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

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from** AstraZeneca
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Make 2nds Count, Patient organisation submission
   b. Breast Cancer Now, Patient organisation submission
   c. METUPUK, Patient organisation submission

4. **Expert personal statements from:**
   a. Prof. Nicholas Turner, nominated by AZ, Clinical expert
   b. Dr Katie Spencer nominated by METUPUK, Patient expert
   c. Dr Charlotte Moss nominated by Breast Cancer Now, Clinical expert
   d. Eleanor Pearce Willis nominated by Breast Cancer Now, Patient expert

5. **External Assessment Report** prepared by Kleijnen Systematic Reviews (KSR) Ltd.

6. **External Assessment Report – factual accuracy check**

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

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

[ID 6370]

Document B

Company evidence submission

July 2024

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Contents

Tables and figures

Abbreviations

ADP	Adenosine diphosphate
AE	Adverse event
AFT	Accelerated failure time
AI	Aromatase inhibitor
AIC	Akaike information criterion
AJCC	American Joint Committee on Cancer
AKT	Serine/threonine kinase AKT (aka Protein kinase B)
AKT1	Isoform 1 of AKT
AQS	Absolute QALY shortfall
ATP	Adenosine triphosphate
BC	Breast cancer
BIC	Bayesian information criterion
BICR	Blinded independent central review
BNF	British National Formulary
CDF	Cancer Drugs Fund
CDK4/6	Cyclin-dependent kinase 4 and 6
CI	Confidence interval
CL	Consultant led
CPI	Consumer price inflation
CrI	Credible interval
CR	Complete response
CRD	Centre for Reviews and Dissemination
CSR	Clinical study report
ChT	Chemotherapy
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
DCO	Data cut off
DIC	Deviance information criterion
E+E	Everolimus plus exemestane
EAG	Evidence assessment group
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EEPRU	Policy Research Unit in Economic Evaluation of Health and Care Interventions
EMA	European Medicines Agency
eMIT	Drugs and pharmaceutical electronic market information tool
EORTC - QLQ - C30	European Organisation for Research and Treatment of Cancer - Quality of Life Questionnaire (30 item)
EORTC - QLQ - BR23	European Organisation for Research and Treatment of Cancer - Quality of Life Questionnaire for Breast Cancer (23 item)
EQ-5D-3L / 5L	Euroqol-5 dimension- 3 level / 5 level
ER	Oestrogen receptor
ERG	Evidence review group

ESMO	European Society for Medical Oncology
ET	Endocrine therapy
FAS	Full analysis set
FDA	(US) Food & Drug Administration
FFPE	Formalin-fixed paraffin-embedded
GP	General practitioner
HCRU	Health care resource use
HER2	Human epidermal growth factor receptor 2
HR	Hormone receptor / Hazard ratio
HRG	Healthcare resource group
HS	Health state
HSU / HSUV	Health state utility / Health state utility value
HTA	Health technology assessment
ICER	Incremental cost effectiveness ratio
IHC	Immunohistochemistry
IQR	Interquartile range
ISH	In situ hybridisation
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
IWRS	Interactive web response system
KM	Kaplan-Meier
LHRH	Luteinizing hormone-releasing hormone
LY	Life year
LYG	Life year gained
mg	milligram
MHRA	Medicines and Healthcare product Regulatory Agency
ml	millilitre
MMRM	Mixed effects repeated measures
MRI	Magnetic resonance imaging
MS	Manufacturer submission
mTOR	Mammalian target of rapamycin
NCCN	National comprehensive cancer network
NGS	Next generation sequencing
NHB	Net health benefit
NHS	National health service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
ONS	Office for National Statistics
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PARP	Poly (ADP-ribose) polymerase

PASLU	Patient Access Scheme Liaison Unit
PD	Progressed disease
PF	Progression free
PFS	Progression-free survival
PH	Proportional hazards
PI3K	Phosphatidylinositol-3-kinase
PIK3CA	Catalytic alpha -subunit of PI3K
PQS	Proportional QALY shortfall
PR	Partial response
PSA	Probabilistic sensitivity analysis
PSS	Personal and social services
PSSRU	Personal Social Services Research Unit
PTEN	Phosphatase and Tensin Homolog
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response evaluation criteria in solid tumours
REML	Restricted maximum likelihood
SAE	Serious adverse event
SAS	Safety analysis set
SD	Standard deviation
SE	Standard error
SERD	Selective oestrogen receptor degrader
SLR	Systematic literature review
SmPC	Summary of product characteristics
TA	Technology appraisal
TFSC	Time to first subsequent chemotherapy or death
TSD	Technical support document
TTD	Time to discontinuation
tx	Treatment
UK	United Kingdom
US	United States
UTI	Urinary tract infection
VAS	Visual analogue scale
WHO	World Health Organisation

B.1. Decision problem, description of the technology and clinical care pathway

Disease overview

- Breast cancer is the most common cancer in the UK. Over 99% of cases occur in women; around 56,400 women and 390 men are diagnosed with breast cancer in the UK each year.[1,2]
- Advanced breast cancer is incurable breast cancer that has grown directly into nearby tissues and cannot be completely removed by surgery (locally advanced, stage III), or has spread to other parts of the body such as the bones, liver, and lungs (metastatic disease, stage IV):[1,2]
    - Five-year survival rates are >70% in people with locally advanced, stage III disease, but reduce to 25% in those with metastatic, stage IV disease.
    - Early diagnosis and rapid access to targeted effective and tolerable therapies that can prevent or delay disease progression is therefore essential.
- HR+/HER2- advanced breast cancer describes advanced breast cancer that is stimulated by endocrine hormones (primarily oestrogen) but is not responsive to HER2-directed therapy. This is the most common type, occurring in ~70% of all advanced breast cancer cases.[3,4]
    - HR+ cancer is treated with endocrine therapy to block the stimulatory effects of oestrogen, but development of resistance to endocrine therapy is inevitable over time for many patients.[5]
- Around 40-50% of people with HR+/HER2- advanced breast cancer have PI3K/AKT-pathway altered tumours, meaning they have specific genomic alterations (PIK3CA, AKT1, or PTEN) in their tumour cells that promote cancer growth and cancer cell survival and can lead to resistance to endocrine therapy used in HR+/HER2- advanced breast cancer.[6–9]
- People with PI3K/AKT-pathway altered tumours experience more rapid disease progression and poorer outcomes.[10–13]

Current treatment pathway based on NICE guidance and ESMO clinical guidelines

- The aims of therapy in advanced, metastatic breast cancer are to relieve symptoms, prolong survival and maintain a good quality of life with minimal adverse events.[14]
- Initial therapy for people with HR+/HER2- advanced breast cancer is with a CDK4/6 inhibitor plus aromatase inhibitor (AI) endocrine therapy, per ESMO guidelines[15] and NICE TA495, TA496, TA563.[16–18]
- Following disease progression, treatment options are everolimus plus exemestane (TA421) [19] or, in people with breast cancer with a confirmed PIK3CA mutation, alpelisib plus fulvestrant (TA816).[20]
- Due to significant toxicity, chemotherapy is reserved for use in people with imminently life-threatening or significantly symptomatic organ involvement, or when people experience disease progression after two or more lines of endocrine therapy.[15]
    - Clinicians and patients have a strong desire to delay use of chemotherapy for as long as possible due to its toxicity and significant impact on QoL.[16,17,20–23]

Unmet needs

- Treatment options for patients with HR+/HER2- advanced breast cancer and PI3K/AKT-pathway alterations (PIK3CA/AKT1/PTEN) are very limited following disease progression on initial CDK4/6 inhibitor plus endocrine therapy.

- Alpelisib plus fulvestrant is limited only to people with PIK3CA-mutated tumours;[20] there are no current targeted therapies for AKT1 or PTEN-altered tumours.
- Everolimus plus exemestane is an mTOR inhibitor which is non-specific to PI3K/AKT pathway-altered tumours.
- Adverse event profiles of these therapies are seen as better than with chemotherapy due to their targeted mechanism of action; however, both regimens are still associated with considerable toxicities that are considered by clinicians to be challenging.[20]

- Initial CDK4/6 inhibitor plus endocrine therapy (either fulvestrant or AI) can lead to endocrine therapy resistance.[24–26] As activation of the PI3K/AKT pathway is heightened in HR+/HER2- breast cancer, inhibition of this signalling pathway may help overcome resistance to ET.
- There is a significant unmet need for an effective and tolerable targeted treatment option for patients with PI3K/AKT pathway alterations that has a differentiated mode of action, enhances sensitivity to endocrine therapy following failure of CDK4/6 inhibitor therapy, and enables patients with PI3K/AKT pathway alterations to remain on endocrine-based treatments for longer before progression to cytotoxic chemotherapy.

Proposed positioning of capivasertib plus fulvestrant

- Capivasertib (TRUQAP®) is the first AKT inhibitor to be licensed for the treatment of breast cancer. It was granted an Innovation Passport by the UK MHRA in February 2024.[27]
- Capivasertib plus fulvestrant simultaneously targets the PI3K/AKT and endocrine receptor signalling pathways, leading to a synergistic antitumour effect[28] that may also preserve endocrine therapy sensitivity.
- On this basis, and the significant improvements in progression-free survival (PFS) demonstrated robustly in its pivotal trial CAPItello-291[6] (see section B.2), capivasertib plus fulvestrant offers a true step change in therapy for patients with HR+/HER2- advanced breast cancer with PI3K/AKT pathway alterations (PIK3CA/AKT1/PTEN-altered tumours) and should be considered by NICE as an innovative therapy.
- The proposed positioning of capivasertib plus fulvestrant is for use in the treatment of advanced, HR+/HER2- breast cancer in patients with PI3K/AKT pathway-altered (PIK3CA, AKT1, or PTEN-altered) tumours whose disease has progressed following CDK4/6 inhibitor therapy plus endocrine therapy.
    - This positioning is aligned with clinician-anticipated use of capivasertib plus fulvestrant in UK clinical practice and addresses an area of significant unmet need.

B.1.1. Decision problem

Capivasertib (TRUQAP®) is indicated in combination with fulvestrant for the treatment of adult patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative (defined as IHC 0 or 1+, or IHC 2+/ISH-) locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following recurrence or progression on or after an endocrine based regimen.[28] This submission presents compelling evidence of the clinical and cost effectiveness of capivasertib plus fulvestrant in the subgroup of patients meeting its licensed indication whose disease has progressed on or following cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitor therapy. This positioning reflects the anticipated use of capivasertib plus fulvestrant within the current UK treatment pathway and

addresses an area of significant unmet need. The alignment of the decision problem addressed in this submission with the NICE scope for this appraisal is summarised in Table 1.

Table 1. The decision problem

	Final scope issued by NICE[14]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer after endocrine treatment	Adults with HR+/HER2- advanced and metastatic breast cancer with PI3K/AKT pathway-altered tumours (PIK3CA, AKT1, or PTEN), whose disease has progressed on or following CDK4/6 inhibitor plus endocrine therapy	Capivasertib is indicated in combination with fulvestrant for the treatment of adult patients with HR+/HER2- (defined as IHC 0 or 1+, or IHC 2+/ISH-) locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN alterations following recurrence or progression on or after an endocrine based regimen.[28] This submission focuses on the subgroup of patients meeting the licensed indication and who have received prior CDK4/6 inhibitor therapy + AI as part of their initial endocrine based regimen. This positioning for use after CDK4/6 inhibitor therapy reflects the anticipated use of capivasertib plus fulvestrant within the current UK treatment pathway and addresses an area of significant unmet need.
Intervention	Capivasertib with fulvestrant	Capivasertib with fulvestrant	N/A
Comparator(s)	• CDK4/6 inhibitors in combination with fulvestrant • Everolimus and exemestane • Exemestane • Tamoxifen • Fulvestrant • Alpelisib plus fulvestrant (PIK3CA-mutated breast cancer)	• Everolimus and exemestane For people whose breast cancer is PIK3CA-mutated: • Alpelisib plus fulvestrant	The proposed positioning of capivasertib plus fulvestrant is for use following CDK4/6 inhibitor plus endocrine therapy. UK clinical expert opinion confirms that:[29] • Retreatment with CDK4/6 inhibitors is not routinely an option, per ESMO and NCCN guidelines,[15,30] and is not reimbursed by the NHS.[31] CDK4/6 inhibitors in combination with fulvestrant are therefore not relevant comparators.

	Final scope issued by NICE[14]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			• Exemestane without everolimus, tamoxifen, and fulvestrant may be included in NICE CG81 as first-line therapy options in HR+ advanced breast cancer[32] but endocrine therapy alone has been superseded by CDK4/6 inhibitor plus AI combination therapy in all but the small proportion of patients who have comorbidities or poor performance status that precludes use of CDK4/6 inhibitors.[15] In the proposed positioning of capivasertib (post CDK4/6 inhibitor therapy), single agent endocrine therapy with exemestane, tamoxifen or fulvestrant is not a treatment option. • In clinical practice, capivasertib plus fulvestrant would be used where everolimus plus exemestane or alpelisib plus fulvestrant would be used. The only relevant comparators for capivasertib plus fulvestrant in the proposed positioning are therefore: • Everolimus plus exemestane • Alpelisib plus fulvestrant in patients with breast cancer containing PIK3CA mutations. As the majority of patients with PI3K/AKT pathway-altered tumours have PIK3CA mutations (>75% of patients with PI3K/AKT pathway-altered tumours have PIK3CA mutations in the CAPItello-291 trial[6]), alpelisib plus fulvestrant is the comparator that is most

	Final scope issued by NICE[14]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			likely to be displaced by capivasertib plus fulvestrant.
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life.	• overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life.	-
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account. The economic modelling should include the costs associated with PIK3CA/AKT1/PTEN mutations in people with hormone receptor-positive HER2-negative locally advanced or metastatic breast cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 4.8 of the guidance development manual (available here: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation).	The economic model conforms to the NICE reference case.	The NICE guidance development manual, section 4.8, states: "If a diagnostic test to identify patients or establish the presence or absence of a particular biomarker is not routinely used in the NHS but is introduced to support the treatment decision for the specific technology, include the associated costs of the diagnostic in the assessments of clinical and cost effectiveness. Provide a sensitivity analysis without the cost of the diagnostic test".[33] PI3K/AKT pathway alterations (PIK3CA/AKT1/PTEN) occur in around 40-50% of patients with HR+/HER2- advanced breast cancer.[6] Of these, PIK3CA mutations account for >75%.[6] PIK3CA testing is included in the National Genomic Test Directory for Cancer[34] and is in routine use following the approval of alpelisib plus fulvestrant in NICE TA816.[20] The costs of genomic testing for PIK3CA/AKT1/PTEN-altered tumours are excluded on the basis that testing for PIK3CA alterations (the most common of all PI3K/AKT pathway alterations) is routinely performed in UK clinical practice following the NICE recommendation for alpelisib plus fulvestrant [TA816] in 2022. Furthermore, [redacted]

	Final scope issued by NICE[14]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			[redacted]
Subgroups to be considered	If the evidence allows the following subgroups should be considered: • PIK3CA/AKT1/PTEN-altered subgroup	The licensed indication is for use in patients with PI3K/AKT pathway-altered (PIK3CA, AKT1, or PTEN) tumours.[28] As the proposed positioning of capivasertib plus fulvestrant is for use following a CDK4/6 inhibitor plus endocrine therapy, analyses are provided for this subgroup where data allow.	
Special considerations including issues related to equity or equality	-	• Capivasertib is an innovative therapy. It is the first licensed inhibitor of all three AKT isoforms in breast cancer and provides significant benefit to patients with advanced and metastatic disease who have limited therapy options. It was licensed following priority review by the FDA in the US in November 2023,[35,36] and was granted an Innovation Passport by the UK MHRA in February 2024.[27] • Capivasertib in combination with fulvestrant is licensed for use in breast cancer in women and men.[28] Breast cancer is rare in men and, consequently, data for capivasertib plus fulvestrant in men with breast cancer are limited. This should not preclude or limit the use of capivasertib plus fulvestrant in men in line with its licensed indication and proposed clinical positioning.	

Abbreviations: AKT, serine/threonine kinase; CDK4/6, cyclin-dependent kinases 4 and 6;ESMO, European Society for Medical Oncology; FDA, US Food and Drug Administration; HR+/HER2-, hormone receptor-positive, human epidermal growth factor receptor 2-negative; MHRA, UK Medicines and Healthcare products Regulatory Agency; NCCN, National Comprehensive Cancer Network; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN, phosphatase and tensin homolog.

B.1.2. Description of the technology being evaluated

Capivasertib (TRUQAP®) is a first-in-class protein kinase B (AKT) inhibitor therapy for the treatment of metastatic breast cancer. It is licensed in the UK in combination with fulvestrant for the treatment of adult patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative (defined as IHC 0 or 1+, or IHC 2+/ISH-) locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following recurrence or progression on or after an endocrine based regimen.[28] Capivasertib plus fulvestrant was licensed following priority review by the FDA in the US in November 2023,[35,36] and was granted an Innovation Passport by the UK MHRA, February 2024.[27] It was licensed on 17th July 2024 by the UK MHRA under Project Orbis.

Capivasertib is a potent, oral adenosine triphosphate (ATP)-competitive inhibitor of all three AKT isoforms (AKT1/2/3). AKT is a pivotal node in the phosphatidylinositol 3-kinase (PI3K) signalling cascade regulating multiple cellular processes, including cellular survival, proliferation, cell cycle, metabolism, gene transcription and cell migration. Activation of AKT promotes breast cancer tumour survival and proliferation. AKT activation in breast cancer and other tumours occurs due to upstream activation from other signalling pathways, mutations of AKT, loss of Phosphatase and Tensin Homolog (PTEN) function and mutations in the catalytic subunit of phosphatidylinositol 3-kinase ([PI3K], PIK3CA). By inhibiting AKT activation, capivasertib reduces the growth of PIK3CA, AKT1, or PTEN-altered tumours.[28]

HR+ breast cancer tumours are stimulated by endocrine hormones, including oestrogen. Endocrine therapy with fulvestrant, as an ER antagonist that blocks and downregulates ER, results in inhibition of ER signalling in HR+ tumours.[37] There is significant crosstalk between the ER signalling pathway targeted by fulvestrant and the PI3K/AKT signalling pathway targeted by capivasertib.[24,25] The PI3K/AKT pathway may be upregulated following exposure to ER antagonists, leading to endocrine therapy resistance, and the therapeutic benefit of inhibiting PI3K/AKT signalling may be limited by ER signalling. By simultaneously targeting the PI3K/AKT and ER signalling pathways, capivasertib plus fulvestrant may exert a synergistic antitumour effect that may also preserve endocrine therapy sensitivity. On this basis, and the significant improvements in progression-free survival (PFS) demonstrated in its pivotal trial (see section B.2), for patients with PI3K/AKT pathway-altered tumours, capivasertib plus fulvestrant offers a true step change in therapy and should be considered by NICE as an innovative therapy.

The UK Summary of Product characteristics is provided in Appendix C. A summary of capivasertib is provided in Table 2.

Table 2. Technology being evaluated

UK approved name and brand name	Capivasertib (TRUQAP®)
Mechanism of action	Capivasertib is a potent, selective inhibitor of the kinase activity of all 3 isoforms of serine/threonine kinase AKT (AKT1, AKT2 and AKT3). By inhibiting AKT, capivasertib reduces the growth of PI3K/AKT pathway-altered (PIK3CA, AKT1, or PTEN) tumours.[28] Fulvestrant is an endocrine therapy that blocks oestrogen receptor signalling in HR+ tumours.[37] Capivasertib plus fulvestrant exerts a synergistic antitumour effect and may reduce development of endocrine therapy resistance.
Marketing authorisation	A UK marketing authorisation was granted 17th July 2024.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Capivasertib (TRUQAP®) is indicated in combination with fulvestrant for the treatment of adult patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative (defined as IHC 0 or 1+, or IHC 2+/ISH) locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following recurrence or progression on or after an endocrine based regimen.[28]
Method of administration and dosage	Capivasertib is administered orally as tablets in strengths of 160mg or 200mg. The recommended dose in combination with fulvestrant is 400 mg (two 200 mg tablets) taken orally twice daily approximately 12 hours apart (total daily dose of 800 mg) with or without food, for 4 days followed by 3 days off treatment. The recommended dose of fulvestrant is 500 mg administered on Days 1, 15, and 29, and once monthly thereafter. In pre/perimenopausal women, capivasertib plus fulvestrant should be combined with a LHRH agonist.[28]
Additional tests or investigations	Testing for HR+/HER2- status is routinely undertaken in practice. Genomic testing is required to identify patients with PIK3CA/AKT1/PTEN-alterations; however, PIK3CA testing is already included in the National Genomic Test Directory for Cancer[34] and is in routine use following the approval of alpelisib plus fulvestrant in NICE TA816.[20] The same sample and assay that is currently being used for PIK3CA testing can be used for AKT1 and PTEN testing, and so no additional testing is required beyond that which is conducted routinely. AstraZeneca anticipate inclusion of the AKT1 and PTEN reporting with the same PIK3CA assay prior to the reimbursement decision for capivasertib with fulvestrant. Therefore, no additional genomic testing beyond that which is already undertaken in practice is required.
List price and average cost of a course of treatment	The list price of capivasertib is £[redacted] (excluding VAT) per pack (64 x 200mg tablets). Based on the drugs and pharmaceutical electronic market information tool, fulvestrant costs £55.32 for 2 x 250 mg / 5 ml solution for injection. This makes the monthly cost of treatment with capivasertib plus fulvestrant £[redacted] in the first month and £[redacted] in the subsequent months on treatment. These costs are not adjusted for relative dose intensity. Given the median treatment duration in the CAPItello-291 trial for patients with PI3K/AKT-pathway alterations for the capivasertib and fulvestrant elements was [redacted] months and [redacted] months, respectively, the average

	cost of a course of treatment with capivasertib plus fulvestrant is [redacted] (excluding VAT).
Patient access scheme (if applicable)	[redacted]
Abbreviations: AKT, serine/threonine kinase AKT; HR+/HER2-, hormone receptor-positive, human epidermal growth factor receptor 2-negative; LHRH, luteinizing hormone releasing hormone; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PIK3, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homolog.	

B.1.3. Health condition and position of the technology in the treatment pathway

B.1.3.1. Disease overview

Breast cancer is a malignant disease that forms in tissues of the breast, most commonly the ducts or lobules.[38] It is the most common cancer in the UK, with an estimated 600,000 prevalent diagnosed cases.[1,2] Over 99% of cases occur in women; around 56,400 women and 390 men are diagnosed with breast cancer each year. Most cases (80%) occur in people over 50 years of age.[1,2]

Every year around 11,500 women and 85 men die from breast cancer in the UK.[1] The prognosis for individuals with breast cancer is determined by several factors, including the stage of cancer, the type of cancer and whether there are specific receptors on the cancer cells and/or genetic mutations in cancer cells, previous treatments received, as well as general health and fitness.[2]

The stage of cancer indicates the size and how far the tumour has spread. Early-stage disease (stages I and II) indicates the cancer has little or no spread (limited to nearby lymph nodes), is amenable to surgery and can often be considered effectively cured. Five-year survival rate in early-stage breast cancer is 90-100%.[1,2] This submission relates to advanced breast cancer, in which it has grown directly into nearby tissues and cannot be completely removed by surgery (locally advanced, stage III), or has spread to other parts of the body such as the bones, liver, and lungs (metastatic disease, stage IV). Approximately 30% of women diagnosed with early-stage breast cancer will progress to metastatic disease at some point.[39] Around 15% of people with breast cancer have advanced stage disease at diagnosis, and in around 5% of cases the cancer has already spread by the time it is diagnosed.[1,2] Five-year survival rates are greater than 70% in people with locally advanced, stage III disease, but

reduce to around 25% in those with metastatic, stage IV disease.[1,2] Early diagnosis and rapid access to targeted effective and tolerable therapies that can prevent or delay disease progression is therefore essential.

In addition to the stage of the disease, prognosis can be influenced by the presence or absence of specific receptors on tumour cells, which influence tumour development, proliferation and survival, and response to treatment.[3,4] Some people have breast cancer tumours that are stimulated by endocrine hormones (oestrogen and/or progesterone). This is referred to as hormone receptor-positive (HR+) disease. In these people, endocrine therapy can be used to block the stimulatory effects of hormones and so reduce the risks of disease progression. However, over time, resistance to endocrine therapy often develops.[5] Another type of receptor is human epidermal growth factor receptor 2 (HER2) and therapies have been developed specifically to target HER2-positive disease. Based on the presence or absence of these two receptor types, it is possible to define breast cancer as being: HR+/HER2−, HR+/HER2+, HR−/HER2+ and HR−/HER2−. This submission relates to people with HR+/HER2− breast cancer, which is the most common subtype, occurring in ~70% of all advanced breast cancer cases.[3,4]

A further factor that can influence prognosis and response to initial or subsequent treatment is the presence or development of genetic mutations that can alter signalling pathways within tumour cells. Many signalling pathway genetic alterations have been identified, and genomic testing of tumours is increasingly used to identify these and guide targeted treatment.[34] Given the licensed indication for capivasertib,[28] this submission relates to people with PI3K/AKT pathway-altered tumours with alterations in the PIK3CA, AKT1, or PTEN gene. PI3K/AKT is a pivotal node in the PI3K signalling cascade regulating multiple cellular processes, including cellular survival, proliferation, cell cycle, metabolism, gene transcription and cell migration. PI3K/AKT activation promotes breast cancer tumour survival and proliferation and occurs due to upstream activation from other signalling pathways, mutations of AKT, loss of PTEN function and mutations in the catalytic subunit of PI3K (PIK3CA).

Around 40-50% of people with HR+/HER2- breast cancer have PI3K/AKT pathway alterations,[6–9] of which >75% include PIK3CA alterations.[6] As noted in section B.1.2, there is significant crosstalk between the ER and PI3K/AKT signalling pathways, meaning that

PI3K/AKT signalling may be upregulated following exposure to ER antagonists, leading to endocrine therapy resistance.[24–26] Given these mechanisms, patients with PI3K/AKT pathway-altered tumours may experience more rapid disease progression and poorer outcomes than those without.[10–13] People with alterations in PIK3CA have a shorter period of time between diagnosis and metastasis compared with patients without PIK3CA mutations,[11] and these alterations are also linked to increased lung metastases.[13] Additionally, HR+/HER2− breast cancer patients with tumours containing PIK3CA and PTEN alterations have been found to have worse overall PFS and OS compared to patients without these tumour alterations.[10,12]

Given that advanced breast cancer is incurable, a diagnosis of advanced breast cancer can have a profound impact on the health-related quality of life (HRQoL) of patients, which deteriorates with disease progression.[40,41] Patients with advanced disease may also experience debilitating symptoms, such as pain, fatigue, nausea, appetite loss, anxiety and depression. A higher symptom burden is associated with reduced HRQoL, including physical, social, emotional and functional wellbeing,[42] and can impact their ability to work and carry out daily activities.[42–44] Caregivers of patients diagnosed with cancer and going through cancer treatment can also experience significant burden such as anxiety and depression, and reduced work productivity.[45]

As disease recurs and progresses, patients require sequential lines of therapy, as described in section B.1.3.2. There is a strong desire from clinicians and patients to delay cytotoxic chemotherapy for as long as possible due significant adverse effects, such as diarrhoea, vomiting, weight loss and cardiac dysfunction,[20] which also contribute to the burden of disease and further impair HRQoL. Preventing or delaying disease progression and allowing patients to stay on endocrine therapy for as long as possible with targeted tolerable and effective therapies is therefore essential to preserve HRQoL as well as to prolong survival.

B.1.3.2. Current treatment pathway and unmet needs

B.1.3.2.1. Current treatment pathway

Advanced breast cancer is generally considered to be incurable. Current treatments for advanced breast cancer therefore aim to relieve symptoms, prolong survival and maintain a good quality of life with minimal adverse events.[14] The NICE Clinical Guideline on advanced breast cancer (CG81) recommends initial treatment of HR+ breast cancer using endocrine

therapy, with chemotherapy only offered as an initial therapy in people whose disease is imminently life-threatening or requires early relief of symptoms because of significant visceral organ involvement and provided they understand and are prepared to accept the associated toxicity.[32] Similarly, European Society of Medical Oncology (ESMO) guidelines recommend chemotherapy is only offered as an initial therapy in people with imminent organ failure.[15] Endocrine therapy in NICE CG81 is stated to consist of AI therapy (either non-steroidal such as letrozole or anastrozole, or steroidal such as exemestane) in postmenopausal women, or tamoxifen in men and pre- or peri-menopausal women.[32] However, these NICE CG81 recommendations were made in 2009 and these treatments have been superseded in practice by newer therapy regimens, as described below.

Based on NICE technology appraisals TA495, TA496 and TA563, issued in 2017-2019,[16–18] and in line with current international treatment guidelines produced by ESMO[15] and the National Comprehensive Cancer Network (NCCN),[30] the recommended routine initial endocrine therapy for men and postmenopausal women with advanced HR+/HER2- breast cancer is with a CDK4/6 inhibitor (palbociclib, ribociclib or abemaciclib) in combination with AI. Pre- or peri-menopausal women are usually offered ovarian function suppression therapy to mimic a natural menopause, so they are also eligible for initial CDK4/6 inhibitor and AI therapy.[15,30] Per ESMO guidelines, endocrine therapy without CDK4/6 inhibitor therapy in the first-line setting should be reserved only for the small group of patients with comorbidities or performance status that preclude the use of CDK4/6 inhibitors.[15] As confirmed by UK clinicians,[29] the vast majority of patients (70%) therefore receive initial therapy consisting of a combination of CDK4/6 inhibitor and AI.

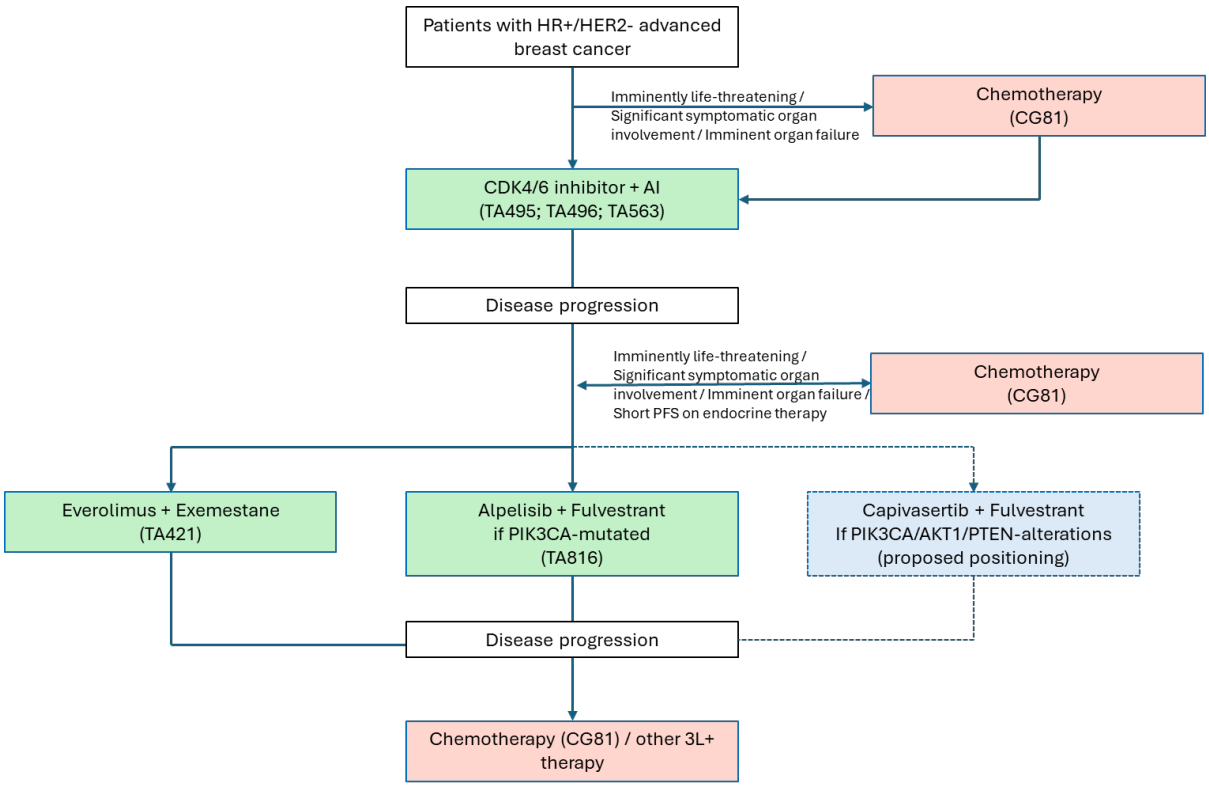
Following progression on CDK4/6 inhibitor-containing endocrine therapy, current treatment options are limited. Alpelisib plus fulvestrant is recommended in TA816 as an option for treating HR+/HER2-, PIK3CA-mutated advanced breast cancer that has progressed after CDK4/6 inhibitor plus AI,[20] with genomic testing for PIK3CA mutations now routinely available.[34] NICE technology appraisal TA421 recommends everolimus in combination with exemestane as an option in postmenopausal women with HR+/HER2- breast cancer without symptomatic visceral disease;[19] however, clinical expert opinion in NICE TA816 noted that adverse events associated with everolimus can limit its use.[20] Although the CDK4/6 inhibitors (palbociclib, ribociclib or abemaciclib) are also recommended in NICE TA836, TA687 and

TA725 for use in combination with fulvestrant following progression on initial endocrine therapy,[21–23] ESMO and NCCN guidelines,[15,30] and UK clinical expert opinion[29] indicate they would only be used for fast progressors (progression within 12 months of adjuvant endocrine therapy) and if CDK4/6 inhibitors were not previously prescribed. Furthermore, UK clinical expert opinion reported in NICE TA725 specifically notes CDK4/6 inhibitors would not be used twice in the treatment pathway due to the potential for tumours to develop resistance.[23] Retreatment with CDK4/6 inhibitors following progression on initial CDK4/6 inhibitor-containing endocrine therapy is therefore not an option clinically and is not currently reimbursed in UK clinical practice.[31]

Recent NICE technology appraisals of therapies for advanced HR+/HER2- breast cancer consistently emphasise clinician and patient desire to delay or even avoid the use of chemotherapy due to its significant toxicity profile and poor tolerability.[16,17,20–23] Furthermore, ESMO clinical guidelines recommend that at least two lines of endocrine-based therapy are preferred before moving to chemotherapy unless patients are at imminent risk of organ failure or have tumours that are endocrine resistant.[15] In patients not at imminent risk of organ failure, chemotherapy would therefore not be offered routinely in the second-line setting following failure of initial CDK4/6 inhibitor plus AI therapy.

The current routine treatment pathway for the large majority of people with HR+/HER2- advanced breast cancer in the UK, based on existing NICE guidance, ESMO and NCCN guidelines, and confirmed by clinical expert opinion sought by AstraZeneca UK Ltd[29] is summarised in Figure 1.

Figure 1. Current treatment pathway for HR+/HER2- advanced breast cancer (and expected positioning of capivasertib plus fulvestrant)



Notes: Based on current NICE guidance (specific NICE guidance in parenthesis), ESMO and NCCN guideline recommendations. Pre- and peri-menopausal women also receive ovarian function suppression therapy.
CDK4/6 inhibitor plus AI and endocrine monotherapy with exemestane, fulvestrant or tamoxifen are not relevant comparators as explained in Table 1.
White boxes reflect disease state; green boxes reflect current NICE recommended therapies at this point in the pathway; red boxes reflect chemotherapy; blue box reflects proposed positioning of capivasertib plus fulvestrant

B.1.3.2.2. Unmet needs

Advanced breast cancer is an incurable disease that exerts a heavy symptom and health-related quality of life (HRQoL) burden on patients, whilst significantly limiting life expectancy (see B.1.3.1). Patients with PI3K/AKT pathway-altered (PIK3CA/AKT1/PTEN) tumours experience more rapid disease progression and poorer outcomes than those without.[10–13] Patients with breast cancer (all stages, all subtypes) with PIK3CA alterations are significantly more likely to have more aggressive clinical features such as bone marrow infiltration, de novo advanced breast cancer, endocrine resistance, and are more likely to have PR-positive and ER-positive disease, compared to patients without PIK3CA alterations.[46–50] In addition, a large meta-analysis of published clinical trials in advanced HR+/HER2- metastatic breast cancer

showed that PIK3CA alterations were associated with shorter PFS and OS outcomes, suggesting a potential negative prognostic value of PIK3CA status in advanced disease.[51]

The aims of therapy in advanced disease are to relieve symptoms, prolong survival and maintain a good HRQoL with minimal adverse events.[14] Initial endocrine therapy with CDK4/6 inhibitor plus AI has significantly improved outcomes compared with endocrine monotherapy; however, patients can develop resistance to CDK4/6 inhibitors plus AI. Therefore, overcoming ET resistance and maintaining sensitivity to endocrine therapy and CDK4/6 inhibitor treatment is an important consideration for later line therapies.[5,52]

As chemotherapy is associated with significant toxicities, leading to poor tolerability, there is a strong desire from clinicians and patients to delay its use for as long as possible.[16,17,20–23] Furthermore, time to disease progression with chemotherapy is low.[53–55] However, following progression or recurrence after recommended initial CDK4/6 inhibitor plus AI, for HR+/HER2- advanced breast cancer patients not at imminent risk of organ failure, everolimus plus exemestane or alpelisib plus fulvestrant are the only current treatment options available before moving to cytotoxic chemotherapy (Figure 1).

Alpelisib plus fulvestrant is a treatment option only for patients with PIK3CA mutations per NICE TA816.[20] Clinical experts contributing to TA816 noted that not everyone can tolerate alpelisib plus fulvestrant and the adverse event profile and the need for additional monitoring due to the high rate of grade 3 or 4 hyperglycaemia is a burden to both patients and clinicians.[20] An alternative treatment option for those with PIK3CA mutations is therefore needed. As there are currently no PI3K/AKT pathway-targeted treatment options for patients with AKT1 or PTEN alterations without PIK3CA alterations, everolimus plus exemestane remains the only combination treatment option for these patients following progression on a CDK4/6 inhibitor-based regimen; however, whilst usually tolerated better than cytotoxic chemotherapy, everolimus is also recognised to be associated with challenging adverse events.[20]

There is a significant unmet need for an effective and tolerable PI3K/AKT-altered pathway targeted treatment option that has a differentiated mode of action and adverse event profile, enhances sensitivity to endocrine therapy following failure of CDK4/6 inhibitor therapy, and

enables patients with PI3K/AKT pathway alterations to remain on endocrine-based treatments for longer before progression to cytotoxic chemotherapy.

B.1.3.3. Positioning of capivasertib plus fulvestrant in the treatment pathway

Capivasertib plus fulvestrant has the potential to meet this significant unmet need for a highly effective and tolerable PI3K/AKT-altered pathway targeted therapy, with a different mode of action and adverse event profile, that enhances sensitivity to endocrine therapy following failure of CDK4/6 inhibitor therapy, and enables patients with PI3K/AKT pathway alterations to remain on endocrine-based treatments for longer before progression to cytotoxic chemotherapy. The proposed positioning of capivasertib plus fulvestrant is for use in the treatment of locally advanced or metastatic, HR+/HER2- breast cancer in people with PI3K/AKT- (PIK3CA- and/or, AKT1-, and/or PTEN-) altered tumours whose disease has progressed following CDK4/6 inhibitor plus AI therapy (see Figure 1). This positioning is aligned with clinicians' anticipated use of capivasertib plus fulvestrant in the current UK treatment pathway and addresses this area of significant unmet need.

The relevant clinical and economic comparators for capivasertib plus fulvestrant in this positioning are alpelisib plus fulvestrant in those patients with PIK3CA-mutated tumours (who account for >75% of people with PI3K/AKT-altered pathway tumours[6]), or everolimus plus exemestane.

B.1.4. Equality considerations

Capivasertib plus fulvestrant is licensed for use in breast cancer in women and men.[28] Breast cancer is rare in men and, consequently, data for capivasertib plus fulvestrant in men with breast cancer are limited. This should not preclude or limit the use of capivasertib plus fulvestrant in men in line with its licensed indication and proposed clinical positioning.

B.2. Clinical effectiveness

Summary of phase 3 RCT data

- The efficacy and safety of capivasertib plus fulvestrant was determined in the CAPItello-291 randomised controlled trial (RCT), conducted in patients with HR+/HER2- advanced breast cancer. The trial compared capivasertib 400mg plus fulvestrant 500mg against placebo plus fulvestrant 500mg, and was specifically designed to determine PIK3CA/AKT1/PTEN-altered status post randomisation, as well as to assess the primary endpoint in both the ITT and the PI3K/AKT pathway-altered populations.[6] The trial was determined to be at low risk of bias in the ITT and the PI3K/AKT pathway-altered populations.
- 289 of the 708 enrolled patients had tumours containing PI3K/AKT pathway alterations and met the subsequent licensed indication for capivasertib plus fulvestrant.[6]
- The primary endpoint was investigator assessed progression-free survival (PFS). Capivasertib plus fulvestrant reduced the risk of progression events or death by 50% in the PI3K/AKT pathway-altered population (HR 0.50; 95%CI 0.38, 0.65, P<0.001). Median PFS in the capivasertib plus fulvestrant arm was more than double that in the placebo plus fulvestrant arm, at 7.3 months versus 3.1 months.[6] Similar PFS results were observed in those with prior use of CDK4/6 inhibitor therapy.[6]
- Overall survival (OS) was a key secondary endpoint. At the primary PFS analysis (DCO1) formal testing of OS was not planned, as the number of deaths was anticipated to be insufficient to permit formal analysis; however, the data show a clear trend towards improvement in OS with capivasertib plus fulvestrant in the PI3K/AKT pathway-altered population (HR 0.69; 95% CI 0.45, 1.05). Kaplan–Meier curves diverged early and remained separated over time.[6]
- Additional secondary and exploratory endpoints including objective response rates, second PFS (PFS2) and time to first subsequent chemotherapy supported these findings,[6] with the latter indicating a delay in the use of chemotherapy or death by approximately 5 months with capivasertib plus fulvestrant.[56]
- The majority of adverse events were mild-to-moderate and were manageable with dose modifications; the rate of discontinuations of capivasertib due to adverse events was low and acceptable for this patient population.[6]
- HRQoL assessments suggested that, overall, capivasertib plus fulvestrant did not materially reduce patient quality of life[57,58] and may have helped to preserve overall quality of life over the course of treatment.

Summary of indirect comparative evidence

- Network meta-analyses using the most robust and relevant RCT data possible provide compelling evidence of the relative effects of capivasertib plus fulvestrant and the comparators of interest (alpelisib plus fulvestrant and everolimus plus exemestane) in patients with HR+/HER2- advanced breast cancer with PI3K/AKT pathway alterations (see section B.2.9).
- All three treatments of interest (capivasertib plus fulvestrant, alpelisib plus fulvestrant and everolimus plus exemestane) were significantly superior to fulvestrant 500mg in terms of PFS and OS (see B.2.9.1).

- Capivasertib plus fulvestrant plausibly improved PFS and OS to a greater, albeit not statistically significant, degree compared with alpelisib plus fulvestrant in patients with PIK3CA mutated tumours.
- Capivasertib plus fulvestrant in patients with PI3K/AKT pathway-altered tumours was numerically superior for PFS and was significantly superior for OS when compared to everolimus plus exemestane in the statistically-preferred fixed effects model.

Conclusion

- Capivasertib plus fulvestrant can address the need for an effective and tolerable targeted treatment option for patients with PI3K/AKT pathway alterations that has a differentiated mode of action, enhances sensitivity to endocrine therapy following failure of CDK4/6 inhibitor therapy, and enables patients with PI3K/AKT pathway alterations to remain on endocrine-based treatments for longer before progression to cytotoxic chemotherapy.

B.2.1. Identification and selection of relevant studies

A systematic literature review (SLR), described in Appendix D, identified the phase 2 FAKTION trial[59] and the phase 3 registrational CAPItello-291 trial[6] as the only studies providing comparative data for capivasertib plus fulvestrant in people with HR+/HER2- advanced breast cancer who had relapsed or experienced disease progression during or after endocrine therapy with an AI. Of these, only the CAPItello-291 trial[6] provides data specifically in the relevant population for this appraisal: patients with HR+/HER2- advanced breast cancer who have PI3K/AKT pathway (PIK3CA-, AKT1-, or PTEN-) altered tumours and have experienced relapse or disease progression during or after treatment with CDK4/6 inhibitor plus endocrine therapy.

As both studies were placebo-controlled trials, efficacy and safety data for the relevant comparators (alpelisib plus fulvestrant in people with PIK3CA mutations, or everolimus plus exemestane) for use in an indirect treatment comparison were also identified in the SLR (see B.2.9).

B.2.2. List of relevant clinical effectiveness evidence

FAKTION was a phase 2 proof of concept study conducted in postmenopausal women before the routine use CDK4/6 inhibitors was common practice. Although not specifically powered for the analysis, in a subgroup of patients with PIK3CA or PTEN alterations this trial showed a numerical benefit of capivasertib plus fulvestrant over placebo plus fulvestrant in PFS.[59]

CAPItello-291[6] was the pivotal phase 3 trial supporting the UK licensing of capivasertib plus fulvestrant, and provides the most robust efficacy and safety data for use of capivasertib in the population of interest. The clinical effectiveness evidence for capivasertib is therefore presented based on the CAPItello-291 trial (Table 3). Details and results from the FAKTION trial, and trials of relevant comparators included in the indirect treatment comparison, are provided in Appendix D1.2.

Table 3. Clinical effectiveness evidence: CAPItello-291 study

Study	CAPItello-291 (NCT04305496)
Study design	Phase 3, multicentre, randomised, double-blind, placebo-controlled trial
Population	Overall population included people with locally advanced (inoperable) or metastatic HR+/HER2− breast cancer following recurrence or progression on or after treatment with an AI, with or without PI3K/AKT pathway–altered (PIK3CA, AKT1, or PTEN) tumours (prespecified for determination after randomisation), with or without previous CDK4/6 inhibitor therapy. The PFS primary endpoint was prespecified for assessment in both the overall (ITT) population and the PI3K/AKT pathway-altered population.
Intervention(s)	Capivasertib 400 mg (2 tablets of 200 mg) orally twice daily (total daily dose 800 mg) on Days 1–4 in each week of a 28-day treatment cycle plus Fulvestrant 500 mg (2 intramuscular injections) on Day 1 of Weeks 1 and 3 of cycle 1, and then on Day 1, Week 1 of each cycle thereafter
Comparator(s)	Placebo plus fulvestrant as above
Indicate if study supports application for marketing authorisation	Yes – the PI3K/AKT pathway-altered population of the trial reflects the licensed population.
Indicate if study used in the economic model	Yes
Rationale if study not used in model	n/a
Reported outcomes specified in the decision problem	**Overall survival*** **Progression-free survival*** Response rate **Adverse effects of treatment*** **Health-related quality of life*.**
All other reported outcomes	Second progression-free survival (PFS2) Time to deterioration in ECOG performance status Time to first subsequent chemotherapy or death

Study	CAPItello-291 (NCT04305496)
	Time to treatment discontinuation*

Notes: *Outcome included in economic model
Source: Turner et al 2023.[6]

B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1. Methodology of pivotal trial

The CAPItello-291 trial methodology, and results from the primary analysis, have recently been published in a manuscript by Turner et al 2023.[6] The trial methodology is summarised in Table 4. [redacted] patients were recruited from the UK.[57] As prespecified in the protocol, the primary and secondary endpoints were assessed in both the overall population and in the population of patients with PI3K/AKT pathway-altered tumours in whom the UK marketing authorisation has been granted. The study was powered to show a statistically significant difference between capivasertib plus fulvestrant and placebo plus fulvestrant in PFS in the Overall Population and the PI3K/AKT pathway altered population (dual primary endpoints).

Table 4. Summary of pivotal trial methodology

Trial number (acronym)	CAPItello-291 (NCT04305496)
Location	Multinational study: 19 countries including UK ([redacted])
Trial design	Phase 3, multicentre, randomised (1:1), double-blind, placebo-controlled trial
Eligibility criteria for participants	**Key inclusion criteria:** • Aged ≥18 years (≥20 years in Japan). • Pre- or postmenopausal female, or male. Pre-menopausal women could be enrolled if amenable to treatment with an LHRH agonist. • Histologically confirmed HR+/HER2− breast cancer. To fulfil the requirement of HR+ disease, a breast cancer must express ER with or without co-expression of progesterone receptor. Therefore, tumours must be: o ER+ defined as ≥1% of tumour cells stain positive for ER on immunohistochemistry (IHC) or, if no percentage is available, then an Allred IHC score of ≥3/8, o Progesterone receptor positive defined as ≥1% of tumour cells stain positive for progesterone receptor on IHC or, if no percentage is available, then an Allred IHC score of ≥3/8; or progesterone receptor negative defined as <1% of tumour cells stain positive for progesterone receptor on IHC or, if no percentage is available, then an Allred IHC score of ≤2/8; or progesterone receptor unknown, and o HER2− defined as 0 or 1+ intensity on IHC, or 2+ intensity on IHC and no evidence of amplification on in situ hybridisation (ISH), or if IHC not done, no evidence of amplification on ISH. • Metastatic or locally advanced disease.

	• Disease progression during prior treatment with an AI-containing regimen (single agent or combination), either:
	  ○ Recurrence or progression while on, or within 12 months of the end of (neo)adjuvant treatment with an AI; or,
	  ○ Progression while on prior AI administered as a treatment line for locally advanced or metastatic disease.
	• At least one lesion or bone lesion that could be accurately measured at baseline with CT or MRI.
	• Eligible for fulvestrant therapy.
	• Consent to provide an FFPE tumour block (primary or recurrent cancer) or at least 20 freshly cut, unstained serial tumour slides, for central (NGS) testing.
	• Able to swallow and retain oral medication.
	• ECOG/WHO performance status of 0 or 1 with no deterioration over the previous 2 weeks, and life expectancy of ≥12 weeks
	• Agreement to use effective contraception, where relevant, for 2 years after the last dose of fulvestrant or 16 weeks after discontinuing capivasertib/ placebo.
	
	Key exclusion criteria:
	• Prior treatment with fulvestrant or other selective oestrogen receptor degraders (SERDs), or AKT serine/threonine kinase (AKT), phosphatidylinositol-3-kinase (PI3K), or mammalian target of rapamycin (mTOR) inhibitors.
	• Clinically significant abnormalities of glucose metabolism as defined by diabetes mellitus requiring insulin treatment, and/or glycosylated haemoglobin ($HbA1_C$) ≥ 8.0% (63.9 mmol/mol).
	• More than 2 lines of endocrine therapy for inoperable locally advanced or metastatic disease.
	• More than 1 line of chemotherapy for inoperable locally advanced or metastatic disease.

Settings and locations where the data were collected	Tertiary centres: • Region 1 (112 centres in United States, Canada, Western Europe, Australia, and Israel: 395 patients). • Region 2 (23 centres in Latin America, Eastern Europe and Russia: 136 patients). • Region 3 (46 centres in Asia, 177 patients).
Trial drugs	**Intervention:** Capivasertib 400 mg twice daily (total daily dose 800 mg) on Days 1–4 in each week of a 28-day treatment cycle; Fulvestrant 500 mg on Day 1 of Weeks 1 and 3 of cycle 1, and then on Day 1, Week 1 of each cycle thereafter **Comparator:** Placebo matching Capivasertib; Fulvestrant matching administration received in the Intervention arm In the **overall population**, n=355 were randomised to the intervention, and n= 353 were randomised to the comparator. In the **PI3K/AKT-pathway altered population,** n= 155 were randomised to the intervention and n=134 were randomised to the comparator.
Primary outcomes	Dual primary end point (assessed in the overall population and in the PI3K/AKT pathway–altered population): • Investigator-assessed PFS (assessed according to RECIST, version 1.1). (PFS was also assessed by blinded independent central review [BICR] as a sensitivity analysis in overall population).

Other outcomes used in the economic model/specified in the scope	Secondary endpoints (assessed in the overall population and in the PI3K/AKT pathway–altered population): • OS: the length of time from randomisation until the date of death due to any cause • ORR: the percentage of patients with at least one complete response (CR) or partial response (PR) per RECIST v1.1 criteria, as assessed by the investigator at the local site • Safety and tolerability: evaluated in terms of AEs/SAEs, vital signs, clinical chemistry/haematology/glucose metabolism parameters and electrocardiogram (ECG) parameters • Health-related quality of life (HRQoL): Evaluation of EORTC QLQ-C30, EORTC QLQ-BR23, scale/item score, including change from baseline and time to deterioration. Exploratory endpoints: • Health state utility using EQ-5D-5L
Pre-planned subgroups	Analyses of primary and secondary outcomes were pre-specified in the trial protocol for both the overall population and for the PI3K/AKT pathway-altered subpopulation. Trial randomisation was stratified by prior use of CDK4/6 inhibitors (yes/no), liver metastases (presence or absence) and geographic area. Randomisation was not stratified by PI3K/AKT pathway-altered status to allow inclusion of patients with more aggressive disease who might otherwise not have enrolled in the trial if they had to wait for tissue-testing results before randomisation. Subgroup analyses for PFS were conducted by stratification factors, age (<65 vs ≥65 years), and in a range of other exploratory analyses (see section B.2.7).
Abbreviations: AI, aromatase inhibitor; ChT, chemotherapy; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; EQ-5D-5L, Euroqol 5 dimension 5 level tool; FFPE, formalin-fixed paraffin-embedded; HR+/HER2–, hormone receptor-positive, human epidermal growth factor receptor 2-negative; IHC, immunohistochemistry; ISH, in situ hybridisation; LHRH, luteinizing hormone-releasing hormone; MRI, magnetic resonance imaging; mTOR, mammalian target of rapamycin; NGS, next-generation sequencing; RECIST, Response Evaluation Criteria in Solid Tumours; SERD, selective oestrogen receptor degrader; WHO, World Health Organization. **Source:** Turner et al 2023;[6] CAPItello-291 CSR[57]	

B.2.3.2. Baseline characteristics

Baseline characteristics for the PI3K/AKT pathway-altered population of the CAPItello-291 trial, and for the subgroup with prior use of CDK4/6 inhibitor therapy (the population of interest based on the current treatment pathway in the UK – see section B.1.3.3) are summarised in Table 5. The baseline characteristics of the overall trial population are provided in the trial manuscript by Turner et al 2023.[6]

PIK3CA/AKT1/PTEN alterations were detected in tumour samples from 289 patients (40.8% of the overall trial population), of which 208 patients had previously received CDK4/6 inhibitor therapy. Baseline characteristics were broadly well balanced between the intervention and comparator arms of each population, and across the PI3K/AKT pathway-altered population and PI3K/AKT pathway-altered population who had received prior CDK4/6 inhibitor therapy.

Prior CKD 4/6 inhibitor use was a stratification factor and similar proportions of the PI3K/AKT pathway-altered population had prior use of CDK4/6 inhibitor in the capivasertib plus fulvestrant and the placebo plus fulvestrant arms (72.9% vs 69.4%, respectively).

Table 5. Baseline characteristics of patients with PI3K/AKT pathway-altered tumours enrolled in CAPItello-291

Characteristic		PI3K/AKT-altered population		PI3K/AKT-altered population with prior CDK4/6 inhibitor use	
		Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)	Capivasertib + fulvestrant (N=114)	Placebo + fulvestrant (N=94)
Age	Median, years (range)	58 (36–84)	60 (34–90)	[redacted]	[redacted]
Sex, n (%)	Female	153 (98.7)	134 (100)	[redacted]	[redacted]
Race/ethnic group, n (%)*	Black or African American	2 (1.3)	1 (0.7)	[redacted]	[redacted]
	Asian	48 (31.0)	35 (26.1)	[redacted]	[redacted]
	White	75 (48.4)	76 (56.7)	[redacted]	[redacted]
	Other	30 (19.4)	22 (16.4)	[redacted]	[redacted]
Genetic mutation status, n (%)	Altered	155 (100)	134 (100)	[redacted]	[redacted]
	PIK3CA only†‡	110 (71.0)	92 (68.7)	[redacted]	[redacted]
	AKT1 only†‡	18 (11.6)	15 (11.2)	[redacted]	[redacted]
	PTEN only†‡	21 (13.5)	16 (11.9)	[redacted]	[redacted]
	PIK3CA and AKT1†	2 (1.3)	2 (1.5)	[redacted]	[redacted]
	PIK3CA and PTEN†	4 (2.6)	9 (6.7)	[redacted]	[redacted]
Disease classification	Metastatic	155 (100)	132 (98.5)	[redacted]	[redacted]
	Locally advanced	0	2 (1.5)	[redacted]	[redacted]
	Missing	0	0	[redacted]	[redacted]
WHO/ECOG performance status	(0) normal activity	93 (60.0)	97 (72.4)	[redacted]	[redacted]
	(1) restricted activity	62 (40.0)	36 (26.9)	[redacted]	[redacted]
	(2) in bed ≤50% of the time	0 (0)	1 (0.7)	[redacted]	[redacted]
AJCC	Stage IV	50 (32.3)	44 (32.8)	[redacted]	[redacted]
Menopausal status	Pre-/perimenopausal	23 (14.8)	29 (21.6)	[redacted]	[redacted]
	Postmenopausal	130 (83.9)	105 (78.4)	[redacted]	[redacted]
Receptor status	ER+/PR+	116 (74.8)	101 (75.4)	[redacted]	[redacted]
	ER+/PR−	35 (22.6)	31 (23.1)	[redacted]	[redacted]
	ER+/PR unknown	4 (2.6)	2 (1.5)	[redacted]	[redacted]
	ER−§	0 (0)	0 (0)	[redacted]	[redacted]
Type of endocrine resistance	Primary	60 (38.7)	55 (41.0)	[redacted]	[redacted]
	Secondary	95 (61.3)	79 (59.0)	[redacted]	[redacted]
Diabetic status	Diabetes	18 (11.6)	8 (6.0)	[redacted]	[redacted]
	No diabetes	137 (88.4)	126 (94.0)	[redacted]	[redacted]
Prior CDK4/6 inhibitor, n (%)		113 (72.9)	93 (69.4)	114 (100)	94 (100)

Notes: *Race data for Belgium, France and Hungary were not permitted to be collected per local regulations and were recorded as 'other'.
†Mutually exclusive groups.
‡Patients with co-occurring mutations were excluded from single gene count.
§Due to the very limited number of patients expected under this category, patients with different PR status are reported together.

Abbreviations: AJCC, American Joint Committee on Cancer; CDK4/6, Cyclin-Dependent Kinase 4/6; ECOG, Eastern Cooperative Oncology Group; ER, oestrogen resistant; PR, progesterone receptor; WHO, World Health Organization.
Source: CAPItello-291 CSR;[57] Data on file.[60]

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1. Statistical analysis

The co-primary objectives of the CAPItello-291 trial were to compare the effect of capivasertib plus fulvestrant relative to placebo plus fulvestrant by assessment of investigator-assessed progression-free survival (PFS) in the overall population and in the PI3K/AKT-altered (PIK3CA/AKT1/PTEN-altered) subgroup. The null hypotheses for the primary endpoint (PFS) in each population was: there is no difference between capivasertib plus fulvestrant and placebo plus fulvestrant in the probability of a progression event.[6,57]

A total sample of 700 patients was planned for the overall trial population. PFS was to be analysed at approximately 77% maturity in the overall population (when 542 progression or death events had occurred) and in the PI3K/AKT pathway–altered population (when 217 events had occurred), under an assumption that 40% of the trial population would have PI3K/AKT pathway–altered tumours. Assuming a PFS hazard ratio (HR) of 0.64 in both populations, it was estimated that the trial would have >99% power to show a significant difference in favour of the capivasertib plus fulvestrant group in the overall population (at a two-sided P<0.035) and 91% power in the PI3K/AKT pathway–altered population (at a two sided P<0.05), with recycling of the remaining 1.5% alpha.[6,57] At data cut-off (DCO) for the primary analysis of PFS (DCO1, 15th August 2022), the required level of maturity was achieved (actual maturity was 77.8% (551 events) in the overall population, and 81.7% (236 events) in the PI3K/AKT pathway-altered subgroup.[6]

Analyses in both populations were based on their full analysis sets (FAS) on an intention to treat (ITT) basis in all patients randomised into the study. The dual primary end points were tested using a log-rank test, with stratification according to the presence of liver metastases (yes vs. no), previous use of a CDK4/6 inhibitor (yes vs. no), and geographic area (assessed in the overall population only: Region 1: United States, Canada, Western Europe, Australia, and Israel, Region 2: Latin America, Eastern Europe and Russia, Region 3: Asia). HRs and

associated 95% confidence intervals (Cis) were calculated from a stratified Cox proportional-hazards model. Overall survival assessments of no detriment (i.e., with the HR not favouring the placebo = fulvestrant group) in the overall and PI3K/AKT pathway–altered populations were conducted at the time of the primary analysis, as requested by the US FDA. The percentage of patients with an objective response was analysed with the use of a logistic-regression model with adjustment for the randomisation stratification factors in both populations. Sensitivity analysis included PFS assessed by blinded independent central review (BICR).[6,57]

The safety analysis set (SAS) for each population comprised all patients included in the FAS who received at least one dose of study drug (fulvestrant, capivasertib or placebo), analysed according to the treatment received. Patients who received only fulvestrant were also included in the SAS and were included in the treatment arm to which they were randomised (capivasertib or placebo).

B.2.4.2. Patient disposition

Patient disposition for the overall population are presented in Turner et al 2023.[6] Patient disposition in the PI3K/AKT-altered population was similar to that seen in the overall population, as presented in the Consort diagram in Appendix D.1.3. At the time of the primary analysis (DCO1; 15 August 2022), a total of 289 patients with PI3K/AKT pathway alterations had been randomised to receive treatment with capivasertib plus fulvestrant (n=155) or placebo plus fulvestrant (n=134). One patient in the placebo plus fulvestrant group died before their first dose.[57] Of these patients with PI3K/AKT pathway alterations, 114/155 (73.5%) patients randomised to capivasertib plus fulvestrant and 94/134 (70.1%) patients randomised to placebo plus fulvestrant had received prior CDK4/6 inhibitor therapy.[6]

At the primary analysis in the PI3K/AKT pathway-altered population, [redacted] patients ([redacted]%) were continuing to receive treatment with capivasertib plus fulvestrant, and [redacted]%) and [redacted]%) were continuing to receive placebo and fulvestrant, respectively. Capivasertib plus fulvestrant was discontinued in [redacted] patients ([redacted]%), and in the placebo arm, placebo was discontinued in [redacted] patients ([redacted]%), and fulvestrant was discontinued in [redacted] patients ([redacted]%). The main reason for discontinuation of capivasertib or placebo was disease progression, which occurred in [redacted] ([redacted]%) and [redacted]%) patients, respectively.[6,57] Only [redacted] was lost to follow

up in the capivasertib plus fulvestrant arm, and [redacted] in the placebo plus fulvestrant arm.[57]

B.2.5. Critical appraisal of the relevant clinical effectiveness evidence

CAPItello-291 was a phase 3, randomised, double-blind, controlled registrational trial.[6] Using the NICE-recommended quality assessment based on University of York Centre for Reviews and Dissemination guidance,[33] the CAPItello-291 trial was at a low risk of bias (Table 6).

Table 6. Quality assessment of pivotal trial

Trial number (acronym)	CAPItello-291 (NCT04305496)[6]
Was randomisation carried out appropriately?	Yes - Patients were randomly assigned to treatment in a 1:1 ratio using a randomisation scheme loaded into an IWRS database. The PI3K/AKT pathway-altered population was pre-specified to be determined after randomisation, and there were no obvious imbalances in baseline characteristics or prognostic factors between treatment arms in this or the overall population to suggest randomisation issues. Prior CDK4/6 inhibitor use was a stratification factor ensuring randomisation was maintained in this population of interest.
Was the concealment of treatment allocation adequate?	Yes – IWRS
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes – within each of the populations the intervention and comparator arms were well balanced in terms of baseline characteristics and for potential effect modifiers. Baseline characteristics were also balanced across the treatment arms in the post-CDK4/6 inhibitor population of interest.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes - double-blind RCT. Primary analysis was investigator-assessed PFS but investigators were blind to treatment allocation. Blinded independent central review of PFS was highly consistent with investigator assessment.
Were there any unexpected imbalances in drop-outs between groups?	No – drop out rates were low (<1%) and balanced across populations and treatment arms.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No – clinical study report includes all outcome assessments included in protocol.

Trial number (acronym)	CAPItello-291 (NCT04305496)[6]
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes – ITT analysis in both the overall and the PI3K/AKT pathway-altered populations.
Notes: Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination), per the NICE Company Evidence Submission user guide.[33] **Abbreviations:** ITT, intention to treat; IWRS, interactive web response system; PFS, progression-free survival; RCT, randomised controlled trial.	

The CAPItello-291 trial enrolled [redacted] in the UK.[57] Clinical experts consulted by AstraZeneca have confirmed that the broad characteristics of patients enrolled in the trial and the treatment effects observed with capivasertib, are likely to be generalisable to patients meeting the licensed indication, and the subgroup of interest in UK clinical practice (see section B.3.14).

Quality assessment of relevant comparator trials included in an indirect treatment comparison is discussed in Appendix D1.2.

B.2.6. Clinical effectiveness results of the relevant studies

Capivasertib is licensed in the UK in combination with fulvestrant for the treatment of adult patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative (defined as IHC 0 or 1+, or IHC 2+/ISH-) locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following recurrence or progression on or after an endocrine based regimen.[28] As this submission relates specifically to the subgroup of patients who have previously received treatment with CDK4/6 inhibitors, results for the licensed population and key results (PFS and OS) for the subgroup with prior CDK4/6 inhibitor exposure are presented here. Results for the overall trial population, which includes patients who do not meet the licensed indication, have been published in Turner et al 2023.[6]

B.2.6.1. Primary endpoint: Progression free survival in PI3K/AKT-altered population

At the primary analysis (DCO1, 15 August 2022), investigator-assessed PFS events had been reported in the PI3K/AKT pathway-altered population in 121 patients (78.1%) in the capivasertib arm and 115 patients (85.8%) in the placebo arm.[6]

There was a 50% reduction in the risk of progression or death in favour of capivasertib plus fulvestrant (HR 0.50; 95%CI 0.38, 0.65, *P*<0.001). Median PFS in the capivasertib plus fulvestrant arm was more than double that in the placebo plus fulvestrant arm, at 7.3 months versus 3.1 months (Table 7).[6]

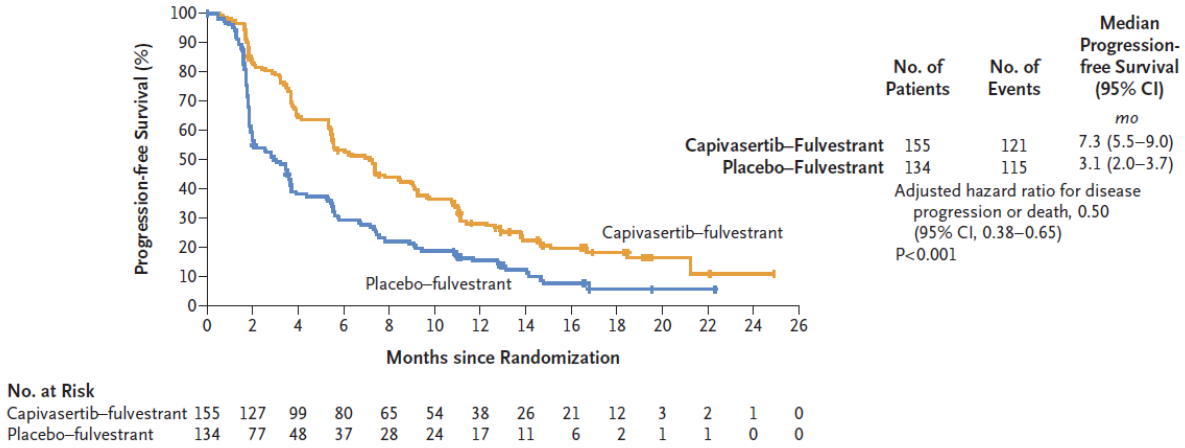
Table 7. PFS by investigator assessment in the PI3K/AKT pathway-altered-population FAS (DCO1)

Progression or death	Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)
Total number of patients with events, n (%)*	121 (78.1)	115 (85.8)
Median PFS (months)†	7.3	3.1
95% CI for median PFS†	5.5, 9.0	2.0, 3.7
2-sided *P*-value‡	<0.001	
Hazard ratio§	0.50	
95% CI for hazard ratio§	0.38, 0.65	

Notes: Progression determined by RECIST v1.1.
*Does not include RECIST progression events that occur after 2 or more missed visits or death after 2 visits of baseline where the patient has no evaluable visits or does not have a baseline assessment.
†Kaplan–Meier estimate.
‡Stratified log-rank test.
§Stratified Cox proportional hazards model. A hazard ratio (HR) < 1 favours capivasertib plus fulvestrant. For the altered population, the log-rank test and Cox model are stratified by presence of liver metastases (yes vs no), and prior use of CDK4/6 inhibitors (yes vs no).
Source: Turner et al 2023; Clinical study report[6,57]

Kaplan–Meier analysis (Figure 2) demonstrated clear separation in the incidence of PFS events from the time of first tumour assessment at 2 months, and favoured capivasertib plus fulvestrant across the whole follow-up period.

Figure 2. Kaplan–Meier plot of PFS by investigator assessment in the PI3K/AKT-altered-population FAS (DCO1)



Notes: Censored observations are indicated by: +
Progression was determined by investigators based on RECIST v1.1 criteria. These data do not include RECIST progression events that occur after 2 or more missed visits or within 2 visits of baseline where the patient has no evaluable visits or did not have a baseline assessment. *P*-values are 2-sided. The hazard ratio was calculated using the stratified Cox proportional hazards model. The log-rank test and Cox model were stratified by presence of liver metastases (yes vs no), and prior use of CDK4/6 inhibitors (yes vs no). A hazard ratio < 1 favours capivasertib plus fulvestrant.
Source: Turner et al 2023[6]

Results based on blinded independent central review were highly consistent with the investigator-assessed analyses (HR 0.51; 95% CI, 0.38 to 0.68), demonstrating the robustness of the primary, investigator-assessed outcomes.[6] Results were also consistent irrespective of the specific tumour alterations (i.e., in patients with tumours containing either PIK3CA alterations, or AKT1 alterations or PTEN alterations), as shown in section B.2.7.

B.2.6.2. Exploratory endpoint: Progression free survival in the PI3K/AKT pathway-altered population with prior CDK4/6 inhibitor use

Results in the PI3K/AKT pathway-altered population with prior use of CDK4/6 inhibitors was consistent with results in the broader PI3K/AKT pathway-altered population. Investigator-assessed median PFS was more than doubled with capivasertib plus fulvestrant compared with placebo plus fulvestrant ([redacted] months [95% CI: [redacted]] versus [redacted] months [95% CI: [redacted]];[61] HR 0.49 [95% CI: 0.36 to 0.66]).[6] There was clear, rapid separation in the incidence of PFS events from the time of first tumour assessment at 2 months, which was maintained across the whole follow-up period (Figure 3).[61]

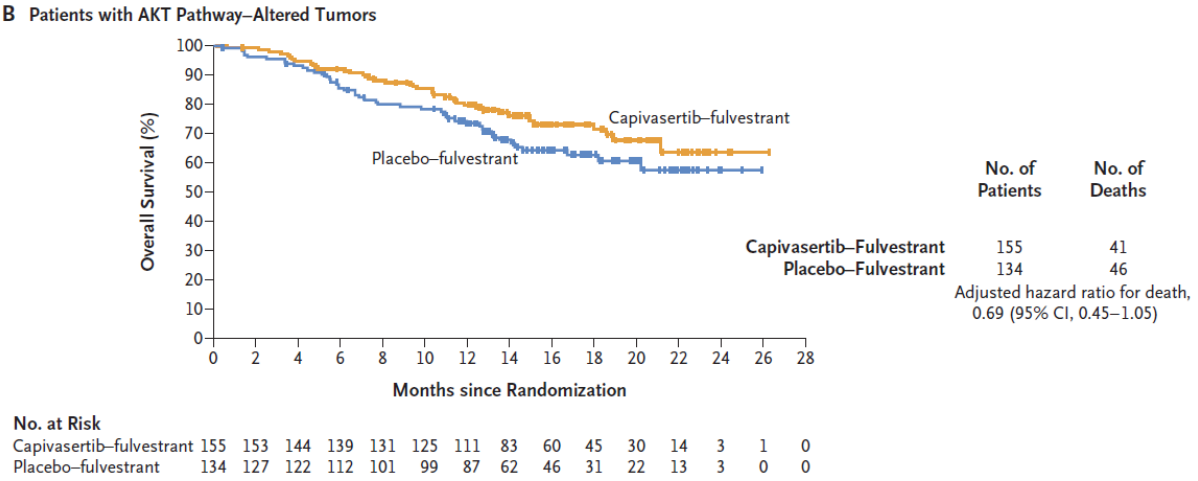
Figure 3. Kaplan–Meier plot of PFS by investigator assessment in the PI3K/AKT pathway-altered-population, prior CDK4/6 inhibitor FAS (DCO1)

Notes: Progression determined by RECIST v1.1. CDK 4/6 = Cyclin-dependent kinases 4 and 6.
HR = Hazard ratio. CI = Confidence interval. Does not include RECIST progression events that occur after two or more missed visits or death after two visits of baseline where the patient evaluable visits or does not have a baseline assessment.
Source: Data on file[61]

B.2.6.3. Secondary endpoint: Overall survival in PI3K/AKT pathway-altered population

Formal testing of OS at DCO1 was not planned, as the number of deaths was anticipated to be insufficient to permit formal analysis. Nonetheless, in the PI3K/AKT pathway-altered population, the data show a clear trend towards improvement in OS with capivasertib plus fulvestrant (HR 0.69; 95% CI 0.45, 1.05). At 18 months, the OS rate in the capivasertib plus fulvestrant arm was 73.2%, compared with 62.9% in the placebo plus fulvestrant arm, and at 24 months was 63.8% and 57.7%, respectively. Kaplan–Meier curves diverged early and remained separated over time (Figure 4).[6]

Figure 4. Kaplan–Meier plot of OS in the PI3K/AKT-altered-population FAS (DCO1)



Notes: A 0.01% alpha penalty was assigned to OS analyses of no detriment. Formal analysis was not prespecified. Censored observations are indicated by: +
Patients not known to have died at the time of analysis are censored at the last recorded date on which the patient was last known to be alive. The *P*-value is 2-sided, and the hazard ratio (HR) was calculated using the stratified Cox proportional hazards model. The log-rank test and Cox model were stratified by prior use of CDK4/6 inhibitors (yes vs no). A HR <1 favours capivasertib plus fulvestrant.
Source: Turner et al 2023[6]

B.2.6.4. Exploratory endpoint: Overall survival in PI3K/AKT pathway-altered population with prior CDK4/6 inhibitor use

At the time of DCO1 (August 15th, 2022), there were [redacted] OS events ([redacted] data maturity) in the PI3K/AKT pathway altered population (post-CDK4/6 inhibitor setting) in the CAPItello-291 trial, with more events observed in the placebo plus fulvestrant arm than the capivasertib plus fulvestrant arm ([redacted] Median OS was [redacted] months for patients in the placebo plus fulvestrant arm, whereas the median OS was [redacted] for patients in the capivasertib plus fulvestrant arm [redacted] There was clear, early separation in the incidence of OS events which was maintained across the whole follow-up period (Figure 5).[62]

Figure 5. Kaplan–Meier plot of OS in the PI3K/AKT pathway-altered-population, prior CDK4/6 inhibitor FAS (DCO1)

Abbreviations: DCO: data cut-off; CDK4/6 inhibitor: cyclin-dependent kinase 4 and 6 inhibitor; KM: Kaplan-Meier; OS: overall survival.
Source: Data on file[62]

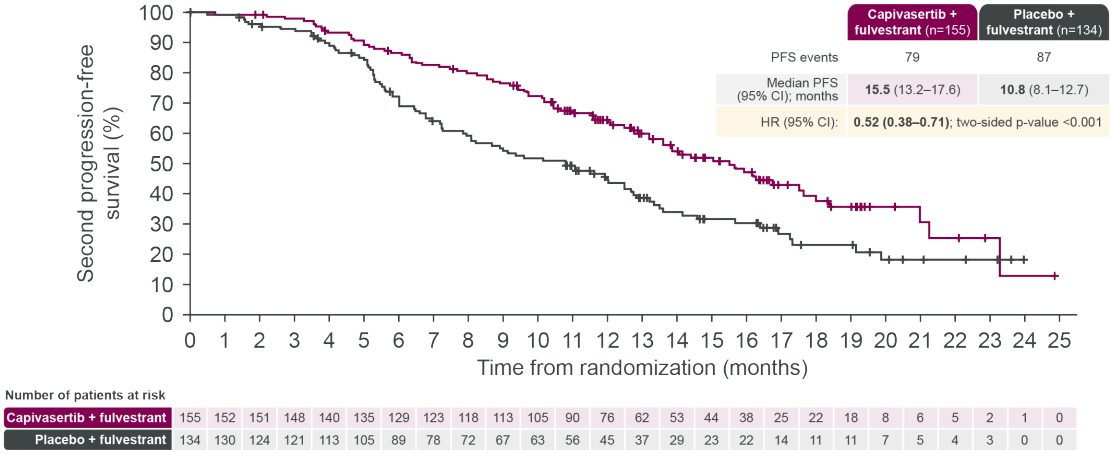
B.2.6.5. Secondary endpoint: Second progression-free survival (PFS2) in PI3K/AKT pathway-altered population

Treatment of advanced (inoperable or metastatic) HR+/HER2− breast cancer with anti-cancer agents may affect the drug resistance profile of the target tumour(s), which may impact on the activity of next-line therapies.[63] For this reason, PFS2 was measured to ascertain the effect of treatment with capivasertib plus fulvestrant on patients' survival following treatment with a subsequent regimen. At the time of DCO1, PFS2 data from CAPItello-291 were over 50% mature in the PI3K/AKT pathway-altered population.[56]

In the PI3K/AKT pathway-altered population, there was a 48% reduction in the risk of second progression in favour of capivasertib plus fulvestrant (HR 0.52; 95% CI 0.38, 0.71). Median PFS2 was 4.7 months longer for patients with PIK3CA/AKT1/PTEN alterations in the capivasertib plus fulvestrant arm compared with the placebo plus fulvestrant arm (15.5 vs 10.8 months). The reduced risk of PFS2 was apparent early (Figure 6).[56] Given the clear trends towards improved OS based on data of limited maturity (see B.2.6.3 and B.2.6.4), these

PFS2 data provide a further indication of an early and sustained clinical benefit with capivasertib plus fulvestrant over placebo plus fulvestrant beyond first progression.

Figure 6. Kaplan–Meier plot of investigator-assessed PFS2 for the PI3K/AKT pathway-altered-population FAS (DCO1)



Notes: Censored observations are indicated by: +
Progression was determined by investigator assessment. The *P*-value is 2-sided, and the hazard ratio (HR) was calculated using the stratified Cox proportional hazards model. The log-rank test and Cox model were stratified by the presence of liver metastases (yes vs no), and prior use of CDK4/6 inhibitors (yes vs no). A HR < 1 favours capivasertib plus fulvestrant.
Source: Rugo et al 2024[56]

B.2.6.6. Secondary endpoint: Objective response rate in PI3K/AKT pathway-altered population

Although not planned for formal analysis at DCO1, the investigator-assessed objective response rate (ORR) by RECIST v1.1 criteria was higher for patients with measurable disease at baseline in the capivasertib plus fulvestrant arm compared with the placebo plus fulvestrant arm (28.8% vs 9.7%; OR 3.93 [95%CI 1.93 to 8.04]) (Table 8).[6] Alongside the PFS data, these ORR data demonstrate the clear benefits of capivasertib plus fulvestrant in reducing tumour burden and disease progression.

Table 8. Logistic regression of investigator-assessed ORR for the PI3K/AKT pathway-altered-population FAS (DCO1)

Group	N	No. (%) patients with response	Adjusted response rate (%)*	Comparison between groups	
				Odds ratio	95% CI
Capivasertib + fulvestrant	132	38 (28.8)	32.1	3.93	1.93, 8.04
Placebo + fulvestrant	124	12 (9.7)	10.7		

Abbreviations: ORR, objective response rate;
Source: Turner 2023[6]

B.2.6.7. Secondary endpoint: EORTC QLQ-C30 and EORTC QLQ-BR23 in the PI3K/AKT pathway-altered population

For European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items (EORTC QLQ-C30), an outcome variable consisting of a score from 0 to 100 was derived for each of the symptom scales/scores, each of the functional domains, and the global measure of health status scale. Changes from baseline were analysed using a mixed model repeat measures analysis. The model included treatment, visit, treatment by visit interaction, and the stratification factors liver metastases, prior use of CDK4/6 inhibitors and geographic region as explanatory variables, and the baseline score and baseline score by visit as covariates; patient was included as a random effect. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire breast cancer specific module (EORTC QLQ-BR23) multi-item scores were transformed to a 0 to 100 scale. Time to deterioration was analysed using a stratified log-rank test as used for PFS.[57]

EORTC QLQ-C30 data for the PI3K/AKT pathway-altered population were available up to cycle 10, beyond which, data from this population were excluded from analysis as there were fewer than 20 observations in the placebo arm. Over the first 10 cycles of treatment in patients with at least one post-baseline score, global health status and quality of life were maintained in both the capivasertib plus fulvestrant group and the placebo plus fulvestrant group (least squares mean change from baseline in the QLQ-C30 score, [redacted] and [redacted], respectively; difference, [redacted]; 95% CI, [redacted] to [redacted]) (Figure 7).[57] Global health status and quality of life were maintained for longer with capivasertib plus fulvestrant than with placebo plus fulvestrant. The median time to deterioration (defined as a sustained decrease of ≥10 points in the score from baseline) was increased with capivasertib plus fulvestrant vs placebo plus fulvestrant

([redacted] months vs [redacted] months; HR [redacted]; 95% CI[redacted]).[57] For reference, in the SOLAR-1 trial, median time to deterioration was 14.8 months with both alpelisib plus fulvestrant and with placebo plus fulvestrant (HR 1.03, 95% CI 0.72 to 1.48),[64] suggesting alpelisib plus fulvestrant did not delay deterioration in global health status and quality of life vs placebo plus fulvestrant.

Figure 7. Change from baseline for EORTC QLQ-C30, by visit, LS Mean (95% CI) (PI3K/AKT pathway-altered subgroup FAS)

Notes: Visits at each cycle are taken on week 1 day 1. Only on treatment assessments are included.
For the symptom scales, a negative change from baseline value indicates improvement of symptoms. For functional scales and Global health status/QoL score a positive change from baseline value indicates improvement in functioning and health status.
Abbreviations: n = Number of patients included in analysis. LS = Least square. CI = Confidence interval. QoL = Quality of Life. EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items.
Source: Clinical study report, Figure 14.2.9.1.32 [57]

For EORTC QLQ-BR23, the risk of clinically meaningful deterioration were similar but numerically favoured capivasertib plus fulvestrant for all subscales that were calculable, except for systemic therapy side effects, which with a HR of [redacted] (95%CI, [redacted]) numerically favoured placebo plus fulvestrant.[57]

These results may indicate that, overall, capivasertib plus fulvestrant does not materially reduce patient quality of life and may help to preserve overall quality of life over the course of treatment.

B.2.6.8. Secondary endpoint: Time to deterioration in ECOG performance status in the PI3K/AKT pathway-altered population

The results of time to deterioration of ECOG performance status favoured capivasertib plus fulvestrant, with a [redacted] reduction in the risk of deterioration compared with the placebo plus fulvestrant arm (HR: [redacted]; 95% CI: [redacted]). However, these results should be interpreted with caution, as there was a high rate of censoring (approximately [redacted] in both treatment arms).[57]

B.2.6.9. Exploratory endpoint: Time to first subsequent chemotherapy or death in the PI3K/AKT pathway-altered population

Consistent with the primary PFS analysis, there was an improvement in time to first subsequent chemotherapy or death (TFSC) with capivasertib plus fulvestrant compared with placebo plus fulvestrant. The median TFSC was delayed by 5.0 months in the capivasertib plus fulvestrant arm (from 6.0 months in the placebo plus fulvestrant arm to 11.0 months in the capivasertib plus fulvestrant arm; HR: 0.56; 95% CI: 0.42 – 0.74).[56] As chemotherapy is associated with significant toxicities, leading to poor tolerability, and there is a strong desire from clinicians and patients to delay its use for as long as possible,[16,17,20–23] these results suggest capivasertib plus fulvestrant may help to achieve this aim.

B.2.6.10. Exploratory endpoint: EQ-5D-5L in the PI3K/AKT pathway-altered population

From baseline EQ-5D-5L index scores of [redacted] and [redacted], and from baseline VAS mean scores of [redacted] and [redacted], in the capivasertib plus fulvestrant and with placebo plus fulvestrant arms, respectively, there were no clear differences in changes from baseline between arms.[57] These results support the cancer-specific quality of life data from the EORTC QLQ tools, indicating that capivasertib plus fulvestrant does not materially reduce overall patient quality of life.

Figure 8. Change from baseline in EQ-5D-5L index score by visit, Mean (SD), in PI3K/AKT pathway-altered population

Source: Clinical study report, Fig 14.2.9.6.5[57]

Figure 9. Change from baseline in EQ-5D-5L VAS score by visit, Mean (SD), in PI3K/AKT pathway-altered population

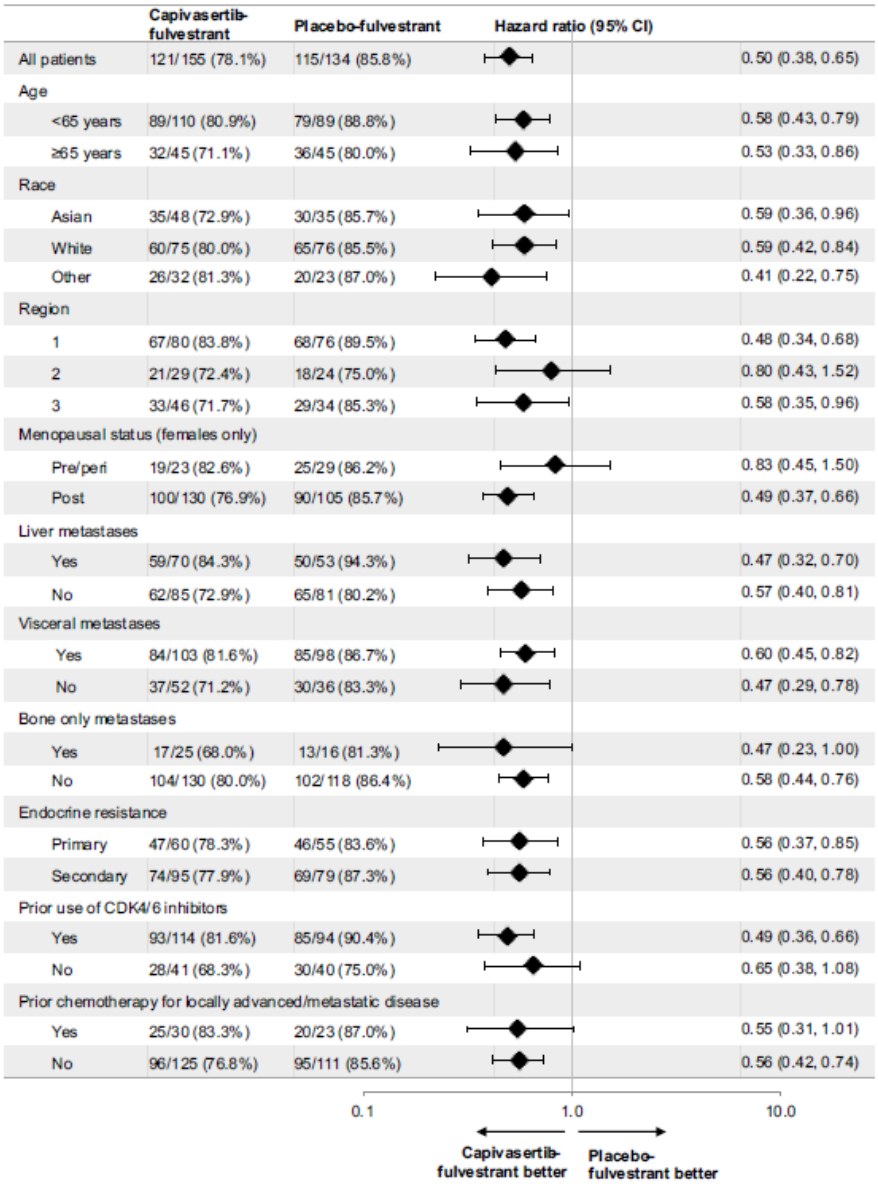
Source: Clinical study report, Fig 14.2.9.7.4 [57]

B.2.7. Subgroup analysis

Subgroup analyses for PFS were planned and conducted by stratification factors, age (<65 vs ≥65 years), and across a range of other exploratory analyses in the PI3K/AKT pathway-altered population. Although some of the resulting subgroups are small, leading to wide confidence intervals around HR point estimates, these analyses demonstrate that the superior efficacy of capivasertib plus fulvestrant in reducing progression events or death is consistent across patients, irrespective of: prior treatment with CDK4/6 inhibitors; prior chemotherapy; endocrine resistance; presence of liver, visceral or bone metastases; age; and race (Figure 10).[6] PFS analyses by the specific tumour alteration also demonstrate consistent treatment effects in patients with PIK3CA alterations (HR 0.51, 95%CI 0.37-0.70), AKT1 alterations (HR 0.51, 95%CI 0.22-1.12) or PTEN alterations (HR 0.43, 95%CI 0.21-0.88) (Figure 11).[65]

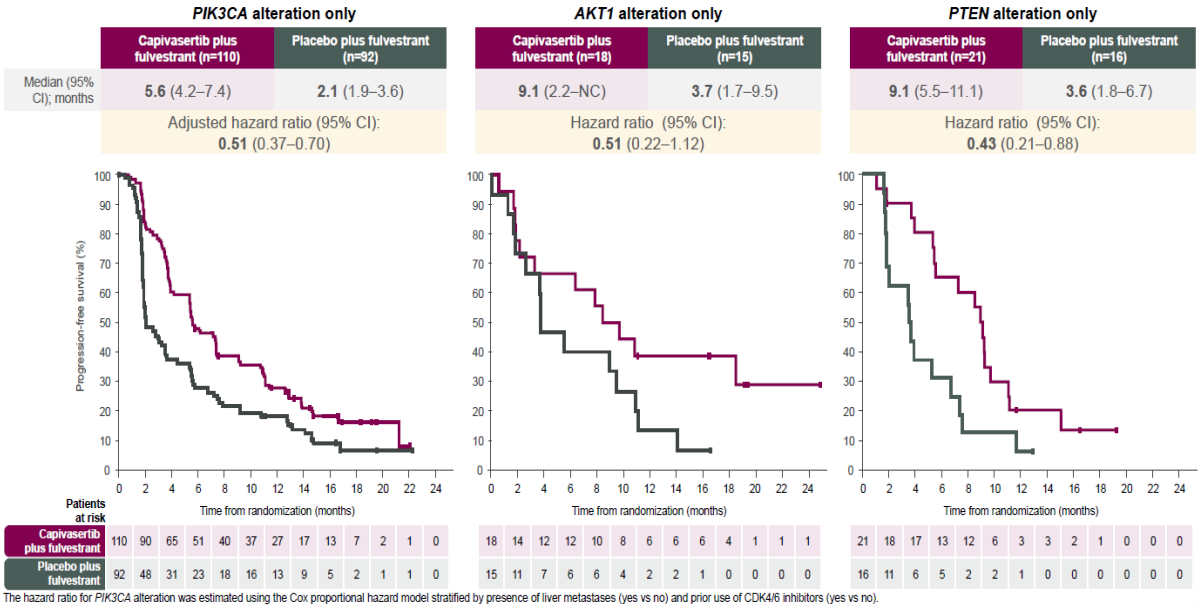
PFS and OS data specifically in the PI3K/AKT pathway-altered population are provided in sections B.2.6.2 and B.2.6.4, respectively, and a discussion of potential treatment effect modifiers and prognostic factors is included in the description of the network meta-analysis (NMA) in Appendix D1.2.

Figure 10. Subgroup analyses of PFS in the PI3K/AKT pathway-altered population



Source: Turner et al 2023[6]

Figure 11. PFS analyses by specific tumour alteration



The hazard ratio for *PIK3CA* alteration was estimated using the Cox proportional hazard model stratified by presence of liver metastases (yes vs no) and prior use of CDK4/6 inhibitors (yes vs no).

Source: Howell et al 2023[65]

B.2.8. Meta-analysis

As capivasertib plus fulvestrant data for the population of interest are available only from the placebo-controlled CAPItello-291 trial, meta-analysis of capivasertib trials has not been undertaken. Network meta-analyses of capivasertib and comparator trial data have been conducted as discussed in section B.2.9.

B.2.9. Indirect and mixed treatment comparisons

As there are no direct comparative data for capivasertib plus fulvestrant vs the relevant comparators (alpelisib plus fulvestrant and everolimus plus exemestane), adjusted indirect comparisons were conducted. Appendix D1.2 provides full details of the methodology and results of these indirect comparisons, including details on the identification of relevant RCT data for the intervention and comparators, a feasibility assessment and resulting statistical methods. A Bayesian network meta-analysis (NMA) approach was taken, and a summary of the results and discussion of uncertainty is provided below.

B.2.9.1. Results of the NMA

The NMA was conducted using the pivotal trials of capivasertib plus fulvestrant (CAPItello-291,[6] FAKTION[59]), alpelisib plus fulvestrant (SOLAR-1[66]) and everolimus plus exemestane (BOLERO-2,[67,68] BOLERO-5[69]). Other trials were also required to connect the network. These are summarised in the network plots for the PFS outcome in Figure 12 and the OS outcome in Figure 13.

Figure 12. Trial network for PFS outcome

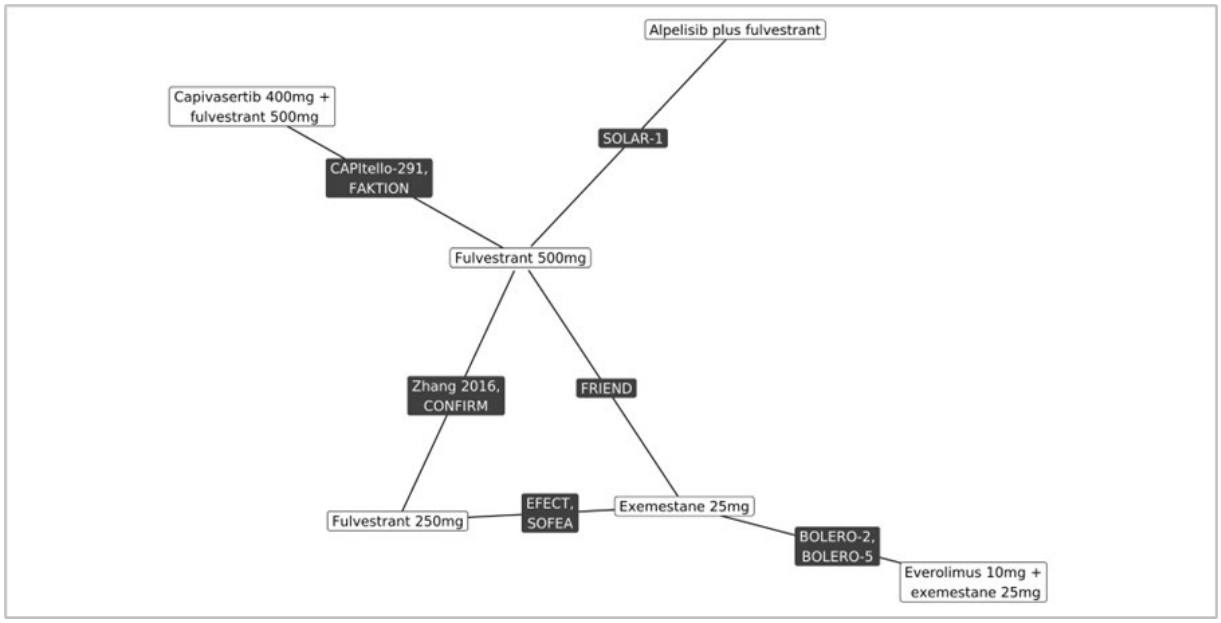
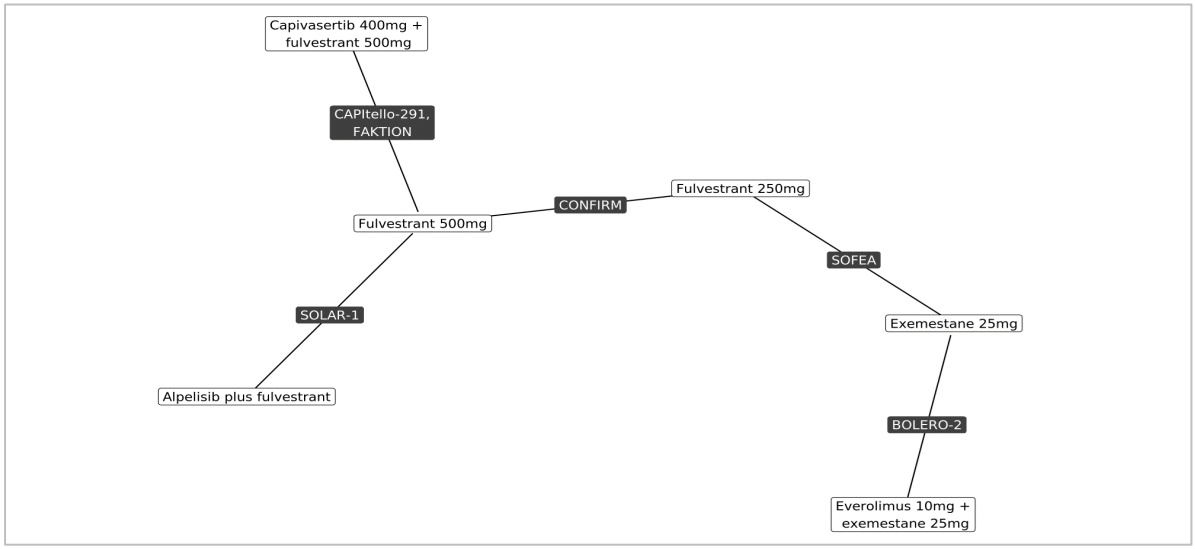


Figure 13. Trial network for OS outcome



The NMAs were performed using the PI3K/AKT pathway-altered subgroup results from the CAPItello-291 and FAKTION trials for capivasertib plus fulvestrant, and the PIK3CA results from the SOLAR-1 trial for alpelisib plus fulvestrant. The remaining trials in the network do not report patient characteristics or results for patients with PIK3CA/AKT1/PTEN alterations specifically. Whilst there is evidence that PIK3CA, AKT1 and PTEN alterations are treatment effect modifiers for capivasertib plus fulvestrant,[6] and PIK3CA is a treatment effect modifier for alpelisib plus fulvestrant,[66] there is no evidence that PIK3CA, AKT1 and PTEN alterations are treatment effect modifiers for the other treatments included in the network (see discussion of treatment effect modifiers and prognostic factors in Appendix D1.2).

B.2.9.1.1. PFS results

The forest plot of the PFS results of the fixed and random effects (with informative prior) NMA using fulvestrant 500mg as the reference treatment (per the economic model - see B.3) is shown in Figure 14. A forest plot using capivasertib plus fulvestrant as the reference treatment is also provided in Figure 15. Based on a nominal two-sided 5% level and their 95% credible intervals (CrI) not spanning one, all three treatments of interest were significantly superior to fulvestrant 500mg. Compared to the treatments of interest for this decision problem, treatment with capivasertib plus fulvestrant was associated with a numerically improved PFS versus everolimus plus exemestane, with a lower 95% credible limit that is close to one ([redacted]), and is

also associated with numerically improved PFS versus alpelisib plus fulvestrant, although not statistically significant.

Results based on random effects models were similar but with wider 95% credible intervals, as would be expected. According to goodness of fitness statistics (deviance information criterion [DIC], included in Appendix D1.2), the preferred model is the fixed effects model followed by the random effects models with informative and vague priors, respectively. The difference in DIC between the fixed effect and random effect model with informative prior was not judged meaningful (less than 3 points).

Figure 14. Forest plot - PFS - comparison with fulvestrant 500mg

Abbreviations: CrI: credible interval; HR: hazard ratio; PFS: progression-free survival; SLR: systematic literature review

Figure 15: Forest plot - PFS - comparison with capivasertib plus fulvestrant

Abbreviations: CrI: credible interval; HR: hazard ratio; PFS: progression-free survival; SLR: systematic literature review

B.2.9.1.2. OS results

The forest plot of the OS fixed and random effects (with informative prior) NMA models with fulvestrant 500mg as the referent (per the economic model – see B.3) is shown in Figure 16. A forest plot using capivasertib plus fulvestrant as the reference treatment is also provided in Figure 17. Based on a nominal two-sided 5% level and their 95% credible intervals not spanning one, only capivasertib plus fulvestrant was significantly superior to fulvestrant 500mg (fixed effects HR [redacted]; 95% CrI: [redacted]); alpelisib plus fulvestrant was numerically superior to fulvestrant 500mg and the point estimate for everolimus plus exemestane indicated no improvement. Compared to the treatments of interest for this decision problem, treatment with capivasertib plus fulvestrant is associated with significantly improved OS versus everolimus plus exemestane (fixed effects only) and numerically improved OS versus alpelisib plus fulvestrant (although not statistically significant).

Figure 16. Forest plot - OS - comparison with fulvestrant 500mg

Abbreviations: CrI: credible interval; HR: hazard ratio; OS: overall survival; SLR: systematic literature review

Figure 17: Forest plot - OS - comparison with capivasertib plus fulvestrant

Abbreviations: CrI: credible interval; HR: hazard ratio; OS: overall survival; SLR: systematic literature review

B.2.9.2. Uncertainties in the indirect and mixed treatment comparisons

The NMA was conducted based on trial data that was obtained from a large and comprehensive systematic review of clinical trials in metastatic breast cancer. A feasibility assessment was undertaken, and the most suitable methodology was applied. Given the presence of heterogeneity between the studies, and the limited number of links with multiple studies in the NMA, the random effects NMAs were performed using informative priors for between-study heterogeneity to support estimation of treatment effects.

However, it is acknowledged that the NMA is subject to some limitations that have the potential to bias results.

Primarily, there are several sources of heterogeneity across trials that may have influenced results. Whilst all the trials were conducted in HR+ or ER+ advanced breast cancer, HER2 status was not reported in 4 of the 10 trials included in the PFS network, which has an uncertain impact on the results (see Appendix D1.2). The majority of trials (8 out of 10) reported in patients with no history of CDK4/6 inhibitor treatment. It was therefore necessary to conduct the NMAs on the assumption that prior CDK4/6 inhibitor use is not a treatment effect modifier. Although prior CDK4/6 inhibitor use may be a prognostic factor, prespecified analyses of the CAPItello-291 trial indicate consistent relative treatment effects of capivasertib plus fulvestrant whether or not CDK4/6 inhibitor therapy was previously used (see B.2.6.1 and B.2.6.2). The assumption that prior CDK4/6 inhibitor use is not a treatment effect modifier therefore seems to be reasonable. Furthermore, only two studies of capivasertib plus fulvestrant (CAPItello-291,[6] FAKTION[59]) and one study of alpelisib plus fulvestrant (SOLAR-1[66]) reported outcomes for patients with PI3K/AKT pathway (PIK3CA, PTEN and AKT1) alterations and PIK3CA alterations, respectively. Hence, the NMA relied on data from the biomarker unselected populations of other comparator studies, i.e., assuming no influence of PI3K/AKT pathway alteration status on the relative effect of these therapies. For other treatments, due to their different mechanism of action, there is no *a priori* expectation of treatment effect modification and there is also no empirical evidence of treatment effect modification by PI3K/AKT pathway alterations.

The NMA correspondingly assumed that, whilst a PI3K/AKT pathway alteration is a prognostic factor for patients with HR+/HER2- advanced breast cancer, it is not a treatment effect modifier for any other treatments included in the network. Other potential sources of heterogeneity included differences in region of enrolment, line of therapy, and menopausal status. As described in detail in Appendix D1.2, although there is no direct evidence that this heterogeneity will introduce bias into the NMA, the true influence of these factors on the results is unknown. Nonetheless, having considered the evidence that is available for capivasertib plus fulvestrant and the comparators, the most robust evidence has been employed to address the decision problem.

Several comparisons in the NMA were based on the results of more than two studies linked together in the network (e.g., BOLERO-2 to SOFEA to CONFIRM to CAPItello-291), which led to increased uncertainty around the relative effects of treatment. The absence of a statistically significant difference between treatments may therefore be partially attributed to the network geometry and the number of steps needed to perform each comparison.

Finally, the PFS and OS NMAs were conducted on the (log) HR scale, which relies on the proportional hazards (PH) assumption. This assumption was tested using log-log plots and the Global Schoenfeld Test. There is a potential appearance of non-proportionality from some of the data, including the CAPItello-291 data; however, based on a review of the Kaplan-Meier plots, it is not clear that there were material deviations from PH (see Appendix D1.2). The possibility of non-PH was most noticeable for PFS, where events tend to occur around the timing of scheduled scans. Departures from non-PH observed on log-log plots may therefore be plausibly driven by interval censoring for the PFS endpoint. Additionally, as follow-up for PFS was almost complete, confounding by variation in trial follow up in the presence of non-PH is likely to be low. For OS, there was weaker, inconsistent evidence of non-PH. In the absence of clear evidence that complex analyses such as fractional polynomials or restricted splines would lead to better estimates, it was deemed reasonable to conduct an NMA on the (log) HR scale.

B.2.9.3. Conclusions from the NMA

In conclusion, the NMAs provide robust evidence of the relative effects of capivasertib plus fulvestrant and the other comparators of interest in the population of interest. The results suggest that capivasertib plus fulvestrant plausibly improves PFS and OS compared with the relevant comparators (alpelisib plus fulvestrant or everolimus plus exemestane) in patients with PI3K/AKT-altered HR+/HER2- advanced breast cancer. As prior CDK4/6 inhibitor therapy is not a treatment effect modifier, the results are applicable to the population of patients with PI3K/AKT pathway-altered HR+/HER2- advanced breast cancer following treatment with CDK4/6 inhibitor and AI therapy. The results of the analyses using fulvestrant 500mg as the common referent are appropriate to use in the economic model (see B.3).

B.2.10. Adverse reactions

As there is no reason to suspect that adverse events would be different in those with versus those without prior exposure to CDK4/6 inhibitor therapy, this section focuses on the larger, and so more robust dataset from the PI3K/AKT pathway-altered population meeting the licensed indication for capivasertib plus fulvestrant.

B.2.10.1. Treatment exposure

Treatment durations and relative dose intensities in the PI3K/AKT pathway-altered population are summarised in Table 9. Mean total intended treatment duration for capivasertib was longer than for placebo ([redacted] months), and the duration of concomitant fulvestrant treatment was longer in the capivasertib arm than in the placebo arm ([redacted] months). Although dose interruptions were observed in [redacted]% of patients on capivasertib, primarily due to adverse events, the mean actual treatment duration of capivasertib (total treatment duration minus the total duration of dose interruptions; [redacted] months) was similar to the mean total treatment duration ([redacted] months), indicating that capivasertib dose interruptions were short-lived. Based on median doses delivered, relative dose intensity was [redacted]% with capivasertib and [redacted]% with fulvestrant in the capivasertib plus fulvestrant arm.[57]

Table 9. Summary of treatment exposure in the PI3K/AKT pathway-altered population

	Capivasertib + Fulvestrant N=155		**Placebo + Fulvestrant N=133**	
	Capivasertib	**Fulvestrant**	**Placebo**	**Fulvestrant**
Total intended treatment duration, Mean (SD), (months)	[redacted]	[redacted]	[redacted]	[redacted]
Total actual treatment duration, Mean (SD), (months)	[redacted]	[redacted]	[redacted]	[redacted]
Relative dose intensity, Mean % (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Number of treatment cycles received, Mean / Median (IQR)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with dose reduction, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with dose interruption, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Notes: Total treatment duration = (date of last dose date where dose > 0 - first dose date + 1) / (365.25/12)

	Capivasertib + Fulvestrant N=155		Placebo + Fulvestrant N=133	
	Capivasertib	Fulvestrant	Placebo	Fulvestrant
Actual treatment duration = total treatment duration minus the total duration of dose interruptions Relative dose intensity = the percentage of the actual dose delivered relative to the intended dose through treatment discontinuation **Abbreviations:** IQR, interquartile range; SD, standard deviation **Source:** Clinical Study report, Tables 14.3.1.1.2, 14.3.1.3.2, 14.3.1.4.3, 14.3.1.4.4, 14.3.1.5.2 [57]				

B.2.10.2. Overall adverse events

As would be expected in a study with a targeted agent added to an endocrine backbone therapy, the incidence of any adverse events (AEs) of any grade was higher in the capivasertib plus fulvestrant arm than in the placebo plus fulvestrant arm (Table 10). In the PI3K/AKT pathway-altered population, AEs of any grade were reported by [redacted]% patients in the capivasertib plus fulvestrant arm and [redacted]% patients in the placebo plus fulvestrant arm. The majority of these were of Grade 2 or lower severity. Serious AEs occurred in [redacted]% patients on capivasertib plus fulvestrant and [redacted]% with placebo plus fulvestrant. Serious AEs involving fatal outcomes were reported in [redacted] in the capivasertib plus fulvestrant arm and [redacted] in the placebo plus fulvestrant arm; none of these were assessed by the investigator as related to treatment. AEs were managed with dose modifications as needed, and the rate of discontinuation of capivasertib due to AEs was relatively low at [redacted]%, demonstrating a manageable and tolerable safety profile of capivasertib plus fulvestrant therapy.[57]

Table 10. Summary of overall adverse events in the PI3K/AKT pathway-altered population

	Number (%) of patients [a]	
	Capivasertib + Fulvestrant (N = 155)	Placebo + Fulvestrant (N = 133)
Any AE	[redacted]	[redacted]
Any AE possibly related to capivasertib/placebo	[redacted]	[redacted]
Any AE possibly related to capivasertib/placebo only [b]	[redacted]	[redacted]
Any AE possibly related to both capivasertib/placebo and fulvestrant [b]	[redacted]	[redacted]
Any AE possibly related to fulvestrant only [b]	[redacted]	[redacted]
Any AE of CTCAE Grade 3 or higher	[redacted]	[redacted]
Any SAE with outcome of death	[redacted]	[redacted]

	Number (%) of patients [a]	
	Capivasertib + Fulvestrant (N = 155)	Placebo + Fulvestrant (N = 133)
Any SAE (including events with outcome of death)	[redacted]	[redacted]
Any AE leading to discontinuation of capivasertib/placebo	[redacted]	[redacted]
Any AE leading to discontinuation of capivasertib/placebo only	[redacted]	[redacted]
Any AE leading to discontinuation of both capivasertib/placebo and fulvestrant	[redacted]	[redacted]
Any AE leading to discontinuation of fulvestrant only	[redacted]	[redacted]
Any AE leading to dose modification of capivasertib/placebo	[redacted]	[redacted]
Any AE leading to dose interruption of capivasertib/placebo [c]	[redacted]	[redacted]
Any AE leading to dose interruption of capivasertib/placebo only	[redacted]	[redacted]
Any AE leading to dose interruption of both capivasertib/placebo and fulvestrant	[redacted]	[redacted]
Any AE leading to dose interruption of fulvestrant only	[redacted]	[redacted]
Any AE leading to dose reduction of capivasertib/placebo only [c]	[redacted]	[redacted]

Notes: [a]Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
[b]As assessed by the investigator.
[c]Differences in the number of dose modifications due to AEs in the exposure summary and the number of AEs resulting in a dose modification are due to the differences in data capture between the exposure and AE eCRFs.
Source: Clinical study report, Table 39[57]

B.2.10.3. Most common AEs

Overall, the AEs reported in the PI3K/AKT pathway-altered population were consistent with the known safety profiles of capivasertib and fulvestrant, or due to underlying disease. AEs of any grade occurring in >10% patients in any treatment arm are summarised in Table 11. The most frequently reported AEs were: diarrhoea ([redacted] with capivasertib plus fulvestrant vs [redacted] with placebo plus fulvestrant); nausea ([redacted] vs [redacted]); fatigue ([redacted] vs [redacted]); maculo-papular rash ([redacted] vs [redacted]); vomiting ([redacted] vs [redacted]); and rash ([redacted] vs [redacted]). As noted above, most of these AEs were of Grade 2 or less severity, were managed by dose modification, and few led to treatment discontinuation. Grade 3 or 4 severity AEs occurring in >2% of patients in any treatment arm were limited to diarrhoea ([redacted] vs [redacted]), maculo-papular rash ([redacted] vs [redacted]) and anaemia ([redacted] vs [redacted]).[57]

Table 11. Most common AEs in the PI3K/AKT pathway-altered population (Frequency >10% in either treatment arm)

MedDRA Preferred term	Number (%) of patients [a]	
	Capivasertib + Fulvestrant (N = 155)	Placebo + Fulvestrant (N = 133)
Diarrhoea	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Rash maculo-papular	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]

Notes: [a] Number (%) of patients with AEs, sorted in descending frequency of preferred term in the capivasertib plus fulvestrant treatment group.
Patients with multiple events in the same preferred term are counted only once in that preferred term.
AEs with an onset date on/after date of first dose; AEs with onset date prior to dosing which worsen after dosing; AEs occurring up to 30 days (+7 days) following date of last dose are reported.
AE = Adverse Event. N = Number of patients in treatment group. MedDRA version 25.0.
Source: Clinical study report, Table 14.3.2.4.2[57]

B.2.10.4. AE causality

AEs of any grade possibly related to capivasertib or placebo in patients with PI3K/AKT pathway alterations were reported in [redacted]% of the capivasertib plus fulvestrant arm and [redacted]% of the placebo plus fulvestrant arm. The most common AEs possibly related to capivasertib in patients were gastrointestinal disorders (diarrhoea [redacted]%], nausea [redacted]%], stomatitis [redacted]%], vomiting [redacted]%]), skin disorders (maculo-papular rash [redacted]%], rash [redacted]%]), and metabolism and nutrition disorders (decreased appetite [redacted]%], hyperglycaemia [redacted]%]. AEs possibly related to both capivasertib and fulvestrant occurred in [redacted]% of patients in the capivasertib plus fulvestrant arm, and mainly in the same categories.[57]

Dose modification of capivasertib or placebo due to AEs occurred in patients with PI3K/AKT pathway alterations in [redacted]% of patients in the capivasertib plus fulvestrant arm and 13.5% of patients in the placebo plus fulvestrant arm. The most common AE leading to capivasertib dose modification was diarrhoea ([redacted]%). There were no discontinuations of capivasertib due to diarrhoea.[57] Although diarrhoea possibly related to capivasertib occurred in [redacted]% of

patients receiving capivasertib plus fulvestrant, it is clear that diarrhoea was low grade and manageable.

B.2.10.5. Adverse events of special interest

Adverse events of special interest specified in the CAPItello-291 protocol included: diarrhoea, hyperglycaemia, infective pneumonia, QT prolongation, rash (including maculo-papular rash), stomatitis and urinary tract infection (UTI). The incidence and severity of diarrhoea, hyperglycaemia, rash and stomatitis are discussed above. QT prolongation occurred in [redacted] patients with PI3K/AKT pathway alterations receiving capivasertib plus fulvestrant vs [redacted] with placebo plus fulvestrant. Infective pneumonia occurred in [redacted] vs [redacted], respectively, and UTI occurred in [redacted] vs [redacted].[57]

B.2.11. Ongoing studies

Capivasertib is currently only being evaluated in the CAPItello-291 trial for patients with HR+/HER2- breast cancer. [redacted]

B.2.12. Interpretation of clinical effectiveness and safety evidence

B.2.12.1. Context and decision problem

Advanced breast cancer is an incurable disease that exerts a heavy symptom and HRQoL burden on patients, whilst significantly limiting life expectancy (see B.1.3.1). Patients with PI3K/AKT pathway alterations (PIK3CA/AKT1/PTEN) experience more rapid disease progression and poorer outcomes than those without.[10–13]

In HR+/HER2- advanced breast cancer patients who progress on or after CDK4/6 inhibitor plus endocrine therapy and are not at imminent risk of organ failure, alpelisib plus fulvestrant in patients with PIK3CA mutations, or everolimus plus exemestane, are the only current treatment options available before moving to cytotoxic chemotherapy (see B.1.3.2). However, given clinician views on the toxicity profile of alpelisib plus fulvestrant in TA816,[20] an alternative targeted treatment option for those with PIK3CA mutations, with an improved adverse event

profile, would be valuable. As there are currently no targeted treatment options for patients with tumours harbouring AKT1 or PTEN alterations without PIK3CA mutations, everolimus plus exemestane is the only endocrine-based treatment option for these patients following progression on a CDK4/6 inhibitor-based therapy; however, whilst usually tolerated better than cytotoxic chemotherapy, everolimus is also recognised by clinicians to be associated with challenging adverse events.[20]

There is therefore a significant unmet need for an effective and tolerable treatment option targeting the PI3K/AKT pathway that has a differentiated mode of action, enhances sensitivity to endocrine therapy following failure of CDK4/6 inhibitor therapy, and enables patients with PIK3CA/AKT1/PTEN alterations to remain on endocrine-based treatment for longer before progression to cytotoxic chemotherapy. Capivasertib plus fulvestrant, as the first AKT inhibitor therapy to be licensed, is an innovative therapy that provides a much-needed novel therapy option for patients with HR+/HER2- advanced breast cancer harbouring PI3K/AKT pathway alterations.

B.2.12.2. Summary of clinical evidence base

B.2.12.2.1. Efficacy and safety data in CAPItello-291

The CAPItello-291 trial was a robust phase 3 trial, at low risk of bias. The trial demonstrated that targeting tumours containing PI3K/AKT pathway alterations with capivasertib plus fulvestrant reduced the risk of progression or death by 50% (HR 0.50; 95%CI 0.38 to 0.65) and more than doubled median PFS (7.3 months vs 3.1 months) compared with fulvestrant monotherapy (see B.2.6.1), with similar relative treatment effects in patients with previous use of CDK4/6 inhibitor therapy (see B.2.6.2). Secondary and exploratory endpoints including objective response rates (B.2.6.6), PFS2 (B.2.6.5) and time to first subsequent chemotherapy or death (B.2.6.9) supported these findings, with the latter indicating the potential to delay use of chemotherapy in line with patient and clinician preferences (see B.1.3.2.2). Although OS, as a key secondary endpoint, was only 28% mature at the primary data cut off, the data show a clear trend towards improvement in OS with capivasertib plus fulvestrant in the PI3K/AKT pathway-altered population (HR 0.69; 95% CI 0.45, 1.05), with early and sustained benefit apparent in the Kaplan-Meier curves (see B.2.6.3 and B.2.6.4). The majority of adverse events were mild-to-moderate and were manageable with dose modifications; the rate of discontinuations of capivasertib due to adverse events was low and acceptable for this patient

population (B.2.10.2). HRQoL assessments suggest that, overall, capivasertib plus fulvestrant does not materially reduce patient quality of life and may help to preserve overall quality of life over the course of treatment (B.2.6.7).

B.2.12.2.2. Comparative evidence

The NMAs discussed in B.2.9 and Appendix D1.2 provide robust evidence of the relative effects of capivasertib plus fulvestrant and the comparators of interest (alpelisib plus fulvestrant and everolimus plus exemestane) in patients with PI3K/AKT-altered HR+/HER2- advanced breast cancer following recurrence or progression on CDK4/6 inhibitor and AI therapy. Based on a nominal two-sided 5% level and their 95% credible intervals not spanning one, all three treatments of interest (capivasertib plus fulvestrant, alpelisib plus fulvestrant and everolimus plus exemestane) were significantly superior to fulvestrant 500mg in terms of PFS and OS. The results further suggest that capivasertib plus fulvestrant plausibly improves PFS and OS to a greater, albeit not statistically significant, degree compared with alpelisib plus fulvestrant in patients with PIK3CA mutations. PFS for patients with PI3K/AKT-pathway altered tumours receiving capivasertib plus fulvestrant was numerically superior to everolimus plus exemestane and was significantly superior to everolimus plus exemestane for OS in the statistically preferred fixed effects model.

B.2.12.3. Generalisability and relevance of clinical evidence base

The collective evidence base for capivasertib plus fulvestrant is reflective of its anticipated use in clinical practice.

B.2.12.3.1. Patient populations

The CAPItello-291 trial recruited premenopausal, perimenopausal and postmenopausal women, and men, with HR+/HER2- advanced breast cancer, reflecting the broad population of adults who develop advanced breast cancer in clinical practice. The study was designed specifically to include patients with or without PI3K/AKT pathway alterations, and the majority (~70%) had previously used CDK4/6 inhibitor plus AI therapy,[6] reflecting the current recommended first-line treatment of HR+/HER2- advanced breast cancer patients in UK clinical practice (see UK treatment pathway in Figure 1). Clinical experts consulted by AstraZeneca UK Ltd have confirmed the enrolled patient populations in CAPItello-291, including the subgroup with tumours with PI3K/AKT pathway alterations meeting the licensed

indication, are reflective of patients who would be eligible to receive capivasertib plus fulvestrant in clinical practice. Genomic testing for PIK3CA mutations is routinely undertaken in patients who have progressed on CDK4/6 inhibitor plus AI therapy, and it is anticipated that genomic testing for AKT1 and PTEN mutations will be added to the national genomic test directory and therefore reimbursed on the NHS to enable the appropriate use of capivasertib in all eligible patients by the time of the final capivasertib plus fulvestrant NICE recommendation.

There may be some heterogeneity in the patient populations enrolled in the trials included in the NMA. Whilst the relevant subgroups of the CAPItello-291 trial of capivasertib plus fulvestrant (PIK3CA/AKT1/PTEN alterations) and the SOLAR-1 trial of alpelisib plus fulvestrant (PIK3CA mutations) are reflective of their use in patients in clinical practice, the BOLERO-2 and BOLERO-5 trials of everolimus plus exemestane were conducted before testing for PIK3CA mutations was available through the NHS. Similarly, due to the evolution of treatment patterns, patients in the trials conducted before the CAPItello-291 trial did not have the opportunity to receive first-line therapy with a CDK4/6 inhibitor, as the CDK4/6 inhibitor-based combination treatments were not available at the time these trials were conducted. As discussed in Appendix D1.2, there is no evidence to suggest that these differences would render the results of the NMA inapplicable to patients in current clinical practice.

B.2.12.3.2. Intervention and comparators

The CAPItello-291 trial[6] compared capivasertib plus fulvestrant against placebo plus fulvestrant at the same doses and frequency as the licensed regimen, and the regimen that will be used in clinical practice. Due to shifting trends in treatment practices, and the clear desire to delay the use of chemotherapy for as long as clinically appropriate (see B.1.3.2), the fulvestrant 500mg comparator is an appropriate trial comparator to demonstrate the efficacy and safety of capivasertib added onto fulvestrant (as was the case in the SOLAR-1 trial of alpelisib plus fulvestrant). However, fulvestrant 500mg is not regarded as a relevant comparator for capivasertib plus fulvestrant in its proposed position in current UK clinical practice. For this reason, the NMA discussed in B.2.9 and Appendix D1.2 specifically compared capivasertib plus fulvestrant against the relevant comparators in UK clinical practice, namely alpelisib plus fulvestrant and everolimus plus exemestane (B.1.3.3).

B.2.12.3.3. Outcomes

The co-primary endpoint of the CAPItello-291 trial was investigator-assessed PFS in the ITT population and in the PI3K/AKT pathway-altered population,[6] with the latter forming the licensed patient population in the UK.[28] PFS is a well-accepted primary endpoint in oncology trials, it was used as a primary endpoint in the key trials of the relevant comparators alpelisib and everolimus that are recommended as options by NICE,[19,20] and was accepted by regulatory authorities as the appropriate primary endpoint for the CAPItello-291 trial.[36] PFS assessed by blinded independent central review was conducted as a sensitivity analysis on the overall population and demonstrated that the investigator assessment of PFS was reliable and valid (see section B.2.6.1).

OS was a key secondary endpoint of the CAPItello-291 trial, and although OS data had not reached maturity at the time of the primary analysis of the PFS endpoint, based on current data there was a clear early and sustained trend towards an OS benefit with capivasertib plus fulvestrant (B.2.6.4). Treatment effects were additionally assessed by time to first subsequent chemotherapy or death in the PI3K/AKT pathway-altered population, which showed that treatment with capivasertib plus fulvestrant resulted in a nominally significant delay in the use of subsequent chemotherapy by 5 months (B.2.6.9). PFS2 also showed a trend towards improvement with capivasertib plus fulvestrant (see section B.2.6.5). HRQoL, which is a particularly important outcome in the advanced breast cancer setting where treatment is given with palliative rather than curative intent, was assessed using multiple cancer-specific instruments that consistently demonstrated quality-of-life was preserved with use of capivasertib plus fulvestrant (see section B.2.6.7).

Collectively, CAPItello-291 assessed a comprehensive, clinically relevant set of outcomes that are of direct relevance to patients with advanced breast cancer and their management. Results across these outcomes consistently support the benefit of capivasertib plus fulvestrant, with no detriment to HRQoL.

B.2.12.4. Strengths and limitations of clinical evidence

B.2.12.4.1. CAPItello-291 trial of capivasertib plus fulvestrant

The CAPItello-291 trial was a robust phase 3 trial, at low risk of bias and provided valid results that are generalisable to patients with PI3K/AKT pathway-altered HR+/HER2- advanced

breast cancer anticipated to receive capivasertib plus fulvestrant in clinical practice. The trial demonstrated that the risk of progression or death was halved, and PFS was doubled for capivasertib plus fulvestrant compared with fulvestrant monotherapy. These clinically and statistically significant results were supported by the sensitivity analysis of PFS by BICR, which indicates that the investigator assessed PFS used in the primary endpoint is reliable. Secondary and exploratory endpoints consistently supported these results. The adverse event profile was very manageable, with few discontinuations due to AEs, and HRQoL was preserved. The trial therefore demonstrates the meaningful benefits of capivasertib plus fulvestrant on outcomes that are clinically relevant and important to patients.

Limitations of the evidence from the CAPItello-291 trial include the use of fulvestrant monotherapy as a comparator. Fulvestrant monotherapy was an appropriate trial comparator in the context of a global RCT at the time of trial design, reflecting SoC at the time and enabling robust assessment of the contribution of components in the doublet regimen under study. However, fulvestrant no longer represents UK SoC for second line treatment of HR+/HER2- advanced breast cancer and is not currently recommended by NICE or nationally reimbursed for patients with advanced breast cancer.

OS data from the CAPItello-291 trial were only 28% mature at the time of the primary efficacy analysis.[57] Nonetheless, the available data from CAPItello-291 provide compelling evidence that capivasertib plus fulvestrant is an effective and tolerable targeted treatment option for tumours harbouring PIK3CA/AKT1/PTEN alterations that has a differentiated mode of action, enhances sensitivity to endocrine therapy following failure of CDK4/6 inhibitor therapy, and enables patients with PI3K/AKT pathway alterations mutations to remain on endocrine-based treatments for longer before progression to cytotoxic chemotherapy.

B.2.12.4.2. Indirect comparison

The NMA provides robust evidence to specifically address the comparative effectiveness of capivasertib plus fulvestrant against the relevant comparators in practice. The trial network includes the most robust and relevant trial data possible; however, a key assumption required to construct the trial network was that PIK3CA/AKT1/PTEN altered status and prior CDK4/6 inhibitor therapy use are not significant treatment effect modifiers for everolimus plus exemestane or other therapies required to link to capivasertib plus fulvestrant or alpelisib plus fulvestrant. On the available evidence, this seems to be reasonable (B.2.9 and Appendix

D1.2). The NMA focuses on PFS and OS, which are key outcomes of concern for patients and clinicians and are required to parameterise the economic model. The results suggest that capivasertib plus fulvestrant plausibly improves PFS and OS compared with the relevant comparators (alpelisib plus fulvestrant or everolimus plus exemestane) in patients with PI3K/AKT-altered HR+/HER2- advanced breast cancer following initial therapy with CDK4/6 inhibitor and AI therapy.

B.2.12.5. Conclusions from clinical evidence

Based on robust phase 3 trial data, capivasertib plus fulvestrant provides clinically meaningful and statistically significant improvements in PFS compared with fulvestrant monotherapy in patients with HR+/HER2- advanced breast cancer with PI3K/AKT pathway alterations. These data are supported by consistent results on secondary and exploratory endpoints in the PI3K/AKT pathway-altered population, and for PFS and OS in the PI3K/AKT-altered population who had received prior therapy with CDK4/6 inhibitor plus AI. NMAs using the most robust trial data available indicate that capivasertib plus fulvestrant plausibly improves PFS and OS compared with the relevant comparators (alpelisib plus fulvestrant or everolimus plus exemestane) in patients with PI3K/AKT pathway-altered HR+/HER2- advanced breast cancer following treatment with CDK4/6 inhibitor and AI.

B.3. Cost effectiveness

Summary of cost effectiveness

- A three health-state partitioned survival model was developed in Microsoft Excel® to assess the cost effectiveness of capivasertib plus fulvestrant. The health states included progression-free, progressed disease and death states (see B.3.2).
- The model is aligned with the NICE reference case and compares capivasertib plus fulvestrant against alpelisib plus fulvestrant and everolimus plus exemestane in patients with PI3K/AKT pathway-altered HR+/HER2- locally advanced or metastatic breast cancer whose disease has progressed following CDK4/6 inhibitor plus endocrine therapy.
- The relative treatment effects of capivasertib plus fulvestrant and the comparators are derived from a network meta-analysis using data from their pivotal trials (see B.2.9).
- These relative treatment effects are applied to the baseline PFS and OS curves derived from the fulvestrant monotherapy arm of the CAPItello-291 trial, which are extrapolated over a lifetime horizon using robust parametric modelling that was informed and validated by clinical experts.
- Health state utility values are derived from EQ-5D-5L data collected directly from patients in the CAPItello-291 trial and mapped to EQ-5D-3L.
- The proportional QALY shortfall with current comparator treatments in people with PI3K/AKT-altered HR+/HER2- locally advanced or metastatic breast cancer that has progressed following CDK4/6 inhibitor plus endocrine therapy exceeds 85%. Capivasertib plus fulvestrant qualifies for consideration under the NICE severity modifier, with a QALY weighting of 1.2 versus both relevant comparators.
- Compared with alpelisib plus fulvestrant (the treatment most likely to be displaced), capivasertib plus fulvestrant has a base case ICER at list prices and using a 1.2x QALY weighting of [redacted]/QALY.
- Compared with everolimus plus exemestane, capivasertib plus fulvestrant has a base case ICER at list prices and using a 1.2x QALY weighting of [redacted]/QALY.
- In fully incremental analysis, capivasertib plus fulvestrant extendedly dominated alpelisib plus fulvestrant, indicating that capivasertib plus fulvestrant would, on average, be the clinically and economically preferred of these two therapies in patients with PIK3CA altered tumours.
- Pairwise probabilistic results were consistent with the deterministic results.
- Extensive sensitivity and scenario analyses demonstrate that the base case model is robust to most parameters and assumptions. As may be expected, the model is sensitive to the parameters that influence total drug acquisition costs and the parametric distributions assumed for extrapolation of PFS and OS over the long term. However, selection of the base case parametric distributions followed recommended guidance and was validated by clinical expert opinion.

Conclusion

- Capivasertib plus fulvestrant is a plausibly cost-effective therapy option in its clinician-confirmed place in the current treatment pathway. As a clinically effective and plausibly cost-effective therapy that can address the significant unmet needs of patients with incurable PI3K/AKT pathway altered HR+/HER2- advanced or metastatic breast cancer, capivasertib plus fulvestrant should be recommended for routine commissioning.

B.3.1. Published cost-effectiveness studies

A systematic literature review of economic evaluations of therapies for HR+/HER2- advanced breast cancer was conducted to 05 April 2024 (see Appendix G). This identified a total of 125 published cost effectiveness analyses across multiple therapies and different lines of treatment. Markov cohort models (N=49) and partitioned survival models (N=38) were the most common modelling approaches; in particular, three-state models consisting of a pre-progression state, progressed disease state, and death.

Where reported, the countries that had the most health economic evaluations available were the United Kingdom (n=30), the United States (n=26) and Canada (n=25). Most economic evaluations were European (n=57) or North American (n=53).

There were 46 studies of health economic evaluations reporting first-line only treatment options, and 41 studies reporting first-line vs. second-line treatment only. The most common treatments in second-line studies were fulvestrant combinations (n=17), including abemaciclib, alpelisib, ribociclib, everolimus and palbociclib. Several health economic evaluations were identified of treatments spanning multiple treatment lines (n=22), later treatment lines (including multiple treatment lines; n=12), or with no treatment line specified (n=23).

No published economic evaluations of capivasertib plus fulvestrant were identified. Eight previous HTAs of alpelisib plus fulvestrant and everolimus plus exemestane in HR+/HER2- advanced breast cancer (i.e., the relevant comparators for capivasertib plus fulvestrant) were identified, including two NICE appraisals (TA816 and TA421).[19,20] A summary of the cost effectiveness analyses conducted for the NICE appraisals of these relevant comparators is provided in Table 12. NICE appraisals of other therapies for HR+/HER2- advanced breast cancer were also identified and informed consideration of other model inputs where relevant.

Table 12. Summary of published cost effectiveness analyses in HTAs relevant to this appraisal

NICE TA	Summary of model	Intervention / comparator	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)
TA816 (2022)[20]	**Model type:** Partitioned survival model with 3 health states: progression-free, progressed, and death. The committee considered that the partitioned survival model is a standard approach to estimate the cost effectiveness of cancer drugs and is suitable for decision making. **Key source of efficacy data:** BYLieve, SOLAR-1 **Source of utilities:** SOLAR-1 **Time horizon:** 40 years (lifetime) **Perspective:** NHS/PSS **Cycle length:** 28 days **Discount rate for cost:** 3.5% **Discount rate for outcomes:** 3.5%	**Intervention:** Alpelisib plus fulvestrant **Comparator:** Everolimus plus exemestane	Patients with HR+/HER2− advanced breast cancer with a PIK3CA mutation who have received prior CDK4/6i therapy	NR	NR	NR (But ICER comfortably below £50,000/QALY) **End-of-life criteria met** **Commercial arrangement in place**
TA421 (2016, post CDF and TA295)[19]	**Model type:** Markov model with 3 health states: stable disease, progressed disease, and death **Key source of efficacy data:** BOLERO-2 **Source of utilities:** Lloyd et al 2006 **Time horizon:** 15 years (adjusted to 20 years by ERG) **Perspective:** NHS **Cycle length:** 1 month **Discount rate for cost:** 3.5% **Discount rate for outcomes:** 3.5%	**Intervention:** Everolimus plus exemestane **Comparator:** Exemestane alone*	Post menopausal women with HR+/HER2- advanced breast cancer without symptomatic visceral disease	ERG corrected model*: Everolimus plus exemestane: 1.786 Exemestane: 1.57	ERG corrected model*: Everolimus plus exemestane: NR Exemestane: £44,293	NR (But ERG's ICER estimate of £68,000/QALY for everolimus plus exemestane vs exemestane alone was viewed as more plausible than the company's base case) **End-of-life criteria not met** **Commercial arrangement in place**

Notes: * Ultimate comparator considered by committee
** Adjusted by ERG, values presented at committee meeting (https://www.nice.org.uk/guidance/ta421/documents/committee-papers)
Abbreviations: CDF, cancer drugs fund; ERG, evidence review groups; ICER, incremental cost-effectiveness ratio; NR, not reported; QALYs, quality-adjusted life years

B.3.2. Economic analysis

In the absence of published cost effectiveness analyses of capivasertib plus fulvestrant in the indication of interest, a *de novo* cost effectiveness model was developed to conduct a cost-utility analysis in line with the NICE reference case. An overview of the model is provided in Table 13.

Table 13. Overview of economic model

Aspect	Value	Justification
Model structure	Partitioned survival model with 3 health states: progression free (PF), progressed disease (PD), death.	Consistent with previous models in advanced breast cancer[20,22]
Type of economic evaluation	Cost utility analysis including fully incremental analysis.	In line with NICE reference case[33]
Perspective on outcomes	All health effects for patients.	In line with NICE reference case[33]
Perspective on costs	UK NHS and PSS.	In line with NICE reference case[33]
Population	Adult patients with HR+/HER2- locally advanced or metastatic breast cancer and one or more PIK3CA/AKT1/PTEN-alterations, following recurrence or progression on or after an endocrine-based regimen including CDK4/6 inhibitor.	Based on the licensed indication for capivasertib plus fulvestrant in the PI3K/AKT pathway-altered population and in line with anticipated clinical positioning of capivasertib plus fulvestrant in clinical practice.
Time Horizon	Estimated 20 years (lifetime horizon, when <1% of population alive).	Long enough to reflect all important differences in costs or outcomes between the technologies being compared, in line with NICE reference case.
Intervention	Capivasertib plus fulvestrant, regimen as per the CAPItello-291 trial and the licensed indication.	Technology under appraisal.
Comparators	• Alpelisib plus fulvestrant (patients with PIK3CA mutated tumours only). • Everolimus plus exemestane.	The relevant comparators amongst those listed in the NICE scope (see Table 1). Aligned with international guidelines and NICE guidance on HR+/HER2- advanced breast cancer in the proposed positioning of capivasertib plus fulvestrant.
Cycle length	1 month (30.44 days) with half cycle correction.	Chosen to reflect the monthly dosing schedule of treatment and considered short enough to capture any meaningful changes in cost and health outcomes. Aligned with previous models in this area (e.g., models in NICE TA816 and TA421).
Discount rate	3.5% per annum for costs, QALYs and LYs.	In line with NICE reference case[33]
Synthesis of evidence on health effects	Systematic literature review identified relevant studies for capivasertib plus fulvestrant and the comparators, Subsequently, an NMA of identified RCTs provides indirect comparative PFS and OS data for capivasertib plus fulvestrant, alpelisib plus fulvestrant and everolimus plus exemestane vs fulvestrant.	In line with NICE reference case[33]

Aspect	Value	Justification
Measuring and valuing health effects	Health effects expressed in terms of QALYs using EQ-5D-3L.	In line with NICE reference case[33]
Source of data for measurement of HRQoL	Based on EQ-5D-5L data reported directly by patients in CAPItello-291 trial, mapped to 3L.	In line with NICE reference case[33]
Source of preference data for valuation of changes in HRQoL	Hernandez Alava et al value set estimated in a representative sample of UK population.[70]	In line with NICE reference case[33]
Costs	Costs relate to NHS resource use and drug costs, and are valued using recent NHS reference costs, eMIT and BNF drug prices.	In line with NICE reference case[33]
Equity considerations	QALYs relate only to patients. A 1.2x QALY weighting is applicable (see section B.3.6).	In line with NICE reference case[33]

Abbreviations: HRQoL, health-related quality of life; LY, life years; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; OS, overall survival; PD, progressed disease; PF, progression free; PSS, Personal Social Services; QALY, quality-adjusted life-year.

B.3.2.1. Patient population

The population in the model is patients with HR+/HER2-, PI3K/AKT pathway-altered, locally advanced or metastatic breast cancer following progression on or after CDK4/6 inhibitor plus endocrine therapy. This reflects the population in which capivasertib plus fulvestrant will be used in clinical practice (see B.1.3.1). In the CAPItello-291 trial these patients make up >70% of the PI3K/AKT pathway-altered population,[6] and the characteristics of these patients are broadly similar to the patients in the PI3K/AKT-altered pathway population enrolled in the CAPItello-291 trial irrespective of prior CDK4/6 inhibitor use (see Table 5 in B.2.3.2). Whilst prior CDK4/6 inhibitor use is not a treatment effect modifier, there is some evidence it is prognostic, as discussed in Appendix D1.2.

Whilst alpelisib plus fulvestrant is only licensed and recommended for use in patients with PIK3CA mutations (per TA816) [20], capivasertib plus fulvestrant is licensed and is anticipated to be used in practice in patients with PI3K/AKT pathway alterations including PIK3CA and/or AKT1 and/or PTEN. Of these pathway alterations, PIK3CA alterations are the most common, accounting for >75%[6] (see B.1.3.1). As described in section B.2.9 and Appendix D1.2, whilst there is evidence that having PI3K/AKT pathway-altered tumours does modify treatment effect compared to non-altered tumours, there is no evidence that PIK3CA mutations are prognostic or modify treatment effect to any greater or lesser extent compared with other PI3K/AKT-mutations (see consistent treatment effects for capivasertib plus fulvestrant across PIK3CA, AKT1 and PTEN altered tumours in section B.2.7). Therefore, the model compares

capivasertib plus fulvestrant in the PI3K/AKT-altered population with alpelisib plus fulvestrant in the PIK3CA population, and results are assumed to be constant across these populations.

A full overview of the demographics and baseline characteristics in the PI3K/AKT pathway-altered population (overall) can be found in section B.2.3.2. Table 14 below outlines the key demographics used in the economic model.

Table 14: Key demographics and baseline patient characteristics in the economic model

Characteristic		PI3K/AKT pathway-altered population
Median age; years (range)		59.0 (34-90)
Sex, n (%) (female)		287 (99.3%)
Body surface area ($m^{2)}$	Male	[redacted]
	Female	[redacted]

Abbreviations: AKT: Akt Murine Thymoma Viral Oncogene; n: number

Source: Turner 2023;[6] Clinical study report[57]; note the average body weight and body surface area are based on the ITT population data

B.3.2.2. Model structure

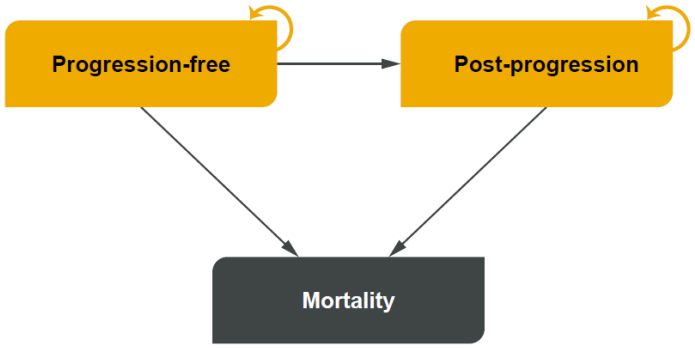
A *de novo* three-state partitioned survival model was developed in Microsoft Excel® to assess the cost effectiveness of capivasertib plus fulvestrant versus the relevant comparators (alpelisib plus fulvestrant and everolimus plus exemestane). This model structure was deemed the most appropriate based on the clinical data available and the widely accepted suitability of this approach in oncology,[71] and has been used in previous HR+/HER2- breast cancer appraisals (e.g. TA816, TA687).[20,22] The model structure directly leverages the primary and key secondary time-to-event endpoints in the CAPItello-291 study, namely OS and PFS. This reflects the natural disease course and the primary objectives of treatment for patients with advanced breast cancer in the form of delaying progression, with its associated treatment costs and impact on length and quality of life (see section B.1.3.1).

The structure of the model is summarised in Figure 18, with the mutually exclusive health states in the model including:

- **Progression free (PF):** patients who are alive with no disease progression; patients can remain in this state, or progress to the progressed disease (PD) or death states at the end of each cycle.
- **Progressed disease (PD):** patients who are alive with PD; patients in the PD state can either remain in this state or enter the death state.

- **Death:** patients who transition from PF and PD to death from any cause; patients remain in the death state for the remainder of the time horizon.

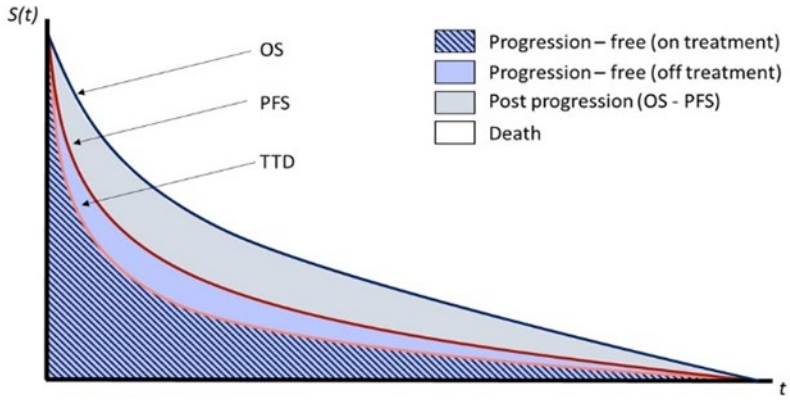
Figure 18. Health states of the partitioned survival model



All patients entered the model in the PF health state and were assumed to initiate treatment with capivasertib plus fulvestrant or the comparators. In each model cycle, patients could either remain in the health state, progress, or die. The proportion of patients who were progression free over time was calculated from the cumulative survival probabilities for investigator-assessed PFS from the fulvestrant arm of the CAPItello-291 trial, which forms the baseline risk to which the relative effects of capivasertib plus fulvestrant and the comparators, obtained from the NMA (section B.2.9), are applied. Although fulvestrant monotherapy is not a relevant comparator for capivasertib plus fulvestrant in the model, this was the common comparator linking the therapies of interest in the NMA and was considered a suitable reference treatment for the model.

The PD health state consists of patients who are alive but whose disease has progressed. Consistent with the natural history of progressive advanced breast cancer, it was assumed that disease progression is irreversible, meaning patients could move from the PF to PD health state but were not able to move from PD to PF. In each model cycle, the proportion of patients with progressed disease was calculated as the difference between the cumulative survival probabilities of OS and PFS (i.e., patients who are alive but not progression-free) (Figure 19).

Figure 19. Partitioned survival model estimation of health state occupancy



Abbreviations: OS, overall survival; PFS, progression-free survival; t, time

The death state is an absorbing state; patients who entered the death state remain in that state until the end of the time horizon. The state occupancy for death was calculated as 1 – OS (i.e., all patients who are not alive). To avoid negative state membership, PFS is constrained to values that are less than or equal to OS over the lifetime of the model. The hazard for death is also constrained to values that are greater than or equal to the background all-cause mortality rate from the general population matched on age and gender. Both OS and PFS were extrapolated beyond the follow-up of CAPItello-291 to a lifetime horizon using parametric survival functions.

Outcomes in the model included life years and QALYs accrued in the PF and PD health states. The PF state represents the period of relatively better quality of life while the disease is under control, and PD represents the period with new and worsening symptoms. The efficacy of subsequent treatment post-discontinuation of initial therapy is not explicitly captured in the model; however, as OS is fully captured in the model, varying the composition of subsequent treatment only impacts subsequent treatment costs, an approach that is consistent with other Health Technology Assessment (HTA) submissions for oncology therapies.

Cost and health outcomes were modelled over an appropriate lifetime horizon, which was assumed to be 20 years (i.e., lifetime, with <1% of patients remaining alive in model) and discounted at an annual rate of 3.5% as per the NICE reference case.[33] The model cycle length is 1 month (30.44 days), which is considered the shortest time period in which a change in the disease course or symptoms would be observed in clinical practice. Half-cycle correction is applied in the model to estimate mid-cycle estimates in each health state, by taking the average between the number of patients present at the beginning of each cycle and the number of patients at the end of each cycle. This accounts for the fact that events and transitions can occur at any point during the cycle, not

necessarily at the start or end of each cycle, and prevents under or overestimation when calculating QALYs or costs.

A comparison of key features of the current model and earlier models used to support the NICE appraisals of alpelisib plus fulvestrant (TA816)[20] and everolimus plus exemestane (TA421),[19] which are the relevant comparators for this appraisal, is provided in Table 15.

Table 15. Comparison of features of the economic analysis vs models of relevant comparators

	Previous evaluations		Current evaluation	
Factor	**TA816 (Alpelisib plus fulvestrant[20]**	**TA421 (Everolimus plus exemestane)[19]**	**Chosen values**	**Justification**
Time horizon	Lifetime (40 years)	15 years (adjusted to 20 years by ERG)	Lifetime (20 years)	Lifetime horizon appropriate for disease associated with risk of death. <1% alive at 20 years in model
Treatment waning effect	5-year duration of treatment effect for alpelisib plus fulvestrant (then switched to everolimus plus exemestane treatment effect)	Not employed (ERG assumed patients would not gain survival benefit from everolimus after disease progression and treatment discontinuation)	Treatment waning has not been applied	Survival analysis and treatment comparisons were conducted in line with NICE DSU TSDs[72,73] and validated by clinical opinion[29]
Source of utilities	SOLAR-1 trial for PF and terminal disease; Mitra et al 2016 for PD	Literature	EQ-5D-5L data collected directly from patients in CAPItello-291 trial mapped to EQ-5D-3L	Using data directly collected from the trial participants is more robust than using external sources
Source of costs	NHS reference costs and previous NICE TA496 and TA687	Unclear	NHS reference costs, eMIT and BNF	Relevant sources used to reflect costs perspective of NHS and PSS

Abbreviations: ERG, evidence review group; NHS, national health service; PD, progressed disease state; PF, progression free state; PSS, personal and social services

B.3.2.3. Intervention technology and comparators

Capivasertib plus fulvestrant is compared in the model against alpelisib plus fulvestrant and everolimus plus exemestane (see section B.1.3.3). The comparison to alpelisib plus fulvestrant is made in the PI3K/AKT pathway altered population, although as alpelisib plus fulvestrant is only recommended in the PIK3CA mutated population, it is assumed that the result holds across these populations. These comparators reflect the relevant comparators from the NICE scope.[14] All technologies are administered and dosed in the model in line with their summaries of product characteristics and clinical trials, and are continued until either disease progression, discontinuation due to intolerability, adverse events, or death. No other clinical continuation or stopping rules are employed.

B.3.3. Clinical parameters and variables

The clinical parameters in the economic analysis include:

- Overall survival (OS)
- Progression-free survival (assessed by the study investigator) (PFS)

Modelling of time to discontinuation of capivasertib plus fulvestrant and the comparators is discussed in section B.3.5.1, and adverse events are considered in terms of their impact on costs and health-related quality of life in section B.3.4.5.

B.3.3.1. Overview of the clinical data sources and approach to survival modelling

The primary data sources for the model are the CAPItello-291 trial[6] described in section B.2.6 and the NMAs described in section B.2.9. As part of the feasibility assessment for the NMA, the assumption of proportional hazards (PH) was explored using a review of the Kaplan-Meier (KM) plots, log-log plots and the Global Schoenfeld Test. This was tested for each comparator and each endpoint and is presented in Appendix D1.2.

For both endpoints the assessment showed that, whilst there is a potential appearance of non-proportionality from some of the data, overall there is no consistent evidence of significant departures from a PH assumption. For PFS, whilst the log-log plots and Schoenfeld residuals suggest some evidence of non-PH, based on a review of the KM plots it is not clear that there were material deviations from PH. The interpretation of log-log plots is inherently subjective, and earlier time points are more prominent on the plots (more data ink) due to the logarithmic scales. Furthermore, apparent departure from non-proportionality observed on the log-log plots for PFS is primarily driven by the interval censoring for the PFS endpoint, e.g., progression events can only be observed when scheduled assessments occur, resulting in 'jumps' in the KM curves at the timepoints where assessments are scheduled. For OS, there is some evidence of non-PH across several trials, although the trends are less pronounced than for PFS, and it was concluded that there was weak-to-moderate evidence of non-PH. With the data available, the use of more complex methods, for example using time-varying hazards, would be challenging, might lead to further uncertainty in the outcome, and thus was not considered appropriate.

Given these findings, and given the other challenges associated with performing an ITC in this setting due to the heterogeneity across trials (see section B.2.9 and Appendix D1.2), a pragmatic approach was taken when calculating the efficacy of the treatments included in the decision problem. Although fulvestrant monotherapy is not a relevant comparator for capivasertib plus fulvestrant in the model (see section B.1.3.3), this was the common comparator linking the therapies of interest in the NMA. The placebo plus fulvestrant arm of the CAPItello-291 trial therefore provides the reference arm in the model. From this reference arm, the outcomes of the comparators are modelled using the HR of treatment versus fulvestrant 500mg from the NMAs. To ensure consistency used with alpelisib plus fulvestrant and everolimus plus exemestane, the capivasertib plus fulvestrant curve is also estimated by applying a HR from the NMA to the extrapolated placebo plus fulvestrant arm from CAPItello-291, instead of fitting parametric survival models directly to the individual patient level data from the capivasertib plus fulvestrant arm in CAPItello-291.

To summarise the approach, the modelling of PFS and OS was therefore conducted in two steps:

1. Fit parametric survival models to the PFS and OS endpoints for the placebo plus fulvestrant arm from CAPItello-291 to predict outcomes during the follow-up of the CAPItello-291 trial, and up to a lifetime horizon. This defines fulvestrant monotherapy as the reference curve in the model, in line with the NMA.

2. Apply HRs estimated from the NMA to the extrapolated placebo plus fulvestrant survival curve to derive the survival curves for capivasertib plus fulvestrant, alpelisib plus fulvestrant and everolimus plus exemestane.

The parametric survival analysis conducted in Step 1 was conducted following NICE DSU guidance TSD14.[72] A series of parametric survival models (exponential, log-normal, Weibull, log-logistic, gamma, generalised gamma, and Gompertz) were fitted to the patient-level data for each endpoint (OS and PFS). To identify the best model fit the following were considered:

- Akaike information criterion (AIC) and Bayesian information criterion (BIC): model fits were evaluated using the AIC and BIC statistical criteria. Lower AIC and BIC values demonstrate a better statistical fit of the survival curve.

- Visual inspection of model fit to the trial data (both to the KM curves and the observed hazards)

- An assessment of the clinical plausibility of extrapolation.

All survival analyses were conducted in R using the flexsurv package, and models were fitted using the standard parameterisation of flexsurv.[74]

B.3.3.2. Progression-free survival modelling – fulvestrant monotherapy reference arm

PFS data for patients with PI3K/AKT-altered tumours, who had received prior endocrine therapy plus CDK4/6 inhibitor therapy in CAPItello-291 are presented in section B.2.6.2. The PFS Kaplan-Meier plot shows a clear early and continued separation between the capivasertib plus fulvestrant and the placebo plus fulvestrant arms over time (Figure 3).

Only survival extrapolations for the fulvestrant plus placebo arm of CAPItello-291 were required given that capivasertib outcomes were to be based on the results of the NMAs. The statistical goodness of fit of each of the standard parametric models fit to the data were reported in terms of the Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) scores in Table 16, where a lower score indicates a more parsimonious fit to the CAPItello-291 trial data. Based on these statistics, log-logistic, log-normal, and generalised gamma were considered to provide good fits to the trial data.

Table 16: AIC and BIC values for the parametric survival models fitted to the PFS fulvestrant data CAPItello-291 (PI3K/AKT pathway-altered populations, DCO1)

Model	PI3K/AKT pathway-altered, post-CDK4/6 inhibitor	
	AIC	BIC
Exponential	425.4	428.0
Weibull	425.8	430.9
Log-normal	406.5	411.6
Log-logistic	402.3	407.4
Gompertz	426.4	431.5
Generalised gamma	408.2	415.8
Gamma	422.5	427.6

Abbreviations: AIC: Akaike Information Criteria; AKT: Akt Murine Thymoma Viral Oncogene; BIC: Bayesian Information Criteria; DCO: data cut-off; PFS: progression-free survival

The fit of the models to the observed data is shown in Figure 20. The log-normal, log-logistic and generalised gamma seem to fit the observed data better visually, although as the trial data is relatively mature for PFS (85.6%), all models provide similar extrapolated projections.

Figure 20: Fit of the parametric survival models to the fulvestrant only KM data for PFS in the PI3K/AKT altered-pathway population in CAPItello-291 (post-CDK4/6i) (DCO1)

Abbreviations: DCO: data cut-off; CDK4/6i: cyclin-dependent kinase 4 and 6 inhibitor; KM: Kaplan-Meier; PFS: progression-free survival

A comparison of the modelled and observed smoothed hazard rates is also shown in Figure 21. The log-normal, log-logistic and generalised gamma models all capture the increase and following decrease in the trial hazards. The final increase in the observed hazards may be overly influenced by the low number at risk at later timepoints (e.g., N=[redacted] at [redacted] months) and so is not considered to be informative.

Figure 21: Modelled and observed smoothed hazard rate for the parametric survival models to the fulvestrant only KM data for PFS in the PI3K/AKT altered-pathway population in CAPItello-291 (post-CDK4/6i, DCO1)

Abbreviations: DCO: data cut-off; CDK4/6i: cyclin-dependent kinase 4 and 6 inhibitor; KM: Kaplan-Meier; PFS: progression-free survival

Clinical validation was sought from five UK clinicians to gain insight into the long-term expectations of PFS in UK clinical practice (see section B.3.14). The PFS KM data for the placebo plus fulvestrant arm from CAPItello-291 and the three best-fitting standard parametric models (lognormal, generalised gamma, loglogistic) over a 5-year time period was provided to clinicians and they were asked to comment on the proportion of patients they would expect to be alive at different time points. Three clinicians commented that the generalised gamma or loglogistic were the most plausible, as both modelled a very small proportion [redacted] to be progression-free at 60 months, compared to lognormal which predicted [redacted] progression-free at 60 months. One clinician commented that lognormal was the most appropriate. The remaining clinician commented that that they would expect less than [redacted] to be progression-free after 12 months, which is an outlier view compared with the views of the other four clinicians and is inconsistent with the observed data from the CAPItello-291 trial data. This comment was therefore not taken into consideration. Clinicians were also asked to comment on the resulting PFS extrapolations for capivasertib plus fulvestrant as a result of selecting a model of the placebo plus fulvestrant arm.

Overall, for the PI3K/AKT pathway-altered post-CDK4/6 inhibitor population, the log-normal and log-logistic models consistently provided the best fit to the PFS data in CAPItello-291 and were therefore considered the primary candidate models for the base case to extrapolate the long-term PFS for the fulvestrant only reference arm. The generalised gamma model is a suitable alternative option with a plausible fit to the data. Based on goodness-of-fit statistics, visual inspection of the trial data to the model predictions, and clinical opinion, the log-normal distribution was selected in the base case, and loglogistic was tested in the scenario analyses.

B.3.3.3. Overall survival modelling – fulvestrant monotherapy reference arm

OS data for patients with PI3K/AKT pathway-altered tumours, who had received prior CDK4/6 inhibitor and endocrine therapy in CAPItello-291 are presented in section B.2.6.4. The OS Kaplan-Meier plot shows a clear early and continued separation between the capivasertib plus fulvestrant and the placebo plus fulvestrant arms over time (Figure 5).

As was done for PFS, a series of independent parametric survival models were fitted to patient-level OS data from the placebo plus fulvestrant arm from CAPItello-291 in patients who had received prior CDK4/6 inhibitor therapy. The statistical goodness of fit was reported in terms of the AIC and BIC scores in Table 17. All models, except for generalised gamma, were considered to provide a reasonable fit to the data (AIC scores between 347.1-348.9, BIC scores between 349.6-353.9).

Table 17: AIC and BIC values for the parametric survival models fitted to the OS fulvestrant data CAPItello-291 (PI3K/AKT pathway-altered populations, DCO1)

Model	PI3K/AKT pathway altered, post-CDK4/6i	
	AIC	BIC
Exponential	347.1	349.6
Weibull	348.0	353.1
Log-normal	347.1	352.2
Log-logistic	347.2	352.3
Gompertz	348.9	353.9
Generalised gamma	349.0	356.6
Gamma	347.1	349.6

Abbreviations: AIC: Akaike Information Criteria; BIC: Bayesian Information Criteria; DCO: data cut-off; OS: overall survival

The fit of the models to the observed data is shown in Figure 22, and extrapolated out over the trial time horizon in Figure 23. Most distributions seem to provide a reasonable fit to the data in the within-trial period, but there are notable differences between distributions in the extrapolated period over the model time horizon (20 years); generalised gamma, log-logistic and log-normal all providing more optimistic survival predictions in the long-run, compared to more pessimistic survival predictions with Gompertz, Weibull, gamma and exponential.

Figure 22: Fit of the parametric survival models to the fulvestrant only KM data for OS in the PI3K/AKT altered-pathway population in CAPItello-291 (post-CDK4/6i) (DCO1) – within-trial period

Abbreviations: DCO: data cut-off; CDK4/6i: cyclin-dependent kinase 4 and 6 inhibitor; KM: Kaplan-Meier; OS: overall

Figure 23 Fit of the parametric survival models to the fulvestrant only KM data for OS in the PI3K/AKT altered-pathway population in CAPItello-291 (post-CDK4/6i) (DCO1) – extrapolated period

The resulting landmark survival probabilities from each model are presented in Table 18. The lognormal, log-logistic and generalised gamma models suggest quite high survival outcomes beyond 10 years versus the Weibull, Gompertz, gamma and exponential models.

Table 18: OS landmark survival probabilities predicted by each parametric model for fulvestrant (PI3K/AKT-altered population, post-CDK4/6i)

Model	Years				
	1	2	5	10	20
Observed (KM)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Model	Years				
	1	2	5	10	20
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CDK4/6i: cyclin-dependent kinase 4 and 6 inhibitor; KM: Kaplan-Meier; OS: overall survival

A comparison of the modelled and observed smoothed hazard rates is also shown in Figure 24. Weibull, Gompertz and gamma all predict increasing hazards with time, whilst log-normal, log-logistic, and generalised gamma predict decreasing hazards with time. The sudden drop and plateau in the trial hazard was not considered as informative due to the low number at risk at later time points (N=[redacted] at [redacted] months). Weibull, Gompertz and gamma appear to follow the observed hazards the closest.

Figure 24: Modelled and observed smoothed hazard rate for the parametric survival models to the fulvestrant only KM data for OS in the PI3KAKT altered-pathway population in CAPItello-291 (post-CDK4/6i, DCO1)

Abbreviations: DCO: data cut-off; CDK4/6i: cyclin-dependent kinase 4 and 6 inhibitor; KM: Kaplan-Meier; OS: overall survival

As statistical and visual goodness-of-fit was comparable across distributions, clinical opinion was considered the most important factor in determining the base case distribution.

Clinical validation was sought from five UK clinicians to gain insight into the long-term expectations of OS in UK clinical practice (see section B.3.14). The OS KM data for the placebo plus fulvestrant arm from CAPItello-291 and six of the standard parametric models (lognormal, generalized gamma, loglogistic, gamma, Weibull, Gompertz) over a 20-year time period were provided to clinicians and they were asked to comment on the proportion of patients they would expect to be alive at different time points. The responses were varied, but four of the clinicians said that the more pessimistic selections (gamma/Weibull/Gompertz) were more reflective of UK clinical practice. Two clinicians said that gamma was the most plausible, one clinician said Gompertz, and one clinician said Gompertz or Weibull. The remaining clinician did not select a distribution but said they would expect [redacted] to be alive at 10 years.

As patients are expected to experience an increased risk of dying over time, Weibull, Gompertz and gamma were considered the most clinically plausible. In addition, over time patients with more severe and aggressive disease pass away, leaving the longer-term survivors, meaning that there is an expectation of a steady but less steep incline of the curve, which is reflected in both the Weibull and gamma, and less so with the Gompertz distribution.

Based on these assessments, the Weibull or gamma models seemed to be the most suitable options for the base-case analysis. Given the feedback from the clinicians, the gamma distribution was selected in the base case and the Weibull distribution was tested in a scenario analyses.

B.3.3.4. Overall survival and progression-free survival for capivasertib plus fulvestrant and external comparators

The efficacy of all treatment regimens of interest in the post-CDK4/6 inhibitor population (i.e., capivasertib plus fulvestrant, alpelisib plus fulvestrant and everolimus plus exemestane) were modelled based on treatment effect estimates versus fulvestrant monotherapy obtained from the NMAs detailed in section B.2.9 and Appendix D1.2. The results of these analyses, in the form of a constant HR of treatment versus fulvestrant monotherapy, were applied to the

extrapolated fulvestrant PFS and OS data (outlined in the previous sections) from CAPItello-291 to estimate the respective survival curves for these treatments in the population of interest.

As described in B.2.9.1, the fixed effects model provided the best statistical fit to the trial data based on the deviance information criterion, and hence the HR estimates obtained from the fixed effect model were incorporated in the model (Table 19).

Table 19: Summary of HRs for treatments versus fulvestrant used in the economic model

Treatment vs. fulvestrant	PI3K/AKT pathway-altered population
PFS (HR <1.0 favours comparator and >1.0 favours fulvestrant)	
Capivasertib + fulvestrant	[redacted]
Everolimus + exemestane	[redacted]
Alpelisib + fulvestrant	[redacted]
OS (HR <1.0 favours comparator and >1.0 favours fulvestrant)	
Capivasertib + fulvestrant	[redacted]
Everolimus + exemestane	[redacted]
Alpelisib + fulvestrant	[redacted]

Abbreviations: AKT: Akt Murine Thymoma Viral Oncogene; HR, hazard ratio; N/A: not applicable; OS: overall survival; PFS: progression-free survival

It should be noted that the gamma and log-normal distributions selected for OS and PFS, respectively, for fulvestrant monotherapy are both accelerated failure time (AFT) models. The combining of HRs from the NMA with survival probabilities estimated from an AFT model is technically mixing assumptions on how treatment effects would (theoretically) be applied in the survival model (acting on the time scale for an AFT model) and how they are modelled in the comparative analysis (acting on the hazard scale). However, we believe that there is no reason to artificially constrain the comparator curves to the same form. If the estimated curves for the comparators are clinically valid, there is no obvious reason why the new survival curves would be biased. All five clinicians commented that the extrapolations for capivasertib plus fulvestrant were plausible when presented with the KM data for the capivasertib plus fulvestrant arm from CAPItello-291 and the resulting extrapolations based on the fulvestrant selection.

B.3.4. Measurement and valuation of health effects

B.3.4.1. Health-related quality of life data from literature

A SLR was undertaken to identify published estimates of health state utility values (HSUVs) for patients with HR+/HER2- advanced breast cancer, as described in Appendix H. The evidence retrieved by this review was supplemented by an overview of HSUVs used in past NICE appraisals of treatments for advanced breast cancer, which were identified by the SLR of previously published economic evaluations described in Appendix G.

Whilst the SLR identified a number of publications reporting HSUVs, few met the requirements of the NICE reference case. Searches of NICE appraisals of other therapies recommended for HR+/HER2- advanced breast cancer following endocrine therapy identified additional EQ-5D data (see Table 20); however, no HSUVs were identified specifically for patients with HR+/HER2- advanced breast cancer with PI3K/AKT pathway-altered tumours following recurrence or progression on or after an endocrine based regimen (note NICE TA816 for alpelisib plus fulvestrant[20] in patients with PIK3CA alterations does not report actual utility values that were adopted and NICE TA421 for everolimus plus exemestane[19] provides limited data). For this reason, the data from CAPItello-291 was considered to be the most relevant for consideration in the first instance as it aligns with the population of interest, but the values identified from the literature were considered as supplementary data to help inform scenario analyses.

Table 20 Identified HSUV data in HR+/HER2- advanced breast cancer after endocrine therapy (previous NICE HTAs)

NICE TA	Treatment regimen	PF HSUV	Source	PD HSUV	Source
TA816[20]	Alpelisib with fulvestrant	NR	SOLAR-1.[64] Utilities were by on/off tx (and tx specific) and progression status	NR	SOLAR-1.[64] Utilities were by on/off tx (and tx dependent) and progression status
TA421[19]	Everolimus with exemestane	0.798	EAG scenarios using tx-specific values E+E: 0.7644; E: 0.7571	0.496, scenario using 0.65	EAG scenario with Lloyd 2006[75]
TA619 (since updated to TA836)[21]	Palbociclib with fulvestrant	Palbo+Ful: 0.74 (0.72 – 0.76); Placebo+Ful: 0.69 (0.67 – 0.72)	PALOMA-3[76]	0.56 (0.5-0.6)	Lloyd 2006[75]

NICE TA	Treatment regimen	PF HSUV	Source	PD HSUV	Source
TA579 (since updated to TA725)[23]	Abemaciclib with fulvestrant	NR	MONARCH-2[77]	0.505	Lloyd 2006[75] EAG scenarios using Mitra et al 2016 (0.67) and MONARCH-2[7]
TA593 (since updated to TA687)[22]	Ribociclib with fulvestrant	NR	MONALEESA-3[78]	NR	MONALEESA-3[78]

Abbreviations: EAG: Evidence Assessment Group; E+E, everolimus plus exemestane; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; HSUV: health state utility value; NICE: National Institute of Health and Care Excellence; NR, not reported PF: progression-free; PD: progressed disease; TA: technology appraisal; tx, treatment

B.3.4.2. Health-related quality of life data from clinical trial

In CAPItello-291, health related quality of life (HRQoL) was assessed using the EORTC QLQ-C30 instrument (see B.2.6.7) and supplemented by the EQ-5D-5L questionnaire (see B.2.6.10). EORTC QLQ-C30 data, specifically in the PI3K/AKT pathway-altered population of the CAPItello-291 trial, demonstrated that capivasertib plus fulvestrant did not materially reduce patient quality of life and may help to preserve overall quality of life over the course of treatment compared with placebo plus fulvestrant.[57]

The schedule of assessment for the EQ-5D-5L included assessments at baseline, and every 4 weeks (±3 days) until PFS2 (defined as the time from randomisation until second progression on next-line treatment, as assessed by the investigator at the local site, or death due to any cause). Overall compliance (number of patients with an evaluable questionnaire at baseline and at least one post-baseline time point, divided by number of patients still expected to complete questionnaires; both on- and off-treatment assessments up to study completion are included in the calculation of compliance rate) with the EQ-5D-5L was [redacted]% in the capivasertib plus fulvestrant arm and [redacted]% in the placebo plus fulvestrant arm.[57] Furthermore, as CAPItello-291 was a double-blind RCT, this reduces bias on patient-reported outcomes.

EQ-5D-5L data from the overall population (Figure 25, Figure 26) were highly consistent with the data in the PI3K/AKT pathway-altered population (Figure 8, Figure 9). Furthermore, the substantial majority (~70%) of patients in the PI3K/AKT pathway-altered population (see B.2.3.2) and in the overall population[6] of the CAPItello-291 trial had been treated previously with CDK4/6 inhibitor therapy. Therefore, as the overall population provides substantially more

data points, the EQ-5D-5L data from the overall CAPItello-291 trial population are adopted in the model as a reliable estimate of HRQoL and source of HSUVs for the modelled population of patients eligible for capivasertib plus fulvestrant.

Figure 25. EQ-5D index score, change from baseline, by visit, Mean (SD) (FAS)

Source: Clinical study report, Figure 14.2.9.6.2 [57]

Figure 26. EQ-VAS score, change from baseline, by visit, Mean (SD) (FAS)

Source: Clinical study report, Figure 14.2.9.7.2 [57]. **Note**: patient numbers reflect number of patients providing data at that cycle

HSUVs were estimated from the analysis of EQ-5D-5L domain responses collected throughout study follow-up. In total, [redacted] EQ-5D-5L observations were available from [redacted] patients. Of these, [redacted] observations were recorded while progression-free and [redacted] were recorded after progression.

B.3.4.3. Mapping analysis

As described above, the CAPItello-291 trial collected health status data using the EQ-5D-5L. The 3-level version (EQ-5D-3L) and the UK time trade-off value set is preferred for the NICE reference case. In line with the 2022 NICE Methods Guide,[33] the mapping function developed by the DSU (Hernández Alava et al., 2017),[79] using the 'EEPRU dataset' (Hernández Alava et al., 2020),[70] were used to convert the EQ-5D-5L data to EQ-5D-3L based utility values.

The mapped HSUVs were summarised using descriptive statistics and mixed effects repeated measures regression (MMRM) analysis. The MMRM analysis for the base-case was conducted to assess the impact of randomised group and health state (PF or PD) on HSUVs. This method accounts for the repeated measurement of HSUVs by subject and provides valid results under the assumption that missing data are missing at random. For input to the cost-effectiveness model, the HSUVs for PFS and PD health states was derived from the MMRM analysis using the estimated marginal means (or least squares) method. This provides a model-based estimate of the mean HSUV for each health state that appropriately accounts for the correlation between repeated measures of EQ-5D-5L data in CAPItello-291.

The MMRM analysis was performed using the restricted maximum likelihood method (REML) with the following covariates included as fixed effects:

- (Randomised) Treatment (model 1)
- Progression status (pre-progression, post-progression) (model 2)
- Treatment + Progression status (model 3)
- Treatment + Progression status + Treatment * Progression status (Both terms and their interaction included) (model 4)

Table 21 presents the goodness of fit statistics for each of the models tested. The best fitting model in terms of AIC and BIC was the model including a term for progression status only (model 2).

Table 21: Goodness of fit statistics

Model terms	Converged?	AIC	BIC
trt (model 1)	Yes	-5874.3	-5662.0
PFSFLAG (model 2)	Yes	-5903.7	-5691.5
trt + PFSFLAG (model 3)	Yes	-5897.4	-5678.6
trt * PFSFLAG (model 4)	Yes	-5888.9	-5663.4

Abbreviations: AIC: Akaike Information Criteria; BIC: Bayesian Information

The marginal ('least square') mean provides a model-based estimate of the mean utility score by status (progression) that is averaged over observations and with adjustment for repeated measures (Table 22). The estimated marginal mean and its associated standard error or confidence interval can be used as utility inputs to the cost-effectiveness model. The resulting estimated progression-free and progressed disease utility values are [redacted] and [redacted], respectively, and these trial-based values derived from patients directly using EQ-5D the instrument are used in the base-case analysis, which is in line with the NICE reference case.

Table 22: Marginal means

Progression status	Estimate	95% CI
Pre-progression	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]

Abbreviations: CI: confidence interval

B.3.4.4. Age-related utility

Age-related utility decrements are also included in the base case analysis to account for the natural decline in HSU associated with age. The economic model includes an adjustment of all health state utilities (base case and scenario analyses) over the time horizon to reflect the modelled patient's age, and as such, prevents the health state utilities exceeding those of the age-matched UK population. The adjustment is modelled using the general population HSU norm equation from Ara & Brazier (2010),[80] summarised in Table 23.

Table 23: Parameters for the health state utility by age

Parameter	Estimate
Intercept	0.9508566
Gender, Male	0.0212126
Age	-0.0002587
Age^2	-0.0000332
Equation: HSU = Intercept + Gender (reference =female) + Age + Age^2	

Abbreviations: HSU: health state utility

Source: Ara & Brazier (2010) [80]

Following NICE-recommended methods, these age-related HSUs are applied as a "multiplier" to the HSUVs assigned to each state.[33]

B.3.4.5. Impact of adverse events on health state utility

Whilst the HRQoL data from the CAPItello-291 trial showed no detriment from treatment with capivasertib plus fulvestrant (see section B.2.6.7 and B.2.6.10), it is possible that AEs experienced outside of the scheduled collection of patients' reported outcomes may have impacted on HRQoL. Furthermore, the incidence of some adverse events differed across the treatments, for example 36.7% of patients receiving alpelisib plus fulvestrant in the SOLAR-1 trial experienced Grade 3+ hyperglycaemia[66] compared with [redacted]% in the PI3K/AKT pathway-altered population receiving capivasertib plus fulvestrant in the CAPItello-291 trial.[57]

AE disutilities were incurred as a one-time application during cycle 1 in the model weighted by their assumed duration. AEs utility impacts were included if the AEs were:

- Grade ≥3: Any AEs were included if they were classified as CTCAE Grade 3 or above. The costs and quality of life impact of Grade 1 and 2 events are assumed to be negligible and are therefore omitted from the analysis.
- Observed in ≥5% of patients in CAPItello-291 or in one of the pivotal studies informing the efficacy of the comparators (SOLAR-1 or BOLERO-2) in the populations in which the therapies are licensed, to ensure that key events were captured while ensuring the list of included events was manageable.

A summary of the AEs included in the economic analysis and respective proportions for each comparator are presented in Table 24. Clinicians were asked for feedback with respect to the adverse events reported in CAPItello-291, and the adverse events they have to manage currently in practice. Clinicians commented that whilst the incidence of diarrhoea and rash is notable for capivasertib plus fulvestrant in CAPItello-291, these are relatively easy to manage

in practice, and with appropriate prophylactic care, which was not permitted in the CAPItello-291 trial setting, the rates of such events could even be improved. Clinicians commented that the management of hyperglycaemia, notable with the introduction of alpelisib plus fulvestrant into clinical practice, has been challenging. There was heterogeneity in response to whether hepatologists were involved, with many oncologists reporting that they manage the condition themselves.[29]

Table 24. Incidence of Grade 3+ adverse events occurring in ≥5% in pivotal trials*

Adverse event proportion (n/N)	Capivasertib plus fulvestrant (PI3K/AKT-altered population)	Alpelisib plus fulvestrant (PIK3CA mutated population)	Everolimus plus exemestane**
Diarrhoea	[redacted]	7.7% (13/169)	3.00% (14.5/482)
Rash maculo-papular	[redacted]	13.0% (22/169)	1.00% (4.8/482)
Rash	[redacted]		
Hyperglycaemia	[redacted]	36.7% (62/169)	6.0% (28.9/482)
Stomatitis	[redacted]	3.0% (5/169)	8.0% (38.6/482)
Anaemia	[redacted]	0% assumed as NR	8.0% (38.6/482)
Source	CAPItello-291 Clinical study report Table 14.3.2.8.2 [57]	SOLAR-1 André et al 2019, Table S3 [66]	BOLERO-2 Yardley 2013, Table 4 [81]

Notes: *Refers to incidence of any treatment emergent AEs, regardless of treatment relationship; ** Proportions are reported in Yardley, n is calculated based on the proportions reported and the sample size and hence are not round numbers

No utility data or AE durations were reported in the studies identified through the SLR of HRQoL and utilities (see Appendix H). Utility decrements associated with AEs were instead informed by Hudgens (2016)[82] where available, which follows the same approach used in a previous NICE appraisal in metastatic breast cancer (TA725).[23] Hudgens (2016) obtained EORTC QLQ-C30 data from a large RCT of eribulin vs. capecitabine in locally advanced metastatic breast cancer that had received prior anthracycline- and taxane-based therapy, and mapped this to EQ-5D using the algorithm by Crott et al[83,84] and a UK tariff to estimate health state utilities and decrements associated with AEs. If these values were not available from Hudgens (2016), a utility study conducted in solid tumours was used. Durations were not reported in Hudgens (2016) and were obtained from the NICE technology appraisal of pixantrone (TA306) for the treatment of adults with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma,[85] in which the manufacturer's submission summarised HRQoL data from a number of solid tumour studies. The disutility values and their durations are presented in Table 25.

Table 25: Disutility values associated with AEs, and assumed duration of events

Adverse event	Disutility value	Disutility source	Duration (days)*	Duration source
Diarrhoea	0.006	Hudgens 2016[82]	6.0	TA306 MS[85] (assumption: same as nausea)
Rash maculo-papular	0.03248	Nafees et al. (2008)[86]	4.0	TA306 MS[85] (assumption: same as mucosal inflammation)
Rash	0.03248	Nafees et al. (2008)[86]	3.0	TA306 MS[85] (assumption: same as mucosal inflammation)
Hyperglycaemia	0.119	Swinburn 2010[87] (assumption: same as anaemia)	16.1	TA306 MS[85] (assumption: same as anaemia)
Stomatitis	0.12	Swinburn 2010[87] (disutility for mucositis only)	4.0	TA306 MS[85] (assumption: same as mucosal inflammation)
Anaemia	0.119	Swinburn 2010[87] (assumption: same as anaemia)	16.1	TA306 MS[85] (assumption: same as anaemia)

Abbreviations: AE, adverse event; NICE, National Institute for Health & Care Excellence; TA, technology appraisal
Notes: * Assumption, per TA725

The impact of AEs experienced by patients receiving subsequent treatment are not considered in the analysis. This is a pragmatic approach that would have a minimal influence on the incremental results given it would impact both arms of the model in a similar way.

B.3.4.6. Summary of health state utilities used in the economic model

A summary of the HSUVs used in the base case and the sensitivity analysis are presented in Table 26 below.

Table 26. Base case and scenario analysis health state utility values used in the economic model

State	Utility value: mean	95% confidence interval	Reference in submission (section)	Justification
Health states				
Pre-progression	[redacted]	[redacted]	B.3.4.3	Mapped EQ-5D-3L values directly measured from the CAPItello-291 study population. These values age adjusted in model over time
Progressed disease	[redacted]	[redacted]		
Death	-	-		
Adverse events				
Diarrhoea	0.006	0.005, 0.007	B.3.4.5	Approach taken in NICE TA725
Rash maculo-papular	0.03248	0.026, 0.039		
Rash	0.03248	0.026, 0.039		
Hyperglycaemia	0.119	0.096, 0.142		
Stomatitis	0.12	0.096, 0.144		
Anaemia	0.119	0.096, 0.142		

Notes: Based on the assumption that the standard error is 10% of the mean

B.3.5. Cost and healthcare resource use identification, measurement and valuation

A SLR of health care resource use (HCRU) and costs associated with the treatment and management of patients with unresectable or metastatic breast cancer was undertaken, as detailed in Appendix I.

Despite the availability of cost estimates for the cost/resource use associated with HR+/HER2- advanced or metastatic breast cancer, no unit costs were provided by the included studies, and most reported costs were >5 years old. It was therefore considered most appropriate to derive unit costs from the most recent NHS reference costs (2021-22), the December 2023 drugs and pharmaceutical electronic market information tool (eMIT), the 2023 Unit Costs of Health and Social Care (PSSRU), and the British National Formulary (BNF).

The modelled costs and healthcare resource use associated with the lifetime treatment and management of patients with HR+/HER2- advanced and metastatic breast cancer comprised of the following:

- Drug acquisition and administration costs
- Disease management and monitoring costs

- Adverse event costs
- End of life costs

B.3.5.1. Intervention and comparator costs

B.3.5.1.1. Time on treatment

Capivasertib plus fulvestrant, alpelisib plus fulvestrant and everolimus plus exemestane are all treat-to-progression regimens. In study protocols this means that patients continue to receive treatment until confirmed disease progression, unacceptable toxicity or withdrawal of consent. A comparison of median treatment exposure and PFS shows that median treatment exposure is less than median PFS for all comparators. Therefore, assuming time on treatment is equivalent to PFS would overestimate treatment duration.

Given the relationship between time to treatment discontinuation (TTD) and PFS, and the approach towards modelling efficacy, i.e., applying a HR to the fulvestrant reference curve for all treatments, the most appropriate method to model TTD in the economic analysis was considered to be applying a ratio between TTD and PFS.

For capivasertib + fulvestrant, the relationship between TTD and PFS from CAPItello-291 in the post-CDK 4/6 inhibitor PI3K/AKT-altered population was assessed at various landmarks to inform an appropriate ratio to apply to the respective modelled PFS curve, as described in Section B.3.3.4. Table 27 shows that the observed ratio between PFS and TTD remains relatively constant over the course of the trial (between [redacted] and [redacted]). Therefore, in the model, the average ratio ([redacted]) was applied to the PFS curve as a constant to model the TTD for capivasertib plus fulvestrant. Furthermore, in the absence of any publicly available TTD data for alpelisib plus fulvestrant and everolimus plus exemestane, a pragmatic decision was made to apply the same constant ratio to generate the TTD from the modelled PFS for both treatment regimens. Scenario analyses explore the impact of using [redacted] and [redacted] applied to all treatment arms.

Table 27 PFS and TTD landmark data from CAPItello-291 for capivasertib plus fulvestrant in the post-CDK 4/6i PI3K/AKT-altered group

Months	PFS	TTD from capivasertib	Absolute Difference	Ratio of hazards (TTD vs. PFS)
3	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]

PFS: progression free survival; TTD: time to treatment discontinuation

B.3.5.1.2. Acquisition costs

Drug dosing information and costs for capivasertib plus fulvestrant and the comparators are displayed in Table 28. Most of the comparator treatment regimens were fixed dose and corresponded to integer multiples of available vial/tablet sizes, and hence no wastage is assumed. For oral capecitabine no drug wastage is assumed.

Mean relative dose intensity (RDI) was available for capivasertib plus fulvestrant and everolimus plus exemestane. For alpelisib plus fulvestrant only the median, presumably for the alpelisib component only, was available (82.7%).[66] Therefore, in the base case 100% was assumed, with a scenario analysis included which assumes the median is equivalent to the mean for alpelisib.

Table 28: Drug acquisition costs

Comparator treatment	Unit cost per pack (List prices)	Pack size	Dosage per admin	Admin frequency	Mean relative dose intensity	Total monthly drug cost*
Capivasertib + fulvestrant						
Capivasertib	£[redacted]	64 x 200 mg tablets	400 mg (2 x 200mg tablets)	Twice daily for 4 days, followed by 3 days off	[redacted]57	[redacted]
Fulvestrant	£55.32	2 x 250 mg / 5 ml solution for injection	500 mg	Cycle one: on days 1 & 15 Cycle two onwards: on day 1 only (4-week cycles)	[redacted]57	£115.22 (1st 4 weeks) £60.02 (post-4 weeks)
Alpelisib + fulvestrant						
Alpelisib	£4,082.14	56 x 150 mg tablets	300 mg (2x 150 mg tablets)	Once daily	100%**	£4,437.50

Comparator treatment	Unit cost per pack (List prices)	Pack size	Dosage per admin	Admin frequency	Mean relative dose intensity	Total monthly drug cost*
Fulvestrant	£55.32	2 x 250 mg / 5 ml solution for injection	500 mg	Cycle one: on days 1 & 15 Cycle two onwards: on day 1 only (4-week cycles)	100%**	£115.45 (1st 4 weeks) £60.14 (post-4 weeks)
Everolimus + exemestane						
Everolimus	£362.55	30 x 2.5 mg tablets***	10 mg	Once daily	79.0%[20]	£1,162.37
Exemestane	£4.20	30 x 25 mg tablets	25 mg	Once daily	98.0%[20]	£4.18

Notes: * monthly treatment cycles are per 30.44 days in the economic model ; ** assumption as mean data for alpelisib plus fulvestrant not publicly available; ***Cheapest cost per mg tablet selected from British National Formulary [88] for alpelisib and everolimus, and eMIT [89] for fulvestrant and exemestane

B.3.5.2. Subsequent treatment costs

Patients that experience disease progression or recurrence in the model are assumed to receive additional drug-based interventions.

In the CAPItello-291 trial [redacted]% of patients received post discontinuation disease-related anticancer therapy in the PI3K/AKT pathway-altered population.[57] The proportion receiving subsequent treatments and the types of subsequent treatments received was consistent across arms and thus there is low risk of bias on the OS results. However, the proportion receiving subsequent treatment and the distribution of subsequent treatments received were not reflective of UK clinical practice, and thus a series of interviews were conducted with 6 UK clinical experts to obtain the types of subsequent treatments received in practice and the distribution according to second-line treatment received for HR+/HER2- advanced or metastatic breast cancer (see section B.3.14).

The treatments mentioned and an average of the subsequent proportions received in these interviews are provided in Table 29. Clinicians were asked for the subsequent treatment distributions for third line and beyond, and so the proportions are not expected to sum to 100%. The responses from clinicians were heterogeneous, particularly with respect to doxorubicin ([redacted] vs. [redacted]), eribulin ([redacted]), paclitaxel ([redacted]) and vinorelbine ([redacted]).[29]

Table 29. Subsequent treatment use per UK clinical expert opinion

Post-progression therapy	Capivasertib plus fulvestrant or alpelisib plus fulvestrant	Everolimus plus exemestane
Any subsequent anticancer therapy	[redacted]	[redacted]
Anastrozole	[redacted]	[redacted]
Capecitabine	[redacted]	[redacted]
Cyclophosphamide	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]
Everolimus + exemestane	[redacted]	[redacted]
Letrozole	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]
Tamoxifen	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]

Source: Data on file[29]

Given the targeted patient population, the subsequent therapy distribution for capivasertib plus fulvestrant or alpelisib plus fulvestrant were equivalent, which clinicians confirmed to be a reasonable assumption.[29]

The costs of these subsequent treatments are modelled as a weighted average of costs, and then applied as a one-off treatment cost on progression. This approach is aligned with that taken in multiple previous NICE TAs in advanced breast cancer[16,17,20,22] and is considered justified as the treatment pathway that patients follow in advanced or metastatic breast cancer is varied and will depend on a wide range of different factors. Given the level of complexity required in deriving a specific treatment flow for the progression health state, it was considered that a simple one-off cost would be a reasonable approach. Furthermore, as patients who receive either capivasertib plus fulvestrant or any of the comparator treatment options will have access to the same subsequent therapies and likely receive them in relatively similar proportions, the approach to modelling subsequent treatment costs was deemed to have a negligible impact on the cost-effectiveness results.

An overview of the subsequent treatment options from CAPItello-291 for patients with relapsed HR+/HER2- advanced or metastatic breast cancer and their respective costs as included in the economic model is presented in Table 30 below. It should be noted that for treatment options with multiple available vial/pack sizes, the lowest cost per vial was estimated for inclusion in the model. No drug wastage is assumed for subsequent treatments.

Duration of therapy was based on the duration of therapy reported in the most relevant clinical trial identified for the treatment given the setting, or if not available, based on NHS protocols

for treatment. Administration costs were added, details of these costs are included in section B.3.5.3.

Table 30: Drug acquisition costs for subsequent therapies

Drug	Unit cost per pack (£)	Pack size	Dosage per admin	Admin frequency	Admin route	Total monthly drug costs including admin	Duration of tx (mths)	Source of duration
Anastrozole	0.50	1mg tablets Pack size 28	1 mg	Daily	Oral	15.9	3.95	Assumed same as Letrozole
Capecitabine	22.51	500mg tablets Pack size 120	2 x 1250 mg/m^2	14 days followed by a 7-day rest period	Oral	47.7	4.10	Fumoleau 2004[90]
Cyclophosphamide	13.14	1g powder for solution for injection vials Pack size 1	800 mg/m^2	Every 28 days	IV	191.6	5.52	6 cycles assumed
Doxorubicin	12.15	50mg/25ml solution for injection vials Pack size 1	50 mg/m^2	Every 28 days	IV	194.6	4.37	O'Brien 2004[91]
Eribulin	361	0.88mg/2ml solution for injection vials	1.23 mg/m^2	Days 1 and 8 of every 21-day cycle	IV	2945.2	3.90	Cortes 2011[92]
Everolimus + exemestane	Per Table 28				Oral	1166.5	3.95	Assumed same as Letrozole
Letrozole	0.86	2.5mg tablets Pack size 28	2.5 mg	Daily	Oral	16.3	3.95	Buzdar 2001[93]
Paclitaxel	24.43	300mg/50ml solution for injection vials Pack size 1	175 mg/m^2	Day 1 of 21 day cycle for 6 cycles	IV	264.7	4.14	NHS chemotherapy protocol for paclitaxel in mBC[94]
Tamoxifen	2.87	20mg tablets Pack size 30	20 mg	Daily	Oral	18.3	3.95	Assumed same as Letrozole
Vinorelbine	75.16	10mg/1ml solution for injection vials Pack size 10	30 mg/m^2	Day 1,8 and 15 in 21 day cycles	IV	855.3	4.14	South West Strategic Clinical Network[95]

Abbreviations: BNF: British National Formulary; eMIT: drugs and pharmaceutical electronic market information tool; mBC, metastatic breast cancer; mth: month; NICE: National Institute for Health and Care Excellence; PARPi: poly (ADP-ribose) polymerase inhibitor

Based on the treatment splits above and the monthly treatment costs and duration of therapy in Table 30, the total subsequent treatment cost that is applied as a one-off treatment cost on progression is shown in Table 31 below.

Table 31: Total one-off subsequent treatment cost per progressed patient

Treatment in the economic model	Total one-off subsequent treatment cost
Capivasertib + fulvestrant	£4,714.65
Alpelisib + fulvestrant	£4,714.65
Everolimus + exemestane	£4,344.06

B.3.5.3. Drug administration costs

Administration costs were applied to both oral and IV therapies as detailed in Table 32. Administration costs were sourced from the latest NHS reference costs (2021-22); an overview is presented in Table 32 below.

Table 32: Administration costs

Chemotherapy admin type	Cost per 4 weeks	Description	Source
Oral administration	£15.40	Pharmacist dispensing (12 minutes) [Band 8a-b pharmacist, £73 per hour]	PSSRU (2023)[96]
Initial IV chemotherapy administration	£178.04	Non-consultant led WF01B Non-Admitted Face-to-Face Attendance, First (Service Code = 370, Medical Oncology Service)	NHS Reference Costs, 2021-22, version 3[97]
Subsequent IV chemotherapy administration	£158.50	Non-consultant led WF01C Non-Admitted Face-to-Face Attendance, Follow-up (Service Code = 370, Medical Oncology Service)	

Abbreviations: HRG, healthcare resource group; IV, intravenous; NHS, National Health Service.

B.3.5.4. Health state costs and resource use

Resource use related to the follow-up and monitoring of patients in the progression-free and progressed health states were based on recommendations in NICE CG81,[32] previous NICE technology appraisals in this setting[20] and validated with 6 UK clinicians in series of 1-to-1 interviews[29]. Values were averaged across clinician responses.

Table 33 outlines the resource use related to staffing by health state per month. Values were similar across health states, with slightly more oncology consultant visits and social worker visits in the progressed health state compared to progression free, and slightly more clinical nurse specialist visits in progression free compared to progressed disease. There was heterogeneity in clinician responses on the involvement of clinical nurse specialists in

particular. Costs have been taken from the latest NHS reference costs (2021–22)[97] or the latest PSSRU report (2023)[96] and are presented in Table 34. Resource use related to staffing in each health state is assumed to be the same regardless of treatment received.

Table 33: Resource use related to staffing by health state (frequency per month)

	Progression-free	Progressed disease
GP visit*	[redacted]	[redacted]
Oncology consultant office*	[redacted]	[redacted]
Community nurse*	[redacted]	[redacted]
Clinical nurse specialist*	[redacted]	[redacted]
Social worker *	[redacted]	[redacted]

Abbreviations: CT: computerized tomography; GP: general practitioner; *It is assumed that 100% of patients receive each item

Table 34: Resource use costs related to staffing

Resource item	Cost	Source
GP visit	£56.00	PSSRU 2023 - Unit Costs of Health and Social Care (cost per surgery consultation lasting 10 minutes, including direct care staff cost and with qualification costs). Table 9.4.2.[96]
Oncology consultant office	£159.80	NHS Reference Costs (2021-22). Weighted average (based on frequency) of:[97] • CL WF01A Non-Admitted Face-to-Face Attendance, Follow-up • CL WF01B Non-Admitted Face-to-Face Attendance, First • CL WF01C Non-Admitted Face-to-Face Attendance, Follow-up • CL WF01D Non-Admitted Face-to-Face Attendance, First
Community nurse	£53.00	PSSRU 2023 - Unit Costs of Health and Social Care (cost per working hour, band 5). Table 9.4.2[96]
Clinical nurse specialist	£57.00	PSSRU 2023 - Unit Costs of Health and Social Care (Table 9.2.1, cost per working hour, band 6)[96]
Social worker	£53.00	PSSRU 2023 - Unit Costs of Health and Social Care (cost per working hour, band 5). Table 9.4.2[96]

Abbreviations: CT: computerized tomography; GP: general practitioner; NHS: National Health Service.

Table 35 outlines the resource use related to imaging and monitoring by health state and treatment per month. The requirement for CT scans is the same across treatments. Differences in other monitoring costs across treatments such as fasting plasma glucose are explained by the distinct side-effect profiles of each treatment listed (see section B.3.4.5). A

scenario analysis tests the impact of setting the frequency of resource use related to monitoring and imaging to be the same across treatments in the progression free health state.

Costs have been taken from the latest NHS reference costs (2021–22)[97] and are presented in Table 36. Resource use related to imaging and monitoring in the progressed disease health state is the same irrespective of treatment received whilst in the progression-free health state.

Table 35 Resource use related to monitoring and imaging by health state and treatment (frequency per month)

	Resource use upon treatment initiation			Resource use progression free			Resource use with Progressed disease
	Capi + Ful	Alp + Ful	Evero + Exem	Capi + Ful	Alp + Ful	Evero + Exem	
CT scan*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Complete blood count*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fasting plasma glucose*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HbA1c monitoring*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: *It is assumed that 100% of patients receive each item
Abbreviations: Alp, alpelisib; Capi, capivasertib; Evero, everolimus; Exem, exemestane; Ful, fulvestrant

Table 36: Resource use costs related to monitoring

Resource item	Cost (£)	Source
CT scan	£142	NHS Schedule Costs 2021/22 NHS Trusts and Foundation Trusts. Total HRG RD24Z Computerised Tomography Scan of Two Areas, with Contrast[97]
Complete blood count	£2.96	NHS Schedule Costs 2021/22 NHS Trusts and Foundation Trusts. Directly Accessed Pathology Services. DAPS05. Haematology[97]
Fasting plasma glucose	£2.96	
HbA1c monitoring	£2.96	

Abbreviations: CT: computerized tomography; GP: general practitioner; NHS: National Health Service

B.3.5.5. Adverse event costs

The health effects of treatment-related AEs were included in the base case economic analysis and modelled via the incidence (occurring in at least 5% of the CAPItello-291, BOLERO-2 or SOLAR-1 trials) of Grade ≥ 3 AEs, as described in B.3.4.5. The costs associated with treating and managing AEs in the analysis are presented in Table 37, and were sourced from the NHS reference costs 2021-22.[97]

AE costs were applied as a one-off cost in the analysis. In reality, AEs can occur at any point while a patient receives treatment. The application of the costs at this timepoint in the analysis is expected to result in a slight overestimation of AE costs in the analysis. Nevertheless, the costs associated with AEs are expected to have a negligible impact on the overall cost-effectiveness results.

Table 37: Adverse event costs

Adverse event	Costs	Source (NHS reference costs 2021-22) [97]
Diarrhoea	£164.19	NHS Reference Costs 2021-22 Trusts and Foundation Trusts. Currency code: WF01A, Service code: 800 [Clinical Oncology] Non-admitted face to face attendance, follow-up
Rash	£164.19	NHS Reference Costs 2021-22 Trusts and Foundation Trusts. Currency code: WF01A, Service code: 800 [Clinical Oncology] Non-admitted face to face attendance, follow-up
Rash maculopapular	£164.19	NHS Reference Costs 2021-22 Trusts and Foundation Trusts. Currency code: WF01A, Service code: 800 [Clinical Oncology] Non-admitted face to face attendance, follow-up
Hyperglycaemia	£1,532.85	NHS Reference Costs 2021-22 Trusts and Foundation Trusts. Weighted average (based on frequency) of Diabetes with Hyperglycaemia Disorders (Total HRGs): • KB02G Diabetes with Hyperglycaemic Disorders, with CC Score 8+ (£2,502.64, Frequency: 16,911) • KB02H Diabetes with Hyperglycaemic Disorders, with CC Score 5–7 (£1,557.26, Frequency: 12,569) • KB02J Diabetes with Hyperglycaemic Disorders, with CC Score 2–4 (£1,083.70, Frequency: 17,072) • KB02K Diabetes with Hyperglycaemic Disorders, with CC Score 0–1 (£733.71, Frequency: 11,311)
Stomatitis	£1,273.39	NHS Reference Costs 2021-22 Trusts and Foundation Trusts. Weighted average (based on frequency) (Total HRGs): • CB02A Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, with Interventions, with CC Score 5+ (£5,303.13, Frequency: 6,373) • CB02B Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, with Interventions, with CC Score 1–4 (£3,397.65, Frequency: 6,763) • CB02C Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, with Interventions, with CC Score 0 (£2,854.46, Frequency: 3,290) • CB02D Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, without Interventions, with CC Score 5+ (£1,416.07, Frequency: 71,521) • CB02E Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, without Interventions, with CC Score 1–4 (£745.59, Frequency: 60,751) • CB02F Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, without Interventions, with CC Score 0 (£555.46; Frequency: 32,580)
Anaemia	£694.96	NHS Reference Costs 2021-22 Trusts and Foundation Trusts. SA44A Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over (Total HRGs)

Abbreviations: AE: adverse event; CL: consultant-led; HRG: Healthcare Resource Group; NHS: National Health Service.

B.3.5.6. Miscellaneous unit costs

B.3.5.6.1. End of life costs

The costs of end of life or terminal care are modelled as a one-off cost applied to patients who enter the death state. These costs reflect the additional care required in the months prior to death. These costs have been included in numerous previous cancer HTAs and economic models.[20,21]

These costs are applied as a one-off cost upon entry into the death state by multiplying the estimated cost of terminal care by the marginal death rate in each cycle. In the model, the marginal death rate in cycle t is calculated as:

1 minus OS[t] minus the cumulative death rate since model start.

This cost reflects the additional care required in the months prior to death; an overview of the resource use and unit costs is given in Table 38.

Table 38: Terminal care resource use and unit costs

Clinical setting	% of deaths	Unit cost*	Weighted end of life cost
Terminal care in hospital	40%	£10,885.24	£8,519.22
Terminal care in hospice	10%	£13,570.70	
Terminal care at home with community support	50%	£5,616.10	

Notes: *Costs were originally reported in 2006/2007 prices. These were inflated to the latest 2024 prices using the ONS CPI INDEX 06.3 : HOSPITAL SERVICES[98]

B.3.5.6.2. Genomic testing costs

Next-generation sequencing (NGS) will be conducted prior to initiating treatment with capivasertib plus fulvestrant, to confirm the PIK3CA/AKT1/PTEN alteration status (per the marketing authorisation for capivasertib plus fulvestrant in this patient population).

Testing for PIK3CA mutations is already commonly performed in UK clinical practice since the NICE recommendation of alpelisib plus fulvestrant in 2022.[20] Therefore, genomic testing costs were not included as there would be no incremental cost compared to current UK clinical practice. Due to the advanced technical capabilities of NGS panels used in the NHS setting, AKT1 and PTEN alteration testing is typically already included in the panel kits such as Trusight Oncology 500; the data can be unmasked for analysis when requested by the

consultant, when those two PI3K/AKT pathway alterations are included in the national genomic test directory ([redacted]).

B.3.6. Severity

Advanced breast cancer is an incurable disease that exerts a heavy symptom and HRQoL burden on patients, whilst significantly limiting life expectancy[40,41] (see B.1.3.1). Patients with tumours with PI3K/AKT pathway alterations experience more rapid disease progression and poorer outcomes than those without.[10–13]

In line with the NICE process and methods,[33] the severity of locally advanced or metastatic HR+/HER2- breast cancer, measured by the absolute QALY shortfall (AQS) or the proportional QALY shortfall (PQS) associated with standard of care relative to the general population without locally advanced or metastatic HR+/HER2- breast cancer was calculated. Within the framework, differential QALY weights are applied if the AQS or PQS estimates lie within given cut-off ranges (Table 39).

Table 39. QALY weight referenced within the new NICE process and methods manual

QALY weight	Absolute shortfall	Proportional shortfall
1x	Less than 12	Less than 0.85
1.2x	12–18	0.85–0.95
1.7x	At least 18	At least 0.95

Abbreviations: NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year.
Source: NICE methods guide[33]

The standard of care was assumed to be alpelisib plus fulvestrant for the majority of the PI3K/AKT pathway-altered population, despite this only being an option for patients with PIK3CA mutations,[20] based on the greater frequency of occurrence of PIK3CA alterations in comparison to the frequencies of AKT1 and PTEN alterations. Nonetheless, to inform the total expected QALYs for patients treated with SoC, the discounted QALYs for both alpelisib plus fulvestrant and everolimus plus exemestane were used. Total expected QALYs for patients without locally advanced or metastatic HR+/HER2- breast cancer, but otherwise identical in characteristics, were then calculated. This calculation used population utility norms informed by Ara and Brazier (2010),[80] mortality estimates informed by the most recent Office of National Statistics (ONS) life tables[99] and a discount rate of 3.5% per annum, to align with parameters

used in the cost-effectiveness analysis (Table 40). The expected QALYs for the general population were compared with those in the SoC arm in order to evaluate QALY shortfall.

AQS is estimated to be 10.41 and 10.74 and PQS was estimated to be 85.4% and 88.1% for alpelisib plus fulvestrant and everolimus plus exemestane, respectively (Table 41). These results provide a clear rationale that a 1.2x QALY weight is appropriate for decision making in this appraisal.

No relevant previous appraisals in HR+/HER2- locally advanced or metastatic breast cancer were identified which were evaluated after the introduction of the severity modifier. It is, however, important to highlight that the end-of-life criteria were accepted for the appraisal of alpelisib plus fulvestrant in TA816,[20] further confirming the severity of this stage of the disease.

Table 40. Summary features of QALY shortfall analysis

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

Table 41 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
12.19	Alpelisib plus fulvestrant: 1.78	10.41	**85.4%**	**1.2x**
	Everolimus plus exemestane: 1.45	10.74	**88.1%**	**1.2x**

B.3.7. Uncertainty

The treatment landscape for advanced and metastatic breast cancer, and in particular the targeting of treatment based on the genomic makeup of the tumour, is rapidly evolving. The CAPItello-291 trial provides contemporary, high-quality evidence of the efficacy and safety of capivasertib plus fulvestrant in patients with PI3K/AKT pathway-altered tumours, including in patients with prior use of CDK4/6 inhibitors.[6] Trials of the relevant comparators were conducted earlier, before CDK4/6 inhibitors were routinely used in the first line setting, and

before genomic testing was established in NHS practice. A pragmatic approach to the available comparative evidence is therefore required.

B.3.8. Managed access proposal

This submission proposes capivasertib plus fulvestrant is commissioned for routine use in patients with HR+/HER2- advanced or metastatic breast cancer with PI3K/AKT pathway-altered tumours following disease progression on CDK4/6 inhibitor plus endocrine therapy. A managed access proposal is not provided.

B.3.9. Summary of base-case analysis inputs and assumptions

B.3.9.1. Summary of base-case analysis inputs

A summary of the key variables included in the base case model is provided in Table 42.

Table 42. Key model variables for base case analysis

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
General model parameters			
Time horizon	Lifetime (20 years)	Fixed	B.3.2
Cycle length	30.44 days	Fixed	B.3.2
Discount rate	3.5%	Fixed, tested in scenario analyses only	B.3.2
Population characteristics			
Age	59.3 years	48.5 – 71.7 (log-normal)	B.2.3.2
Proportion female	99.3%	Fixed	B.3.2.1
Body surface area female	1.70	1.39 – 2.06 (log-normal)	B.3.2.1
Body surface area male	1.82	1.49 – 2.02 (log-normal)	B.3.2.1
Extrapolation of outcomes			
OS – placebo plus fulvestrant	Gamma	Cholesky decomposition of variance-covariance matrix used	B.3.3.3
PFS – placebo plus fulvestrant	Log normal		B.3.3.2
OS – HR for Capivasertib plus fulvestrant vs placebo plus fulvestrant	[redacted]	[redacted] (lognormal)	B.3.3.4
OS – HR for Alpelisib plus fulvestrant vs placebo plus fulvestrant	[redacted]	[redacted] (lognormal)	B.3.3.4
OS – HR for Everolimus plus exemestane vs placebo plus fulvestrant	[redacted]	[redacted] (lognormal)	B.3.3.4

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
PFS – HR for Capivasertib plus fulvestrant vs placebo plus fulvestrant	[redacted]	[redacted]	B.3.3.4
PFS – HR for Alpelisib plus fulvestrant vs placebo plus fulvestrant	[redacted]	[redacted]	B.3.3.4
PFS – HR for Everolimus plus exemestane vs placebo plus fulvestrant	[redacted]	[redacted]	B.3.3.4
Ratio between TTD and PFS – Capivasertib plus fulvestrant	[redacted]	[redacted]	B.3.5.1
Ratio between TTD and PFS – Alpelisib plus fulvestrant	[redacted]	[redacted]	B.3.5.1
Ratio between TTD and PFS – Everolimus plus exemestane	[redacted]	[redacted]	B.3.5.1
Adverse event number - Capivasertib plus fulvestrant			
Diarrhoea	[redacted]	[redacted]	B.3.4.5
Rash maculo-papular	[redacted]	[redacted]	B.3.4.5
Rash	[redacted]	[redacted]	B.3.4.5
Hyperglycaemia	[redacted]	[redacted]	B.3.4.5
Stomatitis	[redacted]	[redacted]	B.3.4.5
Anaemia	[redacted]	[redacted]	B.3.4.5
Adverse event number - Alpelisib plus fulvestrant			
Diarrhoea	13	11 – 16 (gamma)	B.3.4.5
Rash maculo-papular	0	0 – 0 (gamma)	B.3.4.5
Rash	22	18 – 27 (gamma)	B.3.4.5
Hyperglycaemia	62	50 – 75 (gamma)	B.3.4.5
Stomatitis	5	4 – 6 (gamma)	B.3.4.5
Anaemia	0	0 – 0 (gamma)	B.3.4.5
Adverse event number - Everolimus plus exemestane			
Diarrhoea	14	12 – 17 (gamma)	B.3.4.5
Rash maculo-papular	0	0 – 0 (gamma)	B.3.4.5
Rash	5	4 – 6 (gamma)	B.3.4.5
Hyperglycaemia	29	24 – 35 (gamma)	B.3.4.5
Stomatitis	39	31 – 46 (gamma)	B.3.4.5
Anaemia	39	31 – 46 (gamma)	B.3.4.5
Health-related quality of life (utility values)			
Progression-free	[redacted]	(0.76-0.79) (Beta)	B.3.4.3
Post-progression	[redacted]	(0.72-0.76) (Beta)	B.3.4.3
Age adjustment	Table 23	Not applicable	B.3.4.4
Adverse event disutility			
Diarrhoea	0.006	0.005 - 0.007 (Beta)	B.3.4.5
Rash maculo-papular	0.03248	0.026 - 0.039 (Beta)	B.3.4.5
Rash	0.03248	0.026 - 0.039 (Beta)	B.3.4.5
Hyperglycaemia	0.119	0.097 - 0.143 (Beta)	B.3.4.5
Stomatitis	0.12	0.098 - 0.145(Beta)	B.3.4.5
Anaemia	0.119	0.097 - 0.143 (Beta)	B.3.4.5
Intervention and comparator acquisition costs (£/month)			
Capivasertib plus fulvestrant: Capivasertib	£5,481.69	Not applicable	B.3.5.1.2

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Capivasertib plus fulvestrant: Fulvestrant first four weeks	£115.22	Not applicable	B.3.5.1.2
Capivasertib plus fulvestrant: Fulvestrant Subsequent four weeks	£60.02	Not applicable	B.3.5.1.2
Alpelisib plus fulvestrant: Alpelisib	£4,437.50	Not applicable	B.3.5.1.2
Alpelisib plus fulvestrant: Fulvestrant	£115.45	Not applicable	B.3.5.1.2
Alpelisib plus fulvestrant: Fulvestrant Subsequent four weeks	£60.14	Not applicable	B.3.5.1.2
Everolimus plus exemestane: Everolimus	£1,162.37	Not applicable	B.3.5.1.2
Everolimus plus exemestane: Exemestane	£4.18	Not applicable	B.3.5.1.2
Administration costs (£/4 weeks)			
Capivasertib + fulvestrant			
Admin cost: Capivasertib	£15.40	12.53 - 18.56 (gamma)	B.3.5.3
Admin cost: fulvestrant (1st 4 weeks)	£178.04	144.86 - 214.59 (gamma)	B.3.5.3
Admin cost: fulvestrant (post 4 weeks)	£158.50	128.96 - 191.04 (gamma)	B.3.5.3
Admin cost: Alpelisib + Fulvestrant			
Admin cost: Alpelisib	£15.40	12.53 - 18.56 (gamma)	B.3.5.3
Admin cost: Fulvestrabt (1st 4 weeks)	£178.04	144.86 - 214.59 (gamma)	B.3.5.3
Admin cost: Fulvestrant (post 4 weeks)	£158.50	128.96 - 191.04 (gamma)	B.3.5.3
Admin cost: Everolimus + Exemestane			
Admin cost: Everolimus	£15.40	12.53 - 18.56 (gamma)	B.3.5.3
Admin cost: Exemestane	£0	0 - 0	B.3.5.3
Intervention and comparator dose intensity			
Capivasertib plus fulvestrant: Capivasertib	[redacted]	83-87% (beta)	B.3.5.1.2
Capivasertib plus fulvestrant: Fulvestrant	[redacted]	99-100% (beta)	B.3.5.1.2
Alpelisib plus fulvestrant: Alpelisib	100%	Fixed	B.3.5.1.2
Alpelisib plus fulvestrant: Fulvestrant	100%	Fixed	B.3.5.1.2
Everolimus plus exemestane: Everolimus	79%	62-92% (beta)	B.3.5.1.2
Everolimus plus exemestane: Exemestane	98%	71-100% (beta)	B.3.5.1.2
Health care resource use and costs			
Administration	Table 32	see below	B.3.5.3
Health state: PF	Table 33, Table 34	see below	B.3.5.4
Health state: PD	Table 33, Table 34	see below	B.3.5.4
Progression free			
GP visit, freq per month-PFS	[redacted]	[redacted]	B.3.5.4
Oncology consultant office, freq per month-PFS	[redacted]	[redacted]	B.3.5.4

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Community nurse, freq per month-PFS	[redacted]	[redacted]	B.3.5.4
Clinical nurse specialist, freq per month-PFS	[redacted]	[redacted]	B.3.5.4
Social worker, freq per month-PFS	[redacted]	[redacted]	B.3.5.4
CT scan, freq per month-PFS Capivasertib + fulvestrant TX initiation	[redacted]	[redacted]	B.3.5.4
Complete blood count, freq per month-PFS Capivasertib + fulvestrant TX initiation	[redacted]	[redacted]	B.3.5.4
Fasting plasma glucose , freq per month-PFS Capivasertib + fulvestrant TX initiation	[redacted]	[redacted]	B.3.5.4
HbA1c monitoring, freq per month-PFS Capivasertib + fulvestrant TX initiation	[redacted]	[redacted]	B.3.5.4
CT scan, freq per month-PFS Capivasertib + fulvestrant PF	[redacted]	[redacted]	B.3.5.4
Complete blood count, freq per month-PFS Capivasertib + fulvestrant PF	[redacted]	[redacted]	B.3.5.4
Fasting plasma glucose, freq per month-PFS Capivasertib + fulvestrant PF	[redacted]	[redacted]	B.3.5.4
HbA1c monitoring, freq per month-PFS Capivasertib + fulvestrant PF	[redacted]	[redacted]	B.3.5.4
CT scan, freq per month-PFS Alpelisib + fulvestrant TX initiation	[redacted]	[redacted]	B.3.5.4
Complete blood count, freq per month-PFS Alpelisib + fulvestrant TX initiation	[redacted]	[redacted]	B.3.5.4
Fasting plasma glucose, freq per month-PFS Alpelisib + fulvestrant TX initiation	[redacted]	[redacted]	B.3.5.4
HbA1c monitoring, freq per month-PFS Alpelisib + fulvestrant TX initiation	[redacted]	[redacted]	B.3.5.4
CT scan, freq per month-PFS Alpelisib + fulvestrant PF	[redacted]	[redacted]	B.3.5.4
Complete blood count, freq per month-PFS Alpelisib + fulvestrant PF	[redacted]	[redacted]	B.3.5.4
Fasting plasma glucose , freq per month-PFS Alpelisib + fulvestrant PF	[redacted]	[redacted]	B.3.5.4
HbA1c monitoring, freq per month-PFS Alpelisib + fulvestrant PF	[redacted]	[redacted]	B.3.5.4

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
CT scan, freq per month-PFS Everolimus + Exemestane TX initiation	[redacted]	[redacted]	B.3.5.4
Complete blood count, freq per month-PFS Everolimus + Exemestane TX initiation	[redacted]	[redacted]	B.3.5.4
Fasting plasma glucose, freq per month-PFS Everolimus + Exemestane TX initiation	[redacted]	[redacted]	B.3.5.4
HbA1c monitoring, freq per month-PFS Everolimus + Exemestane TX initiation	[redacted]	[redacted]	B.3.5.4
CT scan, freq per month-PFS Everolimus + Exemestane PF	[redacted]	[redacted]	B.3.5.4
Complete blood count, freq per month-PFS Everolimus + Exemestane PF	[redacted]	[redacted]	B.3.5.4
Fasting plasma glucose, freq per month-PFS Everolimus + Exemestane PF	[redacted]	[redacted]	B.3.5.4
HbA1c monitoring, freq per month-PFS Everolimus + Exemestane PF	[redacted]	[redacted]	B.3.5.4
Progressed disease			
GP visit, freq per month-PD	[redacted]	[redacted]	B.3.5.4
Oncology consultant office, freq per month-PD	[redacted]	[redacted]	B.3.5.4
Community nurse, freq per month-PD	[redacted]	[redacted]	B.3.5.4
Clinical nurse specialist, freq per month-PD	[redacted]	[redacted]	B.3.5.4
Social worker, freq per month-PD	[redacted]	[redacted]	B.3.5.4
CT scan, freq per month-PD	[redacted]	[redacted]	B.3.5.4
Complete blood count, freq per month-PD	[redacted]	[redacted]	B.3.5.4
Fasting plasma glucose, freq per month-PD	[redacted]	[redacted]	B.3.5.4
HbA1c monitoring, freq per month-PD	[redacted]	[redacted]	B.3.5.4
Unit costs			
GP visit-Unit cost (PF)	£56.00	45.56 - 67.5 (gamma)	B.3.5.4
Oncology consultant office-Unit cost (PF)	£159.80	130.02 - 192.61 (gamma)	B.3.5.4
Community nurse-Unit cost (PF)	£53.00	43.12 - 63.88 (gamma)	B.3.5.4
Clinical nurse specialist-Unit cost (PF)	£57.00	46.38 - 68.7 (gamma)	B.3.5.4
Social worker-Unit cost (PF)	£53.00	43.12 - 63.88 (gamma)	B.3.5.4
GP visit-Unit cost (PD)	£56.00	45.56 - 67.5 (gamma)	B.3.5.4
Oncology consultant office-Unit cost (PD)	£159.80	130.02 - 192.61 (gamma)	B.3.5.4

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Community nurse-Unit cost (PD)	£53.00	43.12 - 63.88 (gamma)	B.3.5.4
Clinical nurse specialist-Unit cost (PD)	£57.00	46.38 - 68.7 (gamma)	B.3.5.4
Social worker-Unit cost (PD)	£53.00	43.12 - 63.88 (gamma)	B.3.5.4
CT scan	£142	115.54 - 171.15 (gamma)	B.3.5.4
Complete blood count	£2.96	2.41 - 3.57 (gamma)	B.3.5.4
Fasting plasma glucose	£2.96	2.41 - 3.57 (gamma)	B.3.5.4
HbA1c monitoring	£2.96	2.41 - 3.57 (gamma)	B.3.5.4
Adverse event costs			
Diarrhoea	£164.19	133.59 - 197.9 (gamma)	B.3.5.5
Rash maculo-papular	£164.19	133.59 - 197.9 (gamma)	B.3.5.5
Rash	£164.19	133.59 - 197.9 (gamma)	B.3.5.5
Hyperglycaemia	£1,532.85	1247.19 - 1847.53 (gamma)	B.3.5.5
Stomatitis	£1,273.39	1036.08 - 1534.8 (gamma)	B.3.5.5
Anaemia	£694.96	565.44 - 837.62 (gamma)	B.3.5.5
AE duration (days)			
Diarrhoea	6.0	4.82 - 7.18 (normal)	B.3.4.5
Rash maculo-papular	4.0	3.22 - 4.78 (normal)	B.3.4.5
Rash	3.0	2.41 - 3.59 (normal)	B.3.4.5
Hyperglycaemia	16.1	12.94 - 19.26 (normal)	B.3.4.5
Stomatitis	4.0	3.22 - 4.78 (normal)	B.3.4.5
Anaemia	16.1	12.94 - 19.26 (normal)	B.3.4.5
Subsequent therapy			
Drugs and proportion of use	Table 29		B.3.5.2
Drug therapy duration and acquisition costs	Table 30		B.3.5.2
Capivasertib + fulvestrant: % PD Pts receiving Any subsequent treatment	[redacted]	[redacted]	B.3.5.2
Alpelisib + Ful: % PD Pts receiving Any subsequent treatment	[redacted]	[redacted]	B.3.5.2
Ev + Ex: % PD Pts receiving Any subsequent treatment	[redacted]	[redacted]	B.3.5.2
Capivasertib + fulvestrant: % PD Pts receiving Anastrozole	[redacted]	[redacted]	B.3.5.2
Capivasertib + fulvestrant: % PD Pts receiving Capecitabine	[redacted]	[redacted]	B.3.5.2
Capivasertib + fulvestrant: % PD Pts receiving Cyclophosphamide	[redacted]	[redacted]	B.3.5.2
Capivasertib + fulvestrant: % PD Pts receiving Doxorubicin	[redacted]	[redacted]	B.3.5.2

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Capivasertib + fulvestrant: % PD Pts receiving Eribulin	[redacted]	[redacted]	B.3.5.2
Capivasertib + fulvestrant: % PD Pts receiving Everolimus + exemestane	[redacted]	[redacted]	B.3.5.2
Capivasertib + fulvestrant: % PD Pts receiving Letrozole	[redacted]	[redacted]	B.3.5.2
Capivasertib + fulvestrant: % PD Pts receiving Paclitaxel	[redacted]	[redacted]	B.3.5.2
Capivasertib + fulvestrant: % PD Pts receiving Tamoxifen	[redacted]	[redacted]	B.3.5.2
Capivasertib + fulvestrant: % PD Pts receiving Vinorelbine	[redacted]	[redacted]	B.3.5.2
Alpelisib + fulvestrant: % PD Pts receiving Anastrozole	[redacted]	[redacted]	B.3.5.2
Alpelisib + fulvestrant: % PD Pts receiving Capecitabine	[redacted]	[redacted]	B.3.5.2
Alpelisib + fulvestrant: % PD Pts receiving Cyclophosphamide	[redacted]	[redacted]	B.3.5.2
Alpelisib + fulvestrant: % PD Pts receiving Doxorubicin	[redacted]	[redacted]	B.3.5.2
Alpelisib + fulvestrant: % PD Pts receiving Eribulin	[redacted]	[redacted]	B.3.5.2
Alpelisib + fulvestrant: % PD Pts receiving Everolimus + exemestane	[redacted]	[redacted]	B.3.5.2
Alpelisib + fulvestrant: % PD Pts receiving Letrozole	[redacted]	[redacted]	B.3.5.2
Alpelisib + fulvestrant: % PD Pts receiving Paclitaxel	[redacted]	[redacted]	B.3.5.2
Alpelisib + fulvestrant: % PD Pts receiving Tamoxifen	[redacted]	[redacted]	B.3.5.2
Alpelisib + fulvestrant: % PD Pts receiving Vinorelbine	[redacted]	[redacted]	B.3.5.2
Everolimus + Exemestane: % PD Pts receiving Anastrozole	[redacted]	[redacted]	B.3.5.2
Everolimus + Exemestane: % PD Pts receiving Capecitabine	[redacted]	[redacted]	B.3.5.2
Everolimus + Exemestane: % PD Pts receiving Cyclophosphamide	[redacted]	[redacted]	B.3.5.2
Everolimus + Exemestane: % PD Pts receiving Doxorubicin	[redacted]	[redacted]	B.3.5.2
Everolimus + Exemestane: % PD Pts receiving Eribulin	[redacted]	[redacted]	B.3.5.2
Everolimus + Exemestane: % PD Pts receiving Everolimus + exemestane	[redacted]	[redacted]	B.3.5.2
Everolimus + Exemestane: % PD Pts receiving Letrozole	[redacted]	[redacted]	B.3.5.2

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Everolimus + Exemestane: % PD Pts receiving Paclitaxel	[redacted]	[redacted]	B.3.5.2
Everolimus + Exemestane: % PD Pts receiving Tamoxifen	[redacted]	[redacted]	B.3.5.2
Everolimus + Exemestane: % PD Pts receiving Vinorelbine	[redacted]	[redacted]	B.3.5.2
Duration (months): Anastrozole	[redacted]	[redacted]	B.3.5.2
Duration (months): Capecitabine	[redacted]	[redacted]	B.3.5.2
Duration (months): Cyclophosphamide	[redacted]	[redacted]	B.3.5.2
Duration (months): Doxorubicin	[redacted]	[redacted]	B.3.5.2
Duration (months): Eribulin	[redacted]	[redacted]	B.3.5.2
Duration (months): Everolimus + exemestane	[redacted]	[redacted]	B.3.5.2
Duration (months): Letrozole	[redacted]	[redacted]	B.3.5.2
Duration (months): Paclitaxel	[redacted]	[redacted]	B.3.5.2
Duration (months): Tamoxifen	[redacted]	[redacted]	B.3.5.2
Duration (months): Vinorelbine	[redacted]	[redacted]	B.3.5.2
Cost per month: Anastrozole	£15.94	12.97 - 19.22 (gamma)	B.3.5.2
Cost per month: Capecitabine	£47.76	38.86 - 57.57 (gamma)	B.3.5.2
Cost per month: Cyclophosphamide	£191.73	156 - 231.1 (gamma)	B.3.5.2
Cost per month: Dox:orubicin	£194.76	158.47 - 234.74 (gamma)	B.3.5.2
Cost per month: Eribulin	£2947.24	2398 - 3552.28 (gamma)	B.3.5.2
Cost per month Everolimus + exemestane	£1166.55	949.15 - 1406.03 (gamma)	B.3.5.2
Cost per month: Letrozole	£16.33	13.29 - 19.69 (gamma)	B.3.5.2
Cost per month: Paclitaxel	£264.86	215.5 - 319.23 (gamma)	B.3.5.2
Cost per month: Tamoxifen	£18.31	14.9 - 22.07 (gamma)	B.3.5.2
Cost per month: Vinorelbine	£855.94	696.43 - 1031.66 (gamma)	B.3.5.2
Miscellaneous costs			
End of life costs	£8519.22	6931.57 - 10268.12 (gamma)	B.3.5.6.1

B.3.9.2. Assumptions

A summary of key model assumptions and justifications is provided in Table 43.

Table 43. Key model assumptions

Model input	Assumption	Rationale / Justification
Perspective	NHS and PSS	NICE reference case
Discounting	3.5% per annum for costs and health outcomes	NICE reference case
Time horizon	Lifetime (20 years)	A lifetime horizon consistent with NICE reference case (<1% patients alive at 20 years)
Cycle length	30.44 days	The cycle length is 30.44 days to capture the costs and events associated with the rapid progression of disease
Efficacy	OS and PFS HRs for capivasertib plus fulvestrant, alpelisib plus fulvestrant and everolimus plus exemestane derived from NMA are applied to the placebo plus fulvestrant arm of the CAPItello-291 trial.	NMA conducted in absence of direct comparative trials of capivasertib plus fulvestrant and the comparators. Placebo plus fulvestrant is a common comparator arm of several trials in the network and so provides the baseline risks to which treatment effects of the intervention and comparators are applied in the model (whilst not being a comparator of interest). NMA conducted on the (log) HR scale in the absence of evidence of material deviations from proportional hazards assumption. Although the CAPItello-291 trial provides direct evidence for capivasertib plus fulvestrant against placebo plus fulvestrant, the HR for capivasertib plus fulvestrant is taken from the NMA so that the intervention and comparators of interest are treated in the same way, using adjusted indirect comparative methods.
	OS and PFS curves for placebo plus fulvestrant arm of the CAPItello-291 trial are extrapolated over model time horizon with best fitting parametric distributions.	Required to extrapolate over an appropriate time horizon of analysis. Parametric distributions selected based on best fit to trial data, supported by UK clinical expert validation.
Health state utility values	Utility values are assumed to differ by health state, but not by treatment arm.	Consistent with the observed HRQoL in the CAPItello-291 study, which provides the most appropriate HSUVs for the population of interest.
	HSUVs are derived directly from the CAPItello-291 trial	The CAPItello-291 trial provides direct assessment of patient quality of life using the EQ-5D instrument, which is the preferred tool of NICE and meets the reference case for utility estimation. EQ-5D-5L data were mapped to EQ-5D-3L values using the NICE-recommended mapping function and data. A systematic review of the literature and past NICE appraisals did not identify any other utilities values that would be more appropriate to use in the model than the trial-based HSUVs.
Costs	Capivasertib plus fulvestrant and the comparators are costed using list prices.	Capivasertib is costed in the base case at list price. The comparators are available via simple discount patient access schemes, which are confidential and necessitate the use of their list prices.
	The relationship between TTD and PFS from CAPItello-291 for capivasertib plus fulvestrant in the post-CDK 4/6 inhibitor PI3K/AKT-altered population was assessed at various landmarks. Average ratio of hazards was applied to all treatments	TTD data are not publicly available for alpelisib plus fulvestrant or everolimus plus exemestane. CAPItello-291 data indicated that PFS was longer than time on treatment, so it would be inappropriate to adopt PFS to represent TTD. Applied same approach to all therapies so all treated fairly in model.
	Health state costs are based on recommendations in NICE CG81,[32] previous NICE technology appraisals in this setting[20] and validated with 6 UK clinicians in series of 1-to-1 interviews.[29] Values were averaged across clinician responses.	Alignment with previous approaches and clinical practice

Model input	Assumption	Rationale / Justification
Subsequent treatment	Subsequent treatments are considered to be a basket of therapies.	The proportion of patients receiving each type of subsequent therapy was informed by interviews with 6 UK clinicians.
	The costs of subsequent treatments are modelled as a weighted average of costs, and then applied as a one-off treatment cost upon progression.	This approach is aligned with that taken in previous NICE TAs of breast cancer therapies, including TA495, TA496, TA503, TA687/TA593 and TA816.
Inclusion of end-of-life care cost	End-of-life costs are applied as a one-time cost upon entry to the Death state in the model. Costs were estimated based on the resource use and unit costs reported in NICE CG81.	Inclusion of these costs reflects the additional care required in the months prior to death, borne by the NHS/PSS. The hospital health services (ONS) index was employed to inflate costs from 2006 to 2023 prices (the most recent year for which the ONS index is available).
Genomic testing costs	Genomic testing costs are excluded.	Testing for PIK3CA mutations is already commonly performed in UK clinical practice since the NICE TA816 recommendation of alpelisib plus fulvestrant in 2022. AKT1 and PTEN testing is anticipated to be added to the National Test Directory by the time final NICE guidance will be issued for capivasertib plus fulvestrant and is not anticipated to materially change the costs of testing over that already taken. Therefore, testing costs were not included.

B.3.10. Base-case results

The base case results are presented in Table 44, Table 45 and Table 46. Clinical outcomes and the disaggregated results are presented in Appendix J. All results presented use the list prices for all treatments. The base case deterministic results are presented with and without the application of the 1.2x QALY weighting and subsequent results are presented with the application of the 1.2x QALY weighting.

The base case deterministic results (Table 44) show that capivasertib plus fulvestrant is associated with an increase of 0.84 life years, and 0.62 QALYs compared with alpelisib plus fulvestrant, and an increase of 1.30 life years, and 0.94 QALYs compared with everolimus plus exemestane. Capivasertib plus fulvestrant is associated with an increase in costs of [redacted] versus alpelisib plus fulvestrant, and an increase in costs of [redacted] versus alpelisib plus fulvestrant. After taking into account the x1.2 severity modifier, the pairwise incremental cost effectiveness ratios (ICERs) of capivasertib plus fulvestrant vs. alpelisib plus fulvestrant and vs. everolimus plus exemestane are [redacted]/QALY and [redacted]/QALY, respectively.

In fully incremental analysis (Table 45) alpelisib plus fulvestrant is extendedly dominated by capivasertib plus fulvestrant, and the ICER for capivasertib plus fulvestrant vs. everolimus plus exemestane is [redacted]/QALY. As alpelisib plus fulvestrant is only recommended for use in patients with breast cancer containing PIK3CA mutations,[20] these results only hold in the population with

PIK3CA-mutated tumours; however, PIK3CA alterations represent the largest component of the PI3K/AKT-altered pathway, and these results indicate that capivasertib plus fulvestrant is the most effective of the treatment strategies and would be economically preferred to alpelisib plus fulvestrant.

The base case net health benefit (NHB) at £20,000/QALY and £30,000/QALY willingness to pay (WTP) thresholds (with the x1.2 severity modifier weighting) are shown in Table 46. In the base case with the severity modifier applied, capivasertib plus fulvestrant has a NHB of [redacted] QALY at the £20,000/QALY (WTP) threshold, and a NHB of [redacted] QALY at the £30,000/QALY WTP threshold vs. alpelisib plus fulvestrant. The base case NHB of capivasertib plus fulvestrant vs. everolimus plus exemestane is [redacted] QALY at the £20,000/QALY WTP threshold, and [redacted] QALY at the £30,000/QALY WTP threshold with the severity modifier applied.

B.3.10.1. Base-case incremental cost-effectiveness analysis results

Table 44. Deterministic pairwise base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER of capivasertib plus fulvestrant versus comparator (£/QALY)	Pairwise ICER of capivasertib plus fulvestrant versus comparator (£/QALY) with 1.2 QALY weighting
Capivasertib + fulvestrant	[redacted]	3.25	2.40					
Alpelisib + fulvestrant	£51,365	2.41	1.78	[redacted]	0.84	0.62	[redacted]	[redacted]
Everolimus + exemestane	£25,714	1.96	1.45	[redacted]	1.30	0.94	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 45 Deterministic fully incremental results

Technologies	Total costs (£)	Total QALYs	ICER of capivasertib plus fulvestrant versus comparator (£/QALY) with 1.2 QALY weighting
Everolimus + exemestane	£25,714	1.45	
Alpelisib + fulvestrant	£51,365	1.78	Extendedly dominated
Capivasertib + fulvestrant	[redacted]	2.40	[redacted]

Table 46. Net Health Benefits

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000 with 1.2 QALY weighting	NHB at £30,000 with 1.2 QALY weighting
Capivasertib + fulvestrant	[redacted]	2.40				
Alpelisib + fulvestrant	£51,365	1.78	[redacted]	0.62	[redacted]	[redacted]
Everolimus + exemestane	£25,718	1.45	[redacted]	0.94	[redacted]	[redacted]

Abbreviations: QALYs, quality-adjusted life years; NHB, net health benefit

B.3.11. Exploring uncertainty

B.3.11.1. Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed by varying all parameters in the model simultaneously by sampling from probability distributions. The ranges of the parameter values and the distributions assumed are shown in Table 42. For parameters where confidence intervals (CIs) and/or standard deviations/standard errors of the mean (SDs/SEs) were available, these were used to estimate parameter uncertainty. For variables where no CIs and/or SDs/SEs were available, the CIs are assumed to be +/-10% of the base case value, or other plausible maximum/minimum plausible ranges if +/-10% is implausible. Cholesky decomposition was employed for survival parameters to account for potential correlations.

The results of the pairwise PSA are shown in Table 47. The cost-effectiveness plane showing these simulations is presented in Figure 27. These results were generated based on 1,000 simulations. The probabilistic pairwise ICERs using a 1.2x QALY severity weighting are [redacted]/QALY for capivasertib plus fulvestrant vs. alpelisib plus fulvestrant, and [redacted]/QALY for capivasertib plus fulvestrant vs. everolimus plus exemestane, both of which are consistent with the deterministic analysis.

The results were plotted in a cost-effectiveness acceptability curve (CEAC) which shows the probability of either treatment being the most cost-effective across a range of WTP thresholds (Figure 28). At a willingness to pay threshold of £36,000/QALY, accounting for the 1.2x QALY severity weighting, capivasertib plus fulvestrant is associated with a [redacted]% probability of being cost effective.

Table 47: Base-case probabilistic incremental cost-effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER of capivasertib plus fulvestrant versus comparator (£/QALY) with 1.2 QALY weighting
Capivasertib + fulvestrant	[redacted]	3.25	2.85				
Alpelisib + fulvestrant	£52,631	2.41	2.12	[redacted]	0.84	0.73	[redacted]
Everolimus + exemestane	£26,114	1.96	1.73	[redacted]	1.30	1.12	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Figure 27. Cost-effectiveness plane, with x1.2 severity modifier applied

Abbreviations: Alp: alpelisib; Ful: fulvestrant; Ev: everolimus; Ex: exemestane

Figure 28 Cost-effectiveness acceptability curve, with x1.2 severity modifier applied

Abbreviations: Ful: fulvestrant; Ev: everolimus; Ex: exemestane

B.3.11.2. Deterministic sensitivity analysis

In the DSA, each input parameter was varied +/-10% (or other plausible maximum/minimum plausible ranges if +/-10% is implausible) to explore the impact of each parameter on model outcomes. Parameters with no associated uncertainty, such as drug costs, are excluded from the analysis. Interdependent variables that cannot be varied individually, such as efficacy extrapolation parameters, were also excluded from the DSA (but are fully captured in the PSA). Uncertainty associated with efficacy parameters is fully explored through alternative distributions in the scenario analyses and is captured in the PSA. The top 10 most influential parameters included in the one-way sensitivity analysis are presented in Table 48 and Table 49 and the results presented graphically in Figure 29 and Figure 30.

The results show that, of the parameters explored, the model is most sensitive to capivasertib relative dose intensity, which also contributes to drug acquisition costs, is an influential parameter, although the ICER range is still relatively small (e.g., [redacted] in the pairwise comparison vs. alpelisib plus fulvestrant). Other areas of health care resource use and costs have little influence on the estimated ICERs.

Table 48. Deterministic sensitivity analysis results: capivasertib plus fulvestrant vs alpelisib plus fulvestrant (x1.2 severity modifier applied)

Parameter label	Lower bound	Upper bound
Capivasertib relative dose intensity	[redacted]	[redacted]
Capivasertib + fulvestrant: % progressed disease patients receiving any subsequent treatment	[redacted]	[redacted]
Alpelisib + fulvestrant: % progressed disease patients receiving any subsequent treatment	[redacted]	[redacted]
Capivasertib + fulvestrant: % progressed disease patients receiving Eribulin	[redacted]	[redacted]
Alpelisib + fulvestrant: % progressed disease patients receiving Eribulin	[redacted]	[redacted]
Progressed disease utility	[redacted]	[redacted]
Admin cost: fulvestrant (post 4 weeks) in the capivasertib plus fulvestrant arm	[redacted]	[redacted]
Admin cost: fulvestrant (post 4 weeks) in the alpelisib plus fulvestrant arm	[redacted]	[redacted]
Progression-free utility	[redacted]	[redacted]
Hyperglycaemia events: Alpelisib + fulvestrant	[redacted]	[redacted]

Abbreviations: PFS, progression free survival; RDI, relative dose intensity; TTD, time to treatment discontinuation

Figure 29 Deterministic sensitivity analysis results: capivasertib plus fulvestrant vs alpelisib plus fulvestrant (x1.2 severity modifier applied)

Abbreviations: ICUR: Incremental cost-utility ratio; ful: fulvestrant; RDI: relative dose intensity; PD: progressive disease; pt: patient; PFS: progression-free survival; CT: computerized tomography; PF: progression-free

Table 49. Deterministic sensitivity analysis results: capivasertib plus fulvestrant vs everolimus plus exemestane (x1.2 severity modifier applied)

Parameter label	Lower bound	Upper bound
Capivasertib relative dose intensity	[redacted]	[redacted]
Everolimus relative dose intensity	[redacted]	[redacted]
Progressed disease utility	[redacted]	[redacted]
Capivasertib + fulvestrant: % progressed disease patients receiving any subsequent treatment	[redacted]	[redacted]
Everolimus + Exemestane: % progressed disease patients receiving any subsequent treatment	[redacted]	[redacted]
Capivasertib + fulvestrant: % progressed disease patients receiving Eribulin	[redacted]	[redacted]
Everolimus + Exemestane: % progressed disease patients receiving Eribulin	[redacted]	[redacted]
Admin cost: fulvestrant (post 4 weeks) in the capivasertib plus fulvestrant arm	[redacted]	[redacted]
Progression-free utility	[redacted]	[redacted]
Oncology consultant office, frequency per month in the progressed disease state	[redacted]	[redacted]

Figure 30. Deterministic sensitivity analysis results: capivasertib plus fulvestrant vs everolimus plus exemestane (x1.2 severity modifier applied)

Abbreviations: ICUR: Incremental cost-utility ratio; ev: everolimus; ex: exemestane; RDI: relative dose intensity; PD: progressive disease; pt: patient; PFS: progression-free survival; CT: computerized tomography; PF: progression-free

B.3.11.3. Scenario analysis

Scenario analyses were conducted to explore key areas of uncertainty and assumptions in the model, including efficacy extrapolation parameters (Table 50). These demonstrate that the assumed distribution for PFS extrapolation, and to a lesser extent for OS extrapolation, can influence the ICER estimates; however, as the survival extrapolations were conducted according to NICE-recommended methods and were validated by clinical experts (see sections B.3.3.2 to B.3.3.4 and B.3.14), the extrapolations adopted in the base case are the most appropriate.

Table 50. Scenario analyses (x1.2 severity modifier applied)

	Capivasertib + fulvestrant vs. Alpelisib + fulvestrant				Capivasertib + fulvestrant vs. Everolimus + exemestane			
	Incremental costs	Incremental QALYs	Pairwise ICER with 1.2 QALY weighting	Change from base case ICER (%)	Incremental costs	Incremental QALYs	Pairwise ICER with 1.2 QALY weighting	Change from base case ICER (%)
Base	[redacted]	0.62	[redacted]	0.00%	[redacted]	0.94	[redacted]	0.00%
PFS distribution: loglogistic	[redacted]	0.64	[redacted]	28.30%	[redacted]	0.96	[redacted]	17.06%
OS distribution: Weibull	[redacted]	0.57	[redacted]	7.06%	[redacted]	0.88	[redacted]	6.82%
Monitoring and imaging resource use same across all arms in model (all equivalent to Capi +Ful)	[redacted]	0.62	[redacted]	0.02%	[redacted]	0.94	[redacted]	-0.02%
HR applied to PFS for TTD (all comparators): 1.10	[redacted]	0.62	[redacted]	6.64%	[redacted]	0.94	[redacted]	5.70%
HR applied to PFS for TTD (all comparators): 1.20	[redacted]	0.62	[redacted]	-5.90%	[redacted]	0.94	[redacted]	-5.08%
RDI using median for alpelisib	[redacted]	0.62	[redacted]	19.15%	[redacted]	0.94	[redacted]	0.00%
Exclusion of all disease management and follow-up costs in PF and PD states	[redacted]	0.62	[redacted]	-8.24%	[redacted]	0.94	[redacted]	-6.77%
Exclusion of subsequent treatment costs	[redacted]	0.62	[redacted]	0.00%	[redacted]	0.94	[redacted]	-0.67%
Exclusion of terminal care cost	[redacted]	0.62	[redacted]	0.93%	[redacted]	0.94	[redacted]	0.73%
Exclusion of AE costs	[redacted]	0.62	[redacted]	2.01%	[redacted]	0.94	[redacted]	0.31%

B.3.12. Subgroup analysis

The base case analyses represent the expected use of capivasertib plus fulvestrant in clinical practice. No subgroup analyses were considered to be relevant for the submission.

B.3.13. Benefits not captured in the QALY calculation

The model is unlikely to fully capture the HRQoL benefits of delaying treatment with cytotoxic chemotherapy, including the psychological impact and inconvenience of its administration.

B.3.14. Validation

Validation of the cost effectiveness analysis considered internal validation of modelled outcomes against trial data, external validation comparing against alternative data sources and using clinical expert opinion, and quality assurance of the model.

B.3.14.1. Internal validation of modelled outcomes

The modelling of baseline PFS and OS with fulvestrant monotherapy, described in section B.3.3.2 and B.3.3.3, included assessment of the fit of the models to the observed data and comparison of the modelled and observed smoothed hazard rates. This showed that the chosen parametric distributions fit those data well.

B.3.14.2. External validation against other data sources

Validating the PFS and OS outcome extrapolations of fulvestrant monotherapy, capivasertib plus fulvestrant, and the relevant comparators is challenging because no trials provide long term benchmark outcomes data in a biomarker selected PI3K/AKT pathway-altered population with prior CDK4/6 inhibitor experience. In the absence of such benchmark data it was important to seek and obtain clinical expert validation, as discussed below.

B.3.14.3. External validation by clinical experts

Clinical expert interviews were conducted to validate the clinical assumptions underpinning the economic model: these took place between April and May 2024. There were six clinical experts and their areas of practice and working location are summarised in Table 51.

Table 51. Summary of clinical validation interviews supporting this submission

Number of clinical experts	6
Area of practice	Medical oncology
Years of experience	21 (11-38)
Geographical spread	London Brighton Southampton Guildford Manchester

The following topics were included in the pre-specified interview agendas:

1. The UK clinical pathway and management of HR+/HER2- advanced breast cancer
    - The clinicians confirmed that the current pathway and the anticipated positioning of capivasertib plus fulvestrant reflected in section B.1.3.2.1 and B.1.3.3 are reflective of what they experience and anticipate in UK clinical practice.
    - The clinicians confirmed that alpelisib plus fulvestrant and everolimus plus exemestane are the relevant comparators for capivasertib plus fulvestrant.
    - The clinicians provided estimates of subsequent treatments in the third-line setting and beyond following discontinuation of capivasertib plus fulvestrant or the comparators (see section B.3.5.2). The heterogeneity in responses provided by clinicians supports the approach adopted for modelling subsequent therapies using a weighted average basket of therapies applied as a one-time cost upon disease progression.
2. CAPItello-291 study design and generalisability to current UK clinical practice
    - The clinicians confirmed that the PI3K/AKT-altered population of the CAPItello-291 study was reflective of patients in which they would anticipate using capivasertib plus fulvestrant in UK clinical practice
3. Extrapolation of PFS and OS outcomes in the context of PI3K/AKT-altered tumours and post CDK4/6 inhibitor therapy.
    - The clinicians reviewed the long term PFS and OS projections for fulvestrant monotherapy with different parametric distributions to determine which were clinically plausible based on their experience and expertise. Only those curves that clinicians indicated were clinically plausible were selected for consideration in the base case model, as discussed in B.3.3.2 and B.3.3.3.
    - The clinicians confirmed that the extrapolations for capivasertib plus fulvestrant were plausible when presented with the KM data for the capivasertib plus fulvestrant arm from CAPItello-291 and the resulting extrapolations based on the fulvestrant monotherapy curve selection (see section B.3.3.4).

B.3.14.4. Quality assurance of model

The model was subject to review and quality control before finalisation. Two health economists not involved in the model development reviewed the model for coding errors, inconsistencies, and plausibility of inputs and outputs. A range of extreme value and logic tests were conducted to examine the behaviour of the model and ensure that the results were logical.

B.3.15. Interpretation and conclusions of economic evidence

The economic model reflects the anticipated use of capivasertib plus fulvestrant in clinical practice, i.e., in adults with locally advanced or metastatic HR+/HER2- breast cancer with PI3K/AKT- (PIK3CA- and/or, AKT1-, and/or PTEN-) altered tumours whose disease has progressed following CDK4/6 inhibitor plus AI therapy. Amongst these patients, PIK3CA alterations are by far the most common (see section B.1.3.1). Following the NICE TA816 recommendation for alpelisib plus fulvestrant in patients with PIK3CA mutations (granted under the then end-of-life criteria),[20] this is the comparator that is most likely to be displaced by capivasertib plus fulvestrant in practice. However, for patients with AKT1 and PTEN alterations, everolimus plus exemestane is a relevant comparator (see section B.1.3.2 and B.1.3.3). Based on both these standard of care comparator therapies, capivasertib plus fulvestrant meets the criteria for consideration under the NICE severity modifier, with a QALY weighting of 1.2x (see B.3.6).

Compared with alpelisib plus fulvestrant, capivasertib plus fulvestrant has an ICER of £[redacted]/QALY. Compared with everolimus plus exemestane, capivasertib plus fulvestrant has an ICER of £[redacted]/QALY. In a fully incremental analysis, capivasertib plus fulvestrant extendedly dominated alpelisib plus fulvestrant, indicating that capivasertib plus fulvestrant would, on average, be the clinically and economically preferred of these two therapies in patients with the most common PI3K/AKT-altered tumours (PIK3CA-altered tumours). However, it is acknowledged that these analyses are based on the current list prices of capivasertib and the comparators, and ICER estimates may change with the incorporation of relevant confidential discounts.

Extensive sensitivity and scenario analyses demonstrate that the base case model is robust to most parameters and assumptions. Results of PSA, which accounts for the joint parameter uncertainty, including uncertainty in relative treatment effects derived from the NMA, were of

consistent with the (deterministic) base case results. As may be expected, the results of the analysis were sensitive to parameters that influence the assumed total drug acquisition costs. The distribution assumed for extrapolation of PFS and OS over the long term also influences the results, as may be expected; however, it should be noted that the selection of the base case parametric distributions followed recommended guidance and was validated by clinical expert opinion (see section B.3.14). The parametric distributions adopted in the base case models are therefore the most plausible and appropriate.

Limitations of the model include the limitations relating to comparative effectiveness derived from the NMA. Due to differences in modelling approaches and incomplete information, it is not possible to directly compare the current model outputs for alpelisib plus fulvestrant and everolimus plus exemestane against the outputs of previous models supporting their NICE recommendations in TA816[20] and TA421.[19] However, we can be confident that a robust approach, using the most robust data possible, has been adopted to model the cost effectiveness of capivasertib plus fulvestrant in its anticipated use in clinical practice. The model is aligned with the NICE reference case and the NICE methods manual, has undergone validation with clinical experts, and compares capivasertib plus fulvestrant against the relevant comparators listed in the NICE scope.

Notwithstanding the fact that [redacted] capivasertib plus fulvestrant is a plausibly cost-effective therapy option in its clinician-confirmed anticipated place in the current treatment pathway. As a clinically effective and plausibly cost-effective therapy that can address the significant unmet needs of patients with incurable PI3K/AKT pathway altered HR+/HER2- advanced or metastatic breast cancer, capivasertib plus fulvestrant should be recommended for routine commissioning.

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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

[ID 6370]

Summary of Information for Patients (SIP)

August 2024

File name	Version	Contains confidential information	Date
ID6370 Capivasertib_CAPItello291 SIP_7Aug24	2.0	No	7th August 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

Note to those filling out the template: Please complete the template using plain language, taking time to explain all scientific terminology. Do not delete the grey text included in each section of this template as you move through drafting because it might be a useful reference for patient reviewers. Additional prompts for the company have been in red text to further advise on the type of information which may be most relevant and the level of detail needed. You may delete the red text.

1a) Name of the medicine (generic and brand name):

Capivasertib (TRUQAP®)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Capivasertib in combination with fulvestrant is anticipated to be licensed for the treatment of adult patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative (defined as IHC 0 or 1+, or IHC 2+/ISH-) locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following recurrence or progression on or after an endocrine based regimen.[1] Based on European clinical guidelines[2] and existing NICE guidance,[3–5] initial therapy for people with HR+/HER2- advanced or metastatic breast cancer in the UK is with a class of drugs called CDK4/6 inhibitors that are used in combination with a type of endocrine therapy called aromatase inhibitor (AI). UK Clinical experts therefore expect that capivasertib in combination with fulvestrant will be used in patients who have previously received CDK4/6 inhibitor in combination with AI therapy.

This is the proposed place in therapy for capivasertib in combination with fulvestrant (see section 2).

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Capivasertib plus fulvestrant received UK marketing authorisation on 17th July 2024.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

AstraZeneca UK has engaged with the following patient groups relevant to this medicine with the aims of strengthening patient insights and responding to requests for information: Breast Cancer Now; MET UP UK; Make Seconds Count; UK Charity for TNBC. All patient group contributions are published annually on AstraZeneca UK's website: https://www.astrazeneca.co.uk/partnerships/working-with-patient-groups

As of 1st July 2024, the following payments have been awarded in the past 10 years:

- Breast Cancer Care: £15,000 Donation to support the ongoing activities of Breast Cancer Care including the Nursing Network and teleconference training sessions (2015)
- Breast Cancer Now: £12,000 for support for an educational event: 1st UK interdisciplinary Breast Cancer Symposium (2018)
- Breast Cancer Care: £5,000 running costs for telephone helpline for breast
- cancer patients (2018)
- Breast Cancer Now: £32,000 grant contributions towards helpline (2021)
- Breast Cancer Now: £43,314.55 grant contributions towards helpline (2023)
- MET UP UK: £5,000 grant contribution towards Metastatic Breast Cancer Conference in Manchester (June 2023)
- UK Charity for TNBC: £11,100 sponsorship contribution towards patient experience roundtables (2024)
- UK Charity for TNBC: £4,911 grant contribution towards establishment of Patient Forum (2024)
- Make2nds Count: £25,000 sponsorship contribution towards Patient Summit (11th - 13th July 2024)

SECTION 2: Current landscape

Note to authors: This SIP is intended to be drafted at a global level and typically contain global data. However, the submitting local organisation should include country-level information where needed to provide local country-level context.

Please focus this submission on the **main indication (condition and the population who would use the treatment)** being assessed by NICE rather than sub-groups, as this could distract from the focus of the SIP and the NICE review overall. However, if relevant to the submission please outline why certain sub-groups have been chosen.

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England. Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.
• Breast cancer is the most common cancer in the UK. Over 99% of cases occur in women; around 56,400 women and 390 men are diagnosed with breast cancer in the UK each year.[6,7] • Advanced breast cancer is incurable breast cancer that has grown directly into nearby tissues and cannot be completely removed by surgery (locally advanced, stage III), or has spread to other parts of the body such as the bones, liver, and lungs (metastatic disease, stage IV):[6,7] • A diagnosis of advanced breast cancer can have a profound impact on the health-related quality of life (HRQoL) of patients, which deteriorates with disease progression [8,9]. Patients may also experience debilitating symptoms, such as pain, fatigue, nausea, appetite loss, anxiety and depression, which reduce HRQoL[10] and can impact their ability to work and carry out daily activities.[10–12] • Five-year survival rates are >70% in people with locally advanced, stage III disease, but reduce to 25% in those with metastatic, stage IV disease. • Early diagnosis and rapid access to targeted effective and tolerable therapies that can prevent or delay disease progression is therefore essential. • HR+/HER2- advanced breast cancer describes advanced breast cancer that is stimulated by endocrine hormones (primarily oestrogen) but is not responsive to HER2 directed therapy. This is the most common type, occurring in approximately 70% of all advanced breast cancer cases.[13,14] • HR+ cancer is treated with endocrine therapy to block the stimulatory effects of oestrogen, but development of resistance to endocrine therapy is inevitable over time for many patients.[15]

- Around 40-50% of people with HR+/HER2- advanced breast cancer have PI3K/AKT pathway-altered tumours, meaning the tumours have specific mutations (PIK3CA, AKT1, or PTEN alterations) that promote cancer growth and cancer cell survival and can lead to resistance to endocrine therapy used in HR+/HER2- advanced breast cancer.[16–19]
- People with PI3K/AKT pathway-altered tumours experience more rapid disease progression and poorer outcomes.[20–23]

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

- Diagnosis of breast cancer can occur following breast screening for women as part of the national screening programme, or following GP referral for tests in people who notice unusual changes in their breast.
- Breast Cancer Now (see: https://breastcancernow.org/about-breast-cancer/awareness/signs-and-symptoms-of-breast-cancer/) and breast cancer UK (see: https://www.breastcanceruk.org.uk/about-breast-cancer/) are charities that provides patient-friendly information about breast cancer, including signs and symptoms , and Cancer Research UK provides a comprehensive summary of the tests involved (see: https://www.cancerresearchuk.org/about-cancer/breast-cancer/getting-diagnosed).
- In those who are found to have breast cancer, the diagnosis includes determining the stage of the cancer (for example whether it is early stage or advanced), and the type of the cancer cells contained in the tumours (for example, HR+ or HER2-, and whether they contain specific mutations such as PIK3CA, AKT1, or PTEN alterations). This can determine the best approach to treatment.

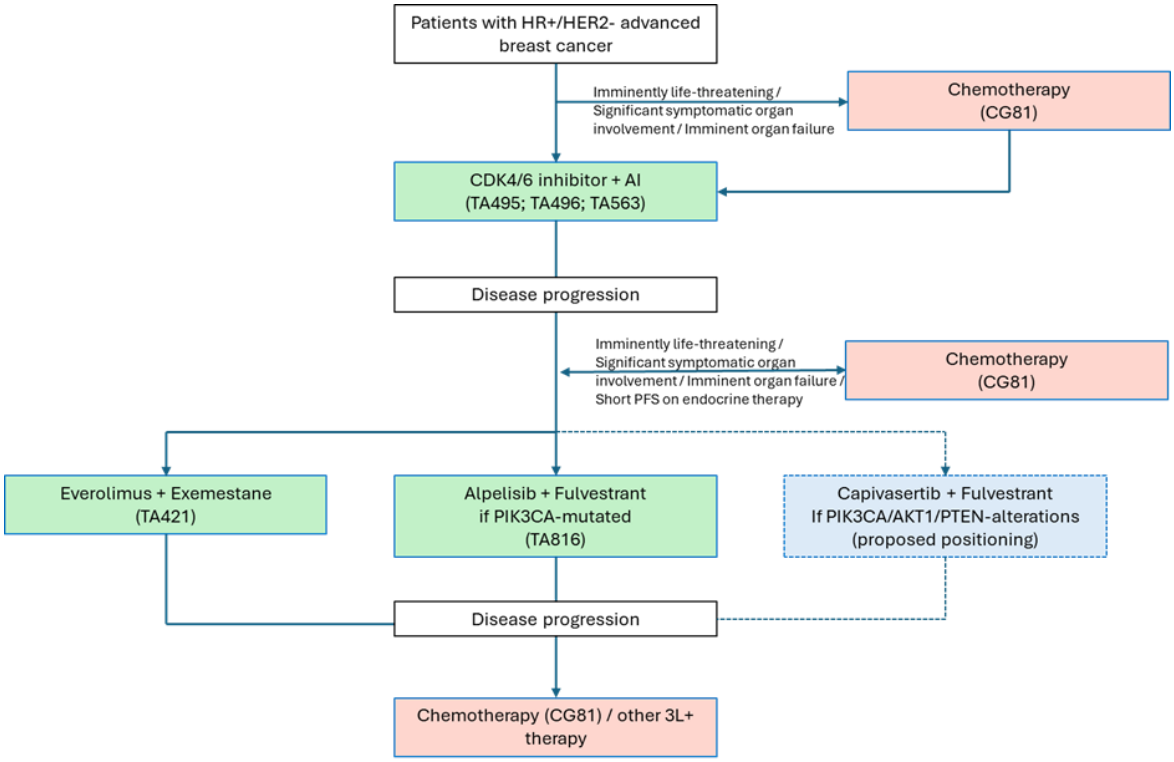
2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

- Treatment options for breast cancer are determined by the stage of the disease and the types of cancer cells contained in the tumours.
- In early-stage disease that has not spread, surgery and radiotherapy may be used, sometimes with chemotherapy or other types of drugs given afterwards to lower the chance of cancer coming back (known as adjuvant therapy). In early-stage disease, treatment is very often curative.
- In people with cancer that has spread to other areas and cannot be completely removed by surgery (locally advanced, stage III), or has spread to other parts of the body such as the bones, liver, and lungs (metastatic disease, stage IV), treatment is given with the aims of delaying further progression, relieve symptoms, prolonging survival and maintaining a good quality of life with minimal adverse events.[24]
- This appraisal relates to capivasertib plus fulvestrant in people with HR+/HER2- advanced or metastatic breast cancer. The current treatment pathway for people with this type and stage of breast cancer, based on current NICE guidance and European clinical guidelines is shown below in Figure 1, along with the expected place in therapy of capivasertib plus fulvestrant.
- It can be seen that treatment options for people with HR+/HER2- advanced breast cancer whose tumours containPI3K/AKT pathway alterations (PIK3CA/AKT1/PTEN) are very limited following disease progression on or after CDK4/6 inhibitor plus AI (**Error! Reference source not found.**):
  - Alpelisib plus fulvestrant is recommended only for people with PIK3CA-altered tumours, per NICE TA816;[25] there are no current targeted therapies for AKT1 or PTEN-altered tumours.
  - Everolimus plus exemestane is a treatment option per NICE TA421[26] but is non-specific to PI3K/AKT pathway-altered tumours.
  - Due to significant toxicity, chemotherapy is reserved for use in people with imminently life-threatening or significantly symptomatic organ involvement, or when people experience disease progression after two or more lines of endocrine therapy.[2] Clinicians and patients have a strong desire to delay use of chemotherapy for as long as possible due to its toxicity and significant impact on HRQoL.[3,4,25,27–29]
  - Adverse events with alpelisib plus fulvestrant and everolimus plus exemestane tend to be less severe than with chemotherapy but are noted by clinicians to still be challenging.[25]
- There is therefore a significant unmet need for an effective and tolerable PI3K/AKT-altered pathway targeted treatment option that has a different mode of action to existing therapies, and enables patients to remain on endocrine-based treatments for longer before progression to cytotoxic chemotherapy.

Figure 1. Current treatment pathway for HR+/HER2- advanced breast cancer (and expected positioning of capivasertib plus fulvestrant)



Notes: Based on current NICE guidance (specific NICE guidance in parenthesis), ESMO and NCCN guideline recommendations.
Pre- and peri-menopausal women also receive ovarian function suppression therapy.
White boxes reflect disease state; green boxes reflect current NICE recommended therapies at this point in the pathway; red boxes reflect chemotherapy; blue box reflects proposed positioning of capivasertib plus fulvestrant

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

- A key aim of therapy in patients with advanced or metastatic breast cancer is to maintain quality of life.[24] The main clinical trial of capivasertib in combination with fulvestrant (CAPItello-291) specifically sought to assess the quality of life of enrolled patients, using cancer-specific questionnaires (called EORTC-QLQ-C30 and EORTC-QLQ-BR23) and a more general questionnaire (called EQ-5D-5L). These found that quality of life was well maintained with capivasertib plus fulvestrant.[16,30]

SECTION 3: The treatment

Note to authors: Please complete each section with a concise overview of the key details and data, including plain language explanations of any scientific methods or terminology. Please provide all references at the end of the template. Graphs or images may be used to accompany text if they will help to convey information more clearly.

3a) How does the new treatment work?

What are the important features of this treatment? Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities. If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.
• Capivasertib is the first therapy to be licensed that specifically targets tumours that have genetic alterations in the PIK3CA, AKT1 and/or PTEN genes. Capivasertib plus fulvestrant was licensed following priority review by the FDA in the US in November 2023,[31,32] and was designated as innovative by the UK drug licensing authority (MHRA).[33] It received its UK marketing authorisation 17th July 2024. • Capivasertib is a potent, selective inhibitor of the growth of PIK3CA, AKT1, and PTEN altered tumours.[1] Fulvestrant is an endocrine therapy that blocks oestrogen receptor signalling in HR+ tumours.[34] When used in combination, the antitumour effect if enhanced and may help to reduce the development of resistance to endocrine therapy.[1] • Capivasertib in combination with fulvestrant has a different mode of action to existing therapies, and a different and possibly improved adverse event profile. It delays disease progression and the need for cytotoxic chemotherapy in patients with PIK3CA, AKT1 and PTEN altered tumours. • As there are no other treatments specifically targeted at three types of genomic alterations in the PI3K/AKT pathway (PIK3CA, AKT1 and/or PTEN), capivasertib plus fulvestrant offers a true step change in therapy and should be considered an innovative therapy. • As capivasertib plus fulvestrant only received its UK marketing authorisation 17th July 2024, the Summary of Product Characteristics is not currently publicly available at the time of writing. Once available, the Summary of Product Characteristics will be posted at: www.medicines.org.uk.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

- This appraisal refers to capivasertib in combination with fulvestrant. When used together, the antitumour effect is enhanced and may help to prevent the development of resistance to endocrine therapy, as described in 3a).
- Like all anticancer medicines, capivasertib plus fulvestrant can have some side effects. The most commonly reported side effects in the trial were diarrhoea; nausea; fatigue; rash and vomiting. The majority of adverse events were mild-to-moderate and were manageable with dose modifications and simple medicines (such as antihistamines, or anti-diarrhoea therapy); the rate of discontinuations of capivasertib due to adverse events was low and acceptable for this patient population.[16]
- Whilst adverse events with other relevant therapies are less severe than with cytotoxic chemotherapy, they can still be challenging and can be difficult to tolerate for some patients. For example, alpelisib plus fulvestrant is associated with a high incidence of hyperglycaemia (high blood sugar levels), which can require additional monitoring and be a burden for patients and clinicians.[25]

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

- As capivasertib plus fulvestrant are taken orally as tablets, this treatment regimen can be taken at home.
- The recommended dose in combination with fulvestrant is 400 mg (two 200 mg tablets) taken orally twice daily approximately 12 hours apart (total daily dose of 800 mg) with or without food, for 4 days followed by 3 days off treatment.
- The recommended dose of fulvestrant is 500 mg administered on Days 1, 15, and 29, and once monthly thereafter.

- In pre/perimenopausal women, capivasertib plus fulvestrant should be combined with a luteinizing hormone releasing hormone (LHRH) agonist,[1] to suppress their ovary function.
- Treatment is continued until progression of disease or unacceptable toxicity.
- For full administration details see the Summary of Product Characteristics and the Patient Information Leaflet, which will be available at: www.medicines.org.uk in due course.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

- The safety and efficacy of capivasertib plus fulvestrant were studied in a pivotal phase III randomised, double-blind, placebo-controlled, multicentre study called CAPItello-291, which enrolled adults with advanced or metastatic HR+/HER2- breast cancer whose tumours contained PIK3CA, AKT1 and/or PTEN alterations.[16]
- Capivasertib plus fulvestrant were dosed as described above. The comparator was placebo plus fulvestrant, dosed as described above.
- The study included patients with or without PIK3CA, AKT1 or PTEN-altered tumours and was specifically designed to test the effects of capivasertib plus fulvestrant both in the whole trial population and in the population with PIK3CA, AKT1 or PTEN-altered tumours. The latter group is the population of interest to this appraisal, and around 70% of this population had received prior treatment with a CDK4/6 inhibitor. The trial population has been confirmed by UK clinical experts to be reflective of patients expected to receive capivasertib plus fulvestrant in clinical practice.[35]
- The primary objective of the trial was to assess the effects of capivasertib plus fulvestrant vs placebo plus fulvestrant for progression-free survival (PFS), which includes clear evidence of progression of the disease or death. Overall survival, which relates to death from any cause, was a secondary endpoint of the trial, as is common in trials of cancer therapies.
- Full trial details are provided in the published manuscript available at: https://www.nejm.org/doi/full/10.1056/NEJMoa2214131.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

CAPItello-291 trial of capivasertib plus fulvestrant vs placebo plus fulvestrant

- The primary endpoint of CAPItello-291 was investigator assessed progression-free survival (PFS), assessed at the first data-cut off (DCO1) after a median follow up of ~13 months. PFS assessed by blinded independent central review (BICR) was analysed in a sensitivity analysis.[16]
- In the population of interest, capivasertib plus fulvestrant more than doubled the time to progression or death compared with placebo plus fulvestrant (7.3 months vs 3.1 months, respectively; hazard ratio [HR] 0.50; 95% CI: 0.38–0.65; p < 0.001). Results for PFS assessed by BICR were highly consistent, confirming the validity of the investigator assessed data.[16]
- Overall survival (OS) was a key secondary endpoint but was not planned for formal analysis at DCO1 as the number of deaths at that time was expected to be too low to show a difference. The OS data should therefore be interpreted with caution. Nonetheless, in the PI3K/AKT-altered population, the data show a clear trend towards improvement in OS with capivasertib plus fulvestrant (HR 0.69; 95% CI 0.45, 1.05).[16]
- Additional secondary and exploratory endpoints including objective response rates, second PFS (PFS2) and time to first subsequent chemotherapy (TTSC) supported the PFS and OS findings,[16,36] indicating an early and sustained benefit for treatment with capivasertib plus fulvestrant. TTSC indicated a delay in the use of chemotherapy or death by approximately 5 months with capivasertib plus fulvestrant.[36]
- HRQoL assessments suggested that, overall, capivasertib plus fulvestrant did not meaningfully reduce patient quality of life and may have helped to preserve overall quality of life over the course of treatment[30] (see section B.2.6 of the company submission).

Efficacy of capivasertib plus fulvestrant vs alpelisib plus fulvestrant and everolimus plus exemestane:

- No clinical trials have compared alpelisib plus fulvestrant, everolimus plus exemestane or capivasertib plus fulvestrant against each other. Therefore, indirect treatment comparisons using a statistical technique called network meta-analysis (NMA) were conducted to assess the relative effects of these therapies on the key outcomes of PFS and OS.
- The NMA was conducted using the most robust and relevant RCTs possible for capivasertib plus fulvestrant (CAPItello-291,[16] FAKTION[37]), alpelisib plus fulvestrant (SOLAR-1[38]) and everolimus plus exemestane (BOLERO-2,[39,40] BOLERO-5[41]), alongside other trials required to form a connected network. It should be noted that, due to the rapidly changing treatment landscape, not all trials included in the network provided data specifically in patients with PIK3CA, AKT1 or PTEN altered tumours, or

following prior CDK4/6 inhibitor therapy; however, in the absence of evidence that these are treatment effect modifiers for the therapies in which these data were missing, the inclusion of these trials in the network is reasonable and justified.

- All three treatments of interest (capivasertib plus fulvestrant, alpelisib plus fulvestrant and everolimus plus exemestane) were compared against fulvestrant 500mg monotherapy in the analysis. All three treatments of interest were significantly better than fulvestrant 500mg for PFS. Capivasertib plus fulvestrant numerically improved PFS to a greater extent than did alpelisib plus fulvestrant and everolimus plus exemestane.
- For OS, only capivasertib plus fulvestrant was significantly superior to fulvestrant 500mg; alpelisib plus fulvestrant was numerically superior to fulvestrant 500mg and the point estimate for everolimus plus exemestane indicated no improvement. Capivasertib plus fulvestrant numerically improved OS to a greater extent than did alpelisib plus fulvestrant and everolimus plus exemestane.
- The results of the NMA suggest that capivasertib plus fulvestrant plausibly improves PFS and OS compared with the relevant comparators (alpelisib plus fulvestrant or everolimus plus exemestane) (see section B.2.9 of the company submission).

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

- Breast cancer negatively affects patients' HRQoL, as noted in 2a). It is important that treatment, particularly in the advanced and metastatic setting where treatment is non-curative, does not further negatively impact HRQoL. CAPItello-291 assessed the HRQoL of participants using cancer specific questionnaires (EORTC-QLQ-C30 and EORTC-QLQ-BR23) and the generic EQ-5D-5L questionnaire. These found that quality of life was well maintained with capivasertib plus fulvestrant.[16,30,42]

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Like all anticancer medicines, capivasertib plus fulvestrant can have some side effects.

- The side effects observed with capivasertib plus fulvestrant in the CAPItello-291 trial were generally mild-to-moderate and were manageable with dose modifications and simple medicines (such as antihistamines or anti-diarrhoea therapy); the rate of discontinuations of capivasertib due to adverse events was low and acceptable for this patient population.[16]
- The most commonly reported side effects in the trial were diarrhoea; nausea; fatigue; rash and vomiting.[16]

3h) Summary of key benefits of treatment for patients

Issues to consider in your

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

- For patients with advanced or metastatic breast cancer harbouring PIK3CA, AKT1 and/or PTEN alterations the only treatment options following progression on CDK4/6 inhibitor and endocrine therapy are alpelisib plus fulvestrant, which is licensed and recommended for use in PIK3CA-mutated tumours only, or everolimus plus exemestane, which is not specifically targeted to these particular genetic alterations, or chemotherapy, which clinicians and patients have a strong desire to delay use of for as long as possible due to its toxicity and significant negative impact on HRQoL. There is a significant unmet need for an effective and tolerable therapy that targets tumours with PIK3CA/AKT1/PTEN alterations, has a different mode of action, enhances sensitivity to endocrine therapy following failure of CDK4/6 inhibitor therapy, and enables patients to remain on endocrine-based treatments for longer before progression to cytotoxic chemotherapy. Capivasertib plus fulvestrant can meet this need.
- In the pivotal clinical trial (CAPItello-291), capivasertib plus fulvestrant significantly improved PFS and OS, delayed use of cytotoxic chemotherapy, was well tolerated and preserved HRQoL in patients with advanced and metastatic disease with PIK3CA/AKT1/PTEN alterations. Compared with alpelisib plus fulvestrant or everolimus plus exemestane, capivasertib plus fulvestrant plausibly improves PFS and OS and has a favourable side effect profile.
- As there are no other treatments specifically targeted at PIK3CA and AKT1 and PTEN altered tumours, capivasertib plus fulvestrant offers a true step change in therapy and should be considered an innovative therapy.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

- Like all anticancer therapies, capivasertib plus fulvestrant is associated with some side effects. The most commonly reported side effects in the trial were diarrhoea, nausea, fatigue, rash, and vomiting,[16] most of which were mild to moderate and manageable with medicines such as antihistamines or anti-diarrhoea therapy, but a minority of patients may experience other side effects. The Summary of Product Characteristics and the Patient Information Leaflet will list the known side effects and will be available at: www.medicines.org.uk in due course. However, on current evidence, side effects with capivasertib plus fulvestrant are generally manageable and possibly less burdensome than those of alternative therapies. For example, clinicians have noted that alpelisib plus fulvestrant is associated with frequent severe hyperglycaemia (raised blood sugar levels) that requires additional monitoring and imposes a burden on patients and clinicians.[25]

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

The treatments compared in the model

- **What are the comparators?**
  The model compares capivasertib plus fulvestrant against alpelisib plus fulvestrant and against everolimus plus exemestane.

How the model reflects the condition

- **What is the structure of the model? Explain how the model reflects the experience of having the condition over time.**

  A three health-state partitioned survival model was developed in Microsoft Excel® to assess the cost effectiveness of capivasertib plus fulvestrant over a lifetime horizon. The health states included progression-free, progressed disease and death. The costs associated with each health state, and the HRQoL patients experiencing each of the health states are included. This is a standard model structure used to model cancer treatments.

Modelling how much a treatment extends life

- **Does the treatment extend life? If so, please explain how (for example. by delaying disease progression, reducing disease severity or complications, reducing disease relapses or life-limiting side effects).**

  Treatment with capivasertib plus fulvestrant delays disease progression and extends life compared with the fulvestrant, as demonstrated in the longer PFS and OS observed in patients receiving capivasertib plus fulvestrant in the CAPItello-291 trial. As explained in response to question 3e above, based on robust indirect comparison methods, capivasertib plus fulvestrant plausibly improves PFS and OS compared with alpelisib plus fulvestrant and everolimus plus exemestane.

- **Describe briefly which trial outcomes feed into the economic model. If trial data used for a certain length of time followed by extrapolation, please note how long the trial data was used for and briefly how the data has been extrapolated.**

  The key clinical parameters from the CAPItello-291 trial that are included in the economic analysis include OS, PFS and time to discontinuation of treatment. The placebo plus fulvestrant arm of the trial provides the baseline OS and PFS data to which the relative treatment effects of capivasertib plus fulvestrant and the comparators, derived from the network meta-analysis, are applied. These treatment effects are extrapolated over a lifetime horizon using NICE-recommended modelling approaches, with the resulting survival curves validated by UK clinical experts.

Modelling how much a treatment improves quality of life

- **How is the treatment modelled to change a person's quality of life compared with the treatments already in use? This should include after stopping treatment if relevant. For example, say if the treatment improves quality of life because of improving symptoms or decreases quality of life because of side effects.**

  HRQoL is captured in the model using utility values derived from data collected in the CAPItello-291 trial. The utility values are specific to the health states and are not dependent on treatment received. The utility values are used to model quality adjusted life years (QALYs) with each treatment, as recommended by NICE. The differences in QALYs between the models arise from the differences in time spent in each health state between the treatments. For example, as capivasertib plus fulvestrant delays time to disease progression compared with the comparators, patients treated with capivasertib plus fulvestrant in the model stay in the progression free health state for longer than

patients treated with the comparators. As patients who are progression free have a higher quality of life than patients who have progressive disease, patients treated with capivasertib plus fulvestrant stay in a higher quality of life state for longer than patients treated with the comparators. Over the lifetime of the model, patients treated with capivasertib plus fulvestrant, on average, live longer than patients treated with the comparators, and so accrue more QALYs than patients treated with the comparators.

The model also accounts for differences quality of life arising form differences in side effects between the treatments.

- **Which quality of life measure(s) did you use to estimate a person's quality of life over time and on treatments? Are there any aspects of the condition or its treatments affecting quality of life which may not have been fully captured by the methods used to estimate quality of life?**

  Utility values in the model are derived from the HRQoL data collected directly from patients using the EQ-5D-5L instrument in the CAPItello-291 trial. In line with NICE's preferred approach, these data were first mapped to EQ-5D-3L data using the appropriate mapping algorithms. The EQ-5D instruments are generic quality of life tools and so it is possible that they are less sensitive to some aspects of the disease compared with disease specific quality of life instruments. However, NICE prefers the use of the EQ-5D instrument. It is unlikely that the model fully captures the HRQoL benefits of delaying treatment with cytotoxic chemotherapy, including the psychological impact and inconvenience or its administration. In addition, the utility arising from availability of choice where previously options were limited is unlikely to be captured.

Modelling how the costs of treatment differ with the new treatment

- **Does the medicine lead to any cost implications (positive or negative) for the health service (e.g., drug costs, number of days in hospital)?**

  The model reflects acquisition costs of all drugs, plus the costs associated with resource use in each of the modelled health states. As capivasertib and the comparators are made available to the NHS at a confidential discount, we are unable to report the total costs. It should be noted that any additional costs of capivasertib plus fulvestrant are also accompanied by clinically meaningful improvements in efficacy, leading to more QALYs.

- **Are there any important differences in the way the medicine is given compared with those already in use that will affect the experience of the patient or costs to the health service or patients (e.g., where it is given or the monitoring that is needed)?**

  There are no major differences in the way capivasertib plus fulvestrant and the comparators are given that would be expected to influence patient experience or costs to the health service. Capivasertib plus fulvestrant is a targeted treatment and so genomic testing is required to target the therapy to appropriate patients; however, genomic testing is already routinely conducted for patients to determine their eligibility for alpelisib plus fulvestrant (PIK3CA testing), and AstraZeneca UK Ltd has applied for

AKT1 and PTEN to be routinely included in this testing. There are therefore no additional costs anticipated to the healthcare setting beyond those that will be used in routine clinical practice. The model does account for the costs of monitoring and the quality-of-life impacts and costs of management of adverse events, which differ between the treatments, but these have very little impact on the total cost and total QALY estimates.

Uncertainty

- **Are there any key assumptions you have made in your model about the medicine's benefits or costs because of lack of data?**

  As explained in response to question 3e, there are no direct comparative data for capivasertib plus fulvestrant and the comparators. Indirect treatment comparisons are therefore required, which are associated with uncertainties due to limitations of the data from earlier conducted trials. Overall survival data available from the capivasertib plus fulvestrant trial are technically immature; however, all available evidence, including additional endpoints assessed in the trial, suggest an early and sustained survival benefit for capivasertib plus fulvestrant.

- **Did you test using alternative assumptions or data in your model? Which had the largest effect on your cost effectiveness estimates?**

  A wide range of sensitivity and scenario analyses were conducted around parameter values and assumptions, which indicated that the base case model estimates were generally robust. The assumptions having the largest effect on the cost effectiveness estimates were the extrapolations of the PFS and OS data from the trial over the longer term, and the extent to which the drug was given as intended (relative dose intensity).

- **Are there any data you have presented to support your modelled outcomes being plausible?**

  Model outputs were tested against the observed data in the CAPItello-291 trial and were shown to be a good match. Clinical experts also validated the modelled survival.

Cost effectiveness results

- **What is the modelled benefit in overall survival, quality adjusted life years and the incremental cost effectiveness ratio?**

  Compared with alpelisib plus fulvestrant, capivasertib plus fulvestrant provided an additional 0.84 life years and an additional 0.62 QALYs. The exact results are considered to be commercially confidential and are presented in Section B.3.10 of the company submission (Document B).

  Compared with everolimus plus exemestane, capivasertib plus fulvestrant provided an additional 1.30 life years and an additional 0.94 QALYs. The exact results are considered to be commercially confidential and are presented in Section B.3.10 of the company submission (Document B).

  Note: the costs and ICERs are based on the (anticipated) list prices of all therapies and do not include confidential discounts that may exist currently or in the future.

Additional factors

- **Have you made a case for a severity modifier being relevant for this condition? If so, please summarise the data presented**

  Yes, using NICE-recommended methods capivasertib plus fulvestrant qualifies for application of a severity modifier. A QALY weighting of 1.2 is applicable and is included in the ICER estimates above.

- **Are there any benefits or disadvantages of the treatment not captured in the modelling?**

  The model is unlikely to fully capture the HRQoL benefits of delaying treatment with cytotoxic chemotherapy, including the psychological impact and inconvenience of its administration.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

- Capivasertib plus fulvestrant provides a step change in therapy for patients with HR+/HER2- advanced breast cancer who have tumours containing PIK3CA/AKT1/PTEN alterations and have experienced disease progression following CDK4/6 inhibitor and endocrine therapy:
- Capivasertib is the first AKT inhibitor to be licensed[32] and the first to target PIK3CA/AKT1/PTEN-altered tumours. None of the existing comparator therapies (alpelisib plus fulvestrant or everolimus plus exemestane) specifically target all three of these alterations.
- The combination of capivasertib plus fulvestrant enhances their antitumour effects and may help to prevent or delay the development of resistance to endocrine therapy, and help delay the use of cytotoxic chemotherapy. In the pivotal CAPItello-291 trial, capivasertib plus fulvestrant delayed the time to subsequent use of chemotherapy or death by 5 months,[36] whilst maintaining patient quality of life. The economic model is unlikely to fully capture the quality-of-life benefits of capivasertib plus fulvestrant form delaying treatment with cytotoxic chemotherapy, including the psychological impact and inconvenience or its administration.
- Whilst acknowledging some limitations, on the available evidence, capivasertib plus fulvestrant plausibly improves progression-free and overall survival compared with alpelisib plus fulvestrant and everolimus plus exemestane.
- The combination was designated as innovative by the granting of an Innovation Passport in January 2024 as part of the UK regulatory authority (MHRA)-led Innovative Licensing and Access Pathway.[33]

- Capivasertib plus fulvestrant provides a much-needed new therapeutic option to address the significant unmet need for an effective and tolerable therapy that targets PIK3CA/AKT1/PTEN-altered tumours, has a different mode of action, enhances sensitivity to endocrine therapy following failure of CDK4/6 inhibitor therapy, and enables patients to remain on endocrine-based treatments for longer before progression to cytotoxic chemotherapy.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

- Capivasertib plus fulvestrant is licensed for use in breast cancer in women and men.[1] Breast cancer is rare in men and, consequently, data for capivasertib plus fulvestrant in men with breast cancer are limited. This should not preclude or limit the use of capivasertib plus fulvestrant in men in line with its licensed indication and proposed clinical positioning.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Useful patient information on breast cancer is available from:

- Breast Cancer Now: https://breastcancernow.org/
- Cancer Research UK: https://www.cancerresearchuk.org/about-cancer/breast-cancer.
- Breast Cancer UK: https://www.breastcanceruk.org.uk/

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/

- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Double-blind. Design feature of a robust randomised controlled trial (RCT) that ensures neither the patient nor the person assessing the patient knows which treatment the patient has received.

EQ-5D-3L/5L. A validated generic quality of life instrument that may be used to assess HRQoL across a range of different diseases. From this utility values can be estimated.

HR+/HER2- breast cancer. A common type of breast cancer. HR+ means that tumour cells have receptors for the hormones oestrogen or progesterone, which can promote the growth of HR+ tumours. HER2 stands for human epidermal growth factor receptor 2. HER2- means these cancer cells are not responsive to therapies that target HER2.

HRQoL – health-related quality of life. A combination of a person's physical, mental and social well-being; not merely the absence of disease. Can be assessed using validated questionnaires or surveys (e.g. EQ-5D-5L instrument), or using quantitative experiments where people reveal their preferences for different situations.

NMA – network meta-analysis. A statistical technique for comparing multiple treatments simultaneously in a single analysis by combining data from randomised controlled trials.

NICE – The National institute for Health and Care Excellence.

NICE TAXXX – NICE technology appraisal number XXX.

OS – overall survival. Typically defined as the time from randomisation in the trial to death from any cause.

Patient information leaflet. Document that provides information for patients on using a medicine safely and correctly.

PIK3CA / AKT1 / PTEN – specific genes that can become mutated in HR+/HER2 breast cancer tumours. Mutations (also called alterations) in these genes can cause cancer cells to grow.

Primary endpoint/outcome. The main outcome for which a clinical trial is designed to evaluate the effects of a treatment.

QALYs – quality adjusted life years. A measure of the state of health of a person or group in which the benefits, in terms of length of life, are weighted using utility values to reflect the quality of life. One quality-adjusted life year (QALY) is equal to 1 year of life in perfect health.

RCT – randomised controlled trial. A type of clinical trial to compare the effects of treatments such as drugs against each other by assigning participants randomly to each of the treatments. This is the most scientifically robust type of clinical trial.

PFS – progression free survival. Typically defined as the time from randomisation in the trial to the first objective evidence of disease progression as assessed using radiography, or death, whichever occurs first.

Secondary endpoint(s)/outcome(s). Specified key outcomes a trial will evaluate that are not the primary endpoint. This does not necessarily mean the secondary endpoints are less important than the primary endpoint; it relates to the ability of the trial design to test for any differences between treatments in their effects on the outcome(s) in the trial.

Summary of Product Characteristics. A document describing the properties and the officially approved conditions of use of a medicines. Forms the basis of information for healthcare professionals on how to use the medicine safely and effectively.

Utility values. A measure of the preference or value that an individual or society gives a particular health state. It is generally a number between 0 (representing death) and 1 (perfect health). Can be used to weight the length of time spent in a given health state to generate QALYs.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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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

[ID 6370]

Clarification questions

August 2024

File name	Version	Contains confidential information	Date
ID6370 Clarification Letter [CIC] - EAG Final_AZ response_REDACTED	1.0	Yes	30 Aug 2024

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

A 1. Please clarify which of the Ovid EBM Reviews resources were searched for the Clinical SLR. In section 2.1.1 of *Astrazeneca_Capivasertib Clinical SLR Report 2024 update_V1 (10 May 2024)_CONFIDENTIAL.doc* it states that the HTA database was searched, but this is not listed in the search strategy documentation (Appendix A). In Appendix A, other EBM Reviews resources are listed as being searched (ACP Journal Club, Cochrane Clinical Answers, Cochrane Methodology Register), but these are not documented in section 2.1.1 of the document above.

The HTA database was searched as part of the Ovid EBM Reviews resources for the original searches which were run on 31 January 2023. As this resource is no longer updated since 2016, it was not included in any of the subsequent updates as no new records would be retrieved in an update.

The information in Appendix A of the company submission Document B for the EBM databases should read: EBM Reviews (Ovid): Cochrane Methodology Register 3rd Quarter 2012, Database of Abstracts of Reviews of Effects 1st Quarter 2016, Health Technology Assessment, 4th Quarter 2016, ACP Journal Club 1991 to January 2023, Cochrane Central Register of Controlled Trials January 2023, Cochrane Database of

Systematic Reviews 2005 to January 31, 2023, Cochrane Clinical Answers January 2023: searched 31 January 2023.

A 2. Please confirm that the EBM Reviews search conducted for the August 2023 update were conducted on 8.8.23, not 28.3.23 as stated in *Astrazeneca_Capivasertib Clinical SLR Report 2024 update_V1 (10 May 2024)_CONFIDENTIAL.doc*.

This was typographic error, the searches were run on 8 August 2023.

A 3. Please confirm the date range and date searched for the February 2024 update of the MEDLINE databases, as these are not provided in Astrazeneca_Capivasertib Clinical SLR Report 2024 update_V1 (10 May 2024)_CONFIDENTIAL.doc.

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions: 1946 to February 06, 2024: searched 7 February 2024.

A 4. Please provide full details (including database name, host, date range, date searched, search terms, hits per line of search and any limits applied) for all of the cost effectiveness/HRQoL/healthcare resource use searches conducted, including the original search (April 2023) and the two update searches (November 2023 and April 2024). Appendix A of *Astrazeneca_Capivasertib Economic SLR Report 2024 update_V1 (06 June 2024)_CONFIDENTIAL* currently only provides one set of search strategies, with no hits per line, and no details of which search update this represents.

The following electronic databases were searched for the original systematic literature review (SLR) and the two updates (November 2023 and April 2024), using the advanced search function available on the respective web interface (listed in parentheses) as the search platform:

- PubMed including MEDLINE (https://pubmed.ncbi.nlm.nih.gov/advanced/)
- Embase (https://www.embase.com/#advancedSearch/default)

- Cochrane Library (https://www.cochranelibrary.com/advanced-search). As clinical studies were not the focus of the SLR, only the Cochrane Database of Systematic Reviews, which includes reviews and protocols, but not the Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Clinical Answers, were searched

- Epistemonikos (https://www.epistemonikos.org/en/advanced_search)

The native web interfaces were used to search each database, as they are directly available to users (subject to subscription/access to the database) and do not require further software or subscriptions to be reproduced.

The full search strategy used to search each database is provided in Appendix I of this document. The same search strategy was used for the original SLR, the November 2023 update and the April 2024 update, with the exception of the timeframe limit applied. No timeframe limit was applied for the original SLR with the earliest study identified dating from 1992. A timeframe limit of 1 April 2023 until present (20 November 2023) was applied for the November 2023 update and a timeframe limit of 1 November 2023 until present (5 April 2024) was applied for the April 2024 update.

The searches for the original SLR were performed on 18 April 2023, on 20 November 2023 for update 1 and 5 April 2024 for update 2. An overview of the number of results identified for each database for the original SLR and two updates is provided in Table 1.

Table 1. Overview of numbers of results identified by database

Database	Original SLR (18 April 2023)	Update 1 (20 November 2023)	Update 2 (5 April 2024)
Cochrane library	38	2	0
Embase	3234	139	150
Epistemonikos	130	5	33
PubMed	1684	89	69

Note: These figures represent the total number of results prior to deduplication.
Abbreviation: SLR, systematic literature review.

The number of hits per line of search for update 1 (20 November 2023) is provided in Appendix I.E of this document. The number of hits per line of search are not available for the original SLR or update 2 (5 April 2024). Search results were

exported into Sourcerer for the original SLR and EndNote for the two updates prior to deduplication. We are confident therefore that all studies identified in database searches are represented in the figures provided in Table 1.

A 5. Please provide full details of all HTA and conference proceedings searches conducted for the cost effectiveness/HRQoL/healthcare resource use SLR, including dates searched, search terms used and numbers of records found for the original search and each of the update searches.

HTA institutions

Websites of the following health technology assessment (HTA) institutions were searched:

- Canadian Agency for Drugs and Technologies in Health (CADTH) and Institut National d'Excellence en Santé et en Services Sociaux (INESSS) in Canada
- Haute Autorité de Santé (HAS) in France
- Institute for Clinical and Economic Review (ICER) in the US
- Institute for Quality and Efficiency in Health Care (IQWiG) in Germany
- National Institute for Health and Care Excellence (NICE), Scottish Medicines Consortium (SMC), and All Wales Medicines Strategy Group (AWMSG) in the UK
- Pharmaceutical Benefits Advisory Committee (PBAC) in Australia.

HTA agencies' websites were searched using the respective in-built functionality for the terms advanced breast cancer, metastatic breast cancer, inoperable breast cancer, and unresectable breast cancer.

The website of the German IQWiG was also searched using the German equivalents of the above terms, namely fortgeschrittener Brustkrebs, metastasierter Brustkrebs, inoperabler Brustkrebs, and nicht-operabler Brustkrebs. The website of the French HAS and Canadian INESSS was searched using the corresponding French terms,

namely cancer du sein avancé, cancer du sein métastatique, cancer du sein métastasé, cancer du sein non résécable, and cancer du sein inoperable.

The same search strategy was used for the original SLR, the November 2023 and April 2024 updates. No date filter was used for the original SLR. If available on the HTA agency website, a date filter was used for the two updates. A timeframe limit of 1 April 2023 until present (21–23 November 2023) was applied for the November 2023 update and a timeframe limit of 1 November 2023 until present (5 April 2024) was applied for the April 2024 update. If a date filter was unavailable, results were sorted from most to least recent and results published before the timeframe limit were not screened. If search results sorting was not supported by the HTA agency website, all results were screened.

An overview of the search dates and the number of results identified for each HTA agency website for the original SLR and two updates is provided in Table 2.

Table 2. Overview of number of results identified for each HTA agency website

HTA agency	Original SLR (18 April 2023)	Update 1 (21–23 November 2023)	Update 2 (5 April 2024)
CADTH	63	0	1
HAS		0	0
INESSS		0	0
ICER		0	0
IQWiG		2*	1
NICE		0	1
SMC		0	1
AWMSG		0	0
PBAC		0	0

*One of the IQWiG reports (abemaciclib) identified in update 1 was a duplicate. The results were extracted as additional cost data was identified which had not been extracted in the original SLR.
Abbreviations: AWMSG, All Wales Medicines Strategy Group; CADTH, Canadian Agency for Drugs and Technologies in Health; HAS, Haute Autorité de Santé; HTA, health technology assessment; ICER, Institute for Clinical and Economic Review; INESSS, Institut National d'Excellence en Santé et en Services Sociaux; IQWiG, Institute for Quality and Efficiency in Health Care; NICE, National Institute for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; SLR, systematic literature review; SMC, Scottish Medicines Consortium.

Abstracts from scientific conferences

For the original SLR, only abstracts published within the previous 2 years (since 2021) were considered relevant. In the two updates, conference websites were only searched if the conference had occurred during the intervening period. An overview

of the search dates and which conference websites were searched for the original SLR and two updates is provided in Table 3.

Table 3. Overview of conference websites searched

Conference	Original SLR (18 April 2023)	Update 1 (21–23 November 2023)	Update 2 (5 April 2024)
ASCO	No searching was conducted as conferences were covered by Embase through 2022	Materials from the 2023 annual conference were searched directly on the ASCO website	No searching was conducted as there had not been a conference since the first update was conducted
ABC	ABC5 (2019) was covered by Embase, but not ABC6 so materials from ABC6 were searched directly on the ABC Global Alliance website	Materials from ABC7 were searched directly on the ABC Global Alliance website	No searching was conducted as there had not been a conference since the first update was conducted
EBCC	No searching was conducted as conferences were covered by Embase through 2022	No searching was conducted as there had not been a conference since the original SLR was conducted	Materials from the 14th EBCC conference were searched directly on the EBCC website
ESMO	No searching was conducted as conferences were covered by Embase through 2023	Materials from the 2023 annual conference were searched directly on the ESMO website	No searching was conducted as there had not been a conference since the first update was conducted
SABCS	Embase covered SABCS through 2021 but not the 2022 edition, which was searched directly on the symposium website	No searching was conducted as there had not been a conference since the original SLR was conducted	Materials from the 2023 SABCS held in December 2023 were searched directly on the SABCS website
SGBCC	SGBCC was not covered by Embase so SGBCC 17 (2021) and 18 (2023) were searched directly on the conference website	No searching was conducted as there had not been a conference since the original SLR was conducted	No searching was conducted as there had not been a conference since the first update was conducted

Abbreviations: ABC, Advanced Breast Cancer; ASCO, American Society of Clinical Oncology; EBCC, European Breast Cancer Council; ESMO, European Society for Medical Oncology; SABCS, San Antonio Breast Cancer Symposium; SLR, systematic literature review; SGBCC, St Gallen International Breast Cancer Conference. Conference websites were searched using the respective in-built functionality for the terms advanced breast cancer, metastatic breast cancer, inoperable breast cancer, and unresectable breast cancer.

An overview of the number of results identified for each conference website for the original SLR and two updates is provided in Table 4.

Table 4. Overview of number of results identified for each conference website

Conference	Original SLR (18 April 2023)	Update 1 (22–23 November 2023)	Update 2 (5 April 2024)
ASCO	1	1*	0
ESMO		3†	0
ABC		0	0
EBCC		0	1
SABCS		0	0

Conference	Original SLR (18 April 2023)	Update 1 (22–23 November 2023)	Update 2 (5 April 2024)
SGBCC		0	0

*This abstract was later excluded during full-text review of abstract and poster.
†These three abstracts were excluded as they were duplicates of those identified during the database search.
Abbreviations: ABC, Advanced Breast Cancer; ASCO, American Society of Clinical Oncology; EBCC, European Breast Cancer Council; ESMO, European Society for Medical Oncology; SABCS, San Antonio Breast Cancer Symposium; SLR, systematic literature review; SGBCC, St Gallen International Breast Cancer Conference.

Decision problem

A 6. **Priority question: The population defined in the NICE final scope is "Adults with hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer after endocrine treatment'." The population in the company submission (CS) is "Adults with HR+/HER2- advanced and metastatic breast cancer with PI3K/AKT pathway-altered tumours (PIK3CA, AKT1, or PTEN), whose disease has progressed on or following CDK4/6 inhibitor plus endocrine therapy." Therefore, the scope of the population in the Decision Problem in the CS was narrower than the population which was defined in the NICE final scope. Please comment on this issue and, please provide further clarification on the difference between the population defined in the NICE final scope and the population in the CS. Please also clarify that the company does not expect capivasertib to be prescribed to patients except those who have progressed on or following CDK4/6 inhibitor plus endocrine therapy.**

The scope for this appraisal was defined before the UK marketing authorisation for capivasertib in combination with fulvestrant was granted. The UK marketing authorisation was granted 17th July 2024 and the wording of the licensed indication, as reflected in our submission, is:

Capivasertib (TRUQAP®) is indicated in combination with fulvestrant for the treatment of adult patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative (defined as IHC 0 or 1+, or IHC 2+/ISH) locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following recurrence or progression on or after an endocrine based regimen.[1]

As discussed in detail in section B.1.3.2 of our submission, based on NICE technology appraisals TA495, TA496 and TA563, issued in 2017-2019,[2–4] and in line with current international treatment guidelines produced by ESMO[5] and the National Comprehensive Cancer Network (NCCN),[6] the recommended first-line standard of care endocrine based therapy for men and postmenopausal women with advanced HR+/HER2- breast cancer is with a CDK4/6i (palbociclib, ribociclib or abemaciclib) in combination with an aromatase inhibitor (AI). As confirmed by UK clinicians approached for their expert opinion by the Company,[7] and the UK clinical experts attending the NICE technology appraisal committee meeting for alpelisib plus fulvestrant (TA816),[8] the majority of patients receive initial therapy with a combination of CDK4/6i and AI.

The positioning of capivasertib plus fulvestrant as stated in our submission – for use in patients with PI3K/AKT pathway-altered tumours (PIK3CA, AKT1, or PTEN) whose disease has progressed on or following CDK4/6i plus endocrine therapy – is therefore aligned with its licensed indication and its anticipated use in current UK clinical practice. This positioning was verified with UK clinicians.[7] We do not anticipate use in patients who have not received prior CDK4/6i therapy.

A 7. **Priority question: The company's decision problem excluded retreatment with CDK4/6 inhibitors as a relevant comparator as the company stated that retreatment with CDK4/6 inhibitors is not routinely an option per ESMO and NCCN guidelines and is not reimbursed by the NHS. Please provide further justification on the exclusion of retreatment with CDK4/6 inhibitors as a relevant comparator on the basis of guidelines in England and Wales.**

In addition to the ESMO and NCCN guideline recommendations, we referenced in section B.1.3.2.1 of our submission the NHS England commissioning policies / BlueTeq criteria for use of CDK4/i. These permit use of CDK4/6i only if one of the following criteria applies: [9]

- No prior treatment with a CDK 4/6i, or

- Previous treatment with another CDK4/6i but treatment has had to be stopped within 6 months of its start solely as a consequence of dose-limiting toxicity and in the clear absence of progressive disease, or
- Previously received adjuvant CDK4/6i for high-risk early breast cancer and treatment with CDK4/6i was completed without disease progression at least 12 months prior to the first diagnosis of recurrent or metastatic disease.

As none of these criteria are relevant to the positioning of capivasertib plus fulvestrant per its licensed indication and in the current treatment pathway, the NHS England commissioning policy effectively precludes CDK4/6i therapy retreatment as a comparator in this appraisal.

The Company also noted in section B.1.3.2.1 of the Company submission that UK clinical expert opinion obtained via 1:1 interviews[7] indicates that retreatment with CDK4/6i therapy is not routinely an option. The company further noted that UK clinical expert opinion reported in NICE TA725 specifically referred to the fact that CDK4/6i would not be used twice in the treatment pathway due to the potential for tumours to develop resistance.[10]

In the NICE appraisal of alpelisib plus fulvestrant (TA816), the technology appraisal committee agreed that the appropriate positioning of alpelisib plus fulvestrant was as a second line therapy after disease progression on a CDK4/6i plus AI. It further agreed that, in this position, the relevant comparator was everolimus plus exemestane.[8] Neither retreatment with CDK4/6i nor any of the other therapies listed as comparators in the scope for the current appraisal of capivasertib plus fulvestrant were deemed to be relevant comparators to address the decision problem for the appraisal of alpelisib plus fulvestrant. As our proposed positioning of capivasertib plus fulvestrant is also for use in patients whose disease has progressed on or following CDK4/6i plus AI therapy, the relevant comparators are alpelisib plus fulvestrant and everolimus plus exemestane.

A 8. **Priority question. The company has only included two comparators and cites the ESMO guideline as part of the justification for the choice. However, the ESMO guideline provides a long list of comparators after progression on a CDK 4/6 inhibitor: *"The optimal sequence of endocrine-***

based therapy is uncertain after progression on CDK4/6 inhibitors. It is dependent on which agents were used previously [in the (neo)adjuvant or advanced settings], duration of response (DoR) to previous ET (for use of second-line single-agent ET), disease burden, patient preference and treatment availability. Evidence-based available options for second line therapy include: fulvestrant alpelisib (for PIK3CAmutated tumours, exemestane everolimus,tamoxifen everolimus, fulvestrant everolimus, AI, tamoxifen, fulvestrant, chemotherapy and poly (ADP-ribose) polymerase (PARP) inhibitors for tumours harbouring gBRCAm." **(p.1478) Please provide evidence that the only treatments currently used in UK clinical practice are the two in the decision problem, or perform clinical effectiveness and cost effectiveness analyses versus all other comparators that are used in UK clinical practice.**

Whilst the ESMO guideline (and the NICE scope for this appraisal) lists several possible treatment options following prior CDK4/6i therapy, the clinical pathway presented in section B.1.3.2 of our submission, which depicted the positioning of capivasertib plus fulvestrant post CDK4/6i therapy, with alpelisib plus fulvestrant (per TA8168) and everolimus plus exemestane (per TA421) as the relevant comparators, was validated by the Company with UK clinical experts.

The Cancer Drugs Fund clinical lead during the appraisal of alpelisib plus fulvestrant (TA816) noted that most people who were potentially likely to have alpelisib plus fulvestrant at that time would have otherwise received everolimus plus exemestane in NHS practice. The technology appraisal committee in TA816 agreed that the relevant comparator for alpelisib plus fulvestrant post CDK4/6i therapy was everolimus plus exemestane.[8] This indicates that none of the other therapies listed in the ESMO guideline were considered by the NICE appraisal committee to be relevant to the decision problem for the appraisal of alpelisib plus fulvestrant post CDK4/6i therapy in NHS practice.

Tamoxifen plus everolimus and fulvestrant plus everolimus, which are not licensed combinations, and single agent endocrine therapy with AI or tamoxifen would not be anticipated to be used routinely instead of NICE-recommended combinations of alpelisib plus fulvestrant (per TA816) or everolimus plus exemestane (per TA421) in

patients who are eligible for these. Similarly, these therapies would not be anticipated to be relevant alternative treatment options to capivasertib plus fulvestrant in patients potentially eligible for this combination.

Single agent fulvestrant is not recommended in the treatment of advanced or metastatic disease per NICE TA239,[11] and so would not be an alternative option to capivasertib plus fulvestrant. PARP inhibitors are targeted at patients with tumours harbouring germline BRCA1/2 mutations, which is a different genomic mutation to the PIK3CA/AKT1/PTEN-alterations targeted by capivasertib plus fulvestrant (and PIK3CA targeted by alpelisib plus fulvestrant). In TA952, the committee agreed that if a patient has a gBRCA mutation, they would be eligible for talazoparib.[12] PARP inhibitors would therefore not be used routinely in patients eligible for capivasertib plus fulvestrant, and would instead be targeted to patients with tumours harbouring germline BRCA1/2 mutations.

As detailed in section B.1.3.2, recent NICE technology appraisals of therapies for advanced HR+/HER2- breast cancer consistently emphasise clinician and patient desire to delay or even avoid the use of chemotherapy due to its significant toxicity profile and poor tolerability.[2,3,8,10,13,14] ESMO clinical guidelines recommend that at least two lines of endocrine-based therapy are preferred before moving to chemotherapy unless patients are at imminent risk of organ failure or have tumours that are endocrine resistant.[5] In patients not at imminent risk of organ failure, chemotherapy would therefore not be offered routinely in the second-line setting following failure of initial CDK4/6i plus AI therapy. Furthermore, clinician feedback has indicated that, in the attempt to delay chemotherapy initiation for as long as possible, chemotherapy is offered when all suitable endocrine options have been exhausted and/or the patient is deemed endocrine-insensitive. According to the ABC guidelines, endocrine insensitivity/resistance is defined as progression within 2 months of later-line ET-based therapy for advanced breast cancer.[15] As patients need to be endocrine treatment-sensitive to benefit from capivasertib and fulvestrant, chemotherapy regimens are not relevant comparators.

In conclusion, only alpelisib plus fulvestrant (per TA816) and everolimus plus exemestane (per TA421) can be considered as relevant alternative options for

patients who would be eligible to receive capivasertib plus fulvestrant in NHS practice. Only alpelisib plus fulvestrant and everolimus plus exemestane are therefore the relevant comparators to address the decision problem.

Systematic review

A 9. **Priority question: The PRISMA flow diagram of the systematic review (Page 22 of Capivasertib Clinical SLR Report 2024 update) showed that 307 studies were included in the systematic review. However, only 10 studies were included in the network meta-analysis. Please provide full details of excluded studies with reasons for exclusion.**

As the inclusion criteria of the SLR were broader than the current decision problem and included several therapies and trial populations that are not relevant to the comparative effectiveness of capivasertib plus fulvestrant in patients with PI3K/AKT pathway-altered HR+/HER2- advanced breast cancer, the feasibility of conducting a NMA using identified RCT data that are relevant to the decision problem was assessed. This consisted of three distinct steps: (1) identification of relevant studies for the decision problem, (2) heterogeneity assessment of study characteristics and (3) generation of outcome-specific networks and tests for proportional hazards.

A total of 271 studies were excluded due to the reasons outlined below:

- Not a comparison of interest in the global NMA: 35
- Not a treatment of interest in the global NMA: 15
- Experimental/non-approved interventions: 93
- Not possible to connect study in base-case (randomised treatments do not fit in the network): 42
- Single arm studies: 82
- Small dose-finding studies excluded following the decision to drop the fulvestrant loading dose from the treatment labels: 4

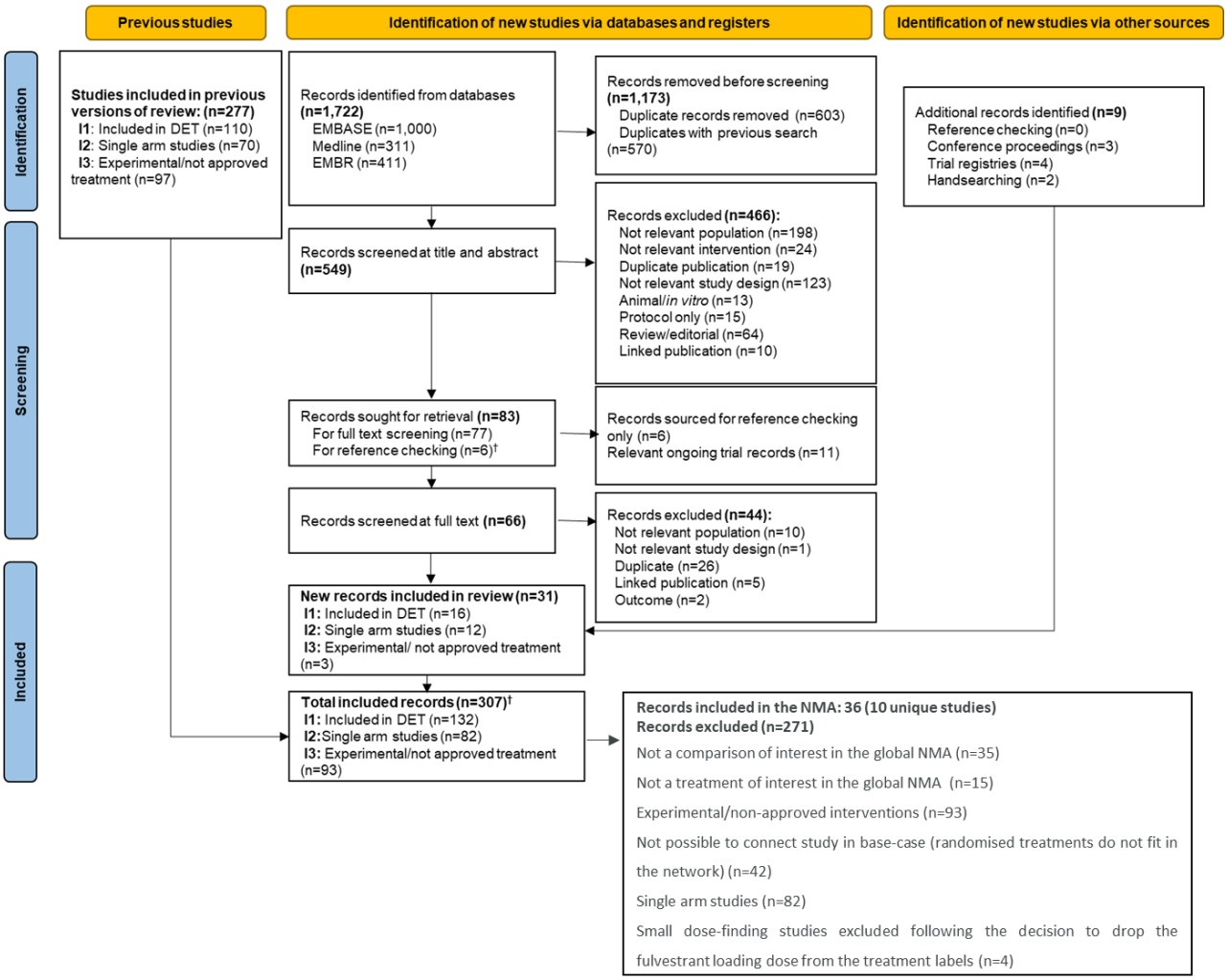
The remaining 36 publications (associated with 10 unique studies) were included in the NMA. Full details on the excluded studies can be found in Appendix II. A Summary of the 10 studies included in the base case NMA can be found in Table 2 of the CS Appendix. CAPItello-291, FAKTION, BOLERO-2, BOLERO-5 and SOLAR-1 provided

data on the interventions and comparators of interest for the decision problem, EFECT, SOFEA, CONFIRM, FRIEND and NCT01300351 were required to form a connected network between the treatments.

A 10. Please revise the PRISMA flow diagram accordingly after providing the details of excluded studies with reasons for exclusion.

The updated PRISMA diagram is provided in Figure 1

Figure 1 Clinical SLR PRISMA diagram



A 11. Please confirm whether quality appraisals were conducted by two independent reviewers and if so how any disagreements were resolved? If not, please describe the approach taken.

A robust procedure was in place to assess the quality of the studies and resolve conflicts. Quality appraisals were conducted by a single reviewer and checked by a

second reviewer. Any disputes were resolved by consensus or by a third reviewer. The specific number of disagreements has not been recorded; as this is not routine practice, and is not required to meet the goals of an SLR for the purposes of a NICE appraisal.

Clinical effectiveness evidence

A 12. **Priority question: Please provide results of subgroup analyses for the overall survival outcome in the PI3K/AKT pathway-altered population of the CAPItello-291 trial.**

Subgroup analyses for PFS (primary endpoint in CAPItello-291) were pre-planned and conducted by stratification factors, age (<65 vs >65 years), and across a range of other exploratory analyses in the PI3K/AKT pathway-altered population (Section B.2.7, Document B). Subgroup analyses for OS were not pre-planned in CAPItello-291, as OS was a secondary endpoint in the trial.

Despite a clear early and sustained trend towards an OS benefit with capivasertib plus fulvestrant (HR 0.69; 95% CI 0.45, 1.05) in the PI3K/AKT-altered population at the time of primary analysis, OS data had reached maturity of 37% in the ITT population and 34.6% in the PI3K/AKT pathway-altered population. Therefore, at the time of the primary analysis, a high enough level of OS maturity was not yet reached to facilitate appropriate subgroup analysis.

Given the maturity of the OS data, any post-hoc subgroup analysis with the data from the primary analysis will likely result in median OS not reached in the large majority of cases. As such, it is not possible to provide OS HRs in the PI3K/AKT pathway altered population per subgroup, as requested.

With OS data showing a promising early and sustained trend, in addition to statistically significant PFS and PFS2 data, and consistent benefit across most subgroups, the evidence available from CAPItello-291 provides a robust basis for reimbursement decision making.

A 13. **Priority question: Please provide subgroup analyses for the overall survival outcome by the specific tumour alteration in the PI3K/AKT pathway-altered population of the CAPItello-291 trial.**

Subgroup analyses for PFS (primary endpoint in CAPItello-291) were pre-planned and conducted by stratification factors, age (<65 vs >65 years), and across a range of other exploratory analyses in the PI3K/AKT pathway-altered population (Section B.2.7, Document B). Subgroup analyses for OS were not pre-planned in CAPItello-291, as OS was a secondary endpoint in the trial.

As outlined above, despite a clear early and sustained trend towards an OS benefit with capivasertib plus fulvestrant (HR 0.69; 95% CI 0.45, 1.05) in the PI3K/AKT-altered population at the time of primary analysis, OS data had reached maturity of 37% in the ITT population and 34.6% in the PI3K/AKT pathway-altered population. Therefore, at the time of the primary analysis, a high enough level of OS maturity was not yet reached to facilitate appropriate subgroup analysis.

It is anticipated that if a post-hoc subgroup analysis were to be conducted with data from the primary analysis, this would not be informative as median OS would not be reached in the large majority of cases, and therefore it would not be possible to provide OS HRs in the PI3K/AKT pathway population, per subgroup.

PFS analysis by specific tumour alteration was conducted and is presented in Figure 11 in Document B, demonstrating consistent treatment effects in patients with PIK3CA alterations (HR 0.51, 95%CI 0.37-0.70), AKT1 alterations (HR 0.51, 95%CI 0.22-1.12) or PTEN alterations (HR 0.43, 95%CI 0.21-0.88).[16] It is notable that while there were 202 patients with PIK3CA alterations in the analysis, there were only 33 patients with AKT1 alterations, and 37 patients with PTEN alterations due to the much lower incidence of these alterations, resulting in larger HR confidence intervals and increased uncertainty. The upper CI in the AKT1 analysis crossed 1 due to the small sample size.

OS for patients with PIK3CA alterations from CAPItello-291 is presented in Figure 2 and Table 5 Source: Data on file 202317

Table 5 below. This was consistent with OS observed in the PI3K/AKT altered population (Figure 4 of Document B), as well as PI3K/AKT altered population with prior CDK4/6i use (Figure 5 in Document B). Restricted mean survival time (RMST) for OS in the capivasertib plus fulvestrant arm was [redacted])[17] (Table 5), which was comparable with RMST for OS in the PI3K/AKT altered population with prior CDK4/6i use ([redacted]) (see response to B19, Table 52). Corresponding analyses for patients with PTEN or AKT1 alterations cannot be generated as these subgroups of patients are very small in CAPItello-291 (please refer to Table 5 in Document B). There is no evidence currently available to suggest outcomes for patients with PTEN or AKT1 alterations would differ from patients with PIK3CA alterations due to the unique mechanism of action of capivasertib, inhibiting AKT – a key node in the PI3K/AKT signalling pathway overactivated in approximately half of patients with HR+/HER2- breast cancer by means of activating mutations in PIK3CA and AKT1 and inactivating alterations in PTEN.[18] By inhibiting AKT activation, capivasertib reduces the growth of PIK3CA, AKT1, or PTEN-altered tumours. Therefore, as observed with the available PFS data (see Figure 11 in Document B), it is expected that OS for patients with PTEN or AKT1 alterations would not differ from those with PIK3CA alterations.

Figure 2 Overall survival in patients with PIK3CA alterations (DCO1)

Source: Data on file 2023[17]

Table 5 Descriptive statistics for overall survival in patients with PIK3CA alterations in CAPItello-291 (DCO1)

Arm	N	Events	Maturity	RMST (95% CI)	Median (95% CI)
Placebo + Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Capivasertib + Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Data on file 2023[17]

A 14. The Investigator assessed progression-free survival (PFS) from CAPItello-291 was one of the clinical parameters to inform treatment effectiveness in the economic model. a) Please provide the definition of investigator-assessed PFS in CAPItello-291. b) Please discuss how the investigator-assessed PFS in CAPItello-291 compares to the definitions of PFS in the other trials included in the NMA. c) If applicable, please elaborate on the potential implications of the discussed differences between definitions in question b.

The definition of PFS from CAPItello-291 can be seen in the table below. The definitions of PFS from the other trials included in the NMA are also located in this table. The definitions of PFS are consistent among the studies, defining PFS as the

time from randomisation until progression or death. The change in RECIST from 1.0 to 1.1 is chronologically consistent with the publication of the new issue of the criteria. We do not anticipate the differences in the RECIST criteria when moving from version 1.0 to version 1.1 to have meaningfully impacted the conclusions that can be drawn from the NMA on the relative treatment effects of the therapies in terms of PFS.

Table 6 Definitions of PFS in the trials included in the NMA

Trial	PFS definition
CAPItello-291	Time from randomisation until progression per RECIST v1.1, as assessed by the investigator at the local site, or death due to any cause[18]
FAKTION	Time from randomisation to either the first documented progression confirmed by RECIST criteria (regardless of whether the patient withdrew from study therapy or received another anti-cancer therapy before progression) or death from any cause.[19]
SOLAR-1	Time from the date of randomisation to the date of the first documented progression or death due to any cause. If a patient has not had an event, PFS will be censored at the date of the last adequate tumour evaluation. Clinical deterioration without objective radiological evidence will not be considered as documented disease progression. The primary analysis for PFS will be performed based on local radiology assessment according to RECIST 1.1.[20]
CONFIRM	Time to progression defined as median time (in months) from randomisation until objective disease progression or death (in the absence of objective progression). RECIST (Response Evaluation Criteria in Solid Tumors) tumour assessments carried out every 12 weeks (+/- 2 weeks) from randomisation for study duration (48 months).[21]
FRIEND	Time from initial randomisation to the first record of disease progression (according to RECIST 1.1 criteria) or death from any cause.[22]
NCT01300351 (Zhang 2016)	Progression defined using Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1), as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, or unequivocal progression of existing non-target lesions, or the appearance of new lesions, or death (by any cause in the absence of progression).[23]
EFECT	Time to progression was defined as the number of days from the date of random assignment until the date of objective disease progression, as per RECIST criteria. If the patient died without documented disease progression, and the date of death was no more than 6 months from the last disease assessment per RECIST, then death was regarded as a progression event.[24]
SOFEA	Time from randomisation to progression of existing disease, new sites of disease, second primary cancer if change in systemic treatment was necessary, or death from any cause. Tumour assessment with Response Evaluation Criteria in Solid Tumors (RECIST; version 1.0) was done every 3 months and at discontinuation or withdrawal from treatment [25]
BOLERO-2	Time from the date of randomisation to the date of first documented radiological progression or death due to any cause. Disease progression was based on the tumour assessment by the local radiologist or investigator using RECIST 1.0 criteria. If a patient did not progress or known to have died at the date of the analysis cut-off or start of another antineoplastic therapy, the PFS date was censored to the date of last adequate tumour assessment prior to cut-off date or start of antineoplastic therapy.[26,27]
BOLERO-5	Time from the date of randomisation to the date of first documented progression or death due to any cause. Disease progression was assessed using the local investigator's tumour assessment per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1.[28,29]
Note: Where the definition of PFS was not clear from the publication, the associated record on clinicaltrials.gov was used to confirm the definition. Time to progression as defined in the trials where this was the stated endpoint is synonymous with PFS	

A 15. The population in the CS (patients with HR+/HER2-, PI3K/AKT pathway-altered, locally advanced or metastatic breast cancer following progression on or

after CDK4/6i plus endocrine therapy) is a subpopulation of the CAPItello-291 trial. a) Please provide patients' characteristics of this subpopulation in the trial and compare these to the characteristics of the full population in the trial. b) Please also justify that this subpopulation is representative for the population in England and Wales in the positioning that is proposed.

Baseline characteristics of the subpopulation of the CAPItello-291 trial meeting the licensed indication were provided in Table 5 of our submission, alongside the baseline characteristics of patients meeting the licensed indication who had received prior CDK4/6i therapy. We noted that the baseline characteristics of the full trial population were provided in the fully published manuscript by Turner et al 2023,[18] which we provided in the reference pack. For the convenience of the EAG we have provided a table below (Table 7), re-presenting the baseline characteristics of the licensed population and the licensed population with prior use of CDK4/6i therapy, and the overall population of the CAPItello-291 trial that includes these patients and those not meeting the licensed indication.

Table 7. Baseline characteristics of the licensed population subgroups and overall trial population of the CAPItello-291 trial

Characteristic		PI3K/AKT-altered population (Licensed population)		PI3K/AKT-altered population (Licensed population) with prior CDK4/6i use		Overall CAPItello-291 trial population	
		Capi + ful (N=155)	Placebo + ful (N=134)	Capi + ful (N=114)	Placebo + ful (N=94)	Capi + ful (N=355)	Placebo + ful (N=353)
Age	Median, years (range)	58 (36–84)	60 (34–90)	[redacted]	[redacted]	59.0 (26–84)	58.0 (26–90)
Sex, n (%)	Female	153 (98.7)	134 (100)	[redacted]	[redacted]	352 (99.2)	349 (98.9)
Race /ethnic group, n (%)*	Black or African American	2 (1.3)	1 (0.7)	[redacted]	[redacted]	4 (1.1)	4 (1.1)
	Asian	48 (31.0)	35 (26.1)	[redacted]	[redacted]	95 (26.8)	94 (26.6)
	White	75 (48.4)	76 (56.7)	[redacted]	[redacted]	201 (56.6)	206 (58.4)
	Other	30 (19.4)	22 (16.4)	[redacted]	[redacted]	55 (15.5)	49 (13.9)
Genetic mutation status, n (%)	Altered	155 (100)	134 (100)	[redacted]	[redacted]	155 (43.7)	134 (38.0)
	PIK3CA only†‡	110 (71.0)	92 (68.7)	[redacted]	[redacted]	110 (31.0)	92 (26.1)
	AKT1 only†‡	18 (11.6)	15 (11.2)	[redacted]	[redacted]	18 (5.1)	15 (4.2)
	PTEN only†‡	21 (13.5)	16 (11.9)	[redacted]	[redacted]	21 (5.9)	16 (4.5)
	PIK3CA and AKT1†	2 (1.3)	2 (1.5)	[redacted]	[redacted]	2 (0.6)	2 (0.6)
	PIK3CA and PTEN†	155 (100)	134 (100)	[redacted]	[redacted]	155 (43.7)	134 (38.0)

Characteristic		PI3K/AKT-altered population (Licensed population)		PI3K/AKT-altered population (Licensed population) with prior CDK4/6i use		Overall CAPItello-291 trial population	
		Capi + ful (N=155)	Placebo + ful (N=134)	Capi + ful (N=114)	Placebo + ful (N=94)	Capi + ful (N=355)	Placebo + ful (N=353)
Disease classification, n (%)	Metastatic	155 (100)	132 (98.5)	[redacted]	[redacted]	349 (98.3)	346 (98.0)
	Locally advanced	0	2 (1.5)	[redacted]	[redacted]	6 (1.7)	6 (1.7)
	Missing	0	0	[redacted]	[redacted]	0	1 (0.3)
WHO/ ECOG performance status, n (%)	(0) normal activity	93 (60.0)	97 (72.4)	[redacted]	[redacted]	224 (63.1)	214 (68.3)
	(1) restricted activity	62 (40.0)	36 (26.9)	[redacted]	[redacted]	131 (36.9)	111 (31.4)
	(2) in bed ≤50% of the time	0 (0)	1 (0.7)	[redacted]	[redacted]	0	1 (0.3)
AJCC, n (%)	Stage IV	50 (32.3)	44 (32.8)	[redacted]	[redacted]	[redacted]	[redacted]
Menopausal status, n (%)	Pre-/perimenopausal	23 (14.8)	29 (21.6)	[redacted]	[redacted]	65 (18.3)	89 (25.2)
	Postmenopausal	130 (83.9)	105 (78.4)	[redacted]	[redacted]	287 (80.8)	260 (73.7)
Receptor status, n (%)	ER+/PR+	116 (74.8)	101 (75.4)	[redacted]	[redacted]	255 (71.8)	246 (69.7)
	ER+/PR−	35 (22.6)	31 (23.1)			94 (26.5)	103 (29.2)
	ER+/PR unknown	4 (2.6)	2 (1.5)	[redacted]	[redacted]	5 (1.4)	4 (1.1)
	ER−§	0 (0)	0 (0)	[redacted]	[redacted]	1 (0.3)	0 (0)
Type of endocrine resistance, n (%)	Primary	60 (38.7)	55 (41.0)	[redacted]	[redacted]	127 (35.8)	135 (38.2)
	Secondary	95 (61.3)	79 (59.0)	[redacted]	[redacted]	228 (64.2)	218 (61.8)
Diabetic status, n (%)	Diabetes	18 (11.6)	8 (6.0)	[redacted]	[redacted]	[redacted]	[redacted]
	No diabetes	137 (88.4)	126 (94.0)	[redacted]	[redacted]	[redacted]	[redacted]
Prior CDK4/6i, n (%)		113 (72.9)	93 (69.4)	114 (100)	94 (100)	247 (69.9)	249 (70.5)

Notes: *Race data for Belgium, France and Hungary were not permitted to be collected per local regulations and were recorded as 'other'.
†Mutually exclusive groups.
‡Patients with co-occurring mutations were excluded from single gene count.
§Due to the very limited number of patients expected under this category, patients with different PR status are reported together.
Abbreviations: AJCC, American Joint Committee on Cancer; Capi, capivasertib; CDK4/6, Cyclin-Dependent Kinase 4/6; ECOG, Eastern Cooperative Oncology Group; ER, oestrogen resistant; Ful, fulvestrant; PR, progesterone receptor; WHO, World Health Organization.
Source: CAPItello-291 CSR;[30] Data on file;[31] Turner et al 2023[18]

A comparison across the baseline characteristics of the full population, and across the subgroup meeting the licensed indication and the subgroup meeting the licensed indication with prior use of CDK4/6i therapy indicates that the populations are broadly similar (with the obvious exception of the proportions with PI3K/AKT alterations and prior use of CDK4/6i therapy).

As we noted in section B.2.5 of our submission, clinical experts consulted by the Company have confirmed that the broad characteristics of patients enrolled in the trial and the treatment effects observed with capivasertib, are likely to be generalisable to patients meeting the licensed indication, and the subgroup of interest in UK clinical practice. This was also discussed in section B.2.12.3 of our submission when discussing the generalisability and relevance of the evidence base.

A 16. In the CAPItello-291 trial, only [redacted] patients were recruited from the UK. Given this, please further comment on the generalisability from the findings of the trial to the population in England and Wales.

As noted in sections B.2.5 and B.2.12.3 of our submission, clinical experts consulted by the Company have confirmed that the broad characteristics of patients enrolled in the trial and the treatment effects observed with capivasertib, are fairly representative of the UK population and therefore generalisable to patients meeting the licensed indication, and the subgroup of interest in UK clinical practice. We are not aware of any reason to suggest that the findings of the CAPItello-291 trial are in any way less generalisable to the population in England and Wales than those of the trials of the relevant comparator therapies that have been accepted by NICE in TA816 and TA421.

Indirect treatment comparison (ITC)

A 17. **Priority question: Based on the assessment of proportional hazard assumption, there was evidence that the assumption of proportional hazards was not valid for progression free survival and overall survival outcomes for studies in the network meta-analysis. However, the company performed the network meta-analysis under proportional hazards. Therefore, the analysis approach used by the company was not appropriate. The EAG considers that given that assumption of proportional hazards was not valid for the progression free survival and overall survival outcomes for studies in the network meta-analysis, time-varying analysis approach would be more appropriate. Please re-conduct the network meta-analyses for progression free survival and overall survival outcomes by using the time-varying analysis approach.**

As part of the feasibility assessment for the network meta-analysis (NMA), the proportional hazards (PH) assumption was assessed for all studies included in the network for each endpoint (progression free survival [PFS] and overall survival [OS]). This was assessed through consideration of the Kaplan Meier (KM) curves, Schoenfeld residual plots and log cumulative hazard plots. The following conditions indicated potential non-PH: a (global) Schoenfeld individual test statistic of $p<0.05$; a non-horizontal line for beta(t) on the Schoenfeld plot; and/or, evidence of non-parallel log cumulative hazard curves between arms.

The summary results of the PH assessment are summarised in Table 8 below (detail is included in the Company Submission Appendix D.1.2.1.1).

For PFS, although there was some evidence of non-PH across several trials (e.g., CAPItello-291, SOFEA and BOLERO-5), based on a review of the Kaplan-Meier plots it is not clear that there were material deviations from PH. Any interpretation of log-log plots is inherently subjective. Earlier time points are more prominent on the plots (more data ink) due to the logarithmic scales. Apparent departure from non-proportionality observed on the log-log plots for PFS is primarily driven by the interval censoring for the PFS endpoint. Progression events can only be observed when scheduled assessments occur. Therefore, 'jumps' in the KM curves occur at the timepoints when assessments are scheduled.

For OS, although there was some evidence of weak-to-moderate non-PH, the trends are less pronounced than for PFS, and thus it is inconclusive as to whether an assumption of proportional hazards is meaningfully violated for this endpoint.

Table 8: Summary of PH assessment across studies (✓ - non-PH conditions met, × PH conditions hold)

	Evidence of non-PH (strong=3, moderate=2, weak=1, none=0)	
Trial	**PFS**	**OS**
BOLERO-2[27]	Weak	Moderate
BOLERO-5[28]	Strong	NA
CAPItello-291[18]	Strong	Weak
CONFIRM[21]	Weak	Weak
EFECT[24]	None	NA
FAKTION[19]	Weak	Weak
FRIEND[22]	Weak	NA
NCT01300351 (Zhang 2016)[23]	Strong	NA
SOFEA[25]	Moderate	Moderate
SOLAR-1[32,33]	Moderate	Weak

Abbreviations: PFS: progression-free survival; PH: proportional hazards; OS: overall survival; NA not applicable

Given there was inconclusive evidence about whether the PH assumption could be considered reasonable for both PFS and OS, the Company considered it was reasonable to conduct an NMA on a hazard ratio scale.

However, the Company recognises that some evidence of non-proportionality was identified and have therefore conducted a time-varying analysis as requested by the EAG. For this analysis, a piecewise approach was adopted. This allowed for a comparison to the Company base case approach, and allowed the results to be incorporated into the model (see Question B6).

The general methodology followed for the piecewise approach was as described in the Company Submission Appendix D.1.2.1 for the original NMA. The NMA was performed using the PI3K/AKT pathway-altered subgroup results of CAPItello-291 and FAKTION, and the PIK3CA mutated subgroup results of SOLAR-1. The NMA used data from the biomarker unselected populations of other comparator studies under the plausible assumption that PI3K/AKT pathway alteration status would not modify the treatment effect of these comparators. For each endpoint, fixed and random effects NMAs were performed using fulvestrant 500mg as the reference treatment in the network. However, for the piecewise approach, cut points were selected based on a visual inspection of the KM curves for all studies included in the network for each endpoint. For OS, 6 months was selected as there was a deviation in some of the curves at this timepoint in selected studies, and it was early enough in the study follow-up for the sample size to be sufficient in most cases. For PFS, 3 months was selected, although as some treatment arms appeared to deviate at 2 months, this alternative was also explored. There were no curves which warranted more than one cut point. The curves evaluated have been included in Appendix III.

The statistical fit of the models was assessed in terms of the posterior mean total residual deviance and the deviance information criterion (DIC). The residual deviance measures the model's ability to accurately predict the data used in the analysis. An accurate fit is denoted by a total mean residual deviance that is approximately equal to the number of data points in the analysis. The DIC provides a comparative measure of model fit that penalizes model complexity. A lower DIC

suggests a more parsimonious model. These measures were used to compare the relative fit of the models. A meaningful difference in model fit was determined by a three point or greater difference in DIC score.

PFS results

The goodness of fit statistics for the NMAs are shown below in Table 9. According to DIC, the preferred model is the fixed effects model followed by the random effects. The difference in DIC between the fixed effect and random effect model with informative prior was not judged meaningful (less than 3 points). The 3-month cut point has a lower DIC than the 2-month cut point, but the difference was not judged to be meaningful.

Table 9: Goodness of fit statistics for the PFS NMA

Model	Number of data points	Total residual deviance	Effect number of parameters	DIC
0-2 months				
Fixed effects	10	10.4	5.0	15.4
Random effects	10	9.1	6.5	15.6
2+ months				
Fixed effects	10	12.5	5.0	17.5
Random effects	10	10.8	7.5	18.3
0-3 months				
Fixed effects	10	9.6	5.0	14.6
Random effects	10	8.5	6.8	15.3
3+ months				
Fixed effects	10	11.0	5.0	16.0
Random effects	10	9.9	7.2	17.1

Abbreviations: DIC: deviance information criterion; NMA: network meta-analysis; PFS: progression-free survival

A forest plot of the results of the fixed and random effects (with informative prior) NMA is shown in Figure 3 for the comparison against fulvestrant 500mg. For completeness, results using capivasertib plus fulvestrant as the reference treatment are provided in Figure 4. The point estimates were similar across models with wider

95% credible intervals for the random versus fixed effects models.

Table 10 provides the HR and 95% credible intervals.

Figure 3 Forest plot - PFS - comparison with Fulvestrant 500mg

Table 10: Summary of PFS HRs for treatments versus fulvestrant

	Timepoint 1 HR (95% CrI)		Timepoint 2 HR (95% CrI)	
	Fixed effects	Random effects	Fixed effects	Random effects
PFS Scenario 1	***0-3 months***		***3+ months***	
Capivasertib + fulvestrant				
Everolimus + exemestane				
Alpelisib + fulvestrant				
Exemestane				
Fulvestrant 250 mg				
PFS Scenario 2	***0-2 months***		***2+ months***	
Capivasertib + fulvestrant				
Everolimus + exemestane				
Alpelisib + fulvestrant				
Exemestane				
Fulvestrant 250 mg				

Abbreviations: HR, hazard ratio; PFS: progression-free survival; CrI: Credible intervals

Figure 4 Forest plot - PFS - comparison with capivasertib plus fulvestrant

Table 11: Summary of PFS HRs for treatments versus capivasertib plus fulvestrant

	Timepoint 1 HR (95% CI)		Timepoint 2 HR (95% CI)	
	Fixed effects	Random effects	Fixed effects	Random effects
PFS Scenario 1	***0-3 months***		***3+ months***	
Fulvestrant 500 mg				
Everolimus + exemestane				
Alpelisib + fulvestrant				
Exemestane				
Fulvestrant 250 mg				
PFS Scenario 2	***0-2 months***		***2+ months***	
Fulvestrant 500 mg				
Everolimus + exemestane				
Alpelisib + fulvestrant				

Exemestane	[redacted]	[redacted]	[redacted]	[redacted]
Fulvestrant 250 mg	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HR, hazard ratio; PFS: progression-free survival

Aligned with the outputs from the originally submitted NMA, the results from this piecewise approach show that capivasertib plus fulvestrant is associated with numerically improved PFS compared to endocrine monotherapy and everolimus plus exemestane across both time periods, regardless of the 2- or 3-month selected cut-off. This result is statistically significant for capivasertib plus fulvestrant versus endocrine monotherapy. When comparing to alpelisib plus fulvestrant, capivasertib plus fulvestrant is associated with numerically improved PFS beyond the 2- or 3-month cut-offs; the HR is only >1.0 for the initial study phase (i.e., first 2- or 3-months).

OS results

The goodness of fit statistics for the NMAs are shown in Table 12 below. According to DIC, the preferred model is the fixed effects model for 0-6 months and the random effects model for 6+ months. The difference in DIC between the fixed effect and random effect model with informative or vague prior was not judged meaningful (less than 3 points).

Table 12: Goodness of fit statistics for the OS NMA

Model	Number of data points	Total residual deviance	Effect number of parameters	DIC
0-6 months				
Fixed effects	6	5.0	5.0	10.0
Random effects	6	5.1	5.1	10.2
6+ months				
Fixed effects	6	7.5	5.0	12.5
Random effects	6	6.8	5.3	12.1

Abbreviations: DIC: deviance information criterion; NMA: network meta-analysis; OS: overall survival

A forest plot of the results of the fixed and random effects (with informative prior) NMA using fulvestrant 500mg as the reference treatment is shown in Figure 5. For completeness, results using capivasertib plus fulvestrant as the reference treatment are provided in Figure 6. As previously, the point estimates were similar across models with the random effects producing wider 95% credible intervals than the fixed effects model.

Figure 5 Forest plot - OS - comparison with Fulvestrant 500mg

Table 13: Summary of OS HRs for treatments versus fulvestrant

	Timepoint 1 HR (95% CI)		Timepoint 2 HR (95% CI)	
	Fixed effects	**Random effects**	**Fixed effects**	**Random effects**
	0-6 months		***6+ months***	
Capivasertib + fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus + exemestane	[redacted]	[redacted]	[redacted]	[redacted]
Alpelisib + fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]
Exemestane	[redacted]	[redacted]	[redacted]	[redacted]
Fulvestrant 250 mg	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HR, hazard ratio; OS: overall survival

Figure 6 Forest plot - OS - comparison with capivasertib plus fulvestrant

Table 14: Summary of OS HRs for treatments versus capivasertib plus fulvestrant

	Timepoint 1 HR (95% CI)		Timepoint 2 HR (95% CI)	
	Fixed effects	Random effects	Fixed effects	Random effects
	0-6 months		*6+ months*	
Fulvestrant 500mg	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus + exemestane	[redacted]	[redacted]	[redacted]	[redacted]
Alpelisib + fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]
Exemestane	[redacted]	[redacted]	[redacted]	[redacted]
Fulvestrant 250 mg	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HR, hazard ratio; OS: overall survival

Similar to the results for PFS, and in line with the originally submitted NMA, the results from this piecewise approach show that capivasertib plus fulvestrant is associated with numerically improved OS across both time points compared to endocrine monotherapy, and everolimus plus exemestane. When comparing to alpelisib plus fulvestrant, capivasertib plus fulvestrant is associated with numerically improved OS beyond the 6-month cut point, with only alpelisib plus fulvestrant showing improved OS during the initial study phase (i.e., 0-6 months).

The impact of using a time-varying approach in the model is explored in the response to question B6.

A 18. **Priority question: Please provide a table that summarizes patient characteristics at baseline for the populations from the included trials in the network meta-analysis. Please also provide baseline data relating to PI3K/AKT pathway alteration, HER2 status, and prior treatment (including CDK) across the trials in the network meta-analysis. It is important to make sure that the assumption of exchangeability for the purpose of the network meta-analysis is acceptable (as highlighted in the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) Technical Support Document). Please further comment on whether these baseline characteristics are prognostic factors and/or treatment effect modifiers, and what the potential implications would be for the cost-effectiveness results.**

The table of baseline characteristics included in Appendix D1.2.1.1 of the company submission detailed all baseline data requested above alongside a full feasibility assessment and details on whether these factors can be considered prognostic, treatment effective modifiers, or both. We have summarised these findings below.

In evidence synthesis, heterogeneity in the patient populations between the included trials can introduce bias into the results. Therefore, it is important to assess the heterogeneity and to identify prognostic factors and treatment effect modifiers. Prognostic factors are covariates (e.g., patient characteristics) that affect (or are prognostic of) outcomes. Treatment effect modifiers are covariates that alter the effect of treatment on outcomes, so that the treatment is effective in different subgroups related to the effect modifier. Treatment effect modifiers are specific to treatments. Prognostic factors are not necessarily treatment effect modifiers, and vice versa.

In an NMA, relative values for different treatments are compared to a selected baseline. Comparative effectiveness is estimated by comparing treatment effects from the contributing trials. *Estimates can therefore only be confounded by variations in treatment effect modifiers, not by variation in prognostic factors.* If there is

heterogeneity in a treatment effect modifier, methods which adjust for this heterogeneity may need to be explored.

Table 15 provides an overview of the studies included in the NMA, and Table 16 provides a summary of key of baseline characteristics.

Table 17 summarises the potential prognostic factors, treatment effect modifiers and the heterogeneity seen among the included studies in the NMA. It also provides a summary of the implications on the findings for the NMA and cost-effectiveness model.

Table 15. Summary of studies included in the base case NMA

Study	PFS	OS	Intervention	Comparator	Sample size	Region	HR status	HER2 status	PI3K/AKT status	Prior treatment
CAPItello-291[18]	✓	✓	Capivasertib + fulvestrant 500	Fulvestrant 500	289	Multi.	HR+	HER2-neg	Altered subgroup	ET +/- CDK
FAKTION[19]	✓	✓	Capivasertib + fulvestrant 500	Fulvestrant 500	59	UK	HR+	HER2-neg	Altered subgroup	ET, no CDK
BOLERO-2[27]	✓	✓	Everolimus + exemestane	Exemestane	724	Multi.	HR+	HER2-neg	NA	ET, no CDK
BOLERO-5[28]	✓	×	Everolimus + exemestane	Exemestane	159	China	HR+	HER2-neg	NA	ET, no CDK
EFECT[24]	✓	×	Fulvestrant 250	Exemestane	693	Multi.	HR+	Mixed/unkn	NA	ET, no CDK
SOFEA[25]	✓	✓	Fulvestrant 250	Exemestane	723	Multi.	HR+	Mixed/unkn	NA	ET, no CDK
CONFIRM[21]	✓	✓	Fulvestrant 500	Fulvestrant 250	736	Multi.	HR+	Mixed/unkn	NA	ET, no CDK
FRIEND[22]	✓	×	Fulvestrant 500	Exemestane	144	China	HR+	HER2-neg	NA	ET, no CDK
NCT01300351 (Zhang 2016)[23]	✓	×	Fulvestrant 500	Fulvestrant 250	221	China	HR+	Mixed/unkn	NA	ET, no CDK
SOLAR-1[32,33]	✓	✓	Alpelisib + fulvestrant 500	Fulvestrant 500	341	Multi.	HR+	HER2-neg	PIK3CA only	ET +/- CDK

Abbreviations: ET, no CDK: Endocrine therapy without prior CDK4/6i therapy; ET +/- CDK: Endocrine therapy with or without prior CDK4/6i therapy use; HER2-neg: HER2-negative; HR+: Hormone receptor positive; Mixed/Unkn: Mixed or unknown HER2 status; Multi: Multinational; NA; not available
Notes: Both PEARL and SOFEA report data for additional non-approved treatment arms not included within the base-case network, SOFEA: Fulvestrant plus anastrozole

Table 16 Summary of baseline data for key sources of heterogeneity in the NMA

Study	Treatment arm	Sample size	Age	ECOG PS=1	Post menopausal %	PI3K/AKT altered	HER2- %	Prior CDK 4/6i use
CAPItello-291 (PI3K/AKT altered population)	Capivasertib + fulvestrant 500	155	58	40%	83.9%	100%	100%	72.9%
	Placebo + fulvestrant 500	134	60	26.9%	78.4%	100%	100%	69.4%
FAKTION[19,34]*	Capivasertib + fulvestrant 500	69	62	36%	100%	45%	100%	0%
	Fulvestrant 500	71	61	24%	100%	39%	100%	0%
BOLERO-2[27]	Everolimus + exemestane	485	62	36%	100%	Unknown	100%	0%
	Exemestane	239	61	35%	100%	Unknown	100%	0%
BOLERO-5[28,29]	Everolimus + exemestane	80	65	61.3%	100%	Unknown	100%	0%
	Exemestane	79	68	68.4%	100%	Unknown	100%	0%
EFECT[24]	Fulvestrant 250	351	63	37.9%	100%	Unknown	Unknown	0%
	Exemestane	342	63	43.6%	100%	Unknown	Unknown	0%
SOFEA[25]	Fulvestrant 250	231	63	Unknown	100%	Unknown	6%	0%
	Exemestane	249	66	Unknown	100%	Unknown	7%	0%
CONFIRM[35]	Fulvestrant 500	362	61	Unknown	100%	Unknown	Unknown	0%
	Fulvestrant 250	374	61	Unknown	100%	Unknown	Unknown	0%
FRIEND[22]	Fulvestrant 500	77	62	37.7	100%	Unknown	100%	Unknown
	Exemestane	67	63	40.3	100%	Unknown	100%	Unknown
NCT01300351 (Zhang 2016)[23]	Fulvestrant 500	111	53.6	Unknown	100%	Unknown	Unknown	Unknown
	Fulvestrant 250	110	53.1	Unknown	100%	Unknown	Unknown	Unknown
SOLAR-1 (PIK3CA mutated cancer)[32,33]	Alpelisib + fulvestrant 500	169	63	33.1	100%	100%	100%	5.3
	Placebo + fulvestrant 500	172	64	33.7	100%	100%	100%	6.4

* No baseline characteristics specifically for the PI3K/AKT pathway altered patients were presented in the FAKTION pivotal publication. The trial included both patients with PIK3CA or PTEN alterations (45% in the capivasertib plus fulvestrant arm, 39% in the placebo plus fulvestrant arm), and patients without PIK3CA or PTEN alterations (55% in the capivasertib plus fulvestrant arm, 61% in the placebo plus fulvestrant arm). The FAKTION phase II trial is an externally-sponsored study by the Velindre NHS Trust. Therefore, the Company does not have access to data beyond the data published in the FAKTION pivotal trial publications by Jones RH in 2020[19] and Howell et al in 2022[34]

Table 17: Summary of prognostic factors / treatment effect modifiers for the NMA

Patient characteristics	Potential prognostic factor	Potential treatment effect modifier (TEM)	Important heterogeneity in studies in NMA	Consequences for NMA and CEM
Prior CDK4/6i	**Yes** In CAPItello-291, the event rates are consistently higher in the prior CDK4/6i population[30] and it was found to be prognostic in RWE for PFS.[36] NICE considered it a prognostic factor in the alpelisib TA.[8]	**No supporting evidence** CAPItello-291 subgroup results: No (see Document B, section B.2.6.1 and B.2.6.2) Other comparators: No data Insufficient patients in SOLAR-1 with prior CDK4/6i to provide any evidence. NICE TA816 treats it as not being a treatment effect modifier.[8]	**Yes** Multiple studies were conducted prior to the uptake of CDK4/6i. Approval of the first CDK4/6i (palbociclib) for treatment of patients with HR+/ HER2- advanced BC was in February 2015.[37] Therefore, any studies in which the primary publication was pre-2016 studies were assumed to have not received prior CDK4/6i. The only study which included patients treated with prior CDK4/6i is CAPItello-291 (SOLAR-1 also included ~5% with prior CDK4/6i).	**NMA** Given that prior CDK4/6i use was identified as a prognostic factor but not a treatment effect modifier, there is no evidence that this heterogeneity would bias the NMA **CEM** Given that prior CDK4/6i use is a prognostic factor and given the expected clinical positioning of capivasertib plus fulvestrant for use after first line treatment with a CDK/46i, the survival data used in the CEM is based on the subgroup of patients from the CAPItello-291 trial with PI3K/AKT pathway alterations that have received a CDK4/6i, which was the majority of patients. The relative effects of other treatments as calculated in the NMA are applied in the model and are expected to hold across populations.
HER2 status	**Yes**[38] HER2 status is an established prognostic factor in breast cancer.[39]	**Unclear** The majority of the more recent studies (N=6) in the network had eligibility criteria which specified that patients had to be HER2-. Three studies did not report HER2 status. One study included mixed HER2 stats (SoFEA), but only 6-7% were HER2+.[25]	**Unclear** For the treatments included in this network, it is unclear whether HER2 status is a TEM. If it was identified as a TEM, HER2 status is not reported in 3 studies in the network, so the direction of bias would still be uncertain.	**NMA** No evidence that it would bias an NMA. Excluding HER2+ patients in SoFEA unlikely to change results due to the small proportion that are not HER2-. **CEM** All patients in CAPItello-291 are HER2-. The relative effects of other treatments as calculated in the NMA are applied in the model and are expected to hold across populations.

Patient characteristics	Potential prognostic factor	Potential treatment effect modifier (TEM)	Important heterogeneity in studies in NMA	Consequences for NMA and CEM
PI3K/AKT pathway alteration (*PIK3CA/AKT1/PTEN*)	**Yes** In CAPItello-291 trial median PFS, and OS at 18 months, were similar in ITT and PI3K/AKT pathway-altered populations.[18] However, literature suggests that patients with PIK3CA/AKT1/PTEN alterations experience worse prognosis and survival outcomes compared to patients without these alterations.	**Yes** Evidence from CAPItello-291 suggests it may be a treatment effect modifier for capivasertib + fulvestrant vs. fulvestrant There is no evidence to suggest that PIK3CA alone vs. PI3K/AKT would result in a different relative treatment effect.	**Unknown** Multiple trials did not report PI3K/AKT pathway alteration status. However, these studies were in treatments that are not PI3K/AKT-targeted agents, and so may have no treatment modifying effect	**NMA** The degree to which this potentially causes bias is unknown. The NMA includes results from the CAPItello-291 and FAKTION PI3K/AKT-altered populations only, and results from the SOLAR-1 PIK3CAm-population only. Whilst all other trials in the network did not report PI3K/AKT pathway alteration status, there is no evidence that PI3K/AKT pathway alteration is a treatment effect modifier for the other treatments in the network. **CEM** Given that PI3K/AKT pathway alteration status is a prognostic factor, the survival data used in the CEM is based on a subgroup of patients from the CAPItello-291 trial with AKT mutation. The relative effects of other treatments as calculated in the NMA are applied in the model and are expected to hold across populations.
Line of treatment	Yes[40,41]	Inconclusive Some numerical differences but no conclusive evidence No studies identified it formally as a treatment effect modifier, inconclusive based on HRs.[20,42,43]	Yes	**NMA** No evidence that it would bias an NMA. While there was important heterogeneity, there is no conclusive evidence of it being treatment effect modifier, and therefore no evidence of risk of bias. **CEM** Given the expected positioning of capivasertib plus fulvestrant, the survival data used in the CEM is

Patient characteristics	Potential prognostic factor	Potential treatment effect modifier (TEM)	Important heterogeneity in studies in NMA	Consequences for NMA and CEM
				based on a subgroup of patients from the CAPItello-291 trial that had received prior CDK4/6i, and would therefore be considered second-line. The relative effects of other treatments as calculated in the NMA are applied in the model and are expected to hold across populations.
Region	Depending on region	Inconclusive Numeric differences mentioned in a few studies.[44,45] Not mentioned in alpelisib NICE TA as concern.[8] In CAPItello-291 the PFS HR was the same for Asia and Australia, Canada, Israel, United States, or Western Europe.[18]	Yes Most studies are multinational except for two Chinese trials[23,46] and FAKTION trial in UK.	No conclusive evidence of significant bias for the NMA or the CEM.
Age	Yes[41]	Evidence of treatment effect modification. Everolimus + exemestane vs. exemestane,[47], fulvestrant 500mg vs. 250mg,[23] fulvestrant vs. exemestane,[24] fulvestrant + anastrozole vs. fulvestrant.[25]	No	No evidence that it would bias the NMA or CEM.
Post-menopausal status	Different treatments can be offered based on menopausal status[5,6]	Evidence of treatment effect modification. CAPItello-291 showed numerical variation in HRs depending on menopausal status.[18]	No Most studies had included post-menopausal patients only	No evidence that it would bias the NMA or CEM.
Sites of metastases (presence of liver	Yes[40,41]	No conclusive evidence.	Yes	No evidence that it would bias the NMA or CEM.

Patient characteristics	Potential prognostic factor	Potential treatment effect modifier (TEM)	Important heterogeneity in studies in NMA	Consequences for NMA and CEM
metastases vs absence)		Numerical differences mentioned in some studies[20,48] but no conclusive evidence.		

Abbreviations: AKT: protein kinase B; CDK4/6: cyclin-dependent kinase 4 and 6; HER2: human epidermal growth factor receptor 2; NMA: network meta-analysis; P13K: phosphoinositide 3-kinase; PTEN: phosphatase and tensin homolog.
Notes: * Includes: tumour grade, poor PS, time to recurrence, progression to advanced breast cancer, disease-free interval, PR- status, higher circulating tumour cell count, Ki67 level, number of metastases (multiple vs single), prior hormone therapy, 1L therapy in early breast cancer, race (black vs. white)

Adverse events

A 19. Please provide a table that summarizes overall adverse events in the PI3K/AKT pathway-altered population from the FAKTION trial.

The FAKTION phase II trial is an externally-sponsored study by the Velindre NHS Trust. Therefore, the Company does not have access to data beyond the data published in the FAKTION pivotal trial publications by Jones RH in 2020[19] and Howell et al in 2022.[34] The safety data provided in these publications was based on the FAKTION ITT population; data specifically in patients with PI3K/AKT pathway alterations is not publicly available and therefore cannot be provided by the Company in response to this clarification question. Similarly to CAPItello-291, the Company does not expect any differences in safety profile by biomarker status, and therefore the FAKTION ITT safety data can be considered applicable and relevant to the PI3K/AKT pathway altered population within the trial.

The pattern of common adverse events observed with capivasertib plus fulvestrant in FAKTION (Table 18) is largely consistent with common adverse events observed in the PI3K/AKT pathway altered population of CAPItello-291 trial (Table 11 of Document B), with diarrhoea, fatigue and nausea being the most prevalent in the capivasertib plus fulvestrant arm in the FAKTION primary analysis.

It is notable that FAKTION is a small UK-based phase II trial which recruited only 140 patients, which did not include patients who have had prior treatment with a CDK4/6i, with no data available specifically in the PI3K/AKT pathway alterations population. More robust data on the safety and effectiveness of capivasertib plus fulvestrant relevant to the decision problem is available from the pivotal multi-national phase III CAPItello-291.

Table 18 Top four most common adverse events of any grade observed in the capivasertib plus fulvestrant arm in FAKTION (ITT population) (Jones 2020)

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Total
Diarrhoea	28 (41%)	18 (26%)	10 (14%)	0	56 (81%)
Fatigue	24 (35%)	15 (22%)	1 (1%)	0	40 (58%)
Nausea	30 (43%)	8 (12%)	0	0	38 (55%)

Note: This table summarises clinical AEs observed in FAKTION, and excludes abnormal lab values reported as AEs, to account for the differences in methodologies for AE reporting between FAKTION and CAPItello-291. In FAKTION, sites were prompted to review results for out of range laboratory test values and to report an adverse event by CTCAE grade if and when CTCAE criteria were met. Some adverse events identified from abnormal blood or biochemistry laboratory testing results might not have had clinical significance. Blood pressure values

were also covered by these reporting requirements. Both clinical and abnormal lab values are summarised in the appendix of Jones 2020. By contrast, the CAPItello-291 CSP Section 8.3.7 states that "Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and ECG abnormalities should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IMP or if they are considered to be clinically relevant as judged by the investigator".

An updated analysis of toxicity and safety data was conducted at the updated analysis (Howell 2022).[34] There was relatively little change in the frequency of adverse events from the primary analysis. This data further reiterates that the AE profile of capivasertib plus fulvestrant in FAKTION is largely consistent with common AE events observed in CAPItello-291, supplementing our understanding of the safety of the regimen based on the findings of the robust pivotal Phase III CAPItello-291.

A 20. Please provide data of serious adverse events and treatment discontinuation due to adverse events in the PI3K/AKT pathway-altered population from the FAKTION trial.

The FAKTION phase II trial is an externally-sponsored study by the Velindre NHS Trust. Therefore, the Company does not have access to data beyond the data published in the FAKTION pivotal trial publications by Jones RH in 2020[19] and Howell et al in 2022.[34] The safety data provided was in the FAKTION ITT population, data specifically in the patients with PI3K/AKT pathway alterations is not publicly available and therefore cannot be provided by the Company in response to this clarification question. Similarly to CAPItello-291, the Company does not expect any differences in safety profile by biomarker status, and therefore the FAKTION ITT safety data can be considered applicable and relevant to the PI3K/AKT pathway altered population within the trial.

Serious adverse reactions (reported only in the capivasertib plus fulvestrant group) were acute kidney injury (two), diarrhoea (three), hyperglycaemia (one), loss of consciousness (one), rash (two), sepsis (one), and vomiting. Serious AEs were rare in both treatment arms (Table 19). One additional serious adverse event (pneumonia) in the capivasertib plus fulvestrant group had occurred subsequent to the primary analysis (Howell 2022).[34] Eight (12%) participants discontinued capivasertib because of adverse events.

Table 19 Serious AEs observed in FAKTION (ITT population)

Serious adverse event	Capivasertib plus fulvestrant N (%)	Placebo plus fulvestrant N (%)
Abdominal pain	1 (1%)	1 (1%)
Anaemia	0	1 (1%)
Back pain	0	2 (3%)
Blocked nephrostomy	1 (1%)	0
Bone pain	1 (1%)	0
Dyspnoea	0	3 (4%)
Fever	0	1 (1%)
Gastroenteritis	0	1 (1%)
Haemorrhage	1 (1%)	0
Hypercalcaemia	0	1 (1%)
Infection	0	1 (1%)
Lower respiratory tract infection	2 (3%)	1 (1%)
Muscle weakness lower limb	1 (1%)	0
Non-cardiac chest pain	1 (1%)	1 (1%)
Pain	1 (1%)	2 (3%)
Pain in extremity	0	1 (1%)
Perineal abscess	1 (1%)	0
Pleural effusion	1 (1%)	0
Radicular pain	0	1 (1%)
Skin infection	1 (1%)	0
Urinary tract infection	1 (1%)	0
Vomiting	0	1 (1%)

Source: Jones et al 2020.[19]

Section B: Clarification on cost-effectiveness data

One minor model error was identified in the process of responding to these questions, this is detailed in Table 20, and has been updated in the model.

Table 20

Sheet and Cell	Previous formula	New formula
Company Submission model: Model!CZ17:CZ375	=IF(E17>=$CY$13,0,$CZ$12*BW16)	=IF(E17>=$CY$13,0,$CZ$12*BW17)

Furthermore, in Question B12 a), the EAG note an inconsistency with the duration of mucosal inflammation (adverse event). This has also now been corrected in the model.

All scenario ICERs in this section are provided with these changes made in the model.

A summary of all changes made in the CEM is provided in Appendix V List of model changes.

Literature reviews

B 1. In CS section B.3.1, eight HTAs of alpelisib plus fulvestrant and everolimus plus exemestane in HR+/HER2- advanced breast cancer were identified, however only the two NICE appraisals were summarised. Further, it is stated that NICE appraisals of therapies outside of the comparator therapies for HR+/HER2- advanced breast cancer were identified and informed the consideration of other model inputs where relevant.

a. Please provide a summary of all identified studies for the relevant comparators.

b. Please provide an overview of the additionally utilised NICE appraisals, highlighting which model inputs were informed by each appraisal.

The published cost effectiveness analyses of the relevant comparators (alpelisib plus fulvestrant and everolimus plus exemestane) identified in the SLR of economic evaluations are summarised in Table 21.

Table 21. Cost effectiveness analyses of relevant comparators identified in SLR

These were taken from Table 2 of the SLR report we referenced in Appendix G to our submission and included in the reference pack as: Astrazeneca_Capivasertib Economic SLR Report 2024 update_V1 (06 June 2024)_CONFIDENTIAL.[49]

We reported in B.3.1 that eight HTAs of the relevant comparators had been identified. To clarify, there were six HTA reports identified relating to eight cost effectiveness comparisons for the relevant comparators (highlighted in yellow in the table below). Of these, the NICE appraisals of alpelisib plus fulvestrant (TA816) and everolimus plus exemestane (TA421) were considered to be the most relevant to inform the NICE appraisal of capivasertib plus fulvestrant and so only these were summarised in section B.3.1 of our submission.

Table 21. Cost effectiveness analyses of relevant comparators identified in SLR

Citation	Model summary	BC indication	Key clinical data source	Comparison (tx1 versus tx2)	QALYs (tx1 vs tx2)	QALYs (delta)	Country, currency	Costs (tx1 vs tx2)	Costs (delta)	ICER, for tx1 versus tx2*
CADTH et al., 2013, https://www.cadth.ca/afinitor-advanced-breast-details	PartSA (‡)	Advanced BC	BOLERO-2	Everolimus + exemestane vs exemestane (2L)	–	0.27	Canada; Canadian dollars	–	43,489	162,049
CADTH et al., 2021, https://www.cadth.ca/alpelisib	Semi Markov cohort model (‡)	HR+ HER2− PIK3CA-mutant mBC	BYLieve	Alpelisib + fulvestrant vs everolimus + exemestane (2L)	1.58 vs 1.42	0.16	Canada; Canadian dollars	129,828 vs 79,119	50,710	319,592
Diaby et al., 2014, 10.1007/s10549-014-3042-3	Markov cohort model (progression-free w/o AE, progression-free with AE, progression)	HR+	BOLERO-2	Everolimus plus exemestane vs exemestane (2L)	21.24 vs 9.36 QAPFW	–	US; US dollars	63,584 vs 3010	60,574	5105.74 (per quality-adjusted progression-free week)
INESSS et al., 2014, https://www.inesss.qc.ca/fileadmin/doc/INESSS/Inscription_medicaments/Avis_au_ministre/Fevrier_2014/Afinitor_2014_02_CAV.pdf	PartSA (‡)	HR+/HER2− ABC/mBC	BOLERO-2	Everolimus + exemestane vs exemestane (≥2L)	–	–	Canada; Canadian dollars	–	–	158,677
NICE et al., 2016, https://www.nice.org.uk/guidance/ta421	Markov cohort model (‡)	HER2− recurrent mBC	BOLERO-2	Everolimus + exemestane vs exemestane (2L)	–	0.155	UK; Pound sterling	–	16,127	104,100
NICE et al., 2016, https://www.nice.org.uk/guidance/ta421	Markov cohort model (‡)	HER2− recurrent mBC	BOLERO-2	Everolimus + exemestane vs exemestane (2L)	–	0.269	UK; Pound sterling	–	18,278	67,909
NICE et al., 2022, https://www.nice.org.uk/guidance/ta816	PartSA (‡)	HR+ HER2− PIK3CA-mutant mBC	BYLieve, SOLAR-1, BOLERO-2, CONFIRM	Alpelisib + fulvestrant vs everolimus + exemestane (2L)	–	–	UK; Pound sterling	–	–	78,538
SMC et al., 2022, https://www.scottishmedicines.org.uk/medicines-advice/alpelisib-piqray-full-smc2481/	PartSA (‡)	HR+ HER2− PIK3CA-mutant LABC/mBC	BYLieve, SOLAR-1	Alpelisib + fulvestrant vs everolimus + exemestane (2L)	–	–	UK; Pound sterling	–	–	70,027
SMC et al., 2022, https://www.scottishmedicines.org.uk/medicines-	PartSA (‡)	HR+ HER2− PIK3CA-mutant LABC/mBC	BYLieve, SOLAR-1	Alpelisib + fulvestrant vs fulvestrant (2L)	–	–	UK; Pound sterling	–	–	200,839

Citation	Model summary	BC indication	Key clinical data source	Comparison (tx1 versus tx2)	QALYs (tx1 vs tx2)	QALYs (delta)	Country, currency	Costs (tx1 vs tx2)	Costs (delta)	ICER, for tx1 versus tx2*
advice/alpelisib-piqray-full-smc2481/										
Xie et al., 2015, 10.1016/j.clbc.2015.04.001	Markov cohort model (‡)	HR+/HER2− ABC	BOLERO-2	Everolimus + exemestane vs exemestane (2L)	1.99 vs 1.60	0.39	US; US dollars	258,648 vs 203,424	55,224	139,740
Xie et al., 2015, 10.1016/j.clbc.2015.04.001	Markov cohort model (‡)	HR+/HER2− ABC	BOLERO-2	Everolimus + exemestane vs fulvestrant (2L)	1.99 vs 1.82	0.17	US; US dollars	258,648 vs 232,457	26,191	157,749
Xie et al., 2015, 10.1016/j.clbc.2015.04.001	Markov cohort model (‡)	HR+/HER2− ABC	BOLERO-2	Everolimus + exemestane vs tamoxifen (2L)	1.99 vs 1.69	0.3	US; US dollars	258,648 vs 224,018	34,630	115,624
Cost-effectiveness studies identified in the SLR update (April–November 2023)										
Soliman et al., 2023, 10.1016/j.jval.2023.03.468	PartSA (‡)	PIK3CA-mutated HR+/HER2− ABC who progressed after CDK4/6i	SOLAR-1 trial	Alpelisib + fulvestrant vs palbociclib + fulvestrant	–	–	$ (country not specified)	–	–	$45,490 per QALY gained
Soliman et al., 2023, 10.1016/j.jval.2023.03.468	PartSA (‡)	PIK3CA-mutated HR+/HER2− ABC who progressed after CDK4/6i	SOLAR-1 trial	Abemaciclib + fulvestrant vs alpelisib + fulvestrant	–	–	$ (country not specified)	–	–	$11,876 per QALY
Soliman et al., 2023, 10.1016/j.jval.2023.03.468	PartSA (‡)	PIK3CA-mutated HR+/HER2− ABC who progressed after CDK4/6i	SOLAR-1 trial	Alpelisib + fulvestrant vs everolimus + exemestane	–	–	$ (country not specified)	–	–	$147,657 per QALY gained
Soliman et al., 2023, 10.1016/j.jval.2023.03.352	PartSA (‡)	PIK3CA-mutated HR+/HER2− ABC	SOLAR-1 trial	Alpelisib + fulvestrant vs palbociclib + fulvestrant	–	–	$ (country not specified)	–	–	Dominant for alpelisib + fulvestrant
Soliman et al., 2023, 10.1016/j.jval.2023.03.352	PartSA (‡)	PIK3CA-mutated HR+/HER2− ABC	SOLAR-1 trial	Alpelisib + fulvestrant vs everolimus + exemestane	–	–	$ (country not specified)	–	–	$117,177 per QALY gained
Wu et al., 2023, 10.1007/s40261-023-01325-z	Markov model (PFS, PD, death)	PIK3CA-mutated HR+/HER2− ABC	SOLAR-1 trial	Alpelisib + fulvestrant vs placebo + fulvestrant	1.59 vs 1.31	0.28	USD	194,984.41 vs 100,638.54	943,45.87	268338.80 per LY

Other technology appraisals that informed the economic model are listed in Table 22.

Table 22. Other NICE technology appraisals informing the economic model

NICE TA	Element of model informed	Reference in Company submission
TA725 - Abemaciclib with fulvestrant	Disutility values for adverse events	Section B.3.4.5; Table 25 Section B.3.4.6; Table 26
TA687 - Ribociclib with fulvestrant	Model structure	Section B.3.2.2
TA836 Palbociclib with fulvestrant	End of life	Section B.3.5.6.1

Model structure

B 2. The company developed a de novo three-state partitioned survival model to assess the cost effectiveness of capivasertib plus fulvestrant versus the relevant comparators (alpelisib plus fulvestrant and everolimus plus exemestane).

a) Please justify the use of a partitioned survival model given the issues highlighted in NICE DSU TSD 19, particularly regarding the extrapolation of progression-free survival and overall survival (OS) while assuming structural independence between these endpoints.

b) Please use state transition modelling to assist in verifying the plausibility of the PSM extrapolations and to address uncertainties in the extrapolation period (NICE DSU TSD 19, recommendation 11).

The partitioned survival modelling approach is a well-established modelling approach for advanced and metastatic cancer therapies that has been used and accepted by NICE in many previous technology appraisals. Indeed, of the 30 economic models of cancer therapies in NICE technology appraisals reviewed in NICE DSU TSD 19, 73% were partitioned survival models.[50] The company submission for the comparator most likely to be displaced by capivasertib plus fulvestrant (alpelisib plus fulvestrant in TA816) used a partitioned survival modelling approach with 3 health states (progression-free, progressed, and dead), which the committee considered: "*…is a standard approach to estimate the cost effectiveness of cancer drugs and is suitable for decision making*."[8] On this basis, and in line with the many other

appraisals of oncology therapies, we adopted this standard partitioned survival modelling approach in our submission.

Although NICE DSU TSD 19 notes potential limitations of the partitioned survival modelling approach, it also notes merits of this approach. These include the use of time to event data for routinely reported clinical endpoints (i.e., PFS and OS) that can be derived from either individual patient data or from summary data. In contrast, the state transition modelling approach requires time to event data for individual transitions (including to/from progressed states) which are often not available, particularly the external comparator data required to inform indirect comparisons versus the relevant comparators. Given the extent of data available to us for the relevant comparators, our partitioned survival modelling approach is appropriate.

We note that recommendation 11 of NICE DSU TSD 19 relates to the use of state transition modelling alongside partitioned survival modelling to verify the plausibility of survival extrapolations. The survival extrapolations in our model are based on data of reasonable maturity from the CAPItello-291 trial and the comparators' trials, and the plausibility of the extrapolations were specifically verified with UK clinical experts.

Intervention and comparators

B 3. Priority question: The company's decision problem excluded retreatment with CDK4/6 inhibitors and (mono)therapy with exemestane, fulvestrant and tamoxifen as relevant comparators.

a. **Please, in addition to your response on question A2 7, also further justify excluding (mono)treatment with exemestane, fulvestrant and tamoxifen.**

b. **Please provide an updated economic model that includes all comparators listed in the final scope and provide all model analyses, including all sensitivity and scenario analyses.**

As detailed in section B.3.1.2 and B.1.3.3 of our submission, and in response to question A 7. and A 8. , only alpelisib plus fulvestrant and everolimus plus exemestane are relevant comparators to address the decision problem in this

appraisal of capivasertib plus fulvestrant. This has been validated by UK clinical experts, and aligns with previous NICE technology appraisal committee views on relevant comparator therapy post CDK4/6 inhibitor therapy in TA816.8

Retreatment with CDK4/6 inhibitor therapy and use of endocrine monotherapy are not routine alternatives in patients eligible for these combination therapies and are not relevant to the decision problem. These therapies are therefore appropriately excluded from the economic model.

B 4. The comparison to alpelisib plus fulvestrant is made in the PI3K/AKT pathway altered population, although alpelisib plus fulvestrant is only recommended in the PIK3CA mutated population. It is assumed that the result holds across these populations. Please provide further justification that this assumption holds.

As capivasertib is an AKT inhibitor, and the PIK3CA and PTEN nodes are upstream from AKT in the PI3K/AKT signalling pathway, there is no biological or clinical reason to assume that results with capivasertib plus fulvestrant would differ by specific alteration within the PI3K/AKT pathway altered cohort overall. Genomic alterations in either of the three nodes of the PI3K/AKT pathway relevant to capivasertib (PIK3CA, PTEN or AKT1) are associated with pathway hyperactivation and endocrine resistance.[18]

As shown in section B.2.7 of the Company submission and in response to question A13, there is a consistent PFS benefit with capivasertib plus fulvestrant across PIK3CA, PTEN and AKT1 alterations, despite the much lower sample sizes of the AKT1 and PTEN altered populations. OS results for patients with PIK3CA alterations from CAPItello-291 are also consistent with the results for the PI3K/AKT pathway-altered population (median not reported and RMST consistent, see response to A13). OS analyses for patients with PTEN or AKT1 alterations cannot be generated as these subgroups of patients are very small in CAPItello-291. However, there is no evidence currently available to suggest OS outcomes for patients with PTEN or AKT1 alterations would differ from patients with PIK3CA alterations due to the unique mechanism of action of capivasertib and it is expected OS for patients with PIK3CA alterations would not differ to that in patients with PTEN or AKT1 alterations.

Evidence from external studies on whether different mutations in the PI3K/AKT altered pathway lead to differential effectiveness of capivasertib plus fulvestrant have not been identified. Overall, the comparison of the capivasertib plus fulvestrant against alpelisib plus fulvestrant in the PI3K/AKT pathway altered population is reasonable.

Treatment effectiveness

B 5. Priority question: The company used conventional methods of parametric survival modelling as outlined in NICE DSU TSD14 for the extrapolation of survival estimates beyond the observed Kaplan-Meier curves of the placebo plus fulvestrant arm from CAPItello-291. Please provide, for PFS and OS separately:

a. Tables with numbers of patients at risk, in 3 months intervals.

The numbers of patients at risk in the placebo plus fulvestrant arm of the post-CDK4/6i PI3K/AKT pathway-altered population from CAPItello-291 trial at 3 month intervals have been provided in Table 23 (OS) and Table 24 (PFS).

Table 23 Number of patients at risk (overall survival) (post-CDK4/6i, PI3K/AKT pathway-altered population, DCO1)

Time (months)	Placebo plus fulvestrant	Capivasertib plus fulvestrant
0	[redacted]	[redacted]
3	[redacted]	[redacted]
6	[redacted]	[redacted]
9	[redacted]	[redacted]
12	[redacted]	[redacted]
15	[redacted]	[redacted]
18	[redacted]	[redacted]
21	[redacted]	[redacted]
24	[redacted]	[redacted]

Table 24 Number of patients at risk (progression-free survival) (post-CDK4/6i, PI3K/AKT pathway-altered population, DCO1)

Time (months)	Placebo plus fulvestrant	Capivasertib plus fulvestrant
0	[redacted]	[redacted]
3	[redacted]	[redacted]
6	[redacted]	[redacted]
9	[redacted]	[redacted]
12	[redacted]	[redacted]
15	[redacted]	[redacted]
18	[redacted]	[redacted]

Time (months)	Placebo plus fulvestrant	Capivasertib plus fulvestrant
21	[redacted]	[redacted]

b.To examine the proportional hazard assumption, provide the plotted scaled Schoenfeld residuals versus time and log cumulative hazard versus log time (as discussed in Appendix D).

Schoenfeld residual plots and log cumulative hazard plots can be used to assess the proportional hazards (PH) assumption, with the following conditions indicating potential non-PH: a (global) Schoenfeld individual test statistic of $p<0.05$; a non-horizontal line for beta(t) on the Schoenfeld plot; and/or, evidence of non-parallel log cumulative hazard curves between arms. A visual assessment of the Kaplan Meier (KM) curves should also be performed.

Overall survival

The Schoenfeld residuals and global test statistic are provided in Figure 7. The Schoenfeld test statistic is >0.05. From graphical inspection of the residuals, there may be some pattern with time. The log cumulative hazard plot is provided in Figure 8. These curves appear to be approximately parallel with time. Overall, the PH assumption was considered to be supported.

The KM curves (see Company submission section B.2.6.4, Figure 5) also indicate PH appears a reasonable assumption for OS.

The Company therefore concluded that the PH assumption is reasonable for OS.

Figure 7 Schoenfeld residuals for overall survival (post-CDK4/6i, PI3K/AKT pathway-altered population, DCO1)

Figure 8 Log cumulative hazard plot for overall survival (post-CDK4/6i, PI3K/AKT pathway-altered population, DCO1)

Progression-free survival

The Schoenfeld residuals and global test statistic are provided in Figure 9. The Schoenfeld test statistic is <0.05, and from the graphical inspection, there may be some pattern with time.

The log cumulative hazard plot is provided in Figure 10. There is some evidence of non-parallel lines.

The KM curves (see Company submission section B.2.6.2, Figure 3) indicate no material deviation from PH. Where there is a possibility that there are non-PH for PFS, this is notable at timepoints where events tend to occur around the timing of scheduled scans. Observed departures from PH may therefore be plausibly driven by interval censoring for the PFS endpoint. The company therefore concluded that there is an absence of evidence of material deviations from the proportional hazards assumption for PFS.

Figure 9 Schoenfeld residuals for progression-free survival (post-CDK4/6i, PI3K/AKT pathway-altered population, DCO1)

Figure 10 Log cumulative hazard plot for progression-free survival (post-CDK4/6i, PI3K/AKT pathway-altered population, DCO1)

c. To examine the heuristics of the hazard function over time, plot the smoothed hazards over time.

Overall survival

A plot of the smoothed hazards over time for OS have been provided in

Figure 11. For capivasertib plus fulvestrant, these show increasing hazards over time. For placebo plus fulvestrant these show increasing hazards, followed by a sudden drop around 18 months. However, the numbers at risk are quite low at and after this timepoint (N= [redacted] at 18 months, N= [redacted] at 20 months), and any inference about these hazards should be taken with caution as are likely not informative about the trajectory of the risk of death. The numbers at risk are provided in Table 23.

Figure 11 Plot of smoothed hazards for overall survival (post-CDK4/6i, PI3K/AKT pathway-altered population, DCO1)

Progression free survival:

A plot of the smoothed hazards over time for PFS have been provided in Figure 12. For capivasertib plus fulvestrant, these show plateuing and decreasing hazards over time. For placebo plus fulvestrant these show sharply increasing hazards, followed by decreasing hazards and a sudden increase around 9 months. However, the numbers at risk are quite low at and after this timepoint (N= [redacted] at 10 months and N= [redacted] at 12 months), and any inference about these hazards should be taken with caution as are likely not informative about the trajectory of the risk of progression. The numbers at risk are provided in Table 24.

Figure 12 Plot of smoothed hazards for progression-free survival (post-CDK4/6i, PI3K/AKT pathway-altered population, DCO1)

d.To examine diagnostics of parametric survival models (using the observed data):

1.Plot the cumulative hazard versus time

The plot of cumulative hazard versus time for OS is provided in Figure 13, which suggests that hazards in both arms are relatively constant with time.

The plot of cumulative hazard versus time for PFS is provided in Figure 14. For the placebo plus fulvestrant arm the cumulative hazard initially increases quite sharply until 2 months. After 2 months the rate of increase decreases. The increase in the rate at the end of the trial period is likely influenced by low numbers at risk. For the capivasertib plus fulvestrant arm, the hazard appears relatively constant with time.

Figure 13 Plot of cumulative hazards for overall survival (post-CDK4/6i, PI3K/AKT pathway-altered population, DCO1)

Figure 14 Plot of cumulative hazards for progression-free survival (post-CDK4/6i, PI3K/AKT pathway-altered population, DCO1)

2. Plot the log smoothed hazard versus time

The plot of the log smoothed hazard versus time for OS is provided in Figure 15. The observations are the same with those made in the response to B5 part c). That is, for capivasertib plus fulvestrant, the plot shows increasing hazards over time, and for placebo plus fulvestrant the plot shows increasing hazards, followed by a sudden drop around 18 months. However, the numbers at risk are quite low at and after this timepoint (N= [redacted] at 18 months, N= [redacted] at 20 months).

Figure 15 Plot of log smoothed hazards for overall survival (post-CDK4/6i, PI3K/AKT pathway-altered population, DCO1)

The plot of the log smoothed hazard versus time for OS is provided in Figure 16. The observations are similar to those made in the response to B5 part c). That is, for capivasertib plus fulvestrant, the plot shows plateuing and decreasing hazards over time. For placebo plus fulvestrant these show sharply increasing hazards, followed by decreasing hazards and a sudden increase. However, the numbers at risk are quite low at and after this timepoint (N= [redacted] at 10 months and N= [redacted] at 12 months).

Figure 16 Plot of log smoothed hazards for progression-free survival (post-CDK4/6i, PI3K/AKT pathway-altered population, DCO1)

3. Plot the standard normal quartiles versus log time

The EAG confirmed in the clarification questions meeting that this was a typo and they were intended to request a quintiles-quintiles plot (QQ plot).

The QQ plot for OS is provided in Figure 17 and for PFS is provided in Figure 18. Both plots indicate that the data may not be normally distributed.

Figure 17 QQ plot for overall survival (post-CDK4/6i, PI3K/AKT pathway-altered population, DCO1)

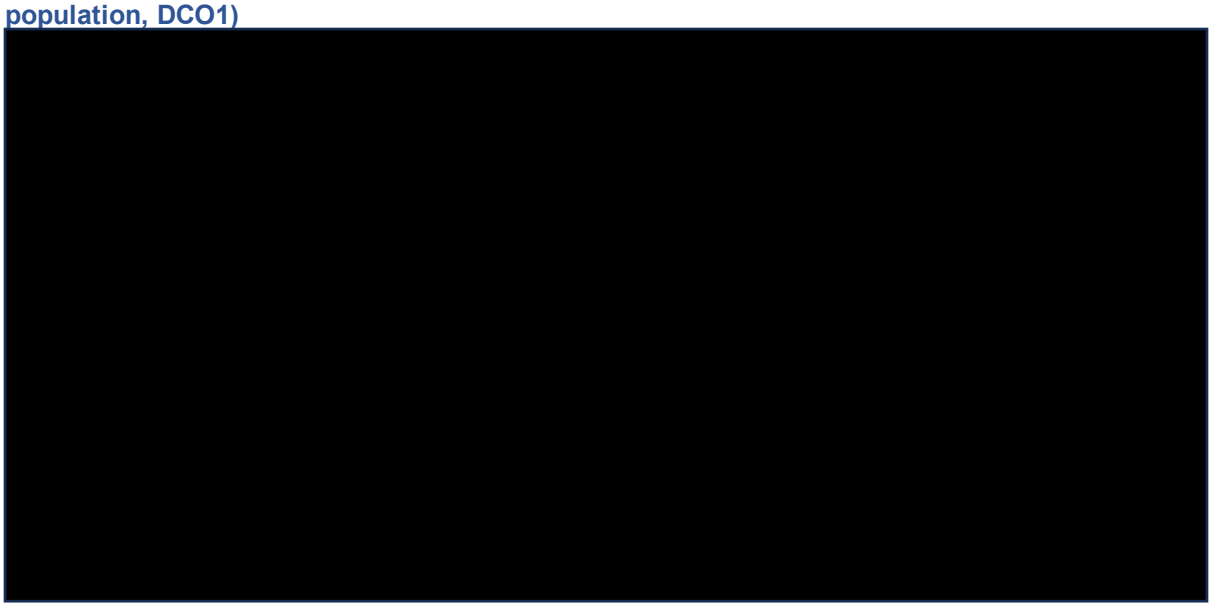
Figure 18 Figure 13 QQ plot for progression-free survival (post-CDK4/6i, PI3K/AKT pathway-altered population, DCO1)

4. Plot the log survival odds versus log time

The log odds plot for OS is provided in Figure 19 and for PFS is provided in Figure 20. In the log odds plot, parallel lines indicate proportional odds. Lines are approximately parallel for the majority of the trial period for OS. For PFS, there are some deviations at the beginning of the trial period, but lines are approximately parallel at later timepoints.

Figure 19 Log odds plot for overall survival (post-CDK4/6i, PI3K/AKT pathway-altered population, DCO1)

Figure 20 Log odds plot for progression-free survival (post-CDK4/6i, PI3K/AKT pathway-altered population, DCO1)



e.The standard parametric survival curves for the extrapolation of PFS do not seem to fit very well to the observed data. Please describe whether the use of spline-based models was explored. Please provide these analyses including 1 and 2 knot models (with default knot location) using the hazard, odds as wells as normal scales. Please elaborate on the appropriateness of these spline

models and provide an updated economic model as well as scenario analyses enabling the use of these spline models.

As presented in Question B5c, the plot of the smoothed hazards for PFS for placebo plus fulvestrant shows sharply increasing hazards, following by decreasing hazards and a sudden increase around 9 months, although the numbers at risk are quite low at and after this timepoint (N= [redacted] at 10 months and N= [redacted] at 12 months). As such, parametric distributions that can appropriately capture this trend in the underlying hazards for PFS were considered when developing the economic model.

In Figure 21 below, which was also provided in Document B of the Company Submission, it is clear that three of the standard parametric models (loglogistic, lognormal and the generalised gamma) are sufficiently flexible in modelling PFS and already capture and reflect the observed trends in the hazards. Furthermore, interviews conducted with clinical experts confirmed that the log-normal distribution selected to extrapolate PFS in the base case was clinically the most plausible. Given this, it was not considered warranted to explore spline-based models.

Figure 21: Modelled and observed smoothed hazard rate for the parametric survival models to the fulvestrant only KM data for PFS in the PI3K/AKT altered-pathway population in CAPItello-291 (post-CDK4/6i, DCO1)

Abbreviations: DCO: data cut-off; CDK4/6i: cyclin-dependent kinase 4 and 6 inhibitor; KM: Kaplan-Meier; PFS: progression-free survival

f. The validity of the extrapolations beyond the KM data was examined using clinical expert estimates. The CS stated that "Clinicians were also asked to comment on the resulting PFS extrapolations for capivasertib plus fulvestrant as a result of selecting a model of the placebo plus fulvestrant arm". The clinical expert interview minutes only state that "[redacted]". Please provide more detailed clinical expert comments.

In the interviews conducted, there was a consensus on the clinical plausibility of the presented PFS extrapolations for capivasertib plus fulvestrant.[7] Three clinicians explicitly stated the extrapolations are clinically plausible. In addition to agreeing the extrapolations appear plausible, two clinicians commented on specific landmarks in the extrapolation data presented, anticipating ~12% and ~10% of patients on capivasertib plus fulvestrant to be progression-free at 24 months, which is in alignment with the landmarks presented. One clinician specifically commented on

the tail end of the extrapolation, noting that it is plausible that a small number of patients on capivasertib plus fulvestrant would still be progression-free at 60 months.

g. In addition to clinical expert validation, please also examine the validity of the extrapolations beyond the Kaplan-Meier data with supporting evidence that the extrapolations are consistent with relevant external data.

Although there is a paucity of evidence in the PI3K/AKT altered-pathway population who have received a prior CDK4/6i, a recently published abstract has been identified which reports relevant evidence on this patient population in those who have received fulvestrant in the real-world. This may be used to further validate the survival models fit to the placebo + fulvestrant arm in CAPItello-291 used in the economic model.

Specifically, the DREAM-US study[51] is a real-world evidence study, which analysed data from the Flatiron Health electronic health records to identify patients with HR+/HER2– mBC who received fulvestrant monotherapy following progression on CDK4/6i plus AI between January 1, 2011, and January 31, 2021. Despite this study being US-based, the patient population and treatment pathway is considered to be generally similar to the UK. The reported medians in DREAM-US are compared to the CAPItello-291 trial and the model in Table 25. This shows close alignment between the trial, the model and the external evidence, and indicates that the model is accurately predicting both OS and PFS over the observed period. Datapoints at other timepoints in the DREAM-US study were not reported, including those beyond the CAPItello-291 trial follow-up period.

Table 25 Comparison of CAPItello-291 and modelled survival to external data

	DREAM-US (N=152)	CAPItello-291 placebo plus fulvestrant arm* (N=94)	Modelled
Median PFS, months (95% confidence interval)	3.8 (3.6–4.5)	[redacted]	[redacted]
Median OS, months (95% confidence interval)	20.2 (14.8–22.7)	[redacted]	[redacted]

* PI3K/AKT altered-pathway population in CAPItello-291 (post-CDK4/6i, DCO1)

h. Please justify the selection of the approaches to estimate and extrapolate PFS and OS, taking into account the responses to the preceding questions as

well as the "Survival Model Selection Process Algorithm" provided in NICE DSU TSD 14.

The process outlined in NICE DSU TSD 14 was followed.

The first step in the algorithm is to assess the diagnostic plots to evaluate whether the PHA is reasonable (indicating that PH/AFT models can be utilised) and whether more flexible models (such as spline-based models) are warranted.

Given the approach taken in the CEM of applying the HRs calculated in the NMA for capivasertib plus fulvestrant, alpelisib plus fulvestrant and everolimus plus exemestane to the fulvestrant arm from CAPItello-291, it was already established that independent models required fitting to the fulvestrant data. This was considered to be the most consistent approach across comparators.

As explained in B5d, standard parametric models were considered appropriately flexible to capture the trial hazards, as indicated by consideration of the observed hazard plots versus the modelled hazards, and therefore spline-based models were not considered.

As outlined in Document B Sections B.3.3.1 to B.3.3.3, goodness of fit (AIC/BIC) statistics, visual assessment of the KM curves and hazard plots, and consideration of clinical validity and clinical opinion were all considered as part of the model selection process.

B 6: Priority question: To derive PFS and OS for capivasertib plus fulvestrant, alpelisib plus fulvestrant and everolimus plus exemestane, HRs estimated from the NMA were applied to the extrapolated placebo plus fulvestrant survival curve. The company performed the network meta-analysis under proportional hazards, despite that there was evidence suggesting that the proportional hazards assumption does not hold for PFS and OS in studies included in the NMA.

a. In line with question A16, please provide an updated economic model and scenario analysis informing the treatment effectiveness of capivasertib plus

fulvestrant, alpelisib plus fulvestrant, and everolimus plus exemestane using a time-varying hazards approach.

The efficacy of all treatment regimens of interest in the post-CDK4/6i population (i.e., capivasertib plus fulvestrant, alpelisib plus fulvestrant and everolimus plus exemestane) were modelled based on treatment effect estimates versus fulvestrant monotherapy obtained from the NMAs detailed in Question A17. The results of these analyses were applied to the extrapolated fulvestrant PFS and OS data (outlined in the Company Submission Sections B.3.3.2 and B.3.3.3) from CAPItello-291 to estimate the respective survival curves for all treatments in the population of interest. This ensures consistency with the approach used to estimate the survival curves for all comparators.

As described in Question A17, the fixed effects model provided the best statistical fit to the trial data based on the deviance information criterion for PFS and for the 0-6 month timepoint for OS, and hence the HR estimates obtained from the fixed effect model were incorporated in the model (Table 26). Point estimates were similar between the fixed and random effects models. For PFS, although the 3-month cut point appeared to provide a better fit to the data, both cut points were assessed in the model.

Table 26: Summary of HRs for treatments versus fulvestrant used in the economic model

Treatment vs. fulvestrant	PI3K/AKT pathway-altered population	
	Timepoint 1	Timepoint 2
PFS Scenario 1 – Timepoints: 0-3 months, 3+ months		
Capivasertib + fulvestrant	[redacted]	[redacted]
Everolimus + exemestane	[redacted]	[redacted]
Alpelisib + fulvestrant	[redacted]	[redacted]
PFS Scenario 2 – Timepoints: 0-2 months, 2+ months		
Capivasertib + fulvestrant	[redacted]	[redacted]
Everolimus + exemestane	[redacted]	[redacted]
Alpelisib + fulvestrant	[redacted]	[redacted]
OS – Timepoints: 0-6 months, 6+ months		
Capivasertib + fulvestrant	[redacted]	[redacted]
Everolimus + exemestane	[redacted]	[redacted]

Treatment vs. fulvestrant	PI3K/AKT pathway-altered population	
Alpelisib + fulvestrant	[redacted]	[redacted]

Abbreviations: AKT: Akt Murine Thymoma Viral Oncogene; HR, hazard ratio; N/A: not applicable; OS: overall survival; PFS: progression-free survival

The deterministic results are presented in Table 27 (cut points at 3 months and 6 months for PFS and OS, respectively) and Table 28 (cut points at 2 months and 6 months for PFS and OS, respectively).

Implementation of a time-varying HR approach has reduced the pairwise ICERs compared to the Company base case (in the base case, capivasertib plus fulvestrant vs. alpelisib plus fulvestrant: [redacted]; capivasertib plus fulvestrant vs. everolimus plus exemestane[redacted]). Total QALYs in the capivasertib plus fulvestrant arm were stable compared to the base case analysis (2.40 in the base case vs. 2.39 across both scenarios). Incremental QALYs increased slightly but were also relatively stable (0.61 and 0.94 in the base case vs. alpelisib + fulvestrant and everolimus plus exemestane, vs. 0.62-0.63 and 0.86-0.87).

Table 27. Deterministic pairwise base-case results (Scenario 1)*

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER of capivasertib plus fulvestrant versus comparator (£/QALY)	Pairwise ICER of capivasertib plus fulvestrant versus comparator (£/QALY) with 1.2 QALY weighting
Capivasertib + fulvestrant	[redacted]	3.26	2.39					
Alpelisib + fulvestrant	£48,405	2.40	1.77	[redacted]	0.86	0.62	[redacted]	[redacted]
Everolimus + exemestane	£25,598	2.06	1.53	[redacted]	1.20	0.86	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; *After revisions described at the beginning of Section B

Table 28. Deterministic pairwise base-case results (Scenario 2)*

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER of capivasertib plus fulvestrant versus comparator (£/QALY)	Pairwise ICER of capivasertib plus fulvestrant versus comparator (£/QALY) with 1.2 QALY weighting
Capivasertib + fulvestrant	[redacted]	3.26	2.39					
Alpelisib + fulvestrant	£45,884	2.40	1.77	[redacted]	0.86	0.63	[redacted]	[redacted]
Everolimus + exemestane	£24,718	2.06	1.52	[redacted]	1.20	0.87	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; *After revisions described at the beginning of Section B

b. **To ensure consistency with alpelisib plus fulvestrant and everolimus plus exemestane, the capivasertib plus fulvestrant curve was also estimated by applying a HR from the NMA to the extrapolated placebo plus fulvestrant arm from CAPItello-291. Please provide an updated economic model and scenario analysis fitting parametric survival models directly to the individual patient level data from the capivasertib plus fulvestrant arm in CAPItello-291. For selection of the most suitable parametric survival models, please provide the information as requested in question B5 above.**

The Company believe the motivation behind this request is to explore independent fits to the capivasertib plus fulvestrant data, as has been performed for the placebo plus fulvestrant data in the Company base case. For this reason, jointly fit models have not been explored.

However, before presenting this scenario analysis, the Company would maintain that given the external comparator survival curves are generated using the results from the NMA, the most appropriate methodology to ensure consistency in the analysis is to model the capivasertib plus fulvestrant survival using the same approach, as is adopted in the Company base-case. This also allows for all relevant evidence to be incorporated into the model (e.g., UK-specific data from FAKTION).

For this reason, when independently fitted curves for the capivasertib plus fulvestrant arm are selected in the economic model as a scenario analysis, the HRs for alpelisib plus fulvestrant and everolimus plus exemestane from the NMA versus capivasertib plus fulvestrant are applied to the capivasertib plus fulvestrant curve, which then becomes the new reference curve in the analysis. These HRs are detailed in the Company Submission Document B, Section B.2.9.1 Figure 15 and Figure 17. This ensures consistency with the approach used across all comparators, and aligns with the Company base-case, with the main difference being the switch from fulvestrant monotherapy to capivasertib plus fulvestrant as the reference arm.

The model selection process for the most appropriate and clinically plausible distribution to extrapolate PFS and OS for the capivasertib plus fulvestrant arm

follows that used for the placebo plus fulvestrant arm and aligns with the guidance in NICE DSU TSD 14.[52]

Progression-free survival

The PFS Kaplan-Meier plot for patients with PI3K/AKT-altered tumours, who had received prior endocrine therapy plus CDK4/6i therapy in CAPItello-291 shows a clear early and continued separation between the capivasertib plus fulvestrant and the placebo plus fulvestrant arms over time (see Company submission Document B Figure 3).

Standard models were considered sufficiently flexible to capture the shape of the trial hazards (plateauing and decreasing hazards over time as shown in Figure 12). Spline-based models were not explored.

The statistical goodness of fit of each of the standard parametric models fit to the data were reported in terms of the Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) scores in Table 29, where a lower score indicates a more parsimonious fit to the CAPItello-291 trial data. Based on these statistics, log-normal, generalised gamma and log-logistic were considered to provide good fits to the trial data.

Table 29: AIC and BIC values for the parametric survival models fitted to the PFS capivasertib plus fulvestrant data CAPItello-291 (PI3K/AKT pathway-altered populations, DCO1)

Model	PI3K/AKT pathway-altered, post-CDK4/6i	
	AIC	BIC
Exponential	591.4	594.1
Weibull	588.6	594.1
Log-normal	576.7	582.2
Log-logistic	580.0	585.5
Gompertz	593.0	598.5
Generalised gamma	577.9	586.1
Gamma	585.9	591.4

Abbreviations: AIC: Akaike Information Criteria; AKT: Akt Murine Thymoma Viral Oncogene; BIC: Bayesian Information Criteria; DCO: data cut-off; PFS: progression-free survival

The fit of the models to the observed data is shown in Figure 22. The log-normal, log-logistic and generalised gamma fit the observed data the best visually.

Figure 22 Fit of the parametric survival models to the capivasertib plus fulvestrant KM data for PFS in the PI3K/AKT altered-pathway population in CAPItello-291 (post-CDK4/6i) (DCO1)

A comparison of the modelled and observed smoothed hazard rates is also shown in Figure 23. The log-normal, log-logistic and generalised gamma models all capture the decrease followed by plateau in the trial hazards.

Figure 23 Modelled and observed smoothed hazard rate for the parametric survival models to the capivasertib plus fulvestrant KM data for PFS in the PI3K/AKT altered-pathway population in CAPItello-291 (post-CDK4/6i, DCO1)

The clinical validation exercise performed prior to the submission confirmed the company base case (applying a HR on to the placebo plus fulvestrant extrapolation) for capivasertib plus fulvestrant was plausible. The distribution most aligned to this base case is the generalised gamma (Figure 24).

Considering goodness of fit, a visual comparison of the trial data to the modelled data (KM curve and hazards), and the previously performed clinical validation, the generalised gamma model was selected for PFS in this scenario analysis.

Figure 24 Comparison of the best fitting models for PFS with validated extrapolation in Company base case

Overall survival

The OS Kaplan-Meier plot for patients with PI3K/AKT-altered tumours, who had received prior endocrine therapy plus CDK4/6i therapy in CAPItello-291 shows a clear early and continued separation between the capivasertib plus fulvestrant and the placebo plus fulvestrant arms over time (see Company submission Document B Figure 5).

Standard models were considered sufficiently flexible to capture the shape of the trial hazards (increasing hazards over time as shown in

Figure 11). Spline-based models were not explored.

The statistical goodness of fit was reported in terms of the AIC and BIC scores in Table 30. As with the independently fit fulvestrant extrapolations, all models, except

for generalised gamma, were considered to provide a reasonable fit to the data (AIC scores between 322.8-324.4, BIC scores between 326.9-329.9).

Table 30: AIC and BIC values for the parametric survival models fitted to the OS capivasertib plus fulvestrant data CAPItello-291 (PI3K/AKT pathway-altered populations, DCO1)

Model	PI3K/AKT pathway-altered, post-CDK4/6i	
	AIC	BIC
Exponential	324.2	326.9
Weibull	323.1	328.6
Log-normal	322.9	328.4
Log-logistic	322.8	328.3
Gompertz	324.4	329.9
Generalised gamma	324.7	332.9
Gamma	322.9	328.4

Abbreviations: AIC: Akaike Information Criteria; AKT: Akt Murine Thymoma Viral Oncogene; BIC: Bayesian Information Criteria; DCO: data cut-off; PFS: progression-free survival

The fit of the models to the observed data and extrapolated out over the trial time horizon are shown in Figure 25. Most distributions provide a reasonable fit to the data in the within-trial period, but there are notable differences between distributions in the extrapolated period over the model time horizon (20 years); generalised gamma, log-logistic and log-normal all providing more optimistic survival predictions in the long-run, compared to more pessimistic survival predictions with Gompertz, Weibull, gamma and exponential.

Figure 25 Fit of the parametric survival models to the capivasertib plus fulvestrant KM data for OS in the PI3K/AKT altered-pathway population in CAPItello-291 (post-CDK4/6i) (DCO1)

A comparison of the modelled and observed smoothed hazard rates is also shown in Figure 26. Weibull, Gompertz and gamma all predict increasing hazards with time, whilst log-normal, log-logistic, and generalised gamma predict decreasing hazards with time. Whilst Gompertz appears to follow the observed hazards the closest, it does predict that the hazard rate will increase monotonically with time, which may not be clinically plausible. Therefore, comparison to the clinically validated curve is important.

Figure 26 Modelled and observed smoothed hazard rate for the parametric survival models to the capivasertib plus fulvestrant KM data for OS in the PI3K/AKT altered-pathway population in CAPItello-291 (post-CDK4/6i, DCO1)

As statistical and visual goodness-of-fit was comparable across distributions, clinical opinion was considered the most important factor in determining the base case distribution. Clinicians said that the distribution selected in the Company base case appears clinically plausible (data presented in Table 31 under 'Company base case'; a detailed overview of clinician responses is presented in Question B5f), and this has been overlaid with the other distributions in Figure 27. The validated Company base case curve for capivasertib plus fulvestrant falls in the middle of the gamma and exponential/generalised gamma distribution. The gamma consistently underestimates survival in the extrapolated period, and whilst the generalised gamma may be considered optimistic, it provides a clinically plausible extrapolation up to ~4 years. Given this, the ICERs have been generated using generalised gamma. The constant hazard assumed with the exponential distribution was not considered plausible.

Figure 27 Comparison of the independently fit OS models with validated extrapolation in Company base case

Table 31 Overall survival for capivasertib plus fulvestrant relative to fulvestrant, extrapolated to 120 months (based on subgroup of patients from CAPItello-291 who had PI3K/AKT pathway alterations and had received prior CDK 4/6i)

		Months					
		12	24	60	120	180	240
Kaplan Meier data from CAPItello-291 (Capivasertib + fulvestrant arm, PI3K/AKT subgroup who had received prior CDK4/6i)		[redacted]	[redacted]	NA	NA	NA	NA
Company base case	Capivasertib + fulvestrant extrapolation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG request	Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The deterministic results are presented in Table 32. These results show approximate consistency with the Company base case, with only small differences in the total QALY gain, primarily driven by slightly higher extrapolated OS.

Table 32. Deterministic pairwise base-case results (Scenario 1 – generalised gamma for OS)*

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER of capivasertib plus fulvestrant versus comparator (£/QALY)	Pairwise ICER of capivasertib plus fulvestrant versus comparator (£/QALY) with 1.2 QALY weighting
Capivasertib + fulvestrant	[redacted]	3.52	2.58					
Alpelisib + fulvestrant	£51,698	2.50	1.84	[redacted]	1.02	0.74	[redacted]	[redacted]
Everolimus + exemestane	£25,895	1.97	1.46	[redacted]	1.55	1.12	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; *After revisions described at the beginning of Section B

B 7. Priority question: Patients on capivasertib plus fulvestrant, alpelisib plus fulvestrant and everolimus plus exemestane all continue to receive treatment until confirmed disease progression, unacceptable toxicity or withdrawal of consent. To derive TTD for capivasertib plus fulvestrant, alpelisib plus fulvestrant and everolimus plus exemestane in the economic model, a HR of [redacted] was applied to their modelled PFS curves. However, reported treatment discontinuation rates due to disease progression and AEs in the relevant trials (i.e. CAPItello-291, SOLAR-1 and BOLERO-2) differed substantially between capivasertib plus fulvestrant (58.9% due to PD, 13% due to AEs), alpelisib plus fulvestrant (37% due to PD, 25% due to AEs), and everolimus plus exemestane (55% due to PD, 19% due to AEs).

a. **Please justify the assumption of pragmatically applying the same HR for all three treatment options, despite the observed treatment discontinuation differences in the corresponding trials.**

Assessment of the proportions who discontinued due to PD and AE does not provide a way to calculate the ratio between TTD and PFS. The methodology adopted in the original submission was seen as a pragmatic approach given the lack of publicly available TTD data for alpelisib plus fulvestrant and everolimus plus exemestane. Considering a ratio of median treatment duration to median PFS was not considered appropriate as it only reflects one point in time.

b. **To assess the impact of pragmatically applying the same HR to the modelled PFS curves for all three treatment options, please provide an updated economic model and scenario analysis exploring TTD by:**

   (1) **applying a HR of [redacted] to the modelled PFS curve of capivasertib plus fulvestrant and a HR of 1.20 to the modelled PFS curve of alpelisib plus fulvestrant and everolimus plus exemestane**

   (2) **applying a HR of [redacted] to the modelled PFS curve of capivasertib plus fulvestrant and a HR of 1.30 to the modelled PFS curve of alpelisib plus fulvestrant and everolimus plus exemestane**

c. **Please provide an updated economic model and scenario analysis estimating TTD by applying different HRs to their modelled PFS curves, in line with what would be expected from the observed discontinuation rates from the trials (i.e. higher HRs for alpelisib plus fulvestrant and everolimus plus exemestane compared to capivasertib plus fulvestrant).**

d. **Please provide an updated economic model and scenario analysis assuming TTD is equal to PFS for capivasertib plus fulvestrant, alpelisib plus fulvestrant and everolimus plus exemestane (i.e. assuming a HR of 1.0).**

The response to part b-d combined is provided here. Question b and c seem to be duplicated, as both are requesting scenario analyses to be performed with a shorter time on treatment for alpelisib plus fulvestrant and everolimus plus exemestane.

In the submission, the Company performed a scenario analysis which tested the impact of changing this ratio to 1.10 and 1.20 for all comparators. The Company have performed the analyses requested by the EAG but would highlight that there is no strong supporting evidence as to why alpelisib plus fulvestrant and everolimus plus exemestane would have the same ratio, and capivasertib plus fulvestrant have another. Furthermore, scenario analyses should test the impact of a parameter on all model comparators, and therefore the requested values (1.20 and 1.30) have also been explored for the capivasertib plus fulvestrant arm.

The requested scenario assuming a HR between TTD and PFS of 1 has also been explored, however this is considered a clinically implausible scenario given that treatment duration is less than PFS for all comparators across the studies.[18,27,33,53]

The pairwise deterministic results for all scenarios are provided in Table 33 (capivasertib plus fulvestrant vs. alpelisib plus fulvestrant) and Table 34 (capivasertib plus fulvestrant vs. everolimus plus exemestane). The Company believe that applying a HR of [redacted] across comparators is the most pragmatic approach, and that exploring nominal increases in the HR for individual comparators is arbitrary and not based on strong evidence.

Table 33 Scenario analyses testing the HR applied to PFS to reflect TTD (capivasertib plus fulvestrant vs. alpelisib plus fulvestrant)

HR applied to PFS for TTD for:		ICER* (capivasertib plus fulvestrant vs. alpelisib plus fulvestrant)	% change from base case
Capivasertib plus fulvestrant arm	Alpelisib plus fulvestrant		
[redacted] (base case)	[redacted] (base case)	[redacted]	-
1.15	1.20	[redacted]	+5.4%
1.20	1.15	[redacted]	-11.4%
1.15	1.30	[redacted]	+14.7%
1.30	1.15	[redacted]	-30.7%
1.00	1.00	[redacted]	+22.8%

*including 1.2 weighting and after revisions described at the beginning of Section B

Table 34 Scenario analyses testing the HR applied to PFS to reflect TTD (capivasertib plus fulvestrant vs. everolimus plus exemestane)

HR applied to PFS for TTD for:		ICER* (capivasertib plus fulvestrant vs. everolimus plus exemestane)	% change from base case
Capivasertib plus fulvestrant arm	Everolimus plus exemestane		
[redacted] (base case)	[redacted] (base case)	[redacted]	-
1.15	1.20	[redacted]	+0.7%
1.20	1.15	[redacted]	-5.8%
1.15	1.30	[redacted]	+1.9%
1.30	1.15	[redacted]	-15.6%
1.00	1.00	[redacted]	19.5%

*including 1.2 weighting and after revisions described at the beginning of Section B

e. **Please provide an updated economic model and scenario analysis fitting parametric survival models directly to the TTD individual patient level data from the capivasertib plus fulvestrant arm in CAPItello-291. For selection of the most suitable parametric survival model, please provide the information as requested in question B5 above.**

The Company maintain that when OS and PFS data is generated for capivasertib plus fulvestrant through applying a HR to the placebo plus fulvestrant extrapolated curves, as has been done in the Company base case, using independently fit models to the TTD data for capivasertib plus fulvestrant is inconsistent. Despite this inconsistency in the methodology, the results presented below show that this is not a driver of the ICER and there is a high level of consistency with the base case analysis.

To perform this analysis, models were independently fit to the fulvestrant and capivasertib elements of the capivasertib plus fulvestrant arm in the model. Proportional hazards were not assessed between the two elements in the treatment arm. Furthermore, as the TTD data for placebo plus fulvestrant is not used in the model, an assessment of proportional hazards was also not performed between treatment arms.

The plots in the subsequent sections have been generated with the placebo plus fulvestrant curve plotted, but this curve should be disregarded.

Capivasertib (capivasertib plus fulvestrant arm)

The capivasertib Kaplan-Meier plot is provided in Figure 28. Median TTD was [redacted] months (95% CI: [redacted]). The smoothed hazard plot is provided in Figure 29 which shows a plateauing and declining hazard with time. Standard models were considered sufficiently flexible to capture the shape of the trial hazards and spline-based models were not explored.

Figure 28 KM curve for capivasertib TTD from capivasertib plus fulvestrant arm in CAPItello-291 (post-CDK4/6i, PI3K/AKT pathway-altered population, DCO1)

Figure 29 Plot of smoothed hazards for TTD (capivasertib in capivasertib plus fulvestrant arm) (post-CDK4/6i, PI3K/AKT pathway-altered population, DCO1)

The statistical goodness of fit of each of the standard parametric models fit to the data were reported in terms of the AIC and BIC scores in Table 35. Based on these statistics, the log-logistic and log-normal models were considered to provide the best fits to the trial data.

Table 35 AIC and BIC values for the parametric survival models fitted to the TTD capivasertib plus fulvestrant data (capivasertib arm) CAPItello-291 (PI3K/AKT pathway-altered populations, DCO1)

Model	PI3K/AKT pathway-altered, post-CDK4/6i	
	AIC	BIC
Exponential	622.1	624.9
Weibull	621.1	626.6
Log-normal	618.8	624.3
Log-logistic	617.2	622.6
Gompertz	623.9	629.3
Generalised gamma	619.0	627.2
Gamma	619.7	625.2

Abbreviations: AIC: Akaike Information Criteria; AKT: Akt Murine Thymoma Viral Oncogene; BIC: Bayesian Information Criteria; DCO: data cut-off

The fit of the models to the observed data is shown in Figure 30. The log-normal and loglogistic models are associated with longer tails compared to other models.

A comparison of the modelled and observed smoothed hazard rates is also shown in Figure 31. The log-normal, log-logistic and generalised gamma models all capture the decrease followed by plateau in the trial hazards. The loglogistic, log-normal and generalised gamma models all capture the observed hazards.

Based on the goodness of fit statistics, visual assessment of the KM curve to the data and the hazard plots, the loglogistic distribution was selected for this scenario analysis.

Figure 30 Fit of the parametric survival models to the capivasertib plus fulvestrant KM data for TTD (capivasertib) in the PI3K/AKT altered-pathway population in CAPItello-291 (post-CDK4/6i) (DCO1)

Figure 31 Modelled and observed smoothed hazard rate for the parametric survival models to the capivasertib plus fulvestrant KM data for TTD (capivasertib) in the PI3K/AKT altered-pathway population in CAPItello-291 (post-CDK4/6i, DCO1)

Fulvestrant (capivasertib plus fulvestrant arm)

The fulvestrant Kaplan-Meier plot is provided in Figure 32. Median TTD was [redacted] months (95% CI: [redacted]). The smoothed hazard plot is provided in Figure 33 which shows plateauing followed by declining hazard with time. Standard models were considered sufficiently flexible to capture the shape of the trial hazards and spline-based models were not explored.

Figure 32 KM curve for fulvestrant TTD from capivasertib plus fulvestrant arm in CAPItello-291 (post-CDK4/6i, PI3K/AKT pathway-altered population, DCO1)

Figure 33 Plot of smoothed hazards for TTD (fulvestrant in capivasertib plus fulvestrant arm) (post-CDK4/6i, PI3K/AKT pathway-altered population, DCO1)

The statistical goodness of fit of each of the standard parametric models fit to the data were reported in terms of the AIC and BIC scores in Table 36. Based on these statistics, the exponential and loglogistic models provide the best fits to the trial data.

Table 36: AIC and BIC values for the parametric survival models fitted to the TTD capivasertib plus fulvestrant data (fulvestrant arm) CAPItello-291 (PI3K/AKT pathway-altered populations, DCO1)

Model	PI3K/AKT pathway-altered, post-CDK4/6i	
	AIC	BIC
Exponential	608.6	611.3
Weibull	610.5	616.0
Log-normal	616.9	622.4
Log-logistic	609.6	615.0
Gompertz	610.2	615.6
Generalised gamma	611.1	619.3
Gamma	610.4	615.8

Abbreviations: AIC: Akaike Information Criteria; AKT: Akt Murine Thymoma Viral Oncogene; BIC: Bayesian Information Criteria; DCO: data cut-off

The fit of the models to the observed data is shown in Figure 34. The exponential model visually fits the KM curve the best as the loglogistic seems to be overpredicting the tail of the curve.

A comparison of the modelled and observed smoothed hazard rates is also shown in Figure 35. Whilst the trial hazards do appear to decline at the end of the trial period,

this may be overly influenced by the low numbers at risk at later timepoints (N= [redacted] at 12 months, N= [redacted] at 14 months).

Based on the goodness of fit statistics, visual assessment of the KM curve to the data and the hazard plots, the exponential distribution was selected for this scenario analysis.

Figure 34 Fit of the parametric survival models to the capivasertib plus fulvestrant KM data for TTD (fulvestrant) in the PI3K/AKT altered-pathway population in CAPItello-291 (post-CDK4/6i) (DCO1)

Figure 35 Modelled and observed smoothed hazard rate for the parametric survival models to the capivasertib plus fulvestrant KM data for TTD (fulvestrant) in the PI3K/AKT altered-pathway population in CAPItello-291 (post-CDK4/6i, DCO1)

The pairwise results for this EAG-requested scenario are presented in Table 37. These are highly consistent with the pragmatic approach adopted in the Company base case.

Table 37 Deterministic pairwise results from scenario using TTD for capivasertib plus fulvestrant

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER* of capivasertib plus fulvestrant versus comparator (£/QALY) with 1.2 QALY weighting
Capivasertib + fulvestrant	[redacted]	3.25	2.40				
Alpelisib + fulvestrant	£51,365	2.42	1.79	[redacted]	0.83	0.61	[redacted]
Everolimus + exemestane	£25,714	1.96	1.45	[redacted]	1.30	0.94	[redacted]

* after revisions described at the beginning of Section B

B 8. No treatment waning was assumed in the company's base-case analysis:

a. Please provide implied hazard ratio plots for PFS and OS versus time with numbers of patients at risk over time to justify this assumption.

The calculation of time-varying HRs was not a pre-specified analysis in the SAP and are not considered appropriate as a post-hoc analysis for the PFS or OS data from CAPItello-291.

However, to reflect the impact of potential changes in the HR over time, a time-varying NMA was explored and adopted as a scenario approach (see responses to question A17 and B7). This analysis demonstrates that even with different HRs over time, capivasertib plus fulvestrant is associated with numerically improved PFS and OS vs. all comparator treatment regimens over the majority of the time periods assessed.

b. If indicated by the implied hazard ratio plots, please provide an updated economic model and scenario analyses exploring treatment waning to kick in at earlier time points.

The application of time-varying hazards accounts for treatment waning, as all HRs estimated in the time-varying NMA increase with time (relative to fulvestrant). The impact of this has been provided in response to Question B6 and demonstrates that the pairwise ICERs for capivasertib plus fulvestrant compared to everolimus plus exemestane and alpelisib plus fulvestrant remain stable or fall.

Health-related quality of life

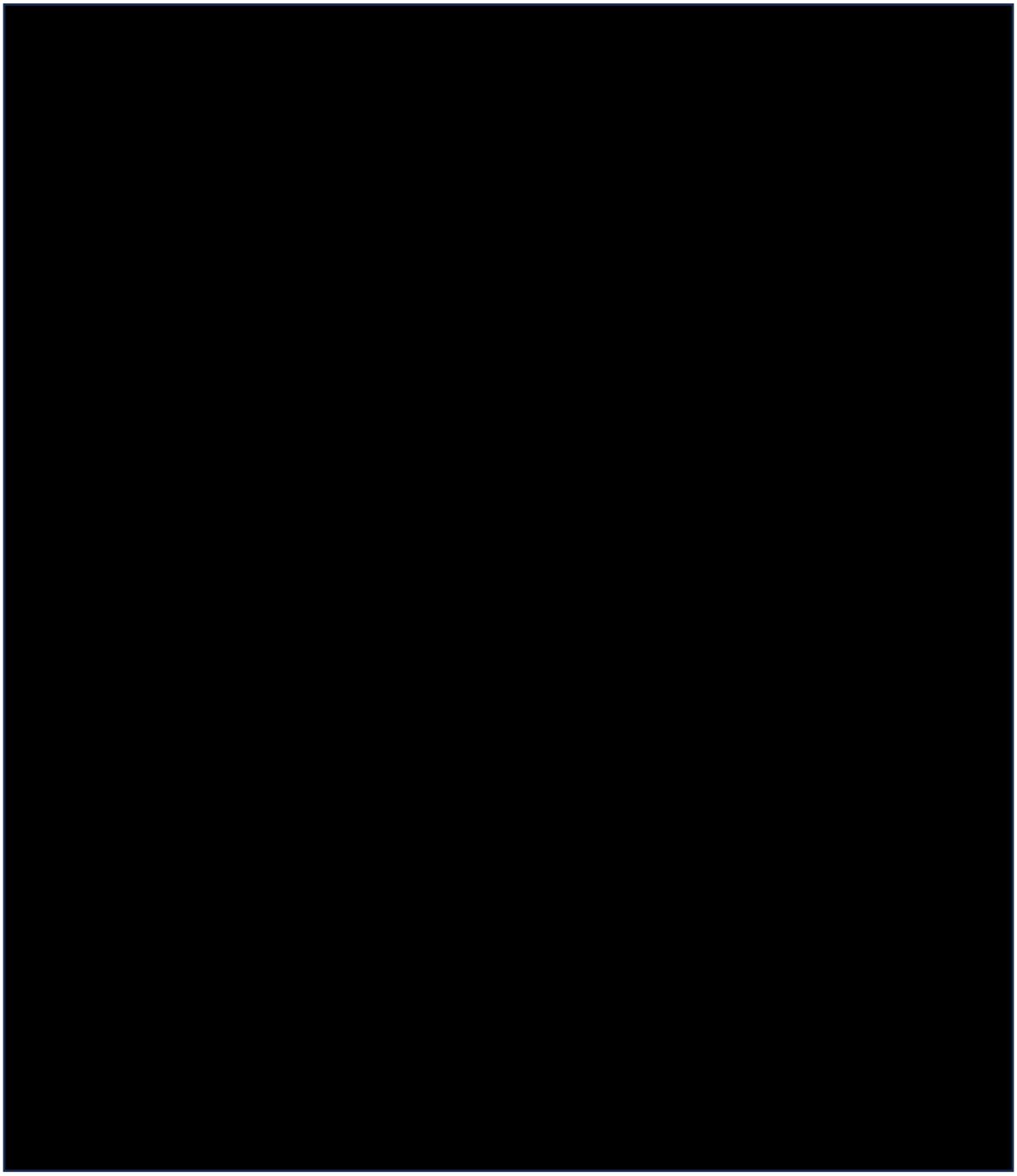
B 9. Priority Question: The company used EQ-5D-5L data from the overall population in the CAPItello-291 trial to inform health state utilities in the economic model. Health state utilities were estimated using MMRM analysis, in which four different models were explored including different (combinations of) fixed effects covariates.

a. It was stated in the CS that the utilised MMRM analysis handles missing data under the missing at random assumption. Please provide the amount of missing data (per arm and time point for the overall

population and the subgroup) and justify the assumption that these data are missing at random, particularly provided that compliance deteriorates overtime within the CAPItello-291 study.

The differences in baseline EQ5D response/missingness across various baseline characteristics was assessed and no noteworthy relationships were identified (Figure 36). This indicates that the data can be treated as missing at random.

Figure 36 Baseline EQ-5D missingness by characteristic



b. Please provide the full results for each explored model and elaborate on how diagnostics of the model were assessed, how the (candidate) covariates as well as interaction terms were selected (with rationale) and how the model accounted for nesting effects.

As detailed in Company Submission Section B.3.4.3., to account for the repeated measurements in the study, a mixed model for repeated measures (MMRM) method was used to model EQ-5D-5L health state utilities. The MMRM analysis was performed on a dataset excluding any observations recorded after the time of censoring for progression since observations obtained during this period have an unknown/missing health status.

The MMRM analysis was performed using the restricted maximum likelihood method (REML) with the following covariates included as fixed effects:

- (Randomised) Treatment
- Progression status (pre-progression, post-progression)
- Treatment + Progression status
- Treatment + Progression status + Treatment * Progression status (both terms and their interaction included)

These covariates were selected as they were believed to be the largest drivers of utility.

Accounting for nested effects

The correlation of repeated utility measurements within subjects over time was captured via the specification of a covariance structure for the MMRM.

The hierarchy of covariance structures tested, in order of most to least flexible, is shown below:

1. Unstructured – each visit is allowed to have a different variance, and each combination of visits is allowed to have a different covariance.
2. Toeplitz with heterogeneity – each visit is allowed to have a different variance, covariances between measurements depend on how many visits apart they are.

3. Autoregressive, order 1 (AR(1)) with heterogeneity – each visit is allowed to have a different variance, and covariances decrease based on how many visits apart they are. Covariances decrease towards zero as the number of visits between observations increases.

4. Toeplitz – as above for number 2, but each visit shares the same variance.

5. Autoregression, order 1 (AR(1)) – as above for number 3, but each visit shares the same variance.

For the analysis of values from CAPItello-291, the most flexible correlation structure for which all 4 models converged was the autoregressive order 1 with heterogeneity ('AR(1)H'). This correlation structure assumes a correlation between adjacent visits and that this correlation decreases exponentially across visits. The 'heterogeneity' aspect of the structure allows for different variances at each visit.

The best-fitting model was assessed by AIC

This was the model with a term for progression status (pre / post-progression).

There are N subjects indexed by i ($i = 1, \ldots, N$).

The model equation is as follows:

$$\mathbf{y_i} = \mathbf{X_i}\boldsymbol{\beta} + \boldsymbol{\epsilon_i}$$

Where $\boldsymbol{\beta}$ represents the coefficients for pre/post-progression, and $\mathbf{X_i}$ is a design matrix for subject i.

The vector of within-subject residuals, $\boldsymbol{\epsilon_i}$, is assumed to have a multivariate normal distribution, where the variance-covariance matrix accommodates correlations between residuals. Vectors of residuals are assumed to be independent between subjects.

Results of all models

The results of all models are provided in Table 38.

Table 38 Results from MMRM analysis (CAPItello-291 ITT)

Parameter	Marginal means (95% CI)	P-Value
Model 1. (Randomised) Treatment		
Placebo + Fulvestrant	[redacted]	< 0.0001
Capivasertib + Fulvestrant	[redacted]	< 0.0001
Model 2. Progression status (pre-progression, post-progression)		
Pre-progression	[redacted]	< 0.0001
Post- progression	[redacted]	< 0.0001
Model 3. Treatment + Progression status		
Placebo + Fulvestrant Pre-progression	[redacted]	< 0.0001
Capivasertib + Fulvestrant Pre-progression	[redacted]	< 0.0001
Placebo + Fulvestrant Post- progression	[redacted]	< 0.0001
Capivasertib + Fulvestrant Post- progression	[redacted]	< 0.0001
Model 4. Treatment + Progression status + Treatment * Progression status		
Placebo + Fulvestrant Pre-progression	[redacted]	< 0.0001
Capivasertib + Fulvestrant Pre-progression	[redacted]	< 0.0001
Placebo + Fulvestrant Post- progression	[redacted]	< 0.0001
Capivasertib + Fulvestrant Post- progression	[redacted]	< 0.0001

c. **The company stated that EQ-5D-5L data from the overall population were highly consistent with the data in the PI3K/AKT pathway-altered population (also in terms of prior CDK 4/6i). Please estimate HSUVs using MMRM analysis based on the PI3K/AKT pathway-altered subgroup (with prior treatment with CDK 4/6i therapy) in the CAPItello-291 trial. Please also provide details as requested in question b.**

The Company submission used data from the overall population (ITT) as there is no clinical rationale as to why patients' safety profile would differ between mutation subgroups, and it provided substantially more data points.

The statement made by the Company that EQ-5D-5L data from the overall population were highly consistent with the data in the PI3K/AKT pathway-altered population was supported by plots of change in EQ-5D-5L index score and VAS score (Company Submission Document B: Figure 8, Figure 9 and Figure 25, Figure 26). This is further supported with the additional MMRM analyses conducted on the AKT pathway altered prior CDK4/6i subgroup; goodness of fit statistics are presented in Table 39 and the results for all models in Table 40. The best fitting model is the same across populations (model 2. progression status), and the

marginal means are similar (based on a comparison between Table 38 and Table 40).

Table 39: Goodness of fit statistics (CAPItello-291 AKT pathway altered, with prior CDK4/6i)

Model terms	Converged?	AIC	BIC
trt (model 1)	Yes	-1410.7	-1325.3
PFSFLAG (model 2)	Yes	-1412.6	-1327.1
trt + PFSFLAG (model 3)	Yes	-1407.4	-1321.9
trt * PFSFLAG (model 4)	Yes	-1404.6	-1319.1

Abbreviations: AIC: Akaike Information Criteria; BIC: Bayesian Information

Table 40 Results from MMRM analysis (CAPItello-291 AKT pathway altered, with prior CDK4/6i)

Parameter	Marginal means (95% CI)	P-Value
Model 1. (Randomized) Treatment		
Placebo + Fulvestrant	[redacted]	< 0.0001
Capivasertib + Fulvestrant	[redacted]	< 0.0001
Model 2. Progression status (pre-progression, post-progression)		
Pre-progression	[redacted]	< 0.0001
Post- progression	[redacted]	< 0.0001
Model 3. Treatment + Progression status		
Placebo + Fulvestrant Pre-progression	[redacted]	< 0.0001
Capivasertib + Fulvestrant Pre-progression	[redacted]	< 0.0001
Placebo + Fulvestrant Post- progression	[redacted]	< 0.0001
Capivasertib + Fulvestrant Post- progression	[redacted]	< 0.0001
Model 4. Treatment + Progression status + Treatment * Progression status		
Placebo + Fulvestrant Pre-progression	[redacted]	< 0.0001
Capivasertib + Fulvestrant Pre-progression	[redacted]	< 0.0001
Placebo + Fulvestrant Post- progression	[redacted]	< 0.0001
Capivasertib + Fulvestrant Post- progression	[redacted]	< 0.0001

d. Please provide an updated model and scenario analysis informing the health state utilities based on the PI3K/AKT pathway-altered subgroup (with prior treatment with CDK 4/6i therapy), using the best fitting model from question c.

Using the utility values in Table 40 for the best fitting model (model 2, by progression status) for the PI3K/AKT pathway-altered subgroup with prior treatment with CDK4/6i data from CAPItello-291 in the model results in the pairwise ICERs presented in Table 41, which are very similar to the Company base case ICERs.

Table 41 Pairwise deterministic ICER

	Capivasertib plus fulvestrant versus*	
	Alp+Ful	E+E
Base case	[redacted]	[redacted]
Scenario	[redacted]	[redacted]

*Including the 1.2 severity modifier weighting and after revisions described at the beginning of Section B
Abbreviations: Apl+Ful, alpelisib plus fulvestrant; E+E, everolimus plus exemestane

e. **Please outline the differences in HSUVs between the overall trial population and the PI3K/AKT pathway-altered population that received prior CDK 4/6 inhibitor therapy. Please discuss the impact of utilising utilities derived from the overall population on modelled results, as compared with the specified subgroup.**

The response to this request is covered in B9, question c and d.

B 10. Priority question: Within the economic model, the decrement between HSUVs in pre- and post-progression is relatively small (difference of [redacted]). Table 20 of the CS highlighted HSUVs identified in previous NICE TAs for HR+/HER2- advanced breast cancer after endocrine therapy. PF and PD HSUVs were available for TA421 and TA619 (since updated to TA836). Further, PD HSUV was available for TA579 (since updated to TA725) also with a significantly lower HSUV was the post-progression health state.

a. **Please discuss the plausibility of the relatively small utility decrement from the pre- to post-progression health state.**

The Company Submission complies with the NICE reference case and utilises utility values from the CAPItello-291 trial in the base case. MMRM utility analysis was conducted on a comprehensive dataset, so any derived values should not be immediately scrutinized with the assumption that patients who experience progression immediately drop to a significantly lower utility value, even if even if this differs from assumptions made in previous appraisals. The values derived from the CAPITello-291 trial were [redacted] and [redacted] for the progression-free and progressed disease health state, respectively, and it is challenging to pinpoint what is driving the progressed disease value. It could potentially be explained by the fact that once patients progress on capivasertib plus fulvestrant, a large proportion of them will continue on many additional lines of therapy. As such, not all patients will experience

a significant decline in QoL following discontinuation on capivasertib plus fulvestrant over the duration of the trial period, and many will continue to live and have relatively good QoL on other subsequent anti-cancer therapies before it declines. Additional sensitivity analyses exploring alternative, lower values for the progressed disease state were explored to understand the impact of this on ICER results (Table 42). As anticipated, lower progressed disease utility values result in an increase in the ICER; however, the ICER is relatively stable within this range indicating this parameter is not a key driver if decision uncertainty.

Table 42 Testing lower progressed disease utility values

Progressed disease utility	ICER for capivasertib plus fulvestrant versus (% change from Company base case):	
	Alpelisib plus fulvestrant	Everolimus plus exemestane
[redacted] (Company base case)	[redacted]	[redacted]
0.70	[redacted]	[redacted]
0.65	[redacted]	[redacted]
0.60	[redacted]	[redacted]

Within the previous NICE appraisals of CDK4/6i and everolimus + exemestane (TA619, TA579, TA593, TA496, TA495) the utility value for the post-progression health state was assumed to be 0.56 or lower (based on the Lloyd et al. SG study), leading to a much larger decrement between the progression-free and post-progression states (this is discussed in the response to part b). Issues with the use of Lloyd et al. in this setting are discussed in response to Question B10 b. Three previous appraisals (TA503, TA639 and TA725) have applied comparatively higher utility values in the post-progression state and values used are more in line, albeit slightly lower, with the utility values used in the base-case analysis described here. Despite the limitations in estimation of post-progression utility, utilising the EQ-5D data from CAPItello-291 was considered to be the most suitable approach (and one that aligns to the NICE reference case).

b. Please compare the identified HSUVs with those utilised in the CS base case and discuss differences in the absolute values as well as the respective decrements between PF and PD HSUVs.

For reference, the identified HSUVs are provided in Table 43. Many of these values were redacted, so it is not possible to comment on the absolute value or respective decrements in all cases.

Table 43 HSUV identified as part of the Company Submission

NICE TA	Treatment regimen	PF HSUV	Source	PD HSUV	Source
TA816[8]	Alpelisib with fulvestrant	NR	SOLAR-1.[54] Utilities were by on/off tx (and tx specific) and progression status	NR	SOLAR-1.[54] Utilities were by on/off tx (and tx dependent) and progression status
TA421[55]	Everolimus with exemestane	0.798	EAG scenarios using tx-specific values E+E: 0.7644; E: 0.7571	0.496, scenario using 0.65	EAG scenario with Lloyd 2006[56]
TA619 (since updated to TA836)[13]	Palbociclib with fulvestrant	Palbo+Ful: 0.74 (0.72 – 0.76); Placebo+Ful: 0.69 (0.67 – 0.72)	PALOMA-3[57]	0.56 (0.5-0.6)	Lloyd 2006[56]
TA579 (since updated to TA725)[10]	Abemaciclib with fulvestrant	NR	MONARCH-2[58]	0.505	Lloyd 2006[56] EAG scenarios using Mitra et al 2016 (0.67) and MONARCH-2[7]
TA593 (since updated to TA687)[14]	Ribociclib with fulvestrant	NR	MONALEESA-3[44]	NR	MONALEESA-3[44]
CAPItello-291 NICE submission ID6370	Capivasertib with fulvestrant	[redacted]		[redacted]	

Across those which reported values, the progression-free utility values are aligned across technology appraisals. In the progressed disease state, most published values utilise the vignette study conducted by Lloyd et al 2006.[56] The Company considers it inappropriate to use Lloyd et al in the base case for a number of reasons:

- It is not in line with the NICE reference case as it uses vignettes to describe the health states and the standard gamble technique to estimate the utility values;

- The use of vignettes derived from the general population have been found to estimate a larger impact of disease progression on utilities compared to utilities which have been collected (directly or indirectly) in patients with breast cancer;[59]

- The use of Lloyd et al would result in two different methods being used to estimate utilities in the PF state vs. PD state, i.e., EQ-5D-5L measured directly in advanced breast cancer patients vs. vignettes describing health states related with metastatic BC, valued by the general public using the standard gamble approach;

- Lloyd was published in 2006, and there have been advances in the treatment and management of breast cancer patients since this time period, making the health state vignettes described not reflective of current clinical practice. The Lloyd values were collected at time when death was often imminent. It is likely not reflective of utility now when even in the metastatic stage many patients live for a longer period of time maintaining improved quality of life to that reflected in Lloyd.

Therefore, the progressed disease value estimated using the EQ-5D data from CAPItello-291 was considered the most appropriate.

c. Please provide an updated economic model and scenario analyses informing HSUVs with those identified in TA421, TA619, and TA579:

i. Utilising absolute utility values for PF and PD health states separately from each trial.

A scenario has been provided using the values published in the TA421 submission. It is not appropriate to provide a scenario using TA619, as it only reports treatment-specific values in the progression-free health state, and the Lloyd et al 2006 value used in progressed disease (i.e., not a trial-derived value). It is also not possible to provide a scenario using TA579 as the submission does not report the value used in the progression-free health state.

It is important to note that TA421 did not use the quality-of-life data collected in the primary clinical trial informing the submission (BOLERO-2) but used adjusted values from Lloyd et al 2006[56] for progression-free and Launois et al. 1997[60] for progressed disease. This does not align to the NICE reference case. Furthermore, the evidence review group for TA295 (the original appraisal of everolimus with exemestane prior to TA421) noted that Launois et al 1997 provided utility values that were derived from a small sample size that was not representative of the general UK population. The committee for that appraisal noted that both Lloyd et al 2006 and Launois et al 1997 were subject to uncertainty.[55]

Given that the values used in TA421 were not the utility values from the BOLERO-2 trial and given the issues identified with Lloyd et al 2006 in the response to part b of this question, the Company believe it is not reasonable to provide a scenario using these values.

ii. Utilising PF utility from the CS base case and informing the PD decrement from TA421 (i.e., utility decrement of 0.302 from PF to PD HSUV).

The Company does not believe that this represents a reasonable scenario, particularly applied as an absolute decrement.

The PD utility in this scenario would be [redacted], which lacks clinical validity, is lower than Lloyd et al 2006 and the other appraisals in this area.

B 11. No AE disutilities were reported in the studies identified through the SLR. Utility decrements were informed by Hudgens (2016), metastatic breast cancer, Nafees et al. (2008), a study in non-small cell lung cancer, and Swinburn (2010), a study in metastatic renal cell carcinoma.

a. Please elaborate on why AE data collected in the CAPItello-291 study was not explored as a source of estimating AE disutilities (i.e., why collected AE data was not included in the MMRM to estimate AE utility decrements).

Utility data related to specific adverse events were not collected in the CAPItello-291 trial. Disutilities related to adverse events are not a driver of model results (as

demonstrated in the response to B11, part d), and thus there is a minimal impact in using disutilities from external sources.

b. Please provide an updated economic model and scenario analysis informing AE disutilities from data collected in the CAPItello-291 trial.

Utility data related to specific adverse events were not collected in the CAPItello-291 trial and so this has not been performed.

c. Please provide justification for assumptions made when selecting proxy AEs as a source of AE disutility (i.e., hyperglycaemia assumed the same as anaemia, stomatitis assumed the same as mucositis).

Given that the costs and disutilities associated with adverse events are not drivers in the model, it was considered a reasonable and pragmatic approach to assume values were equivalent across conditions when there was a lack of reporting, e.g. stomatitis and mucositis are both inflammatory conditions of the mouth.

d. Please discuss the validity of informing AE disutilities from studies by Hudgens (2016), Nafees et al. (2008), and Swinburn (2010), provided the differences in populations (i.e., metastatic breast cancer, non-small cell lung cancer, and metastatic renal cell carcinoma).

No utility data or AE durations were reported in the studies identified through the SLR of HRQoL and utilities (see Company Submission Appendix H). Utility decrements associated with AEs were instead informed by evidence from other oncology areas where available. Hudgens (2016) is in metastatic breast cancer,[59] which is closely aligned to the population for this appraisal. It also follows the approach used in a previous NICE appraisal in metastatic breast cancer (TA725).[10] This same appraisal uses Swinburn (2010)[61] when values from Hudgens (2016) were not available. Nafees (2008)[62] is a commonly used source across a number of oncology appraisals. There is also no strong rationale as to why the disutility associated with an adverse event in one oncology setting should differ from another.

The model is insensitive to AE durations as evidenced by testing two extremes presented in Table 44 below. Given that the costs and disutilities associated with

adverse events are not drivers in the model, it was considered a reasonable approach to assume values were equivalent across conditions when there was a lack of reporting.

Table 44 Testing adverse event duration impact in CEM

	ICER vs capivasertib plus fulvestrant (including x1.2 modifier)	
	Alpelisib plus fulvestrant	**Everolimus plus exemestane**
Company base case*	[redacted]	[redacted]
Setting all AE disutilities to 0	[redacted] (+0.29%)	[redacted] (+0.06%)
Multiplying each disutility by 10	[redacted] (-2.50%)	[redacted] (-0.55%)

*After revisions described at the beginning of Section B

Adverse Events

B 12. Durations of AEs were informed by TA306 (non-Hodgkin lymphoma). None of the sourced durations, with the exception of anaemia, corresponded to the AE to which they were applied. That is, a duration of: 6.0 days (nausea) was used to inform diarrhoea in the model; 4.0 days (mucosal inflammation) was used to inform rash maculo-papular in the model; 3.0 days (mucosal inflammation) was used to inform rash in the model; 16.1 days (anaemia) was used to inform hyperglycaemia in the model, and; 4.0 days (mucosal inflammation) was used to inform stomatitis in the model, as per CS Table 25.

a. CS table 25 suggests that duration for mucosal inflammation in TA306 was used to inform rash macular-papular (4.0 days), rash (3.0 days), and stomatitis (4.0 days). Please clarify why there is a discrepancy in the duration for rash, compared with the durations for rash-papular and stomatitis (3.0 vs 4.0 days), provided that they were sourced from the same AE duration in TA306.

There was an error in the value used for rash in the model. The duration of mucosal inflammation in TA306 was 4 days. This has now been corrected in the model (updating the rash duration from 3 days to 4 days). The impact on the deterministic results is shown in Table 45. The impact on the ICER for both pairwise comparisons is less than 0.01%.

Note that these results also include the correction outlined at the beginning of Section B.

Table 45 Updated deterministic pairwise base-case results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Pairwise ICER of capivasertib plus fulvestrant versus comparator (£/QALY)	Pairwise ICER of capivasertib plus fulvestrant versus comparator (£/QALY) with 1.2 QALY weighting
Capivasertib + fulvestrant	[redacted]	2.40				
Alpelisib + fulvestrant	£51,365	1.79	[redacted]	0.61	[redacted]	[redacted]
Everolimus + exemestane	£25,714	1.45	[redacted]	0.94	[redacted]	[redacted]

*after other revisions described at the beginning of Section B

b. Please clarify whether data regarding AE durations was collected in the CAPItello-291 trial. If available, please provide justification for not utilising durations of AEs collected in the trial and provide an overview of these durations.

Data on adverse event durations were not collected in the CAPItello-291 trial.

c. Please provide justification as to the plausibility of the chosen proxy AEs used to inform durations.

Adverse event durations were taken from TA306 because they were not collected in CAPItello-291 and because this is aligned with other recent appraisals in this disease area (TA725).

The model is insensitive to AE durations as evidenced by testing two extremes presented in Table 44 above (the impact of multiplying adverse event durations by 10 had the same impact as multiplying the disutilites by 10).

B 13. AEs were modelled if they were ≥ grade 3 and observed in ≥ 5% of patients in the CAPItello-291 or in any of the studies informing comparator efficacy. Further, CS Section B.2.10 suggests that there is no reason to suspect deviations between those that have received prior CDK 4/6 inhibitor therapy and those that

have not, in terms of AEs. As such, AEs were informed by the PI3K/AKT-altered pathway population, irrespective of prior CDK 4/6 inhibitor therapy status.

a. Please provide a justification and empirical support for the chosen cut-offs for inclusion.

The approach used in the Company base case has captured all adverse events that have the potential to have an impact on costs and utility in the model. Costs and disutility for grade 1-2 adverse events are negligible and are often associated with low-to-no cost. Inclusion of grade ≥3 utilities is a commonly accepted approach in NICE technology appraisals. [2–4,10,13,14] Similarly, using a ≥ 5% is a commonly used cut-off in appraisals.[4,10,14]

b. For the CAPItello-291 trial, please provide an overview of the incidence rates for all AEs recorded in the capivasertib plus fulvestrant arm, separated by grade. Please provide this for both the utilised population (PI3K/AKT-altered population) and the PI3K/AKT-altered population with prior CDK 4/6 inhibitor therapy.

Appendix IV contains an overview of incidence rates for grade ≥3 AEs recorded in CAPItello-291, by system organ class (Table 64) and by preferred term (Table 65). Data for both the PI3K/AKT-altered population as well as PI3K/AKT-altered population with prior CDK4/6i use is presented as requested. Grade ≥3 AE frequency in patients with prior CDK4/6i use is in alignment with the overall PI3K/AKT altered population, with no notable deviations in observed frequencies. This also complements the AE data presented in Section B.2.10.3 of Document B.

Data by AE grade is not available and therefore cannot be provided in response to this clarification question. Therefore, incidence rates for grade ≥3 AEs are provided, with no cut-off by observed patient numbers applied. We believe this approach provides a comprehensive overview of severe, life-threatening or disabling, and death-related AEs captured in the CAPItello-291 trial. Presenting the safety data by individual AE grade is not anticipated to be informative for the CE model beyond what has been provided.

Costs and resource use

B 14: Priority question: Mean relative dose intensity (RDI) was modelled for capivasertib ([redacted]) plus fulvestrant ([redacted]) and everolimus (79%) plus exemestane (98%) to account for delayed and/or reduced doses. For alpelisib plus fulvestrant a 100% RDI was assumed as only the median RDI (82.7%) was available (explored in a scenario analysis).

a) Please justify why modelling the median RDI for alpelisib plus fulvestrant was deemed unsuitable for the company base-case analysis.

Means and medians are not the same, and this difference is greater if the data is skewed. The mean value is typically used for RDI in economic analyses rather than the median due to this skew. The mean value was not publicly available for alpelisib plus fulvestrant. While only the median RDI is publicly available for alpelisib,[20] in their submission to NICE TA816, the company used mean RDI.[8] Median RDI was not tested by the Company or the EAG in this appraisal.

b) Please provide an updated economic model and scenario analysis also using the median RDI for capivasertib plus fulvestrant.

As the median is not appropriate to use for RDI, the Company has provided a scenario analysis whereby the mean RDI for capivasertib plus fulvestrant has been used for alpelisib plus fulvestrant in Table 46.

Table 46 Impact of using median RDI versus mean RDI on the ICER for capivasertib plus fulvestrant vs alpelisib plus fulvestrant

Scenario	RDI for Capivasertib plus fulvestrant (Capivasertib/fulvestrant)	RDI for Alpelisib plus fulvestrant (Alpelisib/fulvestrant	ICER*
Company base case using means	[redacted]	100%	[redacted]
Scenario using same mean RDI in both arms	[redacted]	[redacted]	[redacted]

*After revisions described at the beginning of Section B

B 15: Priority question: Patients experiencing disease progression in the economic model were assumed to receive subsequent treatments. According to the company, the proportion of patients receiving subsequent treatments and the distribution of subsequent treatments received were not

reflective of UK clinical practice. Therefore, a series of interviews were conducted with 6 UK clinical experts to obtain the types of subsequent treatments received in practice and the distribution according to second-line treatment received for HR+/HER2- advanced or metastatic breast cancer. A weighted average cost of these subsequent treatments was calculated and the applied as a one-off treatment cost on progression.

a) **The CS stated that "*the proportion receiving subsequent treatments and the types of subsequent treatments received was consistent across arms and thus there is low risk of bias on the OS results*". For capivasertib plus fulvestrant, alpelisib plus fulvestrant, and everolimus plus exemestane, please provide an overview of all (types of) subsequent treatments and the proportions of patients that received these treatments in the corresponding clinical trials.**

This statement in the Company Submission (Section B.3.5.2.) is in reference to the CAPItello-291 trial only. The statement in full is: *"In the CAPItello-291 trial [redacted] of patients received post discontinuation disease-related anticancer therapy in the PI3K/AKT pathway-altered population. The proportion receiving subsequent treatments and the types of subsequent treatments received was consistent across arms and thus there is low risk of bias on the OS results."*

Please note: the original percentage from CAPItello-291 quoted above ([redacted]) was based on an initial analysis where certain drugs started were excluded during the safety follow-up window. As such, an erratum was submitted as part of the CSR with all subsequent treatments included. The distribution of subsequent treatments from CAPItello-291 provided in Table 47 below is based on an erratum to the CSR.

The distribution of subsequent treatments in BOLERO-2 and SOLAR-1 is not expected to bias the OS results, unless there is an imbalance between treatment arms *within* each study, given the fact that the HR calculated from the NMA are used in the CEM, rather than the absolute OS results from these studies. There was not judged to be an imbalance in the subsequent treatments received between arms within the BOLERO-2 and SOLAR-1 studies.

Regardless, the subsequent treatments received in each trial is provided in Table 47. There are differences in the data reported for each study which can make comparisons difficult:

- Data available for CAPItello-291 is that related to the PI3K/AKT-pathway altered population, of which 72.9% received previous treatment with a CDK4/6i prior to study entry. The numbers in the table reflect the fact that patients may have had more than 1 cancer therapy;
- Data for SOLAR-1 is that related to the PIK3CA cohort, of which 5% of patients had received previous treatment with a CDK4/6i. The numbers in the table are for the first new antineoplastic medication after discontinuation of study treatment only;
- Data for BOLERO-2 is related to the ITT population, of which no patients received previous treatment with a CDK4/6i. Treatment may have been received as first post-study anticancer therapy (data collected for all patients unless they were lost to follow-up or withdrew consent), or as subsequent therapies (data available for a subset of patients).

Ultimately, treatment practice has changed since these trials were conducted, and the numbers included in Table 47 do not reflect current UK clinical practice. However, common across all three trials is that most subsequent therapies consist of chemotherapy and/or hormonal therapy.

Table 47 Distribution of subsequent treatments received in the active treatment arms of CAPItello-291, SOLAR-1 and BOLERO-2

	CAPItello-291 (capivasertib plus fulvestrant arm; PI3K/AKT altered population, N= 155)[7]	SOLAR-1 (alpelisib plus fulvestrant arm, PIK3CA mutated population, N= 169)[53]	BOLERO-2 (everolimus plus exemestane arm, N=485)[63]
Patients starting subsequent medication	[redacted]	116 (68.6%)	84%
Of those that received subsequent therapy:			
Chemotherapy	[redacted]	38 + 20 (50.0%)*	45%**
Hormonal therapy	[redacted]	20 + 37 (49.1%)*	39.5%**

Immunotherapy	[redacted]	NR	<1%
Targeted therapy	[redacted]	Targeted therapy alone: 1 (<1%)	8.4%
CDK4/6i		17 (11.5%)	NR
Everolimus		20 (17.2%)	NR
Radiation therapy	NR	NR	7.6%

*includes chemotherapy or hormonal therapy in combination with 'other'
**BOLERO-2 does not report sample sizes; these values were calculated by multiplying the proportion who received subsequent medication by the proportion in the total population who received each subsequent medication.

b) For capivasertib plus fulvestrant, alpelisib plus fulvestrant, and everolimus plus exemestane, please comment on how the modelled types of subsequent treatments and proportions of patients (as shown in CS Table 29) compare to the types of subsequent treatments and proportions of patients that received these treatments from the clinical trials.

The absolute overall survival data is not used from the comparator trials, only the relative effects, which is incorporated into the model through the NMA in the form of hazard ratios. As the distribution of subsequent treatments received across arms within CAPItello-291,[7] SOLAR-1[53] and BOLERO-2[63] trials is considered balanced, this is expected to not have an impact on the estimates of relative overall survival.

A comparison of the distribution of subsequent therapies across trials is provided in response to question B15 part a).

The model is intended to capture all subsequent treatments received, beyond third line and over the lifetime of the patient which can extend beyond the duration of a clinical trial. In the model, 81% of patients entering the progressed disease health state receive a subsequent treatment. Of this 81%, 159.1% receive a chemotherapy and 18.5% - 22.8% receive a hormonal therapy (including in combination with a targeted therapy). These numbers were attained through a clinical validation exercise with UK clinicians. As demonstrated in the response to Question B15 part d, subsequent therapies are not a key driver of results in the CEM.

c) **For capivasertib plus fulvestrant, alpelisib plus fulvestrant, and everolimus plus exemestane, please provide an updated economic model and scenario analysis modelling the types of subsequent treatments and proportions of patients according to what was observed in the corresponding clinical trials.**

Given that treatment practice has changed since the initiation of these trials and does not reflect current UK clinical practice, this is considered inappropriate.

As explained in the response to part a and b, the absolute overall survival data is not used from SOLAR-1 or BOLERO-2, only the relative effects, which is incorporated into the model through the NMA in the form of hazard ratios. Given that subsequent treatments are balanced between treatment arms within these trials, there was judged to be a low risk of bias on the OS hazard ratio from these trials. In the CAPItello-291 trial the proportion receiving subsequent treatments and the types of subsequent treatments received was also consistent across arms and thus there is low risk of bias on the OS results.

As demonstrated in the response to Question B15 part d, subsequent therapies are not a key driver of results in the CEM, and this scenario is anticipated to have limited impact on the results.

d) **Responses of the clinicians regarding the proportions of patients that would receive each subsequent treatment were heterogeneous (e.g. doxorubicin ([redacted]), eribulin ([redacted]), paclitaxel ([redacted]) and vinorelbine ([redacted])). Please provide an updated economic model and scenario analyses exploring the lower and upper ranges of the clinician responses regarding the proportions of patients receiving each subsequent treatment.**

The ranges provided in this question were tested in the model. These result in non-significant changes to the ICER as presented in Table 48.

Table 48 Scenarios testing subsequent therapy distributions

	ICER vs Alpelisib + fulvestrant*	ICER vs Everolimus + exemestane*
Base	[redacted]	[redacted]
Doxorubicin: 0 – 10%	[redacted]	[redacted]

Eribulin: 10 - 80%	[redacted]	[redacted]
Paclitaxel: 20-50%	[redacted]	[redacted]
Vinorelbine: 5-60%	[redacted]	[redacted]

*after revisions described at the beginning of Section B
Abbreviations: Alp+ful, alpelisib plus fulvestrant; E+E, everolimus plus exemestane

B 16. Priority question: Next-generation sequencing (NGS) will be conducted prior to initiating treatment with capivasertib plus fulvestrant, to confirm the PIK3CA/AKT1/PTEN alteration status. It is stated in the CS that testing for PIK3CA mutations is already commonly performed and testing for AKT1 and PEN alteration status is requested.

a) Please provide evidence to support your statement that testing for PIK3CA is common, more specifically provide evidence on the proportion of patients in the eligible population that is currently tested for PIK3CA alteration status.

The NHS Strategy for embedding genomic medicine in the NHS which commenced in 2022 has four priority areas, with the ambition of accelerating the use of genomic medicine across the NHS, providing a world leading, equitable service to populations and individuals:

- Embedding genomics across the NHS, through a world leading innovative service model from primary and community care through to specialist and tertiary care.
- Delivering equitable genomic testing for improved outcomes in cancer, rare, inherited and common diseases and in enabling precision medicine and reducing adverse drug reactions.
- Enabling genomics to be at the forefront of the data and digital revolution, ensuring genomic data can be interpreted and informed by other diagnostic and clinical data.
- Evolving the service through cutting-edge science, research and innovation to ensure that patients can benefit from rapid implementation of advances.

Alpelisib plus fulvestrant is a therapy which is recommended by NICE for patients with confirmed PIK3CA mutations (TA816)[8]. As a result of this recommendation,

PIK3CA has been added to the National Genomic Test Directory under test code M3.6. This allows routine NHS-funded testing of all eligible patients for PIK3CA alterations via filling in a Whole Genome Sequencing (WGS) Test Request Form. Based on clinician feedback, the vast majority of consultants test all their patients with HR+/HER2- breast cancer who are potentially eligible for alpelisib, and for whom the benefits of second line treatment with such a combination therapy is anticipated to outweigh risks in terms of toxicity. Therefore, following the addition of PIK3CA to the National Genomic Test directory, testing for PIK3CA mutations in the NHS has now become common. There is no published data available on the exact proportion of patients with advanced HR+/HER2- breast cancer who are tested for PI3K/AKT pathway alterations in the UK via the National Genomic Test Directory route; however, given alpelisib plus fulvestrant is an established treatment option and testing is required for access, it can be inferred that testing for PIK3CA mutations is a common clinical practice.

b) **As testing for AKT1 and PEN alteration status is currently not common, please provide the base case results as well as all sensitivity and scenario analysis including the costs of genomic testing.**

The Final Appraisal Determination Document for TA816 stated that “genomic testing for PIK3CA mutation is now included in the National Genomic Test Directory and so should be funded in the NHS”.[8] The committee for TA816 also noted that, while PIK3CA mutation testing had not been routinely available prior to the appraisal, this situation is changing and PIK3CA mutation status will soon be routinely identified in clinical practice, as targeted treatment options for identifiable mutations are valued by people with advanced breast cancer and clinicians. As stated in the CS, due to the advanced technical capabilities of NGS panels used in the NHS setting, AKT1 and PTEN alteration testing is typically already included in the panel kits such as Trusight Oncology 500; the data can be unmasked for analysis when requested by the consultant, when those two PI3K/AKT pathway alterations are included in the national genomic test directory.

[redacted]

[redacted]

The Company have provided a scenario with testing costs applied to the capivasertib plus fulvestrant and alpelisib plus fulvestrant arms in the model. As this is a scenario analysis itself it was not considered necessary to provide all sensitivity and scenario analysis with this cost applied also.

The total testing cost per eligible patient was calculated based on the data in Table 49.

Table 49: Testing costs used in the model

Parameter	Value	Reference
Proportion of PIK3CA/AKT1/PTEN - altered tumour tissue	40.8%	CAPItello-291 data: The overall proportion of patients with PIK3CA/AKT1/PTEN alterations detected in their tumour samples (i.e., the Altered Population) was 40.8% (289 of 708 patients) - Table 20, CAPItello-291 CSR[30]
Number of patients needed to test to identify one eligible patient	2.45	Calculation: 1/0.408
Cost of NGS	£487.10	Hamblin, et al (2017)[64]: NGS cost inflated to the latest 2024 prices using the ONS CPI INDEX 06.3 : HOSPITAL SERVICES[65]
Total testing cost per eligible patient	£1,193.31	-

Abbreviations: CPI: Consumer price inflation, NGS: Next generation sequencing

The ICERs for this scenario are presented in Table 50. The inclusion of testing costs has minimal impact on the estimated ICER.

Table 50 Scenario including testing costs: Deterministic pairwise results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Pairwise ICER of capivasertib plus fulvestrant versus comparator (£/QALY)	Pairwise ICER of capivasertib plus fulvestrant versus comparator (£/QALY) with 1.2 QALY weighting
Capivasertib + fulvestrant	[redacted]	2.40				
Alpelisib + fulvestrant	£52,559	1.79	[redacted]	0.61	[redacted]	[redacted]

Everolimus + exemestane	£25,714	1.45	[redacted]	0.94	[redacted]	[redacted]

*after other revisions described at the beginning of Section B

B 17. CS Table 35 reports resource use related to monitoring and imaging by health state and treatment.

a) Please provide details of the source(s) used to inform the resource use in Table 35.

Resource use related to the follow-up and monitoring of patients in the progression-free and progressed health states were based on recommendations in NICE CG81,[66] previous NICE technology appraisals in this setting[8] and validated with 6 UK clinicians in series of 1-to-1 interviews.[7] Values were averaged across clinician responses.

b) Where resource use differs between treatment options, please provide a justification.

Differences between treatments was driven by feedback from clinicians and their experience managing patients on these treatments, particularly monitoring for the potential adverse events associated with alpelisib plus fulvestrant and everolimus plus exemestane. For example, the general trend observed towards increased fasting plasma glucose and HbA1c monitoring with alpelisib plus fulvestrant is due to the high rates of hyperglycemia observed with this regimen.[53] Similarly, increased rates of complete blood count monitoring with everolimus plus exemestane can be attributed to commonly observed decreased haemoglobin, lymphocytes, neutrophils and platelets with everolimus, which led to a recommendation for blood count monitoring for patients on the regimen.[67]

The Company submission included a scenario analysis which tests the impact of setting the frequency of resource use related to monitoring and imaging to be the same across treatments in the progression free health state. This showed a very minor difference in the ICER, and has been included in Table 51 below, including the revisions described at the beginning of Section B.

Table 51 Scenario setting all PFS monitoring and imaging resource use equal across all arms

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Pairwise ICER of capivasertib plus fulvestrant versus comparator (£/QALY)*	Pairwise ICER of capivasertib plus fulvestrant versus comparator (£/QALY) with 1.2 QALY weighting*
Capivasertib + fulvestrant	[redacted]	2.40				
Alpelisib + fulvestrant	£51,361	1.79	[redacted]	0.61	[redacted]	[redacted]
Everolimus + exemestane	£25,726	1.45	[redacted]	0.94	[redacted]	[redacted]

*after other revisions described at the beginning of Section B

Severity and uncertainty

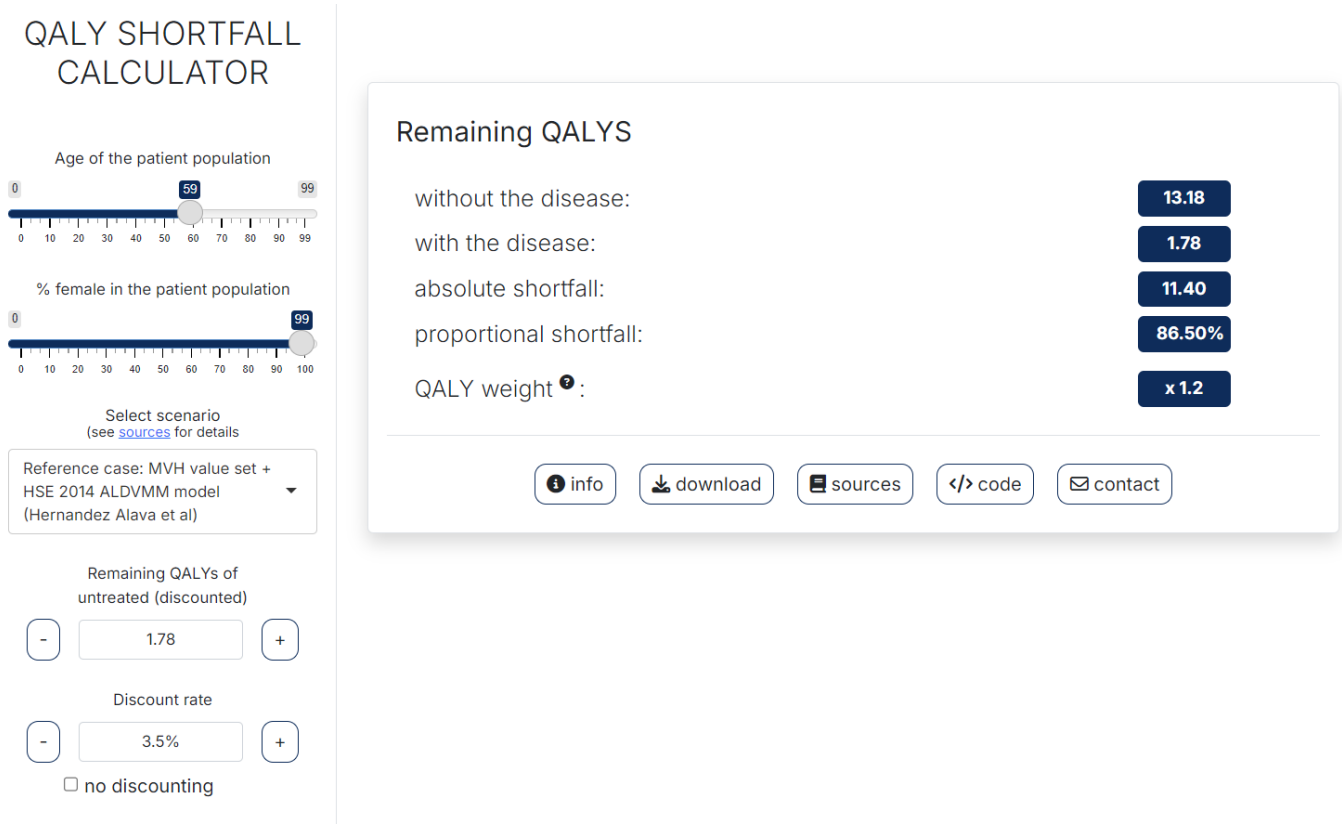
B 18. Priority Question: Absolute and proportional QALY shortfall were calculated within the economic model. The EAG were unable to reproduce the presented results utilising the QALY shortfall calculator (Schneider et al., 2021: https://shiny.york.ac.uk/shortfall/#) and inputs provided in CS Tables 40 and 41.

a. Please utilise the QALY shortfall calculator by Schneider et al. (2021) to calculate absolute and proportional QALY shortfall and ensure that results from the QALY shortfall calculator are replicable in the model calculation for absolute and proportional shortfall.

Absolute and proportional QALY shortfall calculations were provided in the model. This has the benefit of using the most up-to-date mortality data. Other minor differences in calculations may have existed between the two calculators, but this has not been extensively explored.

The calculations for the absolute and proportional QALY shortfall have also been explored with the Schneider et al. (2021) tool. Using this tool the x1.2 modifier is still met across all value sets. A screenshot of the output from the tool has been provided in Figure 37 showing the age and gender settings, using the discounted QALYs from the alpelisib plus fulvestrant arm.

Figure 37 Schneider severity modifier calculator output for comparison to alpelisib plus fulvestrant



The model has now replaced the QALYs calculated 'without the disease' with 13.18 as calculated in the Schneider tool.

b. **A severity modifier weight of x1.2 was calculated for both comparator arms. However, the severity weight may vary depending on uncertainty in the results (i.e. total modelled QALY gains in the comparator arms). Please calculate the severity weight for each PSA iteration and report on the percentage of simulations with a 1.0x, 1.2x and 1.7x severity weight for all comparators.**

NICE does not require the severity weight to be calculated probabilistically.

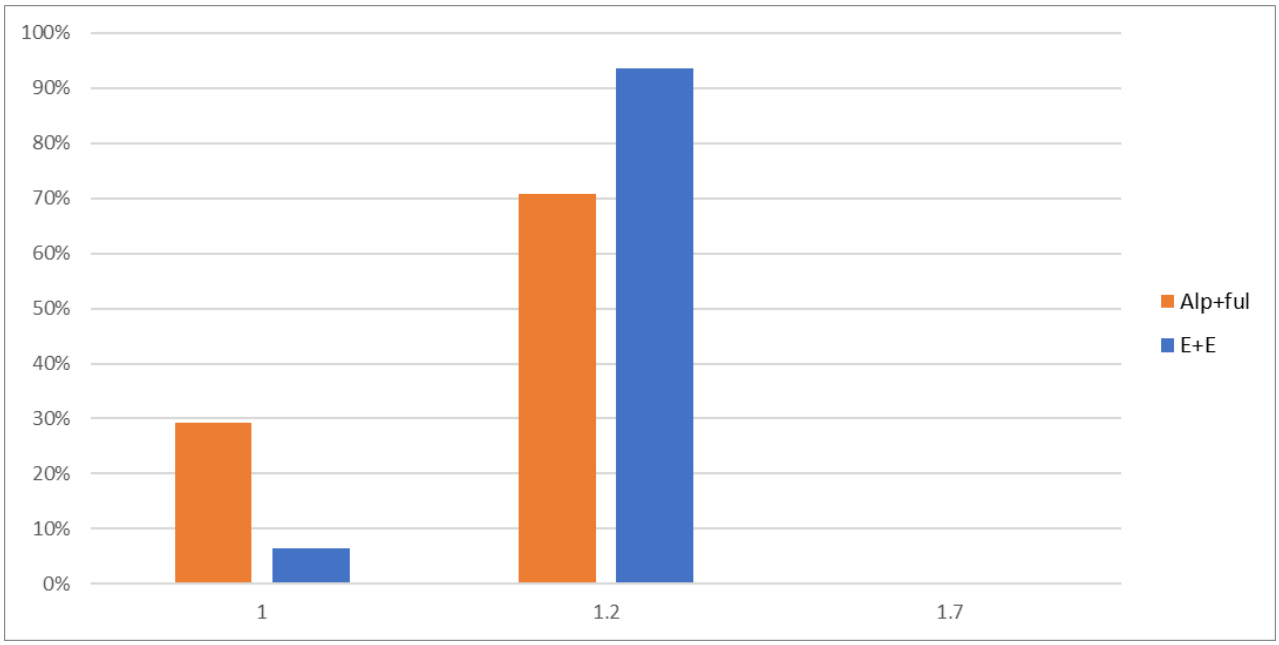
This request has been performed using the Schneider calculator for the severity modifier- i.e., the Schneider tool calculated the expected QALYs without the disease

to be 13.18 as shown in Figure 37, and the severity weight for each PSA iteration has been calculated based on this.

Figure 38 reports the distribution of the severity weight across the PSA iterations, showing that 94% of the simulations qualify for the x1.2 weight in the comparison to everolimus plus exemestane and 71% of the simulations qualify for the x1.2 weight in the comparison to alpelisib plus fulvestrant.

As Question B21 asks for a version of the CEM with a fixed seed for the PSA, the PSA has been rerun in the updated Company model and this distribution is based on this updated PSA.

Figure 38 Distribution of severity weight in the PSA



Results

B 19. Priority Question: Considering the CS base-case results.

a. Please provide a comparison of the observed OS as well as PFS (e.g. using restricted mean survival time; RMST), and the undiscounted life years (LYs) as well as undiscounted progression free LYs (estimated in the model) by filling out the Table below using different periods/truncation points (with justification) to calculate the RMST.

In the clarification questions meeting the EAG advised that the table originally provided was only for guidance, and that the Company could provide their own table.

The trial with the shortest follow-up was used for the cut-off points to calculate the RMST for the comparison to the observed data. This was 24.1 months for OS and 19.5 months for PFS (the maximum follow-up time for the capivasertib plus fulvestrant arm from the CAPItello-291 trial).

Observed RMST for BOLERO-2 and SOLAR-1 was calculated in R using the survival package,[68] after digitizing the data the from the published Kaplan-Meier curves using the Guyot algorithm.[69]

The observed RMST and modelled RMST are provided in Table 52.

Table 52 Comparison of observed vs. modelled RMST

	Endpoint	Observed RMST (months)	Modelled RMST (months) over same timeframe
Capivasertib plus fulvestrant (PI3K/AKT+prior CDK4/6i pop from CAPItello-291)	OS	[redacted]	[redacted]
	PFS	[redacted]	[redacted]
Everolimus plus exemestane (BOLERO-2)	OS	19.8	16.2
	PFS	9.5	6.3
Alpelisib plus fulvestrant (SOLAR-1)	OS	20.7	17.5
	PFS	11.5	6.3

Importantly, Table 52 above shows that the observed and modelled RMST for capivasertib plus fulvestrant from CAPItello-291 are aligned. Values observed in BOLERO-2 and SOLAR-1 are different from the model-calculated RMST, but this is expected given that these trials are in prognostically different patient populations to the one modelled (i.e., not in post-CDK4/6i patients, with post-CDK4/6i patients having markedly prognostically worse outcomes). Furthermore, all comparator survival data in the model is informed by the NMA, which is based on synthesized data from multiple studies beyond CAPItello-291, BOLERO-2 and SOLAR-1. It is therefore unlikely to be reflective of the standalone pivotal trial output of each individual trial and the comparison provided in Table 52 is uninformative.

The lifetime modelled RMST and undiscounted LYs are presented in Table 53. It is not feasible to informatively comment on whether the incremental gain in RMST of capivasertib plus fulvestrant compared to alpelisib plus fulvestrant and everolimus

plus exemestane beyond the observed period for both PFS or OS is clinically plausible based on the comparison between the observed RMST (Table 52) and modelled and extrapolated RMST (Table 53). However, the long-term RMST gain beyond the observed period for all of the trials is realistic when considering longer-term survival data in HR+ mBC and the fact that an increasing number of patients with mBC survive for >8 years.[70] The NMA results indicate that capivasertib plus fulvestrant is associated with numerically improved OS and PFS compared to all other comparators, and therefore it is expected that this would translate into a larger RMST proportion gained beyond the observed data for CAPItello-291 compared to the extrapolated data for alpelisib plus fulvestrant and everolimus plus exemestane. The observation holds across both the Company base case NMA and the time-varying analysis provided in response to Question A17.

Table 53 RMST over model time horizon and undiscounted LY breakdown

	Capivasertib plus fulvestrant	Alpelisib plus fulvestrant	Everolimus plus exemestane
Undiscounted PF LY (months)	[redacted]	[redacted]	[redacted]
Undiscounted PD LY (months)	[redacted]	[redacted]	[redacted]
Undiscounted LY (months)	[redacted]	[redacted]	[redacted]
Modelled RMST – lifetime (PFS)	[redacted]	[redacted]	[redacted]
Modelled RMST – lifetime (OS)	[redacted]	[redacted]	[redacted]

b. Please elaborate on the plausibility of the differences between observed and modelled outcomes (proportion accumulated beyond observed data) for:

i. Capivasertib + fulvestrant

ii. Alepelisib + fulvestrant

iii. Everolimus + exemestane

iv. The increment

The NMA results indicate that capivasertib plus fulvestrant is associated with improved OS and PFS compared to all other comparators, and therefore it is

expected that this would translate into an incremental benefit compared to alpelisib plus fulvestrant and everolimus plus exemestane in the model. The observation holds across both the Company base case NMA and the time-varying analysis provided in response to Question A17. It also means that the proportion of the benefit accumulated beyond the observed data is expected to be greater given the improved OS and PFS.

Observed absolute outcomes from BOLERO-2 and SOLAR-1 should not be compared to the model-predicted outcomes for the reasons outlined in part a.

c. **Regarding the model estimated differences between the intervention and the comparators (in terms of PFS, LYs and quality-adjusted life years (QALYs)); please provide an explanation of the mechanism by which the model generated these differences as well as a justification for why they are plausible based upon available evidence (NICE DSU TSD 19 recommendation 13).**

A tabulation in terms of PFS, LYs and QALYs was provided by the Company in the submission, which is aligned with recommendation 13 in the NICE DSU TSD 19. This is provided in Table 54.

Table 54 Comparison of LYs and QALYs accrued in the CEM

	Capivasertib plus fulvestrant	Alpelisib plus fulvestrant	Everolimus plus exemestane
Total LY	3.25	2.41	1.96
Progression-free (LY)	0.95	0.61	0.61
Progressed disease (LY)	2.30	1.80	1.34
Total QALYs	2.40	1.78	1.45
Progression-free (QALY)	0.73	0.47	0.47
Progressed disease (QALY)	1.66	1.31	0.98

A clinical validation exercise confirmed that the extrapolations used for capivasertib plus fulvestrant could be considered plausible. The results of both the original NMA and the time-varying NMA report that capivasertib plus fulvestrant is associated with numerically improved OS and PFS compared to everolimus plus exemestane and alpelisib plus fulvestrant. The model applies the HRs from the NMA to the placebo plus fulvestrant curve in the model for all comparators, and so given the finding in the

NMA, the fact that the model predicts greater LY and QALY gains in the progression free and progressed disease states for capivasertib plus fulvestrant is aligned with expectations.

B 20. Priority question: CS Appendix J Table 16 provides the clinical outcomes in the informing trials for each comparator, as compared with the respective model results. Particularly for alpelisib plus fulvestrant, the modelled median PFS and OS are significantly lower than the median PFS and OS derived from the clinical trial. The company highlight that the discrepancy between trial and model results for OS and PFS are expected, given the cross-trial differences in prognostic factors for SOLAR-1 and BOLERO-2.

a. **For each modelled treatment (capivasertib plus fulvestrant, alpelisib plus fulvestrant, everolimus plus exemestane), please discuss the discrepancy between modelled vs trial OS and PFS, highlighting all relevant (potential) prognostic and treatment effect modifiers (given in Appendix D Table 7) that differ between the trial and modelled populations. Please comment on the expected influence for each factor on the modelled vs trial clinical outcomes.**

b. **Provided the given response to part a., please elaborate on the validity of discrepancies in trial vs modelled OS and PFS as presented in CS Appendix J Table 16.**

As touched on in the Company response to A18 and B19 in particular, it is not expected that the modelled outcomes would align with the absolute values reported in the BOLERO-2 and SOLAR-1 trials.

The response to A18 outlines all known prognostic factors and treatment effect modifiers in this patient population, and their anticipated impact on the NMA and CEM. The decision problem and the CEM is in the following population: adults with HR+/HER2- advanced and metastatic breast cancer with PI3K/AKT pathway-altered tumours (PIK3CA, AKT1, or PTEN), whose disease has progressed on or following CDK4/6i plus endocrine therapy. Data from the CAPItello-291 trial which relates to this patient population is used in the CEM. The modelled outcomes are generated by

applying the HR calculated in the NMA to the fulvestrant plus placebo arm from the CAPItello-291 trial for this population. The BOLERO-2 and SOLAR-1 trials have prognostically different patient populations to CAPItello-291, one key prognostic difference being prior treatment with a CDK4/6i. Populations in which patients had received prior CDK4/6i were identified to have worse absolute outcomes compared to those that had not received a prior CDK/46i in CAPItello-291 (event rates consistently higher in the prior CDK4/6i population), in a real-world evidence study reporting on PFS,[36] and in the NICE appraisal for alpelisib plus fulvestrant.[8] Whilst prior CDK4/6i use was associated with a worse prognosis, it was not found to be a treatment effect modifier (see Table 17). This means that cross-trial differences should not bias the outcome of an NMA. Therefore, outcomes from CAPItello-291, BOLERO-2 and SOLAR-1 can be synthesised and compared in an NMA, but their absolute outcomes (e.g., median OS and median PFS) should not be compared naively as trials with higher levels of prior CDK4/6i use (i.e., CAPItello-291) are likely to report worse absolute outcomes than those with little to no prior CDK4/6i use (i.e., BOLERO-2 and SOLAR-1). PI3K/AKT pathway alteration was also identified as a potential prognostic factor and is also known to be a treatment effect modifier for capivasertib plus fulvestrant, and the extent to which this impacts the comparison to the absolute outcomes from BOLERO-2 is unknown. Furthermore, an NMA synthesises data from multiple studies beyond CAPItello-291, BOLERO-2 and SOLAR-1, and the results HR applied to the fulvestrant plus placebo extrapolation in the model is unlikely to be reflective of the standalone pivotal trial output of each individual trial.

Sensitivity and scenario analyses

B 21. Within the economic model, a random seed is included for the probabilistic sensitivity analysis (PSA). For the reproducibility of PSA results, please provide an updated economic model with a fixed seed functionality.

This has been provided in the updated Company model.

Validation

B 22. As per CS section B.3.14.4., the model was reviewed by health economists not involved in the model development. Please provide a clear overview of the tests performed by the reviewers, as well as the outcomes of these tests.

The quality-check included a detailed review of all result calculations, and testing the model across various scenarios and settings options. A series of tests and checks were conducted on the model engine.

- Confirmed that model inputs were correctly linked to the engine.
- Checked cells with “IF logic”, confirming that the statements provided the correct value for each condition.
- Traced links between the calculation sheets and results sheet to make sure that the proper outputs were displayed in the correct location.
- Searched for common Microsoft Excel® errors (e.g., #REF errors, unused named ranges, broken links, links to external workbooks, copy/paste errors).
- Checked text and formatting to ensure that there were minimal typographical errors or formatting irregularities.
- Checked unused ranges or formulas and hidden sheets.
- An extreme-value sensitivity analysis was also conducted on many model inputs. While conducting the analysis, the validator noted the direction and magnitude of change for each extreme value tested and confirmed that this aligned with the expected result (e.g., if all drug cost inputs are set to 0, the model should output total drug costs of 0 as well).

Any issues identified in the review were provided to the model builder, which were subsequently addressed prior to submitting to NICE.

The TECH-VER checklist was also guided the quality control process, as explained in the response to question B23.

B 23. Priority question: Please complete the TECH-VER checklist (Büyükkaramikli et al. 2019, https://pubmed.ncbi.nlm.nih.gov/31705406/) and provide the results.

e) Bx. Further external validation of modelled effectiveness would be desirable. Please assess the validity of model outcomes by comparing them with:

a. Evidence used to develop the economic model (e.g., the pivotal trial)

b. Evidence not used to develop the economic model (e.g., registry data)

f) Bx. For all relevant NICE TAs focussed on similar, potentially relevant, diseases, please provide cross-validations and elaborate on the differences regarding:

a. Model structure and assumptions

b. Input parameters related to:

   i. Clinical effectiveness

   ii. Health state utility values

   iii. Resource use and costs

c. Estimated (disaggregated) outcomes per comparator/intervention

   i. Life years

   ii. QALYs

   iii. Costs

The model was reviewed for coding errors, inconsistencies, and the plausibility of model inputs and assumptions using a comprehensive checklist. The TECH-VER checklist guided the quality control process, which, among others checks, included extreme value analysis and tracing of calculations. The TECH-VER checklist consists of five verification stages:

- Model input (pre-analysis) calculations

- Event/state calculations
- Result calculations
- Uncertainty analysis calculations
- Overall validation/other supplementary checks

The pre-analysis checks were performed via double-programming and/or independent quality checks of the survival, network meta-analysis and utility inputs. The clinical inputs were cross checked against the output from R.

The implementation of the model, as per stages 2-4 of the checklist, was assessed using black-box, white-box and replicated based tests.

- Black-box testing: This involves checking if the related model calculations show results in line with a priori expectations, not only for plausible parameter inputs but also for extreme value parameters or probabilistic inputs.
- White-box testing: This involves checking the detailed model calculations that are being inspected, such as by going through the related code carefully, line by line, or by scrutinizing the formulae in all related ranges in a spreadsheet, cell by cell.
- Replication-based tests: These involve replication efforts of the calculations being inspected. The reviewer will try to replicate/re-perform the calculations using the same or different software (or even by pen and paper, if possible).

A summary of the black-box tests are shown below (tests that are not applicable to the model were omitted). White-box testing was performed through visual inspection of the appendix trace sheet, which contains all the models cost, QALY and LY calculations.

To validate the survival projections in the model, a replication-based test was performed by independently estimating the survival functions of one arm in a separate Excel file using an alternative calculation method. The mean survival in the

model, after removing lifetable adjustments, was also validated against the restricted mean survival of key functions (log-normal and log-logistic) in R.

Other supplementary checks were performed to identify issues with the model interface.

Table 55. TECH-VER checklist applied to the CEM

Test description	Expected result of test	Actual rest of test
Does the technology (drug/device, etc.) acquisition cost increase with higher prices?	Yes	Yes
Does the drug acquisition cost increase for higher weight or body surface area?	Yes	Not relevant
Does the probability of an event, derived from an OR/RR/HR and baseline probability, increase with higher OR/RR/HR?	Yes	Yes
In a partitioned survival model, does the progression-free survival curve or the time on treatment curve cross the overall survival curve?	No	No
If survival parametric distributions are used in the extrapolations or time-to-event calculations, can the formulae used for the Weibull (generalized gamma) distribution generate the values obtained from the exponential (Weibull or Gamma) distribution(s) after replacing/transforming some of the parameters?	Yes	Yes
Is the HR calculated from Cox proportional hazards model applied on top of the parametric distribution extrapolation found from the survival regression?	No	No
Calculate the sum of the number of patients at each health state	Yes	Yes
Check if all probabilities and number of patients in a state are greater than or equal to 0	Yes	Yes
Check if all probabilities are smaller than or equal to 1	Yes	Yes
Compare the number of dead (or any absorbing state) patients in a period with the number of dead (or any absorbing state) patients in the previous periods?	Yes	Yes
In case of lifetime horizon, check if all patients are dead at the end of the time horizon	Yes	Yes
Set all utilities to 1	The QALYs accumulated at a given time would be the same as the life years accumulated at that time	Yes
Set all utilities to 0	No QALYs will be accumulated in the model	Yes
Decrease all state utilities simultaneously	Lower QALYS will be accumulated each time	Yes
Set all costs to 0	No costs will be accumulated in the model at any time	Yes
Put mortality rates to 0	Patients never die, LYs equal to time horizon	Yes
Put mortality rate at extremely high	Patients die in the first few cycles	Yes
Set the effectiveness-, utility-, and safety-related model inputs for all treatment options equal	Same life-years and QALYs should be accumulated for all treatment at any time	Yes
In addition to the inputs above, set cost-related model inputs for all treatment options equal	Same costs, life-years, and QALYs should be accumulated for all treatment at any time	Yes
Check if the time conversions for probabilities were conducted correctly.	Yes	Yes
Increase the treatment acquisition cost	X	Yes
Check the incremental life-years and QALYs gained results. Are they in line with the comparative clinical effectiveness evidence of the treatments involved?	Check the incremental cost results. Are they in line with the treatment costs?	Yes
Total life years greater than the total QALYs	Yes	Yes
Undiscounted results greater than the discounted results	Yes	Yes
Divide undiscounted total QALYs by undiscounted life years	This value should be within the outer ranges (maximum and minimum) of all the utility value inputs	Yes for PD value
Do the total life-years, QALYs, and costs decrease if a shorter time horizon is selected?	Yes	Yes

If disentangled results are presented, do they sum up to the total results (e.g. different cost types sum up to the total costs estimate)?	Yes	Yes
Set discount rates to 0	Discounted equal to undiscounted	Yes
Put the consequence of adverse event/discontinuation to 0 (0 costs and 0 mortality/utility decrements)	Zero cost and QALYs from AEs	Yes
Divide total undiscounted treatment acquisition costs by the average duration on treatment	This should be similar to treatment-related unit acquisition costs	Yes
Set discount rates to a higher value	Total discounted results should decrease	Yes
Set discount rates of costs/effects to an extremely high value	Total discounted results should be more or less the same as the discounted results accrued in the first cycles	Yes
Are all necessary parameters subject to uncertainty included in the OWSA?	Yes	Yes
Check if the OWSA includes any parameters associated with joint uncertainty (e.g., parts of a utility regression equation, survival curves with multiple parameters)	No	No
Are the upper and lower bounds used in the one-way sensitivity analysis using confidence intervals based on the statistical distribution assumed for that parameter?	Yes	Yes
Are the resulting ICER, incremental costs/QALYs with upper and lower bound of a parameter plausible and in line with a priori expectations?	Yes	Yes
Check that all parameters used in the sensitivity analysis have appropriate associated distributions – upper and lower bounds should surround the deterministic value (i.e. upper bound≥mean≥lower bound)	Yes	Yes
Standard error and not standard deviation used in sampling	Yes	Yes
Lognormal/gamma distribution for HRs and costs/resource use	Yes	Yes – normal used for resource use
Beta for utilities and proportions/probabilities	Yes	Yes
Dirichlet for multinomial	Yes	Yes
Multivariate normal for correlated inputs (e.g. survival curve or regression parameters)	Yes	Yes
Normal for other variables as long as samples do not violate the requirement to remain positive when appropriate	Yes	Yes
Check PSA output mean costs, QALYs, and ICER compared with the deterministic results. Is there a large discrepancy?	No	No
If you take new PSA runs from the Microsoft Excel model do you get similar results?	Yes	Yes
Is(are) the CEAC line(s) in line with the CE scatter plots and the efficient frontier?	Yes	Yes
Does the PSA cloud demonstrate an unexpected behavior or have an unusual shape?	No	No
Is the sum of all CEAC lines equal to 1 for all WTP values?	Yes	Yes
Do the explored scenario analyses provide a balanced view on the structural uncertainty (i.e. not always looking at more optimistic scenarios)?	Yes	Yes
Are the scenario analysis results plausible and in line with a priori expectations?	Yes	Yes
Check the correlation between two PSA results (i.e. costs/QALYs under the SoC and costs/QALYs under the comparator)	Should be very low (very high) if different (same) random streams are used for different arms	Yes
Check if all sampled input parameters in the PSA are correctly linked to the corresponding event/state calculations	Yes	Yes

B 24. Clinical expert interviews were conducted to validate or inform various input parameters, a report of which was included within the CS. Please confirm whether the compiled report was approved by the clinical experts in question. If this is not the case, to validate the information provided, please ensure that the report is checked and approved by all interviewed clinical experts, and provide detail of any adjustments to the report if/where applicable.

The Company applied robust methodology in line with the ABPI code of practice to conduct six 1-hour interviews with breast cancer experts from the UK to further understand the UK breast cancer treatment landscape and validate model assumptions. Topics of discussion included:

- Current management, treatment pathway and positioning of capivasertib
- Subsequent treatments
- Perceptions of the CAPItello-291 trial data and cost-effectiveness model assumptions
- Healthcare resource use

The discussion guide used and resulting consolidated outputs can be found in the report provided as part of the company submission reference pack.[7]

Clinicians were briefed that the outputs of the discussions will be documented and used to inform and support the patient pathway and management of patients in UK clinical practice in an HTA submission. Clinicians were renumerated for their time preparing for the interviews as well as the interview duration, the contract did not include allowance for reviewing the final report as this is not a standard practice. Sharing the final blinded report with individual clinicians for review and adjustments could lead to potential bias due to the risk of clinicians changing their originally expressed unbiased opinions in cases where they identify themselves as the outliers, in a groupthink-like behaviour.

According to NICE DSU TSD 14,[52] external validation of the model via exploring the clinical plausibility of assumptions and extrapolations should be conducted with clinical experts; however no precise methodology is proposed. Therefore, the Company leveraged methodology previously used and accepted by NICE for validating model assumptions in numerous submissions.

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Appendix I Complete search string for literature databases

A. PubMed

Table 56 Pubmed search strategy

#	Search
Population	
1	("Breast adenocarcinoma advanced"[tiab:~1] OR "Breast adenocarcinoma inoperable"[tiab:~1] OR "Breast adenocarcinoma metastases"[tiab:~1] OR "Breast adenocarcinoma metastasis"[tiab:~1] OR "Breast adenocarcinoma metastasised"[tiab:~1] OR "Breast adenocarcinoma metastasized"[tiab:~1] OR "Breast adenocarcinoma metastatic"[tiab:~1] OR "Breast adenocarcinoma secondary"[tiab:~1] OR "Breast adenocarcinoma unresectable"[tiab:~1] OR "Breast adenocarcinomas advanced"[tiab:~1] OR "Breast adenocarcinomas inoperable"[tiab:~1] OR "Breast adenocarcinomas metastases"[tiab:~1] OR "Breast adenocarcinomas metastasis"[tiab:~1] OR "Breast adenocarcinomas metastasised"[tiab:~1] OR "Breast adenocarcinomas metastasized"[tiab:~1] OR "Breast adenocarcinomas metastatic"[tiab:~1] OR "Breast adenocarcinomas secondary"[tiab:~1] OR "Breast adenocarcinomas unresectable"[tiab:~1] OR "Breast cancer advanced"[tiab:~1] OR "Breast cancer inoperable"[tiab:~1] OR "Breast cancer metastases"[tiab:~1] OR "Breast cancer metastasis"[tiab:~1] OR "Breast cancer metastasised"[tiab:~1] OR "Breast cancer metastasized"[tiab:~1] OR "Breast cancer metastatic"[tiab:~1] OR "Breast cancer secondary"[tiab:~1] OR "Breast cancer unresectable"[tiab:~1] OR "Breast cancers advanced"[tiab:~1] OR "Breast cancers inoperable"[tiab:~1] OR "Breast cancers metastases"[tiab:~1] OR "Breast cancers metastasis"[tiab:~1] OR "Breast cancers metastasised"[tiab:~1] OR "Breast cancers metastasized"[tiab:~1] OR "Breast cancers metastatic"[tiab:~1] OR "Breast cancers secondary"[tiab:~1] OR "Breast cancers unresectable"[tiab:~1] OR "Breast carcinoma advanced"[tiab:~1] OR "Breast carcinoma inoperable"[tiab:~1] OR "Breast carcinoma metastases"[tiab:~1] OR "Breast carcinoma metastasis"[tiab:~1] OR "Breast carcinoma metastasised"[tiab:~1] OR "Breast carcinoma metastasized"[tiab:~1] OR "Breast carcinoma metastatic"[tiab:~1] OR "Breast carcinoma secondary"[tiab:~1] OR "Breast carcinoma unresectable"[tiab:~1] OR "Breast carcinomas advanced"[tiab:~1] OR "Breast carcinomas inoperable"[tiab:~1] OR "Breast carcinomas metastases"[tiab:~1] OR "Breast carcinomas metastasis"[tiab:~1] OR "Breast carcinomas metastasised"[tiab:~1] OR "Breast carcinomas metastasized"[tiab:~1] OR "Breast carcinomas metastatic"[tiab:~1] OR "Breast carcinomas secondary"[tiab:~1] OR "Breast carcinomas unresectable"[tiab:~1] OR "Breast malignancies advanced"[tiab:~1] OR "Breast malignancies inoperable"[tiab:~1] OR "Breast malignancies metastases"[tiab:~1] OR "Breast malignancies metastasis"[tiab:~1] OR "Breast malignancies metastasised"[tiab:~1] OR "Breast malignancies metastasized"[tiab:~1] OR "Breast malignancies metastatic"[tiab:~1] OR "Breast malignancies secondary"[tiab:~1] OR "Breast malignancies unresectable"[tiab:~1] OR "Breast malignancy advanced"[tiab:~1] OR "Breast malignancy inoperable"[tiab:~1] OR "Breast malignancy metastases"[tiab:~1] OR "Breast malignancy metastasis"[tiab:~1] OR "Breast malignancy metastasised"[tiab:~1] OR "Breast malignancy metastasized"[tiab:~1] OR "Breast malignancy metastatic"[tiab:~1] OR "Breast malignancy secondary"[tiab:~1] OR "Breast malignancy unresectable"[tiab:~1] OR "Breast neoplasm advanced"[tiab:~1] OR "Breast neoplasm inoperable"[tiab:~1] OR "Breast neoplasm metastases"[tiab:~1] OR "Breast neoplasm metastasis"[tiab:~1] OR "Breast neoplasm metastasised"[tiab:~1] OR "Breast neoplasm metastasized"[tiab:~1] OR "Breast neoplasm metastatic"[tiab:~1] OR "Breast neoplasm secondary"[tiab:~1] OR "Breast neoplasm unresectable"[tiab:~1] OR "Breast neoplasms advanced"[tiab:~1] OR "Breast neoplasms inoperable"[tiab:~1] OR "Breast neoplasms metastases"[tiab:~1] OR "Breast neoplasms metastasis"[tiab:~1] OR "Breast neoplasms metastasised"[tiab:~1] OR "Breast neoplasms metastasized"[tiab:~1] OR "Breast neoplasms metastatic"[tiab:~1] OR "Breast neoplasms secondary"[tiab:~1] OR "Breast neoplasms unresectable"[tiab:~1] OR "Breast tumor advanced"[tiab:~1] OR "Breast tumor inoperable"[tiab:~1] OR "Breast tumor metastases"[tiab:~1] OR "Breast tumor metastasis"[tiab:~1] OR "Breast tumor metastasised"[tiab:~1] OR "Breast tumor metastasized"[tiab:~1] OR "Breast tumor metastatic"[tiab:~1] OR "Breast tumor secondary"[tiab:~1] OR "Breast tumor unresectable"[tiab:~1] OR "Breast tumors

	advanced"[tiab:~1] OR "Breast tumors inoperable"[tiab:~1] OR "Breast tumors metastases"[tiab:~1] OR "Breast tumors metastasis"[tiab:~1] OR "Breast tumors metastasised"[tiab:~1] OR "Breast tumors metastasized"[tiab:~1] OR "Breast tumors metastatic"[tiab:~1] OR "Breast tumors secondary"[tiab:~1] OR "Breast tumors unresectable"[tiab:~1] OR "Breast tumour advanced"[tiab:~1] OR "Breast tumour inoperable"[tiab:~1] OR "Breast tumour metastases"[tiab:~1] OR "Breast tumour metastasis"[tiab:~1] OR "Breast tumour metastasised"[tiab:~1] OR "Breast tumour metastasized"[tiab:~1] OR "Breast tumour metastatic"[tiab:~1] OR "Breast tumour secondary"[tiab:~1] OR "Breast tumour unresectable"[tiab:~1] OR "Breast tumours inoperable"[tiab:~1] OR "Breast tumours metastases"[tiab:~1] OR "Breast tumours metastasis"[tiab:~1] OR "Breast tumours metastasised"[tiab:~1] OR "Breast tumours metastasized"[tiab:~1] OR "Breast tumours metastatic"[tiab:~1] OR "Breast tumours secondary"[tiab:~1] OR "Breast tumours unresectable"[tiab:~1] OR "mammary adenocarcinoma advanced"[tiab:~1] OR "mammary adenocarcinoma inoperable"[tiab:~1] OR "mammary adenocarcinoma metastases"[tiab:~1] OR "mammary adenocarcinoma metastasis"[tiab:~1] OR "mammary adenocarcinoma metastasised"[tiab:~1] OR "mammary adenocarcinoma metastasized"[tiab:~1] OR "mammary adenocarcinoma metastatic"[tiab:~1] OR "mammary adenocarcinoma secondary"[tiab:~1] OR "mammary adenocarcinoma unresectable"[tiab:~1] OR "mammary adenocarcinomas advanced"[tiab:~1] OR "mammary adenocarcinomas inoperable"[tiab:~1] OR "mammary adenocarcinomas metastases"[tiab:~1] OR "mammary adenocarcinomas metastasis"[tiab:~1] OR "mammary adenocarcinomas metastasised"[tiab:~1] OR "mammary adenocarcinomas metastasized"[tiab:~1] OR "mammary adenocarcinomas metastatic"[tiab:~1] OR "mammary adenocarcinomas secondary"[tiab:~1] OR "mammary adenocarcinomas unresectable"[tiab:~1] OR "mammary cancer advanced"[tiab:~1] OR "mammary cancer inoperable"[tiab:~1] OR "mammary cancer metastases"[tiab:~1] OR "mammary cancer metastasis"[tiab:~1] OR "mammary cancer metastasised"[tiab:~1] OR "mammary cancer metastasized"[tiab:~1] OR "mammary cancer metastatic"[tiab:~1] OR "mammary cancer secondary"[tiab:~1] OR "mammary cancer unresectable"[tiab:~1] OR "mammary cancers advanced"[tiab:~1] OR "mammary cancers inoperable"[tiab:~1] OR "mammary cancers metastases"[tiab:~1] OR "mammary cancers metastasis"[tiab:~1] OR "mammary cancers metastasised"[tiab:~1] OR "mammary cancers metastasized"[tiab:~1] OR "mammary cancers metastatic"[tiab:~1] OR "mammary cancers secondary"[tiab:~1] OR "mammary cancers unresectable"[tiab:~1] OR "mammary carcinoma advanced"[tiab:~1] OR "mammary carcinoma inoperable"[tiab:~1] OR "mammary carcinoma metastases"[tiab:~1] OR "mammary carcinoma metastasis"[tiab:~1] OR "mammary carcinoma metastasised"[tiab:~1] OR "mammary carcinoma metastasized"[tiab:~1] OR "mammary carcinoma metastatic"[tiab:~1] OR "mammary carcinoma secondary"[tiab:~1] OR "mammary carcinoma unresectable"[tiab:~1] OR "mammary carcinomas advanced"[tiab:~1] OR "mammary carcinomas inoperable"[tiab:~1] OR "mammary carcinomas metastases"[tiab:~1] OR "mammary carcinomas metastasis"[tiab:~1] OR "mammary carcinomas metastasised"[tiab:~1] OR "mammary carcinomas metastasized"[tiab:~1] OR "mammary carcinomas metastatic"[tiab:~1] OR "mammary carcinomas secondary"[tiab:~1] OR "mammary carcinomas unresectable"[tiab:~1] OR "mammary malignancies advanced"[tiab:~1] OR "mammary malignancies inoperable"[tiab:~1] OR "mammary malignancies metastases"[tiab:~1] OR "mammary malignancies metastasis"[tiab:~1] OR "mammary malignancies metastasised"[tiab:~1] OR "mammary malignancies metastasized"[tiab:~1] OR "mammary malignancies metastatic"[tiab:~1] OR "mammary malignancies secondary"[tiab:~1] OR "mammary malignancies unresectable"[tiab:~1] OR "mammary malignancy advanced"[tiab:~1] OR "mammary malignancy inoperable"[tiab:~1] OR "mammary malignancy metastases"[tiab:~1] OR "mammary malignancy metastasis"[tiab:~1] OR "mammary malignancy metastasised"[tiab:~1] OR "mammary malignancy metastasized"[tiab:~1] OR "mammary malignancy metastatic"[tiab:~1] OR "mammary malignancy secondary"[tiab:~1] OR "mammary malignancy unresectable"[tiab:~1] OR "mammary neoplasm advanced"[tiab:~1] OR "mammary neoplasm inoperable"[tiab:~1] OR "mammary neoplasm metastases"[tiab:~1] OR "mammary neoplasm metastasis"[tiab:~1] OR "mammary neoplasm metastasised"[tiab:~1] OR "mammary neoplasm metastasized"[tiab:~1] OR "mammary neoplasm metastatic"[tiab:~1] OR "mammary neoplasm secondary"[tiab:~1] OR "mammary neoplasm unresectable"[tiab:~1] OR "mammary neoplasms advanced"[tiab:~1] OR "mammary neoplasms inoperable"[tiab:~1] OR "mammary neoplasms metastases"[tiab:~1] OR "mammary neoplasms metastasis"[tiab:~1] OR "mammary neoplasms metastasised"[tiab:~1] OR "mammary neoplasms metastasized"[tiab:~1] OR "mammary neoplasms metastatic"[tiab:~1] OR "mammary neoplasms secondary"[tiab:~1]

	OR "mammary neoplasms unresectable"[tiab:~1] OR "mammary tumor advanced"[tiab:~1] OR "mammary tumor inoperable"[tiab:~1] OR "mammary tumor metastases"[tiab:~1] OR "mammary tumor metastasis"[tiab:~1] OR "mammary tumor metastasised"[tiab:~1] OR "mammary tumor metastasized"[tiab:~1] OR "mammary tumor metastatic"[tiab:~1] OR "mammary tumor secondary"[tiab:~1] OR "mammary tumor unresectable"[tiab:~1] OR "mammary tumors advanced"[tiab:~1] OR "mammary tumors inoperable"[tiab:~1] OR "mammary tumors metastases"[tiab:~1] OR "mammary tumors metastasis"[tiab:~1] OR "mammary tumors metastasised"[tiab:~1] OR "mammary tumors metastasized"[tiab:~1] OR "mammary tumors metastatic"[tiab:~1] OR "mammary tumors secondary"[tiab:~1] OR "mammary tumors unresectable"[tiab:~1] OR "mammary tumour advanced"[tiab:~1] OR "mammary tumour inoperable"[tiab:~1] OR "mammary tumour metastases"[tiab:~1] OR "mammary tumour metastasis"[tiab:~1] OR "mammary tumour metastasised"[tiab:~1] OR "mammary tumour metastasized"[tiab:~1] OR "mammary tumour metastatic"[tiab:~1] OR "mammary tumour secondary"[tiab:~1] OR "mammary tumour unresectable"[tiab:~1] OR "mammary tumours inoperable"[tiab:~1] OR "mammary tumours metastases"[tiab:~1] OR "mammary tumours metastasis"[tiab:~1] OR "mammary tumours metastasised"[tiab:~1] OR "mammary tumours metastasized"[tiab:~1] OR "mammary tumours metastatic"[tiab:~1] OR "mammary tumours secondary"[tiab:~1] OR "mammary tumours unresectable"[tiab:~1])
Study Type	
2	((("Cost-Benefit Analysis"[Mesh:NoExp] OR "Quality-Adjusted Life Years"[Mesh:NoExp] OR "Markov Chains"[Mesh:NoExp] OR "Models, Economic"[Mesh] OR cost*[ti] OR "cost utility"[tiab:~2] OR "cost utilities"[tiab:~2] OR "cost utilitarian"[tiab:~2] OR "cost utilitarianism"[tiab:~2] OR "cost utilitarians"[tiab:~2] OR "cost utilizable"[tiab:~2] OR "cost utilization"[tiab:~2] OR "cost utilize"[tiab:~2] OR "cost utilized"[tiab:~2] OR "cost utilizes"[tiab:~2] OR "cost utilizing"[tiab:~2] OR "costs utility"[tiab:~2] OR "costs utilities"[tiab:~2] OR "costs utilitarian"[tiab:~2] OR "costs utilitarianism"[tiab:~2] OR "costs utilitarians"[tiab:~2] OR "costs utilizable"[tiab:~2] OR "costs utilization"[tiab:~2] OR "costs utilize"[tiab:~2] OR "costs utilized"[tiab:~2] OR "costs utilizes"[tiab:~2] OR "costs utilizing"[tiab:~2] OR "costly utility"[tiab:~2] OR "costly utilities"[tiab:~2] OR "costly utilitarian"[tiab:~2] OR "costly utilitarianism"[tiab:~2] OR "costly utilitarians"[tiab:~2] OR "costly utilizable"[tiab:~2] OR "costly utilization"[tiab:~2] OR "costly utilize"[tiab:~2] OR "costly utilized"[tiab:~2] OR "costly utilizes"[tiab:~2] OR "costly utilizing"[tiab:~2] OR "costlier utility"[tiab:~2] OR "costlier utilities"[tiab:~2] OR "costlier utilitarian"[tiab:~2] OR "costlier utilitarianism"[tiab:~2] OR "costlier utilitarians"[tiab:~2] OR "costlier utilizable"[tiab:~2] OR "costlier utilization"[tiab:~2] OR "costlier utilize"[tiab:~2] OR "costlier utilized"[tiab:~2] OR "costlier utilizes"[tiab:~2] OR "costlier utilizing"[tiab:~2] OR "costliest utility"[tiab:~2] OR "costliest utilities"[tiab:~2] OR "costliest utilitarian"[tiab:~2] OR "costliest utilitarianism"[tiab:~2] OR "costliest utilitarians"[tiab:~2] OR "costliest utilizable"[tiab:~2] OR "costliest utilization"[tiab:~2] OR "costliest utilize"[tiab:~2] OR "costliest utilized"[tiab:~2] OR "costliest utilizes"[tiab:~2] OR "costliest utilizing"[tiab:~2] OR "costliness utility"[tiab:~2] OR "costliness utilities"[tiab:~2] OR "costliness utilitarian"[tiab:~2] OR "costliness utilitarianism"[tiab:~2] OR "costliness utilitarians"[tiab:~2] OR "costliness utilizable"[tiab:~2] OR "costliness utilization"[tiab:~2] OR "costliness utilize"[tiab:~2] OR "costliness utilized"[tiab:~2] OR "costliness utilizes"[tiab:~2] OR "costliness utilizing"[tiab:~2] OR "cost assessment"[tiab:~2] OR "cost analyzed"[tiab:~2] OR "cost analyzing"[tiab:~2] OR "cost analys"[tiab:~2] OR "cost analysis"[tiab:~2] OR "cost assessed"[tiab:~2] OR "cost benefit"[tiab:~2] OR "cost benefits"[tiab:~2] OR "cost effective"[tiab:~2] OR "cost effectiveness"[tiab:~2] OR "cost evaluation"[tiab:~2] OR "cost evaluations"[tiab:~2] OR "cost evaluated"[tiab:~2] OR "cost evaluating"[tiab:~2] OR "cost evaluat"[tiab:~2] OR "cost expens"[tiab:~2] OR "cost expense"[tiab:~2] OR "cost expenses"[tiab:~2] OR "cost model"[tiab:~2] OR "cost modeled"[tiab:~2] OR "cost modeling"[tiab:~2] OR "cost models"[tiab:~2] OR "cost quality"[tiab:~2] OR "cost reduc"[tiab:~2] OR "cost reduce"[tiab:~2] OR "cost reduced"[tiab:~2] OR "cost reducing"[tiab:~2] OR "cost reduction"[tiab:~2] OR "cost saving"[tiab:~2] OR "cost savings"[tiab:~2] OR "cost threshold"[tiab:~2] OR "cost thresholds"[tiab:~2] OR "costs assessment"[tiab:~2] OR "costs analyzed"[tiab:~2] OR "costs analyzing"[tiab:~2] OR "costs analys"[tiab:~2] OR "costs analysis"[tiab:~2] OR "costs assessed"[tiab:~2] OR "costs benefit"[tiab:~2] OR "costs benefits"[tiab:~2] OR "costs effective"[tiab:~2] OR "costs effectiveness"[tiab:~2] OR "costs evaluation"[tiab:~2] OR "costs evaluations"[tiab:~2] OR "costs evaluated"[tiab:~2] OR "costs evaluating"[tiab:~2] OR "costs evaluat"[tiab:~2] OR "costs expens"[tiab:~2] OR "costs expense"[tiab:~2] OR "costs expenses"[tiab:~2] OR "costs model"[tiab:~2] OR "costs modeled"[tiab:~2] OR "costs

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	"quality-adjusted years"[tiab:~2] OR "quality-adjusted-year"[tiab:~2] OR "quality-adjusted-years"[tiab:~2]))
3	#1 AND #2
4	#3 timeframe limit: (please refer to “Response to Question A” for timeframe limits applied for the original SLR and each update)

B. Embase

Table 57 Embase search strategy

#	Search
Population	
1	((breast OR mammary) NEAR/2 (adenocarcinoma* OR cancer* OR carcinoma* OR neoplasm* OR tumor* OR tumour* OR malignan*) NEAR/2 (advanced OR inoperable OR metasta* OR secondary OR unresectable)):ti,ab,kw
Study type	
2	(('cost benefit analysis'/de OR 'quality adjusted life year'/de OR 'Markov chain'/de OR 'economic model'/exp OR cost*:ti OR (cost* NEAR/2 utilit*):ti,ab,kw OR (cost* NEAR/2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)):ti,ab,kw OR (economic* NEAR/2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)):ti,ab,kw OR (qualit* NEAR/2 adjust* NEAR/2 life*):ti,ab,kw OR QALY*:ti,ab,kw OR (incremental* NEAR/2 cost*):ti,ab,kw OR ICER:ti,ab,kw OR utilities:ti,ab,kw OR markov*:ti,ab,kw OR (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY):ti,ab,kw OR ((utility or effective*) NEAR/2 analys*):ti,ab,kw OR (willing* NEAR/2 pay*):ti,ab,kw OR ('EQ.5D*' or 'EQ-5D*'):ti,ab,kw OR ((euroqol or euro-qol or euroquol or 'euro-quol' or eurocol or 'euro-col') NEAR/2 (“5” or five)):ti,ab,kw OR (european* NEAR/2 quality NEAR/2 (“5” or five)):ti,ab,kw) OR ((cost* NEAR/2 (illness OR disease OR sickness)):ti,ab,kw OR (burden* NEAR/2 (illness OR disease* OR condition* OR economic*)):ti,ab,kw OR ('quality-adjusted life years' OR 'quality adjusted life years' OR QALY*):ti,ab,kw OR 'quality adjusted life year'/exp OR 'cost of illness'/exp OR 'health care cost'/exp OR (out-of-pocket NEAR/2 (payment* OR expenditure* OR cost* OR spending OR expense*)):ti,ab,kw OR (expenditure* NEAR/3 (health OR direct OR indirect)):ti,ab,kw OR ((adjusted OR quality-adjusted) NEAR/2 year*):ti,ab,kw) OR ('quality adjusted life year'/exp OR ('quality adjusted':ti,ab,kw OR 'adjusted life year*':ti,ab,kw OR qaly* OR qald* OR qale* OR qtime* OR 'illness state' OR 'health state*' OR hui OR hui1 OR hui2 OR hui3 OR multiattribute* OR multi attribute*):ti,ab,kw OR (utility NEAR/3 (score* OR valu* OR health* OR cost* OR measur* OR disease* OR mean OR gain OR gains OR index*)):ti,ab,kw OR utilities:ti,ab,kw OR ('eq-5d' OR 'eq5d' OR 'eq-5' OR 'eq5' OR 'euroqual' OR 'euroqual' OR 'euro qual5d' OR 'euroqual5d' OR 'euro qol' OR 'euroqol' OR 'euro qol5d' OR 'euroqol5d' OR 'euro quol' OR 'euroquol' OR 'euro quol5d' OR 'euroquol5d' OR 'eur qol' OR 'eurqol' OR 'eur qol5d' OR 'eur qol5d' OR 'eur?qul' OR 'eur?qul5d' OR 'euro* quality of life' OR 'european qol'):ti,ab,kw OR (euro* NEAR/3 ('5 d' OR 5d OR '5 dimension*' OR 5dimension* OR '5 domain*' OR 5domain*)):ti,ab,kw OR (sf36* OR sf 36* OR 'sf thirtysix' OR 'sf thirty six'):ti,ab,kw OR ('time trade off*' OR 'time tradeoff*' OR tto OR timetradeoff*):ti,ab,kw OR ('quality of life'/exp AND (('quality of life' OR qol) NEAR/1 (score* OR measure*)):ti,ab,kw) OR ('quality of life'/exp AND (health NEAR/3 status):ti,ab,kw) OR (('quality of life' OR qol):ti,ab,kw AND 'cost benefit analysis'/exp) OR (((qol OR hrqol OR 'quality of life'):ti,kw OR 'quality of life'/exp) AND ((qol OR hrqol* OR 'quality of life') NEAR/2 (increas* OR decrease* OR improv* OR declin* OR reduc* OR high* OR low* OR effect OR effects OR worse OR score OR scores OR change* OR impact* OR impacted OR deteriorat*)):ab) OR ('cost benefit analysis'/exp AND ('cost-effectiveness ratio*' AND (perspective* OR 'life expectanc*')):ti,ab,kw) OR ('quality of life'/exp AND ('quality of life' OR qol):ti) OR ('quality of life'/exp AND (('quality of life' OR qol) NEAR/3 (improv* OR chang*)):ti,ab,kw) OR ('quality of life'/exp AND 'health-related quality of life':ti,ab,kw) OR 'economic model'/exp))
3	#1 AND #2
4	#3 timeframe limit: (please refer to “Response to Question A” for timeframe limits applied for the original SLR and each update)

C. Cochrane Library

Table 58: Cochrane Library search strategy

#	Search
Population	
1	((breast OR mammary) NEAR/2 (adenocarcinoma* OR cancer* OR carcinoma* OR neoplasm* OR tumor* OR tumour* OR malignan*) NEAR/2 (advanced OR inoperable OR metasta* OR secondary OR unresectable)):ti,ab,kw
2	#1 timeframe limit: (please refer to “Response to Question A” for timeframe limits applied for the original SLR and each update)

D. Epistemonikos

Table 59: Epistemonikos search strategy

#	Search
Population	
1	(title:(advanced breast cancer OR metastatic breast cancer OR unresectable breast cancer OR inoperable breast cancer) OR abstract:(advanced breast cancer OR metastatic breast cancer OR unresectable breast cancer OR inoperable breast cancer))
Study type	
2	((title:((cost* OR economic* OR quality adjusted life OR QALY* OR ICER OR utilities OR markov* OR dollar* OR USD OR cents OR pound OR pounds OR GBP OR sterling* OR pence OR euro OR euros OR yen OR JPY OR "willingness to pay" OR EQ.5D OR EQ-5D OR euro-qol)) OR abstract:((cost* OR economic* OR quality adjusted life OR QALY* OR ICER OR utilities OR markov* OR dollar* OR USD OR cents OR pound OR pounds OR GBP OR sterling* OR pence OR euro OR euros OR yen OR JPY OR "willingness to pay" OR EQ.5D OR EQ-5D OR euro-qol))) OR (title:("cost of illness" OR "cost of disease" OR "burden of illness" OR "burden of disease" OR expenditure OR out-of-pocket) OR abstract:("cost of illness" OR "cost of disease" OR "burden of illness" OR "burden of disease" OR expenditure OR out-of-pocket)))
3	#1 AND #2
4	#3 timeframe limit: (please refer to “Response to Question A” for timeframe limits applied for the original SLR and each update)

E. Number of hits per line of search for update 1 (20 November 2023)

Table 60. Number of hits per line of PubMed search string for update 1 (20 November 2023)

Search number	Filter	Results
#1	Population search string	43,150
#2	Study type	815,126
#1 AND #2	Population and study type	1767
#3	Publication date filter applied from 01 April 2023	89

Table 61. Number of hits per line of Embase search string for update 1 (20 November 2023)

Search number	Filter	Results
#1	Population search string	60,600
#2	Study type	1,307,267
#1 AND #2	Population and study type	3374
#3	Limit publication year to 2023	198
#4	Records added to Embase filter applied from 1 April 2023	139

Table 62. Number of hits per line of Cochrane search string for update 1 (20 November 2023)

Search number	Filter	Results
#1	Population search string	10,050
#2	Publication date filter applied from 01 April 2023	305
#3	Limit to Cochrane reviews and protocols	2

Table 63. Number of hits per line of Epistemonikos search string for update 1 (20 November 2023)

Search number	Filter	Results
#1	Population search string	6,072
#2	Study type	371,456
#1 AND #2	Population and study type	150
#3	Custom year range applied as 2023	8
#4	Added to database data range applied from 1 April 2023	5

Appendix II Clinical SLR – summary of excluded studies

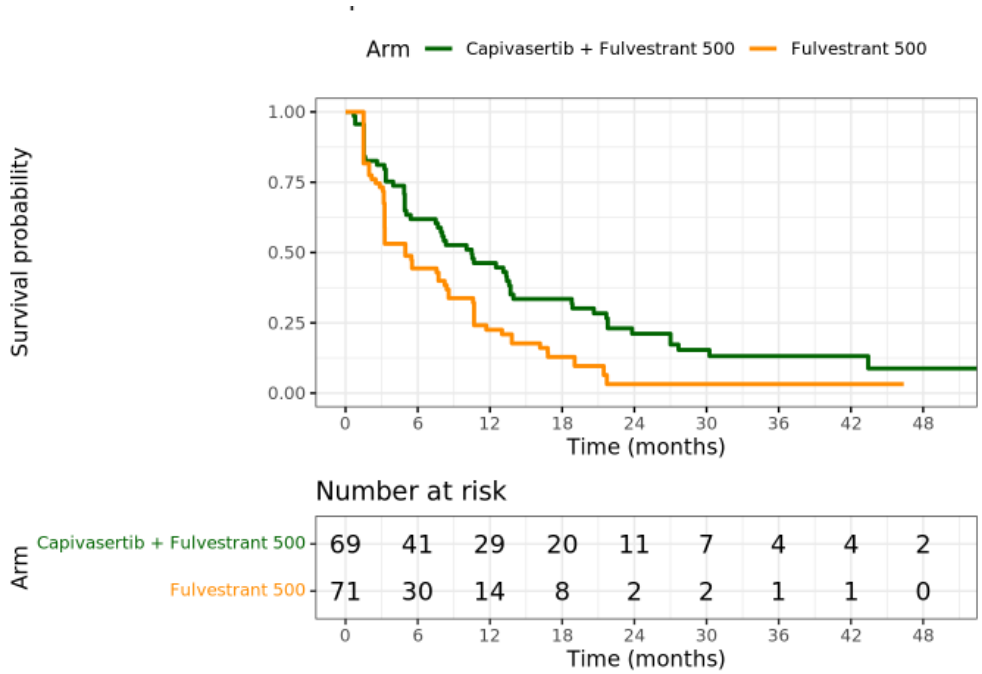
MtA_capivasertib_list of SLR includes_v1.xls

Appendix III PFS KM curves for studies included in the NMA

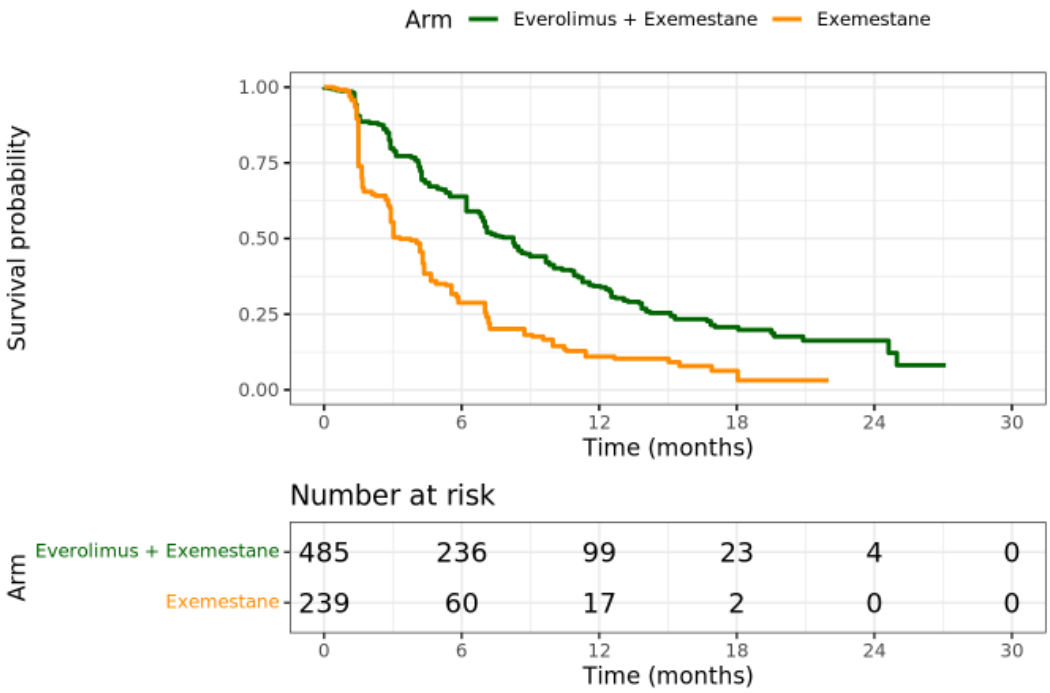
F. CAPItello-291

[redacted]

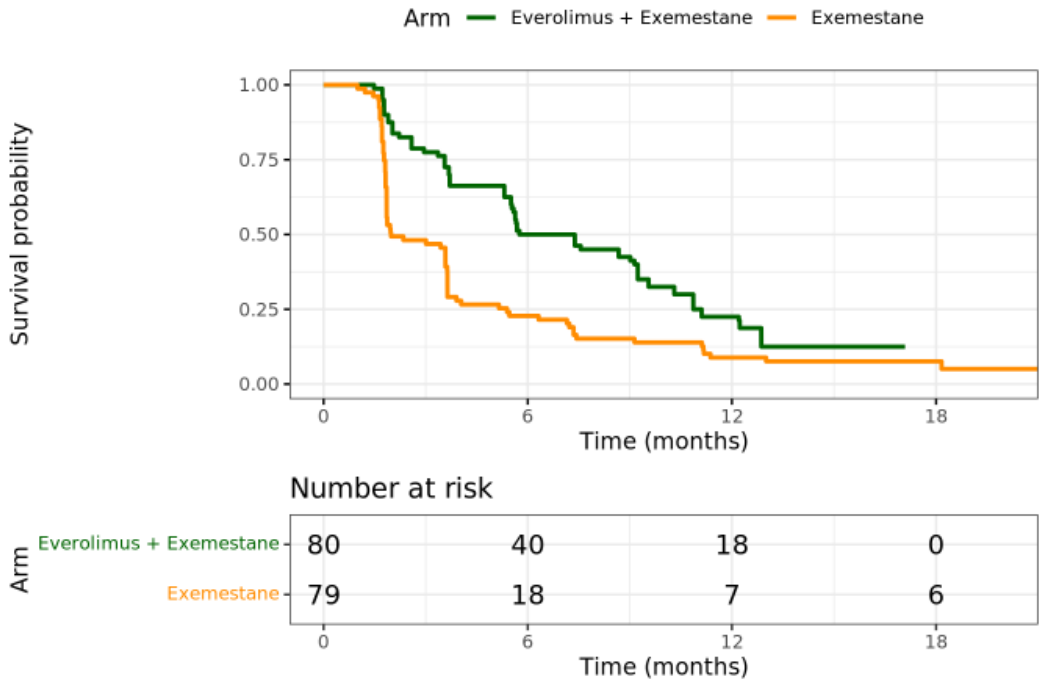
G. FAKTION



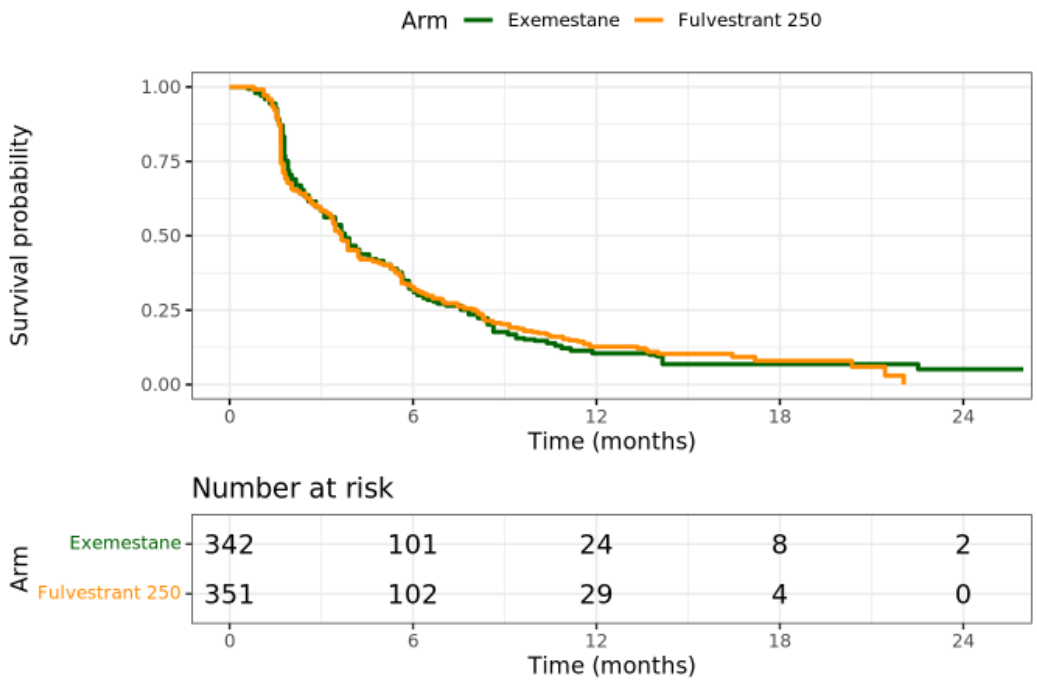
H. BOLERO-2



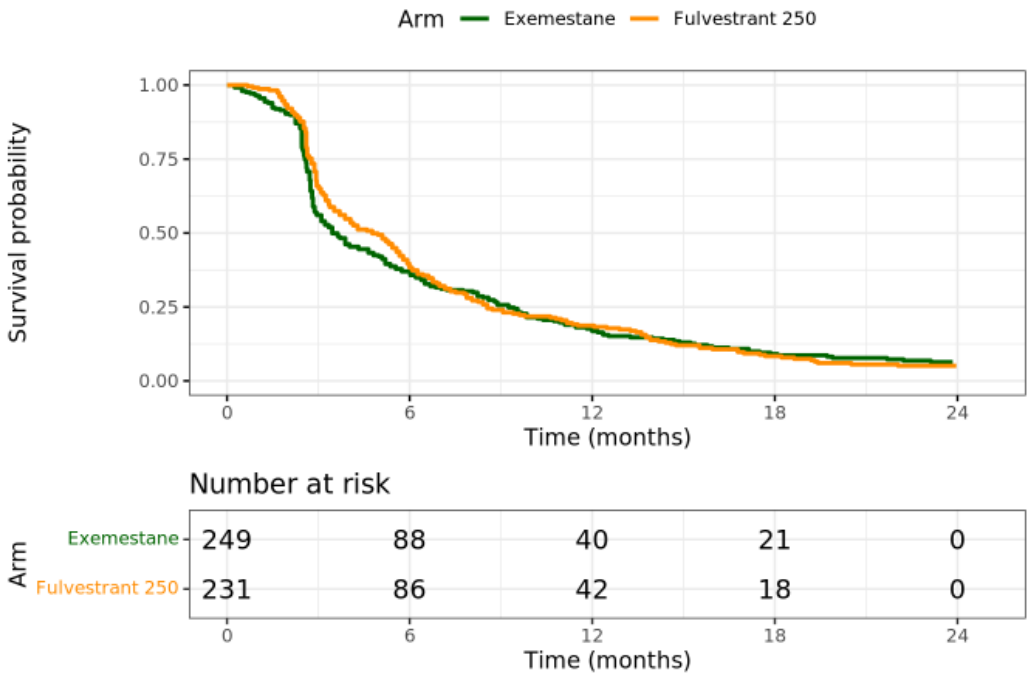
I. BOLERO-5



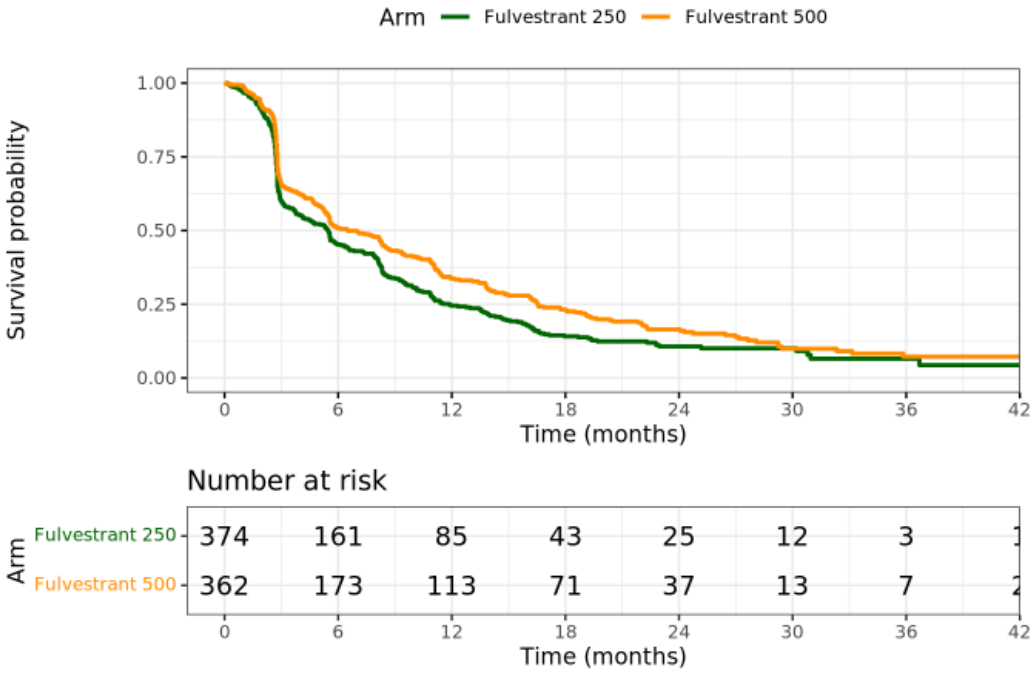
J. EFECT



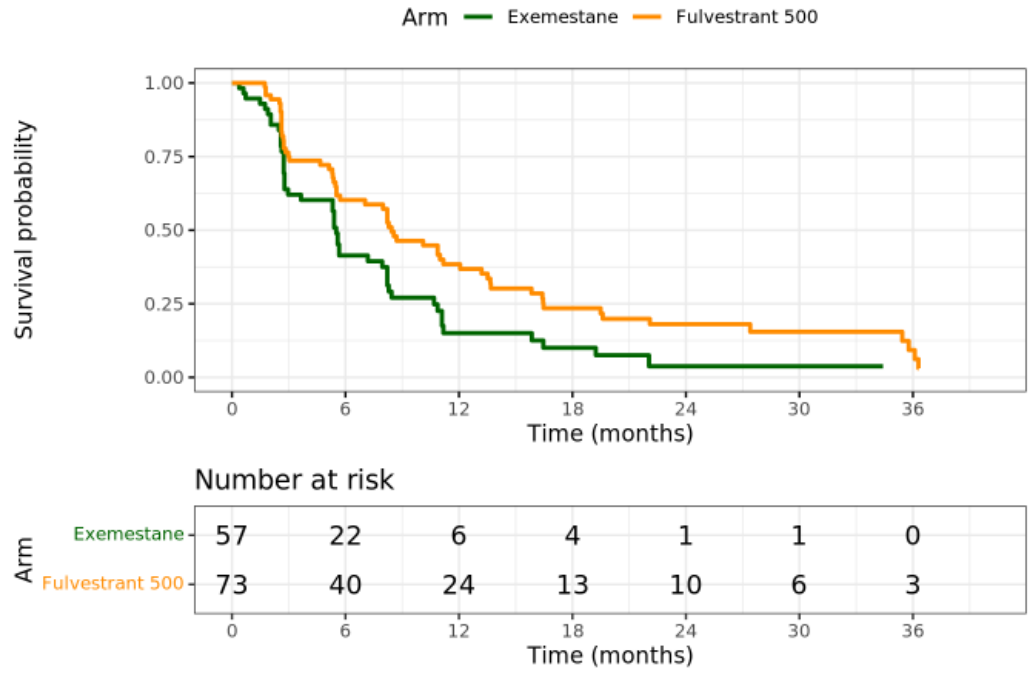
K. SOFEA



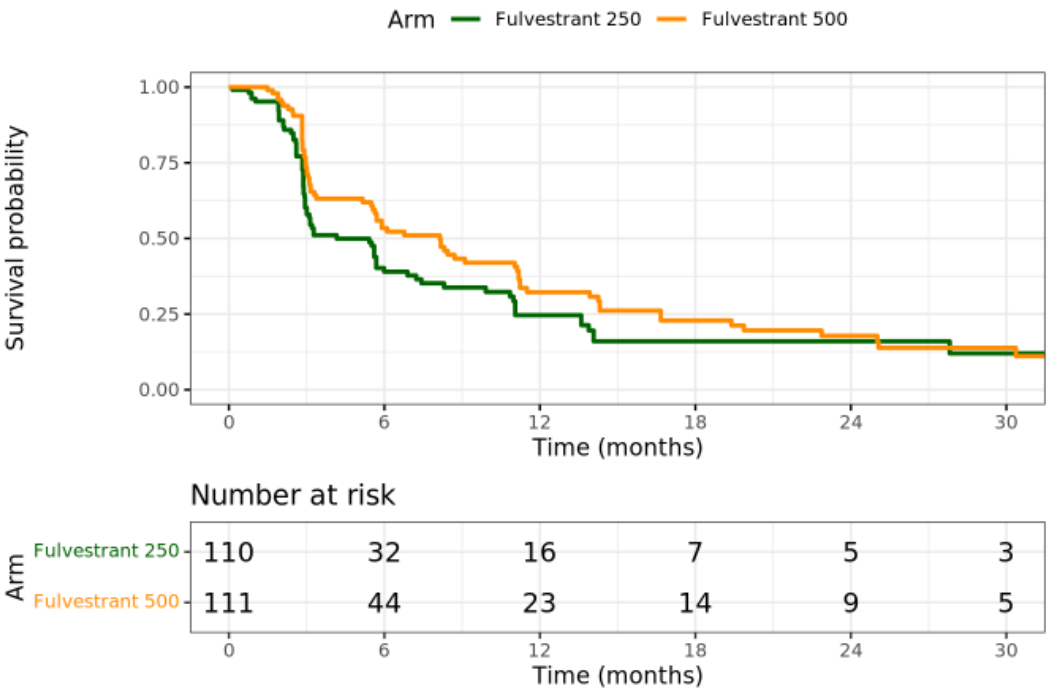
L. CONFIRM



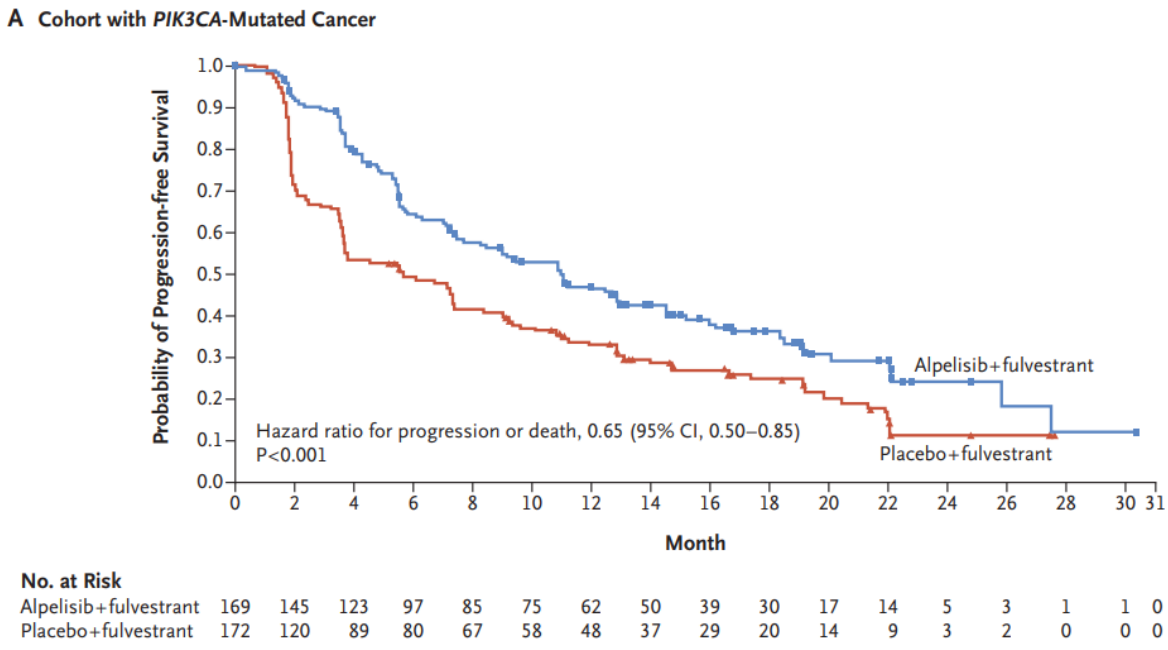
M. FRIEND



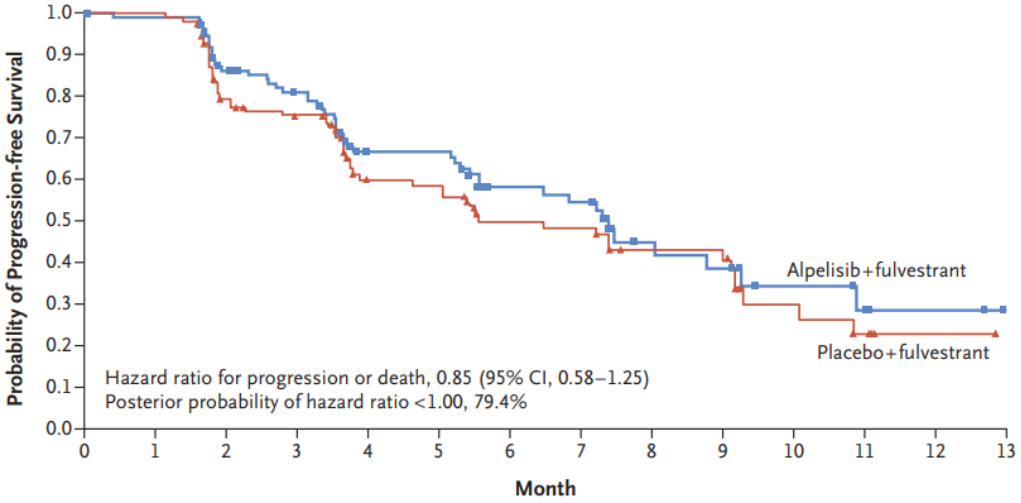
N. NCT01300351 (Zhang 2016)



O. SOLAR-1



B Cohort without *PIK3CA*-Mutated Cancer



No. at Risk

Alpelisib+fulvestrant	115	110	86	76	48	48	31	29	14	12	7	5	3	0
Placebo+fulvestrant	116	110	79	72	43	42	31	30	20	20	8	5	1	0

Appendix IV Overview of the incidence rates for grade ≥3 AEs recorded in CAPItello-291

Table 64 Adverse events of CTCAE grade 3 or higher, by system organ class

Adverse event class	PI3K/AKT- altered population		PI3K/AKT- altered population (post CDK4/6i)	
	Capivasertib + Fulvestrant (N=155), n (%)	Placebo + Fulvestrant (N=133), n (%)	Capivasertib + Fulvestrant (N=114), n (%)	Placebo + Fulvestrant (N=94), n (%)
Patients with AE of CTCAE grade 3 or higher	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]

Source: AstraZeneca data on file, capi291_iemt0521_safety_summ_gr; AstraZeneca Clinical study report, Table 14.3.2.8.2

Table 65 Adverse events of CTCAE grade 3 or higher, by preferred term

Adverse event	PI3K/AKT- altered population		PI3K/AKT- altered population (post CDK4/6i)	
	Capivasertib + Fulvestrant (N=155), n (%)	Placebo + Fulvestrant (N=133), n (%)	Capivasertib + Fulvestrant (N=114), n (%)	Placebo + Fulvestrant (N=94), n (%)
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Rash maculo-papular	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]

Hyperglycaemia	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypocalcaemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]	[redacted]	[redacted]
Rash papular	[redacted]	[redacted]	[redacted]	[redacted]
Urticaria	[redacted]	[redacted]	[redacted]	[redacted]
Drug eruption	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Skin infection	[redacted]	[redacted]	[redacted]	[redacted]
Bacterial colitis	[redacted]	[redacted]	[redacted]	[redacted]
Device related infection	[redacted]	[redacted]	[redacted]	[redacted]
Peritonitis	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia aspiration	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia bacterial	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia pneumococcal	[redacted]	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]	[redacted]
Adenocarcinoma of colon	[redacted]	[redacted]	[redacted]	[redacted]
Endometrial cancer	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Anaphylactic reaction	[redacted]	[redacted]	[redacted]	[redacted]
Dehydration	[redacted]	[redacted]	[redacted]	[redacted]
Seizure	[redacted]	[redacted]	[redacted]	[redacted]
Syncope	[redacted]	[redacted]	[redacted]	[redacted]
Acute myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]
Acute respiratory failure	[redacted]	[redacted]	[redacted]	[redacted]
Periodontal disease	[redacted]	[redacted]	[redacted]	[redacted]
Retroperitoneal fibrosis	[redacted]	[redacted]	[redacted]	[redacted]
Dermatitis allergic	[redacted]	[redacted]	[redacted]	[redacted]
Purpura	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]
Osteonecrosis of jaw	[redacted]	[redacted]	[redacted]	[redacted]

Proteinuria	[redacted]	[redacted]	[redacted]	[redacted]
Nephrolithiasis	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Mucosal inflammation	[redacted]	[redacted]	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]	[redacted]	[redacted]
Blood alkaline phosphatase increased	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Electrocardiogram QT prolonged	[redacted]	[redacted]	[redacted]	[redacted]
Body temperature increased	[redacted]	[redacted]	[redacted]	[redacted]
Femur fracture	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]
Hypercalcaemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypertriglyceridaemia	[redacted]	[redacted]	[redacted]	[redacted]
Agitation	[redacted]	[redacted]	[redacted]	[redacted]
Confusional state	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Pneumothorax	[redacted]	[redacted]	[redacted]	[redacted]
Atelectasis	[redacted]	[redacted]	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory failure	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Dry skin	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Bone pain	[redacted]	[redacted]	[redacted]	[redacted]
Renal impairment	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Blood creatine phosphokinase increased	[redacted]	[redacted]	[redacted]	[redacted]
Clostridium test positive	[redacted]	[redacted]	[redacted]	[redacted]
Hepatic enzyme increased	[redacted]	[redacted]	[redacted]	[redacted]
Fall	[redacted]	[redacted]	[redacted]	[redacted]
Femoral neck fracture	[redacted]	[redacted]	[redacted]	[redacted]
Forearm fracture	[redacted]	[redacted]	[redacted]	[redacted]

Source: AstraZeneca data on file, capi291_iemt0521_safety_summ_gr; AstraZeneca Clinical study report, Table 14.3.2.8.2

Appendix V List of model changes

Table 66 provides guidance on the changes made to the CEM following the questions from the EAG.

Table 66 Summary of changes made to the CEM

Question reference	Change in model
NA – minor model error identified	Sheet and cell reference: Model!CZ17:CZ375 Formula incorrectly referenced cell, corrected to: =IF(E17>=$CY$13,0,$CZ$12*BW17)
B6 a) Incorporating time-varying hazard ratios	User dropdown added to Settings!U21 Time-varying inputs can amended in the 'Relative efficacy' sheet, columns R:AL
B6 b) Independent fits for OS and PFS for capivasertib plus fulvestrant added	User dropdown added to Settings!U19 Sheet added: Capi_Ind – this is where the model parameters are stored, and whether the user can change the drop down (in row 20)
B7 d) Parametric models fit to TTD data for capivasertib plus fulvestrant added	User dropdown added to Settings!U20 Sheet added: Capi_Ind – this is where the model parameters are stored, and whether the user can change the drop down (in row 20)
B12 a) Updated rash duration	Sheet and cell reference: Utilities!J25 Updated value to 4
B16 b) Ability to include testing costs	User dropdown added to Settings!U22 Testing costs can be amended in the Costs_Other sheet, rows 21:32
B18 b) Severity modifier distribution	PSA_calcs sheet, columns FH:FP
B19 a)	RMST sheet added for calculations
B21	Necessary changes made to VBA code, PSA module and Parameters tab column Q

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

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Your response should not be longer than 10 pages

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	Make 2nds Count (Registered Charity Number: SC048268), Gyleworks, 34 South Gyle Crescent, Edinburgh, EH12 9EB
3. Job title or position	Research & Education Content Creator (Part-Time)
4a. Brief description of the organisation (including who funds it). How many members does it have?	Make 2nds Count is a UK-wide patient and family focussed charity dedicated to giving hope to women and men living with secondary breast cancer. Our fundraising income mainly relies on individual fundraising efforts through marathons, skydiving, dance challenges and events, and grants provided by trusts and foundations. Our online patient support group has 1500 members. You can learn more about Make 2nds Count by visiting our website: https://make2ndscount.co.uk/
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company,**	Yes, as follows: AstraZeneca - £25,000 - sponsorship of the Make 2nds Count Secondary Breast Cancer Patient Summit, a patient education event being held on 9-11th July 2024 in Liverpool. Pfizer - £25,000 - educational grant to support the Make 2nds Count Secondary Breast Cancer Patient Summit, a patient education event being held on 9-11th July 2024 in Liverpool. The Secondary Breast Cancer Patient Summit, organised by Make 2nds Count, will be the first national patient-focused conference in the UK for secondary breast cancer. You can read more about this conference here.

amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	A Google Survey was provided to our community group on social media during late-May to mid-June 2024. This survey included the questions noted in this form. Thirty one patients completed the survey. Each response was read and themes extracted. The data from this survey has been used to populate the answers in this form.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	The prevailing theme identified from patient survey responses is having to live with the uncertainty associated with an incurable disease. Particularly, patients discussed fear and anxiety knowing that their health will deteriorate, but not knowing when and that they are "living scan to scan". Below are some patient answers to this question: "It is so challenging, we live with fear and anxiety as well as the physical complications, and we are always aware that our time is limited and none of us know how much time we have left." "Emotionally it's like living on a knife edge. Trying to live each day and always the creeping anxiety at the back of my mind that the cancer will start growing again and kill me." "It's terrifying, I was diagnosed de novo at 50 and felt as though my life was over. I don't know if I will live 1 month, 6 months a year, five years or be really lucky and make it to 10 years. It's stolen my future and I can't make plans, because I don't know how I will feel, what treatment I'll need." "It is physically and mentally debilitating. Even if you are "well", you live with the very real fear that progression can happen at any time, at the same time watching your peers have progression, get ill and die. The more drug options we have available, the better, as the longer it will allow us to live." The prevailing theme identified for carers is that of worry, sadness and helplessness. "It is extremely difficult to watch someone you love and care about go through this, and to only feel like you can make plans 3 months at a time." "Carers are often close family members. They are sad for the person with incurable cancer, feel helpless as there is nothing that they can do to get rid of the disease or provide real support for the side effects." "My partner is my carer, he also works full time, it is hard for him and he is often exhausted."

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	The prevailing theme from patient responses is gratitude for the NHS care they receive, but patients feel that limited treatment options are available to them. Example responses include: "I have received nothing but great care from the NHS - they literally saved my life. Having said that, we need more options for treatment, because there are currently not enough." "It's uncertain. First lines of treatment are clear but none is a cure and we can quickly run out of options." "We need drugs and treatments that cure the disease and prevent it. Until these are available we need more drug options which enable us to live longer and with a better quality of life and less side effects." "We need more treatments to give patients as much hope and life expectancy as possible." "There is always a need for more drugs to be added - particularly for secondary or metastatic cancers."
8. Is there an unmet need for patients with this condition?	Patient answers had similar themes with question 7 with an emphasis on the limited number of treatment options available to patients and that treatments only last for a certain period of time before further disease progression. "Each treatment only lasts for so long so more options are needed to maintain life." "There is a limited number of current treatments and it's important to have many treatment options to increase longevity." "When hormone therapy fails, chemotherapy is gruelling and limits normal life. More options are needed."

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Patient answers focussed on the advantage of an increase in progression free survival and the ease of taking a tablet at home: “Improving the length of life.” “Give us more time with our children.” “Ease of use as it’s a tablet.” “It will free up time and space in overcrowded chemo units as it’s a tablet and can be taken at home.”

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Overall, patients stated they were either unaware of any disadvantages or could not think of any. The only disadvantage noted was the potential for side effects. “Don’t know.” “Not sure.” “I do not see any.” “None.” “There will be side effects, but all medicines have side effects.” “I can’t think of any, but I don’t know the side effect profile.”

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients note that as this medicine is for a subset of HR+ HER2- patients with specific gene mutations, this group will benefit the most and non-eligible patients will not benefit. “It will benefit those who are ER+ and are getting through treatments too quickly.” “Patients with HR+ HER2- breast cancer with specific gene mutations will benefit more.” “The drug is only suitable for a specific subtype.”

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Make 2nds Count is not aware of any potential equality issues.

Other issues

13. Are there any other issues that you would like the committee to consider?	Patients used this response to reiterate the importance of approving new treatments that have the potential to increase progression free survival. They also noted the emotional toll faced by them when such medicines don't get approved. Patients also commented on the change of how secondary breast cancer is rated by the NICE severity modifier. "Just how much it would mean to patients to have the chance of more life, better health, time with family and friends, the chance to make more memories, and to have hope." "Understanding the stress that withholding drugs for certain conditions causes." "Imagine you were told that your plans had to be put on hold, and that your time with those you love was cut short, even though there was something that could have saved your life, but you couldn't have it because it cost slightly more than was available." "I was horrified to understand recently that secondary breast cancer has been downgraded by NICE as a disease from high severity to medium severity. As a result this will likely mean that more drugs will be declined on cost grounds."

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	● Patients discussed fear and anxiety knowing that their health will deteriorate, but not knowing when and that they are "living scan to scan". For example, when describing what it is like when living with this condition one patient said "It is so challenging, we live with fear and anxiety as well as the physical complications, and we are always aware that our time is limited and none of us know how much time we have left". ● When asked about current treatments and if there are unmet needs, patients discussed the need for more treatment options that could improve life expectancy. E.g., "We need more treatments to give patients as much hope and life expectancy as possible". ● When asked about the advantages of this medicine, patient responses focussed on the extension of progression free survival and the fact that this is a tablet based medicine that could be taken at home. Responses of deemed advantages included: "Give us more time with our children" and "Ease of use as it's a tablet". ● Overall, patients stated they were either unaware of any disadvantages or could not think of any. The only disadvantage noted was the potential for side effects, but this was caveated e.g., "There will be side effects, but all medicines have side effects". ● Patients made note of the emotional toll of when medicines known to improve life expectancy are not approved, particularly when they are approved in other countries. For example, when asked if there is anything else the committee should consider one patient said "Understanding the stress that withholding drugs for certain conditions causes".

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Breast Cancer Now
3. Job title or position	Policy Manager
4a. Brief description of the organisation (including who funds it). How many members does it have?	Breast Cancer Now is the UK charity that's steered by world-class research and powered by life-changing care. We provide support for today and hope for the future.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	In the last 12 months (from June 2023), Breast Cancer Now has received the following funding from manufacturers listed in the appraisal matrix. • Novartis - £109,985 to support our Service Pledge programme, £46,000 to support our Living with Secondary Breast Cancer service and £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. Breast Cancer Now hosts the UK Interdisciplinary Breast Cancer Symposium (UKIBCS) alongside a number of partners including professional bodies and charities. The meeting is held every 2 years and the UKIBCS provides a space to bring together those with an interest in breast cancer research and treatment to advance understanding of the disease. The event is managed by a third party who receive and process sponsorship on behalf of the host and partners. Sponsors have no control over the running of the event and editorial control has been retained by the UKIBCS executive board. In the past 12 months (since June 2023), this has included the following listed on this appraisal matrix:

	• AstraZeneca - £3,000 for a stand • Novartis - £50,000 for advertising space • Pfizer - £6,000 for an exhibitor package
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	At Breast Cancer Now we use our various networks of people affected by breast cancer including those with a diagnosis of secondary breast cancer to gather information about patient experience. This includes our online Breast Cancer Now Forum and our online and face to face services.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Secondary breast cancer, also known as advanced, metastatic or stage 4 breast cancer, occurs when cancer originating in the breast spreads to other parts of the body, most commonly the lungs, brain, bones or liver. Patients can be diagnosed with secondary breast cancer from the start, or they can be diagnosed with the condition subsequent to a primary breast cancer diagnosis. There is currently no cure for secondary breast cancer. Treatment at this stage aims to control and slow the spread of the cancer, relieve symptoms and give people the best quality of life for as long as possible. Hormone Receptor (HR)-positive, HER2-negative is the most common sub-type of breast cancer, accounting for 70-80% of cases. These cancers are currently treated with a combination of endocrine therapies (including aromatase inhibitors) and targeted therapies. If patients experience progression following several lines of endocrine therapy and targeted therapies, they will generally be treated with chemotherapy. AKT pathway activation occurs in around half of HR-positive, HER2-negative breast cancers, as a result of activating mutations in PIK3CA or AKT1, or inactivating mutations in PTEN. These mutations may be present from the diagnosis of secondary breast cancer, or they may occur during treatment. AKT pathway activation has been linked to endocrine resistance, which is a significant problem for people receiving standard treatment for HR-positive, HER2 negative secondary breast cancer. Secondary breast cancer symptoms can have a major impact on a person's quality of life. General symptoms can include feeling constantly tired, nausea, weight loss and loss of appetite. Specific symptoms will vary depending on where the cancer has spread to - bone pain and bone fractures can occur if cancer has spread to the bones. Symptoms such as breathlessness and pain while breathing can also occur if cancer has spread to the lungs. Breast cancer treatments themselves can also cause side effects, which is a significant source of concern for patients, especially when starting new treatments. These side effects can have a major impact on people's day-to-day lives, quality of life, health and wellbeing. Different patients will react differently to drugs, so side-effects are not easy to predict, which can add to patient's anxiety. A diagnosis of secondary breast cancer can have a significant emotional toll and practical implications for those diagnosed and their families and friends. After their diagnosis, patients may feel overwhelmed, anxious,

	depressed and isolated. The condition may impact their relationships and could fundamentally change their perspective on life. The practicalities of managing secondary breast cancer alongside day-to-day activities like work, household and family responsibilities can be difficult. Patients may have to travel to regular hospital appointments. Patients tell us they often feel worn down by this attempt to balance treatment with the rest of their lives. Many patients at this stage of their treatment for secondary breast cancer have a significant desire to find treatments that will halt progression and extend life for as long as possible. They also have a strong desire to retain quality of life and spend time with their loved ones.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Patients diagnosed with HR positive, HER2 negative secondary breast cancer, will typically be treated with an aromatase inhibitor (such as anastrazole, exemestane or letrozole) and a CDK 4/6 inhibitor (such as abemaciclib, ribociclib or palbociclib). If they experience progression on this combination of drugs, they may be offered everolimus and exemestane, or fulvestrant and alpelisib (if they show a PIK3CA mutation). If they experience progression after several lines of endocrine therapy and targeted therapies, they will typically be offered chemotherapy. In some parts of England, fulvestrant is available as a single agent, as a second line treatment for women who have already received hormone therapy, although we understand it is not available across the vast majority of England and it has not been recommended for use on the NHS. Understandably, patients are keen for more and better options to be available to treat secondary breast cancer, particularly those that halt progression, extend life for as long as possible and allow them to retain good quality of life.
8. Is there an unmet need for patients with this condition?	Yes – These patients have experienced progression after at least one endocrine treatment. They currently have limited options for further treatment other than chemotherapy. While some patients with a PIK3CA mutation do have a further targeted treatment option in combination with endocrine therapy (alpelisib with fulvestrant), those with other mutations on the AKT pathway do not.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	The CAPItello-291 phase III trial was a randomised, double-blind trial. It enrolled 708 pre-, peri- and post-menopausal women and men with HR-positive, HER2-negative secondary breast cancer who had relapsed or experienced disease progression during or after treatment with an aromatase inhibitor, with or without a previous CDK4/6 inhibitor. They were randomised to capiversatib plus fulvestrant or placebo plus fulvestrant. Of the patients recruited, 40.8% had AKT pathway alterations. For the overall population, median progression free survival was 7.2 months in the capivasertib plus fulvestrant group, and 3.6 months in the placebo plus fulvestrant group. For the AKT pathway altered population, median progression free survival was 7.3 months in the capivasertib plus fulvestrant group, and 3.1 months in the placebo plus fulvestrant group. We are not aware of any overall survival data currently available. In the clinical trial, capivasertib was administered orally, twice daily on an intermittent schedule of four days on and three days off. Patients have told us that oral treatments are appealing as they require less frequent hospital visits. It should be noted however that fulvestrant is injected intramuscularly every 14 days for the first three injections, then every 28 days thereafter. Patients at this stage in their treatment for secondary breast cancer face limited options for further treatment. Capivasertib, in combination with fulvestrant, offers an additional option, beyond chemotherapy, that may offer benefits for these patients.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Secondary breast cancer patients are often concerned about potential side-effects when starting a new medication, and the potential for these to impact on their quality of life. In the CAPItello-291 clinical trial, patients receiving capivasertib with fulvestrant commonly reported side effects including diarrhoea, rash and nausea. These sorts of side-effects can impact on patients lives if they cannot be appropriately managed. Serious adverse events occurred in 57 patients receiving capivasertib and fulvestrant and 28 receiving placebo and fulvestrant. Every treatment for breast cancer has side effects and each patient's situation will be different, with side effects impacting some patients more than others. Patients' willingness to receive treatments will vary, however, as long as all the side effects are clearly discussed with the patient, they will be able to make their own informed choice as to the level of risk they will be willing to take balanced against the potential benefit of that treatment option.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Those with AKT-pathway mutations may experience greater progression free survival.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None that we are aware of.

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Secondary breast cancer, its symptoms, and the side-effects of its treatment have a major impact on patients' lives. HR-positive, HER2 negative is the most common type of breast cancer and AKT pathway activation occurs in around half of people with this type. • Patients with this type of secondary breast cancer who have experienced progression after at least one line of endocrine treatment currently have limited options for further treatment, other than chemotherapy. • In the CAPItello-291 clinical trial, median progression free survival was 7.2 months in the capivasertib plus fulvestrant group, and 3.6 months in the placebo plus fulvestrant group. For the AKT pathway altered population, median progression free survival was 7.3 months in the capivasertib plus fulvestrant group, and 3.1 months in the placebo plus fulvestrant group. • Patients at this stage in their treatment for secondary breast cancer are keen for more and better options to treat their secondary breast cancer. The approval of capivasertib with fulvestrant could offer an additional option for patients to delay progression of their disease. • All treatments for breast cancer have side-effects. Patients receiving capivasertib with fulvestrant as part of the clinical trial commonly reported side effects including diarrhoea, rash and nausea. These sorts of side-effects can impact on patients lives if they cannot be appropriately managed.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	METUPUK
3. Job title or position	Trustee
4a. Brief description of the organisation (including who funds it). How many members does it have?	METUPUK is a volunteer led patient advocacy organisation working to address the unmet needs of patients with metastatic breast cancer (MBC). Our three main objectives are: raising MBC awareness and education; campaigning for equitable treatment across the UK, including access to drugs; and improvements in patient care and outcomes. Our services aim to inform patients with primary breast cancer, their family and friends and clinicians of the red flag signs and symptoms of metastatic breast cancer. For patients with metastatic breast cancer, we campaign for improved access to drugs and treatments. This may include addressing disparities and inequalities in accessing treatment and clinical trials in the four nations of the UK, or between different commissioning groups within a given nation. We have created and maintain a clinical trials dashboard on our website showing a breakdown of current MBC trials in the UK by location and trial type. We also campaign for access to new therapeutics and radiotherapy treatments, so that patient outcomes are improved. We call on Trusts to collect accurate and timely data on their patients with MBC. We are members of the Audit Advisory Committee for NAoMe, the National Audit of Metastatic Breast Cancer for England and Wales. Through our social media channels, we provide signposting for peer support and to other charitable organizations that also offer support. We registered with the Charity Commission for England and Wales in 2021 (Charity number 1196494), but the organisation began as a small group of patients frustrated by the poor prognosis for MBC in 2016 and has grown since then. We are not a membership organisation, but we do reach out to the metastatic patient community with over 9000 followers on social media platforms. Our funding is mainly from public donations, and our accounts are published on the Charity Commission website. All our trustees and volunteers are unpaid.
4b. Has the organisation received any funding from the company bringing the	No

treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We used our patient networks and social media channels of Facebook, Instagram and Twitter to gather experiences of patients with hormone receptor-positive HER2-negative metastatic breast cancer. We created a survey to confidentially and anonymously collect information on what a new oral treatment in combination with fulvestrant targeted to a mutation in their cancer would mean to patients. Almost 70 members of the patient community took time to share their opinions with us to pass on to NICE.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Metastatic breast cancer is a severe disease, and the majority of patients die within five years of diagnosis. Many of the patients who responded to our survey used the words terrifying, horrifying, scary, exhausting and limiting to describe life with metastatic breast cancer. One patient described it as the roller coaster of terror. The theme of uncertainty recurred frequently in patient responses: “We live from scan to scan, and even if our treatment appears to be working well, we never know if our cancer is progressing. It is incredibly difficult to plan anything beyond three or six months in the future. Feeling cheated that the word palliative is used as soon as you’re diagnosed, the word gives no hope. It's living with uncertainty, restrictions, hope, fear, side effects, more hope, frustration, feelings of being forgotten, neglected, dismissed. Feeling that the energy and research is going into the curable patients.” Patients noted the effect of treatment schedules on their quality of life: “Exhausting. I struggle to be the same leader I was in work, my energy is compromised through treatment. I struggle to keep up my positive energy for my 3 teenage sons. I struggle to keep my emotional wellbeing in check.” “My life and my families have been forever turned upside down. The harsh chemo, the lack of drugs, the lack of trials and the hoops to jump through to get on them if you are lucky enough, the mental pain and the physical pain.” “Living with oestrogen positive breast cancer means living with the knowledge that your treatment will eventually fail. More lines of treatment means more options and more time. Time to meet my grandchildren, time to make memories, time with my family.” A METUPUK patient advocate describes living with MBC: “Living with MBC brings a level of sadness which is always there and cannot be shifted. The psychological benefits of knowing that medical advancements continue to be pursued and will be made available cannot be emphasised enough- it reduces the mental stress of MBC and brings real hope.” MBC is also incredibly difficult for carers. Partners find their role in the family changes quite suddenly from lover to carer for the patient, often balancing this with the financial need to work and sometimes manage childcare. Many patients have children under 18 living with them who face the considerable difficulties of being a young carer while balancing their studies and losing out on their youth. Patients’ parents face the awful prospect of their children dying before them, with very little support. One young carer wrote, “My family cannot take any more loss. All I think about is that we will run out of treatments. My mum has the PIK3CA gene and I wake every night in terror and every morning it’s the first thing on my mind!”

	A supporter whose wife has metastatic breast cancer describes how “our lives are turned upside-down, organised around treatments and care. We make plans we hope will come to pass but do not presume. We value the life of those we love like we have never done before, and knowing it will not last, we cherish what we have” A young newly married man explained, “There are so many compromises to be made that you don’t even think about. I love my wife and spending time with her, so it’s largely positive although being on call when she’s sick is challenging. The mental side is very hard. I don’t like seeing her so sick. It makes me sad.” His wife has died since this statement was written. She was 32.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Patients with hormone receptor-positive HER2-negative metastatic breast cancer value targeted treatments over untargeted chemotherapy. They are excited by precision treatments which target mutations in their cancer. Patients generally prefer treatments which are taken as a tablet at home, as opposed to injections and infusions which must be administered in hospital settings. Patients feel frustrated when new more effective treatments with reduced side effects take a long time to reach routine NHS care. Most patients with hormone receptor-positive HER2-negative metastatic breast cancer will get two lines of endocrine treatment on the NHS. Many patients would prefer more lines of endocrine treatment, particularly treatments which can circumvent endocrine resistance in their cancer. Capivasertib offers the promise of an additional line of endocrine treatment in patients with alterations in PIK3CA, AKT1 or PTEN. There is frustration about lack of personalised care in many NHS treatments. A patient wrote, “Current treatments are offered without standard genomic testing. This testing should be routinely done so that we move away from a one size fits all approach. The fact that capivasertib targets ATK is a welcome additional layer to the CDK4/6 inhibitor drugs offered at first line treatment.” Patients are also concerned about treatment line restrictions. One person who is currently on alpelisib with fulvestrant wrote “If we are genuine about improving survival then we need to look at the restrictions placed on treatment eligibility and allow such decisions to be based solely upon what treatment will work, regardless of prior treatment lines.” Many other patients who are on combinations of CDK4/6 inhibitors with fulvestrant also expressed concern that their current treatment would bar them from receiving capivasertib if it is approved. Most patients value targeted treatments over untargeted cytotoxic chemotherapy. Chemotherapy means that patient’s lives revolve around long hospital visits for treatment. One patient who had previously been on endocrine treatment writes: “I am now on IV chemotherapy, which is much harder on my body with several harsh side effects. It is also difficult to lead a normal life when I have weekly treatments, as it is impossible to plan ahead, especially for things like holidays, which are really important for making memories and enjoying life. At the moment, chemotherapy seems to be the only treatment that will be available to me for the foreseeable future.”

8. Is there an unmet need for patients with this condition?	Yes there is an unmet need for capivasertib with fulvestrant. After progression on first and second line endocrine treatment, there are limited options for patients with oestrogen receptor-positive HER2-negative metastatic breast cancer. Capivasertib is a first in class AKT inhibitor and therefore addresses an unmet need offering a precision treatment which is valued by patients.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Feedback from patients about the appraisal of capivasertib with fulvestrant has been very positive. "I really hope this is approved by NICE; it will give us another option after our first line and so longer without having IV chemo". The patients we consulted with were conscious that every line of treatment is vital for them to extend their lives. "It would be great to know there was another possible hormone treatment in the pipeline. I'm nearly 5 years in (after de novo diagnosis). I started on letrozole + palbociclib and have been on fulvestrant for the last 18 months but fear it's getting to the end of its efficacy. Obviously, without being tested it's impossible to know if we have the necessary gene but it's something to keep us having a closer to normal life and give us hope." "This would be amazing, to have another treatment option for stage 4 breast cancer, every single treatment option means so much to me as a stage 4 patient. They all mean time with my son seeing him grow up, reaching milestones that without these new and extra treatment lines wouldn't be possible." Genomic testing is an important part of this appraisal for patients. If patients test negative for alternations in the AKT1, PIK3CA or PTEN genes, it is easier for them to accept that capivasertib is unlikely to be of benefit to them. If they test positive for alterations in these genes, then they can be reassured that they are receiving an evidence based treatment targeted to their particular cancer. For patients with a PIK3CA mutation, capivasertib could be an alternative treatment choice to alpelisib. The availability of both treatments would enable oncologists to select the most appropriate treatment for their patient, taking into account their medical history and preferences. Support for genomic testing in cancer among the patient community is summarised by this quote from our consultation: "I think testing each cancer is important as the drugs are very targeted and we should all be benefiting from this. Progressive cancer needs to be slowed down and stopped, too many people are suffering. Oncologists need to know more about each cancer and offer what is on offer!!!" Another patient comments, "This is true personalised care and what the aim should be in the NHS."

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	As with all drugs capivasertib with fulvestrant has side effects. The most commonly reported side effects are diarrhoea, nausea, high blood sugar and skin reactions. Fulvestrant is given as an intramuscular injection into the buttocks and many patients find it painful. The treatment is generally given in a hospital setting which ties patients into travelling to receive their treatment. In the CAPItello-291 Phase III trial capivasertib with fulvestrant was shown to double the time it took cancer to progress compared to fulvestrant alone in patients with alterations in PIK3CA, AKT and PTEN. Fulvestrant monotherapy is not a standard of care NHS treatment in England, so it is difficult for patients to infer how these results will compare to what is currently available to them. Alterations in PIK3CA, AKT and PTEN affect up to approximately 50% of patients with hormone receptor positive metastatic breast cancer. Therefore, around half of all patients with hormone receptor positive MBC will not benefit from this combination. For most patients increasing overall survival time is highly valued, and data for OS is immature. However, patients do also value increasing progression free survival, which can delay the need for chemotherapy. For many patients, increased PFS translates to reduced tumour load and better management of symptoms. Metastatic breast cancer is a severe disease with a very short life expectancy. Treatments which increase quality of life so remaining time can be spent in a way that reflects individual's preferences are very important. CAPItello-291 Study Group (2023), 'Capivasertib in Hormone Receptor-Positive Advanced Breast Cancer', *The New England Journal of Medicine*, vol. 388, no. 22, pp. 2058-2070.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	No comments, patient selection is a clinical decision.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No issues noted

Other issues

13. Are there any other issues that you would like the committee to consider?	Patients would like clarity about how alterations in the AKT1, PIK3CA or PTEN genes will be assessed. If a tissue sample is used will a new sample be required or can an archived sample be used? A final comment from a patient: Whilst it's important to spend money on prevention and treatments for early stage curable breast cancer, it's also vital to acknowledge that 30% of early breast cancer patients go on to develop metastatic breast cancer. Please help make Metastatic breast cancer a chronic disease in the future. "

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Capivasertib addresses an unmet need as a first in class AKT inhibitor. • Capivasertib with fulvestrant increases progression free survival, delaying the need for patients to receive cytotoxic chemotherapy. • Companion diagnostics used with capivasertib with fulvestrant will increase the provision of genomic testing in the NHS. Targeting treatment to those most likely to gain benefit is a more efficient use of NHS resources. • Capivasertib with fulvestrant offers an alternative treatment to alpelisib with fulvestrant for patients with PIK3CA mutated tumours. • Patients particularly value treatments which increase overall survival. Overall survival data is immature. If more information on how the drugs work over a longer time frame is required, capivasertib with fulvestrant could be a candidate for the Cancer Drug Fund.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Clinical expert statement

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

NICE National Institute for Health and Care Excellence

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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 also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **<insert deadline>.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

Clinical expert statement

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

NICE National Institute for Health and Care Excellence

Part 1: Treating hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment – current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Nicholas Turner
2. Name of organisation	Royal Marsden Hospital and Institute of Cancer Research
3. Job title or position	Consultant Medical Oncologist and Professor of Molecular Oncology
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with hormone receptor-positive HER2-negative advanced breast cancer? ☒ A specialist in the clinical evidence base for hormone receptor-positive HER2-negative advanced breast cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here.	☐ Yes

(If you tick this box, the rest of this form will be deleted after submission)	
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To prolong life, delay progression of disease, and shrink the cancer, whilst minimizing side effects of treatment so that quality of life is maintained or improved
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	As defined by the RECIST criteria
10. In your view, is there an unmet need for patients and healthcare professionals in hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment?	Yes, current endocrine based treatment is relatively ineffective, after patients have been treated with prior endocrine treatment with a CDK4/6 inhibitor. The vast majority of patients are now treated with endocrine treatment and a CDK4/6 inhibitor in the UK. Treatments that make endocrine based treatment more effective, after prior progression on endocrine therapy and CDK4/6 inhibitor, are highly important. Patients strongly value long durations of disease control, and long durations of disease control are more likely to result in improvements in survival. If endocrine based treatment fails, patients have chemotherapy as their main treatment option, and delaying chemotherapy is highly important for patients given the toxicity this involves.

11. How is hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Clinicians do not generally follow NICE guidance for specific recommendations, as this is outdated last updated in 2017. Clinicians generally therefore follow ESMO and ASCO guidance, adapted for the availability of treatments and biomarker tests on the NHS. First line therapy for advanced breast cancer is the combination of endocrine therapy and a CDK4/6 inhibitor. A small proportion of patients do not have a CDK4/6 inhibitor as they are not fit to receive one. This technology assessment is predominantly relevant to those patients who progress on first line endocrine therapy and CDK4/6 inhibitor, so called the "second line" setting. Available current treatment options for these patients are single agent endocrine therapy (for example fulvestrant or tamoxifen), exemestane and everolimus, and fulvestrant and alpelisib for cancers with *PIK3CA* mutations. Guidance is not to give chemotherapy unless the cancer is at risk of causing a life threatening complications (often called a visceral crisis). Guidance is to continue with endocrine based therapy in the second line instead of using chemotherapy, due to the toxicity of chemotherapy. For a very small minority of patients with germline *BRCA1/2* mutations, talazoparib is an option. Single agent endocrine therapy has low activity after progression on prior endocrine therapy and CDK4/6 inhibitors, and recent guidance has shifted against the use of single agent endocrine therapy in the second line setting, and more towards using combinations of endocrine therapy with a targeted therapy, such as exemestane everolimus or fulvestrant and alpelisib.

	Both currently endocrine based targeted therapycombinations have challenges to their use in clinical practice 1) Fulvestrant and alpelisib for *PIK3CA* mutant cancer – this combination comes with high toxicity. In the registration trial SOLAR1 25% of patients discontinued due to toxicity, and multiple real word study studies have shown higher discontinuation rates in standard clinical practice. The main problematic side effects are acute hyperglycaemia and rash. Many oncologists in the UK do not broadly use alpelisib due to the side effects, and therefore they also do not do molecular testing for their patients even through *PIK3CA* testing is on the test directory. This has greatly impacted the adoption of precision medicine in the UK breast cancer population. 2) Exemestane and everolimus - there is no clinical trial data on this combination in patients with prior CDK4/6 inhibitor exposure. The registration study BOLERO2 was conducted well before CDK4/6 inhibitors became available. In addition, the rate of clinical response with this combination is low (9.5% in the registration trial BOLERO2), which substantially undermines the patient experience of the combination (patients value tumours shrinking on scans). In addition, this patient population has a high rate of mutations in the oestrogen receptor gene (*ESR1*), with approximately 40-50% of patients having cancers with *ESR1* mutations. The endocrine therapy exemestane does not work in cancers with *ESR1* mutations, and in my opinion should not be used in a setting where *ESR1* mutations are so common. However, the alternative combination of fulvestrant and everolimus is not funded in the NHS (fulvestrant has a different mechanism of action to exemestane and does have activity in *ESR1* mutant cancer).

	There is therefore a substantial need for a second line endocrine-targeted therapy combination, that is based on fulvestrant and is less toxic than alpelisib. This is what fulvestrant and capivasertib will give to patients in the NHS.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Fulvestrant and capivsertib will be used in the same way as existing second line therapies, there will be no significant differences. This is a secondary care technology, that should be prescribed only by oncologists.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	I expect fulvestrant and capivasertib to lengthen life, as the substantial increase in progression free survival and substantial increase in response rates, would be expected to translate through to increase in survival. I expect fulvestrant and capivasertib to improve quality of life more than the current standard of fulvestrant and alpelisib. In the registration trial of alpelisib (SOLAR1) 25% of patients discontinued therapy due to adverse effects. In the registration trial of capivasertib (Capitelo291) 13% of patients discontinued

	therapy due to adverse effects. This provides evidence that overall capivasertib is better tolerated than alpelisib.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Capivasertib is for tumours with *PIK3CA/AKT1/PTEN* alterations. Capivasertib is not for patients with poorly controlled diabetes.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Capivasertib will be substantially easier to use than alpelisib. The discontinuation rates of alpelisib are highlighted above. Alpelisib causes substantially higher rates of hyperglycaemia (37% grade 3 or higher) than capivaseritb (2% grade 3 or higher). Alpelisib causes higher rates of rash (20% grade 3 or higher) than capivasertib (12% grade 3 or higher). Due to these side effects alpelisib is not used by many oncologists in the UK, as they consider it too toxic. Capivasertib is therefore a substantial practical improvement on alpelisib. Capivaserib does have higher rates of diarrhoea (72% overall, 9% grade 3 or higher) than alpelisib (58% overall, 7% grade 3 or higher), but oncologist are well used to managing diarrhoea as diarrhoea is caused by many of our treatments (eg abemaciclib, chemotherapy, etc) All percentages are from the registrational trails in combination with fulvestrant. The approval of capivasertib will therefore have substantial practical benefits. It will enable more wide adoption of therapies that target *PIK3CA* (as well as *AKT1* and *PTEN*), and in turn this will allow patients to more widely access

	molecular testing of their cancer. *PIK3CA* testing is on the test directory, but is not widely adopted as alpelisib is not widely used.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No change to current practice
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Yes, as I have highlighted above.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes, this will lead to a step change in the management of *PIK3CA/AKT1/PTEN* altered breast cancer. I have outlined my reasons for this in the prior sections. The approval would drive more molecular testing for breast cancer in the UK, and drive more adoption of effective targeted therapy combinations with fulvestant.

19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Capivasertib is generally well tolerated. The main side effect is diarrhoea, but the management of this side effect is very familiar to oncologists. Some patients do have side effects of rash, although again the management of this side effect is well knowns. Quality of life was maintained despite side effects.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA421 (everolimus with exemestane) and TA816 (alpelisib with fulvestrant)?	Discussed above. It is highly important to note that the registration clinical trials that led to the approval of these therapies (everolimus/alpelisib), and therefore the data in the NICE technology appraisals, were **before** the approval and adoption of CDK4/6 inhibitors. Therefore, there can be no direct comparison of absolute response rates and progression free survival between these studies (BOLERO2 and SOLAR1 respectively), and Capitello291 (capivasertib). As I highlight above, it has become clear that single agent endocrine therapy is less effective after

	progression on prior endocrine therapy and a CDK4/6 inhibitor. This can be seen most evidently in the performance of the fulvestrant control arm in Capitello291 (capivsertib, 69% prior CDK4/6 inhibitor) fulvestrant median PFS 3.6 months, compared to SOLAR1 (alpelisib, 2% prior CDK4/6 inhibitor) fulvestrant median PFS 5.7 months. Any trial-to-trial comparisons must carefully consider this.
23. How do data on real-world experience compare with the trial data?	Limited real-world data yet for capivasertib
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation	None

• lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Capivasertib and fulvestant is a highly effective new treatment for advanced breast cancer with alterations in *PIK3CA/AKT1/PTEN* that has progressed on prior endocrine therapy

Alternative comparators have limitations in clinical practice. Fulvestrant and alpelisib has significant challenges with toxicity that has substantially limited the adoption of this therapy in routine practice in the NHS.

Alternative comparators have limitations in clinical practice. Exemestane and everolimus has low response rates, and uses exemestane in a setting where *ESR1* mutations are present in up to 50% of cancers. Exemestane is ineffective in cancers with *ESR1* mutations.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

Your privacy

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Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment or caring for a patient with hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment.

The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Wednesday 6 November 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

Patient expert statement

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

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment

Table 1 About you, hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment, current treatments and equality

1. Your name	[redacted]
2. Are you (please tick all that apply)	☒ A patient with hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	METUP UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing

Patient expert statement

5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment? **If you are a carer (for someone with hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment) please share your experience of caring for them**	I write this statement, not just as myself but representing a substantial cohort of ER+ HER2- women who find themselves in a similar position to me. **My experience:** Within a year of my initial primary diagnosis in 2018, I developed red flag symptoms of recurrent breast cancer which I reported. Unfortunately, my symptoms were repeatedly dismissed by my breast specialist and I was refused any medical investigation. When I challenged this, I was sent for psychological counselling. Moving away from London in 2020, my new GP listened to my concerns, asked me some questions and immediately referred me for a biopsy and ultrasound. Substantial recurrence of disease was confirmed and a further FDG PET/CT scan evidenced extensive metastatic disease throughout all of my proximal appendicular and axial skeleton. Every day at some point there will be a relentless reminder that I am going to be **forced to abandon** my daughter, my family and loved ones. I worry who will look after my daughter, how will she be guided into and through her teenage years. She will need to navigate going to upper school and the numerous social complexities

	the young are required to cope with today without a mother's experience to calm, guide and develop her resilience. It is particularly distressing to know that access to potentially life-saving and certainly life-extending treatments may simply not be accessible to women in the NHS health system. If women progress quickly (a year or less) through their first line of treatment, and/or develop co-mutations (I am one of those women who progressed quickly and had co-mutations of ESR1 and PI3K), then their therapeutic options are immediately limited and outcome poor. I realised that I had an ESR1 mutation (Y537S) – particularly insensitive to Fulvestrant and would struggle to find an effective second line of treatment with the NHS England. Despite visiting a top specialist in London at the Marsden, I was unable to access any trials. I was consistently given advice to take Fulvestrant with Alpelisib but from my understanding of the research around this combination for my particular disease, I felt I had to go for a different option if I wanted to live. My friend however did take this combination and she did not survive. I decided with my oncologist to go on Capecitabine and just hope this lasts until a treatment, effective against **both** arms of mutated PI3K and ESR1 disease becomes available. Additionally, from my own and others experience, the treatment for cancer itself can be stressful as breast cancer patients are aware that as well as destroying the cancer, **they are poisoning themselves** in the process. There is very little if any support with side effects. As a classical musician it was devastating to have a physiological reaction to a certain brand of letrozole and subsequently develop lymphoedema (for which there is little support). Brand can really matter. It is just brutal out there. **Targeted treatments with kinder toxicity profiles are very important to patients**. We often have issues with walking, carrying out normal parental duties, joining in sport. Sometimes maintaining any basic fitness can be very difficult due

	to pain and various side effects of hormonal therapy, being slammed into the menopause overnight, there is just so much to deal with. A loss of physical condition can give rise to a host of other issues too. **Patient voice in metastatic breast cancer:** “It honestly feels like your life isn’t that important and you're just going to die anyway." “I feel at times I am just been left to die. My first line offered was capecitabine nothing mentioned about hormonal treatment and no explanation given. So I have no idea of what options will or will not be available to me.” “ More time for us is not considered as cost worthy”. “Poor how there are such strict rules/protocols to follow. Terrifying that an extra 6 months of my life seems to mean nothing... The harsh outdated chemotherapies used when there are other options you don’t “qualify “ for if you’ve had certain other drugs." **Metastatic Breast Cancer is the leading cause of death for women aged 35-64 in England and Wales (ONS, 2023).** I want to know why people are continually shocked to find this fact out, almost as if it is a secret. Women are systematically broken down by the disease and the toxicity of harsh medications before dying, often in what should be the prime of their working lives, often juggling work and children or grandchildren, looking after elderly parents and running a house and their families. We need to diminish the power of metastatic breast cancer to destroy women by advocating for those women stricken with the terminal disease to access the most

	appropriate treatment. Being honest about the extent of this disease and the people succumbing to it would be a good or at least an honest start. **References:** Office for National Statistics (ONS), released 15 December 2023, ONS website, statistical bulletin; Deaths registered in England and Wales: 2022
7a. What do you think of the current treatments and care available for hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	**7a.** Current treatments for PI3K mutated disease post oestrogen therapy with CDK 4/6 have **harsh toxicity profiles which can exclude many patients** from being able to tolerate them and leave others quite ill. Additionally, a substantial cohort of co-mutated ESR1 and PI3K patients seem overlooked and the synergistic effect of fulvestrant is highly questionable. **We can and must do better for our breast cancer patients and their families!** **7b.** Patients may not always be aware of what disease they have or available medications. This could be for a number of factors but there also seems to exist a huge imbalance of power in consultation rooms. Patients, already beaten down with the horror of what they face, may lack the confidence and experience to even begin to address the consequences of choices and treatment. **Patient voice who have been on Truqap (Capivasertib);** "I'm on Truqap and Orserdu. Not a trial, just the way my Doctor prescribed. Truqap for me is miles above Piqray on side effects. Piqray almost killed me, shut my kidneys down…". "Piqray was the worst for me in 5 treatment regimens…. I'm on Enhertu now" **"I have been on it (Truqap) for 10 months. Tumor markers dropped a lot."**

	Patient voice from United Kingdom; “Current treatments are offered without standard genomic testing and this should be routinely done so that we move away from a one size fits all approach. The fact that Capivasertib targets ATK is a welcome addition layer to the CDK4/6 inhibitor drugs offered at first line treatment.” “I think it’s disgusting that we are limited non treatment options based on prior therapies. Unless there is a scientific, research based evidence for exclusion then why are we prevented from trying available drug combinations? I'm a classic example.. I'm currently on Piqray and Fulvestrant so my disease would be eligible for Capivasertib. However, I'm pretty certain that if/when it is approved I would be excluded from this treatment because I have already received Piqray and Fulvestrant! This is devastating.. the drugs, whilst targeting similar mutations target mutations at different cellular levels… Considering the time, effort and money that is put into developing these drugs why not make them available to anyone who is eligible in terms of their disease! The USA allow this.. granted insurance pays but if there was no chance of the treatment working it wouldn't be allowed. If we are genuine about improving survival then we need to look at the restrictions placed on treatment eligibility and allow such decisions to be based solely upon what treatment will work, regardless of prior treatment lines… not enough is done for secondary patients, we are forgotten about” “Great to extend life without needing iv treatments.” “I'm aware of Capivasertib but not how it works. I'm stable on Palbociclib and Fulvestrant. My next line is Exemestane & Everolimus. Highly likely it won't work for me as Exemestane is the same group of AI's as Letrozole and Letrozole didn't work

	for me. I probably wouldn't be offered Capivasertib anyway as already on Fulvestrant. That's just morally wrong to remove a potentially life extending option." "Probably side effects…as with all of these drugs. Fulvestrant is a horrible drug to have. Can Capivasertib not be partnered with an oral equivalent?" Often overwhelmed, patients progress on standardised treatments to their death, or until the medicine has made them so ill they can take no more treatment, none the wiser of what disease they even have. They suffer being brushed off at their most vulnerable and simply unable to access optimum treatment. Other patients may question or advocate (fight) for themselves and to access treatment. If lucky, they may have an activist oncologist who will find them a trial or advocate for them to receive optimum treatment and they may extend their lives because of this. From my Charity work, patients tell me they feel access to timely and optimum treatment is where the real fight of cancer lies. Metastatic patients feel constantly abandoned Private patients may have better access to timely care and a more flexible approach and better choice of treatment pathway. I spend much time considering whether this is acceptable and get very anxious when 'societal preferences' are mentioned because it seems to me society does not understand the extent of metastatic breast cancer, who is getting it and what it means to have the disease. The inequity of treatment access is certainly not fair but in terms of what is sustainable, equity of access to treatment and with it fairness and justice seems to take a back seat.
8. If there are disadvantages for patients of current NHS treatments for hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment (for example, how they are given or taken,	The are some disadvantages of current NHS treatments for patients with ER+ and HER2- disease because there is a lack of ability to initiate targeted treatments. Many advanced metastatic breast cancer patients are not tested for even the most common mutations they may have after progressing on 1st line endocrine and CDK

side effects of treatment, and any others) please describe these	4/6 inhibition. Oncologists are left following guidelines and retrospectively working out what may or may not work for that individual patient. **Patients themselves may waste their health and precious months of their lives** progressing on treatments that were **not efficacious for them from the outset**. The analysis of the **BYLieve study** in which all patients had prior CDK4/6 inhibitor therapy, the current SoC of **Alpelisib and Fulvestrant was less effective for ESR1 and PI3K co-mutated disease (**Kaklamani and Mallarmé, 2024). There is a **substantial cohort of patients** with advanced ER+ metastatic breast cancer that have **co-mutations in the AKT/PIK3 pathway AND ESR1.** These patients may struggle to access effective treatment against both these pathways of disease in the U.K. Patients feel frustrated that co-mutated disease is being overlooked and we are too slow to combine treatments in clinic. Guidelines may not always receive timely updates, for example recommendations on chemotherapy for people with advanced breast cancer have not been updated since 2009 (NICE, 2018). Guidelines may be treated as rules and serve as excellent barriers to access drugs for patients. They seem to be applied with inconsistency across the country. Another disadvantage is a lack of genomic testing. We know from trials that some patients with identical diagnosis of ER+ MBC with similar prognostic and predictive biomarkers can progress on the same hormonal therapy almost immediately, whereas others can remain on therapy without relapse for years (Robertson *et al.,* 2009; Mauri *et al.,* 2006; Nabholtz *et al.,* 2003; Bonneterre *et al.*, 2000). Every breast cancer is highly individual to its host, you simply don't know what is in the patient's genome until you look at it.

	Access to optimum treatment and meaningful timely intervention can vastly influence both life quality and expectancy outcomes for the patient. **References:** Bonneterre, J. *et al.* (2000) 'Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: Results of the tamoxifen or ARIMIDEX randomized group efficacy and Tolerability Study', *Journal of Clinical Oncology*, 18(22), pp. 3748–3757. doi:10.1200/jco.2000.18.22.3748. Kaklamani, V. and Mallarme, F., 2024. '*Treatment Strategies and sequencing after Endocrine Therapy plus CDK 4/6 inhibitors in Patients with ER+/HER2-Advancer/Metastatic breast cancer.*' European Medical Journal Onc. 2024;12[1]:27-38. https://doi.org/10.33590/emjoncol/YFWE5597. Mauri, D. *et al.* (2006) 'Survival with aromatase inhibitors and inactivators versus standard hormonal therapy in Advanced breast cancer: Meta-analysis', *JNCI: Journal of the National Cancer Institute*, 98(18), pp. 1285–1291. doi:10.1093/jnci/djj357. Nabholtz, J.M. *et al.* (2003) 'Anastrozole (ArimidexTM) versus Tamoxifen as first-line therapy for Advanced Breast Cancer in Postmenopausal women: Survival analysis and updated safety results', *European Journal of Cancer*, 39(12), pp. 1684–1689. doi:10.1016/s0959-8049(03)00326-5. NICE (2018) Surveillance decision: Evidence: *'Early and locally advanced breast cancer: Diagnosis and management: Guidance*, NICE. Available at: https://www.nice.org.uk/guidance/ng101/resourc'es/2023-surveillance-of-early-and-locally-advanced-breast-cancer-diagnosis-and-management-nice-guideline-ng101-

	and-advanced-breast-cancer-diagnosis-and-treatment-nice-guideline-cg81-11321031709/chapter/Surveillance-decision?tab=evidence#advanced-breast-cancer (Accessed: 06 November 2024). Robertson, J.F.R. *et al.* (2009) 'Activity of fulvestrant 500 mg versus Anastrozole 1 mg as first-line treatment for advanced breast cancer: Results from the first study', *Journal of Clinical Oncology*, 27(27), pp. 4530–4535. doi:10.1200/jco.2008.21.1136.
9a. If there are advantages of Capivasertib with fulvestrant over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does Capivasertib with fulvestrant help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	**9a.** The advantages of using Capivasertib for ER+/HER2- breast cancer for patients following on from an anti-oestrogen treatment and CDK 4/6 inhibitor seems to be a reduced toxicity profile. Although Alpelisib and Fulvestrant and Everolimus and Exemestane are potentially offered, the toxicity profile of these combinations mean that the take up of them may be less than expected. Some patients reported that they had refused the alpelisib-fulvestrant combination altogether due to the substantial toxicities potentially incurred (hyperglycemia). CAPItello-291 trial showed that taking capivasertib with fulvestrant effectively targeting the AKT-PTEN-PI3K pathway, resulted in a significant improvement in progression-free survival among patients with hormone receptor–positive, HER2-negative advanced breast cancer that had progressed during previous aromatase inhibitor therapy with or without a CDK4/6 inhibitor (Turner *et al.,* 2023). Better health means better ability to continue on with life. **9b.** The advantages of Capivasertib according to patients appear to be that; • Resulted in a significant progression free survival • The safety profile showed that diarrhoea and rash were the most common side effects and manageable • The incidence of discontinuation due to adverse events was relatively low.

	9c. It should be noted that this trial used an intermittent dosing schedule of Capivasertib which may be attractive to patients and doctors alike as it appeared to reduce the toxic-effect profile of this type of inhibitor, with a low incidence of hyperglycemia. Anecdotally, at ESMO 2024 this year when faced with co-mutated ER+/HER2- metastatic patients a whole panel of Oncologists unanimously chose Capivasertib and Fulvestrant over Alpelisib and Fulvestrant or Exemestane and Everolimus. **References;** Turner, N.C. *et al.* (2023) 'Capivasertib in hormone receptor–positive advanced breast cancer', *New England Journal of Medicine*, 388(22), pp. 2058–2070. doi:10.1056/nejmoa2214131.
10. If there are disadvantages of Capivasertib with fulvestrant over current treatments on the NHS please describe these. For example, are there any risks with Capivasertib with fulvestrant? If you are concerned about any potential side effects you have heard about, please describe them and explain why	**10.** None noted
11. Are there any groups of patients who might benefit more from Capivasertib with fulvestrant or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility,	**11.** None noted

dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment and Capivasertib with fulvestrant? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	**12.** None noted
13. Are there any other issues that you would like the committee to consider?	**13. Patients have raised concerns that they may not be able to access capivasertib with fulvestrant because they have already been given fulvestrant in an earlier line of treatment.** Oncologists must be enabled to use better targeted treatments for each patient. Even with the drugs we have available on the NHS, there is capacity for much greater tailoring of treatment towards individual disease. There is a need for more open discussion between oncologists and patients and honesty about when treatments may not be helpful.

	Patients with **Invasive Lobular Breast** cancer where molecular differences have treatment implications (Barroso-Sousa and Metzger-Filho, 2016) are at a disadvantage. Despite this sub-type being quite a different entity to NST/ductal cancers with a distinct genomic profile (Ciriello *et al,* 2015; Desmedt *et al.,* 2016) and impacting more women than cancers of the kidney, brain, pancreas, liver and ovaries, many study conclusions where standard of care guidelines are created are driven by NST/ductal breast cancers (Mouabbi *et al.,* 2022). Regrettably, many lobular breast cancers are still receiving standard of care chemotherapy, despite a comprehensive review showing there is little clinical benefit. There seems to be a gap in treatment **for ESR1 mutated patients and also co-mutated PI3K and ESR1 disease**. I hope going forward we will be looking to combine drugs for co-mutated disease with known efficacy against ESR1 part of it. Drugs partnerships using Elacestrant, Lasofoxifene, Camizestrant, Imlunestrant etc already used in America and in Europe by the private sector and in trials need to be urgently translated into NHS clinics. Cancer does not discriminate about within whom it resides and can almost laugh at the strict guidelines that may be insensitive to the current scientific body of knowledge. The NHS and patients may suffer waste of financial (for the NHS) and metabolic (for the patient) resources where **patients are offered treatments that may not be effective for their disease yet lie within the guidelines**. It is really important to **drive this home to the people making decisions over our lives**. There needs to be **better access to targeted drugs** such as **Capivasertib** for patients on the NHS with ER+/ HER2- breast cancer so the oncologist can target the disease they see before them. How valuable is progression free survival with a high toxicity treatment offering no overall survival? Treatment, as far as possible,

	needs to be **based on targeting existing disease and measured by both survival outcomes and quality of life.** **References:** Barroso-Sousa, R. and Metzger-Filho, O. (2016) 'Differences between invasive lobular and invasive ductal carcinoma of the breast: Results and therapeutic implications', *Therapeutic Advances in Medical Oncology*, 8(4), pp. 261–266. doi:10.1177/1758834016644156. Ciriello, G. *et al.* (2015) 'Abstract S2-04: Comprehensive Molecular Characterization of invasive lobular breast tumors', *Cancer Research*, 75(9_Supplement). doi:10.1158/1538-7445.sabcs14-s2-04. Desmedt, C. *et al.* (2016) 'Genomic characterization of Primary Invasive Lobular Breast Cancer', *Journal of Clinical Oncology*, 34(16), pp. 1872–1881. doi:10.1200/jco.2015.64.0334. Mouabbi JA, Hassan A, Lim B, Hortobagyi GN, Tripathy D, Layman RM. '*Invasive lobular carcinoma: an understudied emergent subtype of breast cancer'.* Breast Cancer Res Treat. 2022 Jun;193(2):253-264. doi: 10.1007/s10549-022-06572-w. Epub 2022 Mar 26. PMID: 35347549.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Patients are concerned over lack of access to capivasertib with fulvestrant because they have already been given fulvestrant in an earlier line of treatment.
- Patient disease profile, if not fully assessed from the outset, prevents targeted treatment.
- Current treatment for PI3K mutations has high toxicity resulting in significant side effects that need to be treated separately (higher costs). Whereas, Capivasertib targeting AKT-PTEN-PI3K disease pathway for ER+ HER2- metastatic breast cancer patients uses a novel dosing schedule for (4 days on, 3 days off) which may make this drug more tolerable option for patients
- The ESR1 arm of PI3K/ESR1 co-mutated disease (specifically ESR1-Y537S) may not be effectively targeted due to use of fulvestrant in the combination. Analysis of with the BYLieve study showed current SoC of Alpelisib and Fulvestrant was less effective for ESR1 and PI3K co-mutated disease.
- Access to optimum treatment and drugs targeting a patient's metastatic breast cancer continues to be challenging under the current system.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Patient expert statement

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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Clinical expert statement

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

NICE National Institute for Health and Care Excellence

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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 also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **<insert deadline>.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

Clinical expert statement

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

NICE National Institute for Health and Care Excellence

Part 1: Treating hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment – current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Charlotte Moss
2. Name of organisation	Breast Cancer Now
3. Job title or position	Consultant Medical Oncologist, Kent Oncology Centre
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with hormone receptor-positive HER2-negative advanced breast cancer? ☐ A specialist in the clinical evidence base for hormone receptor-positive HER2-negative advanced breast cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here.	☐ Yes

(If you tick this box, the rest of this form will be deleted after submission)	
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To prolong survival with best quality of life.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A delay in median time to progression of 3 months or more. Since progression may mean an increase in symptoms and/or escalation to more toxic treatment, including chemotherapy. Benefit needs to weighed against the risks of adverse effects from treatment.
10. In your view, is there an unmet need for patients and healthcare professionals in hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment?	Multiple agents are available for treatment for hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment but this condition remains incurable and debilitating. There is an unmet need for improvement in effectiveness and reduction in toxicity of available treatments.
11. How is hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	NICE Guidelines and Technology Appraisals / CDF funding dictate the NHS pathway – relevant guidelines: Advanced breast cancer diagnosis and treatment (2009; updated 2017) NICE guideline CG81 Alpelisib with fulvestrant for treating hormone receptor positive, HER2-negative, PIK3CA-mutated advanced breast cancer (2022) NICE technology appraisal guidance 816. Everolimus with exemestane for treating advanced breast cancer after endocrine therapy (2016) NICE technology appraisal 421.

• What impact would the technology have on the current pathway of care?	International Guidelines: ESMO, ABC4, ASCO and NCCN guidelines There is a consensus around the current NHS standard of care for hormone receptor-positive HER2-negative advanced breast cancer 1st line vast majority receive endocrine therapy & CDKi (ribo/palbo/abema) Minority may have 1st line chemotherapy then maintenance endocrine & CDKi Few, usually frail women may have 1st line single endocrine agent 2nd Line Options: Fulvestrant and CDKi (if not given 1st line) Everolimus and Exemestane Single Agent endocrine: Tamoxifen or Exemestane (only if frail) If PIK3CA activating mutation & previous CDKi: Alpelisib and fulvestrant Or chemotherapy (oral or iv) A "postcode lottery" exists for access to single agent Fulvestrant, (despite thorough NICE appraisal of it's clinical utility: Fulvestrant was not deemed cost effective when it cost >£500 per injection in 2018. But currently as a generic drug it costs £64 per injection Technology appraisal guidance Published: 31 January 2018 www.nice.org.uk/guidance/ta503) Capivasertib with fulvestrant would offer a further option in the 2nd line setting for those with a mutation in the AKT pathway (PIK3CA, AKt1 or PTEN) who have had previous CDKi in the metastatic setting

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Due to current guidance (Alpelisib with fulvestrant for treating hormone receptor-positive, HER2-negative, PIK3CA-mutated advanced breast cancer (2022) NICE technology appraisal guidance 816). Patients on first line endocrine and CDKi are tested for PIK3CA mutation. Capivasertib use would require extra testing of stored tissue for mutation in the AKT pathway (PIK3CA, AKt1 or PTEN). My understanding is that the different Genome Laboratory Hubs have approached PiK3CA testing in different ways in different regions: some GLHs have carried out PIK3CA test in isolation others use a panel comprising PIK3CA, AKt1 or PTEN . So there will be an initial period of adjustment if Capivasertib is approved with retesting (on stored tissue) in some areas and re-reporting of test results in other areas.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Current evidence doesn't show increase in length of life but from CAPItello 291 clinical trial there was a meaningful delay in disease progression (7.3m median PFS for Alpelisib with fulvestrant) vs 3.1m mPFS for Fulvestrant alone). From reported clinical trial data, a reduction in hyperglycaemia and stomatitis is a meaningful benefit in terms of quality of life compared with Alpelisib and Fulvestrant combination (G3 hyperglycaemia with Capivasertib in CAPItello 291 was 2% while with Alpelisib in BYLieve 30%)
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The reduction in rates of hyperglycaemia may reduce the risks of treatment for those aged over 75, BMI>30, diabetic or pre-diabetic patients.

15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Capivasertib should be easier to manage and tolerate since it causes less hyperglycaemia and stomatitis. Blood sugar monitoring is arduous for patients and may be a barrier to treatment. Blood sugar monitoring requires HCP time spent training patients, provision of blood glucose monitors, test strips, needles and facilities for their safe disposal. For those who develop significant hyperglycaemia, further diabetes medications are prescribed whose adverse effects can affect quality of life (diarrhoea, poor appetite, renal impairment). Those on Metformin have extra blood tests to monitor renal function prior to CT scans with iv contrast. Stomatitis can affect quality of life painful mouth ulcers reduce ability to enjoy food, can restrict oral intake. Treating and preventing stomatitis is also time consuming for patients with regular mouthwashes 4 times a day.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Monitoring and management of blood sugars will follow the SPC and the company resources - which may be less testing than for Alpelisib. Monitoring of treatment efficacy will be the same as Alpelisib.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	No

18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes - due to the improvement in side effect profile vs Alpelisib with reduction in hyperglycaemia and stomatitis
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Common AEs: hyperglycaemia, rash, diarrhoea, stomatitis, nausea, fatigue, anaemia. Trial data indicates lower rates of hyperglycaemia and stomatitis with capivasertib and Fulvestrant (vs Alpelisib and fulvestrant) (G3 hyperglycaemia with Capivasertib in Capitello 291 was 2% while with Alpelisib in BYLIEVE Cohort A 30%) Blood sugar monitoring is arduous for patients and may be a barrier to treatment. Blood sugar monitoring requires HCP time spent training patients, provision of blood glucose monitor, test strips, needles and facilities for their safe disposal. For those who develop significant hyperglycaemia, diabetes medications are prescribed whose adverse effects can affect quality of life (eg diarrhoea, poor appetite, renal impairment). Those on Metformin have extra blood tests to monitor renal function prior to CT scans with iv contrast. Stomatitis can affect quality of life: painful mouth ulcers reduce enjoyment of food & can restrict oral intake. Treating and preventing stomatitis is time consuming requiring mouthwashes 4 times a day.

20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes - CAPItello 291 trial population broadly reflects current practice / UK population for second line treatment for hormone receptor-positive HER2-negative advanced breast cancer . Comparator arm of single agent fulvestrant isn't available throughout UK – but the same comparator arm was used in BYlieve to establish clinical utility of Alpelisib and fulvestrant in this setting. Outcomes: Yes PFS, OS and toxicity were reported N/A
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA421 (everolimus with exemestane) and TA816 (alpelisib with fulvestrant)?	https://ascopubs.org/doi/pdf/10.1200%2FJCO.2023.41.16_suppl.1078 Chia et al Update on BYLieve study – with longer follow up, mature data overall survival benefit with Alpelisib and Fulvestrant established vs fulvestrant alone. (ASCO abstract **JOURNAL OF CLINICAL ONCOLOGY** Volume 41 • Number 16_suppl • June 2023 **Pages: 1078)**
23. How do data on real-world experience compare with the trial data?	I'm not aware of any RWE data
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this	Not that I'm aware of

treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Activity of Capivasertib Fulvestrant combination appears similar to Alpelisib Fulvestrant for treating hormone receptor-positive, HER2-negative, PIK3CA-mutated advanced breast cancer

Capivasertib should be easier to manage and tolerate since it causes less hyperglycaemia and stomatitis.

Capivasertib use should allow greater access to treatment and reduced burden of toxicity management, reduced emergency hospital admissions and hospital visits due to hyperglycaemia and stomatitis

Capivasertib use will require extra testing of tumour samples for AKT pathway alterations (looking for PIK3CA, AKt1 or PTEN mutations rather than just PIK3CA mutation).

According to GLH practice: looking for AKT pathway alterations on stored tissue may require either re-testing or re-reporting of PIK3CA test results.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with hormone receptor-positive HER2-negative advanced breast cancer or caring for a patient with hormone receptor-positive HER2-negative advanced breast cancer. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **<insert deadline>.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

Patient expert statement

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

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment

Table 1 About you, hormone receptor-positive HER2-negative advanced breast cancer, current treatments and equality

1. Your name	Eleanor Pearce Willis
2. Are you (please tick all that apply)	☐ A patient with hormone receptor-positive HER2-negative advanced breast cancer? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with hormone receptor-positive HER2-negative advanced breast cancer? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Breast Cancer Now
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☒ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☒ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☒ I have not completed part 2 of the statement
6. What is your experience of living with hormone receptor-positive HER2-negative advanced breast cancer? **If you are a carer (for someone with advanced breast cancer) please share your experience of caring for them**	
7a. What do you think of the current treatments and care available on the NHS for hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	
8. If there are disadvantages of current NHS treatments for hormone receptor-positive HER2-negative advanced breast cancer (for example, how they are given or taken, side effects of treatment, and any others) please describe these	

9a. If there are advantages of capivasertib with fulvestrant over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does capivasertib with fulvestrant help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	
10. If there are disadvantages of capivasertib with fulvestrant over current treatments on the NHS please describe these. For example, are there any risks with capivasertib with fulvestrant? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from capivasertib with fulvestrant or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering hormone	

receptor-positive HER2-negative advanced breast cancer after endocrine treatment and capivasertib with fulvestrant? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

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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]

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

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Confidential (CON) data are highlighted in blue throughout the report.

Confidential comparator prices are highlighted in green throughout the report.

Any de-personalised data are highlighted in pink throughout the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors:

Huiqin Yang acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Sabine Grimm acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Willem Witlox, Manuela Joore and Bradley Sugden acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Mubarak Patel and Kevin McDermott acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Xiaoyu Tian acted as systematic reviewer as well as health economist on this assessment. Nigel Armstrong acted as systematic reviewer and health economist on this assessment, critiqued the company's submission, contributed to the writing of the report and provided general guidance. Robert Wolff critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

AACR	American Association for Cancer Research
ABC	Advanced breast cancer
ACP	American College of Physicians
AE	Adverse events
AEMPS	Agencia Espanola d Medicamentos y Productos Sanitarios
AI	Aromatase inhibitor
AIFA	Agenzia Italiana del Farmaco
AJCC	American Joint Committee on Cancer
ASCO	American Society of Clinical Oncology
AIC	Akaike information criterion
AKT	Serine/threonine kinase
BC	Breast cancer
BIC	Bayesian information criterion
BICR	Blinded Independent Central Review
BNF	British National Formulary
CADTH	Canadian Agency for Drugs and Technologies in Health
CDK	Cyclin-dependent kinase
CDK4/6	Cyclin-dependent kinases 4 and 6
CDK4/6i	Cyclin-dependent kinases 4 and 6 inhibitor
CDSR	Cochrane Database of Systematic Reviews
CG	Clinical guidance
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CiC	Commercial in Confidence
CR	Complete response
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company submission
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DARE	Database of Abstracts of Reviews of Effects
DCO	Data cut-off
DFS	Disease-free survival
DIC	Deviance information criterion
DoR	Duration of response
DOR	Duration of response
DRFI	Distant recurrence-free interval
DSA	Deterministic sensitivity analyses
DSU	Decision Support Unit
EAG	Evidence Assessment Group
EBM	Evidence-Based Medicine Reviews
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EFS	Event-free survival
EMA	European Medicines Agency
eMIT	Electronic market information tool
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 Items
ESMO	European Society for Medical Oncology
EQ-5D-5L	European Quality of Life-5 Dimensions 5-Levels

ER	Oestrogen resistant
ET	Endocrine therapy
EUR	Erasmus University Rotterdam
FAS	Full analysis set
FDA	Food and Drug Administration
FE	Fixing errors
FFPE	Formalin-fixed paraffin-embedded
FV	Fixing violations
HAS	Haute Autorité de Sante
HbA1c	Glycosylated haemoglobin
HER2	Human epidermal growth factor receptor 2
HER2-	Human epidermal growth factor receptor 2-negative
HR	Hazard ratio
HR+	Hormone receptor-positive
HRQoL	Health-related quality of life
HSU	Health state utility
HSUV	Health state utility value
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ICER	Institute for Clinical and Economic Review
ICTRP	International Clinical Trials Registry Platform
iDFS	Invasive disease-free survival
IHC	Immunohistochemistry
iNHB	Incremental net health benefit
IQWiG	Institute for Quality and Efficiency in Health Care
ISH	In situ hybridisation
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
IWRS	Interactive web response system
KM	Kaplan-Meier
KSR	Kleijnen Systematic Reviews Ltd
LHRH	Luteinizing hormone-releasing hormone
LS	Least square
LYs	Life years
mBC	Metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MJ	Matters of judgement
MMRM	Mixed model repeated measures
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin
NA	Not available
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NGS	Next generation sequencing
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NL	The Netherlands
NMA	Network meta-analysis
NR	Not reported
NSAI	Nonsteroidal aromatase inhibitor
NSCLC	Non-small cell lung cancer

ONS	Office of National Statistics
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PAS	Patient Access Scheme
PBAC	Pharmaceutical Benefits Advisory Committee
PD	Progressed disease
PF	Progression-free
PFS	Progression-free survival
PFS2	Second progression-free survival
PH	Proportional hazard
PI3K	Phosphatidylinositol-3-kinase
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PR	Progesterone receptor
PR	Partial response
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PROMs	Patient-reported outcome measures
PSA	Probabilistic sensitivity analyses
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PTEN	Phosphatase and tensin homolog
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumours
RoB 2	Risk of Bias tool
RWE	Real world evidence
SABCS	San Antonio Breast Cancer Symposium
SAE	Serious adverse event
SD	Standard deviation
SERDs	Selective oestrogen receptor degraders
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SR	Systematic review
STA	Single Technology Appraisal
TA	Technology Appraisals
TRAE	Treatment-related adverse event
TSD	Technical Support Document
TTD	Time to treatment discontinuation
TTF	Time to treatment failure
TTP	Time to progression
UK	United Kingdom
UMC+	University Medical Centre+
US	United States
VAS	Visual analogue scale
US	United States
WHO	World Health Organization
WTP	Willingness-to-pay

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1. Executive summary

This summary provides a brief overview of the key issues identified by the Evidence Assessment Group (EAG) as being potentially important for decision making. If possible, it also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem, Section 1.4 issues relate to the clinical effectiveness, and Section 1.5 issues related to the cost effectiveness. A summary in presented in Section 1.6.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main EAG report, see Sections 2 (decision problem), 3 (clinical effectiveness) and 4 (cost effectiveness) for more details.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1.1: Summary of key issues

ID 6370	Summary of issue	Report Sections
1	Decision problem population narrower than in NICE scope, which might overestimate effectiveness if decision not confined to decision problem population.	2.1
2	Comparators from NICE scope and/or recommended by ESMO guideline missing from the decision problem with unknown effect on effectiveness and cost effectiveness.	2.2, 3.3, 3.4, and 4 to 6
3	There was limited comparability of patients' baseline characteristics in terms of PI3K/AKT pathway alteration between included trials in the ITC analysis.	3.3 and 3.4
4	There was a lack of sufficient evidence to support the assumption of exchangeability for the purpose of ITC analysis.	3.3 and 3.4
5	Relative treatment effectiveness of all treatments versus placebo plus fulvestrant may follow a pattern over time, and notably appears to wane over time. This is not sufficiently addressed in the company's model and has a large impact.	4.2.6
6	No data imputation was performed for missing data and the covariate selection process was not sufficiently described.	4.2.8
7	The utility decrement from pre- to post-progression estimated from trial data was relatively low, and it was unclear whether the impact of disease progression was appropriately captured by the trial data, and therefore appropriately reflected in the model.	4.2.8
8	Comparator costs were considered uncertain, as there was no information on time-to-treatment discontinuation for both modelled comparators, and only limited information on relative dose intensity for alpelisib plus fulvestrant.	4.2.9

AKT = serine/threonine kinase; ESMO = European Society for Medical Oncology; ITC = indirect treatment comparison; NICE = National Institute for Health and Care Excellence; PI3K = phosphatidylinositol-3-kinase

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are the use of the company's time-varying piecewise network meta-analysis (NMA) instead of assuming constant hazard ratios (HRs), the use of the log-logistic distribution instead of the lognormal distribution for progression-free survival (PFS), the assumption of treatment effect waning after 24 months for all treatments, and an assumption, in the absence of appropriate evidence that relative dose intensity (RDI) for alpelisib plus fulvestrant was equal to that of capivasertib plus fulvestrant.

1.2 Overview of key model outcomes

NICE Technology Appraisals (TAs) compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increased PFS and overall survival (OS) health state occupancy for capivasertib plus fulvestrant, as compared to either comparator. In the progression-free (PF) health state, the undiscounted QALYs accrued were 0.77 in the capivasertib plus fulvestrant arm, compared with 0.48 in both comparator arms. In the progressed disease (PD) health state, the undiscounted QALYs accrued were 1.84 for the capivasertib plus fulvestrant arms, compared with 1.41 in the alpelisib plus fulvestrant arm, and 1.03 in the everolimus plus exemestane arm.

Overall, the technology is modelled to affect costs by:

- Higher drug acquisition and administration costs for capivasertib plus fulvestrant. Total undiscounted drug costs (deterministic) amounted to [redacted] in the capivasertib plus fulvestrant arm, compared to £30,489 in the alpelisib plus fulvestrant arm and £7,878 in the everolimus plus exemestane arm.
- Higher total resource use costs for capivasertib plus fulvestrant. Undiscounted (deterministic) resource use costs accrued were £9,669 in the capivasertib plus fulvestrant arm, £7,057 for alpelisib plus fulvestrant, and £5,544 for everolimus plus exemestane.

The modelling assumptions that have the greatest effect on the ICER are:

- Assuming a RDI of 100% for alpelisib. In a scenario analysis in the CS, which explored applying the median RDI (82.7%) for alpelisib, the pairwise deterministic ICER for capivasertib plus fulvestrant compared to alpelisib plus fulvestrant increased from the base-case result (including x 1.2 severity modifier) of [redacted] to [redacted].
- Selection of PFS and OS distributions. Scenario analyses in the company submission (CS) explored a) loglogistic PFS distribution and b) Weibull OS distribution. Using a loglogistic PFS distribution, the pairwise deterministic ICERs (including x 1.2 severity modifier) for capivasertib plus fulvestrant increased from [redacted] and [redacted] to [redacted] and [redacted] compared with alpelisib plus fulvestrant and everolimus plus exemestane, respectively. Using a Weibull OS distribution, the pairwise deterministic ICERs (including x 1.2 severity modifier) for capivasertib plus fulvestrant increased from [redacted] and [redacted] to [redacted] and [redacted] compared with alpelisib plus fulvestrant and everolimus plus exemestane, respectively.

1.3 The decision problem: summary of the EAG's key issues

The decision problem addressed in the CS is broadly in line with the final scope issued by NICE. However, the population addressed in decision problem was narrower than in the NICE scope (Table 1.2). Furthermore, the comparators from the NICE scope and/or recommended by the European Society for Medical Oncology (ESMO) guideline were missing from the decision problem (Table 1.3).

Table 1.2: Key issue 1: Decision problem population narrower than in NICE scope

Report Section	**2.1**
Description of issue and why the EAG has identified it as important	Unlike the NICE scope, the decision problem population specifies that patients have disease that has progressed on or following therapy that includes a CDK4/6i, but CDK4/6i therapy is not specified in the marketing authorisation. Therefore, it is possible that there will be some patients in clinical practice who would be eligible for capivasertib who had not previously received a CDK4/6i. This might have implications for choice of comparators given that the company exclude CDK4/6is on the basis of retreatment being inappropriate, but only if the appraisal decision includes those patients who had not previously received a CDK4/6i.
What alternative approach has the EAG suggested?	Clarification that patients with no prior CDK4/6i will not be prescribed capivasertib.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	If the population of the NICE recommendation is restricted to prior CDK4/6i then no further evidence is required. However, if it is broader then consideration needs to be given to clinical effectiveness and cost effectiveness analyses for the no prior CDK4/6i population and therefore versus appropriate comparators including a CDK4/6i.
CDK4/6i = cyclin-dependent kinases 4 and 6 inhibitor; EAG = Evidence Assessment Group; NICE = National Institute for Health and Care Excellence	

Table 1.3: Key issue 2: Comparators from NICE scope and/or recommended by ESMO guideline missing from the decision problem

Report Sections	**2.2, 3.3, 3.4 and 4 to 6**
Description of issue and why the EAG has identified it as important	Given their recommendation in the ESMO guideline and in the absence of evidence as to what patients actually receive in clinical practice, none of the comparators in the NICE scope can be ruled out, except probably retreatment with a CDK4/6i for the population of those who have had a prior CDK4/6i.
What alternative approach has the EAG suggested?	Provide evidence as to which treatments are currently used in UK clinical practice and then conduct clinical effectiveness and cost effectiveness analyses versus all relevant comparators.
What is the expected effect on the cost effectiveness estimates?	Unknown.

Report Sections	2.2, 3.3, 3.4 and 4 to 6
What additional evidence or analyses might help to resolve this key issue?	Provide evidence as to which treatments are currently used in UK clinical practice and then conduct clinical effectiveness and cost effectiveness analyses versus all relevant comparators.
CDK4/6i = cyclin-dependent kinases 4 and 6 inhibitor; EAG = Evidence Assessment Group; ESMO = European Society for Medical Oncology; NICE = National Institute for Health and Care Excellence; UK = United Kingdom	

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

The EAG identified two major concerns with the evidence presented on the clinical effectiveness: limited comparability of patients' baseline characteristics in terms of PI3K/AKT pathway-alteration between included trials in the ITC analysis (see Table 1.4) and the lack of sufficient evidence to support the assumption of exchangeability for the purpose of ITC analysis (see Table 1.5).

Table 1.4: Key issue 3: Limited comparability of patients' baseline characteristics in terms of PI3K/AKT pathway alteration between included trials in the ITC analysis

Report Sections	3.3 and 3.4
Description of issue and why the EAG has identified it as important	The ITC analysis from the CS was based on the PI3K/AKT pathway-altered subgroup of CAPItello-291 and FAKTION trials, the PIK3CA mutated subgroup of the SOLAR-1 trial, the overall populations of BOLERO 2 and BOLERO 5 trials and associated bridging studies. It should be further noted that the subgroup of the CAPItello-291 trial included all patients with PI3K/AKT alteration; however, the subgroup of FAKTION trial included a smaller proportion of patients with PI3K/AKT alteration (39% in the fulvestrant arm and 45% in the capivasertib plus fulvestrant arm). In addition, the remaining trials included in the ITC analysis recruited patients with unknown PI3K/AKT status. Therefore, there was limited comparability of patients' baseline characteristics in terms of PI3K/AKT pathway alteration between the included trials in the ITC analysis.
What alternative approach has the EAG suggested?	The ITC analysis from the CS should be ideally based on the subpopulation with PI3K/AKT pathway alteration from all included studies. However, the company stated that such data are not available beyond the CAPItello-291 and FAKTION trials of capivasertib and the SOLAR-1 trial of alpelisib.
What is the expected effect on the cost effectiveness estimates?	The effect on the cost effectiveness estimates is difficult to predict.
What additional evidence or analyses might help to resolve this key issue?	The EAG recommends that the ITC analysis should be performed on the basis of the data from the PI3K/AKT pathway-altered subpopulation from all included studies if relevant data are available.
AKT = serine/threonine kinase; CS = company submission; EAG = Evidence Assessment Group; ITC = indirect treatment comparison	

Table 1.5: Key issue 4: Lack of sufficient evidence to support the assumption of exchangeability for the purpose of ITC analysis

Report Sections	3.3 and 3.4
Description of issue and why the EAG has identified it as important	Following the assessment of heterogeneity and uncertainty, there was considerable heterogeneity in terms of baseline characteristics including PI3K/AKT pathway alteration, HER2 status, ECOG PS 1 status and prior CDK4/6i use for the included populations from the included trials of the ITC analysis. Therefore, there was a lack of sufficient evidence to support the assumption of exchangeability for the purpose of ITC analysis. Due to this issue, there were uncertainties in the validity of ITC results.
What alternative approach has the EAG suggested?	The assumption of exchangeability for the purpose of ITC analysis should be acceptable.
What is the expected effect on the cost effectiveness estimates?	The effect on the cost effectiveness estimates is difficult to predict.
What additional evidence or analyses might help to resolve this key issue?	The EAG recommends that sufficient evidence should be provided to support the assumption of exchangeability for the purpose of ITC analysis.
AKT = serine/threonine kinase; CDK4/6i = cyclin-dependent kinases 4 and 6 inhibitor; EAG = Evidence Assessment Group; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ITC = indirect treatment comparison	

1.5 The cost effectiveness evidence: summary of the EAG's key issues

A full summary of the cost effectiveness (CE) evidence review conclusions can be found in Section 6.4 of this report. The company's CE results are presented in Section 5, the EAG's summary and detailed critique in Section 4, and the EAG's amendments to the company's model and results are presented in Section 6. The main EAG results are reproduced using confidential Patient Access Schemes (PAS) in a confidential appendix. The key issues in the CE evidence are discussed in Tables 1.6 and 1.7.

Table 1.6: Key issue 5: Relative treatment effectiveness over time

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	The relative treatment effectiveness of all treatments versus placebo plus fulvestrant may follow a pattern over time, and notably appears to wane over time. This is not sufficiently addressed in the company's model and has a large impact, particularly given that most of the QALY gains occur in the extrapolated period.
What alternative approach has the EAG suggested?	Include treatment effect waning (both PFS and OS) for all treatments by setting HRs to 1 at 24 months.
What is the expected effect on the cost effectiveness estimates?	The ICER for capivasertib plus fulvestrant versus both comparators increases when modelling treatment effect waning. It decreases with the company's piecewise NMA.
What additional evidence or analyses might help to resolve this key issue?	NMA using a time-varying parametric model and application of treatment effect waning.

EAG = Evidence Assessment Group; HRs = hazard ratios; ICER = incremental cost-effectiveness ratio; NMA = network meta-analysis; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year

Table 1.7: Key issue 6: Statistical approach for analysing HRQoL

Report Section	**4.2.8**
Description of issue and why the EAG has identified it as important	a. In the MMRM analyses of HRQoL data, no missing data imputation was conducted under the assumption that data are missing at random, which the EAG considered may potentially introduce bias. b. Four MMRM models were explored. There was insufficient reporting on methods, for example no justification was provided as to why additional covariates were not considered and no covariate selection process was mentioned. It remains uncertain which model would be preferred, as the current selection may neglect potentially confounding variables that could influence health state utilities.
What alternative approach has the EAG suggested?	a. Justification regarding the assumption that data is missing at random. Only baseline missingness by different characteristics were provided however, it remains unlikely that the assumption that data is missing at random holds. b. Results for each explored model to be presented. In response, the company provided utility results and corresponding P-values for each utility output. No significance levels were provided for included covariates.
What is the expected effect on the cost effectiveness estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	a. Missing data imputation for the missing EQ-5D-5L data in the CAPItello-291 trial. Different data imputations should be explored according to the potential mechanisms causing the missingness in the data. b. For each model: model intercept, covariate estimates, and corresponding significance levels for each covariate. Further justification regarding the covariate selection process would also be desirable and further justification to support the assumption that no additional covariates should be considered.

EAG = Evidence Assessment Group; EQ-5D-5L = European Quality of Life-5 Dimensions 5-Levels; HRQoL = health-related quality of life; MMRM = mixed model repeated measures

Table 1.8: Key issue 7: Utility decrement from pre- to post-progression

Report Section	**4.2.8**
Description of issue and why the EAG has identified it as important	The utility decrement between pre- and post-progression is relatively small ([redacted]). It is unclear whether sufficiently long enough post-progression utility data was collected, which may lead to biased post-progression HSUVs.
What alternative approach has the EAG suggested?	Scenario analyses informing HSUVs with those identified in TA421, TA619, and TA579. Also, a scenario utilising the PF utility from the CS base-case and a utility decrement equal to that found in TA421 (i.e., decrement of 0.302).

Report Section	4.2.8
What is the expected effect on the cost effectiveness estimates?	The company explore three scenarios reducing PD HSUVs to 0.70, 0.65, and 0.60. The ICER (deterministic including x 1.2 QALY weight) compared to alpelisib plus fulvestrant increased from [redacted] to [redacted], [redacted], and [redacted], respectively. Compared to everolimus plus exemestane, the ICER (deterministic including x 1.2 QALY weight) increased from [redacted] to [redacted], [redacted], and [redacted], respectively. The company suggested that a scenario utilising utility values from TA421 was provided, however, no such results were received by the EAG.
What additional evidence or analyses might help to resolve this key issue?	Further assessment of the EQ-5D-5L data collected with respect to when questionnaires were completed post-progression and durations of follow-up for which questionnaires were completed post-progression. Consider the exploratory scenario analysis utilising a PD utility of 0.60.
CS = company submission; EAG = Evidence Assessment Group; EQ-5D-5L = European Quality of Life-5 Dimensions 5-Levels; HSUVs = health state utility values; ICER = incremental cost-effectiveness ratio; PD = progressed disease; PF = progression-free; QALY = quality-adjusted life year, TA = Technology Appraisal	

Table 1.9: Key issue 8: Uncertainty about comparator costs

Report Section	4.2.9
Description of issue and why the EAG has identified it as important	There is some uncertainty about comparator costs: RDI for alpelisib plus fulvestrant is likely over-estimated. There were no data on mean TTD and therefore the company assumed that the ratio of TTD versus time to progression was the same for comparators as for capivasertib plus fulvestrant. Both may have a moderate impact on the ICER.
What alternative approach has the EAG suggested?	In the absence of better data, assume the same RDI for alpelisib plus fulvestrant as for capivasertib plus fulvestrant. Explore alternative TTDs for comparators.
What is the expected effect on the cost effectiveness estimates?	The ICER versus alpelisib plus fulvestrant increases with the changed RDI. A smaller TTD for alpelisib plus fulvestrant and everolimus plus exemestane increases the ICERs versus both.
What additional evidence or analyses might help to resolve this key issue?	Expert opinion on TTD for alpelisib plus fulvestrant and everolimus plus exemestane in comparison to that of capivasertib plus fulvestrant
EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; RDI = relative dose intensity; TTD = time to treatment discontinuation	

1.6 Summary of the EAG's view

The estimated EAG base-case ICER (probabilistic) of capivasertib plus fulvestrant versus alpelisib plus fulvestrant and everolimus plus exemestane, based on the EAG preferred assumptions highlighted in Section 5.1, was [redacted] and [redacted] per QALY gained respectively, excluding the severity modifier, and [redacted] and [redacted] per QALY gained respectively including the severity modifier. In the EAG base-case, the probability of capivasertib plus fulvestrant being cost-effective versus its comparators at thresholds of £20,000 and £30,000 per QALY gained was [redacted] and [redacted] excluding the severity modifier and [redacted] and [redacted] including the severity modifier. The most influential adjustments were

inclusion of treatment effect waning for all treatments after 24 months, which significantly increased the ICERs and the use of the piecewise NMA which significantly decreased the ICERs. The ICERs increased most in the scenario analyses using the Gompertz for modelling OS for the comparison against alpelisib plus fulvestrant and using a decreased PD utility value for the comparison against everolimus plus exemestane respectively.

Table 1.10: Summary of EAG's preferred assumptions and deterministic ICER

Scenario	Incremental cost (capivasertib + fulvestrant versus)*	Incremental QALYs (capivasertib + fulvestrant versus)*	ICER (pairwise capivasertib + fulvestrant versus)*	ICER (pairwise capivasertib + fulvestrant versus, incl severity modifier)
Company's base-case post clarification				
Alpelisib plus fulvestrant	[redacted]	0.61	[redacted]	[redacted]
Everolimus with exemestane	[redacted]	0.94	[redacted]	[redacted]
1. Time varying NMA PFS 3 months, OS 6 months				
Alpelisib plus fulvestrant	[redacted]	0.62	[redacted]	[redacted]
Everolimus with exemestane	[redacted]	0.86	[redacted]	[redacted]
2. PFS log-logistic				
Alpelisib plus fulvestrant	[redacted]	0.64	[redacted]	[redacted]
Everolimus with exemestane	[redacted]	0.96	[redacted]	[redacted]
3. Treatment effect waning after 24 months for all treatments				
Alpelisib plus fulvestrant	[redacted]	0.25	[redacted]	[redacted]
Everolimus with exemestane	[redacted]	0.45	[redacted]	[redacted]
4. RDI for alpelisib plus fulvestrant equal to capivasertib plus fulvestrant				
Alpelisib plus fulvestrant	[redacted]	0.61	[redacted]	[redacted]
Everolimus with exemestane	[redacted]	0.94	[redacted]	[redacted]
EAG's preferred base-case				
Alpelisib plus fulvestrant	[redacted]	0.23	[redacted]	[redacted]
Everolimus with exemestane	[redacted]	0.44	[redacted]	[redacted]

* Excluding severity modifier

EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; NMA = network meta-analysis; OS = overall survival; PFS = progression-free survival; RDI = relative dose intensity; QALY = quality-adjusted life year

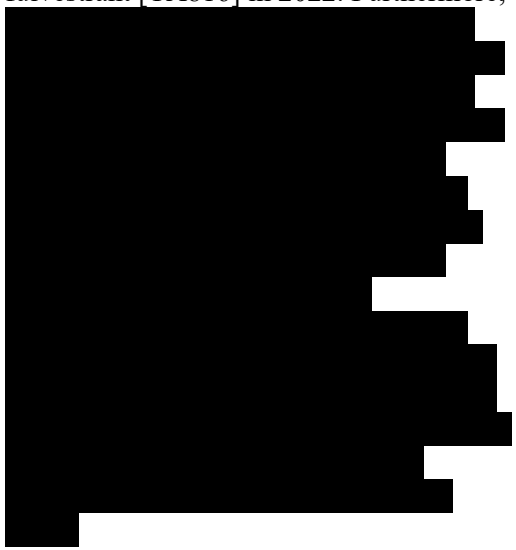
2. Critique of company's definition of decision problem

Table 2.1: Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope
Population	Adults with HR+, HER2-negative locally advanced or mBC after endocrine treatment	Adults with HR+/HER2- advanced and mBC with PI3K/AKT pathway-altered tumours (PIK3CA, AKT1, or PTEN), whose disease has progressed on or following CDK4/6i plus ET	Capivasertib is indicated in combination with fulvestrant for the treatment of adult patients with HR+/HER2- (defined as IHC 0 or 1+, or IHC 2+/ISH-) locally advanced or mBC with one or more PIK3CA/AKT1/PTEN alterations following recurrence or progression on or after an endocrine based regimen. This submission focuses on the subgroup of patients meeting the licensed indication and who have received prior CDK4/6i therapy plus AI as part of their initial endocrine based regimen. This positioning for use after CDK4/6i therapy reflects the anticipated use of capivasertib plus fulvestrant within the current UK treatment pathway and addresses an area of significant unmet need.
Intervention	Capivasertib with fulvestrant	Capivasertib with fulvestrant	N/A
Comparator(s)	CDK4/6i in combination with fulvestrant Everolimus and exemestane Exemestane Tamoxifen Fulvestrant Alpelisib plus fulvestrant (PIK3CA-mutated breast cancer)	Everolimus and exemestane For people whose breast cancer is PIK3CA-mutated: Alpelisib plus fulvestrant	The proposed positioning of capivasertib plus fulvestrant is for use following CDK4/6i plus ET. UK clinical expert opinion confirms that: Retreatment with CDK4/6is is not routinely an option, per ESMO and NCCN guidelines, and is not reimbursed by the

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope
			NHS. CDK4/6is in combination with fulvestrant are therefore not relevant comparators. Exemestane without everolimus, tamoxifen, and fulvestrant may be included in NICE CG81 as first-line therapy options in HR+ advanced breast cancer[32] but ET alone has been superseded by CDK4/6i plus AI combination therapy in all but the small proportion of patients who have comorbidities or poor PS that precludes use of CDK4/6is. In the proposed positioning of capivasertib (post CDK4/6i therapy), single agent ET with exemestane, tamoxifen or fulvestrant is not a treatment option. In clinical practice, capivasertib plus fulvestrant would be used where everolimus plus exemestane or alpelisib plus fulvestrant would be used. The only relevant comparators for capivasertib plus fulvestrant in the proposed positioning are therefore: Everolimus plus exemestane Alpelisib plus fulvestrant in patients with breast cancer containing PIK3CA mutations. As the majority of patients with PI3K/AKT pathway-altered tumours have PIK3CA mutations (>75% of patients with PI3K/AKT pathway-altered tumours have

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope
			PIK3CA mutations in the CAPItello-291 trial), alpelisib plus fulvestrant is the comparator that is most likely to be displaced by capivasertib plus fulvestrant.
Outcomes	The outcome measures to be considered include: • OS • PFS • Response rate • Adverse effects of treatment • HRQoL	• OS • PFS • Response rate • Adverse effects of treatment • HRQoL	-
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.	The economic model conforms to the NICE reference case.	The NICE guidance development manual, Section 4.8, states: *"If a diagnostic test to identify patients or establish the presence or absence of a particular biomarker is not routinely used in the NHS but is introduced to support the treatment decision for the specific technology, include the associated costs of the diagnostic in the assessments of clinical and cost effectiveness. Provide a sensitivity analysis without the cost of the diagnostic test".* PI3K/AKT pathway alterations (PIK3CA/AKT1/PTEN) occur in around 40-50% of patients with HR+/HER2- advanced breast cancer. Of these, PIK3CA mutations account for >75%. PIK3CA testing is included in the National Genomic Test Directory for Cancer and is

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope
	The economic modelling should include the costs associated with PIK3CA/AKT1/PTEN mutations in people with HR+/HER2- negative locally advanced or mBC who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See Section 4.8 of the guidance development manual (available here: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation).		in routine use following the approval of alpelisib plus fulvestrant in NICE TA816. The costs of genomic testing for PIK3CA/AKT1/PTEN-altered tumours are excluded on the basis that testing for PIK3CA alterations (the most common of all PI3K/AKT pathway alterations) is routinely performed in UK clinical practice following the NICE recommendation for alpelisib plus fulvestrant [TA816] in 2022. Furthermore, 
Subgroups to be considered	If the evidence allows the following subgroups should be considered: PIK3CA/AKT1/PTEN-altered subgroup.	The licensed indication is for use in patients with PI3K/AKT pathway-altered (PIK3CA, AKT1, or PTEN) tumours. As the proposed positioning of capivasertib plus fulvestrant is for use following a CDK4/6i plus ET, analyses are provided for this subgroup where data allow.	

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope
Special considerations including issues related to equity or equality	-	Capivasertib is an innovative therapy. It is the first licensed inhibitor of all three AKT isoforms in breast cancer and provides significant benefit to patients with advanced and metastatic disease who have limited therapy options. It was licensed following priority review by the FDA in the US in November 2023 and was granted an Innovation Passport by the UK MHRA in February 2024. Capivasertib in combination with fulvestrant is licensed for use in breast cancer in women and men. Breast cancer is rare in men and, consequently, data for capivasertib plus fulvestrant in men with breast cancer are limited. This should not preclude or limit the use of capivasertib plus fulvestrant in men in line with its licensed indication and proposed clinical positioning.	

Based on Table 1 of CS[1]

AKT = serine/threonine kinase; AI = aromatase inhibitor; AKT = serine/threonine kinase; CDK4/6 = cyclin-dependent kinases 4 and 6; CG = clinical guidance; CS = company submission; ESMO = European Society for Medical Oncology; ET = endocrine therapy; FDA = Food and Drug Administration; HR+ = hormone receptor-positive; HER2- = human epidermal growth factor receptor 2-negative; HRQoL = health-related quality of life; mBC = metastatic breast cancer; MHRA = Medicines and Healthcare products Regulatory Agency; NCCN = National Comprehensive Cancer Network; NICE = National Institute for Health and Care Excellence; NHS = National Health Service; OS = overall survival; PFS = progression-free survival; PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PSS = Personal Social Services; PTEN = phosphatase and tensin homolog; QALY = quality-adjusted life year; UK = United Kingdom; US = United States

2.1 Population

The population defined in the National Institute for Health and Care Excellence (NICE) final scope is *"Adults with hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer after endocrine treatment'."*[2] The population in the company submission (CS) is *"Adults with HR+/HER2- advanced and metastatic breast cancer with PI3K/AKT pathway-altered tumours (PIK3CA, AKT1, or PTEN), whose disease has progressed on or following CDK4/6 inhibitor plus endocrine therapy."*[1] Therefore, the scope of the population in the decision problem in the CS was narrower than the population which was defined in the NICE final scope.

EAG comment: Given this narrower population, which was addressed in the CS, the Evidence Assessment Group (EAG) requested the company to provide clarification on the difference between the population defined in the NICE final scope and the population in the CS.[3] The EAG also requested the company to clarify that the company does not expect capivasertib to be prescribed to patients except those who have progressed on or following CDK4/6i plus endocrine therapy (ET).

In responding to the EAG's request, the company made the following statement:[4]

"The scope for this appraisal was defined before the UK marketing authorisation for capivasertib in combination with fulvestrant was granted. The UK marketing authorisation was granted 17th July 2024 and the wording of the licensed indication, as reflected in our submission, is:

Capivasertib (TRUQAP®) is indicated in combination with fulvestrant for the treatment of adult patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative (defined as IHC 0 or 1+, or IHC 2+/ISH) locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following recurrence or progression on or after an endocrine based regimen." The company went on to say that: *"…the recommended first-line standard of care endocrine based therapy for men and postmenopausal women with advanced HR+/HER2- breast cancer is with a CDK4/6i (palbociclib, ribociclib or abemaciclib) in combination with an aromatase inhibitor (AI)."* The EAG acknowledge that this is consistent with the NICE scope, which also states: *"People who are before menopause or around menopause will have first-line treatment with tamoxifen and ovarian suppression if they have not previously received tamoxifen."*[2] Although the NICE scope does not state that ET has to be accompanied by a CDK4/6i, a CDK4/6i is recommended in the ESMO guidelines for most patients.[5] The exception, where ET would be used alone, is: *"…the small group of patients with comorbidities or a performance status (PS) that prevents the use of CDK4/6 inhibitor combinations; there are no clinical or biomarker data that can help to identify patients suitable for ET alone."* (p. 1478)

Therefore, it is possible that there will be some patients in clinical practice who would be eligible for capivasertib who had not previously received a CDK4/6i. This might have implications for choice of comparators given that the company exclude CDK4/6is on the basis of retreatment being inappropriate, but only if the appraisal decision includes those patients who had not previously received a CDK4/6i. This is therefore a key issue.

2.2 Intervention

The intervention (capivasertib) is in line with the NICE final scope. Capivasertib is administered orally as tablets in doses of 160 mg or 200 mg.[2] The recommended dose of capivasertib in combination with

fulvestrant is 400 mg (two 200 mg tablets) being taken orally twice daily approximately 12 hours apart (total daily dose of 800 mg), for 4 days, which are then followed by 3 days off treatment.

The recommended dose of fulvestrant treatment is 500 mg, which is administered on Days 1, 15, and 29, and once monthly thereafter. For pre/perimenopausal women, capivasertib plus fulvestrant should be administered in combination with a Luteinizing hormone-releasing hormone (LHRH) agonist.

EAG comment: The EAG considers that the intervention (capivasertib) is in line with the NICE final scope.

2.3 Comparators

The description of the comparators in the NICE final scope is as follows:[2]

- CDK4/6is in combination with fulvestrant
- Everolimus and exemestane
- Exemestane
- Tamoxifen
- Fulvestrant
- Alpelisib plus fulvestrant (PIK3CA-mutated breast cancer).

The company addressed the following comparators in the CS:[1]

- Everolimus and exemestane

For people whose breast cancer is PIK3CA-mutated:[1]

- Alpelisib plus fulvestrant

The company made the following statement:[1]

- *"Retreatment with CDK4/6 inhibitors is not routinely an option, per ESMO and NCCN guidelines,15,30 and is not reimbursed by the NHS. CDK4/6 inhibitors in combination with fulvestrant are therefore not relevant comparators.*
- *Exemestane without everolimus, tamoxifen, and fulvestrant may be included in NICE CG81 as first-line therapy options in HR+ advanced breast cancer32 but endocrine therapy alone has been superseded by CDK4/6 inhibitor plus AI combination therapy in all but the small proportion of patients who have comorbidities or poor performance status that precludes use of CDK4/6 inhibitors. In the proposed positioning of capivasertib (post CDK4/6 inhibitor therapy), single agent endocrine therapy with exemestane, tamoxifen or fulvestrant is not a treatment option.*
- *In clinical practice, capivasertib plus fulvestrant would be used where everolimus plus exemestane or alpelisib plus fulvestrant would be used."*

EAG comment: The EAG requested the company to provide further justification on the exclusion of retreatment with CDK4/6is as a relevant comparator on the basis of guidelines in England and Wales, in response to which the company cited the National Health Service (NHS) England commissioning criteria,[4] which *"permit use of CDK4/6i only if one of the following criteria applies:*

- *No prior treatment with a CDK 4/6i, or*

- *Previous treatment with another CDK4/6i but treatment has had to be stopped within 6 months of its start solely as a consequence of dose-limiting toxicity and in the clear absence of progressive disease, or*
- *Previously received adjuvant CDK4/6i for high-risk early breast cancer and treatment with CDK4/6i was completed without disease progression at least 12 months prior to the first diagnosis of recurrent or metastatic disease."*[6]

The EAG acknowledged that none of these apply to the population in either the NICE scope or the decision problem. Nevertheless, the company has only included two comparators and cites the European Society for Medical Oncology (ESMO) guideline as part of the justification for the choice.[1] However, the ESMO guideline provides a long list of comparators after progression on a CDK4/6i:[5] "The optimal sequence of endocrine-based therapy is uncertain after progression on CDK4/6is. It is dependent on which agents were used previously [in the (neo)adjuvant or advanced settings], duration of response (DoR) to previous ET (for use of second-line single-agent ET), disease burden, patient preference and treatment availability. *Evidence-based available options for second line therapy include: fulvestrant alpelisib (for PIK3CAmutated tumours, exemestane everolimus, tamoxifen everolimus, fulvestrant everolimus, AI, tamoxifen, fulvestrant, chemotherapy and poly (ADP-ribose) polymerase (PARP) inhibitors for tumours harbouring gBRCAm."* (p.1478) The EAG therefore requested evidence that the only two treatments used in United Kingdom (UK) clinical practice were those in the decision problem, to which the company responded that these two treatments were:[4] *"…validated by the Company with UK clinical experts."* They also cited the committee opinion in Technology Appraisal 816 (TA816) that everolimus plus exemestane was the appropriate comparator to alpelisib plus fulvestrant. However, the EAG note that the TA816 guidance also stated that:[7] *"People without symptomatic visceral disease can have exemestane plus everolimus…but clinical experts noted that adverse events associated with everolimus limit its use. Because of this, capecitabine chemotherapy is sometimes used instead."*(p. 7-8) The company stated in the clarification letter response that chemotherapy is only recommended in the ESMO guideline for those at risk of imminent organ failure, which the EAG can confirm is shown in Figure 2.[5]

The company ruled out fulvestrant monotherapy on the basis of the negative recommendation in TA239. However, the EAG is not entirely convinced that these are sufficient grounds given that, as well as being recommended in the latest ESMO guideline, it was listed in the NICE scope, which also cited TA239.[2]

The company argue that PARP inhibitors are not appropriate comparators because of the need to be germline BRCA/PALB2m+. However, it seems to the EAG that the coincidence of this genotype and PI3K/AKT pathway-alterations cannot be ruled out.

No evidence was provided to rule out the use of the other treatments recommended in the ESMO guideline, the company stating in response to this clarification request: *"Tamoxifen plus everolimus and fulvestrant plus everolimus, which are not licensed combinations, and single agent endocrine therapy with AI or tamoxifen would not be anticipated to be used routinely instead of NICE-recommended combinations of alpelisib plus fulvestrant (per TA816) or everolimus plus exemestane (per TA421) in patients who are eligible for these."* (p. 11-12)

Therefore, in conclusion, in the absence of evidence as to what patients actually receive in clinical practice, none of the comparators in the NICE scope can be ruled out, except probably retreatment with a CDK4/6i. This is therefore a key issue.

2.4 Outcomes

The NICE final scope lists the following outcome measures:[2]

- Overall survival (OS)
- Progression-free survival (PFS)
- Adverse effects of treatment
- Health-related quality of life (HRQoL)

The outcome measures included in the CS were consistent with those specified by the NICE final scope.

2.5 Other relevant factors

According to the company, no equality issues were related to the use of capivasertib in combination with fulvestrant for second-line treatment in unresectable or metastatic hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2) breast cancer.[1]

3. Clinical effectiveness

3.1 Critique of the methods of review(s)

The company performed a systematic review (SR) to identify and summarise the available randomised controlled trial (RCT) evidence relating to the efficacy and safety of capivasertib in combination with fulvestrant for second-line treatment in unresectable or metastatic HR+, HER2-negative breast cancer.

3.1.1 Searches

The following paragraphs contain summaries and critiques of the searches related to clinical effectiveness presented in the CS.[1] The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS) was used to inform this critique.[8] The EAG has presented only the major limitations of each search strategy in the report.

The CS, Appendix D, an additional report provided by the company and the company's response to the request for clarification detail the systematic literature review (SLR) conducted to identify relevant RCT evidence for therapies used in the treatment of HR+/HER2− unresectable/metastatic breast cancer (mBC).[1, 4, 9, 10] The searches were originally conducted in January and March 2023, and updates were carried out in August 2023 and February 2024.

A summary of the sources searched is provided in Table 3.1.

Table 3.1: Data sources for the clinical effectiveness systematic review (as reported in CS)

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
Embase	Ovid	1974-30.01.23 1974-27.03.23 1974-07.08.23 1974-06.02.24	31.01.23 28.03.23 08.08.23 07.02.24
MEDLINE (inc. In Process & Other Non-Indexed Citations and Daily)	Ovid	1946-30.01.23 1946-27.03.23 1946-07.08.23 1946-06.02.24	31.01.23 28.03.23 08.08.23 07.02.24
CENTRAL	EBM Reviews (Ovid)	To January 2024	31.01.23 28.03.23 08.08.23 07.02.24
CDSR		2005-31.01.24	
Cochrane Methodology Register		To 3rd Q 2012	
DARE		To 1st Q 2016	
HTA Database		To 4th Q 2016	
ACP Journal Club		1991-Jan 24	
Cochrane Clinical Answers		To January 2024	

Resource	Host/Source	Date Ranges	Date searched
Conferences			
ASCO AACR SABCS European Breast Cancer Conference World Congress on Breast Cancer ISPOR	Internet		08.08.23 10.02.23 08.08.23 13.02.23 28.02.24 13.02.23 07.06.23 09.08.24 17.02.23
HTA Agencies			
NICE SMC CADTH PBAC AEMPS AIFA HAS IQWiG ICER FDA EMA	Internet	No date limit applied	17.02.23 07.03.24
Trials registries			
ClinicalTrials.gov WHO ICTRP	Internet	No date limit applied	07.02.23 17.08.23 08.02.23

AACR = American Association for Cancer Research; ACP = American College of Physicians; AEMPS = Agencia Espanola d Medicamentos y Productos Sanitarios; AIFA = Agenzia Italiana del Farmaco; ASCO = American Society of Clinical Oncology; CADTH = Canadian Agency for Drugs and Technology in Health; CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; CS = company submission; DARE = Database of Abstracts of Reviews of Effects; EBM = Evidence-Based Medicing Reviews; EMA = European Medicines Agency; FDA = Federal Drug Administration; HAS = Haute Autorite de Sante; HTA = Health Technology Assessment; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; ICER = Institute for Clinical and Economic Review; IQWiG = Institute for Quality and Efficiency in Health Care; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SABCS: San Antonio Breast Cancer Symposium; SMC = Scottish Medicines Consortium; WHO ICTRP = World Health Organization International Clinical Trials Registry Platform

EAG comment:

- Searches were undertaken in January and March 2023, and updates were carried out in August 2023 and February 2024 to identify relevant RCT evidence for therapies used in the treatment of HR+/HER2− unresectable/mBC. The CS, Appendix D, an additional report provided by the company and the company's response to the request for clarification provided sufficient details for the EAG to appraise the literature searches.[1, 4, 9, 10]

- A good range of bibliographic databases, conferences, Health Technology Assessment (HTA) agency websites and trials registries were searched. Reference checking was conducted. The search documentation was clear and concise, and the searches were well structured, transparent and reproducible.
- The database searches for the clinical effectiveness SLR combined facets for advanced/mBC with terms for HR+. In the Embase and MEDLINE searches, this was then limited using a study design filter for RCTs.
- No date or language limits were applied to the searches.
- Conference proceedings were handsearched for seven key international conferences for the last 3 years. Embase was also searched for conference proceedings published between 2019-2024.
- Separate searches for safety outcomes were not conducted. It is unlikely that efficacy searches that include study design filters for RCTs will be sensitive enough to identify adverse events (AEs) that are long-term, rare or unanticipated. Ideally, searches for AEs should be carried out alongside the searches for efficacy.[11]

3.1.2 Inclusion criteria

The CS states that a SLR was undertaken to identify relevant RCT evidence for therapies used in the treatment of HR+/HER2− unresectable/mBC. The phase 2 FAKTION trial and the phase 3 registrational CAPItello-291 trial were both identified by the SLR. The process for the identification and appraisal of the evidence base in this submission is summarised in this Section.

The eligibility criteria used in the search strategy as described in clinical SLR report[10] to identify relevant evidence is detailed in Table 3.1 below. The EAG notes that there are some conditions to the described inclusion criteria. Specifically, we note that all articles published in any language are of interest. However, it states within the table key that '*English language publications or non-English language publications with an English abstract are of primary interest. Mtech Access will forward a list of potentially relevant non-English language publications to AstraZeneca for review. A decision will then be taken in conjunction with AstraZeneca as to whether translation of these articles is required'.* It is unclear as to why English language articles are of 'primary interest.' Nor is it clear the impact of Mtech Access in determining what is 'potentially relevant', what criteria are used to determine potential relevance, and how a decision taken 'in conjunction with AstraZeneca' as to whether translations are required is determined.

Screening of records at both title and abstract stage, and at full text stage was conducted by two independent reviewers with any disagreements resolved by consensus or the intervention of a third reviewer. This represents the optimal approach for reducing the likelihood of error or bias.

Table 3.2: Eligibility criteria used in search strategy for RCT and non-RCT evidence

	Inclusion	Exclusion
Population	Patients with HR+, HER2-negative, or HER2-mixed/NR/unknown unresectable and/or metastatic BC previously treated with ET in the (neo)adjuvant or advanced setting. Menopausal status PIK3CA/PTEN/AKT mutational status Prior and no prior CT Prior and no prior CDK4/6is	Patients with HER2+ BC.

	Inclusion	Exclusion
	Bone and liver metastases	
Interventions	Any pharmacological treatment for ABC.	
Comparator	No restriction.	
Outcomes	**Efficacy** PFS (or TTP)† OS (including number of deaths)† DFS DDFS iDFS RFS DRFI EFS **Safety** All-Grade AE All-Grade SAE All-Grade TRAE All-Grade serious TRAE AEs leading to death Diarrhoea Rash Hyperglycaemia Tolerability Dose reductions and interruptions Treatment duration Treatment discontinuation (any reason) Discontinuation (due to AEs) **HRQoL‡** Brief Pain Inventory-Short Form Functional Assessment of *Cancer* Therapy-*general* EuroQol 5-Dimension European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire-30 **Other PROMs**	**Efficacy†** DOR (captured within original SLR and removed for subsequent updates) TTF TTD **Safety†** On-treatment deaths/treatment-related deaths – only including deaths due to AE specifically
Study design	Prospective RCTs (Phase 2–4), with no restriction on blinding§ Single-arm clinical trials§ Systematic reviews/meta-analyses¶	Real-world studies of any design In vitro studies and preclinical studies Editorials
Geography	No restrictions.	
Date of publication	No restriction for full publications; last 3 years (2020 onwards) for conference abstracts	
Language restrictions	No restriction††	

Based on Table 1 of the AstraZeneca capivasertib clinical SLR report 2024 update_V1 (10 May 2024)[10]
† Added for clarity during August update.
‡ Data extraction will be restricted to the overall scale scores (data from subscales will not be extracted) and the latest follow-up point.
§ Comments and letters will be captured if they provide additional data not reported in an RCT or single-arm study.
¶ Relevant reviews and meta-analyses will be included at title and abstract stage. The reference lists of reviews will be interrogated for relevant primary publications.

	Inclusion	Exclusion
†† English language publications or non-English language publications with an English abstract are of primary interest. Mtech Access will forward a list of potentially relevant non-English language publications to AstraZeneca for review. A decision will then be taken in conjunction with AstraZeneca as to whether translation of these articles is required. ABC = advanced breast cancer; AE = adverse event; AKT = protein kinase B; BC = breast cancer; CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; CT = chemotherapy; DOR = duration of response; DDFS = distant disease-free survival; DFS = disease-free survival; DRFI = distant recurrence-free interval; EFS = event-free survival; ET = endocrine therapy; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; HRQoL = health-related quality of life; iDFS = invasive disease-free survival; NR = not reported; OS = overall survival; PFS = progression-free survival; PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PROMs = patient-reported outcome measures; PTEN = phosphatase and tensin homolog; RCT = randomised controlled trial; RFS = recurrence-free survival; SAE = serious adverse event; SLR = systematic literature review; TRAE = treatment-related adverse event; TTD = time to treatment discontinuation; TTF = time to treatment failure; TTP = time to progression		

3.1.3 Critique of data extraction

A prioritisation protocol is emphasised within the clinical SLR report update[10] which details the specific aspects of a record that determined its inclusion. It states that '*Due to the large number of included studies within the SLR, AstraZeneca approved a prioritisation strategy to limit data extraction to the most relevant studies for the current project. Records were, therefore, tagged under one of the following inclusion categories in the SLR:*

- *I1 – Include: these studies were extracted in full into the data extraction table (DET)*
- *I2 – Single-arm studies: studies with a single-arm study design only were listed*
- *I3 – Experimental/non-approved interventions: studies randomising patients to experimental or not approved interventions/combinations only were listed*'

It is not clear to by what approach this prioritisation strategy was approved. The particular criteria for '*most relevant*' are not listed and neither is the rationale for such a strategy. It is important that all aspects of data identification, extraction and prioritisation are adequately described and reported to optimise confidence in the data and to reduce risk of bias.

Data extraction for I1 studies was conducted by two independent analysts. Any disputes were resolved by consensus or by a third reviewer. This is an optimal method for data extraction and reduces likelihood of error or bias. No information is provided to describe any processes for data extraction of I2 and I3 categories. Again, the EAG notes the need for clarity and transparency.

3.1.4 Quality assessment

The Cochrane Risk of Bias 2 (RoB 2) tool was used for assessing the quality of studies and according to the clinical SLR report version 1 (10 May)[10] appraisals were conducted by two independent reviewers with any disagreements resolved by consensus or by the involvement of a third reviewer. However, the EAG asked for clarification on this and in their response to the request for clarification[4] the company stated '*A robust procedure was in place to assess the quality of the studies and resolve conflicts. Quality appraisals were conducted by a single reviewer and checked by a second reviewer. Any disputes were resolved by consensus or by a third reviewer*'.

In the clinical SLR report,[10] the quality appraisal results for 39 studies are included (Appendix E). A summary is also provided on page 55 of same report which describes some of the main findings of the RoB 2 appraisals.

EAG comment: There appears to be conflicting information detailed in the Clinical SLR report[10] with the response provided by company to the request for clarification[4] on the matter of quality appraisals. Additionally, it is not entirely clear by which methods data were extracted or by the role of '*Mtech Access'* in the identification and selection of '*potentially relevant'* evidence.

The EAG highlights that clarity, transparency and the robust conducting and reporting of methods are essential components of conducting an SLR. Minimisation of error and bias is optimised by screening, data extraction, and quality appraisals conducted independently and in duplicate. Clear reporting, where readers can follow a flowing process and be informed and reassured that robust methods have been followed are essential. The EAG are of the opinion that there is a lack of clarity around these processes and as a consequence there are uncertainties which mean that a potential risk of bias and error exists.

3.1.5 Evidence synthesis

The CS states that pairwise meta-analysis was not undertaken because data from a direct comparison between capivasertib plus chemotherapy versus chemotherapy for the population of interest was only available from the CAPItello-291 RCT.[1] However, data from other RCTs associated with relevant comparators were combined with the data of the CAPItello-291 trial in an ITC analysis. Further details are provided in Section 3.3 of this report.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Study retrieval

Three hundred and seven relevant publications were identified for inclusion from all combined searches from the electronic database and supplementary handsearching. Based on the prioritisation strategy, records were categorised as follows:

I1 – Include (n=132, reporting on 39 RCTs meeting the broad inclusion criteria)
I2 – List only as single-arm studies (n=82)
I3 – List only as experimental/non-approved interventions (n=93)

The EAG noted that from the initial 307 included records, only 10 studies were included in the network meta-analysis (NMA). It was not clear how prioritisation or exclusion decisions regulated so this process so the EAG asked for clarification on the details and reasons for exclusion of studies that were not include in the NMA. In their response to the request for clarification[4] the company stated the following

"As the inclusion criteria of the SLR were broader than the current decision problem and included several therapies and trial populations that are not relevant to the comparative effectiveness of capivasertib plus fulvestrant in patients with PI3K/AKT pathway-altered HR+/HER2- advanced breast cancer, the feasibility of conducting a NMA using identified RCT data that are relevant to the decision problem was assessed. This consisted of three distinct steps: (1) identification of relevant studies for the decision problem, (2) heterogeneity assessment of study characteristics and (3) generation of outcome-specific networks and tests for proportional hazards.

A total of 271 studies were excluded due to the reasons outlined below:

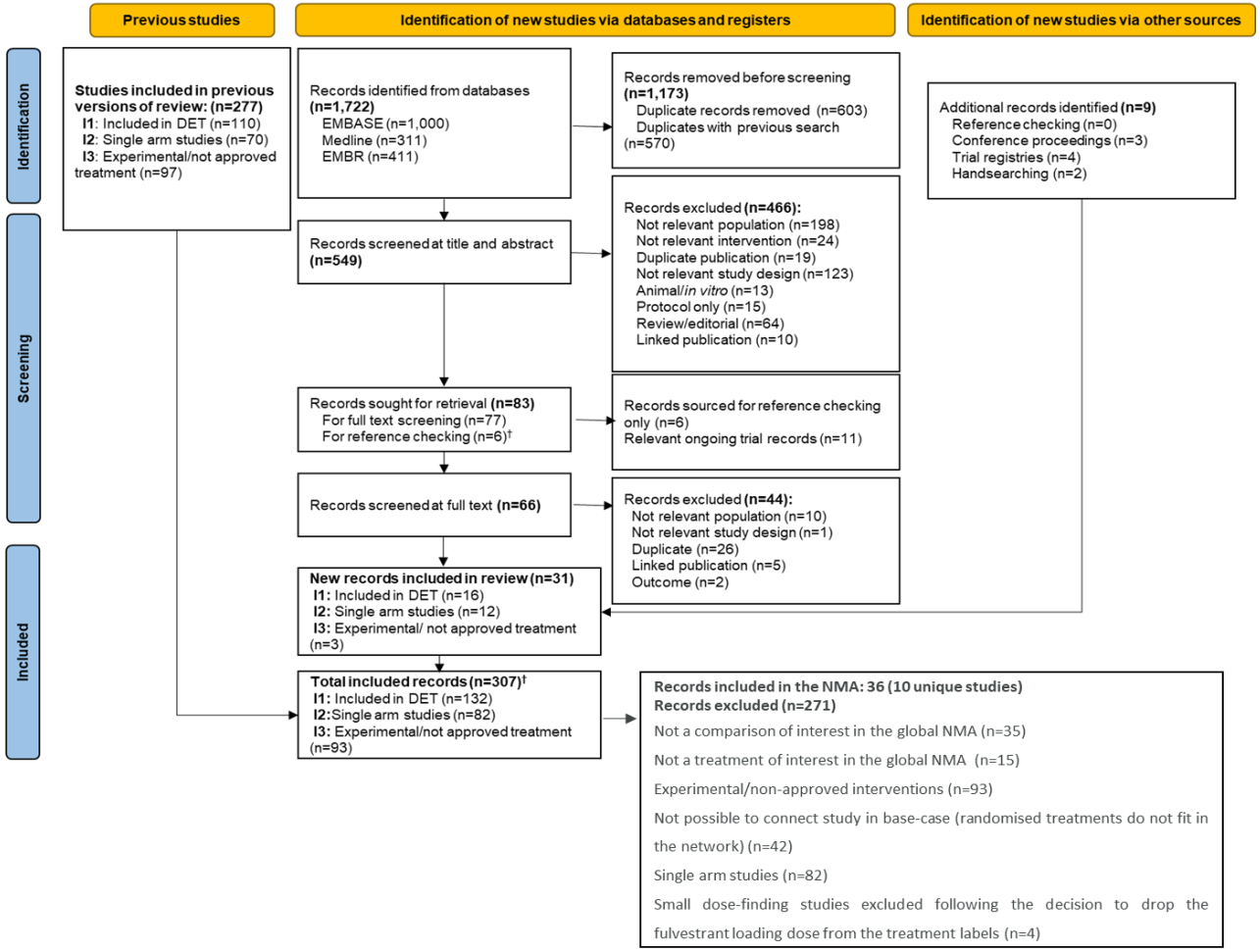
- *Not a comparison of interest in the global NMA: 35*

- *Not a treatment of interest in the global NMA: 15*
- *Experimental/non-approved interventions: 93*
- *Not possible to connect study in base-case (randomised treatments do not fit in the network): 42*
- *Single arm studies: 82*
- *Small dose-finding studies excluded following the decision to drop the fulvestrant loading dose from the treatment labels: 4*

The remaining 36 publications (associated with 10 unique studies) were included in the NMA. Full details on the excluded studies can be found in Appendix II. A Summary of the 10 studies included in the base case NMA can be found in Table 2 of the CS Appendix. CAPItello-291, FAKTION, BOLERO2, BOLERO-5 and SOLAR-1 provided data on the interventions and comparators of interest for the decision problem, EFECT, SOFEA, CONFIRM, FRIEND and NCT01300351 were required to form a connected network between the treatments.

It was also noted that the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow chart included on page 22 of the SLR protocol[10] did not account for the studies excluded from the NMA and so the EAG requested the flowchart be updated to reflect this. In their response to the request for clarification the company[4] provided the flowing flowchart detailed in Figure 3.1 below.

Figure 3.1: Updated clinical SLR flowchart



Based on Appendix C of the clinical SLR report[10]
NMA = network meta-analysis; SLR = systematic literature review

Appendix C of the clinical SLR report[10] describes the flow of evidence identification and selection.

One thousand, seven hundred and twenty-two (1,722) records were obtained by electronic searches. One thousand, seven hundred and seventy-three (1,773) duplicates were excluded, leaving 549 records to be screened. Four hundred and sixty-six (466) records were excluded during the screening and title and abstract stage. Eighty-three (83) records were potentially relevant for full text screening, with six deemed relevant for reference checking only, while 11 ongoing trial records were deemed not relevant for full text screening. The remaining 66 records were obtained for full text screening and of these, 44 were excluded for various reasons (see PRISMA flowchart). An additional nine records were located through manual handsearching. Thirty-one (31) records were eligible for inclusion after the most recent SLR update and were categorised according to a prioritisation strategy determined by AstraZeneca.

Records were, therefore, tagged under one of the following inclusion categories:

- I1 – Include (n=16)
- I2 – List only as single-arm studies (n=12)
- I3 – List only as experimental/non-approved interventions (n=3)

3.2.2 Details of included trials

3.2.2.1 Details of the CAPItello-291 trial

The CS[1] states that the CAPItello-291 was '*the pivotal phase 3 trial supporting the UK licensing of capivasertib plus fulvestrant, and provides the most robust efficacy and safety data for use of capivasertib in the population of interest'*. It is a Phase 3, multicentre, randomised (1:1), double-blind, placebo-controlled trial conducted across 19 countries, of which the UK was one with a total of seven centres and 20 patients.

The clinical effectiveness evidence for capivasertib is therefore presented based on the CAPItello-291 trial, presented in the CS.[1] Details and results from the FAKTION trial, and trials of relevant comparators included in the indirect treatment comparison, are provided in Appendix D1.2.[9]

A summary of the CAPItello-291 trial is described in Table 3.3 below.

Table 3.3: Clinical effectiveness evidence: CAPItello-291 study

Study	CAPItello-291 (NCT04305496)
Study design	Phase 3, multicentre, randomised, double-blind, placebo-controlled trial
Population	Overall population included people with locally advanced (inoperable) or metastatic HR+/HER2− breast cancer following recurrence or progression on or after treatment with an AI, with or without PI3K/AKT pathway–altered (PIK3CA, AKT1, or PTEN) tumours (prespecified for determination after randomisation), with or without previous CDK4/6i therapy. The PFS primary endpoint was prespecified for assessment in both the overall (ITT) population and the PI3K/AKT pathway-altered population.
Intervention(s)	Capivasertib 400 mg (two tablets of 200 mg) orally twice daily (total daily dose 800 mg) on Days 1–4 in each week of a 28-day treatment cycle

Study	CAPItello-291 (NCT04305496)
	plus Fulvestrant 500 mg (two intramuscular injections) on Day 1 of Weeks 1 and 3 of cycle 1, and then on Day 1, Week 1 of each cycle thereafter
Comparator(s)	Placebo plus fulvestrant as above
Indicate if study supports application for marketing authorisation	Yes – the PI3K/AKT pathway-altered population of the trial reflects the licensed population.
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem	OS* PFS* Response rate Adverse effects of treatment* HRQoL*
All other reported outcomes	Second PFS Time to deterioration in ECOG PS Time to first subsequent chemotherapy or death TTD*
Adapted from Table 3 of the CS[1] * Outcome included in economic model AI = aromatase inhibitor; AKT = serine/threonine kinase; CDK4/6i = cyclin-dependent kinases 4 and 6 inhibitor; CS = company submission, ECOG PS = European Cooperative Oncology Group Performance Status; HRQoL = health-related quality of life; HR+ = hormone receptor positive; HER2- = human epidermal growth factor receptor 2-negative; ITT = intention-to-treat; N/A = not applicable; OS = overall survival; PFS = progression-free survival; TTD = time to treatment discontinuation	

The CS[1] confirms that 'Primary and secondary endpoints were assessed in both the overall population and in the population of patients with PI3K/AKT pathway-altered tumours in whom the UK marketing authorisation has been granted. The study was powered to show a statistically significant difference between capivasertib plus fulvestrant and placebo plus fulvestrant in PFS in the Overall Population and the PI3K/AKT pathway altered population (dual primary endpoints).' Table 3.4 below provides a summary of the trial methodology.

Table 3.4: Summary of pivotal trial methodology

Trial number (acronym)	CAPItello-291 (NCT04305496)
Location	Multinational study: 19 countries including UK ([redacted])
Trial design	Phase 3, multicentre, randomised (1:1), double-blind, placebo-controlled trial
Eligibility criteria for participants	**Key inclusion criteria:** • Aged ≥18 years (≥20 years in Japan). • Pre- or postmenopausal female, or male. Pre-menopausal women could be enrolled if amenable to treatment with an LHRH agonist.

	• Histologically confirmed HR+/HER2− breast cancer. To fulfil the requirement of HR+ disease, a breast cancer must express ER with or without co-expression of progesterone receptor. Therefore, tumours must be: • ER+ defined as ≥1% of tumour cells stain positive for ER on IHC or, if no percentage is available, then an Allred IHC score of ≥3/8, • progesterone receptor positive defined as ≥1% of tumour cells stain positive for progesterone receptor on IHC or, if no percentage is available, then an Allred IHC score of ≥3/8; or progesterone receptor negative defined as <1% of tumour cells stain positive for progesterone receptor on IHC or, if no percentage is available, then an Allred IHC score of ≤2/8; or progesterone receptor unknown, and HER2− defined as 0 or 1+ intensity on IHC, or 2+ intensity on IHC and no evidence of amplification on ISH, or if IHC not done, no evidence of amplification on ISH. • Metastatic or locally advanced disease. • Disease progression during prior treatment with an AI-containing regimen (single agent or combination), either: • Recurrence or progression while on, or within 12 months of the end of (neo)adjuvant treatment with an AI; or, • Progression while on prior AI administered as a treatment line for locally advanced or metastatic disease. • At least one lesion or bone lesion that could be accurately measured at baseline with CT or MRI. • Eligible for fulvestrant therapy. • Consent to provide an FFPE tumour block (primary or recurrent cancer) or at least 20 freshly cut, unstained serial tumour slides, for central (NGS) testing. • Able to swallow and retain oral medication. • ECOG/WHO PS of 0 or 1 with no deterioration over the previous 2 weeks, and life expectancy of ≥12 weeks • Agreement to use effective contraception, where relevant, for 2 years after the last dose of fulvestrant or 16 weeks after discontinuing capivasertib/placebo. **Key exclusion criteria:** • Prior treatment with fulvestrant or other SERDs, or AKT serine/threonine kinase, PI3K, or mTOR inhibitors. • Clinically significant abnormalities of glucose metabolism as defined by diabetes mellitus requiring insulin treatment, and/or $HbA1_C$ ≥8.0% (63.9 mmol/mol). • More than two lines of ET for inoperable locally advanced or metastatic disease. • More than one line of chemotherapy for inoperable locally advanced or metastatic disease.
Settings and locations where the data were collected	Tertiary centres: Region 1 (112 centres in US, Canada, Western Europe, Australia, and Israel: 395 patients). Region 2 (23 centres in Latin America, Eastern Europe and Russia: 136 patients).

	Region 3 (46 centres in Asia, 177 patients).
Trial drugs	Intervention: capivasertib 400 mg twice daily (total daily dose 800 mg) on Days 1–4 in each week of a 28-day treatment cycle; fulvestrant 500 mg on Day 1 of Weeks 1 and 3 of cycle 1, and then on Day 1, Week 1 of each cycle thereafter Comparator: placebo matching capivasertib; fulvestrant matching administration received in the intervention arm In the overall population, n=355 were randomised to the intervention, and n= 353 were randomised to the comparator. In the PI3K/AKT-pathway altered population, n= 155 were randomised to the intervention and n=134 were randomised to the comparator.
Primary outcomes	Dual primary end point (assessed in the overall population and in the PI3K/AKT pathway‑altered population): Investigator-assessed PFS (assessed according to RECIST, version 1.1). (PFS was also assessed by BICR as a sensitivity analysis in overall population).
Other outcomes used in the economic model/specified in the scope	Secondary endpoints (assessed in the overall population and in the PI3K/AKT pathway–altered population): OS: the length of time from randomisation until the date of death due to any cause ORR: the percentage of patients with at least one CR or PR per RECIST v1.1 criteria, as assessed by the investigator at the local site Safety and tolerability: evaluated in terms of AEs/SAEs, vital signs, clinical chemistry/haematology/glucose metabolism parameters and ECG parameters HRQoL: evaluation of EORTC QLQ-C30, EORTC QLQ-BR23, scale/item score, including change from baseline and time to deterioration. Exploratory endpoints: Health state utility using EQ-5D-5L
Pre-planned subgroups	Analyses of primary and secondary outcomes were pre-specified in the trial protocol for both the overall population and for the PI3K/AKT pathway-altered subpopulation. Trial randomisation was stratified by prior use of CDK4/6is (yes/no), liver metastases (presence or absence) and geographic area. Randomisation was not stratified by PI3K/AKT pathway-altered status to allow inclusion of patients with more aggressive disease who might otherwise not have enrolled in the trial if they had to wait for tissue-testing results before randomisation. Subgroup analyses for PFS were conducted by stratification factors, age (<65 versus ≥65 years), and in a range of other exploratory analyses.

Adapted from Table 4, CS[1]

AEs = adverse events; AI = aromatase inhibitor; AKT = serine/threonine kinase; CDK4/6i = cyclin-dependent kinases 4 and 6 inhibitor; ChT = chemotherapy; CR = complete response; CT = computed tomography; ECOG =

Eastern Cooperative Oncology Group; ER = oestrogen resistant; EQ-5D-5L = EuroQol 5 dimension 5 level tool; ET = endocrine therapy; FFPE = formalin-fixed paraffin-embedded; HRQoL = health-related quality of life; HR+ = hormone receptor-positive; HER2– = human epidermal growth factor receptor 2-negative; IHC = immunohistochemistry; ISH = in situ hybridisation; LHRH = Luteinizing hormone-releasing hormone; MRI = magnetic resonance imaging; mTOR = mammalian target of rapamycin; NGS = next-generation sequencing; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; PS = Performance Status; RECIST = Response Evaluation Criteria in Solid Tumours; SAEs = serious adverse events; SERD = selective oestrogen receptor degrader; UK = United Kingdom; US = United States; WHO = World Health Organization

The CS[1] contains information on multiple aspects of the trial included in Table 4 of the CS (presented as Table 3.4 above). While this does indeed present an overview, the EAG would have liked to see key parts of this extracted and described. Readability with ease of accessibility to relevant information is important when the EAG reviews such submission and so we draw attention to this for this reason.

3.2.2.2 Baseline characteristics

The CS[1] included details of the baseline characteristics for the PI3K/AKT pathway-altered population of the CAPItello-291 trial, and for the subgroup with prior use of CDK4/6i therapy. These are summarised in Table 3.5 below. The CS states that the baseline characteristics of the overall trial population are provided in the trial manuscript[1] but does not include or describe them in the CS.

PIK3CA/AKT1/PTEN alterations were detected in tumour samples from 289 patients with 208 patients having previously received CDK4/6i therapy. Baseline characteristics across most items, but not all, were generally well balanced between both arms of each population, and across the PI3K/AKT pathway-altered population and PI3K/AKT pathway-altered population who had received prior CDK4/6i therapy. Prior CKD4/6i use was a stratification factor and similar proportions of the PI3K/AKT pathway-altered population had prior use of CDK4/6i in the capivasertib plus fulvestrant and the placebo plus fulvestrant arms (72.9% versus 69.4%, respectively). The EAG however, did comment on noticeable differences below.

Table 3.5: Baseline characteristics of patients with PI3K/AKT pathway-altered tumours enrolled in CAPItello-291

Characteristic		PI3K/AKT-altered population		PI3K/AKT-altered population with prior CDK4/6i use	
		Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)	Capivasertib + fulvestrant (N=114)	Placebo + fulvestrant (N=94)
Age	Median, years (range)	58 (36–84)	60 (34–90)	[redacted]	[redacted]
Sex, n (%)	Female	153 (98.7)	134 (100)	[redacted]	[redacted]
Race/ethnic group, n (%)*	Black or African American	2 (1.3)	1 (0.7)	[redacted]	[redacted]
	Asian	48 (31.0)	35 (26.1)	[redacted]	[redacted]
	White	75 (48.4)	76 (56.7)	[redacted]	[redacted]
	Other	30 (19.4)	22 (16.4)	[redacted]	[redacted]
Genetic mutation status, n (%)	Altered	155 (100)	134 (100)	[redacted]	[redacted]
	PIK3CA only†‡	110 (71.0)	92 (68.7)	[redacted]	[redacted]
	AKT1 only†‡	18 (11.6)	15 (11.2)	[redacted]	[redacted]
	PTEN only†‡	21 (13.5)	16 (11.9)	[redacted]	[redacted]

Characteristic		PI3K/AKT-altered population		PI3K/AKT-altered population with prior CDK4/6i use	
		Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)	Capivasertib + fulvestrant (N=114)	Placebo + fulvestrant (N=94)
	PIK3CA and AKT1†	2 (1.3)	2 (1.5)	[redacted]	[redacted]
	PIK3CA and PTEN†	4 (2.6)	9 (6.7)	[redacted]	[redacted]
Disease classification	Metastatic	155 (100)	132 (98.5)	[redacted]	[redacted]
	Locally advanced	0	2 (1.5)	[redacted]	[redacted]
	Missing	0	0	[redacted]	[redacted]
WHO / ECOG PS	(0) normal activity	93 (60.0)	97 (72.4)	[redacted]	[redacted]
	(1) restricted activity	62 (40.0)	36 (26.9)	[redacted]	[redacted]
	(2) in bed ≤50% of the time	0 (0)	1 (0.7)	[redacted]	[redacted]
AJCC	Stage IV	50 (32.3)	44 (32.8)	[redacted]	[redacted]
Menopausal status	Pre-/perimenopausal	23 (14.8)	29 (21.6)	[redacted]	[redacted]
	Postmenopausal	130 (83.9)	105 (78.4)	[redacted]	[redacted]
Receptor status	ER+/PR+	116 (74.8)	101 (75.4)	[redacted]	[redacted]
	ER+/PR−	35 (22.6)	31 (23.1)	[redacted]	[redacted]
	ER+/PR unknown	4 (2.6)	2 (1.5)	[redacted]	[redacted]
	ER−§	0 (0)	0 (0)	[redacted]	[redacted]
Type of endocrine resistance	Primary	60 (38.7)	55 (41.0)	[redacted]	[redacted]
	Secondary	95 (61.3)	79 (59.0)	[redacted]	[redacted]
Diabetic status	Diabetes	18 (11.6)	8 (6.0)	[redacted]	[redacted]
	No diabetes	137 (88.4)	126 (94.0)	[redacted]	[redacted]
Prior CDK4/6i, n (%)		113 (72.9)	93 (69.4)	114 (100)	94 (100)

Adapted from Table 5, CS[1]
* Race data for Belgium, France and Hungary were not permitted to be collected per local regulations and were recorded as 'other'.
† Mutually exclusive groups.
‡ Patients with co-occurring mutations were excluded from single gene count.
§ Due to the very limited number of patients expected under this category, patients with different PR status are reported together.
AKT = serine/threonine kinase; AJCC = American Joint Committee on Cancer; CDK4/6 = cyclin-dependent kinase 4/6; CS = company submission; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ER = oestrogen resistant; PR = progesterone receptor; WHO = World Health Organization

The EAG was interested in seeing the baseline characteristics of the relevant subpopulation (patients with HR+/HER2-, PI3K/AKT pathway-altered, locally advanced or mBC following progression on or after CDK4/6i plus ET) and requested these data from the company. The EAG also requested that these compared to the whole trial population and that the relevant subpopulation be justified as representative of the relevant population in England and Wales in the positioning that is proposed. In their response to the request for clarification[4] the company stated that '*Baseline characteristics of the subpopulation of the CAPItello-291 trial meeting the licensed indication were provided in Table 5 of our submission, alongside the baseline characteristics of patients meeting the licensed indication who had received prior CDK4/6i therapy. We noted that the baseline characteristics of the full trial population were*

provided in the fully published manuscript by Turner et al 2023, which we provided in the reference pack.'

The company extracted the relevant data from said manuscript and tabulated (see Table 3.6 below) it in their response[4] for the *'convenience of the EAG', which* details *' the baseline characteristics of the licensed population and the licensed population with prior use of CDK4/6i therapy, and the overall population of the CAPItello-291 trial that includes these patients and those not meeting the licensed indication*.'

The EAG is grateful for this information but makes the point that any data or information relevant to a CS should be readable, efficient and have accessibility. It is in the interests of the company to present relevant data within the body of their submission, for the efficiency of access and analysis to justify their position, as well as to provide a comprehensive, flowing submission.

Table 3.6: Baseline characteristics of the licensed population subgroups and overall trial population of the CAPItello-291 trial

Characteristic		PI3K/AKT-altered population (Licensed population)		PI3K/AKT-altered population (Licensed population) with prior CDK4/6i use		Overall CAPItello-291 trial population	
		Capi + ful (N=155)	Placebo + ful (N=134)	Capi + ful (N=114)	Placebo + ful (N=94)	Capi + ful (N=355)	Placebo + ful (N=353)
Age	Median, years (range)	58 (36–84)	60 (34–90)	[redacted]	[redacted]	59.0 (26–84)	58.0 (26–90)
Sex, n (%)	Female	153 (98.7)	134 (100)	[redacted]	[redacted]	352 (99.2)	349 (98.9)
Race /ethnic group, n (%)*	Black or African American	2 (1.3)	1 (0.7)	[redacted]	[redacted]	4 (1.1)	4 (1.1)
	Asian	48 (31.0)	35 (26.1)	[redacted]	[redacted]	95 (26.8)	94 (26.6)
	White	75 (48.4)	76 (56.7)	[redacted]	[redacted]	201 (56.6)	206 (58.4)
	Other	30 (19.4)	22 (16.4)	[redacted]	[redacted]	55 (15.5)	49 (13.9)
Genetic mutation status, n (%)	Altered	155 (100)	134 (100)	[redacted]	[redacted]	155 (43.7)	134 (38.0)
	PIK3CA only†‡	110 (71.0)	92 (68.7)	[redacted]	[redacted]	110 (31.0)	92 (26.1)
	AKT1 only†‡	18 (11.6)	15 (11.2)	[redacted]	[redacted]	18 (5.1)	15 (4.2)
	PTEN only†‡	21 (13.5)	16 (11.9)	[redacted]	[redacted]	21 (5.9)	16 (4.5)
	PIK3CA and AKT1†	2 (1.3)	2 (1.5)	[redacted]	[redacted]	2 (0.6)	2 (0.6)
	PIK3CA and PTEN†	155 (100)	134 (100)	[redacted]	[redacted]	155 (43.7)	134 (38.0)
Disease classification, n (%)	Metastatic	155 (100)	132 (98.5)	[redacted]	[redacted]	349 (98.3)	346 (98.0)
	Locally advanced	0	2 (1.5)	[redacted]	[redacted]	6 (1.7)	6 (1.7)

Characteristic		PI3K/AKT-altered population (Licensed population)		PI3K/AKT-altered population (Licensed population) with prior CDK4/6i use		Overall CAPItello-291 trial population	
		Capi + ful (N=155)	Placebo + ful (N=134)	Capi + ful (N=114)	Placebo + ful (N=94)	Capi + ful (N=355)	Placebo + ful (N=353)
	Missing	0	0	[redacted]	[redacted]	0	1 (0.3)
WHO/ ECOG PS, n (%)	(0) normal activity	93 (60.0)	97 (72.4)	[redacted]	[redacted]	224 (63.1)	214 (68.3)
	(1) restricted activity	62 (40.0)	36 (26.9)	[redacted]	[redacted]	131 (36.9)	111 (31.4)
	(2) in bed ≤50% of the time	0 (0)	1 (0.7)	[redacted]	[redacted]	0	1 (0.3)
AJCC, n (%)	Stage IV	50 (32.3)	44 (32.8)	[redacted]	[redacted]	[redacted]	[redacted]
Menopausal status, n (%)	Pre-/perimenopausal	23 (14.8)	29 (21.6)	[redacted]	[redacted]	65 (18.3)	89 (25.2)
	Postmenopausal	130 (83.9)	105 (78.4)	[redacted]	[redacted]	287 (80.8)	260 (73.7)
Receptor status, n (%)	ER+/PR+	116 (74.8)	101 (75.4)	[redacted]	[redacted]	255 (71.8)	246 (69.7)
	ER+/PR−	35 (22.6)	31 (23.1)	[redacted]	[redacted]	94 (26.5)	103 (29.2)
	ER+/PR unknown	4 (2.6)	2 (1.5)	[redacted]	[redacted]	5 (1.4)	4 (1.1)
	ER−§	0 (0)	0 (0)	[redacted]	[redacted]	1 (0.3)	0 (0)
Type of endocrine resistance, n (%)	Primary	60 (38.7)	55 (41.0)	[redacted]	[redacted]	127 (35.8)	135 (38.2)
	Secondary	95 (61.3)	79 (59.0)	[redacted]	[redacted]	228 (64.2)	218 (61.8)
Diabetic status, n (%)	Diabetes	18 (11.6)	8 (6.0)	[redacted]	[redacted]	[redacted]	[redacted]
	No diabetes	137 (88.4)	126 (94.0)	[redacted]	[redacted]	[redacted]	[redacted]
Prior CDK4/6i, n (%)		113 (72.9)	93 (69.4)	114 (100)	94 (100)	247 (69.9)	249 (70.5)

Adapted from Table 7, response to the request for clarification[4]
* Race data for Belgium, France and Hungary were not permitted to be collected per local regulations and were recorded as 'other'.
† Mutually exclusive groups.
‡ Patients with co-occurring mutations were excluded from single gene count.
§ Due to the very limited number of patients expected under this category, patients with different PR status are reported together.
AKT = serine/threonine kinase; AJCC = American Joint Committee on Cancer; Capi = capivasertib; CDK4/6 = cyclin-dependent kinase 4/6; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ER = oestrogen resistant; Ful = fulvestrant; PR = progesterone receptor; WHO = World Health Organization

On reviewing the baseline characteristics, across the overall population, characteristics are generally well matched. Assuming a difference of >5% as noteworthy some distinctions are present. Pre-/peri menopausal status differs between the arms with the capivasertib arm having 18.4% versus 25.2% in the placebo arm. Post-menopausal status was also different with the capivasertib arm being 80.8% post-menopausal verus 73.7% in the placebo arm.

In the PI3K/AKT-altered (PIK3CA/AKT1/PTEN-altered) subgroup World Health Organization (WHO)/ Eastern Cooperative Oncology Group Performance Status (ECOG PS) differs with a grading of '0' present at [redacted]% in the capivasertib arm versus [redacted]% in the placebo; and a grading of (1) at [redacted]% versus [redacted]% in the placebo arm. Stage IV American Joint Committee on Cancer (AJCC) status was also reduced in the capivasertib arm versus placebo at [redacted]% versus [redacted]% respectively. [redacted]% of the capivasertib arm were post-menopausal versus [redacted]% of the placebo arm, while there were also more diabetics in the capivasertib arm compared to the placebo arm with [redacted]% versus [redacted]% respectively.

In the licenced population, there were less participants with 'white' ethnicity compared to the placebo arm at 48.4% versus 56.7% WHO/ECOG PS differs with a grading of '0' present at 60% in the capivasertib arm versus 72.4% in the placebo and a grading of (1) at 40% versus 26.9% in the placebo arm. There were more pre/peri menopausal women in the placebo arm at 21.6% versus 14.8% respectively, while post-menopausal status was 83.9% in the capivasertib arm versus 78.4% in the placebo arm. There were more diabetics in the capivasertib arm than in the placebo arm, at 11.6% versus 6% respectively.

The company in their response to the request for clarification stated that '*A comparison across the baseline characteristics of the full population, and across the subgroup meeting the licensed indication and the subgroup meeting the licensed indication with prior use of CDK4/6i therapy indicates that the populations are broadly similar (with the obvious exception of the proportions with PI3K/AKT alterations and prior use of CDK4/6i therapy). As we noted in section B.2.5 of our submission, clinical experts consulted by the Company have confirmed that the broad characteristics of patients enrolled in the trial and the treatment effects observed with capivasertib, are likely to be generalisable to patients meeting the licensed indication, and the subgroup of interest in UK clinical practice. This was also discussed in section B.2.12.3 of our submission when discussing the generalisability and relevance of the evidence base.'*

The EAG has highlighted its concerns regarding the CS reliance on clinical opinion and has addressed this in other parts of this report, namely Section 3.2.2.4. There are, however, summarised bulleted points on topics discussed and conclusions reached as well as a table detailing where the clinical experts are located, a range of years' experience, and a designated medical speciality. It is the opinion of the EAG that this is unsatisfactory. It does not provide any form of information that can be scrutinised, audited, challenged or referenced.

EAG comment: The EAG (commenting on population described as 'licenced population' in Table 3.6) has the view that while the groups are well matched in most categories, the EAG highlight some points worth noting. Firstly, it could be suggested that there were more post-menopausal women in the capivasertib arm than in placebo. It is also worth noting that there were more diabetics in the capivasertib arm than in the placebo arm. Racial distribution differs across arms also with less participants defined as 'white' compared to that of the placebo arm meaning that pathology or treatment response characteristics that may be moderated by such aspects were not equal across groups. Additionally, there are less participants in the capivasertib arm with a grading of '0' in the WHO/ECOG

PS which confirms that there are effectively an increased number of 'healthier' or 'fitter' patients in the placebo arm. The EAG do of course note that where differences of >5% exist, this may be a consequence of the smaller sample sizes, rather than any meaningful clinical or physiological differences, and in some cases may reflect differences of only a few participants (i.e. white ethnicity) that might disappear had samples been larger. Nevertheless, these differences are present and notable within this group upon which efficacy and safety data is presented, and some go beyond only a few participants (i.e. post-menopausal status). It must therefore be highlighted and considered in any interpretation of relevant results. The EAG has concerns about the generalisability of these baseline characteristics to the population of England and Wales.

3.2.2.3 Risk of Bias Assessment

The CS provides an overview of the quality appraisal of the CAPItello-291 trial in Section B.2.5[1] and tabulates the relevant results.[1] The company state that '*Using the NICE-recommended quality assessment based on University of York Centre for Reviews and Dissemination guidance, the CAPItello-291 trial was at a low risk of bias*'. Table 3.7 details the findings of the appraisal. The EAG reviewed the appraisal and where appropriate added in our comments. A designation of 'N/A' indicates that there were no major disagreements of note for that item.

Table 3.7: Quality assessment of pivotal trial

Trial number (acronym)	CAPItello-291 (NCT04305496)	EAG comments
Was randomisation carried out appropriately?	Yes - patients were randomly assigned to treatment in a 1:1 ratio using a randomisation scheme loaded into an IWRS database. The PI3K/AKT pathway-altered population was pre-specified to be determined after randomisation, and there were no obvious imbalances in baseline characteristics or prognostic factors between treatment arms in this or the overall population to suggest randomisation issues. Prior CDK4/6i use was a stratification factor ensuring randomisation was maintained in this population of interest.	EAG highlights that the baseline characteristics are not equally distributed across all characteristics for the PI3K/AKT pathway-altered population.
Was the concealment of treatment allocation adequate?	Yes – IWRS	N/A

Trial number (acronym)	CAPItello-291 (NCT04305496)	EAG comments
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes – within each of the populations the intervention and comparator arms were well balanced in terms of baseline characteristics and for potential effect modifiers. Baseline characteristics were also balanced across the treatment arms in the post-CDK4/6i population of interest.	The EAG does not agree with this. We highlight that some differences at the >5% level were present and may reflect characteristics which could moderate disease progression or treatment response. We do not overstate them and acknowledge some may be a consequence of a small sample, but they must be highlighted and considered in any interpretation.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes - double-blind RCT. Primary analysis was investigator-assessed PFS but investigators were blind to treatment allocation. BICR of PFS was highly consistent with investigator assessment.	N/A
Were there any unexpected imbalances in drop-outs between groups?	No – dropout rates were low (<1%) and balanced across populations and treatment arms.	N/A
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No – clinical study report includes all outcome assessments included in protocol.	N/A
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes – ITT analysis in both the overall and the PI3K/AKT pathway-altered populations.	N/A

Adapted from Table 6, CS[1]
Adapted from Systematic Reviews: CRD's guidance for undertaking reviews in health care, per the NICE Company Evidence Submission user guide.
AKT = serine/threonine kinase; BICR = Blinded Independent Central Review; CDK4/6i = cyclin-dependent kinases 4 and 6 inhibitor; CRD = Centre for Reviews and Dissemination; CS = company submission; EAG = Evidence Assessment Group; ITT = intention-to-treat; IWRS = interactive web response system; NICE = National Institute for Health and Care Excellence; PFS = progression-free survival; RCT = randomised controlled trial

EAG comment: We do not fully consider that there was equal distribution of patient characteristics at baseline across all items. We do not conclude these necessarily represent what may be clinically meaningful differences and indeed we note that some differences are a product of small sample size and represent only a few participants, however any differences at baseline >5% reflect the potential to moderate outcomes and so must be identified and considered. The EAG rated the CAPItello-291 trial as being at moderate risk of bias.

3.2.2.4 External validity

The EAG has some concerns about representativeness of this data to the appropriate NHS population in England and Wales. The study had [redacted].[1]

The EAG raised this to the client and asked for clarification on the matters of limited UK based participants, and clinical expert opinion. In their response to submission, the company stated that '*..clinical experts consulted by the Company have confirmed that the broad characteristics of patients enrolled in the trial and the treatment effects observed with capivasertib, are fairly representative of the UK population and therefore generalisable to patients meeting the licensed indication, and the subgroup of interest in UK clinical practice. We are not aware of any reason to suggest that the findings of the CAPItello-291 trial are in any way less generalisable to the population in England and Wales than those of the trials of the relevant comparator therapies that have been accepted by NICE in TA816 and TA421'.* The EAG consider this to be insufficient as a response and does not satisfy our concerns.

The EAG was also concerned that the population as defined in the CS was narrower than in the NICE scope. We raised these concerns to the company, and this is discussed in Section 2.1 of this report. Additionally, we were concerned that the CS did not include all relevant comparators as defined by the NICE scope and again this issue was raised. This is also discussed in Section 2.3 of this report. Our concerns reflected the extent to which deviation from the scope would impact relevance to the clinical population in England and Wales. While the company attempted to provide justification, the EAG did not accept the merits of all these arguments and our comments with rationale can be found across Section 2 of this report.

EAG comment: The EAG therefore takes the view that there are some concerns around the generalisability of this data to the relevant population in England and Wales. Principally that there are (1) limited participants based in England and Wales, (2) it is possible that there will be some patients in clinical practice who would be eligible for capivasertib who had not previously received a CDK4/6i. This might have implications for choice of comparators given that the company exclude CDK4/6is on the basis of retreatment being inappropriate, but only if the appraisal decision includes those patients who had not previously received a CDK4/6i. Finally (3) in the absence of evidence as to what patients actually receive in clinical practice, none of the comparators in the NICE scope can be ruled out, except probably retreatment with a CDK4/6i.

3.2.3 Statistical analysis for the CAPItello-291 trial

The co-primary objectives of the CAPItello-291 trial were to estimate the treatment effect of capivasertib plus fulvestrant compared with placebo plus fulvestrant by the assessment of investigator-assessed PFS in the overall population and in the PI3K/AKT-altered (PIK3CA/AKT1/PTEN-altered) subgroup.[1]

The null hypothesis for the primary endpoint (PFS) in the overall population and in the PI3K/AKT-altered (PIK3CA/AKT1/PTEN-altered) sub-population was that there was no difference between capivasertib plus fulvestrant and placebo plus fulvestrant in the probability of a progression event.[1]

The company made the following statement:[1] *"A total sample of 700 patients was planned for the overall trial population. PFS was to be analysed at approximately 77% maturity in the overall population (when 542 progression or death events had occurred) and in the PI3K/AKT pathway–altered population (when 217 events had occurred), under an assumption that 40% of the trial population would have PI3K/AKT pathway-altered tumours. Assuming a PFS hazard ratio (HR) of 0.64 in both*

populations, it was estimated that the trial would have >99% power to show a significant difference in favour of the capivasertib plus fulvestrant group in the overall population (at a two-sided P<0.035) and 91% power in the PI3K/AKT pathway–altered population (at a two sided P<0.05), with recycling of the remaining 1.5% alpha."

At the data cut-off date for the primary analysis of PFS (15 August 2022), the required level of maturity was achieved: actual maturity for PFS data was 77.8% (551 events) in the overall population, and 81.7% (236 events) in the PI3K/AKT pathway-altered subgroup.[1]

Analyses for the overall population and in the PI3K/AKT-altered (PIK3CA/AKT1/PTEN-altered) sub-population were based on an intention-to-treat (ITT) basis in all patients randomised into the study.[1]

The dual primary outcomes were tested by using a log-rank test, with stratification based on the presence of liver metastases (yes versus no), previous use of a CDK4/6i (yes versus no), and geographic area (which was evaluated in the overall population only based on the following regions: Region 1: United States (US), Canada, Western Europe, Australia, and Israel, Region 2: Latin America, Eastern Europe and Russia, Region 3: Asia).

Hazard ratios (HRs) and associated 95% confidence intervals (95% CIs) were estimated by using stratified Cox proportional-hazards models. The assessments of OS outcomes of no detriment (i.e., with the HR not favouring the placebo plus fulvestrant group) in the overall population and PI3K/AKT pathway–altered sub-populations were conducted at the time of the primary analysis (as requested by the US Food and Drug Administration (FDA).[1]

The percentage of patients with an objective response was analysed by using a logistic-regression model with an adjustment of randomisation stratification factors in both populations. Sensitivity analysis was performed by including PFS outcome assessed by Blinded Independent Central Review (BICR).[1]

The safety analysis dataset for the overall population and the PI3K/AKT-altered (PIK3CA/AKT1/PTEN-altered) sub-population included all patients who received at least one dose of study drug (fulvestrant, capivasertib or placebo).[1] The safety analysis was performed on the basis of the treatment received.[1]

The patients who received fulvestrant only were also included in the safety analysis and were included in the treatment arm to which these patients were randomised (capivasertib or placebo).[1]

EAG comment: The statistical methods appear to be satisfactory.

3.2.4 Efficacy results of the CAPItello-291 trial

3.2.4.1 Progression free survival in PI3K/AKT-altered population

Section B.2.6.1 of the CS[1] included the following statements: "*There was a 50% reduction in the risk of progression or death in favour of capivasertib plus fulvestrant (HR 0.50; 95%CI 0.38, 0.65, P<0.001). Median PFS in the capivasertib plus fulvestrant arm was more than double that in the placebo plus fulvestrant arm, at 7.3 months versus 3.1 months.*" Further details are shown in Table 3.8 below.

The company further confirmed (in Section B.2.6 of the CS[1]) that, "*Kaplan–Meier analysis demonstrated clear separation in the incidence of PFS events from the time of first tumour assessment*

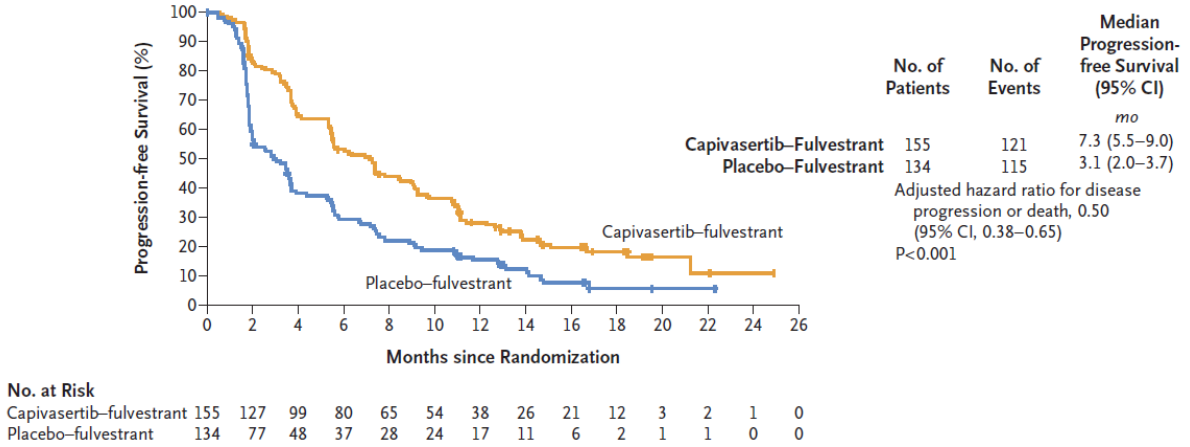
at 2 months, and favoured capivasertib plus fulvestrant across the whole follow-up period." The relevant details are shown in Figure 3.2 below.

Table 3.8: PFS by investigator assessment in the PI3K/AKT pathway-altered-population FAS (DCO1)

Progression or death	Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)
Total number of patients with events, n (%)*	121 (78.1)	115 (85.8)
Median PFS (months)†	7.3	3.1
95% CI for median PFS†	5.5, 9.0	2.0, 3.7
2-sided *P*-value‡	<0.001	
HR§	0.50	
95% CI for HR§	0.38, 0.65	

Based on Table 7 of the CS[1]
Progression determined by RECIST v1.1.
*Does not include RECIST progression events that occur after two or more missed visits or death after two visits of baseline where the patient has no evaluable visits or does not have a baseline assessment.
†Kaplan–Meier estimate.
‡Stratified log-rank test.
§Stratified Cox proportional hazards model. A HR <1 favours capivasertib plus fulvestrant. For the altered population, the log-rank test and Cox model are stratified by presence of liver metastases (yes versus no), and prior use of CDK4/6is (yes versus no).
CDK4/6i = cyclin-dependent kinases 4 and 6 inhibitor; CI = confidence interval; CS = company submission; FAS = full analysis set; HR = hazard ratio; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours

Figure 3.2: Kaplan-Meier plot of PFS by investigator assessment in the PI3K/AKT-altered-population FAS (DCO1)



Based on Figure 2 of the CS[1]
AKT = serine/threonine kinase; CI = confidence interval; CS = company submission; DCO = data cut-off; FAS = full analysis set; PFS = progression-free survival

Progression was determined by investigators based on Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 criteria. These data do not include RECIST progression events that occur after two or more missed visits or within two visits of baseline where the patient has no evaluable visits or did not have a baseline assessment. P-values are 2-sided. The HR was calculated using the stratified Cox proportional hazards model. The log-rank test and Cox model were stratified by presence of liver

metastases (yes versus no), and prior use of CDK4/6is (yes versus no). A HR <1 favours capivasertib plus fulvestrant.

3.2.4.2 Progression free survival in the PI3K/AKT pathway-altered population with prior CDK4/6i use

The company reported the following: "*Investigator-assessed median PFS was more than doubled with capivasertib plus fulvestrant compared with placebo plus fulvestrant ([redacted] months [95% CI: [redacted]] versus [redacted] months [95% CI: [redacted]];[61] HR 0.49 [95% CI: 0.36 to 0.66]).[6] There was clear, rapid separation in the incidence of PFS events from the time of first tumour assessment at 2 months, which was maintained across the whole follow-up period.*"[1] Further details are shown in Figure 3.3 below.

The company also added that "*Results in the PI3K/AKT pathway-altered population with prior use of CDK4/6 inhibitors was consistent with results in the broader PI3K/AKT pathway-altered population*".[1]

Figure 3.3: Kaplan-Meier plot of PFS by investigator assessment in the PI3K/AKT pathway-altered-population, prior CDK4/6i FAS (DCO1)

[redacted]

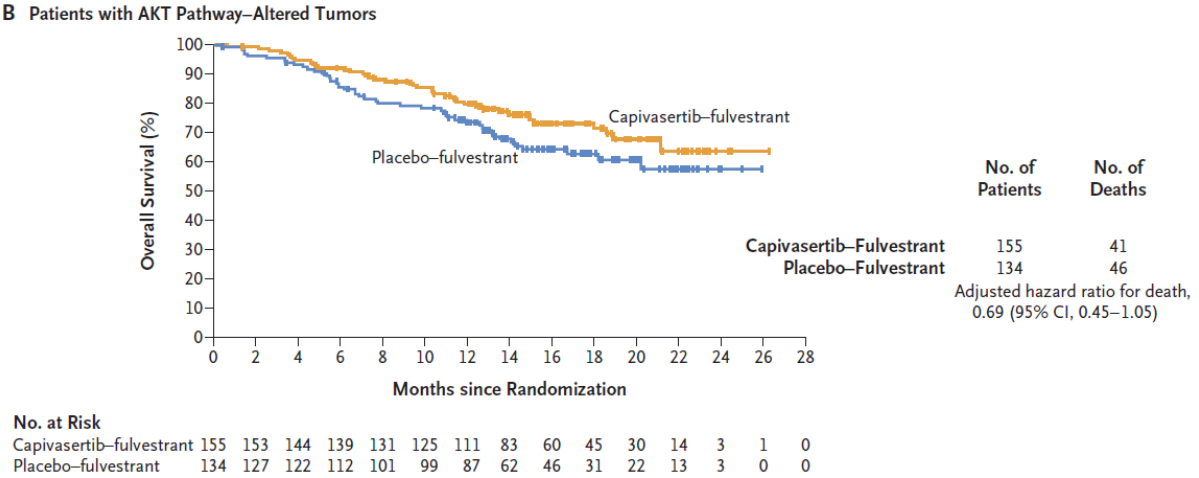
Based on Figure 3 of the CS[1]
Progression determined by RECIST v1.1. Does not include RECIST progression events that occur after two or more missed visits or death after two visits of baseline where the patient evaluable visits or does not have a baseline assessment.
AKT = serine/threonine kinase; CDK 4/6 = cyclin-dependent kinases 4 and 6; CI = confidence interval; CS = company submission; DCO = data cut-off; FAS = full analysis set; HR = hazard ratio; KM = Kaplan-Meier; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours

3.2.4.3 Overall survival in PI3K/AKT pathway-altered population

The company explained that "*Formal testing of OS at DCO1 was not planned, as the number of deaths was anticipated to be insufficient to permit formal analysis.*"[1]

The company demonstrated that "*In the PI3K/AKT pathway-altered population, the data show a clear trend towards improvement in OS with capivasertib plus fulvestrant (HR 0.69; 95% CI 0.45, 1.05). Kaplan–Meier curves diverged early and remained separated over time*."[1] The further details can be found as below in Figure 3.4.

Figure 3.4: Kaplan-Meier plot of OS in the PI3K/AKT-altered-population FAS (DCO1)



Based on Figure 4 of the CS[1]
Censored observations are indicated by +.
Patients not known to have died at the time of analysis are censored at the last recorded date on which the patient was last known to be alive.
AKT = serine/threonine kinase; CS = company submission; DCO = data cut-off; FAS = full analysis set; OS = overall survival

3.2.4.4 Overall survival in PI3K/AKT pathway-altered population with prior CDK4/6i use

The company reported the following "*Median OS was* [redacted] *months for patients in the placebo plus fulvestrant arm, whereas the median OS was* [redacted] *for patients in the capivasertib plus fulvestrant arm* [redacted] *There was clear, early separation in the incidence of OS events which was maintained across the whole follow-up period.*" [1] The further details can be found as below in Figure 3.5.

Figure 3.5: Kaplan-Meier plot of OS in the PI3K/AKT pathway-altered-population, prior CDK4/6i FAS (DCO1)

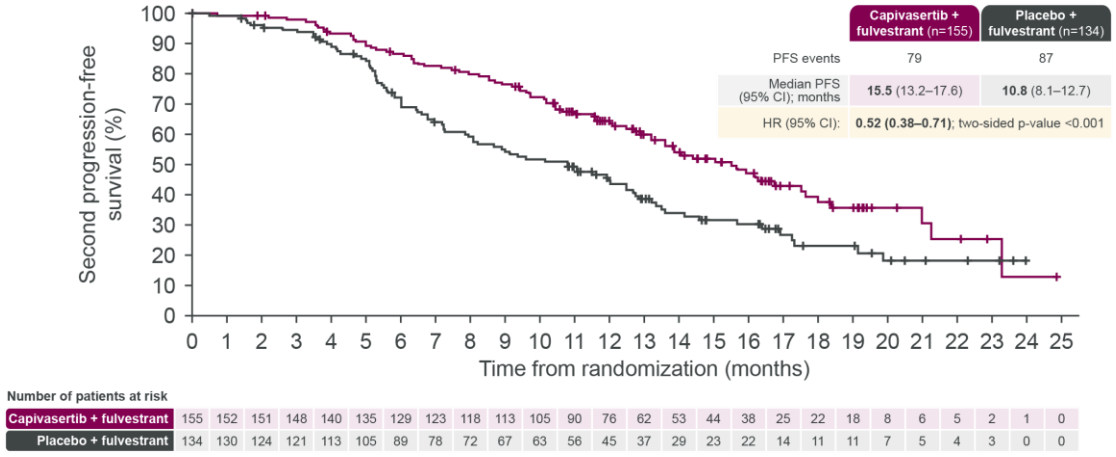
Based on Figure 5 of the CS[1]
AKT = serine/threonine kinase; CS = company submission; DCO = data cut-off; FAS = full analysis set; CDK4/6i = cyclin-dependent kinase 4 and 6 inhibitor; KM = Kaplan-Meier; OS = overall survival

3.2.4.5 Second progression-free survival (PFS2) in PI3K/AKT pathway-altered population

Section B.2.6.5 of the CS[1] included the following statements "*In the PI3K/AKT pathway-altered population, there was a 48% reduction in the risk of second progression in favour of capivasertib plus fulvestrant (HR 0.52; 95% CI 0.38, 0.71). Median PFS2 was 4.7 months longer for patients with PIK3CA/AKT1/PTEN alterations in the capivasertib plus fulvestrant arm compared with the placebo plus fulvestrant arm (15.5 vs 10.8 months).*" The further details can be found as below in Figure 3.6.

The company further pointed out that:[1] "*These PFS2 data provide a further indication of an early and sustained clinical benefit with capivasertib plus fulvestrant over placebo plus fulvestrant beyond first progression.*"

Figure 3.6: Kaplan-Meier plot of investigator-assessed PFS2 for the PI3K/AKT pathway-altered-population FAS (DCO1)



Based on Figure 6 of the CS[1]

AKT = serine/threonine kinase; CI = confidence interval; CS = company submission; DCO = data cut-off; FAS = full analysis set; HR = hazard ratio; PFS = progression-free survival; PFS2 = second progression-free survival

3.2.4.6 Objective response rate in PI3K/AKT pathway-altered population

The company explained that "the investigator-assessed objective response rate (ORR) by RECIST v1.1 criteria was higher for patients with measurable disease at baseline in the capivasertib plus fulvestrant arm compared with the placebo plus fulvestrant arm (28.8% versus 9.7%; odds ratio [OR] 3.93 [95% CI 1.93 to 8.04])."[1] The further details can be found as below in Table 3.9.

The company further pointed out that "These ORR data demonstrate the clear benefits of capivasertib plus fulvestrant in reducing tumour burden and disease progression."

Table 3.9: Logistic regression of investigator-assessed ORR for the PI3K/AKT pathway-altered-population FAS (DCO1)

Group	N	No. (%) patients with response	Adjusted response rate (%)*	Comparison between groups	
				OR	95% CI
Capivasertib + fulvestrant	132	38 (28.8)	32.1	3.93	1.93, 8.04
Placebo + fulvestrant	124	12 (9.7)	10.7		

Based on Table 8 of the CS[1]
AKT = serine/threonine kinase; CI = confidence interval; CS = company submission; DCO = data cut-off; FAS = full analysis set; OR = odds ratio; ORR = objective response rate

EAG comment: The survival data and other efficacy outcomes from the CS were not relatively mature. There was a lack of longer-term follow-up data from the CAPItello-291 trial.

3.2.4.7 EORTC QLQ-C30 and EORTC QLQ-BR23 in the PI3K/AKT pathway-altered population

In Section B.2.6.7 of the CS[1] the company reported that "*EORTC QLQ-C30 data for the PI3K/AKT pathway-altered population were available up to cycle 10, beyond which, data from this population were excluded from analysis as there were fewer than 20 observations in the placebo arm. Over the first 10 cycles of treatment in patients with at least one post-baseline score, global health status and quality of life were maintained in both the capivasertib plus fulvestrant group and the placebo plus fulvestrant group (least squares mean change from baseline in the QLQ-C30 score, [redacted] and [redacted], respectively; difference, [redacted]; 95% CI, [redacted] to [redacted]). Global health status and quality of life were maintained for longer with capivasertib plus fulvestrant than with placebo plus fulvestrant.*" The further details can be found as below in Figure 3.7.

The company also added that "*The median time to deterioration (defined as a sustained decrease of ≥10 points in the score from baseline) was increased with capivasertib plus fulvestrant vs placebo plus fulvestrant ([redacted] months vs [redacted] months; HR [redacted]; 95% CI, [redacted]).57 For reference, in the SOLAR-1 trial, median time to deterioration was 14.8 months with both alpelisib plus fulvestrant and with placebo plus fulvestrant (HR 1.03, 95% CI 0.72 to 1.48),64 suggesting alpelisib plus fulvestrant did not delay deterioration in global health status and quality of life vs placebo plus fulvestrant.*"[1]

The company also mentioned that "*For EORTC QLQ-BR23, the risk of clinically meaningful deterioration were similar but numerically favoured capivasertib plus fulvestrant for all subscales that were calculable, except for systemic therapy side effects, which with a HR of [redacted] (95%CI, [redacted]) numerically favoured placebo plus fulvestrant.*"[1]

The company summarised that "*These results may indicate that, overall, capivasertib plus fulvestrant does not materially reduce patient quality of life and may help to preserve overall quality of life over the course of treatment.*"[1]

Figure 3.7: Change from baseline for EORTC QLQ-C30, by visit, LS Mean (95% CI; PI3K/AKT pathway-altered subgroup FAS)

Based on Figure 7 of the CS[1]
Visits at each cycle are taken on Week 1, Day 1. Only on treatment assessments are included.
For the symptom scales, a negative change from baseline value indicates improvement of symptoms. For functional scales and Global health status/QoL score a positive change from baseline value indicates improvement in functioning and health status.
AKT = serine/threonine kinase; CI = confidence interval; CS = company submission; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; FAS = full analysis set; LS = least square; n = number of patients included in analysis; QoL = quality of life

3.2.4.8 Time to deterioration in ECOG PS in the PI3K/AKT pathway-altered population

In Section B.2.6.8 of the CS[1] the company explained that "*The results of time to deterioration of ECOG performance status favoured capivasertib plus fulvestrant, with a [redacted] reduction in the risk of deterioration compared with the placebo plus fulvestrant arm (HR: [redacted]; 95% CI: [redacted]).*"

3.2.4.9 Time to first subsequent chemotherapy or death in the PI3K/AKT pathway-altered population

The company reported that "*There was an improvement in time to first subsequent chemotherapy or death (TFSC) with capivasertib plus fulvestrant compared with placebo plus fulvestrant. The median TFSC was delayed by 5.0 months in the capivasertib plus fulvestrant arm (from 6.0 months in the placebo plus fulvestrant arm to 11.0 months in the capivasertib plus fulvestrant arm; HR: 0.56; 95% CI: 0.42 – 0.74).*" [1]

3.2.4.10 EQ-5D-5L in the PI3K/AKT pathway-altered population

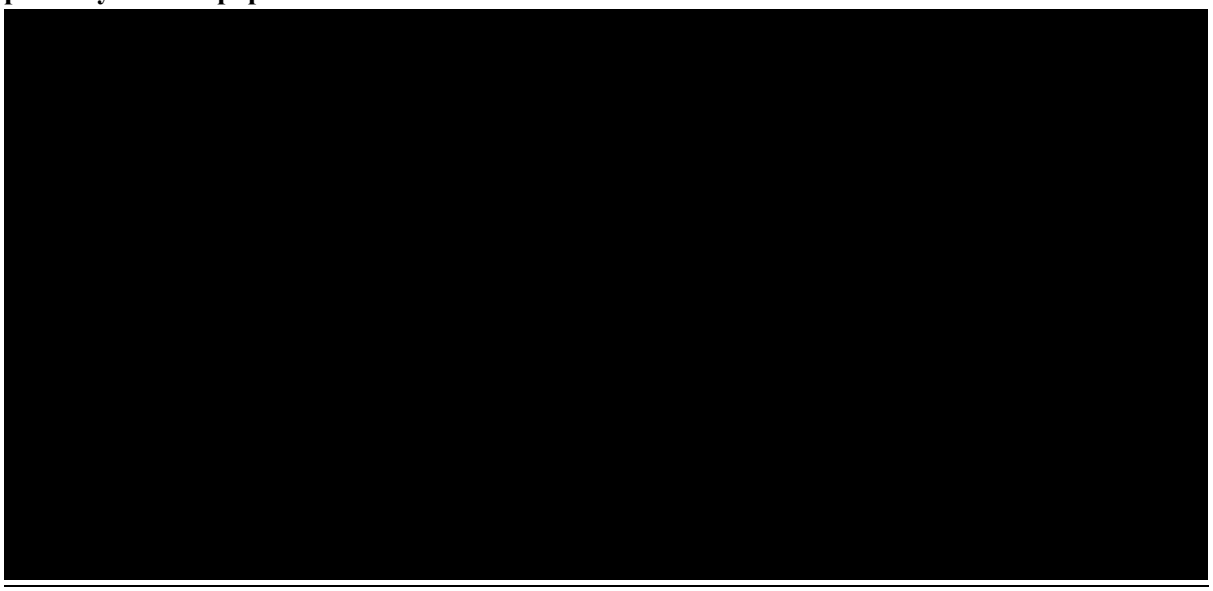
In Section B.2.6.8 of the CS[1] the company reported that, "*From baseline EQ-5D-5L index scores of [redacted] and [redacted], and from baseline VAS mean scores of [redacted] and [redacted], in the capivasertib plus fulvestrant and with placebo plus fulvestrant arms, respectively, there were no clear differences in changes from baseline between arms.*" The further details can be found as below in Figure 3.8 and Figure 3.9.

The company further explained that "*These results support the cancer-specific quality of life data from the EORTC QLQ tools, indicating that capivasertib plus fulvestrant does not materially reduce overall patient quality of life.*"

Figure 3.8: Change from baseline in EQ-5D-5L index score by visit, Mean (SD), in PI3K/AKT pathway-altered population

Based on Figure 8 of the CS[1]
AKT = serine/threonine kinase; CS = company submission; SD = standard deviation; EQ-5D-5L = European Quality of Life-5 Dimensions 5-Levels

Figure 3.9: Change from baseline in EQ-5D-5L VAS score by visit, Mean (SD), in PI3K/AKT pathway-altered population



Based on Figure 9 of the CS[1]
AKT = serine/threonine kinase; CS = company submission; SD = standard deviation; EQ-5D-5L = European Quality of Life-5 Dimensions 5-Levels

EAG comment: It should be noted that only short-term data up to cycle 20 assessed by the European Quality of Life-5 Dimensions 5-Levels (EQ-5D-5L) visual analogue scale (VAS) from the CAPItello-291 trial were provided. There was a lack of long-term follow-up data relating to HRQoL outcomes from the CAPItello-291 trial.

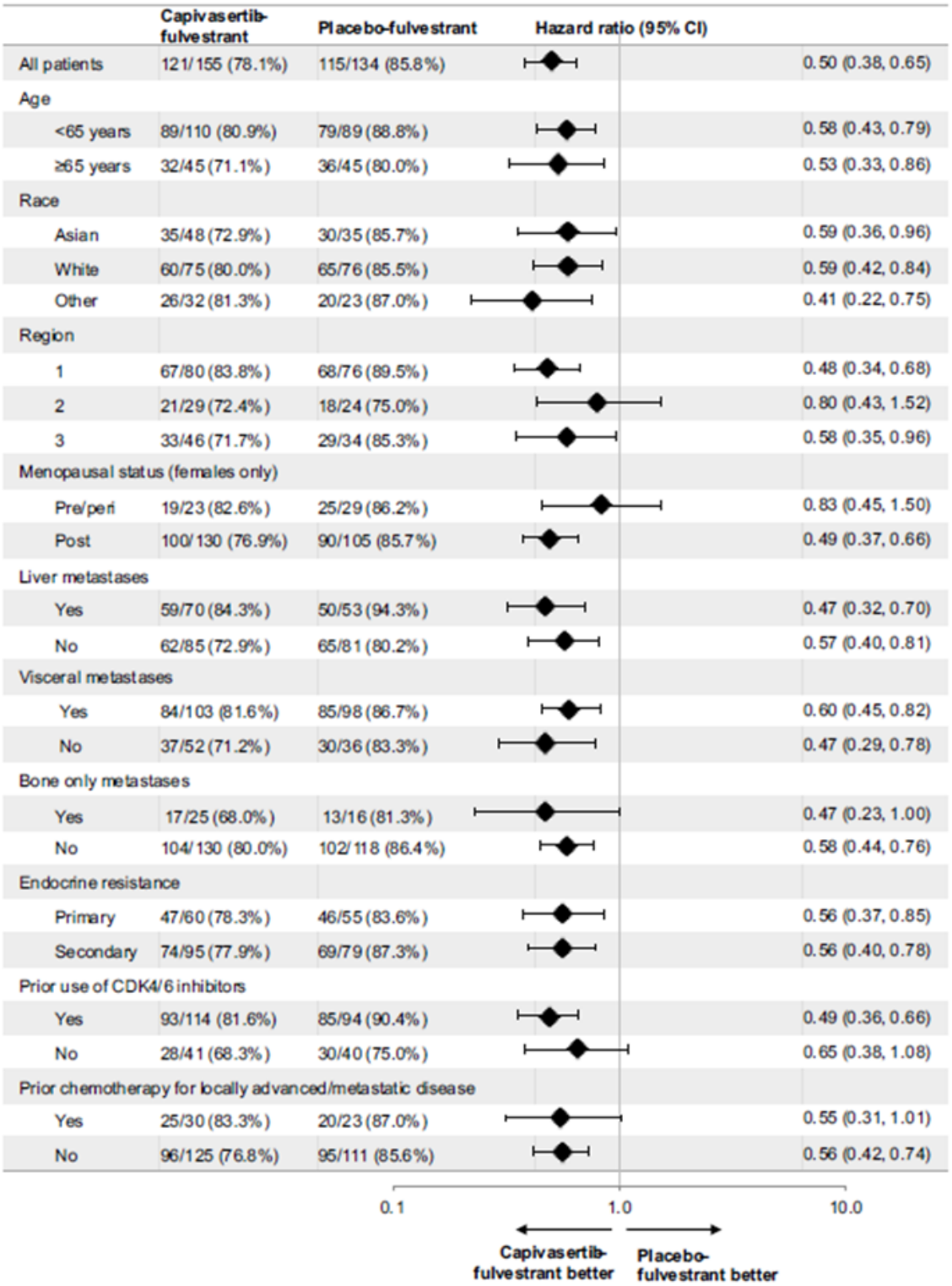
3.2.4.11 Subgroup analyses

Subgroup analyses were conducted for PFS, which were described as planned for stratification factors (prior use of CDK4/6is (yes versus no), liver metastases (presence or absence) and geographic area), age and "…across a range of other exploratory analyses in the PI3K/AKT pathway-altered population." (p. 49)[1] The results are shown in Figure 3.10.

EAG comment: It appears that there is little difference in treatment effect between the subgroups that were analysed. Notably, the treatment effect seems less in those with no prior CDK4/6i use, which means that efficacy estimates might actually be conservative for the decision problem population. However, the treatment effect also seems to be drastically diminished for those who are pre/peri-menopausal, which might have implications for clinical effectiveness if the proportions of pre/per- versus post-menopausal women are different in clinical practice.

The EAG requested subgroup analyses for OS in the clarification letter, to which the company responded that the data were too immature to perform.[4]

Figure 3.10: Subgroup analyses of PFS in the PI3K/AKT pathway-altered population



Based on Figure 10, CS.[1]

AKT = serine/threonine kinase; CI = confidence interval, CS – company submission; PFS = progression-free survival

3.2.5 Adverse events

The following Section will provide detail of the AEs in the PI3K/AKT pathway-altered population, in patients who were treated with either capivasertib plus fulvestrant and placebo plus fulvestrant, which were reported by the company in the CS.

3.2.5.1 Overall adverse events

The company identified a higher incidence of AEs of any Grade in the capivasertib plus fulvestrant arms when compared to placebo plus fulvestrant arm. In the PI3K/AKT pathway-altered population, AEs of any Grade were reported by [redacted] patients in the capivasertib plus fulvestrant arm and [redacted] patients in the placebo plus fulvestrant arm. The majority of AEs were of Grade 2 severity or lower. Serious adverse events (SAEs) occurred in [redacted] of patients on capivasertib plus fulvestrant and [redacted] with placebo plus fulvestrant. With regards to SAEs involving fatal outcomes, these were reported in [redacted] in the capivasertib plus fulvestrant arm and [redacted] in the placebo plus fulvestrant arm. However, none of these were assessed by the investigator as related to treatment. The company stated that the rate of discontinuation of capivasertib due to AEs was relatively low at [redacted]%. Table 3.10 highlights a summary of the overall AEs in the PI3K/AKT pathway-altered population.

Table 3.10: Summary of overall AEs in the PI3K/AKT pathway-altered population

	Number (%) of patients [a]	
	Capivasertib + Fulvestrant (N=155)	**Placebo + Fulvestrant (N=133)**
Any AE	[redacted]	[redacted]
Any AE possibly related to capivasertib/placebo	[redacted]	[redacted]
Any AE possibly related to capivasertib/placebo only[b]	[redacted]	[redacted]
Any AE possibly related to both capivasertib/placebo and fulvestrant[b]	[redacted]	[redacted]
Any AE possibly related to fulvestrant only[b]	[redacted]	[redacted]
Any AE of CTCAE Grade 3 or higher	[redacted]	[redacted]
Any SAE with outcome of death	[redacted]	[redacted]
Any SAE (including events with outcome of death)	[redacted]	[redacted]
Any AE leading to discontinuation of capivasertib/placebo	[redacted]	[redacted]
Any AE leading to discontinuation of capivasertib/placebo only	[redacted]	[redacted]
Any AE leading to discontinuation of both capivasertib/placebo and fulvestrant	[redacted]	[redacted]
Any AE leading to discontinuation of fulvestrant only	[redacted]	[redacted]
Any AE leading to dose modification of capivasertib/placebo	[redacted]	[redacted]
Any AE leading to dose interruption of capivasertib/placebo[c]	[redacted]	[redacted]
Any AE leading to dose interruption of capivasertib/placebo only	[redacted]	[redacted]

	Number (%) of patients [a]	
	Capivasertib + Fulvestrant (N=155)	Placebo + Fulvestrant (N=133)
Any AE leading to dose interruption of both capivasertib/placebo and fulvestrant	[redacted]	[redacted]
Any AE leading to dose interruption of fulvestrant only	[redacted]	[redacted]
Any AE leading to dose reduction of capivasertib/placebo only[c]	[redacted]	[redacted]

Based on Table 10 of the CS[1]

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

[b] As assessed by the investigator.

[c] Differences in the number of dose modifications due to AEs in the exposure summary and the number of AEs resulting in a dose modification are due to the differences in data capture between the exposure and AE eCRFs.

Based on Clinical Study Report, Table 39[12]

AEs = adverse events; AKT = serine/threonine kinase; CS = company submission; CTCAE = Common Terminology Criteria for Adverse Events; SAEs = serious adverse events

3.2.5.2 Most common AEs

The company stated that "*the AEs reported in the PI3K/AKT pathway-altered population were consistent with the known safety profiles of capivasertib and fulvestrant, or due to underlying disease*". The most frequently reported AEs were: diarrhoea ([redacted] with capivasertib plus fulvestrant versus [redacted] with placebo plus fulvestrant); nausea ([redacted] versus [redacted]); fatigue ([redacted] versus [redacted]); maculo-papular rash ([redacted] versus [redacted]); vomiting ([redacted] versus [redacted]); and rash ([redacted] versus [redacted]). When AEs were of Grade 2 or lower severity, dose modification was managed, with only a few leading to discontinuation. Of AEs at Grade 3 and 4 severity occurring in >2% of patients in any treatment arm were limited to diarrhoea ([redacted] versus [redacted]), maculo-papular rash ([redacted] versus [redacted]) and anaemia ([redacted] versus [redacted]) Table 3.11 summarises the AEs of any Grade occurring in >10% patients in any treatment arm.

Table 3.11 Most common AEs in the PI3K/AKT pathway-altered population (frequency >10% in either treatment arm)

MedDRA Preferred term	Number (%) of patients[a]	
	Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=133)
Diarrhoea	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Rash maculo-papular	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]

MedDRA Preferred term	Number (%) of patients[a]	
	Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=133)
Hyperglycaemia	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]

Based on Table 11 of the CS[1]
[a] Number (%) of patients with AEs, sorted in descending frequency of preferred term in the capivasertib plus fulvestrant treatment group.
Patients with multiple events in the same preferred term are counted only once in that preferred term.
AEs with an onset date on/after date of first dose; AEs with onset date prior to dosing which worsen after dosing; AEs occurring up to 30 days (+7 days) following date of last dose are reported.
AE = adverse event; AKT = serine/threonine kinase; CS = company submission; N = number of patients in treatment group; MedDRA version 25.0 = Medical Dictionary for Regulatory Activities

3.2.5.3 Adverse events causality

The company stated that AEs of any Grade possibly related to capivasertib or placebo in patients with PI3K/AKT pathway alterations were reported in [redacted] of the capivasertib plus fulvestrant arm and [redacted] of the placebo plus fulvestrant arm. The most common AEs that could be related to capivasertib in patients were gastrointestinal disorders (diarrhoea [redacted], nausea [redacted], stomatitis [redacted], vomiting [redacted]), skin disorders (maculo-papular rash [redacted], rash [redacted]), and metabolism and nutrition disorders (decreased appetite [redacted], hyperglycaemia [redacted], respectively. AEs that were possibly related to both capivasertib and fulvestrant occurred in [redacted] of patients in the capivasertib plus fulvestrant arm, and mainly in the same categories.[12]

Dose modification of both capivasertib or placebo resulting from AEs among patients with PI3K/AKT pathway alterations in [redacted] of patients in the capivasertib plus fulvestrant arm and 13.5% of patients in the placebo plus fulvestrant arm. The most frequently reported AE leading to dose modification in the capivasertib arm was diarrhoea ([redacted]). The company stated that there were no discontinuations of capivasertib to due diarrhoea.[12] The company suggested that "*although diarrhoea possibly related to capivasertib occurred in [redacted] of patients receiving capivasertib plus fulvestrant, it is clear that diarrhoea was low grade and manageable*".

3.2.5.4 Adverse events of special interest

The company identified AEs of "special interest" which were specified in the CAPItello-291 protocol which included "*diarrhoea, hyperglycaemia, infective pneumonia, QT prolongation, rash (including maculo-papular rash), stomatitis and urinary tract infection (UTI)*". Furthermore, the company stated that "*QT prolongation occurred in [redacted] patients with PI3K/AKT pathway alterations receiving capivasertib plus fulvestrant vs [redacted] with placebo plus fulvestrant. Infective pneumonia occurred in [redacted] vs [redacted], respectively, and UTI occurred in [redacted] vs [redacted]* [12]".

EAG comment: The EAG asked the company to provide a table and summary of the overall AEs in the PI3K/AKT pathway-altered population from the FAKTION trial. The company responded by

declaring that the FAKTION phase 2 trial was externally sponsored by the Velindre NHS Trust, and consequently the company does not have access to data beyond what is presented "*in the FAKTION pivotal trial publications by Jones RH in 2020 [13] and Howell et al in 2022 [14]. The safety data provided in these publications was based on the FAKTION ITT population; data specifically in patients with PI3K/AKT pathway alterations is not publicly available and thereore cannot be provided by the Company in response to this clarification question. Similarly to CAPItello-291, the Company does not expect any differences in safety profile by biomarker status, and therefore the FAKTION ITT safety data can be considered applicable and relevant to the PI3K/AKT pathway altered population within the trial.*"

The company also responded by stating that there was a pattern among frequently observed AEs with capivasertib plus fulvestrant in FAKTION (see Table 3.12) to be largely consistent to AEs observed in the PI3K/AKT pathway altered population of the CAPItello trial (see Table 3.11). In the capivasertib plus fulvestrant arm of the FAKTION primary analysis, diarrhoea, fatigue and nausea were the most prevalent AEs observed.

The company also noted "*that FAKTION is a small UK-based phase II trial which recruited only 140 patients, which did not include patients who have had prior treatment with a CDK4/6i, with no data available specifically in the PI3K/AKT pathway alterations population. More robust data on the safety and effectiveness of capivasertib plus fulvestrant relevant to the decision problem is available from the pivotal multi-national phase III CAPItello-291*".

Table 3.12: Top four most common AEs of any Grade observed in the capivasertib plus fulvestrant arm in FAKTION (ITT population) (Jones 2020)

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Total
Diarrhoea	28 (41%)	18 (26%)	10 (14%)	0	56 (81%)
Fatigue	24 (35%)	15 (22%)	1 (1%)	0	40 (58%)
Nausea	30 (43%)	8 (12%)	0	0	38 (55%)

Based on Jones 2020[13]
Note: This Table summarises clinical AEs observed in FAKTION, and excludes abnormal lab values reported as AEs, to account for the differences in methodologies for AE reporting between FAKTION and CAPItello-291. In FAKTION, sites were prompted to review results for out of range laboratory test values and to report an AE by CTCAE Grade if and when CTCAE criteria were met. Some AEs identified from abnormal blood or biochemistry laboratory testing results might not have had clinical significance. Blood pressure values were also covered by these reporting requirements. Both clinical and abnormal lab values are summarised in the Appendix of Jones 2020. By contrast, the CAPItello-291 CSP Section 8.3.7 states that "Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and ECG abnormalities should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IMP or if they are considered to be clinically relevant as judged by the investigator".
AEs = adverse events; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ITT = intention-to-treat

The company also cited a paper by Howell et al. (2022), which provided an updated analysis of toxicity and safety data. The company stated that there was little change in the occurrence of AEs from the primary analysis. The company further stated that "*this data further reiterates that the AE profile of capivasertib plus fulvestrant in FAKTION is largely consistent with common AE events observed in CAPItello-291, supplementing our understanding of the safety of the regimen based on the findings of the robust pivotal Phase III CAPItello-291*."

Although the EAG had requested a Table that summarises the overall AEs in the PI3K/AKT pathway alterations population from the FAKTION trial, which was not fully provided. The EAG appreciated

that data may not be available and are satisfied with the response and common adverse reported from the capivasertib plus fulvestrant arm of the FAKTION trial. Nevertheless, it should be noted that an overall summary of all AEs would provide greater insight into the AEs suffered.

The EAG also asked the company provide data of SAEs and treatment discontinuation due to AEs in the PI3K/AKT pathway-altered population from the FAKTION trial. The company responded by again explaining how the FAKTION phase 2 trial was externally sponsored by the Velindre NHS Trust and that data was not available as is described above. However, the company did provide a Table of SAEs which were published in the article of Jones 2020[13]. Table 3.13 highlights the SAEs observed in the FAKTION trial provided by the company.

Table 3.13 SAEs observed in FAKTION (ITT population)

SAE	Capivasertib plus fulvestrant N (%)	Placebo plus fulvestrant N (%)
Abdominal pain	1 (1%)	1 (1%)
Anaemia	0	1 (1%)
Back pain	0	2 (3%)
Blocked nephrostomy	1 (1%)	0
Bone pain	1 (1%)	0
Dyspnoea	0	3 (4%)
Fever	0	1 (1%)
Gastroenteritis	0	1 (1%)
Haemorrhage	1 (1%)	0
Hypercalcaemia	0	1 (1%)
Infection	0	1 (1%)
Lower respiratory tract infection	2 (3%)	1 (1%)
Muscle weakness lower limb	1 (1%)	0
Non-cardiac chest pain	1 (1%)	1 (1%)
Pain	1 (1%)	2 (3%)
Pain in extremity	0	1 (1%)
Perineal abscess	1 (1%)	0
Pleural effusion	1 (1%)	0
Radicular pain	0	1 (1%)
Skin infection	1 (1%)	0
Urinary tract infection	1 (1%)	0
Vomiting	0	1 (1%)

Based on Jones 2020[13]
ITT = intention-to-treat; SAE = serious adverse event

Serious adverse events that were reported only in the capivasertib plus fulvestrant group were acute kidney injury (two), diarrhoea (three), hyperglycaemia (one), loss of consciousness (one), rash (two), sepsis (one) and vomiting (one). The company stated that "*serious AEs were rare in both treatment arms*" and this is evident in Table 3.13. An additional SAE of pneumonia "*in the capivasertib plus*

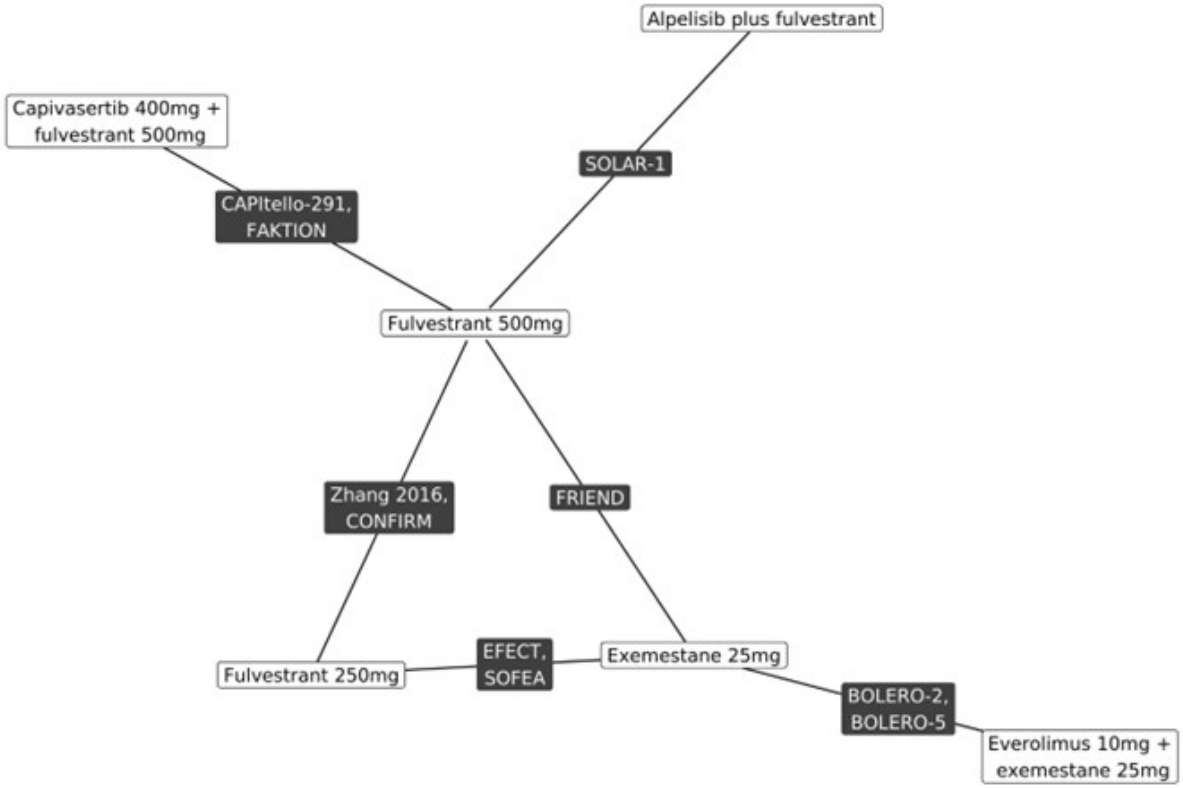
fulvestrant group had occurred subsequent to the primary analysis [14]." Furthermore, the company stated that "*Eight (12%) participants discontinued capivasertib because of adverse events*". The EAG are satisfied with the company's response to the clarification question asked.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Indirect treatment comparison (ITC) was conducted by the company because there were no direct comparative data for capivasertib plus fulvestrant versus relevant comparators (alpelisib plus fulvestrant and everolimus plus exemestane).

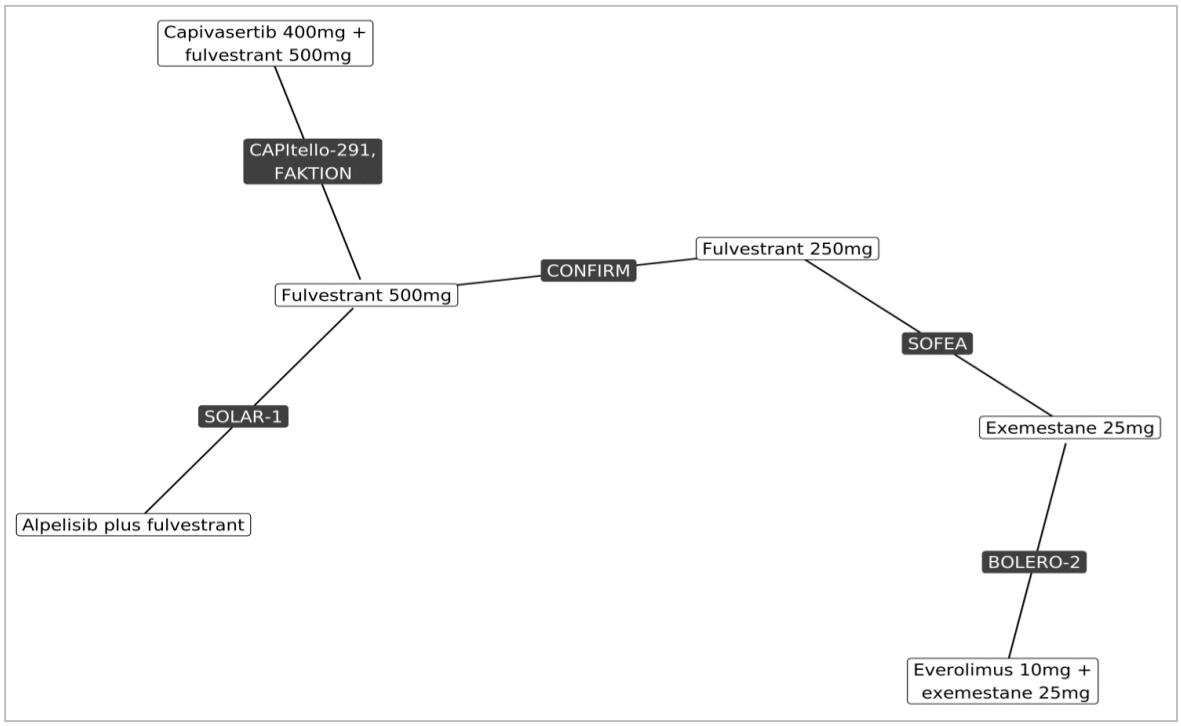
Ten RCTs were identified via the SR and the data from these 10 RCTs were used in the ITC analysis. The ITC analysis was performed by using the pivotal trials of capivasertib plus fulvestrant (CAPItello-291, FAKTION), alpelisib plus fulvestrant (SOLAR-1) and everolimus plus exemestane (BOLERO-2, BOLERO-5). Other studies were also required to connect the network for the ITC analysis. The network plot for the PFS outcome is presented in Figure 3.11. The network plot for the OS outcome is presented in Figure 3.12.

Figure 3.11: Trial network for PFS outcome



Based on Figure 12 of CS.[1]
CS = company submission; PFS = progression-free survival

Figure 3.12: Trial network for OS outcome



Based on Figure 13 of CS.[1]
CS = company submission; OS = overall survival

The NMA was performed on the basis of data of the PI3K/AKT pathway-altered subgroup from the CAPItello-291 and FAKTION trials for capivasertib plus fulvestrant, and the PIK3CA subgroup from the SOLAR-1 trial for alpelisib plus fulvestrant. The remaining trials included the NMA did not report patient characteristics for patients with PIK3CA/AKT1/PTEN alterations.[1] It should be noted that there is evidence that PIK3CA, AKT1 and PTEN alterations are treatment effect modifiers for capivasertib plus fulvestrant, and PIK3CA alteration is a treatment effect modifier for alpelisib plus fulvestrant.[1]

The company presented the data of study characteristics of included trials and baseline data for the key sources of heterogeneity in a figure format in the original submission. However, the company did not present the data of study characteristics of included trials and baseline data for the key sources of heterogeneity in a table in the original submission. Therefore, the EAG requested the company to provide the data of study characteristics of included trials and baseline data for key sources of heterogeneity in a table. In responding to the EAG's request, the company provided the data of study characteristics of included trials and baseline data for key sources of heterogeneity in a table. The summary of studies included in the base-case NMA is presented in Table 3.14. The summary of baseline data for key sources of heterogeneity in the NMA is presented in Table 3.15.

There was heterogeneity of baseline characteristics for the populations in the included studies in the base-case NMA. Of 10 included studies, four studies (EFECT, SOFEA, CONFIRM and NCT01300351) included populations with mixed/unknown characteristics in terms of HER2 status, while the remaining studies recruited all patients with HER2 negative.[4]

In terms of PI3K/AKT status, two trials (CAPItello-291 and FAKTION) included the PI3K/AKT altered subgroup while one trial (SOLAR-1) included the subgroup of PIK3CA alteration only. It should be further noted that the trial of CAPItello-291 included all patients with PI3K/AKT altered population; however, the FAKTION only included a smaller proportion (39% in the fulvestrant arm and 45% in the

capivasertib plus fulvestrant arm) of patients with PI3K/AKT altered population. It should be noted that the remaining trials recruited patients with unknown PI3K/AKT status.[4]

In terms of prior treatment, only two trials (CAPItello-291 and SOLAR-1) recruited patients who received ET and cyclin-dependent kinase (CDK) treatment. It should be further noted that the proportion of patients who received prior CDK4/6i use in the CAPItello-291 trial ranged from 69.4% in the placebo plus fulvestrant arm to 72.9% in the capivasertib plus fulvestrant arm, while the proportion of patients who received prior CDK4/6i use in the SOLAR-1 trial ranged from 5.3% in the alpelisib plus fulvestrant to 6.4% in the placebo plus fulvestrant arm. However, the remaining eight trials recruited patients who received ET treatment but did not receive CDK treatment.

In addition, there was substantial heterogeneity in ECOG PS 1 in the populations of included studies for the ITC analysis. Where reported, the proportion of patients with ECOG (PS = 1) ranged from 24% to 68.4%. However, six studies did not report ECOG (PS = 1) for the population being recruited.[4]

Table 3.14: Summary of studies included in the base-case NMA

Study	PFS	OS	Intervention	Comparator	Sample size	Region	HR status	HER2 status	PI3K/AKT status	Prior treatment
CAPItello-291	✓	✓	Capivasertib + fulvestrant 500	Fulvestrant 500	289	Multi	HR+	HER2-neg	Altered subgroup	ET +/- CDK
FAKTION	✓	✓	Capivasertib + fulvestrant 500	Fulvestrant 500	59	UK	HR+	HER2-neg	Altered subgroup	ET, no CDK
BOLERO-2	✓	✓	Everolimus + exemestane	Exemestane	724	Multi	HR+	HER2-neg	NA	ET, no CDK
BOLERO-5	✓	x	Everolimus + exemestane	Exemestane	159	China	HR+	HER2-neg	NA	ET, no CDK
EFECT	✓	x	Fulvestrant 250	Exemestane	693	Multi	HR+	Mixed/unkn	NA	ET, no CDK
SOFEA	✓	✓	Fulvestrant 250	Exemestane	723	Multi	HR+	Mixed/unkn	NA	ET, no CDK
CONFIRM	✓	✓	Fulvestrant 500	Fulvestrant 250	736	Multi	HR+	Mixed/unkn	NA	ET, no CDK
FRIEND	✓	x	Fulvestrant 500	Exemestane	144	China	HR+	HER2-neg	NA	ET, no CDK
NCT01300351 (Zhang 2016)	✓	x	Fulvestrant 500	Fulvestrant 250	221	China	HR+	Mixed/unkn	NA	ET, no CDK
SOLAR-1	✓	✓	Alpelisib + fulvestrant 500	Fulvestrant 500	341	Multi	HR+	HER2-neg	PIK3CA only	ET +/- CDK

Based on Table 15 of response to the request for clarification.[4]
Notes: Both PEARL and SOFEA report data for additional non-approved treatment arms not included within the base-case network
AKT = serine/threonine kinase; ET = endocrine therapy; no CDK: endocrine therapy without prior CDK4/6i therapy; ET +/- CDK: endocrine therapy with or without prior CDK4/6i therapy use; HER2-neg = HER2-negative; HR+ = hormone receptor positive; Mixed/unkn = mixed or unknown HER2 status; Multi: multinational; NA = not available; NMA = network meta-analysis; OS = overall survival; PFS = progression-free survival; SOFEA = fulvestrant plus anastrozole; UK = United Kingdom

Table 3.15: Summary of baseline data for key sources of heterogeneity in the NMA

Study	Treatment arm	Sample size	Age	ECOG PS = 1	Post menopausal %	PI3K/AKT altered	HER2- %	Prior CDK4/6i use
CAPItello-291 (PI3K/AKT altered population)	Capivasertib + fulvestrant 500	155	58	40%	83.9%	100%	100%	72.9%
	Placebo + fulvestrant 500	134	60	26.9%	78.4%	100%	100%	69.4%
FAKTION*	Capivasertib + fulvestrant 500	69	62	36%	100%	45%	100%	0%
	Fulvestrant 500	71	61	24%	100%	39%	100%	0%
BOLERO-2	Everolimus + exemestane	485	62	36%	100%	Unknown	100%	0%
	Exemestane	239	61	35%	100%	Unknown	100%	0%
BOLERO-5	Everolimus + exemestane	80	65	61.3%	100%	Unknown	100%	0%
	Exemestane	79	68	68.4%	100%	Unknown	100%	0%
EFECT	Fulvestrant 250	351	63	37.9%	100%	Unknown	Unknown	0%
	Exemestane	342	63	43.6%	100%	Unknown	Unknown	0%
SOFEA	Fulvestrant 250	231	63	Unknown	100%	Unknown	6%	0%
	Exemestane	249	66	Unknown	100%	Unknown	7%	0%
CONFIRM	Fulvestrant 500	362	61	Unknown	100%	Unknown	Unknown	0%
	Fulvestrant 250	374	61	Unknown	100%	Unknown	Unknown	0%
FRIEND	Fulvestrant 500	77	62	37.7	100%	Unknown	100%	Unknown
	Exemestane	67	63	40.3	100%	Unknown	100%	Unknown
NCT01300351 (Zhang 2016)	Fulvestrant 500	111	53.6	Unknown	100%	Unknown	Unknown	Unknown
	Fulvestrant 250	110	53.1	Unknown	100%	Unknown	Unknown	Unknown
SOLAR-1 (PIK3CA mutated cancer)	Alpelisib + fulvestrant 500	169	63	33.1	100%	100%	100%	5.3
	Placebo + fulvestrant 500	172	64	33.7	100%	100%	100%	6.4

Based on Table 16 of response to the request for clarification[4]

Study	Treatment arm	Sample size	Age	ECOG PS = 1	Post menopausal %	PI3K/AKT altered	HER2- %	Prior CDK4/6i use
* No baseline characteristics specifically for the PI3K/AKT pathway altered patients were presented in the FAKTION pivotal publication. The trial included both patients with PIK3CA or PTEN alterations (45% in the capivasertib plus fulvestrant arm, 39% in the placebo plus fulvestrant arm), and patients without PIK3CA or PTEN alterations (55% in the capivasertib plus fulvestrant arm, 61% in the placebo plus fulvestrant arm). The FAKTION phase II trial is an externally-sponsored study by the Velindre NHS Trust AKT = serine/threonine kinase; CDK4/6i = cyclin-dependent kinases 4 and 6 inhibitor; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HER2- = human epidermal growth factor receptor 2-negative; NHS = National Health Service; NMA = network meta-analysis								

3.4 Critique of the indirect comparison and/or multiple treatment comparison

The proportional hazard (PH) assumptions of included trials for the NMA were assessed. The PHs assumption was assessed for all included studies in terms of outcomes of PFS and OS. This PH assumption was evaluated by the consideration of the Kaplan-Meier (KM) curves, Schoenfeld residual plots and log cumulative hazard plots.[4]

It should be noted that based on the assessment of PH assumption, there was evidence that the assumption of PHs was not valid for PFS and OS outcomes for studies in the NAM. However, the company performed NMA under PHs in their evidence submission.[1]

The summary results of the PH assumption assessment are summarised in Table 3.16 below.

Table 3.16: Summary of PH assessment across studies

	Evidence of non-PH (strong = 3, moderate = 2, weak = 1, none = 0)	
Trial	**PFS**	**OS**
BOLERO-2	Weak	Moderate
BOLERO-5	Strong	N/A
CAPItello-291	Strong	Weak
CONFIRM	Weak	Weak
EFECT	None	N/A
FAKTION	Weak	Weak
FRIEND	Weak	N/A
NCT01300351 (Zhang 2016)	Strong	N/A
SOFEA	Moderate	Moderate
SOLAR-1	Moderate	Weak

Based on Table 8 of response to the request for clarification.[4]
PFS = progression-free survival; PH = proportional hazards; OS = overall survival; N/A = not applicable

Therefore, the EAG considers that given that assumption of PHs was not valid for the PFS and OS outcomes for studies in the NMA, time-varying analysis approach would be more appropriate. The EAG requested the company to reconduct NMAs for PFS and OS outcomes by using the time-varying analysis approach.

In responding to the EAG's request, the company reconducted NMAs for PFS and OS outcomes by using the time-varying analysis approach. The company provided the updated results of NMA by using the time-varying approach during the response to the request for clarification stage.

The company used a piecewise approach for the time-varying NMA. The time-varying NMA was based on the PI3K/AKT pathway-altered subgroup results of CAPItello-291 and FAKTION, and the PIK3CA mutated subgroup results of SOLAR-1.[4]

Furthermore, the company stated that the updated NMA used data from the biomarker unselected populations of other comparator studies as the company assumed that PI3K/AKT pathway alteration status would not modify the treatment effect of these comparators.[4]

For PFS and OS, both fixed effect and random effect NMAs were performed where fulvestrant 500 mg was used as the reference treatment in the network.[4]

For the piecewise approach, the company stated that cut-off points were selected on the basis of a visual inspection of the KM curves for all studies included in the NMA for each endpoint. The company made the following statement:[4]

- *"For OS, 6 months was selected as there was a deviation in some of the curves at this timepoint in selected studies, and it was early enough in the study follow-up for the sample size to be sufficient in most cases.*
- *For PFS, 3 months was selected, although as some treatment arms appeared to deviate at 2 months, this alternative was also explored. There were no curves which warranted more than one cut point."*

The statistical fit of the models was assessed by using the posterior mean total residual deviance and the deviance information criterion (DIC). A lower DIC suggests a more parsimonious model. These measures were used to compare the relative fit of the models.[4]

3.4.1 Results of progression free survival

The goodness of fit statistics for the NMAs for PFS are shown below in Table 3.17. The company stated that the difference in DIC between the fixed effect model and random effect model was not judged meaningful (less than 3 points).[4] The 3-month cut-off point has a lower DIC than the 2-month cut-off point but the difference was not judged to be meaningful.[4]

Table 3.17 Goodness of fit statistics for the PFS NMA

Model	Number of data points	Total residual deviance	Effect number of parameters	DIC
0-2 months				
Fixed effects	10	10.4	5.0	15.4
Random effects	10	9.1	6.5	15.6
2+ months				
Fixed effects	10	12.5	5.0	17.5
Random effects	10	10.8	7.5	18.3
0-3 months				
Fixed effects	10	9.6	5.0	14.6
Random effects	10	8.5	6.8	15.3
3+ months				
Fixed effects	10	11.0	5.0	16.0
Random effects	10	9.9	7.2	17.1

Based on Table 9 of response to the request for clarification.[4]
DIC = deviance information criterion; NMA = network meta-analysis; PFS = progression-free survival

Figure 3.13 shows the results of PFS where fulvestrant 500 mg was used as the reference treatment. Figure 3.14 shows the results of PFS by using capivasertib plus fulvestrant as the reference treatment. The results showed that the point estimates were similar across models with wider 95% credible intervals (CrIs) for the random-effects models compared to fixed-effects models.[4]

The HR and 95% CrIs for PFS where fulvestrant 500 mg was used as the reference treatment are presented in Table 3.18. The HR and 95% CrIs for PFS by using capivasertib plus fulvestrant as the reference treatment are presented in Table 3.19.

The results from the piecewise approach showed that capivasertib plus fulvestrant was associated with a statistically significant improvement in PFS when compared with endocrine monotherapy (at both 2-month or 3-month cut-off).[4]

However, there were no statistically significant differences in PFS between capivasertib plus fulvestrant and alpelisib plus fulvestrant (at both 2-month or 3-month cut-off). There were also no statistically significant differences in PFS between capivasertib plus fulvestrant and everolimus plus exemestane for all random-effect models and most of fixed-effect models (at both 2-month or 3-month cut-off).[4]

Figure 3.13: Forest plot for PFS for the comparison with fulvestrant 500 mg

Based on Figure 3 of response to the request for clarification[1]
CrI = credible interval; ITC = indirect treatment comparison; PFS = progression-free survival

Figure 3.14: Forest plot for PFS for the comparison with capivasertib plus fulvestrant

Based on Figure 4 of response to the request for clarification[1]
CrI = credible interval; ITC = indirect treatment comparison; PFS = progression-free survival

Table 3.18 Summary of PFS HRs for treatments versus fulvestrant

	Timepoint 1 HR (95% CrI)		Timepoint 2 HR (95% CrI)	
	Fixed effects	**Random effects**	**Fixed effects**	**Random effects**
PFS Scenario 1	***0-3 months***		***3+ months***	
Capivasertib + fulvestrant				
Everolimus + exemestane				
Alpelisib + fulvestrant				
Exemestane				
Fulvestrant 250 mg				
PFS Scenario 2	***0-2 months***		***2+ months***	
Capivasertib + fulvestrant				
Everolimus + exemestane				
Alpelisib + fulvestrant				

	Timepoint 1 HR (95% CrI)		Timepoint 2 HR (95% CrI)	
	Fixed effects	Random effects	Fixed effects	Random effects
Exemestane	[redacted]	[redacted]	[redacted]	[redacted]
Fulvestrant 250 mg	[redacted]	[redacted]	[redacted]	[redacted]
Based on Table 10 of response to the request for clarification[4] HR = hazard ratio; PFS = progression-free survival; CrI = credible intervals				

Table 3.19 Summary of PFS HRs for treatments versus capivasertib plus fulvestrant

	Timepoint 1 HR (95% CI)		Timepoint 2 HR (95% CI)	
	Fixed effects	Random effects	Fixed effects	Random effects
PFS Scenario 1	**0-3 months**		**3+ months**	
Fulvestrant 500 mg	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus + exemestane	[redacted]	[redacted]	[redacted]	[redacted]
Alpelisib + fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]
Exemestane	[redacted]	[redacted]	[redacted]	[redacted]
Fulvestrant 250 mg	[redacted]	[redacted]	[redacted]	[redacted]
PFS Scenario 2	**0-2 months**		**2+ months**	
Fulvestrant 500 mg	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus + exemestane	[redacted]	[redacted]	[redacted]	[redacted]
Alpelisib + fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]
Exemestane	[redacted]	[redacted]	[redacted]	[redacted]
Fulvestrant 250 mg	[redacted]	[redacted]	[redacted]	[redacted]
Based on Table 11 of response to the request for clarification[4] CI = confidence interval; HR = hazard ratio; PFS = progression-free survival				

3.4.2 Results of overall survival

The goodness of fit statistics for OS for the NMAs are shown in Table 3.20. Based on DIC values, the preferred model is the fixed effects model for 0-6 months and the random effects model for 6+ months.[4]

Table 3.20: Goodness of fit statistics for the OS NMA

Model	Number of data points	Total residual deviance	Effect number of parameters	DIC
0-6 months				
Fixed effects	6	5.0	5.0	10.0
Random effects	6	5.1	5.1	10.2
6+ months				
Fixed effects	6	7.5	5.0	12.5
Random effects	6	6.8	5.3	12.1
Based on Table 12 of response to the request for clarification.[4] DIC = deviance information criterion; NMA = network meta-analysis; OS = overall survival				

Figure 3.15 shows the results of OS where fulvestrant 500 mg was used as the reference treatment. Figure 3.16 shows the results of OS by using capivasertib plus fulvestrant as the reference treatment.

The results also showed that the point estimates were similar across models with wider 95% CrIs for the random effects models compared to fixed effects models.[4]

The HR and 95% CrIs for OS where fulvestrant 500 mg was used as the reference treatment are presented in Table 3.21. The HR and 95% CrIs for OS by using capivasertib plus fulvestrant as the reference treatment are presented in Table 3.22.

The results from the piecewise approach showed that there were no statistically significant differences in OS between capivasertib plus fulvestrant and alpelisib plus fulvestrant (at both 6-month or 6+-month cut-off).[4]

Capivasertib plus fulvestrant was associated with a statistically significant improvement in OS when compared with exemestane for fixed-effect models (at both 6-month or 6+ month cut-off). However, there were also no statistically significant differences in OS between capivasertib plus fulvestrant and exemestane for random-effect models (at both 6-month or 6+ month cut-off).[4]

Figure 3.15: Forest plot of OS for the comparison with Fulvestrant 500 mg

Based on Figure 5 of response to the request for clarification[4]
CrI = credible interval; ITC = indirect treatment comparison; OS = overall survival

Figure 3.16: Forest plot of OS for the comparison with capivasertib plus fulvestrant

Based on Figure 6 of response to the request for clarification[4]
CrI = credible interval; ITC = indirect treatment comparison; OS = overall survival

Table 3.21: Summary of OS: HRs for treatments versus fulvestrant

	Timepoint 1 HR (95% CI)		Timepoint 2 HR (95% CI)	
	Fixed effects	Random effects	Fixed effects	Random effects
	0-6 months		*6+ months*	
Capivasertib + fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus + exemestane	[redacted]	[redacted]	[redacted]	[redacted]
Alpelisib + fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]
Exemestane	[redacted]	[redacted]	[redacted]	[redacted]
Fulvestrant 250 mg	[redacted]	[redacted]	[redacted]	[redacted]
Based on Table 13 of company response to the request for clarification[4] CI = confidence interval; HR = hazard ratio; OS = overall survival				

Table 3.22: Summary of OS: HRs for treatments versus capivasertib plus fulvestrant

	Timepoint 1 HR (95% CI)		Timepoint 2 HR (95% CI)	
	Fixed effects	Random effects	Fixed effects	Random effects
	0-6 months		*6+ months*	
Fulvestrant 500 mg	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus + exemestane	[redacted]	[redacted]	[redacted]	[redacted]
Alpelisib + fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]
Exemestane	[redacted]	[redacted]	[redacted]	[redacted]
Fulvestrant 250 mg	[redacted]	[redacted]	[redacted]	[redacted]
Based on Table 14 of response to the request for clarification[4] CI = confidence interval; HR = hazard ratio; OS = overall survival				

EAG comment:

- The ITC base-case analysis in the company evidence submission was based on a NMA consisting of 10 RCTs. The base-case ITC analysis was conducted primarily based on the data of the pivotal

trials of capivasertib plus fulvestrant (CAPItello-291, FAKTION), alpelisib plus fulvestrant (SOLAR-1) and everolimus plus exemestane (BOLERO-2, BOLERO-5). The PH assumption was assessed for PFS and OS for all included studies. This assumption was evaluated by the consideration of the KM curves, Schoenfeld residual plots and log cumulative hazard plots.

- It should be noted that based on the assessment of PH assumption, there was evidence that the assumption of PHs was not valid for PFS and OS outcomes for studies in the NMA. However, the company performed the NMA under PHs in their evidence submission.
- The EAG considers that, given that assumption of PHs was not valid for the PFS and OS outcomes for studies in the NMA, time-varying analysis approach would be more appropriate. The EAG requested the company to reconduct NMAs for PFS and OS outcomes by using the time-varying analysis approach.
- In responding to the EAG's request, the company reconducted NMAs for PFS and OS outcomes by using the time-varying analysis approach. The company provided the updated results based on the time-varying approach during the response to the request for clarification stage. The company used a piecewise approach for the time-varying NMA.
- The EAG considers that the piecewise approach used by the company for ITC seems to be an appropriate approach, given that the PHs assumption for OS and PFS in the included populations was not valid for studies in the ITC analysis.
- However, the company stated that cut-off points for the piecewise approach were selected on the basis of a visual inspection of the KM curves of both OS and PFS outcomes for studies included in the NMA. The EAG considers that the selection of cut-off points was not sufficiently justified. Furthermore, given that only short-term follow-up data were available from each trial when conducting the analysis, short-term follow-up data were used for the base-case NMA. There was a lack of longer-term follow-up data for the base-case NMA.
- For the feasibility analysis, the company provided the data of baseline characteristics for included studies of NMA in a figure format for the original submission. However, the company did not provide the data of baseline characteristics for included studies of NMA in a table. However, given that it is important to ensure the comparability of patients' baseline characteristics between included trials for the purpose of NMA, the EAG requested the company to provide the data of baseline characteristics for included studies of NMA in a table. In responding to the EAG's request, the company provided the data of baseline characteristics for included studies of NMA in a table during the response to the request for clarification stage.
- Heterogeneity of PI3K/AKT status was observed for the baseline characteristics of populations of included studies in the base-case NMA. It should be noted that the data of NMA were based on the PI3K/AKT pathway-altered subgroup of CAPItello-291 and FAKTION trials, and the PIK3CA mutated subgroup of SOLAR-1.
- It should be further noted that the subgroup of CAPItello-291 trial included all patients with PI3K/AKT alteration; however, the FAKTION trial only included a smaller proportion of patients with PI3K/AKT alteration (39% in the fulvestrant arm and 45% in the capivasertib plus fulvestrant arm). The remaining trials included in the NMA recruited patients with unknown PI3K/AKT status.[4]
- Heterogeneity of HER2 status was also observed in the baseline characteristics of populations in the included studies of the base-case NMA. Of 10 included studies, four studies (EFECT, SOFEA, CONFIRM and NCT01300351) included populations with mixed/unknown characteristics in terms of HER2 status, while the remaining six studies recruited all patients with HER2 negative.[4]

- Furthermore, there was substantial heterogeneity in prior treatment received by patients in the included studies of NMA. Only two trials (CAPItello-291 and SOLAR-1) recruited patients who received ET and CDK treatment. It should be further noted that the proportion of patients who received prior CDK4/6i use in the CAPItello-291 trial ranged from 69.4% in the placebo plus fulvestrant arm to 72.9% in the capivasertib plus fulvestrant arm, while the proportion of patients who received prior CDK4/6i use in the SOLAR-1 trial ranged from 5.3% in the alpelisib plus fulvestrant arm to 6.4% in the placebo plus fulvestrant arm. However, the remaining eight trials recruited patients who received ET treatment but did not receive CDK treatment.[4]
- Furthermore, there was considerable heterogeneity in ECOG (PS = 1) in the populations of included studies. Where reported, the proportion of patients with ECOG (PS = 1) in the included trials of NMA ranged from 24% to 68.4%. It should be further noted that six studies in the NMA did not report ECOG (PS = 1) for the population being recruited.[4]
- Following the assessment of heterogeneity and uncertainty, 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. Therefore, 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.
- The EAG considers that while the company provided a discussion of potential prognostic factors and treatment effect modifiers as well as their impact on the results of ITC, there was a lack of sufficient evidence to support the assumption of exchangeability for the purpose of ITC. This issue may have compromised the validity of ITC results.

3.5 Additional work on clinical effectiveness undertaken by the EAG

Not applicable.

3.6 Conclusions of the clinical effectiveness section

The CS, Appendix D, an additional report provided by the company, and the company's response to the request for clarification provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant clinical evidence on therapies used in the treatment of HR+/HER2− unresectable/mBC.[1, 4, 9, 10] Searches were conducted in January and March 2023, and updated in August 2023 and February 2024. Searches were transparent and reproducible, and comprehensive strategies were used. Bibliographic databases, conference proceedings, HTA agency websites and trials registers were searched. Overall, the EAG has no major concerns about the literature searches conducted, although additional searches for AEs may have been useful.

The study selection criteria for participants, interventions, comparators and outcomes in the SR of clinical effectiveness generally encompassed those specified by the NICE final scope.[2] However, it should be noted that the restriction to only RCTs may have resulted in some relevant AE data that were overlooked. The data extraction process was satisfactory and in line with recommended good practice in SRs. The process for the assessment of risk of bias in the included studies was satisfactory. The process of assessing risk of bias and the number of reviewers involved were described. The use of the Cochrane risk of bias tool for the assessment of risk of bias was appropriate.

The company did not provide clear information on the number of studies retrieved, screened and included in their original evidence submission, because there were initially 307 included records but only 10 studies were included in the NMA. The EAG asked for clarification on the details and reasons

for exclusion of studies that were not included in the NMA. The company provided clarification on the details and updated the PRISMA flow chart during the response to the request for clarification stage. The number of studies retrieved, screened and included was clear based on the updated PRISMA flow chart.

One unique RCT was identified as being relevant to the SR: one RCT (CAPItello-291) provided the main source of evidence. The CAPItello-291 trial was an international, phase III, double-blinded RCT that assessed the efficacy and safety of capivasertib plus fulvestrant in patients with unresectable or metastatic HR+, HER2-negative breast cancer. The EAG rated the CAPItello-291 trial as being at moderate risk of bias. The CS focused on the PI3K/AKT pathway-altered subpopulation of CAPItello-291 trial.

At the data cut-off date for primary analysis of PFS (15 August 2022), investigator-assessed PFS was more favourable for capivasertib plus fulvestrant compared with placebo plus fulvestrant in the PI3K/AKT-altered subpopulation of CAPItello-291 trial.

At the data cut-off date (15 August 2022), OS was also more favourable for capivasertib plus fulvestrant compared with placebo plus fulvestrant in the PI3K/AKT-altered subpopulation of CAPItello-291 trial.

In the PI3K/AKT pathway-altered subpopulation of CAPItello-291 trial, there was a higher proportion of patients who experienced any SAEs in the capivasertib plus fulvestrant arm compared with the placebo plus fulvestrant arm. Serious AEs occurred in [redacted] of patients who received capivasertib plus fulvestrant and [redacted] in patients who received placebo plus fulvestrant. In the PI3K/AKT pathway-altered subpopulation, AEs of any Grade were reported by [redacted] patients in the capivasertib plus fulvestrant arm and [redacted] patients in the placebo plus fulvestrant arm. It should be noted that the majority of AEs were of Grade 2 severity or lower.

The ITC base-case analysis in the company evidence submission was based on a NMA consisting of 10 RCTs. The base-case ITC analysis was conducted primarily based on the data of the pivotal trials of capivasertib plus fulvestrant (CAPItello-291, FAKTION), alpelisib plus fulvestrant (SOLAR-1) and everolimus plus exemestane (BOLERO-2, BOLERO-5). The PHs assumption was assessed for PFS and OS of all included studies. Following the assessment of PH assumptions, there was evidence that the assumption of PHs was not valid for PFS and OS outcomes for studies in the NMA. However, the company performed NMA under PHs in their evidence submission.

The EAG considers that, given that the assumption of PHs was not valid for PFS and OS outcomes of studies in the NMA, time-varying analysis approach would be more appropriate. The EAG requested the company to reconduct NMAs for PFS and OS outcomes by using the time-varying analysis approach.

In responding to the EAG's request, the company reconducted NMAs for PFS and OS outcomes by using the time-varying analysis approach. The company provided updated NMA results by using the time-varying approach during the response to the request for clarification stage. The company used a piecewise approach for the time-varying NMA.

The EAG considers that the piecewise approach used by the company for ITC analysis seems to be an appropriate approach, because the PHs assumption for PFS and OS was not valid for studies in the ITC. However, the cut-off points of the pricewise approach were selected on the basis of a visual inspection of the KM curves for PFS and OS outcomes of studies included in the NMA. The EAG considers that the selection of cut-off points for the pricewise approach was not sufficiently justified. Furthermore,

only short-term follow-up data were used for the base-case NMA. There was a lack of longer-term follow-up data for the base-case NMA.

It should be noted that heterogeneity of PI3K/AKT pathway alteration was observed for the included populations of studies in the base-case NMA. The NMA used data of the PI3K/AKT pathway-altered subgroup of CAPItello-291 and FAKTION trials, and the PIK3CA mutated subgroup of SOLAR. While the subgroup of CAPItello-291 trial included all patients with PI3K/AKT alteration, the subgroup of FAKTION trial only included a smaller proportion of patients with PI3K/AKT alteration (39% in the fulvestrant arm and 45% in the capivasertib plus fulvestrant arm). It should be further noted that the remaining trials included in the NMA recruited patients with unknown PI3K/AKT status.

In terms of HER2 status, six studies recruited all patients with HER2 negative. However, four studies (EFECT, SOFEA, CONFIRM and NCT01300351) included populations with mixed/unknown characteristics in terms of HER2 status. Therefore, there was heterogeneity of HER2 status in the baseline characteristics of populations in the included studies of NMA.

Furthermore, there was substantial heterogeneity in prior treatment received by patients in the included studies of NMA. Only two trials (CAPItello-291 and SOLAR-1) recruited patients who received ET and CDK treatment. The proportion of patients who received prior CDK4/6i use in the CAPItello-291 trial ranged from 69.4% in the placebo plus fulvestrant arm to 72.9% in the capivasertib plus fulvestrant arm, while the proportion of patients who received prior CDK4/6i use in the SOLAR-1 trial ranged from 5.3% in the alpelisib plus fulvestrant arm to 6.4% in the placebo plus fulvestrant arm. It should also be noted that the remaining eight trials recruited patients who received ET treatment but did not receive CDK treatment. In addition, considerable heterogeneity in ECOG (PS = 1) was also observed for the included populations across studies of NMA.

Following the assessment of heterogeneity and uncertainty, there was considerable heterogeneity in a range of patients' baseline characteristics including PI3K/AKT status, HER2 status, ECOG (PS = 1) and prior CDK4/6i use for the included populations across trials of NMA. Therefore, there was limited comparability of patients' baseline characteristics between included trials, thereby introducing uncertainties in the findings from the ITC analysis.

The EAG considers that there was a lack of sufficient evidence to support the assumption of exchangeability for the purpose of ITC. This issue may have compromised the validity of ITC results.

4. Cost effectiveness

4.1 EAG comment on company's review of cost effectiveness evidence

This Section pertains mainly to the review of cost effectiveness analysis (CEA) studies. However, the search Section (4.1.1) also contains summaries and critiques of other searches related to cost effectiveness (CE) presented in the CS. Therefore, the following Section includes searches for the CEA review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

4.1.1 Searches performed for cost effectiveness Section

The following paragraphs contain summaries and critiques of all searches related to CE, HRQoL and resource use identification presented in the CS.[1] The CADTH evidence-based checklist for the PRESS, was used to inform this critique.[8] The EAG has presented only the major limitations of each search strategy in the report.

The CS, Appendices G, H and I, an additional report provided by the company, and the company's response to the request for clarification provide details of an SLR conducted to identify relevant studies on CE, HRQoL and cost/health care resource use in HR+/HER2- advanced breast cancer.[1, 4, 9, 15] The searches were conducted in April 2023, and updated in November 2023 and April 2024.

A summary of the sources searched is provided in Table 4.1.

Table 4.1: Data sources searched for economic evaluations, HRQoL and healthcare resource use (as reported in CS)

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
Embase	Embase.com	To April 2023 Apr 2023-20.11.23 01.11.23-05.04.24	18.04.23 20.11.23 05.04.24
MEDLINE	PubMed	To Apr 2023 Apr 2023-20.11.23 01.11.23-05.04.24	18.04.23 20.11.23 05.04.24
CDSR	Cochrane Library	To Apr 2023 Apr 2023-20.11.23 01.11.23-05.04.24	18.04.23 20.11.23 05.04.24
Epistemonikos	Internet	To Apr 2023 Apr 2023-20.11.23 01.11.23-05.04.24	18.04.23 20.11.23 05.04.24
HTA websites			
AWMSG CADTH INESSS NICE ICER HAS	Internet	No date limit applied	18.04.23 21-23.11.23 05.04.24

Resource	Host/Source	Date Ranges	Date searched
IQWiG PBAC SMC			
Conferences			
ASCO ABC Consensus Conference EBCC Conference ESMO SABCS SGBCC	Internet	2021+	18.04.23 21-23.11.23 05.04.24
ABC = advanced breast cancer; ASCO = American Society of Clinical Oncology; AWMSG = All Wales Medicines Strategy Group; CADTH = Canadian Agency for Drugs and Technology in Health; CS = company submission; EBCC = European Breast Cancer Council; ESMO = European Society of Medical Oncology; HAS = Haute Autorite de Sante; HTA = Health Technology Assessment; ICER = Institute for Clinical and Economic Review; INESSS = Institut National d'Excellence en Santé et en Services Sociaux; IQWiG = Institute for Quality and Efficiency in Health Care; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SABCS: San Antonio Breast Cancer Symposium; SGBCC = St. Gallen International Breast Cancer Conference; SMC = Scottish Medicines Consortium			

EAG comment:

- A single set of searches was undertaken in April 2023 and updated in November 2023 and April 2024 to identify relevant studies on CE, HRQoL and cost/health care resource use in HR+/HER2- advanced breast cancer. The CS, Appendices G, H and I, an additional report provided by the company, and the company's response to the request for clarification provided sufficient details for the EAG to appraise the literature searches.[1, 4, 9, 15]
- In addition to bibliographic database searches, a good range of HTA organisation websites, HTA agency websites and conference proceedings were searched. Reference checking did not appear to have been conducted.
- Searches were extensive and well structured, although the number of hits per line of search was not available, so the EAG was unable to verify the search results. In response to the request for clarification the company stated that 'The number of hits per line of search for update 1 (20 November 2023) is provided in Appendix I.E of this document'.[4] Appendix I.E however only provides the total number of hits per facet, rather than for each line of search. Best practice states that bibliographic database search strategies should be copied and pasted exactly as run and in full, together with the search set numbers and the total number of records retrieved by each search strategy for full transparency.[16]
- No date limits were applied, and searches were not limited by language of publication.
- Conference proceedings were handsearched for six key international conferences between 2021 and April 2024. Embase was also searched for conference proceedings.
- The searches contained a population facet for advanced breast cancer. This was then combined with study design filters containing terms for economic evaluations, HSUVs and burden of illness for the MEDLINE and Embase searches. Filters were based on published search filters and adapted as appropriate.
- Overall, the EAG has no major concerns about the literature searches conducted, although it would have been helpful to the EAG to have seen full details of all searches conducted, complete with hits per line of search.

4.1.2 Inclusion/exclusion criteria

Population, intervention/comparator, outcomes and study type in- and exclusion criteria for the review on CE studies, utilities and costs and resource use are presented in Table 1 of the CS Economic SLR Report (June 2024 update).

EAG comment: The EAG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify CE studies. The rationales for excluding CE studies after full paper reviewing are considered appropriate given the defined in- and exclusion criteria.

4.1.3 Findings of the CE review

The combined (health economic evaluations, health state utility studies, and burden of illness studies) PRISMA flow diagram can be found in Figure 1 (Section 3) of the Health Economic Systematic Literature Review report (April 2024 update).

A total of 235 studies, comprised of 125 health economic evaluations, 22 health state utility studies, and 88 burden of illness studies, were included. Included health economic evaluations assessed various treatments across various countries, including 30 in the UK. Markov cohort models (n=49) was the most common modelling approach. However, no published CEAs of capivasertib in combination with fulvestrant were identified. Included HSUV studies assessed HSUVs across various countries including two specifically in the UK. EQ-5D was the only HRQoL instrument utilised in multiple studies (n=19). Included burden of illness studies identified a wide range of cost and HCRU items across various countries, including eight in the UK.

Six previous NICE appraisals in similar populations were identified which could potentially inform the model structure, functionality, assumptions, and data sources.

4.1.4 Conclusions of the CE review

The CS provides an overview of the included CE, utility and resource use and costs studies. The company conclude that despite a wealth of health economic information for patients with unresectable/mBC, information is more limited, particularly HSUVs and costs and healthcare resource utilisation, for patients with HR+/HER2- unresectable/mBC following progression on at least one endocrine-based regimen. Despite this, no clear overview is provided regarding the use of information identified in the SLR to inform the economic model.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 4.2: NICE reference case checklist

Element of HTA	Reference case	EAG comment on CS
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Consistent with the reference case
Perspective on costs	NHS and PSS	Consistent with the reference case

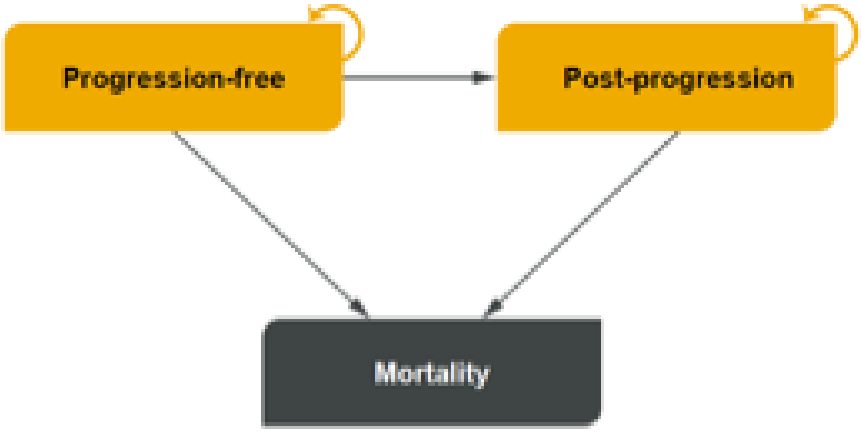
Element of HTA	Reference case	EAG comment on CS
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Consistent with the reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Consistent with the reference case
Synthesis of evidence on health effects	Based on SR	Consistent with the reference case
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Consistent with the reference case
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Consistent with the reference case
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Consistent with the reference case
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Consistent with the reference case, severity modifier of 1.2 was applied to the QALY
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Consistent with the reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Consistent with the reference case

CS = company submission; EAG = Evidence Assessment Group; HTA = Health Technology Assessment; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALY = quality-adjusted life year; SR = systematic review; UK = United Kingdom

4.2.2 Model structure

A de-novo three-state partitioned survival model was developed in Microsoft Excel®. The health states in the model included progression free (PF), progressed disease (PD) and death. Patients in PF can remain in this state, or progress to PD or death. Patients in PD can remain in this state or enter the death state. This model structure has been used in previous HR+/HER2- breast cancer appraisals (e.g. TA816,[7] TA687[17]). Figure 4.1 shows the model structure.

Figure 4.1: Model structure



Based on Figure 18 of the CS
CS = company submission

EAG comment: The main concern of the EAG relates to the use of a partitioned survival model.

The EAG asked for justification for the use of a partitioned survival model given the issues highlighted in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 19,[18] particularly regarding the extrapolation of PFS and OS while assuming structural independence between these endpoints. The company responded that their model structure was in line with many other oncology appraisals and also highlighted the additional data requirements on individual transitions that are often not available. They also mentioned the relative maturity of their data and the fact that UK clinical experts had verified the plausibility of their extrapolations. The EAG agrees with the company that their partitioned survival model approach is appropriate.

4.2.3 Population

The population in the model is *"patients with HR+/HER2-, PI3K/AKT pathway-altered, locally advanced or metastatic breast cancer following progression on or after CDK4/6 inhibitor plus endocrine therapy"*. The population defined in the NICE final scope is *"Adults with hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer after endocrine treatment"*. Hence, the population in the model was narrower than the population which was defined in the NICE final scope.

In the CAPItello-291 trial patients following progression on or after CDK4/6i plus ET make up >70% of the PI3K/AKT pathway-altered population. The company argues that the characteristics of these patients are broadly similar to the patients in the PI3K/AKT-altered pathway population enrolled in the CAPItello-291 trial irrespective of prior CDK4/6i use (see Table 5 in B.2.3.2 in the CS).

Table 4.3: Key baseline patient characteristics in the model

Characteristic		PI3K/AKT pathway-altered population in the CAPItello-291 trial
Median age; years (range)		59.0 (34-90)
Sex, n (%) (female)		287 (99.3%)
Body surface area (m^2)	male	[redacted]
	female	[redacted]

Characteristic	PI3K/AKT pathway-altered population in the CAPItello-291 trial
Based on Table 14, CS AKT = serine/threonine kinase; CS = company submission	

EAG comment: The main concern of the EAG relates to further clarification for the population that is narrower than defined in the final NICE scope, specifically whether capivasertib plus fulvestrant would only be prescribed to patients who have progressed on or following CDK4/6i plus ET. In response to the request for clarification question A.6 the company reiterated that it was verified with UK clinical experts that capivasertib plus fulvestrant is positioned for use in patients with PI3K/AKT pathway-altered tumours (PIK3CA, AKT1, or PTEN) whose disease has progressed on or following CDK4/6i plus ET. They also stated that it is not anticipated that capivasertib plus fulvestrant is used in patients who have not received prior CDK4/6i therapy. However, there remains uncertainty about whether patients in practice may receive capivasertib plus fulvestrant if they had not previously received a CDK4/6i (see key issue 1 and critique in Section 2.1).

4.2.4 Interventions and comparators

The intervention considered in the CS is capivasertib, a protein kinase B (AKT) inhibitor therapy for the treatment of mBC. It is licensed in the UK in combination with fulvestrant for the treatment of adult patients with HR+, HER2- (defined IHC 0 or 1+, or IHC 2+/ISH-) locally advanced or mBC with one or more PIK3CA/AKT1/PTEN-alterations following recurrence or progression on or after an endocrine based regimen. It is administered orally as tablets in strengths of 160 mg or 200 mg. The recommended dose in combination with fulvestrant is 400 mg (two 200 mg tablets) taken orally twice daily approximately 12 hours apart (total daily dose of 800 mg) with or without food, for 4 days followed by 3 days off treatment. The recommended dose of fulvestrant is 500 mg administered on Days 1, 15, and 29, and once monthly thereafter. In pre/perimenopausal women, capivasertib plus fulvestrant should be combined with a LHRH agonist.

The comparators considered in the model are alpelisib plus fulvestrant and everolimus plus exemestane. The comparison to alpelisib plus fulvestrant is made in the PI3K/AKT pathway altered population, although as alpelisib plus fulvestrant is only recommended in the PIK3CA mutated population, it is assumed that the result holds across these populations. The comparators are administered and dosed in the model in line with their summaries of product characteristics and clinical trials, and are continued until either disease progression, discontinuation due to intolerability, AEs, or death. No other clinical continuation or stopping rules are employed.

The company excluded treatments mentioned in the NICE final scope, including retreatment with CDK4/6is, as a relevant comparator, referring to ESMO guidelines.

EAG comment: The main concern of the EAG relates to excluding potentially relevant comparators. In response to the request for clarification question A8, the company highlighted that the included comparators were validated with UK clinical experts. They also highlighted that the TA committee in TA816 agreed that the relevant comparator for alpelisib plus fulvestrant post CDK4/6i therapy was everolimus plus exemestane. Other alternatives would include tamoxifen plus everolimus and fulvestrant plus everolimus, which are both not licensed combinations according to the company. They also stated that single agent ET with aromatase inhibitor (AI) or tamoxifen would not be anticipated to be used routinely instead of NICE-recommended combinations of alpelisib plus fulvestrant (per TA816)

or everolimus plus exemestane (per TA421) in patients who are eligible for these. The EAG thus agrees that alpelisib plus fulvestrant and everolimus plus exemestane are relevant comparators, but also concludes that in the absence of evidence as to what patients actually receive in clinical practice, none of the comparators in the NICE scope can be ruled out, except probably retreatment with a CDK4/6i (see critique in Section 2.3).

4.2.5 Perspective, time horizon and discounting

The analysis is performed from the NHS and PSS perspective. Discount rates of 3.5% are applied to both costs and benefits. The model cycle length is 30.44 days with a lifetime time horizon (20 years) and a half-cycle correction is applied.

EAG comment: No comment.

4.2.6 Treatment effectiveness and extrapolation

The main sources of evidence on treatment effectiveness used for the intervention and comparators are the CAPItello-291 trial and the NMA as discussed in Section 3.4 of this report. The NMA was conducted using the pivotal trials of capivasertib plus fulvestrant (CAPItello-291, FAKTION), alpelisib plus fulvestrant (SOLAR-1) and everolimus plus exemestane (BOLERO-2, BOLERO-5). Other trials were also required to connect the network (CS, Figures 12 and 13).

As part of the feasibility assessment for the NMA, the company explored the assumption of PHs by reviewing the KM plots, log-log plots and the Global Schoenfeld Test. The company concluded that for both PFS and OS that, whilst there is a potential appearance of non-proportionality from some of the data (particularly PFS), overall, there is no consistent evidence of significant departures from a PH assumption. The company stated that with the data available, the use of more complex methods would be challenging (e.g. using time-varying hazards), potentially leading to further uncertainty in the outcome, and thus was not considered appropriate.

Given these findings, and given the other challenges associated with performing an ITC in this setting due to the heterogeneity across trials, a pragmatic approach was taken to estimate treatment effectiveness of capivasertib plus fulvestrant, alpelisib plus fulvestrant, and everolimus plus exemestane. First, parametric survival models (exponential, log-normal, Weibull, log-logistic, gamma, generalised gamma, and Gompertz) were fitted to the PFS and OS patient level data of the placebo plus fulvestrant arm from CAPItello-291 (the common comparator in the NMA) to extrapolate these outcomes to a lifetime horizon. To identify the best model fit the following criteria were considered:

- Statistical model fits were evaluated using the Akaike information criterion (AIC) and Bayesian information criterion (BIC)
- Visual inspection of model fit to the trial data (both to the KM curves and the observed hazards)
- An assessment of the clinical plausibility of extrapolation.

Details of the company's assessment of the best fitting curves for use in their base-case are provided in Table 4.3. With PFS data being quite mature, the different distributions were all relatively similar. The company chose the lognormal distribution in the base-case and explored the log-logistic in a scenario, also noting that the generalised gamma would be a suitable alternative.

For OS, whilst most distributions made a reasonable within-trial fit to the data, there are notable differences between distributions in the extrapolated period over the model time horizon. The company

used the gamma in their base-case and noted that the Weibull would be a suitable alternative and explored this in a scenario.

Table 4.3: Company's assessment of the best fitting curves to extrapolate PFS and OS

	PFS	OS
General considerations	PFS data was relatively mature.	Most distributions seem to provide a reasonable fit to the data in the within-trial period, but there are notable differences between distributions in the extrapolated period over the model time horizon (20 years), generalised gamma, log-logistic and log-normal all providing more optimistic survival predictions in the long-run.
Statistical goodness-of-fit based on AIC BIC for each arm	Log-logistic, log-normal, and generalised gamma were considered to provide good fits to the trial data. The log-logistic had the best fit (AIC and BIC).	All curves had similar statistical fit.
Visual inspection to assess the fit of the extrapolation to the KM curve	The log-normal, log-logistic and generalised gamma seem to fit the observed data better visually, although as the trial data is relatively mature for PFS (85.6%), all models provided similar extrapolated projections	Similar fit.
Visual inspection of the modelled and observed smoothed hazard rates	The log-normal, log-logistic and generalised gamma models all capture the increase and following decrease in the trial hazards. The final increase in the observed hazards may be overly influenced by the low number at risk at later timepoints and so was not considered to be informative.	Weibull, Gompertz and gamma all predict increasing hazards with time, while the remaining curves predict decreasing hazards with time. Weibull, Gompertz and gamma appear to follow the observed hazards the closest.
Assessment of the clinical plausibility of extrapolation	Three clinical experts considered the log-logistic or generalised gamma as the most appropriate (a small proportion progression-free at 60 months).	Four of the clinicians said that the more pessimistic selections (gamma/Weibull/Gompertz) were more reflective of UK clinical practice. Two clinicians said that gamma was the most plausible, one

	PFS	OS
		clinician said Gompertz, and one clinician said Gompertz or Weibull.
Base-case approach	Lognormal	Gamma
Scenario analyses	Log-logistic	Weibull

Based on information provided in Section B3.3 of the CS[1]
AIC = Akaike information criterion; BIC = Bayesian information criterion; CS = company submission; KM = Kaplan-Meier, OS = overall survival; PFS = progression-free survival; UK = United Kingdom

Then, from the placebo plus fulvestrant indepen, PFS and OS of capivasertib plus fulvestrant, alpelisib plus fulvestrant, and everolimus plus exemestane were estimated by applying the HR of these treatments versus placebo plus fulvestrant 500 mg from the NMA. To ensure consistency with alpelisib plus fulvestrant and everolimus plus exemestane, the capivasertib plus fulvestrant curve was estimated using the same approach, instead of fitting parametric survival models directly to the individual patient level data from the capivasertib plus fulvestrant arm in CAPItello-291. The HRs are shown in Table 4.4.

EAG comment: The main concerns of the EAG relate to: a) the selection of parametric survival models, b) the appropriateness of the constant HR NMA, c) the potential for treatment effect waning.

a) The EAG considers the company's choices for standard parametric models and for independent survival modelling per treatment arm as appropriate considering the evidence provided by the company. There remains some uncertainty about the model choice for both OS and PFS and this can be impactful considering that approximately 90% of the modelled health gain occurs in the extrapolated time period. Based on the company's reasoning and input from the company's clinical experts, appropriate candidates for OS were the gamma, Weibull and Gompertz, and for PFS the log-logistic, generalised gamma and lognormal. For OS, while the company chose the gamma in its base-case and the Weibull in a scenario, the EAG considered that the Gompertz was equally plausible as the gamma, considering that it had similar statistical fit, was deemed the most appropriate by two experts (like the gamma), and hazards had a good visual fit, although they were monotonically increasing (Figure 26 in company's response to the request for clarification). The EAG thus explored the Gompertz in a scenario. For PFS, while the company chose the lognormal in its base-case, the EAG used the loglogistic in the EAG base-case and the generalised gamma in a scenario, considering that the loglogistic had the best statistical fit and was also deemed the most appropriate along with the generalised gamma by the experts.
b) Key issue: The EAG was concerned about the appropriateness of a constant HR derived from the NMA as there was some evidence that the proportional hazard assumption did not hold for PFS and potentially also for OS in some studies included in the NMA. In response to the request for clarification question B6, the company argued that there was inconclusive evidence about whether the PH assumption was violated and explained that the fixed effects model provided the best statistical fit to the trial data based on the deviance information criterion for PFS and for the 0-6 month timepoint for OS, and hence the HR estimates obtained from the fixed effects model were incorporated in the model. Nevertheless, upon the EAG's request, the company also explored a time-varying HR approach, using one cut point, i.e. two HRs for the entire model duration for PFS and OS. The resulting HRs are presented in Table 4.4. These cut-off points were selected using visual inspection of the KM curve, and there is some uncertainty about these. The EAG considers that, although a NMA using a time-varying parametric model would likely be preferred (see Section

3.4), the company's piecewise NMA presents an improvement over the constant HR NMA and adopts this NMA in its base-case.

Table 4.4: Hazard ratios versus placebo plus fulvestrant in PI3K/AKT pathway-altered population

Treatment versus fulvestrant	Time-varying HR NMA		Constant HR NMA
	Timepoint 1	Timepoint 2	
PFS Scenario 1 – Timepoints: 0-3 months, 3+ months			**PFS**
Capivasertib + fulvestrant	[redacted]	[redacted]	[redacted]
Everolimus + exemestane	[redacted]	[redacted]	[redacted]
Alpelisib + fulvestrant	[redacted]	[redacted]	[redacted]
PFS Scenario 2 – Timepoints: 0-2 months, 2+ months			**PFS**
Capivasertib + fulvestrant	[redacted]	[redacted]	[redacted]
Everolimus + exemestane	[redacted]	[redacted]	[redacted]
Alpelisib + fulvestrant	[redacted]	[redacted]	[redacted]
OS – Timepoints: 0-6 months, 6+ months			**OS**
Capivasertib + fulvestrant	[redacted]	[redacted]	[redacted]
Everolimus + exemestane	[redacted]	[redacted]	[redacted]
Alpelisib + fulvestrant	[redacted]	[redacted]	[redacted]

Based on Response to the request for clarification Table 26 and CS Table 19
AKT = serine/threonine kinase; CS = company submission; HR = hazard ratio; NMA = network meta-analysis; OS = overall survival; PFS = progression-free survival

c) Key issue: The company did not include treatment effect waning. Implied HR plots over time were not provided by the company. But in response to the request for clarification question B5, the company provided further evidence on their assessment of proportional hazards for capivasertib plus fulvestrant versus placebo plus fulvestrant. The PH assumption was supported by this evidence for OS. To assess the appropriateness of a constant HR and the potential for treatment effect waning, the company provided smoothed hazard plots. For OS, the hazard for capivasertib plus fulvestrant [redacted] placebo plus fulvestrant [redacted] (Figure 11 response to the request for clarification, see below Figure 4.2). The company stated that the drop of hazard in the placebo plus fulvestrant arm was based on small patient numbers (N=[redacted] at 20 months) and should be interpreted with caution. The EAG agrees that the drop in the placebo plus fulvestrant arm is likely an artifact of low patient numbers, but also notes that the hazard in the capivasertib plus fulvestrant arm is [redacted], while the hazard in the placebo plus fulvestrant arm is [redacted]. This appears to imply that a constant HR may not be appropriate past the trial period. The company argued in response to the request for clarification question B8 that their time-varying HR scenario explores the impact of a smaller effect over time. The EAG disagrees that this scenario would be appropriate for estimating treatment effect waning as the HR for the longer term period was derived with a cut-off point of 3 months (2 months in a scenario) for PFS and a cut-off point of 6 months for OS. The EAG also notes that there is some indication of treatment effect waning for everolimus plus exemestane and for alpelisib plus fulvestrant. The EAG considers that treatment effect waning assumptions should be explored and explores treatment effect waning by setting the HR for all treatments versus fulvestrant to 1 after 24 months in the EAG base-case and 36 months in a scenario for OS.

Figure 4.2: Plot of smoothed hazards for OS (post-CDK4/6i, PI3K/AKT pathway-altered population (DCO1)

Based on Response to the request for clarification Figure 11
AKT = serine/threonine kinase; CDK4/6i = cyclin-dependent kinases 4 and 6 inhibitor; DCO = data cut-off; OS = overall survival

For PFS, the Schoenfeld test statistic was <0.05, and Schoenfeld residuals indicated some pattern over time. The company noted that the appearance of non-proportionality of hazards may be a result of the timing of scheduled scans and concluded that there is an absence of evidence of material deviations from the PH assumption for PFS. The EAG broadly agrees with the company's assessment. The shape of the smoothed hazard curve in Figure 12 of the company's response to the request for clarification (reproduced in below Figure 4.3) does not appear to support a constant HR versus placebo plus fulvestrant, however, the numbers of patients at risk are relatively small past 6 months, especially in the placebo plus fulvestrant arm, and the shape past 6 months should be interpreted with caution. There remains some doubt over whether a constant HR is appropriate beyond the trial duration. The EAG also notes that PFS data were 85.6% mature, which means that few patients had not progressed at the end of follow-up. In the company's model base-case, only [redacted] and [redacted] of patients remained in the PF state in the placebo plus fulvestrant and the capivasertib plus fulvestrant arms respectively. Nevertheless, the EAG considers that treatment effect waning should be explored for PFS and set the HR of all treatments to 1 after 24 months in the EAG base-case and 36 months in a scenario.

Figure 4.3: Plot of smoothed hazards for PFS (post-CDK4/6i, PI3K/AKT pathway-altered population (DCO1)

Based on Response to the request for clarification Figure 12
AKT = serine/threonine kinase; CDK4/6i = cyclin-dependent kinases 4 and 6 inhibitor; DCO = data cut-off; PFS = progression-free survival

4.2.7 Adverse events

The main sources of evidence on treatment AEs used for intervention and comparators are CAPItello-291, SOLAR-1, and BOLERO-2. As per the CS, AEs were incorporated into the economic model if, AEs were both:

- Grade ≥3: AEs were included if they were classified as Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or above. The costs and quality of life (QoL) impact of Grade 1 and 2 events were assumed to be negligible and thus omitted, and;
- Observed in ≥5% of patients in CAPItello-291 or in one of the pivotal studies informing the efficacy of the comparators (SOLAR-1 or BOLERO-2) in the populations in which the therapies are licensed, to ensure that key events were captured while ensuring the list of included events was manageable.

Grade ≥3 AEs that occurred in <5% of patients were excluded from the analysis. Therefore, for the PI3K/AKT-altered population (irrespective of CDK4/6i therapy) in the CAPItello-291 trial, [redacted] Grade 3+ AE observations were excluded from the analysis.

Incidence of Grade 3+ AEs (occurring in over 5% of patients) in the pivotal trials are presented in Table 4.5. The impact of AEs was modelled in terms of health effects, as disutilities (Section 4.2.8.3), and costs (Section 4.2.9.3).

Table 4.5: Incidence of Grade 3+ AEs occurring in over 5% patients in at least one of CAPItello-291, SOLAR-1, and BOLERO-2

	Capivasertib plus fulvestrant	Albelisib plus fulvestrant	Everolimus plus exemestane
Population	PI3K/AKT-altered population (irrespective of CDK4/6i therapy)	PIK3CA mutated population	Postmenopausal women with HR+ advanced breast cancer with recurrence/progression on or after NSAIs
Source	CAPItello-291 CSR report, Table 14.3.2.8.2	SOLAR-1 Andre et al., 2019, Table S3	BOLERO-2 Yardley, 2013, Table 4
AE (proportion[n/N])			
Diarrhoea	[redacted]	7.7% (13/169)	3.00% (14.5/482)
Rash maculo-papular	[redacted]	0.0% (NR)	0.0% (NR)
Rash	[redacted]	13.0% (22/169)	1.00% (4.8/482)
Hyperglycaemia	[redacted]	36.7% (62/169)	6.0% (28.9/482)
Stomatitis	[redacted]	3.0% (5/169)	8.0% (38.6/482)
Anaemia	[redacted]	0.0% (NR)	8.0% (38.6/482)

Based on CS Table 24[1]
AE = adverse event; AKT = serine/threonine kinase; CDK4/6i = cyclin-dependent kinases 4 and 6 inhibitor; CS = company submission; CSR = Clinical Study Report; HR+ = hormone receptor-positive; NR = not reported; NSAI = nonsteroidal aromatase inhibitor

EAG comment: The main concern of the EAG relates to the chosen Grade and prevalence cut-offs for inclusion in the economic model. In response to the request for clarification question B13a. the company justified the chosen Grade/prevalence cut-offs as they expect Grade 1-2 AEs to be negligible and associated with low-to-no cost. Further, the cut-offs are supported by the company with reference to the approach being commonly accepted in previous NICE TAs. The EAG accepts that Grade 3+ and/or ≥5% prevalence are often used in TA submissions but notes that such cut-offs are rarely empirically supported. The concern of the EAG regarding the present submission pertains to the chosen cut-offs for inclusion of AEs leading to a high proportion of Grade 3+ AEs being excluded from the analysis ([redacted] Grade 3+ observations). This suggests that the cost and utility impact for the capivasertib plus fulvestrant arm is likely underestimated. The EAG acknowledges that, whilst including all Grade 3+ AEs would be preferable, it is unclear whether all prevalence data for Grade 3+ AEs is available for the comparator arms, given that AE prevalence was only reported in the SOLAR-1 and BOLERO-2 publications if above 15% or 10% of patients, respectively, experienced a given

AE (irrespective of Grade). In conclusion, provided the relatively small impact of AE rates on model results, the EAG believes further analysis is not required.

4.2.8 Health-related quality of life

The utility values were estimated for the following health states: pre-progression and PD.

4.2.8.1 Health-related quality of life data identified in the literature review

According to the CS, the SLR, supplemented by health state utility values (HSUVs) used in previous NICE appraisals of treatments for advanced breast cancer (as identified in the SLR for economic evaluations), identified no studies reporting HSUVs for patients with HR+/HER2- advanced breast cancer with PI3K/AKT pathway-altered tumours following recurrence or progression on or after an endocrine based regimen. Nonetheless, the SLR was conducted to identify utility values for health states relating to patients with unresectable/mBC (excluding triple negative breast cancer), and was therefore broader than the anticipated licensed indication of capivasertib plus fulvestrant, and the NICE-recommended use of the comparators.[1, 9] That is, utility values were irrespective of whether these were conducted in patients with HR+/HER2- or PI3K/AKT pathway-altered breast cancer. HSUVs were reported in 22 identified studies, two of which were specific to the UK. Two studies (one multinational, including the UK, and one in China) reported HSUVs in the HR+/HER2- population. In addition, five previous NICE TAs of other therapies recommended for HR+/HER2- advanced breast cancer following ET and utilised EQ-5D data, were identified, within which, HSUVs were reported in three: TA421,[19] TA619 (since updated to TA836),[20] and TA579 (since updated to TA725).[21]

The company considered the CAPItello-291 trial to be the most relevant source for consideration, provided that the trial aligns with the population of interest. The company stated that values identified from the literature were considered as supplementary data to help form scenario analysis. Despite this, no scenarios were reported utilising alternative utility values, nor were present in the company's economic model.

4.2.8.2 Health state utility values

Health state utility values were sourced from the CAPItello-291 trial. Health-related quality of life was assessed using the EORTC QLQ-C30 instrument and the EQ-5D-5L questionnaire. The EQ-5D-5L data was collected at baseline, and every 4 weeks (± 3 days) until PFS2 (defined as time from randomisation to second progression on next-line treatment, as assessed by the local site investigator, or death due to any cause). Overall compliance was [redacted]% in the capivasertib plus fulvestrant arm and [redacted]% in the placebo plus fulvestrant arm, with progressively lower rates of compliance overtime (as highlighted in CSR Tables 14.2.9.6.3, 14.2.9.6.6, 14.2.9.2.15, and 14.2.9.2.30). To inform HSUVs, EQ-5D-5L data was utilised from the overall ITT trial population from CAPItello-291.

The EQ-5D-5L data were mapped to EQ-5D-3L using the EEPRU dataset from Hernandez Alava et al. 2020[22] and the mapping function developed by Hernandez Alava et al. 2017.[23] Mapped HSUVs were analysed using mixed effects repeated measures regression model (MMRM). MMRM accounts for missing data under the assumption that missing data is missing at random. HSUVs for PF and PD health states were derived from the MMRM using the estimated marginal means (or least squares) method.

Four MMRM models were explored using the restricted maximum likelihood method with the following covariates included as fixed effects:

- Model 1: (randomised) treatment
- Model 2: Progression status (pre-progression, post-progression)
- Model 3: Treatment; progression status
- Model 4: Treatment; progression status; treatment* progression status (both terms and interaction)

As per the CS, Model 2 was the best fitting model in terms of both AIC and BIC (CS Table 21) and was thus selected to inform HSUVs, as presented in Table 4.6.

To note, utilised HSUVs were treatment independent.

Table 4.6: Health state utility values

Health state	Utility value (mean [95% CI])	Reference	Justification
Pre-progression	[redacted]	CAPItello-291	Trial included population relevant to the reference case
Post-progression	[redacted]	CAPItello-291	Trial included population relevant to the reference case

Based on CS Table 22[1]
CI = confidence interval; CS = company submission

4.2.8.3 Disutility values

4.2.8.3.1 Age-related utility decrements

Age-related utility decrements are included in the economic model and applied to all health state utilities in the CS base-case and scenario analyses over the time horizon. The adjustment is modelled using the general population HSU norm equation from Ara and Brazier[24] and applied as a multiplier to the HSUVs assigned to all HSUs over the time horizon. A multiplier of 1 was therefore applied to the first cycle utility estimates and is therefore as described in Section 4.2.8.2.

Utilised equation for age-related utility decrements:

$$HSU = intercept + Gender\ (reference\ value = female) + Age + Age^2$$

4.2.8.3.2 Adverse event disutility

Adverse event disutilities were incorporated through a one-time application during cycle 1 of the model. The CAPItello-291 trial collected EORTC QLQ-C30 data, however disutilities were sourced from existing literature not identified through the CS SLR. The included AE disutilities were weighted by time durations sourced from TA306.[25] Prevalence of AEs were sourced from CAPItello-291 (PI3K/AKT-altered population), SOLAR-1 (PIK3CA mutated population), and BOLERO-2 (Postmenopausal with HR+ advanced breast cancer with recurrence/progression on or after nonsteroidal aromatase inhibitors [NSAIs]) for capivasertib plus fulvestrant, alpelisib plus fulvestrant, and everolimus plus exemestane, respectively. Disutility sources were conducted in mBC (informing diarrhoea), non-small cell lung cancer (NSCLC) (informing rash maculo-papular and rash), and metastatic renal cell carcinoma (informing hyperglycaemia, stomatitis, and anaemia). Proxy AEs were

used to inform hyperglycaemia and stomatitis disutilities. With the exception of anaemia, proxy AEs were used to inform AE durations within the economic model. The impact of AEs experienced by patients receiving subsequent treatments are not considered and is considered by the company as a pragmatic approach that would have minimal impact on incremental results.

Adverse event disutilities, durations, and respective sources are displayed in Table 4.7.

Table 4.7: Adverse event disutility values and durations

Adverse Event	Disutility value	Disutility source /assumption	Duration (days)*	Duration source /assumption
Diarrhoea	0.006	Hudgens 2016[26]	6.0	TA306;[25] assumed same as nausea
Rash maculo-papular	0.03248	Nafees et al. 2008[27]	4.0	TA306;[25] assumed same as mucosal inflammation
Rash	0.03248	Nafees et al. 2008[27]	4.0	TA306;[25] assumed same as mucosal inflammation
Hyperglycaemia	0.119	Swinburn 2010;[28] assumed same as anaemia	16.1	TA306;[25] assumed same as anaemia
Stomatitis	0.12	Swinburn 2010;[28] assumed same as mucotitis	4.0	TA306;[25] assumed same as mucosal inflammation
Anaemia	0.119	Swinburn 2010[28]	16.1	TA306[25]

Based on CS Table 25, and response to the request for clarification
*Assumption as per TA725[21]
CS = company submission; TA = Technology Assessment

EAG comment: The main concerns of the EAG relate to: a) the relatively small utility decrement from pre- to post-progression, b) the statistical approach for analysing HRQoL data, and c) the use of studies in alternative indications and the use of proxy AEs to inform AE disutilities and durations.

a) Key issue: In clarification question B10., the EAG highlighted the relatively small utility decrement between pre- and post-progression ([redacted]) as compared to HSUVs identified in previous NICE TAs for HR+/HER2- advanced breast cancer following ET. In response to the EAGs request for discussion as to the plausibility of the decrement, the company highlight the difficulty in pinpointing the driver for PD utility. The company suggest, as one possible reason, that once patients progress on capivasertib plus fulvestrant, a large proportion will continue on additional lines of therapy meaning that not all patients will experience a significant decline in HRQoL following discontinuation of capivasertib plus fulvestrant. The EAG requested scenarios utilising utilities from TA421, TA619, and TA579, as well as a scenario using PF utility from the company base-case and PD utility from TA421. In response, the company suggested that only a scenario informing PF and PD utility by TA421 was explored, however, the results were not provided and therefore no requested scenarios were received. The company did explore three scenarios, assessing the impact on pairwise incremental cost-effectiveness ratios (ICERs) of reducing PD utility values to 0.70, 0.65, and 0.60. In the scenarios, the ICER (deterministic including x 1.2 QALY weight) compared to alpelisib plus fulvestrant increased from [redacted] to [redacted], [redacted], and [redacted], respectively. Compared to everolimus plus exemestane, the ICER (deterministic including x 1.2 QALY weight) increased from [redacted] to [redacted], [redacted], and [redacted], respectively. The EAG

accept the difficulty in pinpointing causes for differences in utility values compared to previous TAs. However, it is unclear to the EAG whether the utility decrement is a result of not having PD EQ-5D observations for sufficiently long enough to capture the full effect of DP. The CS suggests that of the [redacted] total EQ-5D-5L observations, [redacted] were collected post-progression (overall ITT population). While the Clinical Study Report (CSR) provides EQ-5D-5L data for each collection time point, including mean scores and compliance rates, no distinction is made between patients that completed the questionnaire pre- or post-progression. To assess the reliability of PD utility values, the EAG would like to see further assessment of the EQ-5D-5L data collected with respect to when questionnaires were completed post-progression and durations of follow-up for which questionnaires were completed post-progression. While even the company-provided scenario utilising a PD utility of 0.60 constitutes a smaller pre- to post-progression utility decrement than that found in TA421 ([redacted] versus. 0.302 decrement), the EAG believes that the scenario highlights the impact and direction of influence of a relatively small utility decrement from PF to PD. As such, the EAG performed a scenario analysis utilising a PD utility of 0.60.

b) Key issue: The EAG is concerned about the statistical approach taken for analysing HRQoL data. Concerns specifically pertain to a. the missingness of EQ-5D-5L data and b. the selection of explored covariates in the MMRM analyses and model chosen.
    a. HRQoL data were collected in the CAPItello-291 trial and analysed using an MMRM approach. Four models were considered using different (combinations of) covariates. No missing data imputation was conducted under the assumption that data are missing at random. The assumption that data are missing at random is questionable, particularly provided that compliance rates decreased over time and, as per response to the request for clarification Figure 36, baseline EQ-5D-5L [redacted]. Despite this, the company considered there to be no noteworthy relationships between missingness and the presented baseline characteristics. Although the capivasertib plus fulvestrant overall compliance in the ITT population was 82.5%, there was a significant decrease in the number of participants completing the questionnaire as the trial continued, as shown in Table 14.2.9.6.3 of the CSR. If the assumption that data is missing at random does not hold, then bias is potentially introduced into the analysis, particularly provided that healthier patients are more likely to stay in the trial, increasing the average utility values. Further, provided that compliance rates provided in the CSR do not specify whether patients were pre- or post-progression at the point of completion, an appraisal of the validity of EQ-5D trial results are hindered. As such, the EAG would prefer that the company performed missing data imputation for the missing EQ-5D-5L data in the CAPItello-291 trial. Different data imputations should be explored according to the potential mechanisms causing the missingness in the data.[29,30]
    b. Four models were explored in the CS MMRM analyses, which included covariates that the company believed would be the largest drivers of utility. No further justification was provided as to why additional covariates were not considered. No covariate selection process was mentioned. Model 2 (progression status as covariate) was selected due to having both the lowest AIC and BIC as compared with the other models. In response to the request for clarification question B9., the company provided results from the MMRM analyses for each model explored (Table 38). The company also provided results based on an MMRM analysis utilising the CAPItello-291 AKT pathway altered population with prior CDK4/6i therapy (the CS utilised the overall ITT population from CAPItello-291). Model 2 again displayed the lowest AIC and BIC with pre- and post-progression utilities of [redacted]

and [redacted], respectively. A scenario analysis utilising utilities from the MMRM analyses in the PI3K/AKT pathway-altered population with prior CDK4/6i therapy reduced the pairwise deterministic ICERs to [redacted] compared with alpelisib plus fulvestrant, and [redacted] compared to everolimus plus exemestane. The EAG noted that the displayed P-value for each result (both explored populations) was <0.0001, which corresponded to marginal means results, rather than corresponding to individual/interaction-term covariates. That is, no information regarding the significance of included covariates was presented. This hinders the assessment of the significance of explored covariates. Therefore, it remains uncertain which model would be preferred, as the current selection may neglect potentially confounding variables that could influence health state utilities. The EAG would therefore like to see, for each model explored: the model intercept, covariate estimates, and corresponding significance levels for each covariate. Further justification regarding the covariate selection process would also be desirable and further justification to support the assumption that no additional covariates should be considered. Given the company's scenario analyses assessing the impact of PD utilities of 0.70, 0.65, and 0.60, and the relatively small differences between HSUVs in Model 1 (treatment as covariate), Model 2 (i.e., the selected model with progression status as a covariate), Model 3 (treatment and progression status as covariates), and Model 4 (treatment, progression status, and treatment*progression status interaction term as covariates), the EAG does not believe that further scenario analyses utilising utilities from MMRM Models 1, 3, and 4 are necessary.

c) Adverse event disutilities and durations were informed by studies in alternative indications. Further, AE durations (with the exception of anaemia) were informed using proxy AEs. Hyperglycaemia and stomatitis disutilities were also sourced using proxy AEs: anaemia and mucotitis, respectively. In response to the request for clarification question B11., the company suggest that, provided AE costs and disutilities were not drivers in the model, using proxy AEs as a source of utility was a pragmatic approach. The use of studies in alternative indications to inform AE disutilities and durations was supported due to no utility data or AE durations being reported in the studies identified in the CS SLR. As such, utility decrements were informed by other oncology areas, where available. Further, the company suggest that no strong rationale exists as to why disutilities associated with AEs in one oncology setting should differ from another. The EAG accepts that, given AEs are not a driver of costs or QALYs in the model, no additional analyses are required.
d) When implementing age-related utility decrements, the general population HSU norm equation from Ara and Brazier et al 2010 was utilised. In the 2022 DSU report for "*Estimating EQ-5D By Age and Sex For The UK*", Hernandez Alava et al. recommend the use of the most up-to-date information available that has direct observation of EQ-5D-3L from the Health Survey for England 2014. As such, the EAG would prefer an approach aligned with the latest DSU recommendation.

4.2.9 Resources and costs

The cost categories included in the model were treatment acquisition and administration costs, health state costs, costs of managing AEs, subsequent treatment costs, end of life costs and genomic testing costs.

Unit prices were based on the NHS reference costs (2021-22),[31] the December 2023 drugs and pharmaceutical electronic market information tool (eMIT),[32] the 2023 Unit Costs of Health and Social Care (Personal Social Services Research Unit [PSSRU]),[33] and the British National Formulary (BNF).[34]

4.2.9.1 Resource use and costs data identified in the literature review

According to the CS, the SLR identified eight studies reporting UK relevant resource use and cost information. Out of these, the company considered only one study to be consistent with the NICE reference case. This study, however, included limited cost/resource use data, namely the annual treatment costs per patient for intervention and comparator treatment options at this later line of treatment.

4.2.9.2 Treatment costs (with PAS)

Table 28 of the CS reported the drug dosing and costs for capivasertib plus fulvestrant and the comparators. No wastage was assumed in the economic model, as most comparator treatments had a fixed dose and corresponded to integer multiples of available vial/tablet sizes. Also, for oral capecitabine no drug wastage is assumed. Administration costs were applied to both oral and intravenous (IV) therapies (CS Table 32), and were sourced from the latest NHS reference costs (2021-22).

Patients on capivasertib plus fulvestrant, alpelisib plus fulvestrant and everolimus plus exemestane were expected to receive treatment until confirmed disease progression, unacceptable toxicity or withdrawal of consent. The company modelled time to treatment discontinuation (TTD) by applying a ratio between TTD and PFS.

For capivasertib plus fulvestrant, the average observed ratio ([redacted]) between PFS and TTD from CAPItello-291 was applied to the respective modelled PFS curve. In the absence of any publicly available TTD data for alpelisib plus fulvestrant and everolimus plus exemestane, the company pragmatically applied the same constant ratio to generate the TTD from the modelled PFS for both comparators. The impact of using [redacted] and [redacted] applied to all treatment arms was explored in scenario analyses.

Mean relative dose intensity (RDI) was modelled for capivasertib plus fulvestrant and everolimus plus exemestane. For alpelisib plus fulvestrant only the median RDI was available (82.7%), and the company therefore assumed a 100% RDI in its base-case, with a scenario analysis applying the median RDI.

4.2.9.3 Health state costs

Resource use related to the follow-up and monitoring of patients in the PF and PD health states were based on recommendations in NICE CG81,[35] previous NICE TAs and was validated by six UK clinicians.

Resource use and costs related to staffing were assumed to be the same regardless of treatment received (CS Tables 33 and 34). Costs were taken from the latest NHS reference costs (2021–22) or the latest PSSRU report (2023). Clinician responses were heterogeneous, especially regarding the involvement of clinical nurse specialists.

Resource use and costs related to imaging and monitoring by health state and treatment per month were reported in CS Tables 35 and 36. Differences in monitoring costs across treatments such as fasting plasma glucose were explained by the distinct side-effect profiles of the treatments listed. The company provided a scenario analysis assuming equivalent resource use related to monitoring and imaging across treatments in the PF health state. Resource use related to imaging and monitoring in the PD health state is the same irrespective of treatment received.

4.2.9.4 Adverse event costs

Costs associated with treating and managing AEs, applied as a one-off cost in the company's base-case, were presented in CS Table 37 and were sourced from the NHS reference costs 2021-22.

4.2.9.5 Subsequent treatment costs

Patients experiencing disease progression or recurrence in the economic model were assumed to receive subsequent treatments. In the CAPItello-291 trial [redacted] of patients received subsequent treatments in the PI3K/AKT pathway-altered population. The company stated that the types and proportion receiving subsequent treatments were consistent across arms. However, the distribution and proportion receiving subsequent treatment were not reflective of UK clinical practice. Hence, the modelled types and distribution of subsequent treatments were based on a series of interviews with six UK clinical experts (Table 4.8). Responses from clinicians were heterogeneous, particularly for doxorubicin ([redacted]), eribulin ([redacted]), paclitaxel ([redacted]) and vinorelbine ([redacted]).

The costs of subsequent treatments were modelled as a one-off weighted average cost on progression. Duration of therapy was based on the duration of therapy reported in the most relevant clinical trial identified for the treatment given the setting, or if not available, based on NHS protocols for treatment.

Table 4.8: Modelled subsequent treatments based on UK clinical expert opinion

Subsequent treatment	Capivasertib plus fulvestrant or alpelisib plus fulvestrant	Everolimus plus exemestane
Any subsequent anticancer therapy	[redacted]	[redacted]
Anastrozole	[redacted]	[redacted]
Capecitabine	[redacted]	[redacted]
Cyclophosphamide	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]
Everolimus + exemestane	[redacted]	[redacted]
Letrozole	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]
Tamoxifen	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]

Based on CS, Table 39[1]
CS = company submission; UK = United Kingdom

4.2.9.6 End of life costs

End of life costs were applied as a one-off cost upon entry into the death state by multiplying the estimated cost of terminal care by the marginal death rate in each cycle (CS Table 38). End of life resource use and unit costs were sourced from TA816,[7] in which they were estimated based on NICE CG81.[35]

4.2.9.7 Genomic testing costs

Prior to initiating capivasertib plus fulvestrant treatment, next generation sequencing (NGS) will be conducted to confirm the PIK3CA/AKT1/PTEN alteration status (per the marketing authorisation for capivasertib plus fulvestrant in this patient population). The company did not include genomic testing costs for PIK3CA mutations, as they stated that this is already commonly performed in UK clinical practice. Testing for AKT1 and PTEN alterations are currently not included in the national genomic test directory ([redacted]).

EAG comment: The main concerns of the EAG relate to: a) assumption related to the modelling of RDI, b) assumptions related to the modelling of TTD, c) the modelling of subsequent treatments upon disease progression, and d) the modelling of genomic testing costs.

a) Key issue: The company modelled mean RDI for capivasertib ([redacted]) plus fulvestrant ([redacted]) and everolimus (79%) plus exemestane (98%) to account for delayed and/or reduced doses. For alpelisib plus fulvestrant, however, the company assumed a 100% RDI in its base-case as only the median RDI (82.7%) was available. In its clarification letter, the EAG requested justification for why modelling the median RDI for alpelisib plus fulvestrant was deemed unsuitable for the company base-case analysis. The company responded that because data may be skewed, medians and means are not the same and that therefore the mean values for RDI are typically used. The reported median RDI of 82.7%, however, indicates that alpelisib plus fulvestrant is also associated with delayed and/reduced doses. The EAG is concerned that the company's assumption of a 100% RDI for alpelisib plus fulvestrant in its base-case therefore likely overestimates the total treatment costs of this comparator. The EAG additionally requested a scenario analysis in which the median RDI was also used for capivasertib plus fulvestrant. The company did not provide this but did provide a scenario in which the RDI for capivasertib plus fulvestrant was used for the alpelisib plus fulvestrant arm. The EAG considers the company's assumption of a 100% RDI for alpelisib plus fulvestrant unlikely to be appropriate, and therefore used this scenario in its base-case.
b) Key issue: Patients on capivasertib plus fulvestrant, alpelisib plus fulvestrant and everolimus plus exemestane all continue to receive treatment until confirmed disease progression, unacceptable toxicity or withdrawal of consent. To derive TTD for capivasertib plus fulvestrant, alpelisib plus fulvestrant and everolimus plus exemestane in the economic model, a HR of [redacted] was applied to their modelled PFS curves. The EAG, however, questions this assumption given that reported treatment discontinuation rates due to disease progression and AEs in the relevant trials (i.e. CAPItello-291, SOLAR-1 and BOLERO-2) differed substantially between capivasertib plus fulvestrant (58.9% due to PD, 13% due to AEs), alpelisib plus fulvestrant (37% due to PD, 25% due to AEs), and everolimus plus exemestane (55% due to PD, 19% due to AEs), which would indicate that the relative proportion of patients discontinuing due to reasons other than progression differ per treatment. In response to the request for clarification, the company further justified its assumption by stating that theirs was a pragmatic approach given the lack of available TTD data for alpelisib plus fulvestrant and everolimus plus exemestane. The EAG notes the uncertainty about this assumption and requested scenario analyses in which different HRs were explored for capivasertib plus fulvestrant and the comparators, which were provided by the company. These showed the potential impact of assuming shorter TTD for the comparators than for capivasertib plus fulvestrant to be moderate (Tables 33 and 34 of the company's response to the request for clarification letter). In addition, the company's scenario analysis in which parametric survival models were directly fitted to the TTD individual patient level data from the capivasertib plus fulvestrant arm in CAPItello-291 demonstrated that results were fairly consistent with the company's base-case, although with slightly

increased pairwise ICERs for both comparisons. This indicates that the company's approach works well for the capivasertib plus fulvestrant arm, but the uncertainty about comparator arms remains unresolved. The EAG explores modelling TTD of comparators using a HR of [redacted] in a scenario.

c) In the company's economic model, patients experiencing disease progression were assumed to receive subsequent treatments. Expert interviews were conducted to obtain types and distribution of subsequent treatments, because, according to the company, the proportion of patients and distribution of subsequent treatment following disease progression in the clinical trials were not reflective of UK clinical practice. The EAG was concerned about the potential mismatch between the subsequent treatments from the clinical trials and the subsequent treatments from expert interviews that were used to inform the modelled costs. The company argued in their response to the request for clarification question B15 that the distribution of subsequent treatments in comparator trials would not be expected to bias OS results, unless there was an imbalance within each study (which the company stated was not the case), given that a relative treatment effect was calculated from the NMA. The company provided an updated overview of subsequent treatments in the three trials (unnumbered Table in the company's response to the request for clarification question B15) but highlighted that these were not reflective of UK clinical practice. The company did not provide the requested scenario analysis informing the subsequent treatment costs in the economic model based on the subsequent treatment data from the clinical trials as it considered this inappropriate given that treatment practice has changed since the initiation of the trials and hence this scenario would not reflect current UK clinical practice. Furthermore, the EAG noted that the responses of the clinicians regarding the proportions of patients that would receive each subsequent treatment were heterogeneous and hence requested scenarios in which the lower and upper ranges of these responses were explored. Results of these analyses showed that the impact on the ICER was minor (unnumbered table in the company's response to the request for clarification question B15), indicating that uncertainty in the proportions of patients receiving subsequent treatments is likely not a model driver.

d) The company did not include genomic testing costs in its base-case, as testing for PIK3CA mutations is already commonly performed in UK clinical practice since the NICE recommendation of alpelisib plus fulvestrant in 2022. This was further supported by the company in response to the request for clarification question B16. Testing for AKT and PEN alterations, however, is currently not included in the national genomic test directory. However, the company stated that [redacted] The company performed a scenario analysis including testing costs for AKT1 and PEN alterations, which was deemed appropriate by the EAG and showed that including additional test costs would lead to a minimal impact on the estimated ICER. The EAG considers this issue to be addressed.

4.2.10 Disease severity

The NICE reference case stipulates that the committee will regard all QALYs as being of equal weight. However, the committee may consider the severity of the condition, as determined by the absolute and proportional QALY shortfall (including discounting at the reference case rate), as decision modifier. Severity can thus be taken into account quantitatively in the CEAs through QALY weighting, based on the absolute and proportional shortfall, as shown in Table 4.9. Whichever implies the greater severity

level will be considered, and if either the proportional or absolute QALY shortfall falls exactly on the cut-off between two severity levels, the higher level will apply.[36]

Table 4.9: QALY weightings for disease severity

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
1.0	Less than 0.85	Less than 12
1.2	From 0.85 to 0.95	From 12 to 18
1.7	At least 0.95	At least 18

Based on CS, Table 39[1]
CS = company submission; QALY = quality adjusted life year

The company assessed absolute and proportional QALY shortfall for locally advanced or metastic HR+/HER2- breast cancer. The CS utilised population utility norms informed by Ara and Brazier[24] mortality estimates from the Office of National Statistics (ONS) life tables, and a discount rate of 3.5%. Absolute and proportional QALY shortfall were assessed assuming a) alpelisib plus fulvestrant as standard of care and b) everolimus plus exemestane as standard of care to inform expected QALYs for people living with a condition.

The results of the QALY shortfall analysis provided by the company can be found in Table 4.10.

Table 4.10: Summary of company QALY shortfall analysis

Expected total QALYs for the general population	Total expected QALYs for people with *HR+/HER2-, PI3K/AKT pathway-altered, locally advanced or metastatic breast cancer following progression on or after CDK4/6i plus endocrine therapy* on current SoC	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
12.19	Alpelisib plus fulvestrant: 1.78	10.41	85.4%	1.2
12.19	Everolimus plus exemestane: 1.45	10.74	88.1%	1.2

Based on CS B.3.6 [1]
AKT = serine/threonine kinase; CDK4/6i = cyclin-dependent kinases 4 and 6 inhibitor; CS = company submission; QALY = quality-adjusted life year

EAG comment: The QALY shortfall results presented by the company were validated by the EAG with Schneider et al.[37] The EAG were unable to reproduce the estimates of absolute and proportional QALY shortfall provided in the CS. In response to the request for clarification question B18., the company suggest that observed differences are expected due to calculations for absolute and proportional shortfall being calculated in the model and provided results following exploration of absolute and proportional shortfall versus alpelisib plus fulvestrant using the Schneider et al. QALY shortfall calculator (Table 4.16). The EAG also requested that severity weights were calculated probabilistically, with the proportion of simulations with x1.0, x1.2, and x1.7 being presented for each comparator. For alpelisib plus fulvestrant, 94% of simulations qualified for a x1.2 QALY weight (6% with x1.0 QALY weight). For everolimus plus exemestane, ~71% of simulations qualified for a x1.2 QALY weight (~29% with a x1.0 QALY weight). The EAG further highlights that while proportional shortfall indicates a x1.2 QALY weight (and is therefore applied in the model), the absolute shortfall estimate indicates a x1.0 QALY weight.

5. Cost effectiveness results

5.1 Company's cost effectiveness results

In the fully incremental analyses, alpelisib plus fulvestrant was extendedly dominated by capivasertib plus fulvestrant, which had a deterministic (probabilistic) ICER, without the x1.2 QALY weight applied, of [redacted] ([redacted]) post-clarification. Fully incremental probabilistic CS base-case results are presented in Table 5.1, with ICERs displayed both with and without severity modifiers applied.

Table 5.1: Fully incremental probabilistic base-case results post-clarification (mean [95% CI])

Technology	Total costs (£)	Total QALYs (excluding severity modifier)	Incremental costs	Incremental QALYs	ICER (£/QALY) without 1.2 severity modifier	ICER (£/QALY) with 1.2 severity modifier
Everolimus + exemestane	£26,059	1.48	-	-	-	-
Alpelisib + fulvestrant	£52,681	1.81	Extendedly dominated	Extendedly dominated	Extendedly dominated	Extendedly dominated
Capivasertib + fulvestrant	[redacted]	2.44	[redacted]	0.96	[redacted]	[redacted]
Based on the EAG-run company base-case PSA with 5,000 iterations CI = confidence interval; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year						

Overall, the technology is modelled to affect QALYs by:

- Increased PFS and OS health state occupancy for capivasertib plus fulvestrant, as compared to either comparator. In the PF health state, the undiscounted QALYs accrued were 0.77 in the capivasertib plus fulvestrant arm, compared with 0.48 in both comparator arms. In the PD health state, the undiscounted QALYs accrued were 1.84 for the capivasertib plus fulvestrant arms, compared with 1.41 in the alpelisib plus fulvestrant arm, and 1.03 in the everolimus plus exemestane arm.

Overall, the technology is modelled to affect costs by:

- Higher drug acquisition and administration costs for capivasertib plus fulvestrant. Total undiscounted drug costs amounted to [redacted] in the capivasertib plus fulvestrant arm, compared to £30,489 in the alpelisib plus fulvestrant arm and £7,878 in the everolimus plus exemestane arm.
- Higher total resource use costs for capivasertib plus fulvestrant. Undiscounted resource use costs accrued were £9,669 in the capivasertib plus fulvestrant arm, £7,057 for alpelisib plus fulvestrant, and £5,544 for everolimus plus exemestane.

The modelling assumptions that have the greatest effect on the ICER are:

- Assuming a RDI of 100% for alpelisib. In a scenario analyses in the CS, which explored applying the median RDI (82.7%) for alpelisib, the pairwise deterministic ICER for

capivasertib plus fulvestrant compared to alpelisib plus fulvestrant increased from the base-case result (including x1.2 severity modifier) of [redacted] to [redacted].

- Selection of PFS and OS distributions. Scenario analyses in the CS explored a) loglogistic PFS distribution and b) Weibull OS distribution. Using a loglogistic PFS distribution, the ICERs (including x1.2 severity modifier) for capivasertib plus fulvestrant increased from [redacted] and [redacted] to [redacted] and [redacted] compared with alpelisib plus fulvestrant and everolimus plus exemestane, respectively. Using a Weibull OS distribution, the ICERs (including x1.2 severity modifier) for capivasertib plus fulvestrant increased from [redacted] and [redacted] to [redacted] and [redacted] compared with alpelisib plus fulvestrant and everolimus plus exemestane, respectively.

Following clarification, the company updated the economic model. The implemented changes are presented in Table 5.2.

Table 5.2: Summary of model updates following clarification

Clarification question reference	Change in model
NA – minor model error identified	Sheet and cell reference: Model!CZ17:CZ375 Formula incorrectly referenced cell, corrected to: =IF(E17>=$CY$13,0,$CZ$12*BW17)
B6 a) Incorporating time-varying hazard ratios	User dropdown added to Settings!U21 Time-varying inputs can be amended in the 'Relative efficacy' sheet, columns R:AL
B6 b) Independent fits for OS and PFS for capivasertib plus fulvestrant added	User dropdown added to Settings!U19 Sheet added: Capi_Ind – this is where the model parameters are stored, and where the user can change the drop down (in row 20)
B7 d) Parametric models fit to TTD data for capivasertib plus fulvestrant added	User dropdown added to Settings!U20 Sheet added: Capi_Ind – this is where the model parameters are stored, and where the user can change the drop down (in row 20)
B12 a) Updated rash duration	Sheet and cell reference: Utilities!J25 Updated value to 4
B16 b) Ability to include testing costs	User dropdown added to Settings!U22 Testing costs can be amended in the Costs_Other sheet, rows 21:32
B18 b) Severity modifier distribution	PSA_calcs sheet, columns FH:FP
B19 a)	RMST sheet added for calculations
B21	Necessary changes made to VBA code, PSA module and Parameters tab column Q
Based on Appendix V, Table 66 of the Response to the request for clarification[4]	

EAG comment: The main concerns of the EAG relate to a) the discrepancy between observed versus modelled QALY gains, and b) the probabilistic results displayed in the updated company model, following clarification.

a) In clarification question B19, the EAG requested a comparison of the observed OS, PFS, undiscounted life years (LYs) and undiscounted PF LYs using different (justified) periods/truncation points to calculate the restricted mean survival time. The company utilised cut-off points using the shortest trial follow-up. That is, PFS of 19.5 months and OS of 24.1 months (maximum follow-up time for the capivasertib plus fulvestrant from the CAPItello-291 trial). Table 52 highlights that modelled RMST (months) is largely aligned with the observed RMST for OS ([redacted] versus [redacted], respectively) and PFS ([redacted] versus [redacted], respectively) for the capivasertib plus fulvestrant arm. The modelled OS and PFS are notably lower than the observed values for alpelisib plus fulvestrant and everolimus plus exemestane. Modelled versus observed OS was 17.5 versus 20.7 months for alpelisib plus fulvestrant and 16.2 versus 19.8 months for everolimus plus exemestane. Modelled versus observed PFS was 6.3 versus 11.5 months for alpelisib plus fulvestrant and 6.3 versus 9.5 months for everolimus plus exemestane. The company suggest that the differences seen in the model-calculated RMST compared to those observed in BOLERO-2 and SOLAR-1 are expected, provided that these trials are in prognostically different populations. To elaborate, in response to the request for clarification question B20, the company refer to all known prognostic factors and treatment effect modifiers in response to the request for clarification question A18 (including their anticipated impact on the NMA and CE model). In particular, the company highlight the difference between the CAPItello-291 with the SOLAR-1 and BOLERO-2 trials of the prior CDK4/6i therapy. That is, CDK4/6i therapy is associated with a worse prognosis and therefore the company suggest that median PFS and OS in the NMA should not be compared naively with observed values. Further, the company highlight the use of beyond CAPItello-291, BOLERO-2, and SOLAR-1 which could further impact differences in observed versus modelled OS and PFS. The EAG accepts the company's justification for deviations in observed versus modelled OS and PFS. However, despite this, the EAG remains concerned regarding the extent of the difference in modelled QALY gains between the observed versus extrapolated periods. Indeed, in a crude analysis of observed versus extrapolated gains in the economic model (i.e., setting the time horizon to 15 months), the EAG found that 90.96-91.82% of the incremental QALY gains for capivasertib plus fulvestrant (pairwise comparisons with comparators), are found in the extrapolated period, highlighting substantial uncertainty about long-term OS in the model.
b) In the response to the request for clarification, while the company presented an overview of model changes, in addition to an updated economic model, the updated probabilistic company base-case was not presented. The results displayed in the updated models "PSA" sheet were not reproducible by the EAG, although it is unclear whether these were run by the company with all updated model changes implemented. As such, the company base-case results presented by the EAG were derived from running the PSA in the updated model with fixed seed and 5,000 iterations.

5.2 Company's sensitivity analyses

The company performed and presented the results of probabilistic sensitivity analyses (PSA), deterministic sensitivity analyses (DSA) as well as scenario analyses. The probabilistic CS base-case analyses indicated CE probabilities of 1.3% and 12.8% versus willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY gained. The DSA showed that the results were most sensitive, compared to everolimus plus exemestane, to changes in capivasertib RDI, everolimus relative dose

intensity, and PD HSUV, and compared to alpelisib plus fulvestrant, to changes in capivasertib RDI, proportion of alpelisib plus fulvestrant and proportion of capivasertib plus fulvestrant PD patients receiving subsequent treatments. The company conducted several scenario analyses. The results showed deterministic ICERs (including severity modifier) ranging between [redacted] and [redacted] per QALY gained versus alpelisib plus fulvestrant, and between [redacted] and [redacted] per QALY gained versus everolimus plus exemestane. The three most influential scenarios that increased the ICER were loglogistic PFS distribution, RDI using median for alpelisib and Weibull OS distribution.

EAG comment: The main concerns of the EAG relate to a) the volatility of probabilistic results with 1,000 iterations, and b) the discrepancy between probabilistic and deterministic results when adjusting OS distribution in the model.

a) The EAG noticed that, when running the PSA with 1,000 iterations appeared volatile with variation in costs and QALYs. As such, the probabilistic results displayed by the EAG were run with 5,000 iterations.
b) The EAG noticed that, when adjusting the OS distribution in the economic model (specifically, from gamma to Gompertz), there was a discrepancy between probabilistic and deterministic CE results. The discrepancy was consistent when the adjustment was made to both the EAG base-case and the CS base-case. The mechanism of this discrepancy in the model is unclear to the EAG and would therefore require explanation. As such, in the EAG's analyses, the scenario exploring a Gompertz OS distribution is only presented deterministically.

5.3 Model validation and face validity check

Model validation efforts reported by the company in the CS included internal validation of modelled outcomes against trial data, external validation comparing against alternative data sources and using clinical expert opinion, and quality assurance of the economic model.

5.3.1 Internal validation of modelled outcomes

The modelling of baseline PFS and OS with fulvestrant monotherapy included assessment of the model fit to the observed data and comparison of the modelled and observed smoothed hazard rates.

5.3.2 External validation against external data sources

The company did not externally validate the PFS and OS outcome extrapolations of fulvestrant monotherapy, capivasertib plus fulvestrant, and the relevant comparators to external data sources, stating that this is challenging because no trials provide long term benchmark outcomes data in a biomarker selected PI3K/AKT pathway-altered population with prior CDK4/6i experience. In response to the request for clarification, further external validation was provided comparing model results to the DREAM-US study, a real world evidence (RWE) study, which analysed data from the Flatiron Health electronic health records to identify patients with HR+/HER2– mBC who received fulvestrant monotherapy following progression on CDK4/6i plus AI (Table 25 of the response to the request for clarification). Comparison of reported median OS and PFS indicated alignment between the trial, the model and the external evidence.

5.3.3 External validation by experts

Interviews with six clinical experts were conducted to validate the clinical assumptions underpinning the economic model. Topics that were discussed included the UK clinical pathway and management of HR+/HER2- advanced breast cancer, the CAPItello-291 study design and generalisability to current UK clinical practice, and extrapolation of PFS and OS outcomes in the context of PI3K/AKT-altered tumours and post CDK4/6i therapy.

5.3.4 Quality assurance of the model

Two health economists not involved in the model development reviewed the model for coding errors, inconsistencies, and plausibility of inputs and outputs. A range of extreme value and logic tests were conducted to examine the behaviour of the model and ensure that the results were logical and the TECH-VER checklist was completed.

EAG comment: The EAG considers the company's validation efforts appropriate. A high level comparison with other relevant NICE TAs (TA816 and TA421) was provided in CS, Table 12, but a detailed cross validation including a reflection on model assumptions and input parameters in relation to model outputs was not performed, though it should also be noted that this would be complicated by model outcomes being redacted for TA816.

6. Evidence Assessment Group's Additional Analyses

6.1 Exploratory and sensitivity analyses undertaken by the EAG

Table 6.1 summarises the key issues related to the CE categorised according to the sources of uncertainty as defined by Grimm et al. 2020:[38]

- Transparency (e.g. lack of clarity in presentation, description, or justification).
- Methods (e.g. violation of best research practices, existing guidelines, or the reference case).
- Imprecision (e.g. particularly wide CIs, small sample sizes, or immaturity of data).
- Bias & indirectness (e.g. there is a mismatch between the decision problem and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered).
- Unavailability (e.g. lack of data or insight).

Identifying the source of uncertainty can help determine what course of action can be taken (i.e. whether additional clarifications, evidence and/or analyses might help to resolve the key issue). Moreover, Table 6.1 lists suggested alternative approaches, expected effects on the CE, whether it is reflected in the EAG base-case as well as additional evidence or analyses that might help to resolve the key issues.

Based on all considerations in the preceding Sections of this EAG report, the EAG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous sections. These adjustments made by the EAG form the EAG base-case and were subdivided into three categories (derived from Kaltenthaler et al. 2016):

- Fixing errors (FE) (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (FV) (correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (MJ) (amending the model where the EAG considers that reasonable alternative assumptions are preferred)

6.1.1 EAG base-case

Adjustments made by the EAG, to derive the EAG base-case (using the CS base-case as starting point) are listed below. Table 6.2 shows how individual adjustments impact the results plus the combined effect of all abovementioned adjustments simultaneously, resulting in the EAG base-case. The 'fixing error' adjustments were combined and the other EAG analyses were performed also incorporating these 'fixing error' adjustments given the EAG considered that the 'fixing error' adjustments corrected unequivocally wrong issues.

6.1.1.1 Fixing errors

None.

6.1.1.2 Fixing violations

None.

6.1.1.3 Matters of judgement

1. Time-varying NMA PFS 3 months, OS 6 months (Section 4.2.6)

Instead of a constant HR, two different HRs were used with a cut-off point of 3 months for PFS and 6 months for OS.

2. PFS log-logistic (Section 4.2.6)
   To model PFS, the log-logistic was used instead of the lognormal distribution.
3. Treatment effect waning after 24 months for all treatments (Section 4.2.6)
   The OS and PFS HRs for all treatments versus placebo plus fulvestrant were set to 1 after 24 months in the model.
4. Equal RDI for alpelisib plus fulvestrant to that of capivasertib plus fulvestrant (Section 4.2.9)
   The RDI for alpelisib plus fulvestrant was set equal to that of capivasertib plus fulvestrant instead of assuming 100%.

6.1.2 EAG exploratory scenario analyses

The EAG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the EAG base-case.

6.1.2.1 Exploratory scenario analyses

5. OS Gompertz (Section 4.2.6)
   To model OS, the Gompertz was explored instead of the gamma distribution.
6. PFS generalised gamma (Section 4.2.6)
   To model PFS, the generalised gamma was explored instead of the loglogistic distribution.
7. Treatment effect waning after 36 months for all treatments (Section 4.2.6)
   The OS and PFS HRs for all treatments versus placebo plus fulvestrant were set to 1 after 36 months in the model.
8. TTD HR of 1.3 for comparators (Section 4.2.9)
   A 1.3 HR was applied to PFS for both comparators, instead of [redacted] used for capivasertib plus fulvestrant, to explore the impact of faster treatment discontinuation for the comparators in absence of evidence.
9. PD utility lowered to 0.6 (Section 4.2.8)
   The impact of lowering the PD utility was explored by changing it to 0.6.

6.1.3 EAG subgroup analyses

No subgroup analyses were performed by the EAG.

6.1.4 EAG confidential prices analyses

All the above EAG changes and scenarios are repeated using confidential prices for alpelisib, eribulin and fulvestrant as obtained through the NICE pricing tracker form.

Table 6.1: Overview of key issues related to the CE (conditional on fixing errors highlighted in Section 5.1)

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
Relative treatment effectiveness over time	4.2.6	Unavailability, methods	Employ treatment effect waning, time-varying NMA	+ for treatment effect waning, - for time-varying piecewise NMA	Partly	NMA using a time-varying parametric model
HRQoL	4.2.8	Statistical approach for analysing HRQoL	Missing data imputation, reporting statistical significance	+/-	No	Missing data imputation, reporting statistical significance
HRQoL	4.2.8	Utility decrement from pre- to post-progression	Alternative decrement	+	Explored	Further data assessment, scenarios
Uncertainty about comparator costs	4.2.9	Unavailability	Alternative assumptions about RDI and TTD	+	Yes	Expert opinion on comparator RDI and TTD

[a] Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the EAG and '+' indicates that the EAG believes this issue likely induces bias in favour of the intervention versus at least one comparator
[b] Explored
CE = cost effectiveness; EAG = Evidence Assessment Group; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; NMA = network meta-analysis; RDI = relative dose intensity; TTD = time to treatment discontinuation

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

In Section 6.1, the EAG base-case was presented, which was based on various changes compared to the company base-case. Table 6.2 shows how individual changes impact the results plus the combined effect of all changes simultaneously. The exploratory scenario analyses are presented in Table 6.3. These are all conditional on the EAG base-case. The analyses numbers in Tables 6.2 and 6.3 correspond to the numbers reported in Section 6.1. The submitted model file contains technical details on the analyses performed by the EAG (e.g. the "EAG" sheet provides an overview of the cells that were altered for each adjustment).

Technology	Total costs (£)	Total LYs	Total QALYs (excl. sev mod)	Incremental costs (£) - Capi versus	Incremental LYs - Capi versus	Incremental QALYs (excl. sev mod) - Capi versus	Pairwise ICER (excl. sev mod)	Pairwise ICER (incl. sev mod)	Fully incremental ICER (excl. sev mod)	Fully incremental ICER (incl. sev mod)*	iNHB (£20,000 WTP)	iNHB (£30,000 WTP)
Deterministic												
Company base-case (post-clarification)												
Capivasertib plus fulvestrant	[redacted]	3.25	2.40	[redacted]	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alpelisib plus fulvestrant	£51,365	2.42	1.79	[redacted]	0.83	0.61	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus with exemestane	£25,714	1.96	1.45	[redacted]	1.30	0.94	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1. Time varying NMA PFS 3 months, OS 6 months												
Capivasertib plus fulvestrant	[redacted]	3.26	2.39	[redacted]	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alpelisib plus fulvestrant	£48,405	2.40	1.77	[redacted]	0.86	0.62	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus with exemestane	£25,598	2.06	1.53	[redacted]	1.20	0.86	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2. PFS log-logistic												
Capivasertib plus fulvestrant	[redacted]	3.30	2.44	[redacted]	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technology	Total costs (£)	Total LYs	Total QALYs (excl. sev mod)	Incremental costs (£) - Capi versus	Incremental LYs - Capi versus	Incremental QALYs (excl. sev mod) - Capi versus	Pairwise ICER (excl. sev mod)	Pairwise ICER (incl. sev mod)	Fully incremental ICER (excl. sev mod)	Fully incremental ICER (incl. sev mod)*	iNHB (£20,000 WTP)	iNHB (£30,000 WTP)
Alpelisib plus fulvestrant	£52,709	2.43	1.80	[redacted]	0.87	0.64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus with exemestane	£26,065	1.98	1.47	[redacted]	1.31	0.96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3. Treatment effect waning after 24 months for all treatments (Post-FAC)												
Capivasertib plus fulvestrant	[redacted]	2.62	1.94	[redacted]	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alpelisib plus fulvestrant	£50,227	2.29	1.69	[redacted]	0.33	0.25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus with exemestane	£25,684	2.02	1.50	[redacted]	0.60	0.45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4. Relative dose intensity for alpelisib plus fulvestrant equal to capivasertib plus fulvestrant												
Capivasertib plus fulvestrant	[redacted]	3.25	2.40	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alpelisib plus fulvestrant	£47,275	2.42	1.79	[redacted]	0.83	0.61	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus with exemestane	£25,714	1.96	1.45	[redacted]	1.30	0.94	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technology	Total costs (£)	Total LYs	Total QALYs (excl. sev mod)	Incremental costs (£) - Capi versus	Incremental LYs - Capi versus	Incremental QALYs (excl. sev mod) - Capi versus	Pairwise ICER (excl. sev mod)	Pairwise ICER (incl. sev mod)	Fully incremental ICER (excl. sev mod)	Fully incremental ICER (incl. sev mod)*	iNHB (£20,000 WTP)	iNHB (£30,000 WTP)
EAG Base-case (Post-FAC)												
Capivasertib plus fulvestrant	[redacted]	2.65	1.95	[redacted]	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alpelisib plus fulvestrant	£43,627	2.34	1.73	[redacted]	0.30	0.23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus with exemestane	£25,347	2.05	1.52	[redacted]	0.60	0.44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic												
Company base-case (post-clarification)**												
Capivasertib plus fulvestrant	[redacted]	3.25	2.44	[redacted]	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alpelisib plus fulvestrant	£52,681	2.42	1.81	[redacted]	0.83	0.63	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus with exemestane	£26,059	1.96	1.48	[redacted]	1.30	0.96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base-case (Post-FAC)												
Capivasertib plus fulvestrant	[redacted]	2.65	1.96	[redacted]	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technology	Total costs (£)	Total LYs	Total QALYs (excl. sev mod)	Incremental costs (£) - Capi versus	Incremental LYs - Capi versus	Incremental QALYs (excl. sev mod) - Capi versus	Pairwise ICER (excl. sev mod)	Pairwise ICER (incl. sev mod)	Fully incremental ICER (excl. sev mod)	Fully incremental ICER (incl. sev mod)*	iNHB (£20,000 WTP)	iNHB (£30,000 WTP)
Alpelisib plus fulvestrant	£44,429	2.34	1.73	[redacted]	0.30	0.23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus with exemestane	£25,522	2.05	1.51	[redacted]	0.60	0.45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* 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

** Probabilistic CS base-case, as calculated by the EAG using 5,000 iterations.

Capi = capivasertib plus fulvestrant; CS = company submission; EAG = Evidence Assessment Group; excl. = excluding; ICER = incremental cost-effectiveness ratio; incl.= including; iNHB = incremental net health benefit; LY = life year; OS = overall survival; NMA = network meta-analysis; PFS = progression-free survival; QALY = quality-adjusted life year; sev mod = severity modifier; WTP = willingness-to-pay

Table 6.2: Deterministic/probabilistic EAG base-case

Table 6.3: Deterministic scenario analyses (conditional on EAG base-case)

Technology	Total costs (£)	Total LYs	Total QALYs (excl sev mod)	Incremental costs (£) - Capi versus	Incremental LYs - Capi versus	Incremental QALYs (excl. sev mod) - Capi versus	Pairwise ICER (excl. sev mod)	Pairwise ICER (incl. sev mod)	Fully incremental ICER (excl. sev mod)	Fully incremental ICER (incl. sev mod)*	iNHB (£20,000 WTP)	iNHB (£30,000 WTP)
Deterministic												
EAG base-case (Post-FAC)												
Capivasertib plus fulvestrant	[redacted]	2.65	1.95	[redacted]	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alpelisib plus fulvestrant	£43,627	2.34	1.73	[redacted]	0.30	0.23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus with exemestane	£25,347	2.05	1.52	[redacted]	0.60	0.44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5. OS Gompertz												
Capivasertib plus fulvestrant	[redacted]	2.48	1.83	[redacted]	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alpelisib plus fulvestrant	43,314	2.22	1.64	[redacted]	0.26	0.19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus with exemestane	25,015	1.92	1.43	[redacted]	0.55	0.41	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6. PFS generalised Gamma												
Capivasertib plus fulvestrant	[redacted]	2.64	1.95	[redacted]	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alpelisib plus fulvestrant	44,984	2.34	1.73	[redacted]	0.30	0.23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus with exemestane	25,634	2.05	1.52	[redacted]	0.60	0.44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technology	Total costs (£)	Total LYs	Total QALYs (excl sev mod)	Incremental costs (£) - Capi versus	Incremental LYs - Capi versus	Incremental QALYs (excl. sev mod) - Capi versus	Pairwise ICER (excl. sev mod)	Pairwise ICER (incl. sev mod)	Fully incremental ICER (excl. sev mod)	Fully incremental ICER (incl. sev mod)*	iNHB (£20,000 WTP)	iNHB (£30,000 WTP)
7. Treatment effect waning after 36 months												
Capivasertib plus fulvestrant	[redacted]	2.82	2.08	[redacted]	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alpelisib plus fulvestrant	£43,791	2.37	1.74	[redacted]	0.46	0.34	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus with exemestane	£25,474	2.06	1.52	[redacted]	0.77	0.56	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8. TTD HR of 1.3 for comparators												
Capivasertib plus fulvestrant	[redacted]	2.65	1.95	[redacted]	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alpelisib plus fulvestrant	41,091	2.34	1.73	[redacted]	0.30	0.23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus with exemestane	24,411	2.05	1.52	[redacted]	0.60	0.44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9. PD utility set to 0.6												
Capivasertib plus fulvestrant	[redacted]	2.65	1.68	[redacted]	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alpelisib plus fulvestrant	43,627	2.34	1.48	[redacted]	0.30	0.20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus with exemestane	25,347	2.05	1.32	[redacted]	0.60	0.36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* 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

Technology	Total costs (£)	Total LYs	Total QALYs (excl sev mod)	Incremental costs (£) - Capi versus	Incremental LYs - Capi versus	Incremental QALYs (excl. sev mod) - Capi versus	Pairwise ICER (excl. sev mod)	Pairwise ICER (incl. sev mod)	Fully incremental ICER (excl. sev mod)	Fully incremental ICER (incl. sev mod)*	iNHB (£20,000 WTP)	iNHB (£30,000 WTP)
Capi = capivasertib plus fulvestrant; CS = company submission; EAG = Evidence Assessment Group; excl. = excluding; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; incl.= including; iNHB = incremental net health benefit; LY = life year; OS = overall survival; PFS = progression-free survival; PD = progressed disease; QALY = quality-adjusted life year; sev mod = severity modifier; TTD = time to treatment discontinuation; WTP = willingness-to-pay												

6.3 EAG's preferred assumptions

The estimated EAG base-case ICER (probabilistic) of capivasertib plus fulvestrant versus alpelisib plus fulvestrant and everolimus plus exemestane, based on the EAG preferred assumptions highlighted in Section 5.1, was [redacted] and [redacted] per QALY gained respectively, excluding the severity modifier, and [redacted] and [redacted] per QALY gained respectively including the severity modifier. In the EAG base-case, the probability of capivasertib plus fulvestrant being cost-effective versus its comparators at thresholds of £20,000 and £30,000 per QALY gained was [redacted] and [redacted] excluding the severity modifier and [redacted] and [redacted] including the severity modifier. The most influential adjustments were inclusion of treatment effect waning for all treatments after 24 months, which significantly increased the ICERs and the use of the piecewise NMA which significantly decreased the ICERs. The ICERs increased most in the scenario analyses using the Gompertz for modelling OS for the comparison against alpelisib plus fulvestrant and using a decreased PD utility value for the comparison against everolimus plus exemestane respectively.

6.4 Conclusions of the cost effectiveness section

The CS, Appendices G, H and I, an additional report provided by the company, and the company's response to the request for clarification provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant studies on CE, HRQoL and cost/health care resource use in HR+/HER2- advanced breast cancer.[1, 4, 9, 15] Searches were conducted April 2023, and updated in November 2023 and April 2024. Searches were extensive and well structured. Databases, conference proceedings and HTA resources were searched. Overall, the EAG has no major concerns about the literature searches conducted, although it would have been helpful to the EAG to have seen full details of all searches conducted, complete with hits per line of search.

The company presented a health economic model in line with the NICE reference case. Notable uncertainties in how the CS addressed the decision problem are in the narrower population, where there remains uncertainty about whether patients in practice may receive capivasertib plus fulvestrant if they had not previously received a CDK4/6i; and in the comparators, where the EAG noted an absence of evidence as to what patients actually receive in clinical practice.

Notably, 90.96-91.82% of the incremental QALY gains for capivasertib plus fulvestrant (pairwise comparisons with comparators), are found in the extrapolated period, highlighting substantial uncertainty about long-term relative OS in the model. This means that relative treatment effectiveness of all treatments versus placebo plus fulvestrant is very important. It was noted that relative treatment effectiveness may follow a pattern over time, and notably appears to wane over time. This was not sufficiently addressed in the company's model and has a large impact.

There is remaining uncertainty about whether the impact of the disease and different treatments on HRQoL is appropriately reflected in the CS. The company's analysis assumed data missing at random, which was considered to potentially bias results. There was remaining doubt over the company's model selection. Furthermore, it remained unclear whether the impact of disease progression was appropriately captured by the trial data, and therefore appropriately reflected in the model.

Comparator costs were also considered uncertain, as there was no information on TTD for both modelled comparators, and only limited information on RDI for alpelisib plus fulvestrant.

Three of the four EAG changes to the company's model increased the ICERs, most notably the implementation of treatment effect waning for all treatments versus placebo plus fulvestrant after 24 months. The switch to using the company's piecewise NMA to derive HRs reduced the ICERs.

In conclusion, there is significant uncertainty about the CE of capivasertib plus fulvestrant versus its comparators in this population. It may be possible to address some of this uncertainty with further data collection, collection of expert opinion, and further analyses. Further data collection may help inform the long-term effectiveness of capivasertib plus fulvestrant (with the caveat that unanchored indirect treatment comparisons are prone to bias). Collection of (further) expert opinion may inform the patient population eligible for capivasertib plus fulvestrant, the comparators used in this population, and assumptions regarding time-to-discontinuation for both comparators and RDI specifically for alpelisib plus fulvestrant. Further analyses may help address the uncertainty about HRs at different time points (through a NMA using a time-varying parametric model and exploration of treatment effect waning scenarios), and about the utility estimates (through appropriately addressing missingness and selection of covariates).

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Single Technology Appraisal

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

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Tuesday 8 October 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Issue 1 Comparators - EAG suggest that no evidence was provided to rule out the use of other treatments recommended in the ESMO guidelines

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 13 of the EAG report: *"Given their recommendation in the ESMO guideline and in the absence of evidence as to what patients actually receive in clinical practice, none of the comparators in the NICE scope can be ruled out, except probably retreatment with a CDK4/6i for the population of those who have had a prior CDK4/6i."* Page 26 of the EAG report: *"Nevertheless, the company has only included two comparators and cites*	The Company proposes this text is amended as follows: *"Given their recommendation in the ESMO guideline and the uncertainty around the evidence as to what patients actually receive in clinical practice…"* *"The company has provided the following rationale to rule out the use of the other treatments recommended in the ESMO guideline , the company stating in response to this clarification request: "Tamoxifen plus everolimus and fulvestrant plus everolimus, which are not licensed combinations, and single agent endocrine therapy with AI or tamoxifen would not be anticipated to be used routinely instead of*	The company has provided the EAG with evidence on why the comparators in the NICE draft and final scopes beyond alpelisib plus fulvestrant, and everolimus plus exemestane are not deemed relevant for this decision problem as part of the CS (Section B.1.1 and B.1.3.2), supplemented by a report outlining findings from UK breast cancer expert interviews, and relevant NHS England commissioning criteria and references to recent relevant breast cancer appraisals.[1-7] ESMO guidelines, as the EAG states, were only part of the justification for the choice of comparators, which were viewed through the lens of UK commissioning rules (e.g.	Not a factual inaccuracy.

the European Society for Medical Oncology (ESMO) guideline as part of the justification for the choice" *"No evidence was provided to rule out the use of the other treatments recommended in the ESMO guideline, the company stating in response to this clarification request: "Tamoxifen plus everolimus and fulvestrant plus everolimus, which are not licensed combinations, and single agent endocrine therapy with AI or tamoxifen would not be anticipated to be used routinely instead of NICE-recommended combinations of alpelisib plus fulvestrant (per TA816) or*	*NICE-recommended combinations of alpelisib plus fulvestrant (per TA816) or everolimus plus exemestane (per TA421) in patients who are eligible for these."* *"The EAG deemed the evidence ~~was~~ provided to rule out the use of the other treatments recommended in the ESMO guideline was insufficient in their opinion, the company stating in response to this clarification request: "Tamoxifen plus everolimus and fulvestrant plus everolimus, which are not licensed combinations, and single agent endocrine therapy with AI or tamoxifen would not be anticipated to be used routinely instead of NICE-recommended combinations of alpelisib plus fulvestrant (per TA816) or everolimus plus exemestane (per TA421) in patients who are eligible for these."*	fulvestrant monotherapy is not reimbursed). This evidence also serves to inform what options patients have in UK clinical practice. The company has also provided detailed rationale on the partial applicability of the ESMO guidelines in the UK clinical setting in Question A8 of the clarification questions response document.[8] While the company acknowledges the EAG may wish to further explore uncertainties around comparator choice in the committee meeting, the company consider it is factually incorrect to state no evidence has been provided on what patients receive in clinical practice in the UK, as the company has shared evidence-backed UK specific rationale for each comparator in question.	

everolimus plus exemestane (per TA421) in patients who are eligible for these."			
Page 26 of the EAG report: *"The company argue that PARP inhibitors are not appropriate comparators because of the need to be germline BRCA/PALB2m+. However, it seems to the EAG that the coincidence of this genotype and PI3K/AKT pathway-alterations cannot be ruled out."*	The Company proposes the following text is deleted: ~~*"The company argue that PARP inhibitors are not appropriate comparators because of the need to be germline BRCA/PALB2m+. However, it seems to the EAG that the coincidence of this genotype and PI3K/AKT pathway-alterations cannot be ruled out."*~~	As outlined in the clarification questions document (response to Priority question A 2 8), PARP inhibitors are not expected be used routinely in patients eligible for capivasertib plus fulvestrant, as the presence of a gBRCA mutation to make a patient eligible for a PARP inhibitor is typically identified in early breast cancer or even before breast cancer formation through familial screening. [8, 9] In comparison, eligibility for capivasertib would not be established until advanced or metastatic diagnosis. Therefore while the possibility of co-mutation occurrence cannot be ruled out, this sequence of genomic testing would imply PARPi	Not a factual inaccuracy.

		are not appropriate comparators and should therefore remain excluded from the scope.	

Issue 2 Baseline characteristics of the CAPItello-291 trial – distribution across arms

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 40 of the EAG report: *"The CS states that the baseline characteristics of the overall trial population are provided in the trial manuscript1 but does not include or describe them in the CS"*	The Company proposes this text is amended as follows: *"The CS stated that the baseline characteristics of the overall trial population are provided in the trial manuscript1 but ~~does~~ did not include or describe them in the CS. Upon request, the Company provided these at the clarification question stage"*	A reference to the pivotal publication by Turner, which was provided in the submission reference pack, was made in the CS for the baseline characteristics in the overall trial population. The Company deemed this sufficient given the overall trial population was not the relevant licensed population nor the population relevant to the proposed positioning and decision problem.[10] The company provided a table of the baseline characteristics from the ITT population as part of the response to the clarification	Not a factual inaccuracy. Please note that Table 7 of the clarification questions document presents an overview of adverse events in the SPOTLIGHT, GLOW and FAST trials.

		questions (Table 7 of the Clarification questions document),[8] which we would like to clarify by introducing a wording amendment.	
Page 44-45 of the EAG report: *"… it could be suggested that the distribution of menopausal status may impact on outcomes given that there were more post-menopausal women in the capivasertib arm than in placebo"* *The EAG (commenting on population described as 'licenced population' in Table 3.6) has the view that while the groups are well matched in most categories, the EAG highlight some points worth noting…. The EAG do of course note*	The Company proposes this text is amended as follows: *"… it could be suggested that ~~the distribution of menopausal status may impact on outcomes given that~~ there were more post-menopausal women in the capivasertib arm than in placebo"* *"EAG highlights that the baseline characteristics are not equally distributed across all characteristics for the PI3K/AKT pathway-altered population ~~and may reflect characteristics of physiological or treatment response relevance,~~ although the net direction of potential bias/effect cannot be established"*	The EAG has put forward statements suggesting differences in the baseline characteristics in subgroups of the trial ITT may potentially moderate progression/response. This can be considered inaccurate and potentially misleading due to lack of clarity on the direction of potential bias/effect and lack of robust evidence to support the suggestions (eg the arbitrary >5% difference threshold to deem a difference noteworthy). In addition, uncertainties around matching baseline characteristics in small subgroups cannot be expected to automatically lead to generalisability	Amended.

that where differences of >5% exist, this may be a consequence of the smaller sample sizes, rather than any meaningful clinical or physiological differences, and in some cases may reflect differences of only a few participants (i.e. white ethnicity) that might disappear had samples been larger. Nevertheless, these differences are present and notable within this group upon which efficacy and safety data is presented, and some go beyond only a few participants (i.e. post-menopausal status). It must therefore be highlighted and considered in any interpretation of relevant results"		concerns; and introduces unfounded doubt.	

"EAG highlights that the baseline characteristics are not equally distributed across all characteristics for the PI3K/AKT pathway-altered population and may reflect characteristics of physiological or treatment response relevance"			

Issue 3 Comparability of populations in trials included in ITC and exchangeability (EAG Key issues #3 and #4)

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Table 1.4, page 14 states: ***Description of the issue:*** *"The ITC analysis from the CS was based on the PI3K/AKT pathway-altered subgroup of CAPItello-291 and FAKTION trials, and the PIK3CA mutated subgroup of the SOLAR-1 trial. It should be further noted that the subgroup of the*	The Company proposes this text is amended as follows: ***Description of the issue:*** *"The ITC analysis from the CS was based on the PI3K/AKT pathway-altered subgroup of CAPItello-291 and FAKTION trials, ~~and~~ the PIK3CA mutated subgroup of the SOLAR-1 trial, the overall BOLERO 2 and BOLERO 5 trials of everolimus plus exemestane, and associated bridging studies. ~~It should be further~~*	It is not clear from Table 1.4 of the EAG report that the ITC included everolimus plus exemestane. It is also not clear that the company discussed in detail in section B.2.9.1 of the CS and in Appendix D1.2 to the CS that data for the PI3K/AKT pathway-altered subpopulation were available only for capivasertib plus	Amended for clarity.

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
CAPItello-291 trial included all patients with PI3K/AKT alteration; however, the subgroup of FAKTION trial included a smaller proportion of patients with PI3K/AKT alteration (39% in the fulvestrant arm and 45% in the capivasertib plus fulvestrant arm). In addition, the remaining trials included in the ITC analysis recruited patients with unknown PI3K/AKT status. Therefore, there was limited comparability of patients' baseline characteristics in terms of PI3K/AKT pathway alteration between the included trials in the ITC analysis. ***What alternative approach has the EAG suggested?:*** *"The ITC analysis from the CS should be based on the subpopulation with*	~~*noted that*~~ *The subgroup of the CAPItello-291 trial included all patients with PI3K/AKT alteration; however, the subgroup of FAKTION trial included a smaller proportion of patients with PI3K/AKT alteration (39% in the fulvestrant arm and 45% in the capivasertib plus fulvestrant arm). In addition, the remaining trials included in the ITC analysis recruited patients with unknown PI3K/AKT status. The Company notes there is no evidence to support PI3K/AKT alterations as a treatment effect modifier of everolimus and exemestane. ~~Therefore~~, However, as there was limited comparability of patients' baseline characteristics in terms of PI3K/AKT pathway alteration between the included trials in the ITC analysis, there is a degree of uncertainty in the results of the NMA, which the company would be unable to resolve based on the available trial data for everolimus plus exemestane and the other therapies included in bridging trials."*	fulvestrant and alpelisib plus fulvestrant, and were not available for any other therapy trials included in the network. Evidence of the extent to which PI3K/AKT status was a treatment effect modifier for all therapies included in the network was also discussed. To accurately convey the potential issue raised by the EAG the description of the issue should be reframed to note that the company fully explored the available data and noted it was possible to provide data from the subgroup of patients with PI3K/AKT alterations in the capivasertib plus fulvestrant trials (CAPItello-291 and FAKTION) and alpelisib plus fulvestrant trial (SOLAR-1), but not for the remaining trials it was necessary to include in	

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
PI3K/AKT pathway alteration from all included studies" ***What additional evidence or analyses might help to resolve the key issue?:*** *"The EAG recommends that the ITC analysis should be performed on the basis of the data from the PI3K/AKT pathway-altered subpopulation from all included studies if relevant data are available."*	***What alternative approach has the EAG suggested?:*** *"The ITC analysis from the CS should ideally be based on the subpopulation with PI3K/AKT pathway alteration from all included studies. However, as noted by the Company, such data are not available beyond the CAPItello-291 and FAKTION trials of capivasertib and the SOLAR-1 trial of alpelisib."* ***What additional evidence or analyses might help to resolve the key issue?:*** *"~~The EAG recommends that the ITC analysis should be performed on the basis of the data from the PI3K/AKT pathway-altered subpopulation from all included studies if relevant data are available."~~ In the absence of PI3K/AKT subgroup data from publicly available trial data for all relevant comparators, consideration must be given to the extent to which PI3K/AKT status is an effect modifier*	the network. However, the company also notes there is no evidence to support PI3K/AKT alterations as a treatment effect modifier of everolimus and exemestane. There is therefore a degree of uncertainty in the results of the NMA, which the company would be unable to resolve based on the available trial data for everolimus plus exemestane and the other therapies included in interconnecting trials. This issue also existed in NICE TA 816 (alpelisib plus fulvestrant).[7] The alternative approach suggested by the EAG and the EAG's views of the additional evidence or analyses that might help resolve the key issue should be amended accordingly.	

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
	for everolimus plus exemestane, informed by clinical expert opinion."	As this is a key issue listed in the executive summary of the EAG report, it is important that this accurately conveys the approach taken by the company and does not mislead the reader who may only focus on the executive summary. Only by including the detail proposed here by the Company can the reader interpret the issue and form a judgement on if or the extent to which this influences the results of the ITC.	
Section 3.3, page 65 and Section 3.4, page 77 state: *"The company did not present the data of study characteristics of included trials and baseline data for the key sources of heterogeneity in a table in the original submission"*	The Company proposes this text is amended as follows: *"The company ~~did not~~ presented the data of study characteristics of included trials and baseline data for the key sources of heterogeneity in a detailed figure format in the original submission"*	The way the EAG has presented this point is likely to mislead the reader and the committee. The Company is therefore proposing an amendment. The baseline characteristics of all studies included in the NMA were provided in the original submission in Figure 2 of	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
"For the feasibility analysis, the company did not provide the data of baseline characteristics for included studies of NMA in a table."	*"For the feasibility analysis, the company ~~did not~~ provided the data of baseline characteristics for included studies of NMA in ~~a table~~* Figure 2 of Appendix D1.2 to the CS, alongside a detailed discussion of potential prognostic factors vs treatment effect modifiers*."*	Appendix D1.2 to the CS, alongside a detailed assessment of study heterogeneity and a detailed discussion of potential prognostic factors vs treatment effect modifiers.	
Section 3.3, page 65-69 and Section 3.4, page 77-78 refers to heterogeneity in baseline characteristics including HER2 status, prior use of CDK4/6i therapy, ECOG PS. The EAG concludes (page 78): "…*there was lack of sufficient evidence to support the assumption of exchangeability for the purpose of the ITC. This issue may have compromised the validity of the ITC results."*	The Company proposes this text is amended as follows: *"…while the company provided a detailed discussion of potential prognostic factors and treatment effect modifiers, as well as their impact on the ITC results, ~~there was lack of sufficient~~ the evidence to support the assumption of exchangeability for the purpose of the ITC is still uncertain. ~~This issue may have compromised the validity of the ITC results~~."*	Rather than simply listing potential differences in specific baseline characteristics, the EAG report should acknowledge the detailed discussion of these as potential prognostic factors and treatment effect modifiers, and discuss the assessment of the impact of those on the results of the ITC and the cost effectiveness analysis provided by the Company in the CS. It should also note that data with which to adjust for potential heterogeneity are	Amended for clarity.

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
		lacking in some of the comparator trials. The EAG report fails to highlight the difference between prognostic factors and treatment effect modifiers and excludes discussion of the detailed assessment of the impact of potential prognostic factors and treatment effect modifiers on the results of the ITC, which were provided by the Company in Appendix D1.2 to the original CS. This was provided again by the Company in response to the Priority clarification question A 18, which specifically asked for comment on whether the baseline characteristics were prognostic factors and/or treatment effect modifiers and the implications of these on the cost effectiveness results.[8]	

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
		Only by including the detail proposed here by the Company can the reader and committee interpret the issue and form a judgement on if or the extent to which the differences in some baseline characteristics compromise the validity of the ITC results and influence the cost effectiveness results.	

Issue 4 Clinical validation interviews and generalisability to UK clinical practice

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 44, EAG report states: "*EAG make the point that apart from Section B.3.14.3 in the CS, there is no viable documentation to support the clinical opinions presented within. On reviewing this Section of the CS, there is no information to identify the*	The company proposes that this statement on page 44 is deleted: ~~"*EAG make the point that apart from Section B.3.14.3 in the CS, there is no viable documentation to support the clinical opinions presented within. On reviewing this Section of the CS, there is no information to identify the experts, no recorded minutes of meetings, no*~~	The company proposes removing all suggestions in the EAG report that the clinical opinion stated in the CS is not clearly documented, or that this documentation was not provided; as this is factually inaccurate and has the	Amended to increase accuracy

experts, no recorded minutes of meetings, no clinical or audit data provided, no statements/declarations attesting to opinion or advice, or regarding professional status." Page 45, EAG report states: "*The EAG also has concerns about the generalisability of these baseline characteristics to the population of England and Wales and cannot accept the assertions by the company, based on undocumented expert opinion from currently unidentified experts, that the trial population is generalisable to the population in England and Wales*" Page 47, EAG report states: *"The EAG has some concerns about representativeness of this data to the appropriate NHS population in England and Wales. The study had* [redacted]	~~*clinical or audit data provided, no statements/declarations attesting to opinion or advice, or regarding professional status."*~~ The company proposes that this statement on page 45 is amended to: *"Although the company provided documented consolidated expert opinion from 6 clinicians in support of its assertion that the baseline characteristics are generalisable to the population of England and Wales, the EAG has concerns about the generalisability based on [EAG to insert here what those concerns are]"* The company proposes that this statement on page 47 is amended as follows: *"The EAG has some concerns about representativeness of this data to the appropriate NHS population in England and Wales. The study had* [redacted] ~~*. The company makes the claim that' Clinical experts consulted by*~~	potential to mislead the reader and committee. Furthermore, to avoid misleading the reader about the level of clinical validation conducted, the EAG report should outline that the clinical opinion stated in the CS is reflected in the documented responses of the 6 UK clinical experts including the generalisability of the trial, the current clinical pathway and the positioning of capivasertib plus fulvestrant within that, and their input to the cost effectiveness modelling assumptions.[3] The company would like to clarify that while the experts' opinions were anonymised, they were not unidentified and were selected by the company based on their length and breadth of expertise in breast cancer. A detailed report of the clinical expert opinion of the	

[redacted]. *The company makes the claim that' Clinical experts consulted by AstraZeneca have confirmed that the broad characteristics of patients enrolled in the trial and the treatment effects observed with capivasertib, are likely to be generalisable to patients meeting the licensed indication, and the subgroup of interest in UK clinical practice'. However, no evidence has been provided to support this claim and while in principle the advice of clinical experts carries some impact where appropriate, we would expect to see documentation in support of these expert opinions, including such items as meeting minutes, relevant studies or data (if available/appropriate), written statements etc to ensure such expert opinions can be audited and recorded formally."*	~~*AstraZeneca have confirmed that the broad characteristics of patients enrolled in the trial and the treatment effects observed with capivasertib, are likely to be generalisable to patients meeting the licensed indication, and the subgroup of interest in UK clinical practice'. However, no evidence has been provided to support this claim and while in principle the advice of clinical experts carries some impact where appropriate, we would expect to see documentation in support of these expert opinions, including such items as meeting minutes, relevant studies or data (if available/appropriate), written statements etc to ensure such expert opinions can be audited and recorded formally."*~~ The Company proposes that this statement is deleted: "~~*…It is not the position of the EAG that we necessarily dispute the accuracy of such assertions, but rather that we must have documentary evidence to support, justify, record and audit such assertions. This is lacking and therefore we do not*~~	6 UK clinicians with expertise in the management of breast cancer was provided as reference 29 (AstraZeneca UK Ltd. *Data on File. UK Clinical Expert Interviews. ID: GB-56710. CONFIDENTIAL*.; 2024.) to the original CS and was included in the reference pack uploaded to NICE docs at the time of the Company's submission.[3] This 23-page report, which went through the Company's rigorous medical approval process used for provision of all materials and communications with external audiences, detailed the methodology, the questions asked and the answers across the 6 clinicians, including confirmation of the generalisability of the CAPItello-291 trial population to UK clinical practice and all other areas in the CS where it is stated that UK clinical expert opinion was sought. It	

"…*It is not the position of the EAG that we necessarily dispute the accuracy of such assertions, but rather that we must have documentary evidence to support, justify, record and audit such assertions. This is lacking and therefore we do not accept this to assertion to have been reasonably justified*."	~~*accept this to assertion to have been reasonably justified*."~~	is factually incorrect to state there is no viable documentation to support the clinical opinions presented in the CS or otherwise imply that these are undocumented or that documentation was not provided. The Company would also like the EAG to clarify in the report what its concerns are regarding generalisability of the CAPItello-291 trial beyond the erroneous statement that the detailed clinical expert opinion was not documented. At the moment, the only objection of the EAG included in the report seems to be related to the number of UK sites and UK patients enrolled in the trial, which the Company considers does not in itself speak to whether the trial population is generalisable to UK patients.	

Issue 5 Systematic literature reviews

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 33 of the EAG report: *"The EAG are of the opinion that there is a lack of clarity around these processes and as a consequence there are uncertainties which mean that a high risk of bias and error exists"*	The Company proposes this text is amended as follows: *"The EAG are of the opinion that there is a lack of clarity around these processes and as a consequence there are uncertainties which mean that an ~~high~~ unknown risk of bias and error exists"*	The company believes it is misleading to assume a high risk of bias and error if the level of clarity around processes is deemed insufficiently clear by the EAG. Claiming unknown level of risk would be deemed more appropriate.	Amended.
Page 82 of the EAG report: *"The number of hits per line of search for update 1 (20 November 2023) is provided in Appendix I.E of this document'. This was not the case however, and no search hits/line were provided in either the CS or the response to the request for clarification"*	The Company proposes this text is amended as follows: *"The number of hits per line of search for update 1 (20 November 2023) is provided in Appendix I.E of this document'. ~~This was not the case however, and no search hits/line were provided in either the CS or the response to the request for clarification~~"*	Appendix I.E of clarification questions document did contain the #hits per line from the November 2023 economic SLR update, therefore the wording used by the EAG is factually inaccurate and misleading.	Amended to read "The number of hits per line of search for update 1 (20 November 2023) is provided in Appendix I.E of this document'. Appendix I.E however only provides the total number of hits per facet, rather than for each line of search. Best practice states that bibliographic database search strategies should be copied and pasted

			exactly as run and in full, together with the search set numbers and the total number of records retrieved by each search strategy for full transparency”

Issue 6 Survival extrapolations

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 89 of the EAG report “*The EAG considered that the Gompertz was equally plausible as the gamma, considering that it had similar statistical fit, was deemed the most appropriate by two experts (like the gamma), and followed the observed hazards in a similar fashion*”	The Company proposes this text is amended as follows: “*The EAG considered that the Gompertz was equally plausible as the gamma, considering that it had similar statistical fit and was deemed the most appropriate by two experts (like the gamma), although assumed monotonically increasing hazards which deviates from the observed hazards in the trial ~~which and followed the observed hazards in a similar fashion~~*”	The Gompertz distribution assumes monotonically increasing hazards which does not follow the observed hazards in a similar fashion to the gamma distribution.	Amended to “considering that it had similar statistical fit, was deemed the most appropriate by two experts (like the gamma), and hazards had a good visual fit, although they were monotonically increasing”

Issue 7 Comments on the PSA

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 107 of the EAG report "*The EAG noticed that, when running the PSA with 1,000 iterations appeared volatile with variation in costs and QALYs. As such, the probabilistic results displayed by the EAG were run with 5,000 iterations*."	The Company proposes that the EAG should remove this statement or clarify that it was the EAG's model that was unstable, e.g., "*The EAG noticed that, when running the PSA with 1,000 iterations appeared volatile with variation in costs and QALYs in the EAG's amended model. As such, the probabilistic results displayed by the EAG were run with 5,000 iterations*."	The PSA results were stable at 1,000 iterations in the Company submitted model.	Not a factual inaccuracy.

Issue 8 Network meta-analysis commentary

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 77 of EAG report: "*However, the company stated that cut-off points for the piecewise approach were selected on the basis of a visual inspection of the KM curves of both OS and PFS outcomes for studies included in the NMA. The EAG considers that the selection of cut-off points was not sufficiently justified. Furthermore, only short-term follow-up data were used for the base-case NMA. There was a lack of longer-term follow-up data for the base-case NMA*."	In addition to the proposed change below, it would also be helpful if the EAG could clarify what further justification they were hoping for with respect to selecting cut points for the time-varying analysis. "The longest follow-up data available were used for each trial in the NMA ~~Furthermore, only short-term follow-up data were used for the base-case NMA. There was a lack of longer-term follow-up data for the base-case NMA~~."	Inspection of the KM curves is a common method for assessing where relevant cut points may be for a time-varying analysis. The Company used the longest follow-up available from each trial when conducting the analysis.	Amended to increase accuracy.

Issue 9 Treatment waning

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 90 of EAG report: "*The company argued in response to the request for clarification question B8 that their time-varying HR scenario explores the impact of a smaller effect over time. The EAG disagrees that this scenario would be appropriate for estimating treatment effect waning as the HR for the longer-term period was derived with a cut-off point of 3 months (2 months in a scenario) for PFS and a cut-off point of 6 months for OS*."	The Company proposes this text is amended as follows: "*The company argued in response to the request for clarification question B8 that their time-varying HR scenario explores the impact of a smaller effect over time. ~~The EAG disagrees that this scenario would be appropriate for estimating treatment effect waning as the HR for the longer-term period was derived with a cut-off point of 3 months (2 months in a scenario) for PFS and a cut-off point of 6 months for OS~~*." The last sentence should be removed, or the EAG should explain why an increasing HR does not reflect treatment waning.	The time-varying hazard ratio does account for treatment waning, as the results of the time-varying analysis show that the hazard ratio increases at the second cut point. The proportional hazards assumption was not clearly violated for OS, and it is not clear that the hazards would reduce to 1 over time.	Not a factual inaccuracy.

Page 90 of EAG report: "*The EAG considers that treatment effect waning assumptions should be explored and explores treatment effect waning by setting the HR for all treatments versus fulvestrant to 1 after 24 months in the EAG base-case and 36 months in a scenario for OS."*	The EAG should add rationale for the choice of 24 months and 36 months in a scenario for both endpoints, particularly considering the precedent in this setting.	Treatment waning applied at 24 months is incredibly punitive and not evidence based. It is also not aligned with previous appraisals in the setting (TA816), which applied treatment waning at 5-years. Whilst there may be some evidence of an increasing HR with time, there is no evidence to support reducing the HR to 1, or justification for applying this at such an early timepoint.	Justification was provided in the critique, referring to hazards as shown in the hazard plots.
Application of treatment waning in the EAG model Model file name: *ID6370 Capivasertib CAPItello291 Cost effectiveness model*	If the EAG is to apply treatment waning, this should be done at the same timepoint across comparators. Please amend columns BP and BQ to apply waning from 25 months.	The EAG has inconsistently applied treatment waning across the comparators in the model.	This was an oversight, and has been amended. Results tables are updated.

EAG Analyses CON.xlsm Worksheet: Model For capivasertib plus fulvestrant (OS and PFS) in columns BP and BQ, the EAG apply waning from row 40 (at 24 months); for alpelisib plus fulvestrant and everolimus plus exemestane in columns DS, DT, FZ and GA, the EAG apply waning from row 41 (at 25 months)			

Issue 10 Adverse event calculations

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 92 of EAG report The EAG claims that "*Grade ≥3 AEs that occurred in ≥5% of patients were excluded from the analysis. Therefore, for the PI3K/AKT-altered*	The Company proposes this text is amended as follows: "*Grade ≥3 AEs that occurred in <5% of patients were excluded from the analysis. Therefore, for the PI3K/AKT-altered population (irrespective of CDK4/6i therapy) in the CAPItello-291*	The EAG have mistakenly used greater than or equal to symbol, rather than the less than symbol when describing the Company approach. The EAG approach to present the Grade 3+ AEs	Tracked change 1: Amended. Tracked change 2: Not a factual inaccuracy.

population (irrespective of CDK4/6i therapy) in the CAPItello-291 trial, 71/113 (62.83%) Grade 3+ AE observations were excluded from the analysis."	*trial, 71/113 (62.83%) Grade 3+ AE observations were excluded from the analysis due to their low individual prevalences*."	observed in the CAPItello-291 trial that were excluded from the analysis without also considering the Grade 3+ AEs that would have also been observed in the SOLAR-1 and BOLERO trials and have been excluded from the analysis can be considered misleading. The cut-off point of Grade ≥3 AEs that occurred in ≥5% of patients adopted in the Company's analysis is commonly used in other TAs, and a sizeable proportion of Grade 3+ AEs would be excluded from the SOLAR-1 and BOLERO-2 trials as well, due to low overall prevalences of many individual Grade 3+ AEs. It is notable that the frequency of individual Grade 3+ AEs in the PI3K/AKT altered population of CAPItello-291 was low in contrast to the data on SOLAR-1 and BOLERO-2	

		presented in Table 4.5. Only two Grade 3+ AEs were observed in ≥5% of patients in the capivasertib plus fulvestrant arm of the CAPItello-291 trial, with the remaining four AE categories covered in Table 4.5 of the EAG report being <5%; and three of them <2%. Due to the paucity of Grade 3+ AEs data at lower incidence, the approach taken by the company can be considered aligned with previous NICE TAs and available data, with a focus on the most common Grade 3+ AEs observed with capivasertib plus fulvestrant and the relevant comparators.	

Issue 11 Utility analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
a) Inappropriate conclusion that data cannot be considered missing at random Page 97 of EAG report: The EAG state that the "*assumption that data are missing at random is questionable", based on that observation that compliance rates decreased over time and on the baseline EQ-5D-5L compliance rates being lower in "* [redacted]	The Company proposes: Removal of the concerns around 'the missingness of EQ-5D-5L data', or the EAG should provide in the report justification as to why missing at random cannot be assumed.	The justification behind data not being missing at random is not evidence based. It is common for compliance rates with EQ-5D-5L questionnaires to fall over the duration of a trial, and this is not justification for claiming that data are not missing at random. The Company maintain that there are no noteworthy relationships between missingness and the presented baseline characteristics, and any differences observed by the EAG are minor and are not anticipated to lead to any bias.	Not a factual inaccuracy. The EAG do not assert that missing data is not missing at random.
b) Covariate selection Page 98 of EAG report: The EAG commented that "*no information regarding the*	The Company proposes this text is amended as follows: "*no information regarding the significance of included covariates was presented. This hinders the*	The AIC/BIC information provided in the CS indicated the preferred model from those that tested covariates which	Not a factual inaccuracy.

significance of included covariates was presented. This hinders the assessment of the significance of explored covariates. Therefore, it remains uncertain which model would be preferred, as the current selection may neglect potentially confounding variables that could influence health state utilities."	*assessment of the significance of explored covariates. ~~Therefore, it remains uncertain which model would be preferred, as the current selection may neglect potentially confounding variables that could influence health state utilities~~.*"	were considered the largest drivers of utility. Importantly, it is common practice to only include covariates to distinguish between health states, not baseline covariates, in the modelling of utility scores. As such, it is unclear what the EAG is specifically requesting, or which other covariates should be explored in the assessment of utility values in the model. The Company do not believe this would solve or address any concerns about uncertainty. Instead, the focus should remain on the validity of the generated utility values used in the economic analysis.	

c) Anchoring to inappropriate PD utility values Page 97 of the EAG report: The EAG use TA421 as an anchor and compare the absolute decrement between the PF and PD utility values applied in the Company model with those in TA421: "*While even the company-provided scenario utilising a PD utility of 0.60 constitutes a smaller pre- to post-progression utility decrement than that found in TA421 ([redacted] versus. 0.302 decrement), the EAG believes that the scenario highlights the impact and direction of influence of a relatively small utility decrement from PF to PD*."	The Company proposes this text is amended as follows: "~~While even the company-provided scenario utilising a PD utility of 0.60 constitutes a smaller pre- to post-progression utility decrement than that found in TA421 ([redacted] versus. 0.302 decrement),~~ the EAG believes that the scenario using a 0.60 PD utility value highlights the relatively small impact and direction of influence of a relatively small utility decrement from PF to PD." The EAG should also provide further justification for the use of 0.6 in a scenario, as this value is not evidence based, and the Company provided this scenario alongside other values to evidence the relative stability of the model result.	The EAG does not clarify the magnitude of impact of a smaller PD utility value. Anchoring to the absolute decrement used in TA421[6] fails to recognise that the utility value for PD in TA421[6] is from an external study (Lloyd 2006[11]) which is an inappropriate reference source to use in this appraisal for the following reasons: • It is not in line with the NICE reference case as it uses vignettes to describe the health states and the standard gamble technique to estimate the utility values; • The use of vignettes derived from the general population have been found to estimate a larger impact of disease progression on utilities	Not a factual inaccuracy. Uncertainty remains regarding whether the CS base-case utility decrement from PF to PD is plausible. The EAG recognise that utilising the company-provided scenario (exploring PD utility of 0.60) is crude, the scenario demonstrates the relative importance of this uncertainty. Particularly given that the decrement in TA421 was substantially larger. The EAG requested a scenario in the clarification letter utilising the decrement in TA421. This was never provided.

		compared to utilities which have been collected (directly or indirectly) in patients with breast cancer; • The use of Lloyd et al[11] would result in two different methods being used to estimate utilities in the PF state vs. PD state, i.e., EQ-5D-5L measured directly in advanced breast cancer patients vs. vignettes describing health states related with metastatic BC, valued by the general public using the standard gamble approach; • Importantly, the Lloyd paper was published in 2006, and there have been advances in the treatment and management of breast cancer patients since this time period, making the health state	

		vignettes described not reflective of current clinical practice. The Lloyd values were collected at a time when death was often imminent for patients with metastatic disease. It is likely not reflective of the quality of life (utility) that metastatic breast cancer patients experience today, especially as evidence has shown that many patients live for a longer period of time even after first- or second-line progression, maintaining an improved quality of life vs. that reflected in Lloyd et al[11].	

Issue 12 Discontinuation is related to progression

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 101 of EAG report: The EAG questions the Company assumption of applying a HR of [redacted] to all modelled PFS curves to reflect TTD: "*The EAG, however, questions this assumption given that reported treatment discontinuation rates due to disease progression and AEs in the relevant trials (i.e. CAPItello-291, SOLAR-1 and BOLERO-2) differed substantially between capivasertib plus fulvestrant (58.9% due to PD, 13% due to AEs), alpelisib plus fulvestrant (37% due to PD, 25% due to AEs), and everolimus plus exemestane (55% due to PD, 19% due to AEs), which would indicate that the relative proportion of patients discontinuing due to reasons other than*	The Company proposes this text is amended as follows: "*The EAG, however, questions this assumption given that there were some differences in the reported treatment discontinuation rates due to ~~disease progression and~~ AEs in the relevant trials (i.e. CAPItello-291, SOLAR-1 and BOLERO-2); ~~differed substantially between~~ capivasertib plus fulvestrant (~~58.9% due to PD~~, 13% due to AEs), alpelisib plus fulvestrant (~~37% due to PD,~~ 25% due to AEs), and everolimus plus exemestane (~~55% due to PD~~, 19% due to AEs), which would indicate that the relative proportion of patients discontinuing due to reasons other than progression differ per treatment*."	The EAG is inaccurate in saying that the Company approach does not account for discontinuation due to progression, as the approach used directly ties TTD to PFS – i.e., those who progress earlier will discontinue treatment earlier. The EAG make reference to this feature in the final part of the sentence quoted above. Clarification that the approach used does account for differences in discontinuation due to progression.	Not a factual inaccuracy.

progression differ per treatment."			

Issue 13 Severity calculation

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 103, EAG report states: *"The EAG further highlights that while proportional shortfall indicates a x1.2 QALY weight (and is therefore applied in the model), the absolute shortfall estimate indicates a x1.0 QALY weight."*	The Company proposes this text is amended as follows: *"The EAG ~~further highlights~~ notes that ~~while~~ the proportional shortfall indicates a x1.2 QALY weight ~~(~~and this is therefore applied in the model~~),~~ ~~the absolute shortfall estimate indicates a x1.0 QALY weight~~."*	We are pleased the EAG acknowledges that capivasertib plus fulvestrant meets the criteria for application of a x1.2 QALY weighting on the basis of the proportional QALY shortfall. As the NICE Methods Manual[12] clearly indicates that a severity weighting should be applied on the basis of either the absolute or the proportional QALY shortfall calculation, the Company does not understand the EAG's intent in commenting on the absolute QALY shortfall calculation in this way and believe this may introduce	Not a factual inaccuracy.

		unnecessary and unjustified uncertainty.	

Issue 14 Incorrect confidentiality marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG comment
Page 44, EAG report states: *In the PI3K/AKT-altered (PIK3CA/AKT1/PTEN-altered) subgroup World Health Organization (WHO)/ Eastern Cooperative Oncology Group Performance Status (ECOG PS) differs with a grading of '0' present at [redacted]% in the capivasertib arm versus [redacted]% in the placebo; and a grading of (1) at [redacted]% versus [redacted]% in the placebo arm. Stage IV American Joint Committee on Cancer (AJCC) status was also reduced in the capivasertib arm versus placebo at [redacted]% versus [redacted]% respectively.*	This paragraph refers to data from CAPItello291 population who had PI3K/AKT pathway alterations and has progressed on a CDK4/6i regimen. This data is commercial in confidence and should therefore be highlighted as CIC, as per the CS.	*In the PI3K/AKT-altered (PIK3CA/AKT1/PTEN-altered) subgroup World Health Organization (WHO)/ Eastern Cooperative Oncology Group Performance Status (ECOG PS) differs with a grading of '0' present at [redacted]% in the capivasertib arm versus [redacted]% in the placebo; and a grading of (1) at [redacted]% versus [redacted]% in the placebo arm. Stage IV American Joint Committee on Cancer (AJCC) status was also reduced in the capivasertib arm versus placebo at [redacted]% versus [redacted]% respectively. [redacted]% of the capivasertib arm were post-menopausal*	Amended

[redacted]% of the capivasertib arm were post-menopausal versus [redacted]% of the placebo arm, while there were also more diabetics in the capivasertib arm compared to the placebo arm with [redacted]% versus [redacted]% respectively.		*versus [redacted]% of the placebo arm, while there were also more diabetics in the capivasertib arm compared to the placebo arm with [redacted]% versus [redacted]% respectively.*	
Page 90 of the EAG report: "*For OS, the hazard for capivasertib plus fulvestrant [redacted] of placebo plus fulvestrant [redacted]* And "*…the hazard in the capivasertib plus fulvestrant arm [redacted] while the hazard in the placebo plus fulvestrant arm is [redacted]*	Plot 11 in the Company response to the Clarification questions is marked confidential, and this provides detail on the confidential information in the plot.	"*For OS, the hazard for capivasertib plus fulvestrant [redacted] placebo plus fulvestrant [redacted]*" And "*…the hazard in the capivasertib plus fulvestrant arm is [redacted], while the hazard in the placebo plus fulvestrant arm is [redacted]*."	Amended.

Page 97 "*The assumption that data are missing at random is questionable, particularly provided that compliance rates decreased over time and, as per response to the request for clarification Figure 36, baseline EQ-5D-5L* [redacted]."	Information on baseline EQ-5D-5L compliance rates is confidential	*"The assumption that data are missing at random is questionable, particularly provided that compliance rates decreased over time and, as per response to the request for clarification Figure 36, baseline EQ-5D-5L* [redacted]."	Amended.

References

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4. AstraZeneca UKL. Data on file. Blueteq criteria for CDK4/6 inhibitor use, 2024.
5. National Institute for H, Care E. Technology appraisal guidance [TA239] Fulvestrant for the treatment of locally advanced or metastatic breast cancer. 2011.
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8. AstraZeneca. Clarification questions response document for ID6370, 2024.
9. National Institute for Health and Care Excellence. [CG164] Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer. 2013.
10. Turner NC, Oliveira M, Howell SJ, et al. Capivasertib in Hormone Receptor–Positive Advanced Breast Cancer. New England Journal of Medicine 2023;388:2058-70.
11. Lloyd A, Nefees B, Narewska J, et al. Health state utilities for metastatic breast cancer. British Journal of Cancer 2006;95:683-90.
12. National Institute for H, Care E. National Institute for Health and Care Excellence (NICE) health technology evaluations: the manual (PMG36). National Institute for Health and Care Excellence (NICE) process and methods, 2023.