which there is no evidence of treatment modification) is expected to be negligible. • In conclusion, although there is a level of heterogeneity between the trials included in the NMA, this heterogeneity was considered to be across prognostic factors only, with the exception of AKT-pathway alternations as an effect modifier for capivasertib and alpelisib, for which the appropriate subgroup relative effects were used in the NMA. There is strong rationale to support that the relative effects from each trial are representative for patients with HR+/HER2- AKT-altered mBC in a 2L post-CDK4/6i setting, and that the magnitude of any potential bias in the results is likely minimal. The approach to the NMA reflects the best available clinical evidence, is aligned to the assumptions accepted in TA816, and therefore is appropriate for decision-making in this appraisal.
3	**Modelling of long-term relative treatment effect** • As requested by the committee in the draft guidance document, we have explored the option of using fractional polynomials (FP) as an alternative time-varying analysis for conducting the indirect treatment comparison for PFS and OS. This approach differs from our original company base-case, where we adopted an NMA in which the treatment effect was represented by a constant hazard ratio. We believe our original approach was justified on the basis that there was inconclusive evidence on whether the assumption of proportional hazards holds for both PFS and OS, and thus it was deemed reasonable to conduct an NMA on a constant hazard ratio scale. • Instead, with fractional polynomials, a multi-dimensional approach is taken to model the hazard over time, with the treatment effect being represented with multiple parameters. Specifically, the hazard functions of the treatments compared in the clinical trials included in the NMA are modelled, and the difference between the parameters of these fractional polynomials within a trial are synthesized (and indirectly compared) across studies. This flexibility allows for a potential non-linear relationship between time and hazard to be modelled (1). • The time-varying indirect comparison for both PFS and OS for the purpose of this response was conducted using the FP-NMA methodology by Jansen (2011) (1), and follows the two-step process as outlined in Wiksten et al. (2020) (2). This process was deemed most efficient and appropriate as it allows practitioners to investigate a broad range of models rapidly and achieve a more robust and comprehensive model selection strategy. ▪ The first step is to fit the full set of FP models (8 first-order and 36 second-order models) to the PFS and OS data in a frequentist framework via a standard generalised linear model routine. This enables the selection of the ‘best’ model from the full set of potential structures (44 in total) based on statistical goodness of fit (i.e., Akaike Information Criteria [AIC]), and the clinical plausibility of modelled hazard ratios over time. ▪ The second and final step in the process is to refit the selected ‘best-fitting’ models in a Bayesian framework to capture and propagate any uncertainty for final decision-making and derive the relevant parameters for inclusion in the economic model.

	• In addition to the FP models, two other modelling approaches have been explored: (1) piecewise exponential models with cut points of 3 months for PFS and 6 months for OS and (2) proportional hazards models, with exponential and Weibull baseline hazards. ▪ The piecewise exponential models assume that the treatment effect is constant within a series of segments that are defined by fixed cut points, i.e. at 3 months for PFS and 6 months for OS. This approach is analogous to the piecewise NMA that was provided to NICE as part of the response to the EAG's clarification questions in September 2024. ▪ The proportional hazards models assume that the treatment effect is constant over time, analogous to the constant log-hazard ratio NMA provided in the original submission. These simpler models were included in the analysis to provide a benchmark from which to judge the fit of the more complex FP-NMA models. • The frequentist and Bayesian FP-NMAs were conducted under a fixed effects assumption. Random-effects FP-NMAs were not considered due to the limited number of studies per comparison in the network (i.e., two or fewer), which was deemed insufficient to reliably estimate between-study heterogeneity. This decision aligns with the findings of the random effects constant log-hazard ratio NMA, which used informative priors for between-study heterogeneity to improve model fit. Currently, no informative priors are available to support a random-effects FP-NMA. • The outputs from the FP-NMA of PFS and OS are presented in the Appendix. Please note that only comparisons of capivasertib with fulvestrant, alpelisib with fulvestrant and everolimus with exemestane versus fulvestrant 500mg are considered. Other treatments are included in the NMA but are excluded from the results as they do not contribute to the economic analysis. A full explanation of the methodology, model selection and results is provided in the Appendix, with a summary given below: ▪ **For PFS:** The models that provided the best fit in the frequentist framework, based on statistical criteria and the plausibility of the pattern of hazard ratios over time were the second order FP models with $p1$=-2 and the first order FP model with p=-2. These models yielded time-varying hazard ratios that were similar in value to the results of the piecewise NMA provided to NICE as part of the response to the EAG's clarification questions. However, given that the second order FP model with $p1$=-2 and $p2$=-2 failed to converge when fitted in a Bayesian framework, only the second-best fitting second-order FP ($p1$=-2, $p2$=-1) and the first order fractional polynomial ($p1$=-2) were applied in the Bayesian analysis and implemented in the economic model. ▪ **For OS:** The 'best fitting' models in the frequentist framework according to statistical criteria and the clinical plausibility of hazard ratios over time were the first-order FP models with $p1$=-1 and p=-0.5. These models were subsequently applied in the Bayesian analysis and implemented in the economic model. • The results of the FP-NMA suggest that: ▪ **For PFS:** the treatment effects for everolimus with exemestane and alpelisib with fulvestrant vs. fulvestrant monotherapy are predicted to decline (or wane) over time before stabilizing at a long-term HR value that is close to 1. For capivasertib with fulvestrant, the treatment effect is predicted to [redacted], but the HR [redacted] in the long-term.

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	▪ **For OS:** the treatment effects for everolimus with exemestane and alpelisib with fulvestrant vs. fulvestrant monotherapy are predicted to gradually converge to a HR value close to 1, whilst the effect of capivasertib with fulvestrant is predicted to [redacted] and eventually [redacted] over time. • For the updated economic analysis, the base-case FP models for both PFS and OS were selected based on their statistical fit (best-fitting) and clinical plausibility. They also provide similar long-term survival projections to the previous piecewise NMA submitted to NICE as part of our response to the EAG's clarification questions. ▪ **For PFS:** The second-order model (*p*1=-2 and *p*2=-2) given that it best reflects the converging trends in treatment effect over time across all three treatment regimens and had the highest statistical fit. The first-order model will be explored in scenario analyses. ▪ **For OS:** As both FP models generate almost identical trends in HR over time across all three treatment regimens, the best fitting out of two (first-order, *p*=-1) has been adopted in the updated base-case economic analysis. The second-best fitting (first-order, *p*=-0.5) model will be explored in scenario analyses. • The results from the updated base-case analysis incorporating these FP-NMA models demonstrate that capivasertib with fulvestrant remains a highly cost-effective option vs. both alpelisib with fulvestrant and everolimus + exemestane. These results are also consistent when selecting different FP models for PFS and OS in scenario analyses.
4	**Implementation of treatment waning in the economic model** We remain in strong disagreement with the EAG and the committee that "… *exploring 2- or 3-year treatment waning time points are plausible and useful…*" for the purpose of this appraisal: • First, adopting fractional polynomials as an alternative analysis for conducting the NMA and modelling long-term survival already results in time-varying hazard ratios in which the relative treatment effect of capivasertib, alpelisib and everolimus with exemestane vs. fulvestrant wanes over time. As described above, the outputs from the best-fitting and clinically plausible FP models demonstrate a strong waning effect for alpelisib and everolimus + exemestane vs. fulvestrant across both endpoints, and a [redacted] effect of capivasertib over time. • Incorporating a crude treatment waning assumption in the economic model by setting the HR to 1.0 at an arbitrary timepoint is therefore inappropriate. Furthermore, the selection of a 2-year timepoint for this approach does not reflect the observed treatment effects from the respective trials included in the NMA. It is also inconsistent with the trends in treatment effect over time that are appropriately modelled, tested and validated in the FP-NMA, as any output from this approach beyond the point of HR=1.0 has no impact on the model's results. Instead, the estimated PFS and OS curves will have abrupt kinks at the point at which the HR=1.0 is implemented, which are clinically implausible and do not accurately reflect the expected survival over time for patients with HR+/HER2- aBC. • Importantly, in the appraisal of alpelisib (TA816) – a kinase inhibitor similar to capivasertib that also targets a part of the AKT signalling pathway – a time-limited treatment effect at 5 years was adopted in the final analyses. There is no biological rationale to assume that a different waning of effect would occur with capivasertib. Indeed, the clinical expert during the committee meeting also mentioned that "… *it was reasonable to assume the same*

	treatment waning characteristics would apply for capivasertib plus fulvestrant and its comparators". • Furthermore, it is mentioned in the draft guidance that "…*only a small number of people were still on treatment at 2 years, so it was not implausible to set waning at 2 years*". However, time on treatment is not the sole appropriate indicator for whether a treatment's effect is waning over time, and there is no evidence to suggest the effect of capivasertib vs. fulvestrant would not be sustained for at least a period after discontinuation of treatment. Anchoring the introduction of treatment waning to the point at which most patients have discontinued capivasertib in the model is therefore overly conservative and likely does not reflect what will happen in real-life clinical practice. In our view, the points above demonstrate that adopting the suggested 2- or 3-year treatment waning time point in the economic model is arbitrary and lacks clinical rationale or evidence. With the adoption of the FP-NMA, setting the waning assumption at 2 or 3 years is overly punitive and biases the economic analysis specifically against capivasertib with fulvestrant. Nevertheless, as requested, we have provided an updated base-case with a treatment waning effect (i.e., HR=1.0) introduced at 5 years, which is aligned with the precedent set in this setting (i.e., TA816) and is more consistent with the evidence from the committee-requested FP-NMA. For completeness and to address the request from the committee in the draft guidance document, we are also presenting scenario analyses with a 2- and 3-year treatment waning timepoint. However, we maintain that these scenarios are not reflective of the available evidence, lack clinical plausibility, and are inconsistent with the approaches applied in TA816. It should however be noted that even when adopting a 2-, 3- or 5-year treatment waning assumption, the ICERs of capivasertib with fulvestrant vs. alpelisib + fulvestrant and everolimus + exemestane remain below the relevant WTP thresholds of £30k, demonstrating that capivasertib with fulvestrant remains a cost-effective option vs. both comparators in a scenario where conservatively both a time-varying HR and treatment waning approach are adopted.
5	**Other requested additional analyses** As requested by the committee in the draft guidance document, we have adopted most of the requested changes in our updated base-case analysis, with the exception of adopting a different HSUV for the PD state, which will be explored in scenario analyses only as explained below. All of the inputs have already been fully explored and presented in various scenario analyses prior to the first committee meeting: • **Health state utility value (HSUV) for the progressed disease (PD) state:** The committee accepted that the appropriate utility value for the modelled health state after disease progression is uncertain. It concluded that in the new analyses from the company it would like to see the company and EAG scenarios (which explored the range 0.60 to 0.70), plus a scenario using the 0.69 value from Mitre et al. to explore this uncertainty. As such, we have again provided these scenario analyses in the updated results section below. We would however like to note that the scenarios which include a PD HSUV of 0.60 and 0.65 are highly conservative and there is no recent and relevant empirical evidence suggesting these values appropriately reflect the HRQoL of aBC patients. Again, an appropriate anchor is the post-progression utility value of 0.69 from Mitre et al. (2016), which was used in TA816. Considering capivasertib has improved tolerability vs. alpelisib, which the committee recognized and is summarized accordingly in the draft guidance document, a HSUV of >0.69 for patients progressing on capivasertib with fulvestrant is

	most appropriate for the purpose of the economic model. It should however be noted that varying the HSUV for the PD state has a minimal impact on the ICER. • **Reporting costs for AKT1 and PTEN alterations:** As requested by the committee, we have presented a scenario analysis that includes reporting costs for AKT1 and PTEN alterations at £114.71 per patient. This figure is based on the estimated staffing costs for the analysis of PTEN and AKT1 alterations, informed and estimated based on feedback from 2 GLHs (North East & Yorkshire and South East), additional resource use for allocating the test, report entry, analyses and checks, and the NHS pay scales derived from the NHS Employers website (3). The impact on the cost-effectiveness results of incorporating these additional reporting costs for capivasertib only is negligible. • **Relative dose intensity (RDI) for alpelisib:** In the absence of any other evidence on the appropriate RDI for alpelisib with fulvestrant, we have updated our base-case analysis to include the median RDI of 82.7%, as preferred by the committee. As with the inclusion of the additional AKT1/PTEN reporting costs above, the impact on the cost-effectiveness results of incorporating this RDI for alpelisib with fulvestrant is minimal.
5	**Benefits not captured in the economic model** The draft guidance suggests that uncaptured health benefits and other relevant aspects should be acknowledged when considering the most appropriate ICER threshold for this appraisal. We would like to highlight the following important benefits which are not captured in the ICER, and ask the committee to consider these during decision-making: • As per the committee request, costs for AKT1 and PTEN reporting have been included in the adjusted model base case, as testing for PIK3CA via next generation sequencing (NGS) is already in place following NICE's positive recommendation of alpelisib plus fulvestrant in 2022. Nevertheless, the wider benefits of PIK3CA/AKT/PTEN alterations testing as part of a NGS panel including other significant genetic alterations in advanced breast cancer e.g., HER2 and ESR1 are not captured in the cost-effectiveness analyses. Testing for multiple relevant genomic alterations from a single sample allows clinicians to understand the genetic driver of their patients' disease, which can inform prognosis and optimal management, therefore it is technically inappropriate and an overestimation of costs to allocate the cost of reporting for individual genes to the company since the existing panel reporting procedures can already support this. We believe with the availability of more targeted treatment options in advanced breast cancer medium to large/medium NGS panel testing will become common NHS practice, optimising genomic data analysis through a centrally funded mechanism. • While tissue-based biopsy will remain the gold standard for identifying PIK3CA/AKT1/PTEN alterations where tissue samples are available, developments in the genomic testing space bring further uncaptured benefits. The capivasertib plus fulvestrant MHRA approval does not require the qualifying PI3K/AKT pathway alteration to be detected specifically from a tissue sample, opening an opportunity for circulating tumour DNA (ctDNA) detection as well. Following NICE's positive recommendation of elacestrant in December 2024, ctDNA testing for ESR1 variants is now available through the NHS Genomic Medicine Service (code M3.13) as of January 2025 (4). As part of the associated liquid testing panel, additional findings significant in advanced breast cancer e.g., PIK3CA, AKT1, PTEN can also be reported in this tumour type in pilot genomic laboratory hubs (GLHs) and expected to be widely reported at full rollout. The ctDNA biopsy approach provides information on treatment options including capivasertib plus fulvestrant eligibility through a centrally funded mechanism, offering an alternative, less resource-intensive,

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	more convenient, non-invasive tumour sampling in comparison to tissue biopsy, while also accounting for tumour evolution and heterogeneity. • Another benefit not captured in the QALY calculations is the impact of improved tolerability of capivasertib plus fulvestrant compared to existing therapies on carer burden. Demonstrating a manageable AE profile with few discontinuations and preserved HRQoL, the combination offers a meaningful treatment option which alleviates the significant burden associated with toxicities on both patients as well as carers.
6	**Approach to managing uncertainty** • The draft guidance consultation document concludes that due to "high level of uncertainty" around "differences between the populations in terms of PI3K and AKT pathway status and previous treatment with CDK 4 and 6 inhibitors biased the indirect treatment comparisons", "modelling of long-term overall and progression-free survival", and "the most appropriate utility value to use for the post-progression health state", an acceptable ICER would be around £20,000 per QALY gained. • We recognise that the committee considers uncertainty in determining what is an appropriate threshold to adopt. In light of the changes implemented and additional analyses provided, namely the FP-NMA addressing uncertainties around the treatment effect on the ICER which was demonstrated to be minimal, we believe it would be reasonable for the committee to adopt a higher WTP threshold that reflects the innovative nature of capivasertib plus fulvestrant and the step change in therapy it provides, as recognised by the clinical experts and patients in the first committee meeting.

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.
- 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.

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Updated base-case and scenario analysis results

In line with our response to the draft guidance above, we have updated the Company's base-case analysis with the following changes requested by the committee:

1. Using a log-logistic model to estimate long-term PFS.
2. Adopting fractional polynomials as an alternative time-varying analysis for conducting the NMA for PFS and OS and incorporating the outputs in the model.
3. Incorporating treatment waning at 5 years. We are also presenting two highly conservative scenario analyses with treatment waning introduced at 3 and 2 years, however we maintain that these scenarios are not reflective of the available evidence, lack clinical plausibility, and are inconsistent with the approaches applied in TA816.
4. Presenting scenario analyses using exploratory health state utility values of 0.60, 0.65 and 0.70, and the value of 0.69 from TA816 (Mitre et al., 2016) for the post-progression health state.
5. Incorporating the additional reporting testing cost for AKT1 and PTEN alterations.
6. Incorporating an RDI of 82.7% for alpelisib plus fulvestrant.

We have also re-calculated the QALY shortfall for the severity modifier; the results presented in Table 2 demonstrate that a 1.2x QALY weight remains the most appropriate for decision-making in this appraisal.

Table 1. Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in the original submission document
Sex distribution	99.3% female	B.2.3.2
Starting age	59.3 years	B.2.3.2

Abbreviations: QALY: quality-adjusted life year

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Table 2 summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall	QALY weighting
13.18	Alpelisib plus fulvestrant: 1.80	11.38	86.4%	1.2x
	Everolimus plus exemestane: 1.24	11.94	90.6%	1.2x

Abbreviations: QALY: quality-adjusted life year

Table 3: Deterministic pair-wise updated base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pair-wise ICER of capivasertib + fulvestrant vs. comparator (£/QALY)	Pair-wise ICER of capivasertib + fulvestrant vs. comparator (£/QALY) (1.2 QALY weighting)
Capivasertib + fulvestrant	[redacted]	3.01	2.22	-	-	-	-	-
Alpelisib + fulvestrant	£46,448	2.44	1.80	[redacted]	0.57	0.41	[redacted] *Strongly dominates*	[redacted] *Strongly dominates*
Everolimus + exemestane	£25,236	1.66	1.24	[redacted]	1.35	0.98	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years
Notes: Please note the results above included the updated PAS price for capivasertib at [redacted] per pack.

Table 4: Probabilistic pair-wise updated base-case results

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Capivasertib with fulvestrant for treating hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment [ID6370]

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Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pair-wise ICER of capivasertib + fulvestrant vs. comparator (£/QALY) (1.2 QALY weighting)
Capivasertib + fulvestrant	[redacted]	3.01	2.82				
Alpelisib + fulvestrant	£47,076	2.44	2.32	[redacted]	0.57	0.50	[redacted]
Everolimus + exemestane	£25,022	1.66	1.45	[redacted]	1.35	1.37	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years
Notes: Please note the results above included the updated PAS price for capivasertib at [redacted] per pack.

Table 5: Scenario analyses

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Capivasertib with fulvestrant for treating hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment [ID6370]

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			Pair-wise ICER of capivasertib + fulv vs. alpelisib + fulv (£/QALY)		Pair-wise ICER of capivasertib + fulv vs. everolimus + exemestane (£/QALY)	
Parameters	**Base-case**	**Scenario**	**W/o 1.2 QALY weighting**	**With 1.2 QALY weighting**	**W/o 1.2 QALY weighting**	**With 1.2 QALY weighting**
Updated base-case			[redacted]	[redacted]	[redacted]	[redacted]
FP-NMA model for PFS	Second-order model (*p*1=-2, *p*2=-1)	First-order model (*p*=-2)	[redacted]	[redacted]	[redacted]	[redacted]
FP-NMA model for OS	First-order model (*p*=-1)	First-order model (*p*=-0.5)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment waning	Implemented at 5 years	Implemented at 3 years	[redacted]	[redacted]	[redacted]	[redacted]
		Implemented at 2 years	[redacted]	[redacted]	[redacted]	[redacted]
HSUV for the PD state	0.736	0.60	[redacted]	[redacted]	[redacted]	[redacted]
		0.65	[redacted]	[redacted]	[redacted]	[redacted]
		0.69	[redacted]	[redacted]	[redacted]	[redacted]
		0.70	[redacted]	[redacted]	[redacted]	[redacted]
Additional reporting costs for AKT1 and PTEN	Included	Excluded	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years
Notes: Please note the results above included the updated PAS price for capivasertib at [redacted] per pack.

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Capivasertib with fulvestrant for treating hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment [ID6370]

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Capivasertib with fulvestrant for treating hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment [ID6370]

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Appendix – FP-NMA

Introduction

As requested by the committee in the draft guidance document, we have explored the option of using fractional polynomials (FP) as an alternative time-varying analysis for conducting the indirect treatment comparison for PFS and OS. This approach differs from our original company base-case, where we adopted an NMA in which the treatment effect was represented by a constant hazard ratio. We believe our original approach was justified on the basis that there was inconclusive evidence on whether the assumption of proportional hazards holds for both PFS and OS, and thus it was deemed reasonable to conduct an NMA on a constant hazard ratio scale.

Instead, with fractional polynomials, a multi-dimensional approach is taken to model the hazard over time, with the treatment effect being represented with multiple parameters. Specifically, the hazard functions of the treatments compared in the clinical trials included in the NMA are modelled, and the difference between the parameters of these fractional polynomials within a trial are synthesized (and indirectly compared) across studies. This flexibility allows for a potential non-linear relationship between time and hazard to be modelled.

Methodology

The time-varying indirect comparison for both PFS and OS for the purpose of this response was conducted using the FP-NMA methodology by Jansen (2011) (1). This methodology models the log hazard rate per treatment arm in each study as a function of up to two power parameters, P, where P = {-2, -1, -0.5, 0.5, 1, 2, 3}. Models can be either first-order FP (one power parameter) or second-order FP (two power parameters). The functional forms of these models are shown below:

- **First-order:** $\ln\big(h_{ik}(t)\big) = \beta_0 + \beta_1 t^p$
- **Second-order**, when P1 is not equal to P2: $\ln\big(h_{ik}(t)\big) = \beta_0 + \beta_1 t^{p1} + \beta_2 t^{p2}$
- **Second-order**, when P1 is equal to P2: $\ln\big(h_{ik}(t)\big) = \beta_0 + \beta_1 t^{p1} + \beta_2 t^{p}\log(t)$

The beta parameters are further defined in terms of parameters for baseline treatment (mu) and the treatment effect parameters (d). The FP-NMA focuses on the endpoints of progression-free (PFS) and overall survival (OS). The analysis follows a stepwise approach as described by Wiksten et al. (2020). The first step in this process is to fit the full set of FP models (8 first-order and 36 second-order models) to the PFS and OS data in a frequentist framework using standard generalized linear models. This enables the selection of the 'best' model from the full set of potential structures (44 in total) based on statistical goodness of fit (i.e., Akaike Information Criteria), and the clinical plausibility of the modelled hazard ratios over time.

The second and final step in the process is to refit the selected models in a Bayesian framework to capture and propagate uncertainty for decision-making. This process was deemed most efficient and appropriate as it allows practitioners to investigate a broad range of models rapidly and achieve a more robust and comprehensive model selection strategy.

In addition to the FP models, two other modelling approaches have been explored: (1) piecewise exponential models with cut points of 3 months for PFS and 6 months for OS and (2) proportional hazards models, with exponential and Weibull baseline hazards. These simpler models were included in the analysis to provide a benchmark from which to judge the fit of the more complex FP-NMA models.

- The piecewise exponential models assume that the treatment effect is constant within a series of segments that are defined by fixed cut points, i.e. at 3 months for PFS and 6 months for OS. This approach is analogous to the piecewise NMA that was provided to NICE as part of the response to the EAG's clarification questions in September 2024.
- The proportional hazards models assume that the treatment effect is constant over time, analogous to the constant log-hazard ratio NMA provided in the original submission.

The frequentist and Bayesian FP-NMAs were conducted under a fixed effects assumption, utilizing vague prior distributions for treatment effects when fitting the models in a Bayesian framework, e.g. for second-order models:

$$\text{prior.mean} = [0 \quad 0 \quad 0]$$

$$\text{prior.prec} = \begin{bmatrix} 0.00001 & 0 & 0 \\ 0 & 0.00001 & 0 \\ 0 & 0 & 0.00001 \end{bmatrix}$$

Due to the limited number of studies per comparison in the network (i.e., two or fewer), it was not feasible to implement a random-effects FP-NMA, as this approach requires sufficient data to reliably estimate between-study heterogeneity. This decision is consistent with the findings of the random-effects log-hazard ratio NMA, which employed informative priors for between-study heterogeneity to enhance model fit. At present, no suitable informative priors are available to support the use of a random-effects FP-NMA.

The Bayesian analysis was conducted using the Rjags package and the fractional polynomial code provided by Wiksten et al. (2020) (2). Model fit was performed using Markov Chain Monte Carlo (MCMC) sampling with 4 chains, each with 80,000 iterations including a burn-in period of 20,000 iterations. Additionally, a thinning rate of 3, and an adaptive phase of 20,000 iterations was used to support convergence and minimize autocorrelation. Convergence was evaluated using the potential scale reduction factor, '*r* hat', with scores of less than 1.1 indicating sufficient convergence of the Markov chains. Models with any parameter exceeding this threshold were excluded.

The outputs from the FP-NMA of PFS and OS are presented in the sections below. Please note that only comparisons of capivasertib with fulvestrant, alpelisib with fulvestrant and everolimus with exemestane versus fulvestrant 500mg are considered. Other treatments are included in the NMA but are excluded from the results as they do not contribute to the economic analysis.

Results

The FP-NMA utilized summary data derived from patient-level data from the CAPItello-291 and the CONFIRM trials. Additionally, pseudo patient-level data were recovered from the Kaplan-Meier plots of other trials using the Guyot et al. (2012) method (5).

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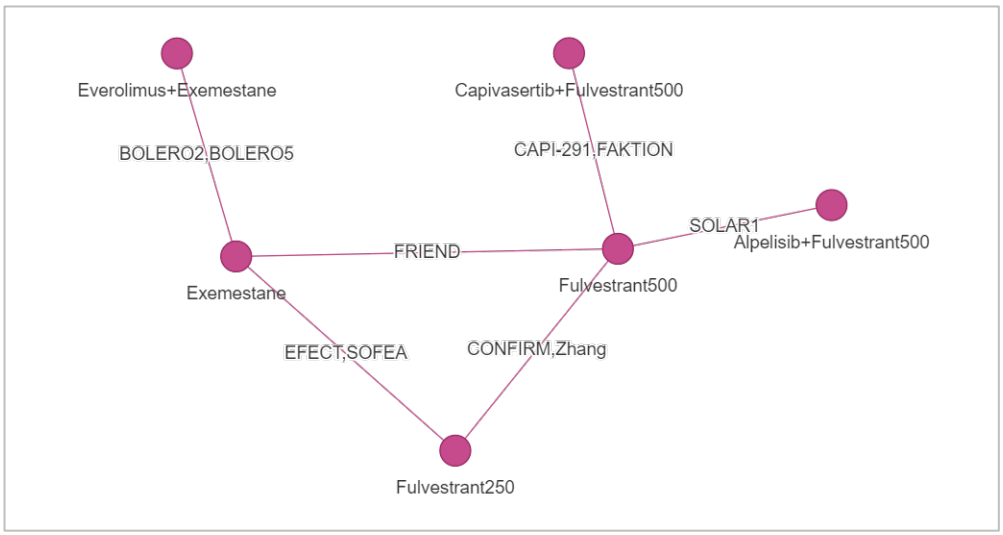
The FP models were fitted to data on the number of patients at risk and the number of events that occur over a series of discrete intervals, each of length 2 months (based on the scan frequency for PFS in CAPItello-291), spanning the duration of study follow-up. The numbers of patients at risk and with events at each interval was estimated from the (pseudo) patient level data using standard Kaplan-Meier estimates.

Progression-free survival (PFS)

The trial network for the PFS FP-NMA is presented in Figure 1 below.

Figure 1: Trial evidence network for PFS



Abbreviations: PFS: progression-free survival

Frequentist analysis

Table 6 presents the AIC scores for the frequentist FP-NMA for PFS. The best fitting models are highlighted in grey. According to AIC score, the best fitting models were all second-order FP models with either *p*1=-2 or *p*1=-1. Similarly, among the first-order models, the best fitting FP model was the model with *p*1=-2. There was strong concordance between AIC and BIC rankings for the 'best-fitting' models.

Table 6: Summary of goodness of fit using ANOVA models for PFS

Model	AIC	BIC	Rank AIC	Rank BIC
Exponential	1671.77	1726.61	47	37
PH with Weibull baseline survival	1652.13	1743.53	46	43
Weibull,p1=0	1626.31	1735.99	45	41
Gompertz,p1=1	1608.13	1717.81	40	33
First order FP, p1=-2	1565.26	1674.94	33	26
First order FP, p1=-1	1610.96	1720.64	41	34
First order FP, p1=-0.5	1624.74	1734.42	44	40
First order FP, p1=0.5	1618.06	1727.73	43	38
First order FP, p1=2	1603.89	1713.57	38	32
First order FP, p1=3	1616.18	1725.85	42	36
Second order FP,p1=-2, p2=-2	1209.17	1373.69	1	1
Second order FP,p1=-2, p2=-1	1233.60	1398.12	2	2
Second order FP,p1=-2, p2=-0.5	1254.06	1418.58	3	3
Second order FP,p1=-2, p2=0	1280.83	1445.35	5	5
Second order FP,p1=-2, p2=0.5	1312.70	1477.22	7	7
Second order FP,p1=-2, p2=1	1346.86	1511.38	10	10
Second order FP,p1=-2, p2=2	1409.89	1574.41	16	16
Second order FP,p1=-2, p2=3	1457.17	1621.69	19	20
Second order FP,p1=-1, p2=-1	1269.10	1433.62	4	4
Second order FP,p1=-1, p2=-0.5	1295.86	1460.38	6	6
Second order FP,p1=-1, p2=0	1328.38	1492.90	9	9
Second order FP,p1=-1, p2=0.5	1364.59	1529.11	12	12
Second order FP,p1=-1, p2=1	1401.29	1565.81	15	15
Second order FP,p1=-1, p2=2	1465.28	1629.80	20	21
Second order FP,p1=-1, p2=3	1511.27	1675.79	26	27
Second order FP,p1=-0.5, p2=-0.5	1325.72	1490.24	8	8
Second order FP,p1=-0.5, p2=0	1360.56	1525.08	11	11
Second order FP,p1=-0.5, p2=0.5	1397.85	1562.37	14	14
Second order FP,p1=-0.5, p2=1	1434.34	1598.86	18	19
Second order FP,p1=-0.5, p2=2	1495.56	1660.08	24	24
Second order FP,p1=-0.5, p2=3	1538.15	1702.67	29	30
Second order FP,p1=0, p2=0	1396.53	1561.05	13	13
Second order FP,p1=0, p2=0.5	1433.40	1597.92	17	18
Second order FP,p1=0, p2=1	1468.05	1632.57	21	22
Second order FP,p1=0, p2=2	1523.42	1687.94	27	28
Second order FP,p1=0, p2=3	1560.29	1724.81	31	35
Second order FP,p1=0.5, p2=0.5	1468.16	1632.67	22	23
Second order FP,p1=0.5, p2=1	1499.31	1663.83	25	25
Second order FP,p1=0.5, p2=2	1546.28	1710.80	30	31
Second order FP,p1=0.5, p2=3	1575.90	1740.42	34	42
Second order FP,p1=1, p2=1	1525.88	1690.40	28	29
Second order FP,p1=1, p2=2	1563.40	1727.92	32	39
Second order FP,p1=1, p2=3	1585.80	1750.32	36	45
Second order FP,p1=2, p2=2	1584.76	1749.28	35	44
Second order FP,p1=2, p2=3	1597.07	1761.59	37	46
Second order FP,p1=3, p2=3	1604.84	1769.36	39	47
PWE, cutpoint @2	1471.78	1581.46	23	17

Abbreviations: FP: fractional polynomials; PFS: progression-free survival; PH: proportional hazards; PWE: piecewise exponential

Figure 2 illustrates the hazard ratios (vs. fulvestrant 500 mg) over time for the best fitting first- and second- order FP models, as well as the proportional hazard and piecewise exponential model. The hazard ratio pattern was consistent across most FP models, showing treatment effects that diminished over time before stabilizing at values close to 1. Similar trends were observed with the piecewise exponential model with a 3-month cut point.

The first-order FP model with *p*1=2 predicted an increasing treatment effect over time, with values exceeding 1 after approximately 12-18 months. The estimated hazard ratios for all therapies at 24 months were greater than 10. This pattern is not clinically plausible for treatments such as capivasertib and alpelisib, as both therapies are given in combination with fulvestrant 500mg and are therefore highly unlikely to cause an increased risk of PFS vs. fulvestrant 500mg alone, as suggested by a hazard ratio above 1.

Figure 2: Hazard ratio versus fulvestrant 500mg over time for PFS

Figure 3 shows an alternative presentation of the hazard ratios over time, grouped by treatment (row) and model (column).

Figure 3: Hazard ratio vs. fulvestrant 500 mg over time (by treatment) for PFS - with 95% CIs

Abbreviations: CI: confidence interval; FP: fractional polynomials; PWE: piecewise exponential

In summary, the models that provided the best fit, based on statistical criteria and the clinical plausibility of the modelled hazard ratios over time, were the:

- **Second-order FP models with *p*1=-2 and *p2*=-2** and,
- **First-order FP model with *p*=-2**

These models yielded time-varying hazard ratios that were similar in value to the results of the piecewise NMA that was provided to NICE as part of the response to the EAG's clarification questions in September 2024. In step 2 of the analysis, these models were refitted in a Bayesian framework.

Bayesian analysis

Table 7 presents a cross tabulation of the treatment names and treatment numbers in the Bayesian analysis. The treatment effect parameters corresponding to each therapy can be identified using this table, i.e., for capivasertib, the effect parameters are d[3,1], d[3,2] and d[3,3] where d[i,j] is the effect of treatment i on parameter j. Convergence was met across all parameters (*r*hat<1.1) for both the second-order FP model (*p*1=-2, *p*2=-2) and the first-order model (*p*1=2).

Table 7: Cross tabulation of treatment name and number in the Bayesian analysis

Capivasertib with fulvestrant for treating hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment [ID6370]

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trtf	trtn
Fulvestrant500	1
Alpelisib+Fulvestrant500	2
Capivasertib+Fulvestrant500	3
Everolimus+Exemestane	4
Exemestane	5
Fulvestrant250	6

Table 8 shows the fitted parameters for the second-order fractional polynomial (*p*1=-2, *p*2=-2), as well as the covariance matrices for the treatment effect parameters.

Table 8: Parameter estimates for the second-order fractional polynomial (*p*1=-2, *p*2=-2)

Abbreviations: L: lower; U: upper

Table 9 shows the fitted parameters for the first-order fractional polynomial (*p*1=-2), as well as the covariance matrices for the treatment effect parameter.

Table 9: Parameter estimates for the first-order fractional polynomial (*p*1=-2)

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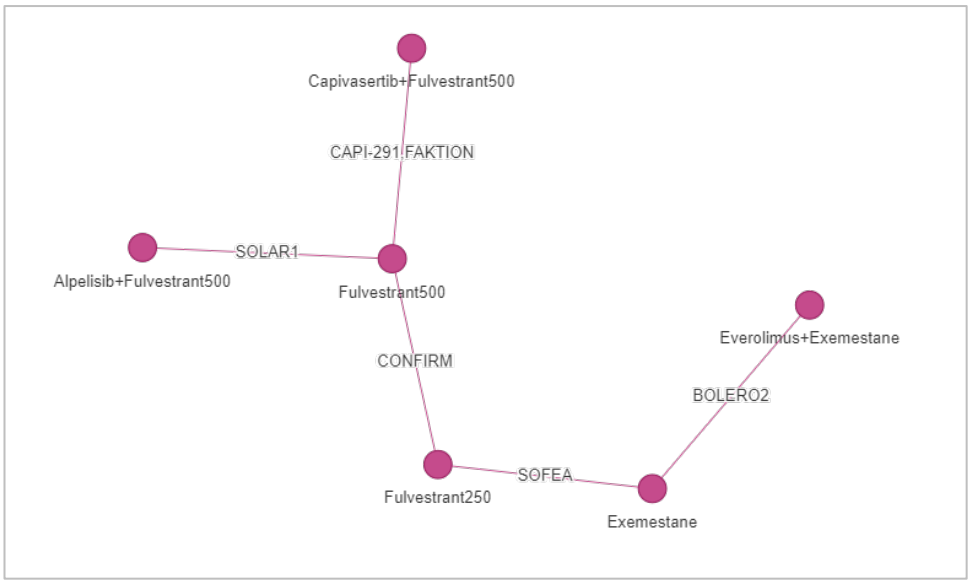
[redacted]

Abbreviations: L: lower; U: upper

Overall survival (OS)

The trial network for the OS FP-NMA is presented in Figure 4 below.

Figure 4: Trial evidence network for OS



Abbreviations: PFS: progression-free survival

Frequentist analysis

Table 10 presents the AIC scores for the frequentist FP-NMAs for OS. The best-fitting models are shaded in grey. According to AIC, the best-fitting models were all second order FP models including models with *P*1=-1 and models with *P*1=-0.5. Additionally, when comparing only first-order models, the models with *P*1=-1 and *P*1=-0.5 yielded the best fit and lowest AIC scores. According to BIC, the best-

fitting models were the proportional hazards model with a Weibull baseline hazard, followed by the first-order FP models.

In contrast to PFS, there was little agreement between AIC and BIC on the best-fitting models for OS. It is important to note that the BIC score applies a greater penalty for additional model complexity compared to the AIC. As a result, BIC scores tended to favour simpler models.

Table 10: Summary of goodness of fit using ANOVA models for OS

Model	AIC	BIC	Rank AIC	Rank BIC
Exponential	1240.35	1280.87	47	42
PH with Weibull baseline survival	1151.37	1214.00	33	1
Weibull,p1=0	1155.52	1236.56	38	5
Gompertz,p1=1	1187.45	1268.49	44	28
First order FP, p1=-2	1149.14	1230.18	26	4
First order FP, p1=-1	1139.62	1220.66	7	2
First order FP, p1=-0.5	1143.19	1224.23	12	3
First order FP, p1=0.5	1172.23	1253.27	41	6
First order FP, p1=2	1206.89	1287.93	45	44
First order FP, p1=3	1216.59	1297.63	46	46
Second order FP,p1=-2, p2=-2	1153.60	1275.16	36	40
Second order FP,p1=-2, p2=-1	1151.80	1273.36	35	39
Second order FP,p1=-2, p2=-0.5	1151.09	1272.65	32	37
Second order FP,p1=-2, p2=0	1150.41	1271.97	30	35
Second order FP,p1=-2, p2=0.5	1149.53	1271.09	28	33
Second order FP,p1=-2, p2=1	1148.34	1269.90	24	30
Second order FP,p1=-2, p2=2	1145.63	1267.19	20	25
Second order FP,p1=-2, p2=3	1143.56	1265.12	15	19
Second order FP,p1=-1, p2=-1	1151.38	1272.94	34	38
Second order FP,p1=-1, p2=-0.5	1150.53	1272.09	31	36
Second order FP,p1=-1, p2=0	1148.97	1270.53	25	31
Second order FP,p1=-1, p2=0.5	1146.70	1268.26	22	27
Second order FP,p1=-1, p2=1	1144.02	1265.58	16	20
Second order FP,p1=-1, p2=2	1138.88	1260.44	5	11
Second order FP,p1=-1, p2=3	1135.29	1256.85	2	8
Second order FP,p1=-0.5, p2=-0.5	1149.44	1271.00	27	32
Second order FP,p1=-0.5, p2=0	1147.55	1269.11	23	29
Second order FP,p1=-0.5, p2=0.5	1145.01	1266.57	18	23
Second order FP,p1=-0.5, p2=1	1142.23	1263.79	10	15
Second order FP,p1=-0.5, p2=2	1137.43	1258.98	3	9
Second order FP,p1=-0.5, p2=3	1134.45	1256.01	1	7
Second order FP,p1=0, p2=0	1145.61	1267.17	19	24
Second order FP,p1=0, p2=0.5	1143.45	1265.01	14	18
Second order FP,p1=0, p2=1	1141.47	1263.03	8	13
Second order FP,p1=0, p2=2	1138.90	1260.46	6	12
Second order FP,p1=0, p2=3	1138.09	1259.65	4	10
Second order FP,p1=0.5, p2=0.5	1142.42	1263.98	11	16
Second order FP,p1=0.5, p2=1	1142.14	1263.70	9	14
Second order FP,p1=0.5, p2=2	1143.38	1264.94	13	17
Second order FP,p1=0.5, p2=3	1145.70	1267.26	21	26
Second order FP,p1=1, p2=1	1144.08	1265.64	17	21
Second order FP,p1=1, p2=2	1149.62	1271.18	29	34
Second order FP,p1=1, p2=3	1155.01	1276.56	37	41
Second order FP,p1=2, p2=2	1162.14	1283.70	39	43
Second order FP,p1=2, p2=3	1171.57	1293.13	40	45
Second order FP,p1=3, p2=3	1182.76	1304.32	42	47
PWE, cutpoint @6	1184.95	1265.98	43	22

Abbreviations: FP: fractional polynomials; OS: overall survival; PH: proportional hazards; PWE: piecewise exponential

Figure 5 shows the hazard ratio over time for the best fitting models for OS. The hazard ratio plots show two distinct patterns across the FP-NMA models. For all first-order FP models, except for Gompertz, the predicted long-term treatment effects for everolimus plus exemestane and alpelisib plus fulvestrant converged to values close to 1. This indicates diminishing differences in the hazard rate over time, compared to fulvestrant 500 mg. In contrast, for capivasertib plus fulvestrant, these models predict an approximately constant effect over time.

In comparison, the second-order FP and Gompertz models exhibited more exaggerated patterns. Specifically, the hazard ratio for capivasertib decreases toward zero, while the hazard ratios for other therapies increases to values greater than 1.

Overall, the exaggerated patterns observed with the Gompertz model and the more complex second-order FP models are considered highly clinically implausible. It is specifically unclear why the effect of one treatment would diminish while others would improve, yielding negative (i.e. >1) long-term hazard ratios for regimens such as everolimus plus exemestane and alpelisib plus fulvestrant (versus fulvestrant 500 mg). Despite achieving the lowest AIC scores, the best-fitting second-order FP models yielded clinically implausible time-varying hazard ratios, with treatment effects improving for some but not for other therapies. These models were therefore excluded from the analysis, and only first-order models were applied in the Bayesian analysis.

Figure 5: Hazard ratio versus fulvestrant 500mg over time for OS

Abbreviations: FP: fractional polynomials; PH: proportional hazards; PWE: piecewise exponential

Figure 6 shows an alternative presentation of the hazard ratios over time, grouped by treatment (row) and model (column).

Figure 6: Hazard ratio vs. fulvestrant 500 mg over time (by treatment) for OS - with 95% CIs

Abbreviations: CI: confidence interval; FP: fractional polynomials; PWE: piecewise exponential

In summary, the 'best fitting' models according to statistical criteria and the plausibility of hazard ratios over time, were the **first-order FP models with *p*1=-1** and ***p*=-0.5**. In step two of the analysis below, these models were refitted in a Bayesian framework.

Bayesian analysis

Table 11 presents a cross tabulation of treatment names and numbers in the Bayesian analysis.

Convergence was met across all parameters (rhat<1.1) for both first-order models.

Table 11: Cross tabulation of treatment name and number in the Bayesian analysis

trtf	trtn
Fulvestrant500	1
Alpelisib+Fulvestrant500	2
Capivasertib+Fulvestrant500	3
Everolimus+Exemestane	4
Exemestane	5
Fulvestrant250	6

Table 12 shows the fitted parameters for the first order fractional polynomial (p1=-1), as well as the covariance matrices for the treatment effect parameters.

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 4 February 2025. Please submit via NICE Docs.

Table 12: Parameter estimates for the first order fractional polynomial (*p*1=-1)

Abbreviations: L: lower; U: upper

Table 13 shows the fitted parameters for the first order fractional polynomial (*p*1=-0.5), as well as the covariance matrices for the treatment effect parameter.

Table 13: Parameter estimates for the first order fractional polynomial (*p*1=-0.5)

Abbreviations: L: lower; U: upper

Capivasertib with fulvestrant for treating hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment [ID6370]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 4 February 2025. Please submit via NICE Docs.

Discussion

The results of the FP-NMA suggest that:

- **Progression-free survival**: the treatment effects for everolimus plus exemestane and alpelisib plus fulvestrant are predicted to decline (or wane) over time before stabilizing at a long-term value that is close to 1. For capivasertib plus fulvestrant, the treatment effect is predicted to [redacted] but [redacted] in the long-term.
- **Overall survival**: the treatment effects for everolimus plus exemestane and alpelisib plus fulvestrant (versus fulvestrant 500 mg) are predicted to gradually converge to a value close to 1, whilst the effect of capivasertib plus fulvestrant is predicted to [redacted] over time.

For both PFS and OS, the best fitting models produced hazard ratios similar to those estimated in the piecewise NMA that was provided to NICE as part of the response to the EAG's clarification questions in September 2024.

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Capivasertib with fulvestrant for treating hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment [ID6370]

Company Draft guidance comments form

Erratum for: Company Draft guidance comments form

The Company had previously stated the following under Comment 3 in the Draft guidance comments form:

- ***For PFS:*** *The models that provided the best fit in the frequentist framework, based on statistical criteria and the plausibility of the pattern of hazard ratios over time were the second order FP models with p1=-2 and the first order FP model with p=-2. These models yielded time-varying hazard ratios that were similar in value to the results of the piecewise NMA provided to NICE as part of the response to the EAG's clarification questions. However, given that the second order FP model with p1=-2 and p2=-2 failed to converge when fitted in a Bayesian framework, only the second-best fitting second-order FP (p1=-2, p2=-1) and the first order fractional polynomial (p1=-2) were applied in the Bayesian analysis and implemented in the economic model.*

There is a factual inaccuracy in this statement. This should be corrected to:

- **For PFS:** The models that provided the best fit in the frequentist framework, based on statistical criteria and the plausibility of the pattern of hazard ratios over time were the second order FP models with *p*1=-2 and *p*2=-2 and the first order FP model with *p*=-2. These models yielded time-varying hazard ratios that were similar in value to the results of the piecewise NMA provided to NICE as part of the response to the EAG's clarification questions. These models were subsequently applied in the Bayesian analysis and implemented in the economic model.

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Capivasertib with fulvestrant for treating hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment [ID6370]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 4 February 2025. 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

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Capivasertib with fulvestrant for treating hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment [ID6370]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 4 February 2025. 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.	In the last 12 months (from January 2024) Breast Cancer Now has received the following funding from manufacturers listed in the appraisal matrix: Novartis – £69,421 to support our Service Pledge programme, £50,000 to support an external research project, £15,000 to support our nursing conference Please note, Breast Cancer Now does not receive any pharmaceutical funding for our Policy, Evidence and Influencing work.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Eleanor Pearce Willis

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 very disappointed that NICE has been unable to recommend capivasertib with fulvestrant for treating HR-positive, HER2-negative advanced breast cancer with PIK3CA, AKT1 and/or PTEN alterations. This outcome is particularly concerning given that the committee recognises in the draft guidance that this is an effective treatment for these patients after a CDK 4/6 inhibitor and aromatase inhibitor.

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Capivasertib with fulvestrant for treating hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment [ID6370]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 4 February 2025. Please submit via NICE Docs.

2	This is the second breast cancer treatment in recent months that has been provisionally rejected in part due to uncertainties as a result of the use of indirect treatment comparisons. This was also an issue in the appraisal of elacestrant for HR+ve, HER2-ve secondary breast cancer with an ESR1 mutation. Given the complexity and fast changing nature of breast cancer treatment pathways we are concerned that indirect treatment comparisons will become increasingly necessary in appraisals for future treatments. To minimise delays to future appraisals we would urge NICE to clearly communicate with companies their specific requirements for information and evidence on indirect treatment comparisons. We note that there was no technical engagement stage for this appraisal, which could have offered an opportunity to surface and potentially address these issues prior to ACM1.
3	Some people with HR-positive, HER2-negative advanced breast cancer with one or more PIK3CA, AKT1 or PTEN alterations who could benefit from this drug don't have any other targeted treatment options available for the particular genetic changes in their tumours. This delay is deeply frustrating for these patients. We hope that NICE and the company are able to work closely together to address the uncertainties and make this treatment available as quickly as possible.
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.
- 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.

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Capivasertib with fulvestrant for treating hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment [ID6370]

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Capivasertib with fulvestrant for treating hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment [ID6370]

Draft guidance comments form

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	METUPUK

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Capivasertib with fulvestrant for treating hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment [ID6370]

Draft guidance comments form

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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:	XXXXXXXX XXXXXXXXXX

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.

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Capivasertib with fulvestrant for treating hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment [ID6370]

Draft guidance comments form

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Example 1	We are concerned that this recommendation may imply that ……..
1	Most Trustees and volunteers at METUPUK have personal experience of breast cancer, either as a patient or a carer, and usually that is experience is of metastatic breast cancer (MBC). MBC remains the largest single cause of death in women aged 35-64 and a significant cause of death in all women (ONS, 2024. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathsregisteredsummarystatisticsenglandandwales [accessed 19 Jan 2025]). METUPUK campaigns for improvement in outcomes for people with MBC, and research and the development of new and better treatments is key to achieving this. The development of capivasertib offers us hope that the research taking place is being translated into new treatments for use in the clinic (ICR, 2022. https://www.icr.ac.uk/about-us/icr-news/detail/capivasertib-a-huge-success-story-for-uk-science [accessed 19 January 2025]). The fundamental biology researching AKT activation which took place in the early 2000's at the Institute of Cancer Research (ICR) led to the development of protype drugs. This in turn led to the development of capivasertib which has been approved by the FDA, EMA and MHRA and is already being used in the clinic internationally. The endeavour of the many scientists involved at the ICR and from industry in this 25 year process gives us hope that incremental steps are taking place to improve the management of MBC and ultimately outcomes for patients. The investment from charities, government grants and industry has resulted in a drug which will benefit patients with MBC. As patients, as charity donors and as taxpayers we applaud their work and hope that it will be available for patients in England and ultimately across the UK.
2	**Has all of the relevant evidence been taken into account?** Capivasertib is a first in class drug which targets the AKT protein molecule. Around 50% of patients with HR+/HER2- MBC could benefit from capivasertib with fulvestrant because they have alterations in PIK3CA, AKT1 or PTEN genes. As a first in class drug combination, there is no alternative AKT inhibitor available on the NHS in England. There is also no alternative therapy which is directed against PTEN mutations. The combination of alpelisib-fulvestrant is available for patients with alterations in the PIK3CA gene. However, around 25% of patients who would be eligible for capivasertib-fulvestrant do not have PIK3CA mutations, and so would not qualify for alpelisib-fulvestrant. Therefore capivasertib-fulvestrant addresses an unmet need. A significant uncertainty in this appraisal relates to differences in clinical trials between capivasertib plus fulvestrant and the trials for alpelisib plus fulvestrant and everolimus plus exemestane. Specifically differences in the populations, prior treatments (prior CKD4/6i use was only 5% in SOLAR-1 but over 70% in CAPItello-291 and data not

	available in BOLERO-2) and in the methods used to compare these trials. A further significant uncertainty relates to the modelling used to extrapolate treatment waning. Indirect Treatment Comparisons will inevitably have different populations and inclusion criteria in trials, and so uncertainties will arise. We hope that the Company will provide the data to address these uncertainties. As patients, treatment waning over time reflects our experience of taking cancer drugs and we would expect the models to reflect this. However, it does seem reasonable that the time for treatment waning should be aligned with TA816, given that comparing capivasertib with fulvestrant to alpelisib with fulvestrant forms part of the ICER calculation. Therefore it is counterintuitive to not apply the same methods to both appraisals. The comparators alpelisib with fulvestrant and everolimus with exemestane are established treatments in NHS practice and there is real world data for PFS, OS and quality of life. The clinical experts spoke about the comparator treatment toxicities and the patient expert echoed their concerns about side effects. We believe that greater weight should be given to concerns expressed by the clinical and patient experts around the toxicity of the comparator treatments which are not always tolerated well. As patients, we understand the importance of accessing effective treatments but also the downsides of taking treatments with a high side effect burden. The poster by de Wilt et al (2024) carried out an anchored safety indirect treatment comparison of capivasertib-fulvestrant and alpelisib-fulvestrant. They found capivasertib-fulvestrant significantly reduced the risk of nausea, vomiting and fatigue compared with alpelisib-fulvestrant. However, capivasertib-fulvestrant increased the risk of diarrhoea compared to alpelisib-fulvestrant. De Wilt et al (2024) also found that patients with PIK3CA alterations taking capivasertib-fulvestrant lived longer before their cancer got worse, compared to patients taking alpelisib-fulvestrant. There was no data for patients with AKT or PTEN mutations, but as patients it is encouraging to see improved outcomes in the PIK3CA alteration cohort. References: De Wilt, E., Hettle, R., Liljas, B. (2024). Indirect treatment comparison of efficacy and safety of capivasertib-fulvestrant versus alpelisib-fulvestrant for *PIK3CA*-altered, HR-positive, advanced breast cancer after disease progression following endocrine-based therapy. Available at: https://www.ispor.org/docs/default-source/intl2024/ispor24liljasco172poster138705-pdf.pdf?sfvrsn=ed46dba7_0 [accessed 2 February 2025]
3	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? It is difficult to comment on cost effectiveness as lay people.

Capivasertib with fulvestrant for treating hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment [ID6370]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 4 February 2025. Please submit via NICE Docs.

4	Are the provisional recommendations sound and a suitable basis for guidance to the NHS? No the recommendations are not a sound and suitable basis for guidance to the NHS. Capivasertib with fulvestrant is a first in class AKT inhibitor. Treatment options for patients with hormone receptor-positive HER2-negative metastatic breast cancer with alterations in PIK3CA, AKT and PTEN are limited after progression on a CDK4/6 inhibitor. Although alpelisib with fulvestrant targets PIK3CA mutations, there are no treatments available which are directed against AKT and PTEN mutations. Around 25% of patients eligible for capivasertib-fulvestrant do not have alterations in PIK3CA and so are not eligible for alpelisib with fulvestrant. Therefore capivasertib with fulvestrant fulfils an unmet need. The comparator treatments alpelisib with fulvestrant and everolimus with exemestane both have significant side effects and many patients find them difficult to tolerate. Alpelisib is known to cause hyperglycaemia and Everolimus with exemestane can cause stomatitis. The clinical experts noted that for most patients capivasertib with fulvestrant is a well tolerated treatment with side effects that are lower grade and easier to manage. Patients taking capivasertib with fulvestrant live for longer before their cancer gets worse, and experience fewer grade 3/4 side effects compared to alpelisib with fulvestrant or everolimus with exemestane. In our patient engagement surveys, patients have a stated preference for targeted treatments over untargeted chemotherapy. They dislike scattergun treatments which can expose their bodies to unnecessary toxicity for little benefit. Patients are excited by precision treatments which target mutations in their cancer. They value effective treatments which are proven to improve outcomes.
5	We would also like you to think about whether there are any aspects of the recommendations that need particular consideration to make sure we avoid unlawful discrimination against any group of people. None noted.
6	
7	

Insert extra rows as needed

Checklist for submitting comments

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Capivasertib with fulvestrant for treating hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment [ID6370]

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- 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.
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Capivasertib with fulvestrant for treating hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment [ID6370]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	

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Capivasertib with fulvestrant for treating hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment [ID6370]

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Kirstin Spencer

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	**Patients are concerned** they may suffer **unsustainable toxicities** from the only currently NHS prescribed treatment for PIK3CA disease of **alpelisib-**fulvestrant combination. Alpelisib can take an unacceptable toll on their metabolic health and ability to tolerate this combination. **Patient voice:**

Please return to: **NICE DOCS**

Capivasertib with fulvestrant for treating hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment [ID6370]

Draft guidance comments form

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	[redacted]
2	Capivasertib meets a significant **unmet need** for a targeted treatment option by **extending the scope of treatment** for the PI3K common pathway to include **AKT1** and **PTEN** genetic alterations. This could enable an additional cohort of **patients currently unable to access targeted treatment for their AKT1/PTEN disease** a **targeted option**.
3	The **post-CDK 4/6 inhibitor metastatic breast cancer** (MBC) **patient** population is challenging to treat effectively as disease progresses. Capivasertib-fulvestrant treatment found significantly better progression-free survival for patients than fulvestrant alone (Turner *et al.,* 2023). DeWilt, Hettle and Lijas (2024) recognised that capivasertib-fulvestrant (CAPItello-291 trial) may perform better and for a wider cohort of patients with advanced mutated disease than alpelisib-fulvestrant (SOLAR-1 trial) where consistency of efficacy across prior CDK 4/6 inhibitor groups was left uncertain due to small (5%) numbers of these patients.
4	The indirect treatment comparison (de Wilt, Hettle and Liljas, 2024) between **CAPItello-291** (capivasertib-fulvestrant) and **SOLAR-1** (alpelisib-fulvestrant) trials concluded **importantly for patients** that **side effects** from capivasertib and fulvestrant are **generally more favourable** than with alpelisib and fulvestrant. Additionally, **patients** are likely to live longer without their disease progressing on the capivasertib-fulvestrant treatment compared to those treated with alpelisib-fulvestrant.
5	For **patients** with PIK3CA disease, the capivasertib-fulvestrant combination appears to offer a more **effective and better tolerated treatment option** than current pathways offered in an NHS clinic at this time. It **additionally allows patients** with **PTEN** and **AKT1** mutations to access a targeted treatment for their disease **for the first time**.
6	**References:** De Wilt, E., Hettle, R. and Liljas, B., (2024a) 'CO172 indirect Treatment Comparison of Efficacy and Safety of Capivasertib-Fulvestrant Versus Alpelisib-Fulvestrant for PIK3CA-Altered, HR-Positive, Advanced Breast Cancer after Disease Progression Following Endocrine-Based Therapy', *Value in Health*, 27(6). Doi:10.12016/j.jval.2024.03.258. Joyce O'Shaughnessy, M. *et al.* (2021) *Managing patients with HR+ MBC on PI3K therapy, OncLive.* Available at: https://www.onclive.com/view/managing-patients-with-hr-mbc-on-pi3k-therapy (Accessed: 01 February 2025). Turner, N.C., Oliveira, M., Howell, S.J., Dalenc, F., Cortes, J., Gomez Moreno, H.L., Hu, X., Jhaveri, K., Krivorotko, P., Loibl, S., Morales Murillo, S., Okera, M., Park, Y.H., Sohn, J., Toi M, Tokunaga E, Yousef S., Zhukova L., de Bruin E.C., Grinsted L., Schiavon G., Foxley A., Rugo, H.S.; CAPItello-291 Study Group. Capivasertib in Hormone Receptor-Positive Advanced Breast Cancer. *N Engl J Med.* 2023 Jun 1;388(22):2058-2070. doi: 10.1056/NEJMoa2214131. PMID: 37256976; PMCID: PMC11335038.

Insert extra rows as needed

Checklist for submitting comments

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Capivasertib with fulvestrant for treating hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment [ID6370]

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Single Technology Appraisal

Capivasertib with fulvestrant for treating hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment [ID6370]

Comments on the draft guidance received through the NICE website

Name	[redacted]
Comments on the DG:	

Has all of the relevant evidence been taken into account?
All the relevant evidence has been taken into account. i have nothing to add

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
yes it is reasonable.

yes it is reasonable.

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

yes it will help the NHS

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

yes it would add that the NHS staff start asking people their pronouns. to avoid discrimination and lawsuits upon this.

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Capivasertib in combination with fulvestrant for second-line treatment in unresectable or metastatic HR-positive, HER2-negative breast cancer [ID6370] – EAG critique of company response to Draft Guidance

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Comment 1: Overall comments on the draft guidance

No response from the EAG required.

Comment 2: Robustness of the indirect treatment comparison

In the EAG report, the EAG highlighted that following the assessment of heterogeneity, there was considerable heterogeneity in a range of baseline characteristics including PI3K/AKT status, HER2 status, ECOG (PS = 1) and prior CDK4/6i use for the included patients from the trials of NMA.[1] Therefore, The EAG considers that there was limited comparability of patients' baseline characteristics between included trials in the NMA. This limitation may have introduced uncertainties the findings from the ITC analysis. Given that the company's response in the draft guidance document did not present additional data, the EAG's concern on considerable heterogeneity in a range of baseline characteristics for the included patients from the trials of NMA remains.

Comment 3: Modelling of long-term relative treatment effect

Following the request by the committee in the draft guidance document, the company explored the option of using fractional polynomials (FP) as an alternative time-varying analysis for conducting the indirect treatment comparison for PFS and OS outcomes. The company stated that 'with fractional polynomials, a multi-dimensional approach is taken to model the hazard over time, with the treatment effect being represented with multiple parameters. Specifically, the hazard functions of the treatments compared in the clinical trials included in the NMA are modelled, and the difference between the parameters of these fractional polynomials within a trial are synthesized (and indirectly compared) across studies. This flexibility allows for a potential non-linear relationship between time and hazard to be modelled.'

The FP time varying NMA was based on the comparisons of capivasertib with fulvestrant, alpelisib with fulvestrant and everolimus with exemestane versus fulvestrant 500mg. For PFS outcome, based on statistical criteria and the visual inspection of the pattern of hazard ratios over time, the company stated that the best fit models were the second order FP models with p1= -2 and p2= -2, and the first order FP model with p1= -2. For OS outcome, based on statistical criteria and the visual inspection of the pattern of hazard ratios over time, the best fit models were the first-order FP models with p1= -1 and p1= -0.5. The company made the following statement:

- **'**For PFS**:** the treatment effects for everolimus with exemestane and alpelisib with fulvestrant vs. fulvestrant monotherapy are predicted to decline (or wane) over time before stabilizing at a long-term HR value that is close to 1. For capivasertib with fulvestrant, the treatment effect is predicted to [redacted], but the HR [redacted] in the long-term.
- For OS: the treatment effects for everolimus with exemestane and alpelisib with fulvestrant vs. fulvestrant monotherapy are predicted to gradually converge to a HR value close to 1, whilst the effect of capivasertib with fulvestrant is predicted to [redacted] and eventually [redacted] over time.'

The EAG considers that the company appropriately used fractional polynomials (FP) as an alternative time-varying analysis for conducting the indirect treatment comparison for PFS and OS outcomes. The approach for the selection of best fit models appears to be appropriate. The results from these FP time

varying NMA were generally consistent visually with those results of the piecewise time varying NMA as part of the company's response to the EAG's clarification questions.[1] However, the EAG notes that, despite the company's statement as to the best fitting model for PFS, another model was stated to have been chosen for their economic model base case, which was the second order p1= -2, p1 = -1. This model had the second best statistical fit, and, although there appears to be little difference between this and the other best fitting models, it might be more clinically plausible. Therefore, the models chosen for the EAG base case are the same as the company base case as stated in the company response to the DG:

- for PFS, second order p1= -2, p2= -1
- for OS, first order p1= -1

After submitting this EAG critique to NICE, the EAG were provided with a correction from the company that the company base case had in fact used the second order p1= -2, p2= -2 for PFS. The EAG still prefer the second order p1= -2, p2= -1 because of its greater clinical plausibility, at least for capivasertib + fulvestrant vs. fulvestrant (turquoise curve in figure 3 of company response to DG): there is a kink with p1 = -2, p2 = -2, where the HR starts at 1 and drops sharply, before rising gradually towards 1. However, the economic model provided by the company does not allow this FP model to be used, and so the EAG requested that company provided an economic model that does. In response, the company stated: *"This means that p1 = -2, p2 = -1 was not explored in a Bayesian framework or included in the CEM. All results provided in the ACD response are in reference to p1= -2, p2= -2, it was just mislabelled. The challenges encountered with convergence reflected an earlier draft of the ACD response, as we initially faced complexities in running the Bayesian model. However, we successfully resolved these complexities."* Therefore, if the 'complexities' have been resolved, it is unclear to the EAG why a version of the economic model that uses the second order p1 = -2, p2 = -1 cannot be provided.

Comment 4: Implementation of treatment waning in the economic model

The company implemented 5-year treatment effect waning for all interventions and explored 2- and 3-year treatment effect waning in scenarios. The FP approach resulted in hazard ratios of [redacted], [redacted] and [redacted] at 24 months for capivasertib, alpelisib and everolimus with exemestane respectively. Since no strong evidence has been presented to show a prolonged treatment effect after the end of follow-up, the EAG considers that 2- or 3-year treatment effect waning assumptions are still appropriate. Given that the estimated hazard ratio for capivasertib at 24 months is still below 1, the EAG adopts treatment effect waning for all interventions at 3 years.

Comment 5: Other requested additional analyses

Health state utility value (HSUV) for the progressed disease (PD) state:

In response to the DG, the company provided additional scenario analyses using different health state utility values for the progressed disease state (of 0.6, 0.65, 0.69 and 0.7), while their base-case estimate did not change. The Mitra et al publication (a poster presentation) does not provide a lot of detail regarding patient characteristics and disease status. The same study results appear to have been published later in Davie et al 2020 (see supplementary information file 5 Table S5), though it is unclear whether the exact same data was used (mean and sd are the same for the 5 EU countries but the reported overall sample size differed). Of note, the utility for the 17 UK patients was 0.79. It is unclear to the EAG whether these values represent progressed disease health state values, or pre-progression values in the context of this appraisal. Noting the uncertainty about utility values in this population, the EAG explores a health state utility of 0.6 in a scenario.

Reporting costs for AKT1 and PTEN alterations:

The company, in response to the DG, included AKT1 and PTEN alterations test costs. The number of patients needed to test to identify one eligible patient was estimated at 2.45 based on the proportion of patients with PIK3CA/AKT1/PTEN altered tumour tissue – no reference was provided for this. The testing cost was estimated at £114.71, based on *"[…] the estimated staffing costs for the analysis of PTEN and AKT1 alterations, informed and estimated based on feedback from 2 GLHs (North East & Yorkshire and South East), additional resource use for allocating the test, report entry, analyses and checks, and the NHS pay scales derived from the NHS Employers website"* (Company's DG response). This resulted in total testing cost per eligible patient of £281.02. It was unclear to the EAG whether these costs were based on an appropriate micro-costing exercise, and therefore the EAG considers this uncertain and tests the impact of double the costs in a scenario. The EAG also notes the relatively small impact of the testing costs on the ICER.

Relative dose intensity (RDI) for alpelisib:

In response to the DG, the company stated to have included the median RDI of 82.7% for alpelisib as was requested by the committee. However, in the model, the RDI of capivasertib of [redacted] appeared to have been used instead. The EAG requested a new model file with this error amended. The company did provide an updated model file, but that still continues to use the capivasertib RDI of [redacted]. The EAG corrected this in their base-case.

Time to treatment discontinuation continues to be estimated based on PFS. With the use of the FP approach, PFS has changed for all treatments and it may be that there is now a disconnect between TTD observed in Capitello and that estimated in the model. For alpelisib, there were already concerns of TTD potentially being over-estimated with the company's estimation method, as non-progression related reasons for discontinuation may vary by treatment. If it is the case that PFS for alpelisib has increased because of the new estimation method, these concerns are exacerbated. The EAG therefore applies a scenario in which TTD is shorter for both comparators.

Company updated base-case

The EAG compared results of the EAG's modified model for ACM1 with the company's updated model using the following settings (**differences in bold**).[2]

- Applying the new PAS in the EAG's model, to align with the company's model
- **The original time-varying NMA in the EAG model vs the new fractional polynomial approach in the company model**
- Using the log-logistic in both models
- 2 year waning in both models (because the EAG model did not include the possibility for 5 year treatment effect waning)
- Original progressed disease utility
- **Test costs for AKT1 and PTEN alterations not included in the EAG model, but included in the company model**
- RDI for alpelisib at [redacted] in both models (the company had not changed this to the median dose intensity for alpelisib that was requested by the committee)

Based on these settings, it would be expected that costs for capivasertib may be slightly higher in the EAG model than in the company's model because of the test costs, and that there may also be an unknown effect on costs, life-years and QALYs for all comparators because of the difference in estimating the relative effects.

Costs for capivasertib and alpelisib plus fulvestrant were higher, while costs for everolimus with exemestane were lower (Table 1). The use of the FP NMA appears to have resulted in an increase / decrease in LYs and QALYs for alpelisib plus fulvestrant / everolimus with exemestane, while it had no effect on QALYs of patients treated with capivasertib plus fulvestrant.

Table 1: Difference between EAG's model and company's updated model results

Technology	Total Costs (£)	Total LYs	Total QALYs (excl sev mod)
Capivasertib plus fulvestrant	[redacted]	-0.003	0.000
Alpelisib plus fulvestrant	£ 2,733	0.078	0.059
Everolimus with exemestane	-£ 318	-0.432	-0.313

The EAG requested from the company a breakdown of the impact of each change in terms of incremental costs, QALYs and the ICER, which the company promptly provided.[3] This supported that the increase in cost difference between capivasertib plus fulvestrant and alpelisib plus fulvestrant was mainly driven by the use of the FP NMA.

However, the reasons for this were not explained by the company. The EAG assumes that the lack of change in QALYs for capivasertib plus fulvestrant may be explained by the time-varying hazard ratios derived from the FP approach being fairly similar to the hazard ratios used in the previous time-varying analysis (where only two hazard ratios were used, before and after 6 and 3 months for OS and PFS respectively). In addition, applying treatment effect waning at 2 years means that any longer term differences between the FP approach and the original time-varying approach have no impact. Further clarification on this should be provided by the company, e.g. by showing PFS and OS curves with and without the use of the FP approach for all treatments.

For alpelisib plus fulvestrant and capivasertib plus fulvestrant, the increase in costs is largely driven by a change in drug treatment costs (i.e., not health state costs), according to the company's disaggregated results in the model file, although part of the increase in the capivasertib plus fulvestrant costs is explained by including the test costs. Without explanation by the company as to why there is such an increase in drug costs for the alpelisib plus fulvestrant arm, the EAG assume that this may have to do with time-to-treatment discontinuation being dependent on PFS. PFS for both treatments has changed with the use of the FP approach. Further clarification on this should be provided by the company, e.g. by showing PFS curves with and without the use of the FP approach for all treatments.

Other company model changes

Effectiveness fulvestrant

In line with the previous EAG base-case and the DG, the company used the log-logistic distribution for modelling PFS in the fulvestrant arm. This issue is resolved.

Relative effects

As detailed above, the company's new FP approach with its preferred specification was deemed appropriate by the EAG, but the EAG noted that cost-effectiveness results were sensitive to the model specification for PFS. The EAG thus explored using the first-order FP (p= -2) model in a scenario.

Severity

The EAG reproduced the company's QALY shortfall analysis and agrees that the severity weighting of 1.2 is appropriate.

EAG analyses in light of the company response to the draft guidance

The EAG made the following changes to the company's model to produce the new EAG base-case (Table 2).

1. Use of median RDI for alpelisib (82.7%).
2. Use of 3-year treatment effect waning

The EAG explored the following scenarios (Table 3).

1. Use progressed disease utility value of 0.6.
2. Use double the company's testing costs
3. Derive TTD by applying a hazard ratio of 1.3 to PFS for comparators
4. Use first-order FP model (p= -2) for PFS

Note, however, that, as explained in Comment 3, the FP model used for PFS in the company base case was the second order p1 = -2, p2 = -2, which is not the FP model preferred by the EAG i.e. second order p1 = -2, p2 = -1. The economic model supplied to the EAG does not permit the FP model preferred by the EAG, and therefore the EAG base-case retains this limitation. This means that the effect of the second order p1 = -2, p2 = -1 FP model on the ICER is unknown.

Table 2: EAG base-case responding to DG response

Technology	Total Costs (£)	Total LYs	Total QALYs (excl sev mod)	Incremental Costs (£) - Capi vs.	Incremental LYs - Capi vs.	Incremental QALYs (excl. sev mod) - Capi vs.	Pairwise ICER (incl. sev mod)	Fully incremental ICER (incl. sev mod)	iNHB (£20,000 WTP)	iNHB (£30,000 WTP)
Company's DG response base-case										
Capivasertib plus fulvestrant	[redacted]	3.010	2.217	-	-	-	-	[redacted]	-	-
Alpelisib plus fulvestrant	£46,448	2.444	1.803	[redacted]	0.566	0.414	[redacted]	[redacted]	0.96	0.81
Everolimus with exemestane	£25,236	1.661	1.235	[redacted]	1.350	0.981	[redacted]	-	0.58	0.78
Use of median RDI for alpelisib										
Capivasertib plus fulvestrant	[redacted]	3.010	2.217	-	-	-	-	[redacted]	-	-
Alpelisib plus fulvestrant	£45,453	2.444	1.803	[redacted]	0.566	0.414	[redacted]	[redacted]	0.91	0.77
Everolimus with exemestane	£25,236	1.661	1.235	[redacted]	1.350	0.981	[redacted]	-	0.58	0.78
Treatment effect waning at 3 years										
Capivasertib plus fulvestrant	[redacted]	2.809	2.073	-	-	-	-	[redacted]	-	-
Alpelisib plus fulvestrant	£46,417	2.437	1.798	[redacted]	0.373	0.275	[redacted]	[redacted]	0.83	0.66
Everolimus with exemestane	£25,132	1.636	1.218	[redacted]	1.173	0.855	[redacted]	-	0.46	0.65
EAG DG response base-case										
Capivasertib plus fulvestrant	[redacted]	2.809	2.073	-	-	-	-	[redacted]	-	-
Alpelisib plus fulvestrant	£45,423	2.437	1.798	[redacted]	0.373	0.275	[redacted]	[redacted]	0.78	0.63

Everolimus with exemestane	£25,132	1.636	1.218	[redacted]	1.173	0.855	[redacted]	-	0.46	0.65
EAG DG response base-case (probabilistic)*										
Capivasertib plus fulvestrant	[redacted]	2.809	2.653	[redacted]	0	0	-	[redacted]		
Alpelisib plus fulvestrant	£45,914	2.437	2.321	[redacted]	0.373	0.332	[redacted]	[redacted]	0.73	0.60
Everolimus with exemestane	£24,827	1.636	1.416	[redacted]	1.173	1.237	[redacted]	-	0.58	0.80
* Fully incremental analyses including the severity modifier are calculated in the model PSA individually for each iteration, rather than applying the severity modifier to aggregated results. Thus, QALYs include the severity modifier.										

Table 3: EAG scenarios

Technology	Total Costs (£)	Total LYs	Total QALYs (excl sev mod)	Incremental Costs (£) - Capi vs.	Incremental LYs - Capi vs.	Incremental QALYs (excl. sev mod) - Capi vs.	Pairwise ICER (incl. sev mod)	Fully incremental ICER (incl. sev mod)	iNHB (£20,000 WTP)	iNHB (£30,000 WTP)
EAG DG response base-case										
Capivasertib plus fulvestrant	[redacted]	2.809	2.073	-	-	-	-	[redacted]	-	-
Alpelisib plus fulvestrant	£45,423	2.437	1.798	[redacted]	0.373	0.275	[redacted]	[redacted]	0.78	0.63
Everolimus with exemestane	£25,132	1.636	1.218	[redacted]	1.173	0.855	[redacted]	-	0.46	0.65
Scenario 1. Use progressed disease utility value of 0.6										
Capivasertib plus fulvestrant	[redacted]	2.809	1.786	-	-	-	-	[redacted]	-	-
Alpelisib plus fulvestrant	£45,423	2.437	1.546	[redacted]	0.373	0.240	[redacted]	[redacted]	0.73	0.59

Everolimus with exemestane	£25,132	1.636	1.081	[redacted]	1.173	0.705	[redacted]	-	0.28	0.47
Scenario 2. Use double test costs										
Capivasertib plus fulvestrant	[redacted]	2.809	2.073	-	-	-	-	[redacted]	-	-
Alpelisib plus fulvestrant	£45,423	2.437	1.798	[redacted]	0.373	0.275	[redacted]	[redacted]	0.76	0.62
Everolimus with exemestane	£25,132	1.636	1.218	[redacted]	1.173	0.855	[redacted]	-	0.44	0.64
Scenario 3. Derive TTD by applying a hazard ratio of 1.3 to PFS for comparators										
Capivasertib plus fulvestrant	[redacted]	2.809	2.073	-	-	-	-	[redacted]	-	-
Alpelisib plus fulvestrant	£43,063	2.437	1.798	[redacted]	0.373	0.275	[redacted]	[redacted]	0.66	0.55
Everolimus with exemestane	£24,212	1.636	1.218	[redacted]	1.173	0.855	[redacted]	-	0.41	0.62
Scenario 4. First-order FP model for PFS										
Capivasertib plus fulvestrant	[redacted]	2.812	2.079	-	-	-	-	[redacted]	-	-
Alpelisib plus fulvestrant	£46,391	2.437	1.799	[redacted]	0.375	0.280	[redacted]	[redacted]	0.70	0.58
Everolimus with exemestane	£24,622	1.636	1.215	[redacted]	1.176	0.863	[redacted]	-	0.32	0.56

[1] Yang H, Grimm S, Witlox W, Joore M, Sugden B, Patel M, et al. *Capivasertib in combination with fulvestrant for second-line treatment in unresectable or metastatic HR-positive, HER2-negative breast cancer [ID6370]: a Single Technology Assessment*. York: Kleijnen Systematic Reviews Ltd., 2024. 124p.

[2] AstraZeneca UK Ltd. *Capivasertib in combination with fulvestrant for second-line treatment in unresectable or metastatic HR-positive, HER2-negative breast cancer [ID 6370]: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA): Cost-effectiveness model v0.4 2 Feb 2025 [Excel spreadsheet provided by Company]*: AstraZeneca UK Ltd., 2025

[3] AstraZeneca UK Ltd. *Capivasertib in combination with fulvestrant for second-line treatment in unresectable or metastatic HR-positive, HER2-negative breast cancer [ID 6370]: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA): Adjustments made to the company base-case economic model 2 Feb 2025 [Word document provided by Company]*: AstraZeneca UK Ltd., 2025

Adjustments made to the company base-case economic model | draft ACD response

Please find below an overview of the adjustments that were made to the original August 30th, 2024, pre-ACM1 economic model. Table 1 presents the pairwise ICERs versus alpelisib with fulvestrant and Table 2 versus everolimus with exemestane. Both tables include the 1.2 severity weighting, and each ICER includes the impact from the previous adjustment(s) (iterative).

Table 1: Adjustments made to the economic model (August 30th, 2024) for the new company base-case and impact on the pairwise ICER vs. alpelisib + fulvestrant

Scenario	Description adjustment	Justification adjustment	Model implementation adjustment	Incr. costs (£)	Incr. QALYs	ICER (£) Incl. x1.2 weighting
ACM1 company base-case	-	-	-	[redacted]	0.61	[redacted]
1.1 - adjustment A*	Log-normal → log-logistic model for PFS	Aligned with committee preference	'SurvivalM' sheet, H31. Please note that in the submitted model, this adjustment can be toggled in the 'ACD response' sheet in cell E9.	[redacted]	0.64	[redacted]
1.2 - adjustment B*	No time-varying HR approach → FP-NMA to model treatment effect	Aligned with committee preference for fractional polynomials	'Model' sheet, columns BR:BW, DX:EF, GH:GP, using the inputs from the FP PFS and FP OS sheets. Please note that in the submitted model, this adjustment can be toggled in the 'ACD response' sheet in cell E10.	[redacted]	0.41	[redacted]
1.3 - adjustment C*	No treatment waning → 5-year treatment waning	Aligned with committee preference for incorporation of	'Model' sheet, columns BT:BU, DZ:EA, GJ:GK. Please note that in the submitted model, this adjustment automatically activates when the FP approach has been	[redacted]	0.41	[redacted]

		treatment waning	selected. Other options for the treatment waning time point can be selected by toggling cell E11 in the 'ACD response' sheet.			
1.4 - adjustment D*	RDI for alpelisib at 100% → RDI for alpelisib equivalent to capivasertib (82.6%)	Aligned with committee preference	'Costs_Tx' sheet, cell AF19. Please note that in the submitted model, this adjustment can be toggled in the 'ACD response' sheet in cell E13.	[redacted]	0.41	[redacted]
1.5 - adjustment E*	No testing costs included → additional reporting costs for AKT1 and PTEN	Aligned with committee preference for incorporation of testing costs	'Settings' sheet, cell U22. Please note that in the submitted model, this adjustment can be toggled in the 'ACD response' sheet in cell E13.	[redacted]	0.41	[redacted]
Revised company base-case			ACM COMPANY BASE-CASE + adjustments 1.1-1.5	[redacted]	0.41	[redacted]

Abbreviations: ACD: appraisal consultation document; ACM: appraisal committee meeting; FP: fractional polynomials; ICER: incremental cost-effectiveness ratio; OS: overall survival; PFS: progression-free survival; QALY: quality-adjusted life year; RDI: relative dose intensity

Table 2: Adjustments made to the economic model (August 30th, 2024) for the new company base-case and impact on the pairwise ICER vs. everolimus + exemestane

Scenario	Description adjustment	Justification adjustment	Model implementation adjustment	Incr. costs (£)	Incr. QALYs	ICER (£) Incl. x1.2 weighting
ACM1 company base-case	-	-	-	[redacted]	0.94	[redacted]
1.1 - adjustment A*	Log-normal → log-logistic model for PFS	Aligned with committee preference	'SurvivalM' sheet, H31. Please note that in the submitted model, this adjustment can be toggled in the 'ACD response' sheet in cell E9.	[redacted]	0.96	[redacted]
1.2 - adjustment B*	No time-varying HR approach → FP-NMA to model treatment effect	Aligned with committee preference for fractional polynomials	'Model' sheet, columns BR:BW, DX:EF, GH:GP, using the inputs from the FP PFS and FP OS sheets. Please note that in the submitted model, this adjustment can be toggled in the 'ACD response' sheet in cell E10.	[redacted]	0.98	[redacted]
1.3 - adjustment C*	No treatment waning → 5-year treatment waning	Aligned with committee preference for incorporation of treatment waning	'Model' sheet, columns BT:BU, DZ:EA, GJ:GK. Please note that in the submitted model, this adjustment automatically activates when the FP approach has been selected. Other options for the treatment waning time point can be selected by	[redacted]	0.98	[redacted]

			toggling cell E11 in the 'ACD response' sheet.			
1.4 - adjustment D*	RDI for alpelisib at 100% → RDI for alpelisib equivalent to capivasertib (82.6%)	Aligned with committee preference	'Costs_Tx' sheet, cell AF19. Please note that in the submitted model, this adjustment can be toggled in the 'ACD response' sheet in cell E13.	N/A	N/A	N/A
1.5 - adjustment E*	No testing costs included → additional reporting costs for AKT1 and PTEN	Aligned with committee preference for incorporation of testing costs	'Settings' sheet, cell U22. Please note that in the submitted model, this adjustment can be toggled in the 'ACD response' sheet in cell E13.	[redacted]	0.98	[redacted]
Revised company base-case			ACM COMPANY BASE-CASE + adjustments 1.1-1.5	[redacted]	0.98	[redacted]

Abbreviations: ACD: appraisal consultation document; ACM: appraisal committee meeting; FP: fractional polynomials; ICER: incremental cost-effectiveness ratio; OS: overall survival; PFS: progression-free survival; QALY: quality-adjusted life year; RDI: relative dose intensity