NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Abemaciclib in combination with endocrine therapy for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer [ID3857]

Committee Papers

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Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission summary** from Eli Lilly
2. **Clarification questions and company responses**
3. **Patient group, professional group and NHS organisation submissions** from:
   a. Breast Cancer Now
   b. NCRI-ACP-RCP-RCR
4. **Evidence Review Group report** prepared by Kleijnen Systematic Reviews
5. **Evidence Review Group report – factual accuracy check**
6. **Technical engagement response from company**
7. **Evidence Review Group critique of company response to technical engagement** prepared by Kleijnen Systematic Reviews

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

Abemaciclib for adjuvant treatment of hormone receptor positive, HER2-negative, node-positive early breast cancer [ID3857]

Document B

Company evidence submission

November 2021

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Contents

Tables and figures

Abbreviations

ABC	Advanced breast cancer
ABE	Abemaciclib
AE	Adverse event
AIC	Akaike Information Criterion
ALN	axillary lymph nodes
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATAC	Arimidex, Tamoxifen, Alone or in Combination
BIC	Bayesian Information Criterion
BID	Twice (two times) a day
BMI	Body mass index
BNF	British National Formulary
BSA	Body surface area
BSC	Best supportive care
CAP	capecitabine
CDK	cyclin dependent kinase
CHMP	Committee for Medicinal Products for Human use
CSR	Clinical study report

CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
DFI	Disease-free interval
DFS	Disease-free survival
DNA	Deoxyribonucleic acid
DRFS	Distant-relapse free survival
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EBC	Early breast cancer
ECHO	Echocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERG	Evidence Review Group
ET	Endocrine therapy
EVE	Everolimus
EXE	Exemestane
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FACT-B	Functional Assessment of Cancer Therapy – Breast
FACT-ES	Functional Assessment of Cancer Therapy – Endocrine Subscale
FDA	Food and Drug Administration
FUL	Fulvestrant
HER2−	Human epidermal growth factor receptor 2 negative
HER2+	Human epidermal growth factor receptor 2 positive
HRG	Healthcare resource group
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IDFS	Invasive disease free survival
ILD	Interstitial lung disease
IPD	Individual patient data
ITT	Intention to treat
IWRS	Interactive, web-based randomisation scheme
LHRH	Luteinising hormone-releasing hormone
LSM	Least-squares mean
LYG	Life years gained
MAA	Marketing Authorisation Application
MBC	Metastatic breast cancer

MDT	Multidisciplinary team
MHRA	Medicines and Healthcare products Regulatory Agency
MID	Minimally important difference
MMRM	Mixed effect Model Repeat Measurement
MOS SF-36	Medical Outcomes Study Short Form Survey
MUGA	Multigated acquisition
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMR	Non-metastatic recurrence
NSAI	Non-steroidal aromatase inhibitor
OFS	Ovarian function suppression
PAL	Palbociclib
PAS	Patient Access Scheme
PFS	Progression-free survival
PHE	Public Health England
PPS	Post-progression survival
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RDI	Relative dose intensity
RIB	Ribociclib
RIBO	Ribociclib
RWE	Real-world evidence
SAE	Serious adverse event
SDF	survival distribution function
SLR	Systematic literature review
SMQ	standardised MedDRA queries
SOC	Standard of care
STA	Single Technology Appraisal
STEEP	Standardised definitions for efficacy end points in adjuvant breast cancer trials
TEAE	Treatment-emergent adverse event
TLR	Targeted literature review
TMX	Tamoxifen
TSD	Technical Support Document

TTD	Time to treatment discontinuation
URTI	Upper respiratory tract infection
UTI	Urinary tract infection
VAS	Visual analogue score
VTE	Venous thrombolytic events
WHO	World Health Organisation

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

B.1.1 *Decision problem*

The submission covers the technology's full marketing authorisation for this indication.

Abemaciclib in combination with endocrine therapy is under review by the European Medicines Agency [redacted]

The decision problem for this submission (Table 1) involves abemaciclib in combination with endocrine therapy (ET) for patients with hormone receptor-positive (HR+), HER2-negative (HER2−), node-positive early breast cancer.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with hormone receptor-positive, HER2-negative, node-positive early breast cancer after definitive surgery of the primary breast tumour at high risk of recurrence.	Adults with hormone receptor-positive, HER2-negative, node-positive early breast cancer after definitive surgery of the primary breast tumour at high risk of recurrence.	NA
Intervention	Abemaciclib in combination with standard endocrine therapy	Abemaciclib in combination with standard endocrine therapy	NA
Comparator(s)	Standard endocrine therapy	Standard endocrine therapy	NA
Outcomes	The outcome measures to be considered include: • overall survival (OS) • invasive disease-free survival (IDFS) • recurrence-free survival • response rate • adverse effects of treatment • health-related quality of life (HRQoL)	• IDFS • Distant relapse free survival (DRFS) • OS (given the early disease stage, OS data will not be mature during the timeframe of the appraisal, which will focus of modelling disease recurrence) • Safety and tolerability (adverse effects of treatment) • PROs related to HRQoL: o FACT-B, FACT-ES, and FACIT-F o EQ-5D-5L and cross-walked to EQ-5D-3L using the van Hout 2012 methodology	NA
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	As per NICE reference case, cost-effectiveness is expressed in terms of incremental cost per QALY, and costs considered from the perspective of the NHS and PSS, with a life-time time horizon.	NA

	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 technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account.		
Special considerations including issues related to equity or equality	The availability and cost of biosimilar and generic products should be taken into account. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	Although breast cancer is predominantly a disease of women, it does occur in men; the trial included, and the anticipated licence will include, both men and women. Therefore, Lilly intend to submit evidence to support appraisal across both sexes. Inherently the evidence will be heavily weighted towards evidence in women, in line with the prevalent sexual distribution of the disease in the general population, but this is not anticipated to be a barrier to appraisal in the overall population of both sexes.	NA

Abbreviations: ALN: axillary lymph nodes; DRFS: distant relapse free survival; EQ-5D-5L: EuroQol-5 Dimensions-5 Levels; FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-B: Functional Assessment of Cancer Therapy – Breast; FACT-ES: Functional Assessment Of Cancer Therapy-Endocrine Symptoms; HER2−: human epidermal growth factor receptor 2; HRQoL: health-related quality of life; HRQoL: health-related quality of life; IDFS: invasive disease-free survival; NA: not applicable; OS: overall survival; PROs: patient-reported outcomes; PSS: personal social services; QALY: quality adjusted life year.

B.1.2 *Description of the technology being appraised*

A description of the technology being appraised (abemaciclib [Verzenios®]) is provided in Table 2. A draft Summary of Product Characteristics (SmPC) is located in Appendix C.

Table 2: Technology being appraised

UK approved name and brand name	Abemaciclib (Verzenios®)
Mechanism of action	Abemaciclib is a selective dual inhibitor of cyclin-dependent kinase 4 and 6 (CDK4 and 6). As an inhibitor of CDK4 and 6, abemaciclib prevents the phosphorylation of retinoblastoma protein, thereby blocking the progression from G1 phase into S phase of the cell cycle. By inhibiting DNA synthesis, cell cycle arrest is induced which has been shown to induce senescence and apoptosis.[1-3] This results in cell proliferation and tumour growth being subsequently suppressed.[3]
Marketing authorisation/CE mark status	• MAA was submitted to EMA in [redacted] • A CHMP opinion is expected in [redacted] • MHRA marketing authorisation is expected to be granted by [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	• [redacted] • [redacted] • Abemaciclib is also licensed in other indications which are not within the scope of this appraisal and which have been previously appraised by NICE[5-7] • Abemaciclib has the following contraindications: o Hypersensitivity to the active substance or to any of the excipients
Method of administration and dosage	• The dose for abemaciclib in this indication is one 150 mg film-coated oral tablet twice daily (a total of 300 mg daily) as a continuous therapy for up to two years, in combination with endocrine therapy, according to the relevant Summary of Product Characteristics, for 5–10 years • Dose adjustments and/or dose interruption are recommended for the management of some adverse reactions (such as haematological toxicities, diarrhoea, increased ALT), and when given in combination with CYP3A inhibitors. See Appendix C for more detailed information. • Abemaciclib should be taken until recurrence, for a maximum of two years, or until unacceptable toxicity occurs
Additional tests or investigations	No additional test or investigations are required to determine eligibility for abemaciclib beyond those routinely conducted in NHS clinical practice
List price and average cost of a course of treatment	• List price of abemaciclib: £2,950.00 per 28-day cycle[8] • For a patient receiving treatment with abemaciclib for one year with no dose pauses or interruptions, abemaciclib would cost £38,481.69
Patient access scheme (if applicable)	A simple discount patient access scheme is in place for abemaciclib. The proposed abemaciclib with-PAS price is £[redacted] per 28-day cycle, equivalent to a discount of [redacted]%.

Abbreviations: ALT: alanine aminotransferase; CDK: cyclin dependent kinase; HER2−: human epidermal growth factor receptor 2 negative; HR+: hormone receptor positive; mg; milligram; NHS: National Health Service; SmPC: Summary of Product Characteristics.

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

Early breast cancer

- Abemaciclib is an orally administered treatment for [redacted]
- Approximately 46,700 women and 350 men are diagnosed with breast cancer each year in the UK. HR+/HER2− disease is the most common breast cancer subtype, representing 70% of all breast cancers[9]
- In the UK, breast cancer causes approximately 11,000 deaths each year, and is the fourth most common cause of cancer death overall, rising to the second most common in women[10-12]

Current clinical management

- Treatment for early breast cancer is of curative intent. NICE Guideline NG101 recommends that patients with early breast cancer should undergo surgery and appropriate (neo)adjuvant therapy.[13] All HR+ breast cancer patients are recommended to receive adjuvant endocrine therapy (ET), such as tamoxifen or an aromatase inhibitor, for up to 10 years[14]
- Regrettably, 30% of patients with HR+ early breast cancer will relapse following primary treatment, and be diagnosed with invasive or distant recurrent disease.[15-17] This proportion is likely to be greater for the patients in this submission who are at high risk of disease recurrence. Some patients will progress to advanced breast cancer, which is no longer curable and leaves patients facing a poor prognosis, with a median overall survival of just three to four years[18-20]
- Disease progression to advanced breast cancer can also be associated with increases in the intensity and frequency of pain, as well as a detrimental impact on HRQoL.[21] Progression is associated with a worsening of physical symptoms such as physical pain, fatigue, trouble sleeping, as well as treatment side effects and acute distress[21]
- It is therefore paramount to employ effective treatment options as early as possible for patients with early breast cancer, to reduce the likelihood of a patient developing advanced disease and to protect them from the substantial associated morbidity and mortality
- There has been a historical lack of innovation of treatments for HR+, HER2− breast cancer – other than the recent introduction of add-on adjuvant treatment with bisphosphonates for some postmenopausal women[13], cytotoxic chemotherapy and/or ET have remained the standard of care for HR+, HER2− breast cancer for over a decade[13]
- There is an unmet need for novel targeted agents that are more effective in reducing the recurrence of invasive or distant disease, and the subsequent associated mortality and decreases in HRQoL

Abemaciclib

- Abemaciclib, an orally administered, potent, and selective small-molecular inhibitor of CDK4 and CDK6, has the potential to address this unmet need
- Treatment with abemaciclib + ET resulted in statistically significant and clinically meaningful improvements in invasive disease free survival (IDFS) and distant relapse free survival (DRFS) versus ET alone in the pivotal monarchE trial (detailed in Section B.2)[22, 23]

B.1.3.1 Breast cancer

Disease overview and pathogenesis

Breast cancer is the most common cancer amongst women in the UK, with an estimated 55,000 new cases of invasive disease diagnosed each year.[24] Breast cancer is responsible for 7% of all cancer deaths in the UK, with a mortality rate of 17.1 per 100,000.[11, 12] In the UK, there are approximately 11,000 breast cancer deaths each year, meaning that breast cancer is the fourth most common cause of cancer death overall, and the second most common in women.[10]

With an annual breast cancer incidence of 0.08%, approximately 46,700 women in England and Wales are diagnosed with breast cancer each year.[15, 25] Whilst predominantly a disease affecting women, breast cancer also occurs at a much lower incidence in men, with an estimated 350 men diagnosed each year in the UK.[26] Breast cancer incidence is strongly age-dependent, with more than 80% of cases occurring in women over the age of 50,[27] and approximately 25% of cases occurring in women aged 75 and over.[28]

Breast cancers are classified according to the cell type from which the tumour arises and are described in terms of oestrogen (*or estrogen*) receptor (ER) status, progesterone receptor (PgR) status and human epidermal growth factor receptor 2 (HER2 status). Collectively, ER and PgR may be referred to as hormone receptors (HR). The HR and HER2 status may be denoted as either positive or negative. HR+/HER2− disease is the most common subtype, representing 70% of all breast cancers, and patients with HR+, HER2− disease are the population addressed in this submission.[9]

Multiple HR+ breast cancer therapies operate by regulating oestrogen signalling, collectively referred to as endocrine therapy (ET).[29] There are two broad types of ET: therapies that target oestrogen receptors, such as selective oestrogen receptor modulators (SERMs; e.g. tamoxifen), and those that reduce the production of oestrogen through the inhibition of enzymatic activity required for the production of oestrogens, termed aromatase inhibitors (e.g. anastrozole, letrozole, and exemestane).[30]

Approximately 90% of incident breast cancer patients have invasive breast cancer.[15] Most patients (87%) are found to have early breast cancer (or locally advanced disease that is amenable to curative surgical treatment) (Stages I–III), while a smaller number of patients (approximately 5%) will be diagnosed with advanced breast cancer (Stage IV disease) at first diagnosis *(the remaining 8% of patients have an unknown stage at diagnosis)*.[31] Early breast cancer resides only in the breast and lymph nodes nearby, whereas locally advanced disease involves cancer in a large part of the breast and lymph nodes.[13]

The goal of early breast cancer treatment is cure.[13] Regrettably, an estimated 30% of cases in the overall early breast cancer population or operable locally advanced disease will relapse following primary treatment, and result in invasive or distant recurrent disease.[15, 17] This proportion is likely higher in the subset of patients at high risk of disease recurrence that this submission focuses on. Some patients may experience their disease progressing to advanced breast cancer, including locally advanced breast cancer that is no longer amenable to curative treatment by surgery. Some patients will also suffer their disease progressing to metastatic cancer, where their disease spreads to other parts of the body, such as the bones, liver, and lungs.[32]

Once breast cancer progresses to advanced disease, it cannot be completely removed by surgery and is considered incurable.[32] At this point, patients face a poor prognosis, with a median overall survival (OS) that has historically been around 2–3 years, though the introduction of CDK4/6 inhibitors in the advanced setting has slightly increased this to approximately 3–4 years.[18-20]

- There are various clinical and pathological features that can be used to identify patients with breast cancer which is at high risk of disease recurrence. These include the number of axillary lymph nodes (ALNs) that the cancer has spread to, the histologic grade, the tumour size and biomarker data
- One of these biomarkers is Ki-67, a protein biomarker that can be used to identify breast cancer at high risk of recurrence, and is widely used in other countries. However, it is currently not routinely tested for throughout the UK, and Lilly are not proposing the introduction of Ki-67 testing in this submission
- It is therefore anticipated that patients with early breast cancer at high risk of recurrence in the UK will be identified by the various routinely collected clinical and pathological features outlined above, such as the number of ALNs and tumour size, in line with the inclusion criteria used in the monarchE trial, the pivotal trial for abemaciclib in this indication

Effect of breast cancer on patients and carers

Breast cancer imparts a substantial humanistic burden across all stages of disease. Patients with early breast cancer suffer from reduced health-related quality of life (HRQoL) compared with patients who are free from breast cancer,[33, 34] and HRQoL deteriorates as the stage of breast cancer progresses from one stage to the next.[33] Patients must manage both symptoms (breast pain), and treatment side effects (fatigue, nausea, depression and hot flushes), both of which reduce quality of life.[21]

In addition to this, patients also suffer psychological effects, which can be related to the risk of progression; one study found 65% of patients reported moderate to severe problems with anxiety/depression within the first year following a diagnosis of primary breast cancer.[35] A further study that evaluated self-reported physical and emotional concerns of breast cancer patients in remission (N=1,013) reported that more than half of the patients reported cognitive issues, fatigue, fear of recurrence, emotional distress, and identity/grief issues.[36]

Patients with early breast cancer are also at risk of suffering disease progression to advanced breast cancer, which is associated with a poor prognosis, as well as increased symptom burden and a detrimental impact on HRQoL.

There is a growing body of evidence that demonstrates the negative effect of disease progression on patient HRQoL; impacting their ability to work and carry out daily activities. In a cross-sectional study, women with metastatic breast cancer (N=235) completed the Functional Assessment of Cancer Therapy - Breast (FACT-B).[37] This is a 37-item instrument designed to measure five domains of HRQoL in breast cancer patients: physical, social, emotional, functional well-being as well as a breast-cancer subscale. Scores for physical, social/family, emotional and functional well-being were markedly lower than normative scores collected from a validation sample of patients of whom only 20% had metastatic breast cancer.[37] Another Primary Care Monitor study of patients with HER2− (HR+ or HR−), Stage IV (advanced) breast cancer (N=102) found that disease progression was associated with a worsening of physical symptoms such as physical pain, fatigue, trouble sleeping, as well as treatment side effects and acute distress.[21]

Pain can also increase in intensity and frequency as breast cancer progresses to advanced stages. A study of patients with HER2− (HR±), Stage IV breast cancer, found that pain significantly increased with disease progression.[21] In advanced breast cancer, metastases are often associated with, and can directly cause, pain. Distant metastases are associated with significantly more pain than local or regional metastases.[21]

It is not only patients themselves that suffer from the detrimental effect of breast cancer on HRQoL. The caregivers of patients with breast cancer also experience decreased QoL, as a result of the life-threatening nature of the disease as well as the distressing side effects that patients experience with treatment, including physical, psychological and financial impacts.[38, 39]

Wagner *et al*. (2006) found that the spouses of women who were receiving breast cancer treatment scored significantly lower on the general health, vitality, role-emotional and mental health subscales of the Medical Outcomes Study Short Form Survey (MOS SF-36), compared with spouses of healthy women,[40] highlighting the burden on carers.

By preventing recurrence and the progression to advanced breast cancer, patients can therefore be protected from the severe pain and the HRQoL detriment associated with advanced or metastatic disease. It is therefore paramount to employ effective treatment options as early as possible for patients with early breast cancer, to reduce the likelihood of a patient developing advanced disease and suffering the substantial associated burden and mortality.

Economic burden of early breast cancer

In addition to the direct effects on patients and their caregivers, breast cancer also places a significant burden on the economy, directly through the cost of treatment, but also indirectly through work absenteeism and presenteeism, as well as caregiver time and their associated costs.[41] A study from the University of Oxford found that breast cancer generates an estimated annual cost of £1.5 billion to the UK economy.[42] Although this is beyond the NICE perspective in terms of economic analysis, it remains a relevant consideration for the broader impact of managing breast cancer in the UK.

Unmet need

Despite treatment for early breast cancer being of curative intent, regrettably, 30% of patients with HR+ early breast cancer will relapse following primary treatment.[17, 43] There is therefore an unmet need for novel targeted agents that are effective in reducing the recurrence of invasive or distant disease, and the subsequent associated mortality and decreases in HRQoL. Effective early breast cancer treatment that can reduce the risk of recurrence may therefore reduce the incidence of, and protect patients from, the substantial burden of advanced and incurable metastatic disease.

This unmet need is heightened by a historical lack of innovation or new treatments for patients with HR+, HER2− early breast cancer, particularly in comparison to other breast cancer subtypes, such as HER2+ early breast cancer. In 2006, trastuzumab was recommended by NICE as a targeted biological treatment for patients with HER2+ early breast cancer,[44] while more recently neratinib[45] and pertuzumab[46] have also been recommended. These targeted treatments have been proven to reduce the risk of cancer returning after surgery in early stage HER2+ cancer.

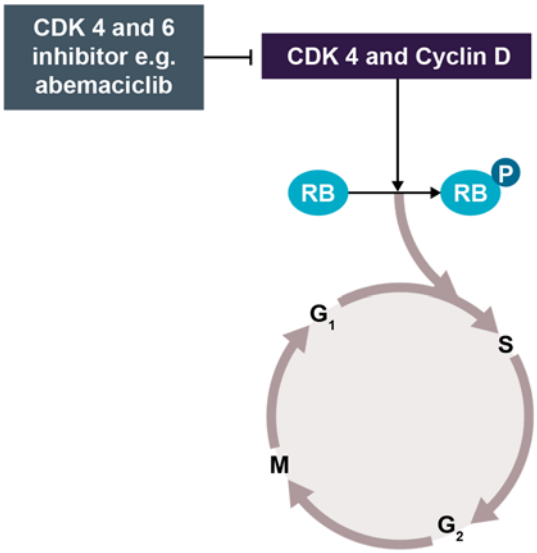
In comparison, there are no similarly effective targeted therapies available for patients with HER2− early breast cancer. Other than the recent recommendation of add-on adjuvant treatment with bisphosphonates, alongside ET, for some postmenopausal women,[13] cytotoxic chemotherapy, radiotherapy, and/or ET have remained the standard of care for these patients for over a decade. There remains an unmet need for the introduction of novel, more effective treatments to help to prevent recurrence and progression to advanced stages of disease.

B.1.3.2 Abemaciclib

Description of abemaciclib

Abemaciclib is an orally administered, potent, and selective small-molecular inhibitor of CDK4 and CDK6.[47] CDKs are a family of enzymes that regulate the progression of the cell cycle through the G1 (growth), S (DNA synthesis), G2 (growth) and M (mitosis) phases. CDKs and cyclins interact at 'checkpoints' between each phase, to tightly control orderly progression of the cycle.[29] The cyclin D-CDK4 and 6 complexes promote phosphorylation of the retinoblastoma (Rb) tumour-suppressor protein, initiating a sequence of events that allows the cell to proceed to S phase and continue through the cell cycle, ultimately promoting cell division and proliferation (Figure 1).[48]

Figure 1: Mechanism of action for CDK 4 and 6 inhibitors



Footnotes: Adapted from Dickson 2014.[49]
Abbreviations: CDK: cyclin dependent kinase; P: phosphorylation; RB: retinoblastoma.

As an inhibitor of CDK4 and 6, abemaciclib prevents the phosphorylation of the Rb protein, thereby blocking the progression from G1 phase into S phase of the cell cycle. By inhibiting DNA synthesis, cell cycle arrest is induced, and cell proliferation and tumour growth is suppressed.[3] Preclinical studies have shown that abemaciclib as a single agent or in combination with endocrine therapies can suppress tumour growth in ER+ xenograft models.[3]

Abemaciclib demonstrates unique pharmacological selectivity. In enzymatic assays, abemaciclib is 14-times more selective and potent for cyclin D1/CDK4 than for cyclin D3/CDK6.[3] Cyclin D1/CDK4 has been frequently implicated in the pathogenesis of HR+ breast cancer, whereas cyclin D3/CDK6 play a large role in the maturation of haematopoietic stem cells within the bone marrow.[50, 51]

Notably, abemaciclib can be dosed continually in clinical practice.[52] UK clinical expert opinion sought by Lilly has highlighted that this may be particularly important in the early breast cancer setting, where smaller tumours are proliferative and potentially grow rapidly. Continuous CDK4/6 blockade may therefore be key to the effective treatment of microscopic disease present in the early breast cancer setting.

Abemaciclib clinical trials

Abemaciclib has previously been investigated across a number of clinical trials, including the pivotal MONARCH 3 and MONARCH 2 trials, which included patients with advanced breast cancer, a different indication which is not within the scope of this appraisal. As a result of these trials, NICE recommended abemaciclib with an aromatase inhibitor as an option for treating locally advanced or metastatic, HR+, HER2−, breast cancer as first-endocrine based therapy (TA563), and abemaciclib with fulvestrant as an option for treating HR+, HER2−, locally advanced or metastatic breast cancer in adults who have had endocrine therapy (TA725).[7]

For the indication of relevance to this submission, abemaciclib was investigated in the monarchE trial:

- monarchE included node positive patients with HR+, HER2−, high-risk early breast cancer, who had received surgery and as indicated, radiotherapy and/or adjuvant/neoadjuvant chemotherapy. Patients were randomly assigned (1:1) to adjuvant ET with or without abemaciclib (150 mg twice daily for two years)
- The primary end point was invasive disease free survival (IDFS), as defined by the STEEP system[23], while secondary end points included distant relapse free survival (DRFS), OS, and safety[23, 53]
- Abemaciclib met the primary IDFS endpoint at interim analysis 2 (IA2) in the ITT population. A statistically significant and clinically meaningful improvement in IDFS was observed for patients treated with abemaciclib + ET versus ET alone; abemaciclib + ET reduced the risk of developing invasive disease by 25.3% (stratified HR=0.747, 95% CI: 0.598, 0.932 versus ET alone, with a clinically meaningful improvement in the 2-year IDFS rates for abemaciclib + ET versus ET; 92.2% vs 88.7%.
- This benefit was sustained with longer-term follow-up through the primary outcome (PO) analysis and the additional follow-up 1 (AFU1) analysis. The AFU1 analysis collected at 36 months showed treatment with abemaciclib + ET reduced the risk of developing invasive disease by 30.4% (stratified HR=0.696, 95% CI: 0.588, 0.823) compared to ET alone and a clinically meaningful improvement in the 3-year IDFS rates for abemaciclib + ET versus ET alone was observed; 88.8% vs 83.4%, respectively demonstrating maintenance of treatment effect
- A clinically meaningful benefit in DRFS was also observed (stratified HR=0.687, 95% CI: 0.571, 0.826), reflecting a 31.3% reduction in the risk of developing distant relapse or death. Abemaciclib reduced the incidence of distant relapse or death at 2 years (94.1% versus 91.6%) and 3 years (90.3% versus 86.1%) versus ET alone
- HRQoL endpoints were similar between treatment arms, with the only notable difference observed after exploring symptoms of interest based on the toxicity profile. Patients treated with abemaciclib plus ET reported mean scores indicating they experienced diarrhoea “a little bit”, whereas patients treated with ET alone reported they did not experience diarrhoea

- The monarchE trial is described in detail in Section B.2

Marketing authorisation and health technology assessment

- MAA was submitted to the EMA in [redacted]
- A CHMP opinion is expected in [redacted]
- MHRA marketing authorisation is expected to be granted by [redacted]

B.1.3.3 Current treatment pathway and the position of abemaciclib

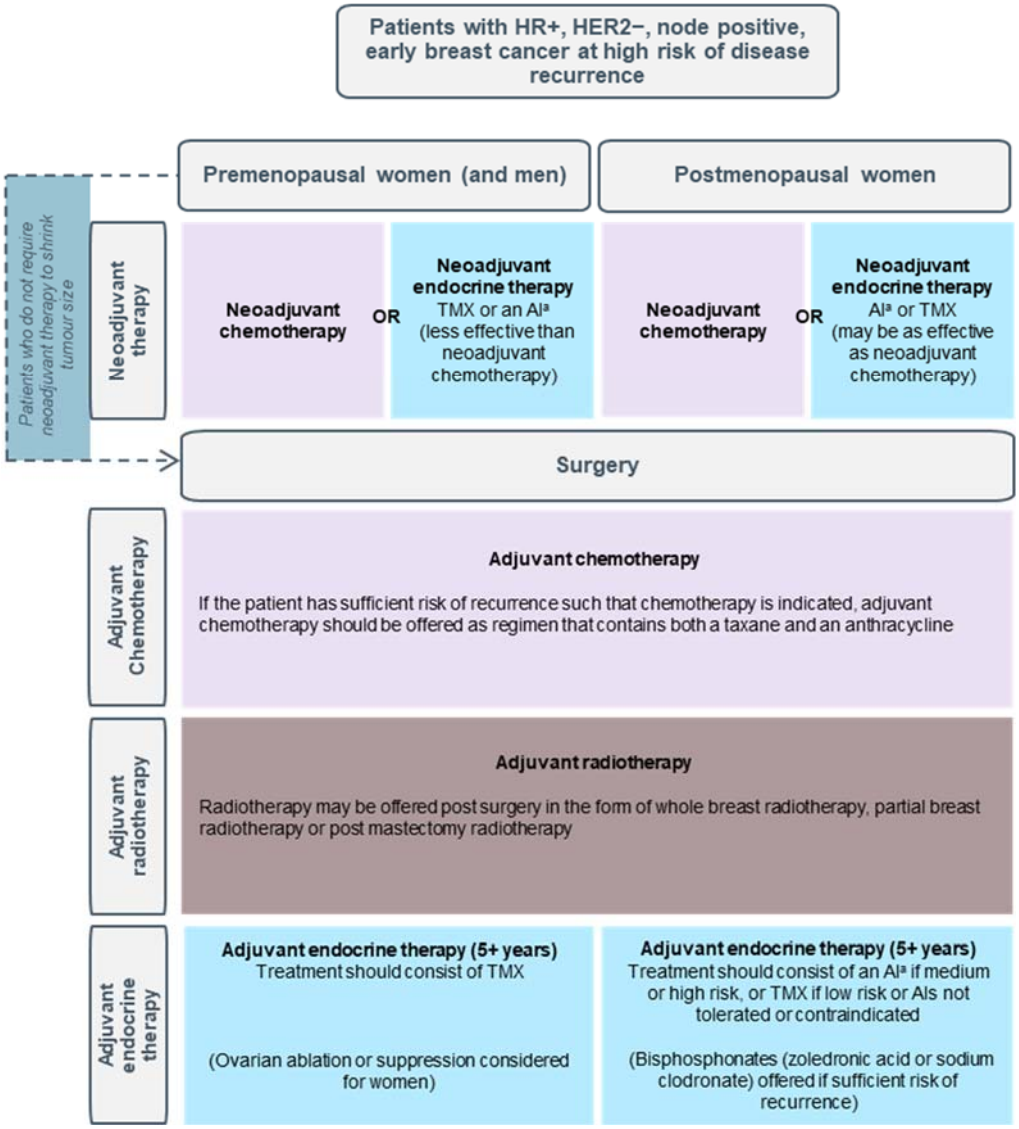
Early breast cancer: current treatment pathway

NICE Guideline NG101 recommends that patients with early breast cancer should undergo surgery and appropriate (neo)adjuvant therapy as treatment for their disease, unless significant comorbidity precludes surgery.[13] Prior to surgery, neoadjuvant chemotherapy may be considered as an option to shrink tumour size to allow surgery with curative intent, if chemotherapy is indicated. Neoadjuvant ET may be considered as an option to shrink tumour size if there is no definite indication for neoadjuvant chemotherapy. Neoadjuvant ET should consist of tamoxifen or an aromatase inhibitor (anastrozole, letrozole or exemestane).[13]

Following surgery, adjuvant therapy is prescribed based on prognostic and predictive factors.[13] For patients with breast cancer that are considered to be at sufficient risk of recurrence such that chemotherapy is indicated, adjuvant chemotherapy should be offered as regimen that contains both a taxane and an anthracycline (in clinical practice it is advised that a regimen contains an anthracycline, a taxane, or a combination).[13] Radiotherapy may be offered in the form of whole breast radiotherapy, partial breast radiotherapy or post mastectomy radiotherapy.[13]

All HR+ breast cancer patients are recommended to receive adjuvant ET as treatment for their disease.[14] Tamoxifen should be offered to men and premenopausal women, while adjuvant ovarian ablation or suppression in combination with ET could also be considered for premenopausal women.[13] Postmenopausal women should be offered an aromatase inhibitor if they are at medium or high risk of disease recurrence, or tamoxifen if they are at low risk or if aromatase inhibitors are not tolerated or are contraindicated. Patients at high risk of recurrence should be offered extended adjuvant ET for at least five years and up to ten years (e.g. treatment with an aromatase inhibitor is recommended for a minimum of five years for postmenopausal women who have been taking tamoxifen for 2–5 years).[13] Additionally, bisphosphonates (zoledronic acid or ibrandronic acid) may be offered as add-on adjuvant therapy for postmenopausal women with node-positive invasive breast cancer.[54] See Figure 2 for a summary diagram of the treatment pathway according to these guidelines.

Figure 2: Current clinical pathway of care for HR+, HER2−, early breast cancer patients



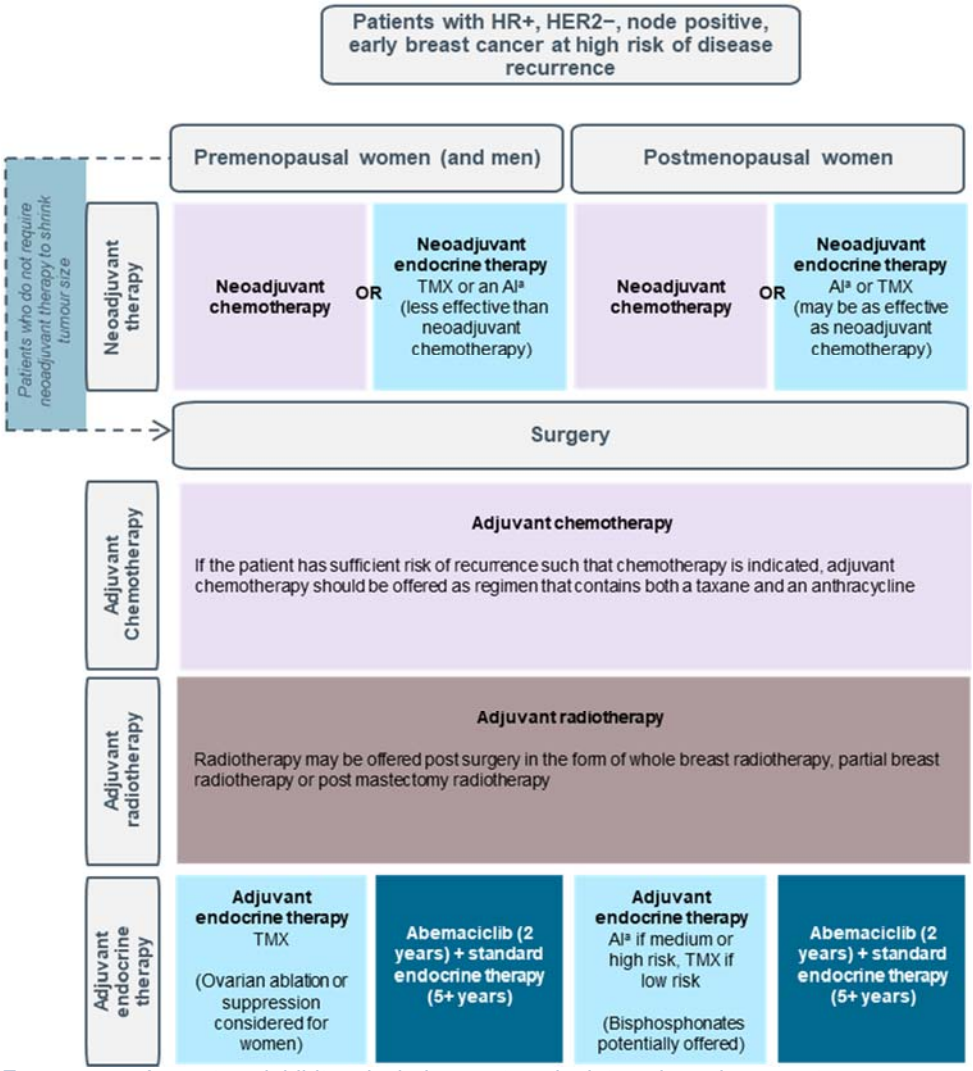
Footnotes: a Aromatase inhibitors include anastrozole, letrozole and exemestane
Abbreviations: AI: aromatase inhibitor; HER2−: human epidermal growth factor receptor 2 negative; HR+: hormone receptor positive; TMX: tamoxifen.
Source: NICE guideline [NG101] Early and locally advanced breast cancer: diagnosis and management[13]

Positioning of abemaciclib relative to the current treatment pathway

Abemaciclib is anticipated to have a marketing authorisation in combination with endocrine therapy [redacted].[4] This is aligned with the NICE final scope, and is aligned with the monarchE inclusion criteria.[55]

The proposed position of abemaciclib is highlighted in Figure 3. It is expected that high risk disease will be defined in clinical practice by clinicopathological features such as the number of ALNs that the cancer has spread to, the histologic grade and size of the tumour. This is aligned with the NICE final scope, and is aligned with the monarchE inclusion criteria.[22]

Figure 3: Proposed positioning of abemaciclib



Footnotes: [a]Aromatase inhibitors include anastrozole, letrozole and exemestane
Abbreviations: AI: aromatase inhibitor; HER2−: human epidermal growth factor receptor 2 negative; HR+: hormone receptor positive; TMX: tamoxifen
Source: NICE guideline [NG101] Early and locally advanced breast cancer: diagnosis and management[13]

Comparators

Adjuvant ET is currently recommended in NICE guidelines for patients with early breast cancer[13]. As such adjuvant ET is considered as the only comparator for this submission, in line with the final scope. The adjuvant ET given in the monarchE trial is consistent with current NHS practice.[13, 23]

Summary

There is a substantial unmet need for a new novel therapy that can reduce disease recurrence and metastasis, and prevent the associated mortality, pain and detriments to HRQoL for the 30% of patients who experience their breast cancer relapsing following therapy for early breast cancer in current practice.[17, 43]

Abemaciclib, an orally administered, potent, and selective small-molecular inhibitor of CDK4 and CDK6 has the potential to address this unmet need. Abemaciclib would provide an additional treatment option, with the potential to reduce disease recurrence and progression to more

advanced stages of disease, demonstrated by the statistically significant and clinically meaningful improvements in IDFS and DRFS observed for patients who received treatment with abemaciclib + ET versus ET alone in the monarchE trial (described in more detail in Section B.2).[22, 23]

B.1.4 *Equality considerations*

The license is anticipated to cover both women and men, and it is not expected that this appraisal will exclude any people protected by equality legislation, nor is it expected to lead to a recommendation that would have a different impact on people protected by equality legislation than on the wider population. Similarly, it is not expected that this appraisal will lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

B.2 Clinical effectiveness

Summary of the clinical evidence

- The Phase III monarchE trial is the pivotal trial for abemaciclib in the indication relevant to this submission. monarchE compared abemaciclib + endocrine therapy (ET) versus ET alone for patients with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2−), node-positive early breast cancer at high risk of recurrence (N=5,637).
- The primary endpoint of monarchE was invasive disease-free survival (IDFS), as defined by the STEEP criteria;[56] secondary endpoints included distant relapse-free survival (DRFS), overall survival (OS), patient reported outcomes (PROs) and safety outcomes

Summary of the clinical effectiveness evidence relevant to the decision problem

- The monarchE study met the primary IDFS endpoint at interim analysis 2 (IA2). This benefit was sustained with longer-term follow-up through the primary outcome (PO) analysis and the additional follow-up 1 analysis 1 (AFU1).
- At the time of the AFU1, a total of 565 patients experienced IDFS events, including 232 (8.3%) in the abemaciclib + ET arm and 333 (11.8%) in the ET alone arm. Abemaciclib + ET reduced the risk of developing invasive disease by 30.4% (stratified HR=0.696, 95% CI: 0.588, 0.823) compared to ET alone, with 2-year and 3-year IDFS rates of 92.7% vs 90.0% and 88.8% vs 83.4%, respectively.
- DRFS was evaluated as a secondary endpoint in monarchE; at the AFU1, the results showed that abemaciclib + ET resulted in a 31.3% reduced risk of a patient experiencing a DRFS event (i.e. metastatic disease or death) (stratified HR=0.687, 95% CI: 0.571, 0.826). There was a clinically meaningful difference of 2.5% in the 2-year DRFS rates (94.1% and 91.6%) for patients treated with abemaciclib + ET, compared to ET alone, and a 4.2% difference in 3-year DRFS rates between abemaciclib + ET and ET alone (90.3% versus 86.1%)
- Given the early stage of cancer on trial entry and the natural timeline of breast cancer progression, OS data are inherently immature at the available data cuts. IDFS and DRFS are strong surrogates for OS and improvements in these measures are expected to translate into improvements in OS with longer-term follow-up.[56] However, establishing evidence will require much longer follow-up, and OS data will not be mature during the timeframe of this appraisal

Summary of the safety evidence

- Overall, abemaciclib + ET was well-tolerated, with a treatment-emergent adverse event (TEAE) profile consistent with previous studies of abemaciclib in advanced breast cancer where it is part of routine NHS clinical practice
- The most frequent TEAEs of any grade reported by the investigator in the abemaciclib + ET arm (versus the ET arm) were diarrhoea (83.5% versus 8.6% in the ET arm), infections/infestations ([redacted]% versus [redacted]% in the ET arm), neutropenia (45.8% versus 5.6% in the ET arm) and fatigue (40.6% versus 17.8% in the ET arm)
- The majority of diarrhoea events were grade 1 or 2 in severity ([redacted]%), with a total of [redacted] patients ([redacted]%) discontinuing abemaciclib or all study treatment (abemaciclib and ET) because of diarrhoea
- In total, 546 (19.6%) patients treated with abemaciclib + ET reported Grade ≥3 neutropenia, compared to 23 (0.8%) patients in the ET alone arm. Overall, neutropenia was manageable with dose modifications, with only [redacted] patients ([redacted]%) discontinuing abemaciclib or all treatment due to neutropenia
- The incidence of serious adverse events (SAEs) was higher in the abemaciclib + ET arm (15.2%) as compared with the ET alone arm (8.8%). Venous thrombolytic events (VTE) and pneumonia were the most commonly reported SAEs by patients treated with abemaciclib + ET

([redacted]% and [redacted]%, respectively). Patients treated with ET alone reported pneumonia ([redacted]%) cellulitis ([redacted]%) and VTE ([redacted]%) most commonly.
- These findings were in line with the known safety profile of abemaciclib: diarrhoea is a recognised side effect of abemaciclib, while neutropenia is a recognised side effect of CDK4/6 inhibitors. It is important to consider that abemaciclib is already an established treatment option for HR+, HER2− advanced breast cancer in the UK,[32] and clinicians have experience managing the known side effects of abemaciclib in clinical practice, including diarrhoea and neutropenia, using anti-diarrhoeal medications and dose modifications.

Innovation and interpretation

- Abemaciclib would represent the first licensed CDK4/6 inhibitor for treating HR+, HER2− early breast cancer at high risk of recurrence, where there have been few fundamental treatment advances for nearly 20 years.[53] The mechanism of action of abemaciclib has previously demonstrated clinically meaningful improvements in progression free survival (PFS) and OS for patients with HR+, HER2− advanced breast cancer[57, 58]
- For patients with HR+, HER2− early breast cancer at high risk of recurrence, abemaciclib + ET has demonstrated statistically significant and clinically meaningful improvements in IDFS versus ET alone, as well as a clinically meaningful improvement in DRFS[53]
- The addition of abemaciclib would represent an important paradigm shift in the management of early breast cancer. It would provide patients with an increased chance of a potential disease cure, thereby avoiding progression to incurable advanced breast cancer and the associated substantial reduction in quality of life and inevitable early death.

B.2.1 *Identification and selection of relevant studies*

Two systematic literature reviews (SLR) were conducted to identify relevant clinical evidence on the efficacy and safety of abemaciclib with ET and other relevant treatment options for patients with early stage, HR+, HER2− breast cancer at high risk of recurrence. Full details of the SLR search strategy, study selection process and results can be found in Appendix D.

B.2.2 *List of relevant clinical effectiveness evidence*

The SLR identified one randomised controlled trial for abemaciclib for which published literature was available, monarchE. In addition, Lilly hold further unpublished data on file which is presented in this appraisal. A summary of clinical effectiveness evidence from monarchE is presented in Table 3.

Table 3: Clinical effectiveness evidence

Study	monarchE		
Study design	Parallel group, active controlled, open-label, global, randomised, phase III trial		
Population	Patients with HR+, HER2−, node-positive eBC at high risk of recurrence (N=5,637) The ITT population in monarchE includes two cohorts: **Cohort 1**, which enrolled 5,120 patients who were considered to be at high risk of recurrence based on clinical and pathological features (Figure 4), defined as pathological tumour involvement in ≥4 ipsilateral ALNs, or pathological tumour involvement in 1–3 ALNs as well as either: • Grade 3 disease (defined as at least 8 points on the Bloom Richardson grading system) • Primary tumour size ≥5 cm[59] **Cohort 2**, which enrolled 517 patients who were considered high risk based on pathological tumour involvements in 1–3 ALNs and a high (≥20%) Ki-67 index. This submission focusses on the ITT population of monarchE as this is generalisable to UK clinical practice and aligned to the monarchE statistical analysis plan.		
Intervention(s)	Abemaciclib (150 mg twice daily on a continuous dosing schedule) for up to 2 years + ET (tamoxifen, toremifene, letrozole anastrozole or exemestane, with or without ovarian suppression) for 5–10 years		
Comparator(s)	ET (tamoxifen, toremifene, letrozole anastrozole or exemestane; with or without ovarian suppression) for 5–10 years		
Indicate if trial supports application for marketing authorisation	Yes	**Indicate if trial used in the economic model**	Yes
Rationale for use/non-use in the model	The pivotal trial for abemaciclib in this indication is the monarchE trial which provides direct head-to-head evidence versus the relevant comparator for this appraisal, for the patient population defined in the final scope of this appraisal.		
Reported outcomes specified in the decision problem	Primary endpoint: Invasive disease-free survival Secondary endpoints: Distant relapse–free survival, overall survival, patient-reported outcomes and safety outcomes.		
All other reported outcomes	Secondary endpoints in the monarchE trial also included two prespecified groups with high Ki-67: • Invasive disease-free survival, as defined by the STEEP system, in patients in the ITT population of monarchE with pre-treatment Ki-67 index ≥20% tested by a central laboratory • Invasive disease-free survival, as defined by the STEEP criteria, in patients in Cohort 1 with pre-treatment Ki-67 index ≥20% tested by a central laboratory		

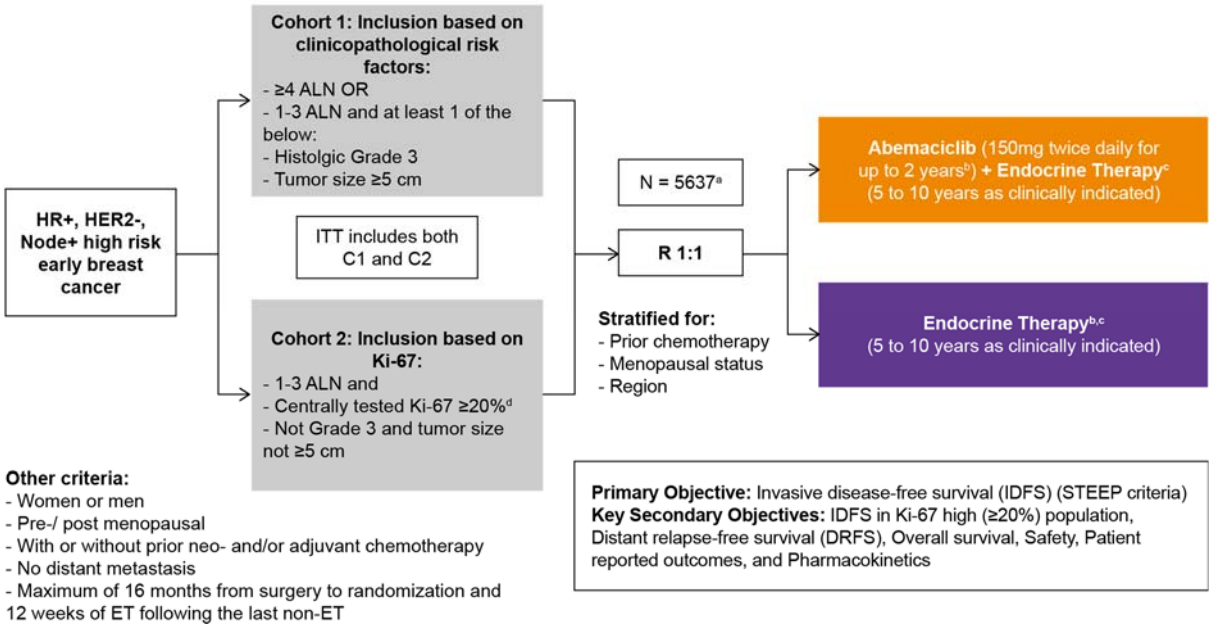
Abbreviations: ALN: axial lymph nodes; eBC: early breast cancer; ET: endocrine therapy; HER2−: human epidermal growth factor receptor-2 negative; HR+: hormone receptor positive; ITT: intention to treat; NA: not applicable.
Source: Lilly Data on File. Clinical Study Report: monarchE [23]

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

B.2.3.1 Summary of trial methodology

An overview of the monarchE study design is presented in Figure 4.

Figure 4: Summary of the study design of monarchE



Footnotes: Full study methodology is presented in Table 4 and full eligibility criteria are presented in Table 5
Abbreviations: ALN: positive axillary lymph nodes; DRFS: distant relapse-free survival; ET: endocrine therapy; HER2−, human epidermal growth factor receptor-2 negative; HR+: hormone receptor positive; IDFS: invasive disease-free survival; ITT: intent-to-treat; R: randomised.
Source: Rastogi *et al.* (2020)[22]

Table 4: Summary of methodology for monarchE

Methodology	Summary
Location	monarchE was an international, multicentre trial conducted in 611 centres across 38 countries: Argentina, Australia, Austria, Belgium, Brazil, Canada, China, Czech Republic, Denmark, Finland, France, Germany, Greece, Hong Kong, Hungary, India, Israel, Italy, Japan, Republic of Korea, Mexico, Netherlands, New Zealand, Poland, Portugal, Puerto Rico, Romania, Russia, Saudi Arabia, Singapore, South Africa, Spain, Sweden, Taiwan, Turkey, Ukraine, **United Kingdom** and United States of America.
Trial design	Phase III, randomised, open-label study of abemaciclib with standard adjuvant endocrine therapy (abemaciclib + ET) versus standard adjuvant endocrine therapy alone (ET alone) in patients with high risk, node-positive, early stage HR+/HER2− breast cancer.
Duration of study	The trial included a two-year on-study treatment period (study Years 1 and 2), in which patients in the abemaciclib + ET arm could receive abemaciclib for up to two years, or until meeting a discontinuation criterion, and all patients received ET. After this on-study treatment period, all patients entered a long-term follow-up period of up to 8 years (overall study Year 10), in which they received ET for at least 3 years (overall study Year 5) if medically appropriate, and for up to 8 years (overall study Year 10) as medically indicated.
Method of randomisation	Patients were randomly assigned to receive abemaciclib with ET or ET alone in a 1:1 ratio. Randomisation was performed using an interactive, web-based randomisation scheme (IWRS) and was stratified according to: • Prior treatment (neoadjuvant chemotherapy versus adjuvant chemotherapy versus no chemotherapy) • Menopausal status (premenopausal versus postmenopausal, as determined by investigator and based on patient's status at the time of diagnosis) • Region (North America and Europe versus Asia versus Other)
Method of blinding	This was an open-label study. Toxicities and laboratory abnormalities related to abemaciclib treatment, such as diarrhoea, neutropenia, and creatinine increase, have the potential to unblind investigators to treatment allocation, justifying an open-label design. In order to maintain the study integrity, the sponsor was blinded to treatment group assignments until the study reached a positive outcome. An independent data monitoring committee was responsible for reviewing the unblinded safety and efficacy analyses. In addition, access to the study data was strictly controlled prior to the study reaching a positive outcome and will continue to be controlled throughout the entire study.
Trial drugs and method of administration	• **ET alone (comparator):** Patients in both study arms received standard adjuvant endocrine therapy of physician's choice, such as letrozole, anastrozole, exemestane or tamoxifen with or without gonadotropin-releasing hormone (GnRH) agonist for ovarian suppression in pre-menopausal women. ET was taken as prescribed during the on-study treatment period (study Years 1 and 2); in Year 3 and beyond, standard adjuvant ET was continued to at least study Year 5 if this was medically appropriate. • **Abemaciclib + ET (intervention):** Patients received the ET as outlined above. In addition, patients received oral abemaciclib 150 mg capsules or tablets twice daily on a continuous dosing schedule for up to two years (study Years 1 and 2), until dose amendments due to adverse event, or until a discontinuation criterion was met. • Dose suspension or delay of study treatment were permitted. When a dose suspension or delay occurred related to toxicity, defined as an AE possibly related to study treatment per investigator judgment, the relevant drug (abemaciclib and/or ET) could be

<table>
<tr><td></td><td colspan="2">suspended or delayed as determined by the investigator's judgment and the other drug could be continued as per pre-specified procedures for patients exhibiting treatment-related toxicities.
• Patients in the abemaciclib + ET arm could discontinue abemaciclib only and continue on ET, or discontinue both treatments at the same time. Patients in either arm could discontinue all components of the study treatment. Patients were allowed to switch from one ET to another within the trial arm as per the investigator's discretion and in the absence of an IDFS event during the on-study treatment period. Patients that discontinued all study treatment (abemaciclib + ET) could restart with another ET.</td></tr>
<tr><td rowspan="2">Permitted and disallowed concomitant medication</td><td colspan="2">All forms of pre-medication, supportive care, concomitant medications and supplements were recorded throughout each patient's participation in the study, including at the time of discontinuation. Please see Section 4.5 of the monarchE CSR for further details.</td></tr>
<tr><td>Permitted therapies
• At the time of study entry, standard adjuvant ET for up to 12 weeks following the last non-endocrine therapy (surgery, chemotherapy or radiation)
• Concurrent treatment with bone-modifying agents, such as bisphosphonates or denosumab
• Full supportive care as judged by the treating physician
• Anti-diarrhoeal agents
• Ovarian suppression with gonadotropin-releasing hormone analogues</td><td>Prohibited therapies
• Anti-breast cancer therapies other than the standard endocrine therapy, such as megestrol acetate and fulvestrant
• Any exogenous reproductive hormone therapy, such as birth control pills, hormone replacement therapy or megestrol acetate
• Grapefruit juice, and inducers or strong inhibitors of CYP3A4
• Any experimental treatment in a clinical trial within the last 30 days or five half-lives, whichever is longer, prior to randomisation</td></tr>
<tr><td>Primary endpoints (including scoring methods and timings of assessments)</td><td colspan="2">o The primary efficacy measure was IDFS, as defined by the STEEP system.[56]
o IDFS time was measured from the date of randomisation to the date of first occurrence of:
o Ipsilateral invasive breast tumour recurrence
o Regional invasive breast cancer recurrence
o Distant recurrence
o Death attributable to any cause
o Contralateral invasive breast cancer
o Second primary non-breast invasive cancer
• IDFS was assessed at every visit and as clinically indicated until distant disease recurrence or death
• Patients for whom no event was observed were censored on the day of their last assessment for recurrence, or date of randomisation if no post-baseline clinic visit occurred.
• Assessments were also performed for patients who discontinued treatment without an IDFS event per STEEP criteria or who were randomised but never received study treatment.</td></tr>
<tr><td>Secondary endpoints</td><td colspan="2">Efficacy:
o Invasive disease-free survival, as defined by the STEEP system, for two prespecified groups with high Ki-67:</td></tr>
</table>

(including scoring methods and timings of assessments)	○ Patients in the ITT population with pre-treated Ki-67 index ≥20% by a central laboratory ○ In patients in Cohort 1 with pre-treated Ki-67 ≥20% by a central laboratory o Distant relapse-free survival, defined as the time from randomisation to distant recurrence or death from any cause, whichever occurred first. For patients who experienced an IDFS event other than distant recurrence or death, assessments continued to be performed until an event of distant recurrence, death, or study completion, whichever occurred first. o Overall survival, defined as the time from randomisation until death from any cause. o PK/PD assessments **Safety:** • During the study, all AEs were recorded and graded at every visit according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Any AEs resulting in dose reduction or discontinuation of treatment was reported and noted. • AEs were assessed at all clinical visits and over the phone between clinical visits • TEAEs, SAEs and hospitalisations. SAEs were defined as any adverse event that resulted in one of the following outcomes: ○ Death ○ Initial or prolonged inpatient hospitalisation ○ A life-threatening experience (that is, immediate risk of dying) ○ Persistent or significant disability/incapacity ○ Congenital anomaly/birth defect ○ Considered significant by the investigator for any other reason: important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered serious, based upon appropriate medical judgment. • Laboratory measurements • Vital signs: signs including blood pressure (systolic and diastolic), pulse rate, respiratory rate, temperature, BMI, and weight were collected at regular intervals during the study. • Physical examinations • PK/PD assessments **Patient-reported outcomes:** • Patients completed paper versions of the PROs questionnaires at the planned visits for administration. The self-reported questionnaires were administered in countries where the questionnaires were translated into the native language of the region and linguistically validated. • PROs were collected on day 1 of the study treatment period, at Months 6, 9, 15, 21 and 27, 30 days post treatment discontinuation and during the first and second long-term follow-up visit

	• FACT-B 37-item questionnaire
	• Endocrine therapy-specific symptoms:
	  o FACT-ES 19-item subscale
	  o 2 FACIT-sourced items of cognitive symptoms
	  o 3 FACIT-sourced items for bladder symptoms
	• Fatigue during abemaciclib, ET, or both via FACIT-F 13-item subscale
	• EQ-5D-5L

Pre-specified subgroup analyses	Subgroup analyses of IDFS were performed for each of the following potential prognostic subgroup variables: • All baseline stratification factors • Primary tumour size by pathology following definitive surgery • Number of involved axillary lymph nodes • Tumour stage • Tumour grade • Progesterone receptor status • Age • Race

Abbreviations: AE: adverse event; CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; CYP3A4: cytochrome P450 3A4; ET: endocrine therapy; EQ-5D-5L: EuroQol-5 Dimensions-5 Levels FACIT: Functional Assessment of Chronic Illness Therapy; FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-B: Functional Assessment of Cancer Therapy – Breast; FACTES: Functional Assessment of Cancer Therapy – Endocrine Subscale; GnRH: gonadotropin-releasing hormone; HER2−: human epidermal growth factor receptor-2 negative; HR+: hormone receptor positive; IDFS: invasive disease-free survival; IWRS: interactive, web-based randomisation scheme; PD: pharmacodynamics; PK: pharmacokinetics; PRO: patient reported outcome; SAE: serious adverse event; STEEP: standardised definitions for efficacy end points in adjuvant breast cancer trials; TEAE: treatment-emergent adverse event.
Source: Lilly Data on File. Clinical Study Report: monarchE[23]

Eligibility criteria

The key eligibility criteria in monarchE are presented in Table 5. The trial included men and women with HR+, HER2−, node-positive, early breast cancer at high risk of recurrence following resection. Full inclusion and exclusion criteria are presented in Appendix L.

Table 5: Key eligibility criteria for monarchE

Key inclusion criteria	Key exclusion criteria
• Male or female aged 18 years or older • Confirmed HR+, HER2−, resected invasive EBC without metastases • Undergone definitive surgery of primary breast tumour and randomised within 16 months of surgery • ECOG PS ≤1 • Adequate organ function • Appropriate washout period for any adjuvant chemotherapy and/or radiotherapy and recovered from acute side effects prior to randomisation • If on standard adjuvant ET at study entry, may receive up to 12 weeks of ET until randomisation following the previous non-ET (surgery, chemotherapy or radiation), whichever is last • Fulfil one of the following criteria: o **Cohort** 1: Pathological tumour involvement in ≥4 ipsilateral axillary lymph nodes, or pathological tumour involvement in 1 to 3 ipsilateral axillary lymph node(s) *and at least one of the following indicating higher risk of recurrence:* Grade 3 disease or primary tumour size ≥5 cm o **Cohort 2:** Pathological tumour involvement in 1 to 3 ipsilateral axillary lymph node(s) *and* Ki-67 index of ≥20%[b]	• Metastatic disease, node-negative BC, inflammatory BC • Previous history of BC with the exception of ipsilateral ductal carcinoma in situ treated by locoregional therapy alone ≥5 years ago • Pregnant or lactating • Concurrent exogenous reproductive hormone therapy (that is, birth control, hormone replacement therapy, or megestrol acetate) • Previous exposure to CDK4 and CDK6 inhibitors • Prior ET for BC prevention or raloxifene • History of any other cancer[a] • Any previous history of venous thromboembolic event • Active systemic infections or viral load

Abbreviations: BC: breast cancer; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ET: endocrine therapy; HER2−: human epidermal growth factor receptor-2 negative; HR+: hormone receptor positive.
Footnote: [a] Exception: nonmelanoma skin cancer or carcinoma in situ of the cervix, unless in complete remission with no therapy for ≥5 years; [b] Ki67 index was measured by a central laboratory.
Source: Lilly Data on File. Clinical Study Report: monarchE[23]

Patient-reported outcomes

The Functional Assessment of Cancer Therapy – Breast (FACT-B) 37-item questionnaire was used to compare treatment arms in terms of general oncology and breast cancer self-reported health-related HRQoL. The FACT – Endocrine Subscale (FACT-ES) 19-item questionnaire was used to evaluate endocrine therapy-specific symptoms. 2 FACIT-sourced items of cognitive symptoms and 3 FACIT-sourced items for bladder symptoms were used to evaluate these specific symptoms. The EQ-5D-5L questionnaire was used to evaluate patients' health status to inform decision modelling for health economic evaluation.

After the baseline assessment, questionnaires for all instruments were next administered to patients at Visit 6 (3 months), Visit 9 (6 months), Visit 15 (12 months), and Visit 21 (18 months). Thus, the timing of assessments did not capture the effects of any AEs the patient might have experienced during the first three months (i.e., prior to Visit 6).

Following discontinuation from study treatment for any reason (including as a result of an IDFS event), questionnaires were administered at the short-term follow-up visit (30 days post study discontinuation), and then at the first and second long-term follow-up study visits every six months following treatment discontinuation. Further details of the collection protocol, instrument scoring, and compliance are available in Appendix L.

B.2.3.2 Participant flow

Patient disposition in monarchE as well as a CONSORT diagram showing patient flow are presented in Appendix D.5.

B.2.3.3 Baseline characteristics

Patients had well-balanced baseline characteristics, with no substantial differences between the abemaciclib + ET and ET alone arms. Full details of the baseline patient demographics are provided in Table 6. The study consisted of over 99% women, with 0.7% men in the abemaciclib + ET arm and 0.5% men in the ET alone arm. In both treatment groups, the median age was 51 years and 56.5% of the women were postmenopausal.

As presented in Table 7, the baseline disease characteristics of the participants included in the monarchE study were well balanced between treatment arms. The majority of patients, [redacted] ([redacted]%), presented with invasive ductal breast carcinoma with approximately 40% of patients in both arms had 1–3 or 4–9 positive lymph nodes, and approximately 20% having 10+. The grade and stage of cancer was varied with similar distributions across both arms, and in both groups, approximately 99% of patients were oestrogen receptor positive while approximately 87% were progesterone receptor positive.

The majority of people in monarchE had their disease treated with prior radiotherapy (95.4% in both arms). In the abemaciclib + ET arm, 36.5% of patients received neoadjuvant chemotherapy, and 61.8% of patients received adjuvant chemotherapy for the disease; in the ET alone arm, this was 36.4% and 61.2%, respectively. A total of [redacted] patients ([redacted]%) in the abemaciclib + ET arm and [redacted] patients ([redacted]%) in the ET alone arm received both adjuvant and neoadjuvant chemotherapy for their disease. Further details of prior therapy and surgery at baseline are provided in Table 8.

Patients received ET for their disease in monarchE as clinically indicated, and the proportions were well balanced between treatment arms (Table 6). Approximately [redacted]% of patients received anti-oestrogen treatment, primarily tamoxifen, at any time, and approximately [redacted]% of patients received aromatase inhibitors at any time for their disease. Ovarian function suppression (OFS) was broadly balanced between treatment arms, with slightly more patients on ET receiving OFS compared to abemaciclib + ET. Disease was treated with gonadotropin releasing hormone (GnRH) analogues in [redacted] patients ([redacted]%) in the abemaciclib + ET arm and [redacted] patients ([redacted]%) in the ET arm. In total, [redacted] patients ([redacted]%) underwent oophorectomies (surgical removal of the ovaries) in the abemaciclib + ET arm, compared to [redacted] patients ([redacted]%) in the ET arm. The choice of endocrine therapy was made by clinicians based on clinical practice and patient preference. The treatment offered is consistent with the ET treatments used in UK clinical practice.

Patients could have also received concurrent treatment with bone-modifying agents, such as bisphosphonates. Bone-modifying agents were balanced between both arms, with 387 (13.9%) patients receiving them in the abemaciclib + ET arm, and 443 (15.8%) patients receiving them in the ET arm. The most commonly used agent in both arms was zoledronic acid [redacted].

In total, [redacted] of patients were recruited from the UK, and the patient baseline characteristics, disease characteristics, prior therapy and surgery at baseline and ET used in the trial population in monarchE are expected to be generalisable to UK clinical practice.

Table 6: Demographics of patients in the monarchE trial

Demographic Parameter[a]	Abemaciclib + ET (N=2,808)	ET alone (N=2,829)
Sex, n (%)	**n=2,808**	**n=2,829**
Female, n (%)	2,787 (99.3)	2,814 (99.5)
Male, n (%)	21 (0.7)	15 (0.5)
Age, years	**n=2,808**	**n=2,829**
Mean (SD)	[redacted]	[redacted]
Median (min, max)	51.0 (23, 89)	51.0 (22, 86)
Race, n (%)	**n=[redacted]**	**n=[redacted]**
American Indian or Alaska Native	[redacted]	[redacted]
Asian	675 (24.4)	669 (24.0)
Black or African American	[redacted]	[redacted]
Native Hawaiian or Other Pacific Islander	[redacted]	[redacted]
White	1,947 (70.3)	1,978 (71.0)
Multiple	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Region, n (%)	**n=2,808**	**n=2,829**
North America/Europe	1,470 (52.4)	1,479 (52.3)
Asia	574 (20.4)	582 (20.6)
Other	764 (27.2)	768 (27.1)
Ethnicity, n (%)[b]	**n=[redacted]**	**n=[redacted]**
Hispanic or Latino	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Menopausal status, n (%)	**n=2,803**	**n=2,829**
Premenopausal	1,221 (43.5)	1,232 (43.5)
Postmenopausal	1,587 (56.5)	1,597 (56.5)
Baseline ECOG PS, n (%)	**n=[redacted]**	**n=[redacted]**
0	2,405 (85.7)	2,369 (83.8)
1	401 (14.3)	455 (16.1)
2	[redacted]	[redacted]
3	[redacted]	[redacted]
Missing	[redacted]	[redacted]

Demographic Parameter[a]	Abemaciclib + ET (N=2,808)	ET alone (N=2,829)
Weight (kg)	**n=**	**n=**
Mean (SD)		
Median (min, max)		
BMI (kg/m^2)	**n=**	**n=**
Mean (SD)		
Median (min, max)		
Missing		
Country, n (%)	**n=**	**n=**
United Kingdom		

Abbreviations: BMI: body mass index; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ET: endocrine therapy; ITT: intent-to-treat; max: maximum; min: minimum; N: number of patients in the ITT population; n: number of patients within category; SD: standard deviation.
Footnotes: [a] Number of patients with non missing data, used as denominator; [b] Only includes responses from US sites, n is the number of subjects with a value of "HISPANIC OR LATINO" or "NOT HISPANIC OR LATINO".
Source: Lilly Data on File. Clinical Study Report: monarchE.[23] Data cut-off: 08 July 2020 (PO analysis)

Table 7: Summary of key baseline disease characteristics in monarchE

Baseline Disease Characteristic, n (%) unless otherwise specified	Abemaciclib + ET (N=2,808)	ET alone (N=2,829)
Initial pathological diagnosis		
Invasive ductal breast carcinoma		
Breast cancer, not otherwise specified		
Invasive lobular breast carcinoma		
Mucinous breast carcinoma		
Invasive papillary breast carcinoma		
Inflammatory carcinoma of the breast		
Medullary carcinoma of the breast		
Tubular breast carcinoma		
Paget's disease of nipple		
Metastatic breast carcinoma		[a]
Missing		
Primary tumour size by radiology prior to any systemic treatment, n	**n=**	**n=**
<20 mm		
≥20 mm but <50 mm		
≥50 mm		
Missing		
Primary tumour size by pathology after definitive surgery	**n=2,760**	**n=2,796**
<20 mm	781 (27.8)	767 (27.1)
≥20 mm but <50 mm	1,372 (48.9)	1,419 (50.2)
≥50 mm	607 (21.6)	610 (21.6)
Missing	48 (1.7)	33 (1.2)

Baseline Disease Characteristic, n (%) unless otherwise specified	Abemaciclib + ET (N=2,808)	ET alone (N=2,829)
Involvement of ipsilateral supraclavicular, ipsilateral infraclavicular, or ipsilateral internal mammary nodes at initial diagnosis		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Axillary lymph node evaluation		
Positive	2,800 (99.7)	2,822 (99.8)
Negative	7 (0.2)	7 (0.2)
Missing	[redacted]	0
Number of positive lymph nodes		
0	7 (0.2)	7 (0.2)
1-3	1,118 (39.8)	1,142 (40.4)
4-9	[redacted]	[redacted]
≥10	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Histopathological diagnosis grade		
G1 – favourable	209 (7.4)	216 (7.6)
G2 – moderately favourable	1,377 (49.0)	1,395 (49.3)
G3 – unfavourable	1,086 (38.7)	1,064 (37.6)
GX – cannot be accessed	126 (4.5)	141 (5.0)
Missing	10 (0.4)	13 (0.5)
Disease stage at initial diagnosis		
Stage IA	2 (0.1)	1 (0.0)
Stage IIA	324 (11.5)	353 (12.5)
Stage IIB	392 (14.0)	387 (13.7)
Stage IIIA	1,029 (36.6)	1,026 (36.3)
Stage IIIB	99 (3.5)	88 (3.1)
Stage IIIC	950 (33.8)	963 (34.0)
Missing	[redacted]	[redacted]
Oestrogen receptor status		
Positive	2,786 (99.2)	2,810 (99.3)
Negative	16 (0.6)	17 (0.6)
Unknown	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Progesterone receptor status		
Positive	2,426 (86.4)	2,456 (86.8)
Negative	298 (10.6)	295 (10.4)
Unknown	[redacted]	[redacted]
Missing	[redacted]	[redacted]
HER2 status at initial diagnosis		

Baseline Disease Characteristic, n (%) unless otherwise specified	Abemaciclib + ET (N=2,808)	ET alone (N=2,829)
Positive	[redacted]	[redacted]
Negative	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Central lab Ki-67 results from untreated tumour (%)		
<20%	953 (33.9)	974 (34.4)
≥20%	1,262 (44.9)	[redacted]
Missing	[redacted]	[redacted]
Not applicable[b]	[redacted]	[redacted]
Not evaluable[c]	[redacted]	[redacted]

Abbreviations: ET: endocrine therapy; G1: low combined histologic grade (favourable); G2: intermediate combined histologic grade (moderately favourable); G3: high combined histologic grade (unfavourable); GX: grade cannot be assessed; HER2: human epidermal growth factor receptor 2; ITT: intent-to-treat; N: number of patients in the ITT population; n: number of patients within category.
Footnotes: [a] This patient was enrolled due to a protocol deviation, as detailed in the CSR; [b] Not applicable was defined as <200 viable tumour cells present, and therefore the test was not performed; [c] Not evaluable was defined as >200 viable tumour cells present, but expression cannot be determined due to issue with section that obscures or prevents an accurate evaluation, such as damage, artifact, or washing off.
Source: Lilly Data on File. Clinical Study Report: monarchE.[23] Data cut-off: 08 July 2020 (PO analysis)

Table 8: Prior therapy and surgery for breast cancer monarchE ITT population

Prior Therapy, n (%)	Abemaciclib + ET (N=2,808)	ET alone (N=2,829)	Total (N=5,637)
Prior anticancer therapy			
Surgical procedure	[redacted]	[redacted]	[redacted]
Radiotherapy	2680 (95.4)	2700 (95.4)	5380 (95.4)
Systemic therapy	[redacted]	[redacted]	[redacted]
Surgical procedure: intent			
Curative intent	[redacted]	[redacted]	[redacted]
Radiotherapy: reason			
Neoadjuvant	71 (2.5)	82 (2.9)	153 (2.7)
Adjuvant	2,620 (93.3)	2,628 (92.9)	5,248 (93.1)
Systemic therapy: reason and type			
Neoadjuvant	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]
ET[a]	[redacted]	[redacted]	[redacted]
Other[b]	[redacted]	[redacted]	[redacted]
Target[c]	[redacted]	[redacted]	[redacted]
Adjuvant	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]
ET[a]	[redacted]	[redacted]	[redacted]
Other[b]	[redacted]	[redacted]	[redacted]
Target[c]	[redacted]	[redacted]	[redacted]
Term to be coded	[redacted]	[redacted]	[redacted]

Footnotes: [a] ET included patients treated with endocrine treatment and/or GnRH analogues; [b] "Other" is any other type of prior therapy not listed above; [c] "Target" is any prior therapy that is target therapy based on compound-wise documentation on systemic drugs.
Abbreviations: ET: endocrine therapy; GnRH: gonadotropin-releasing hormone; ITT: intent-to-treat; N: number of patients in the ITT population; n: number of patients within category.
Source: Lilly Data on File. Clinical Study Report: monarchE.[23] Data cut-off: 16 March 2020 (IA2 analysis).

Table 9: Summary of endocrine treatments in the monarchE safety population

n, (%)	Abemaciclib + ET (N=2,791)		ET (N=2,800)	
	At start of study	Any time	At start of study	Any time
Aromatase inhibitors	[redacted]	[redacted]	[redacted]	[redacted]
Anastrozole	[redacted]	[redacted]	[redacted]	[redacted]
Exemestane	[redacted]	[redacted]	[redacted]	[redacted]
Letrozole	[redacted]	[redacted]	[redacted]	[redacted]
Anti-oestrogens	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	[redacted]	[redacted]	[redacted]	[redacted]
Toremifene	[redacted]	[redacted]	[redacted]	[redacted]
GnRH Analogues	[redacted]	[redacted]	[redacted]	[redacted]
Goserelin	[redacted]	[redacted]	[redacted]	[redacted]
Leuprorelin	[redacted]	[redacted]	[redacted]	[redacted]
Triptorelin	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ET: endocrine therapy; GnRH: gonadotropin-releasing hormone; N: number of patients in the safety population; NA: not applicable.
Source: Lilly Data on File. Clinical Study Report: monarchE.[23] Data cut-off: 08 July 2020 (PO analysis).

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

The study was designed to compare the IDFS for abemaciclib + ET to that for ET alone. The study enrolled 5,637 patients in the intent to treat (ITT) population, with 2,808 assigned to the abemaciclib + ET arm and 2,829 assigned to the ET alone arm.

All efficacy analyses, including the primary endpoint of IDFS, were performed on the ITT population which included all randomised patients, and were performed by treatment arm. Safety was assessed in the safety population, which included patients who received at least one dose of study treatment (N=5,591).

The primary end point was IDFS per the Standardised Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials (STEEP) criteria[56] and was measured from the date of randomisation to the date of first occurrence of ipsilateral invasive breast tumour recurrence, local/regional invasive breast cancer recurrence, distant recurrence, death attributable to any cause, contralateral invasive breast cancer, or second primary non breast invasive cancer. Confirmation by biopsy or imaging was required, when possible.

All patients who experienced local recurrence of their disease continued to be followed for distant recurrence. DRFS, a secondary end point, was defined as the time from randomisation to distant recurrence or death from any cause, whichever occurred first. Patients for whom no event was observed were censored on the day of their last assessment for recurrence or date of

randomisation if no post-baseline assessment for recurrence occurred. Other secondary end points included OS, safety, pharmacokinetics (PK), and patient-reported outcomes (PROs).

The study was powered at approximately 85% to detect the superiority of abemaciclib + ET versus ET alone in terms of IDFS, assuming a hazard ratio (HR) of 0.73 at a cumulative two-sided alpha level of 0.05, with a 5-year IDFS rate of 82.5% in the control arm for this high-risk population.[60-62] This required approximately 390 IDFS events in the ITT population at the time of the primary analysis (PO). There were two planned efficacy interim analyses (IA1 and IA2) at approximately 50% and 75% of the total required events. The second efficacy interim analysis at approximately 293 IDFS events included an efficacy criterion for statistical significance. The overall type I error for the pre-planned interim analyses and primary analysis was maintained using the Lan–DeMets method with an O'Brien–Fleming stopping boundary. Efficacy analyses were performed on the ITT population. At the first efficacy interim analysis, the nominal one-sided alpha level was 0.0015 if exactly 195 IDFS events were observed. At the IA2, the nominal one-sided alpha level was 0.0092 if exactly 293 IDFS events were observed. If the analyses were performed at exactly 195, 293 and 390 events, then the one-sided boundary p-value at the final analysis will be 0.0220.

The primary objective was to test the superiority of abemaciclib + ET versus ET alone on IDFS using a log-rank test stratified by randomisation factors. A stratified Cox proportional hazard model with treatment arm as a variable was used to estimate the HR and the corresponding 95% CI. Analysis of the proportional hazards assumption for each endpoint is detailed in Section B.3.3.

The Kaplan–Meier method was used to estimate both the 2-year and 3-year IDFS rates in each treatment arm. Secondary endpoints in monarchE were IDFS for patients with high Ki-67 across monarchE (Ki67H), and for patients with high Ki-67 in Cohort 1 (C1-Ki67H). A sequential gate-keeping strategy was utilised to control the family-wise type I error at 0.025 (one-sided) for IDFS in the ITT, Ki67H and C1-Ki67H populations. Namely, IDFS was tested hierarchically in the order or ITT, Ki67H and C1-Ki67H, each gated after the former population.

Subgroup analyses of IDFS in the ITT population were performed for potential prognostic subgroup variables prespecified in the statistical analysis plan, including stratification factors and some clinicopathological features. HR estimates were reported within each subgroup, with p values for interaction tests across subgroups.

OS was also included as a gated secondary endpoint. A sequential gate-keeping strategy was utilised to control the overall type I error at 0.025 (one-sided) for the secondary endpoint OS in all randomised patients in Cohort 1 and Cohort 2. This means that OS was only to be tested if IDFS in the ITT, Ki67H and C1Ki67H populations were all significant.

DRFS was included as an additional secondary endpoint, evaluated using similar analyses to those performed for IDFS, but DRFS was not included as a gated secondary endpoint in the testing hierarchy. Safety was analysed in all randomly assigned patients who received at least one dose of study treatment (defined as either abemaciclib or ET after randomisation). Investigator reported terms were mapped to MedDRA terms, and AEs were graded according to Common Terminology Criteria Adverse Events v4.0.[53]

A summary of the trial populations considered in monarchE is provided in Table 10.

Table 10: Trial populations used for the analysis of outcomes of monarchE

Population	Description
Intent to treat (ITT)	All eligible patients enrolled into two cohorts (N=5,637)
Safety population	All included patients who received at least one dose of study treatment (N=5,591)

Abbreviations: ITT: intent to treat.
Source: Lilly Data on File. Clinical Study Report: monarchE[23]

B.2.5 *Quality assessment of the relevant clinical effectiveness evidence*

The monarchE trial and other relevant trials were assessed for quality using the Cochrane Risk-of-Bias assessment tool version 2.0, 2020.[63] The results of these quality assessments are presented in Appendix D. The overall risk of bias in the monarchE trial was considered to be low.

A summary of the quality of the monarchE trial is also presented in Table 11, using the criteria adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).

Table 11: Quality assessment of the monarchE trial

	monarchE
	Risk of bias
Bias arising from randomisation process	Low
Random allocation sequence	Yes
Allocation sequence concealed	Yes
Baseline differences	Probably no
Bias due to deviations from intended interventions – effect of assignment to intervention	Some concerns
Participant awareness	Yes
Delivery awareness	Yes
Deviations due to context	No information
Deviation balancing	NA
Affected outcomes	NA
Appropriate analysis	Yes
Substantial impact	NA
Bias due to deviations from intended interventions – effect of adhering to intervention	Low
Adherence participant awareness	Yes
Adherence delivery awareness	Yes
Adherence balancing	NA
Adherence affected outcome	NA
Non-adherence affected outcome	NA
Appropriate analysis	NA
Risk of bias due to missing outcome data	Low
Data randomised	Yes
No bias from missing data	NA
Missingness dependency	NA
Missingness likelihood	NA
Bias in measurement of the outcome	Low
Inappropriate method	No
Outcome difference	No

Assessor awareness	Yes
Assessment influence	Probably no
Influence likelihood	NA
Bias in selection of the reported result	Low
Appropriate analysis	Probably yes
Multiple outcomes	Probably no
Multiple analyses	Probably no
Overall bias	Some concerns

Abbreviations: NA: not applicable.

B.2.6 *Clinical effectiveness results of the relevant trials*

Summary of the clinical effectiveness evidence relevant to the decision problem

- The results of the monarchE study showed that abemaciclib + ET significantly improved IDFS for patients with hormone receptor positive (HR+), human epidermal growth receptor 2 negative (HER2−) early breast cancer at high risk of disease recurrence, when compared to ET alone
- At the time of the AFU1, abemaciclib + ET reduced the risk of developing invasive disease by 30.4% (stratified HR=0.696, 96% CI: 0.588, 0.823, nominal p-value [redacted]) compared to ET alone, with 2-year and 3-year IDFS rates of 92.7% vs 90.0% and 88.8% vs 83.4%, respectively. A total of 565 patients experienced IDFS events, including 232 (8.3%) in the abemaciclib + ET arm and 333 (11.8%) in the ET alone arm
- The primary IDFS endpoint was reached at the IA2. The IDFS results at the AFU1 were consistent with results observed at previous data cuts which showed a reduced risk of developing invasive disease of 25.3% at IA2 and 28.7% at the PO analysis
- DRFS was evaluated as a secondary endpoint in monarchE; at the AFU1, the results showed that abemaciclib + ET resulted in a 31.3% reduced risk of a patient experiencing a distant relapse (i.e. metastatic disease or death) (stratified HR=0.687, 95% CI: 0.571, 0.826). There was a clinically meaningful difference of 2.5% in the 2-year DRFS rates (94.1% and 91.6%) for patients treated with abemaciclib + ET, compared to ET alone, and a 4.2% difference in 3-year DRFS rates between abemaciclib + ET and ET alone (90.3% versus 86.1%)
- Given the early stage of cancer on trial entry and the natural timeline of breast cancer progression, OS data are inherently immature at the available data cuts, with a total of [redacted] OS events at the time of the AFU1. IDFS and DRFS are strong surrogates for OS and improvements in these measures are expected to translate into improvements in OS with longer-term follow-up. However, establishing evidence will require much longer follow-up, and OS data will not be mature during the timeframe of this appraisal
- HRQoL as measured by the FACT-B, FACT-ES and FACIT-F subscale scores, EQ-5D-5L index and Visual Analogue Score was consistent between treatment arms demonstrating that the addition of abemaciclib to ET did not impact the overall health status of patients during the trial

Data cuts

Following a regulatory request from the FDA for an assessment of the efficacy and safety of abemaciclib + ET with longer follow-up, an additional data cut (AFU1) was made. As such, the results from three data cuts are reported in this submission where relevant: IA2 (16 March 2020), PO (08 July 2020) and AFU1 (01 April 2021). At the time of the IA2, PO analysis and AFU1, the proportion of patients who had completed the 2-year study period was 12.5%, 25.5% and 72.2%, respectively. Results from the most recent data cut for each endpoint are reported in the following sections, and further detail on results from previous data cuts for each endpoint are reported in Appendix L.2.

B.2.6.1 Primary endpoint

Invasive disease-free survival

Summary of IDFS results in monarchE

A summary of IDFS in the ITT population at the time of the IA2, PO and AFU1 are shown in Table 12. The definite IDFS analysis was performed at the time of IA2, on the ITT population of

5,637 patients, of whom 2,808 received abemaciclib + ET and 2,829 received ET alone. The primary endpoint of IDFS was met for this study at the IA2 analysis, demonstrating a statistically significant improvement (two-sided p=[redacted]; stratified HR=0.747, 95% CI: 0.598, 0.932) in IDFS with abemaciclib + ET compared to ET alone. This benefit was greater at the time of the PO analysis (stratified HR=0.713, 95% CI: 0.583, 0.871) and this benefit deepened further with additional follow-up at AFU1.

Table 12: Summary of Investigator-Assessed IDFS Intent-to-Treat Population at IA2, PO and AFU1

	IA2			PO			AFU1		
	Abemaciclib + ET (N=2,808)	ET alone (N=2,829)	Treatment Effect/Difference 2-sided p-Value[e]	Abemaciclib + ET (N=2,808)	ET alone (N=2,829)	Treatment Effect/Difference 2-sided p-Value[e]	Abemaciclib + ET (N=2,808)	ET alone (N=2,829)	Treatment Effect/Difference 2-sided p-Value (nominal)[e]
Median follow up (months)	[redacted]	[redacted]	NA	19.1	19.2	NA	[redacted]	[redacted]	NA
p-value (2-sided) log-rank, stratified[b]	Stratified: p=.00957 [redacted]			Stratified: p=0.00089 [redacted]			[redacted]		
HR (95% CI)	Stratified: 0.747 (0.598, 0.932) [redacted]			Stratified: 0.713 (0.583, 0.871)[b] [redacted]			Stratified: 0.696 (0.588, 0.823) [redacted]		
IDFS rate, % (95% CI)[c]									
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	92.3 (90.9, 93.5)	89.3 (87.7, 90.7)	3.0 [redacted]	92.7 (91.6, 93.6)	90.0 (88.8, 91.1)	2.7 [redacted]
36 months	NE	NE	NE	NE	NE	NE	88.8 (87.0, 90.3)	83.4 (81.3, 85.3)	5.4 [redacted]

Footnotes: [a] Restriction time is defined by the latest time where the standard error of the survival estimates are ≤0.075; [b] Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [c] 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation; [d] 2-sided p-value based on normal approximation; [e] Treatment Effect/Difference/p-values are computed based on comparator ET.
Abbreviations: CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; IDFS: invasive disease-free survival; ITT: intent-to-treat; N: number of patients in the ITT population; NA: not applicable; NE: not evaluable.
Source: Lilly Data on File. Clinical Study Report: monarchE.[23] Data cut-off: 16 March 2020 (IA2), 08 July 2020 (PO analysis) and 01 April 2021 (AFU1 analysis).

IDFS results in monarchE at AFU1

At the AFU1, the benefit of abemaciclib + ET compared to ET alone on IDFS deepened further. A summary of IDFS in the ITT population at the time of AFU1 is shown in Table 13. A total of 565 patients experienced IDFS events, including 232 (8.3%) in the abemaciclib + ET arm and 333 (11.8%) in the ET alone arm. The median follow-up time was [redacted] months in abemaciclib + ET arm and [redacted] months in the ET alone arm. With the additional follow-up, abemaciclib + ET reduced the risk of developing invasive disease by [redacted]% (stratified HR=0.696, 95% CI: 0.588, 0.823) versus ET alone, together with a clinically meaningful improvement in the 2-year and 3-year IDFS rate: 92.7% vs 90.0% and 88.8% vs 83.4%, for abemaciclib + ET versus ET alone respectively.

In order to investigate the effect of abemaciclib over time, a piecewise analysis for IDFS was performed (Table 14). Based on the HRs from this analysis, this confirms that the treatment benefit of abemaciclib is maintained beyond the 2-year study period and the benefit deepens with longer follow-up.

K–M curves of IDFS for patients in the ITT population of monarchE who received either abemaciclib + ET or ET alone are displayed in Figure 5. The figure in the middle shows the curves with a truncated y-axis (70% to 100%) without any censoring ticks to better visualize the separation of curves. Analysis of the proportional hazards assumption between abemaciclib + ET versus ET alone is presented in Section B.3.3.

In summary, the benefit in terms of IDFS observed in the abemaciclib + ET arm, versus ET alone, in the ITT population observed at IA2 and PO continued to deepen, with additional follow-up at the time of the AFU1 IDFS analysis. The magnitude of treatment benefit continued to increase over time in the follow-up period, as reflected by the further improvement in IDFS rates at 3 years and robust effect size beyond the 2-year study treatment period. This treatment benefit was observed over a large sample size, with a total of 565 IDFS events observed.

Table 13: Summary of Investigator-Assessed IDFS ITT Population (AFU1 analysis)

	Abemaciclib + ET (N=2,808)	ET alone (N=2,829)	Treatment Effect/Difference 2-sided p-Value (nominal)[e]
Median follow up (months)	[redacted]	[redacted]	
Number of events, n (%)	232 (8.3)	333 (11.8)	
Deaths without invasive disease	[redacted]	[redacted]	
Invasive disease	[redacted]	[redacted]	
Number of patients censored, n (%)	[redacted]	[redacted]	
Invasive disease prior to randomisation	[redacted]	[redacted]	
No post-baseline assessment	[redacted]	[redacted]	
No documented invasive disease	[redacted]	[redacted]	
p-value (2-sided) log-rank, stratified[b]	[redacted]		
HR (95% CI)	Stratified: 0.696 (0.588, 0.823) [redacted]		
IDFS rate, % (95% CI)[c]			
12 months	[redacted]	[redacted]	[redacted]
24 months	92.7 (91.6, 93.6)	90.0 (88.8, 91.1)	2.7 [redacted]
36 months	88.8 (87.0, 90.3)	83.4 (81.3, 85.3)	5.4 [redacted]

Footnotes: [a] Restriction time is defined by the latest time where the standard error of the survival estimates are ≤0.075; [b] Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [c] 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation; [d] 2-sided p-value based on normal approximation; [e] Treatment Effect/Difference/p-values are computed based on comparator ET.
Abbreviations: CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; IDFS: invasive disease-free survival; ITT: intent-to-treat; N: number of patients in the ITT population.
Source: Lilly Data on File. Clinical Study Report: monarchE.[23] Data cut-off: 01 April 2021 (AFU1 analysis).

Table 14: Piecewise analysis of IDFS – ITT population (AFU1)

Analysis landmark	Number of events		Piecewise HR[a] (95% CI)[b]
	Abemaciclib + ET	ET alone	
Year 0–1	[redacted]	[redacted]	[redacted]
Year 1–2	[redacted]	[redacted]	[redacted]
Year 2+	[redacted]	[redacted]	[redacted]

Footnotes: [a] Piecewise HR was estimated using Bayesian piecewise exponential model for the yearly hazard rate within each treatment arm.; [b] 95% confidence intervals were calculated by equal tails in the posterior samples of Bayesian exponential models
Abbreviations: CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; IDFS: invasive disease-free survival; ITT: intent-to-treat; OS: overall survival.
Source: Lilly Data on File. Clinical Study Report: monarchE.[23] Data cut-off: 01 April 2021 (AFU1 analysis).

Figure 5: Summary of the IDFS results in monarchE (AFU1 analysis)

Abbreviations: ET: endocrine therapy; HR: hazard ratio; IDFS: invasive disease-free survival; ITT: intent-to-treat.
Source: Lilly Data on File. Clinical Study Report: monarchE.[23] Data cut-off: 01 April 2021 (AFU1 analysis).

B.2.6.2 Secondary endpoints for the ITT population in monarchE

A number of secondary endpoints were assessed in monarchE; some endpoints were assessed across both the ITT population and in prespecified groups of patients.

Secondary endpoints that were assessed across the ITT population in monarchE are considered below (Section B.2.6.2). Additional secondary endpoints in monarchE include IDFS for two prespecified groups of patients with high Ki-67, as detailed in Section B.2.4. These endpoints are not relevant for routine NHS clinical practice, but were included in the monarchE trial because they are potentially relevant for other countries worldwide. These endpoints are detailed for reference in Section B.2.6.3.

Distant relapse-free survival

Summary of DRFS results in monarchE

DRFS is an important secondary endpoint, as it measures the impact of treatment on reducing metastatic recurrence, which is incurable. According to the panel of breast cancer experts who developed the STEEP system, distant recurrence is a life-threatening disease and is strongly associated with OS.[56] Thus, the effect in preventing the development of distant recurrence events is expected to translate to the survival benefit, after longer term follow-up and, as such, DRFS is seen as a strong surrogate for subsequent OS outcomes.

A summary of DRFS at the time of the PO and AFU1 is shown in Table 15. At AFU1, the benefit of abemaciclib + ET in reducing the risk of developing a distant relapse was maintained with the longer follow-up time.

Table 15: Summary of Investigator-Assessed DRFS ITT Population at PO and AFU1

	PO			AFU1		
	Abemaciclib + ET (N=2,808)	ET alone (N=2,829)	Treatment Effect/Difference 2-sided p-Value[f]	Abemaciclib + ET (N=2,808)	ET alone (N=2,829)	Treatment Effect/Difference 2-sided p-Value (nominal)[f]
Number of events, n (%)	131 (4.7)	193 (6.8)	NA	191 (6.8)	278 (9.8)	NA
p-value (2-sided) log-rank	Stratified p=0.00088 [redacted]			[redacted]		
HR (95% CI)	Stratified: 0.687 (0.551, 0.858) [redacted]			Stratified: 0.687 (0.571, 0.826) [redacted]		
DRFS rate, % (95% CI)[d]						
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	93.8 (92.6, 94.9)	90.8 (89.3, 92.1)	3.0 [redacted]	94.1 (93.2, 95.0)	91.6 (90.5, 92.6)	2.5 [redacted]
36 months	NE	NE	NE	90.3 (88.6, 91.8)	86.1 (84.2, 87.9)	4.2 ([redacted]

Footnotes: [a] For minimum and maximum, + indicates a censored observation; [b] Restriction time is defined by the latest time where the standard error of the survival estimates is ≤0.075; [c] Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [d] 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation; [e] 2-sided p-value based on normal approximation; [f] Treatment Effect/Difference/p-values are computed based on comparator ET.
Abbreviations: CI: confidence interval; DRFS: distant relapse-free survival; ET: endocrine therapy; ITT: intent-to-treat; IWRS: interactive web-response system; N: number of patients in the ITT population; n: number of patients in the specific population; NE: not evaluable.
Source: Lilly Data on File. Clinical Study Report: monarchE.[23] Data cut-off: 08 July 2020 (PO analysis) and 01 April 2021 (AFU1).

DRFS results in monarchE at AFU1

At AFU1, 496 DRFS events were observed, including 191 in the abemaciclib + ET arm and 278 in the ET alone arm. A summary of DRFS at AFU1 is shown in Table 16. There was a clinically meaningful benefit in DRFS (stratified HR=0.687, 95% CI: 0.571, 0.826), reflecting a 31.3% reduction in the risk of developing distant relapse, and a 2.5% difference in 2-year DRFS rates (94.1% versus 91.6%) for patients treated with abemaciclib + ET, compared to patients treated with ET alone. Additionally, there was a 4.2% difference in 3-year DRFS rates between abemaciclib + ET and ET alone (90.3% versus 86.1%).

A piecewise analysis for DRFS was also performed to explore the impact of abemaciclib on DRFS over time and the results are presented in Table 17. The results showed that the HRs within the first, second and third year indicate that the benefit of abemaciclib deepens with longer-follow up and confirms that the benefit of abemaciclib on DRFS is maintained beyond the two-year study period.

K–M curves of DRFS for patients in the ITT population receiving either abemaciclib + ET or ET alone are displayed in Figure 6. The figure in the middle shows the curves with a truncated y-axis (70% to 100%) without any censoring ticks to better visualize the separation of curves.

In summary, a greater treatment benefit in DRFS was observed in the ITT population for patients treated with abemaciclib + ET, at the time of the AFU1 DRFS analysis. For patients with early breast cancer at high risk of recurrence, this clinically meaningful DRFS effect demonstrates the impact of adding abemaciclib to ET on reducing the risk of developing metastatic recurrence, which is incurable, or death. At the AFU1, there were 278 patients in the ET alone arm who had developed incurable and likely fatal metastatic disease or death, compared to 191 in the abemaciclib + ET arm. According to the panel of breast cancer experts who developed the STEEP system, these benefits in DRFS are expected to translate into OS benefits after longer term follow-up.[56]

Table 16: Summary of Investigator-Assessed DRFS ITT Population (AFU1 analysis)

	Abemaciclib + ET (N=2,808)	ET alone (N=2,829)	Treatment Effect/Difference 2-sided p-Value (nominal)[f]
Number of events, n (%)	191 (6.8)	278 (9.8)	
Death without distant relapse	[redacted]	[redacted]	
Distant relapse	[redacted]	[redacted]	
Number of patients censored, n (%)	[redacted]	[redacted]	
Distant relapse prior to randomisation	[redacted]	[redacted]	
No post-baseline assessment	[redacted]	[redacted]	
No documented distant relapse with regular assessment	[redacted]	[redacted]	
Minimum, months[a]	[redacted]	[redacted]	
25th percentile (95% CI)	[redacted]	[redacted]	
Median (95% CI) months	[redacted]	[redacted]	
75% percentile (95% CI)	[redacted]	[redacted]	
Maximum, months[a]	[redacted]	[redacted]	
p-value (2-sided) log-rank	[redacted]		
HR (95% CI)	Stratified: 0.687 (0.571, 0.826) [redacted]		
DRFS rate, % (95% CI)[d]			
12 months	[redacted]	[redacted]	[redacted]
24 months	94.1 (93.2, 95.0)	91.6 (90.5, 92.6)	2.5 [redacted]
36 months	90.3 (88.6, 91.8)	86.1 (84.2, 87.9)	4.2 [redacted]

			[redacted]

Footnotes: [a] For minimum and maximum, + indicates a censored observation; [b] Restriction time is defined by the latest time where the standard error of the survival estimates is ≤0.075; [c] Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [d] 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation; [e] 2-sided p-value based on normal approximation; [f] Treatment Effect/Difference/p-values are computed based on comparator ET.
Abbreviations: CI: confidence interval; DRFS: distant relapse-free survival; ET: endocrine therapy; ITT: intent-to-treat; IWRS: interactive web-response system; N: number of patients in the ITT population; n: number of patients in the specific population.
Source: Lilly Data on File. Clinical Study Report: monarchE.[23] Data cut-off: 01 April 2021 (AFU1 analysis).

Table 17: DRFS piecewise analysis – ITT population (AFU1)

Analysis landmark	Number of events		Piecewise HR[a] (95% CI)[b]
	Abemaciclib + ET	ET alone	
Year 0–1	[redacted]	[redacted]	[redacted]
Year 1–2	[redacted]	[redacted]	[redacted]
Year 2+	[redacted]	[redacted]	[redacted]

Footnotes: [a] Piecewise HR was estimated using Bayesian piecewise exponential model for the yearly hazard rate within each treatment arm.; [b] 95% confidence intervals were calculated by equal tails in the posterior samples of Bayesian exponential models
Abbreviations: CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; DRFS: distant relapse-free survival; ITT: intent-to-treat; OS: overall survival.
Source: Lilly Data on File. Clinical Study Report: monarchE.[23] Data cut-off: 01 April 2021 (AFU1 analysis).

Figure 6: Summary of the DRFS results in monarchE (AFU1 analysis)

Abbreviations: DRFS: distant relapse-free survival; ET: endocrine therapy; HR: hazard ratio; ITT: intent-to-treat.
Source: Lilly Data on File. Clinical Study Report: monarchE.[23] Data cut-off: 01 April 2021 (AFU1 analysis).

Overall survival

As part of the sequential gate-keeping testing (Section B.2.4) OS in the ITT population was planned to be tested after IDFS in the ITT and the two prespecified high Ki-67 subgroups (Section B.2.6.3) were all statistically significant.

At the time of the PO analysis, there were no significant differences in these OS data between the two treatment arms. Despite the longer duration of follow-up at AFU1 (36 months), the OS data remained immature with a [redacted]% event rate and [redacted]% of the [redacted] events required for the final OS analysis. It should be noted that patients with HR+, HER2− metastatic breast cancer have a median OS ranging between 3 to 5 years, based on RWE and trials of CDK 4/6 inhibitors in the metastatic setting.[20, 51, 64] Considering that patients may first spend a number of years in the early breast cancer setting before progressing to metastatic breast cancer, it is evident that insufficient time has passed for the 3-year OS data in monarchE to capture any treatment effect of abemaciclib on OS.

However, as outlined in Section B.2.6.1 and Section B.2.6.2, while no significant differences in OS were observed, the improvements in IDFS and DRFS observed for abemaciclib + ET versus ET alone would be expected to translate into improvements in OS in the long-term. A summary of OS at AFU1 is shown in Table 18. There were [redacted] deaths ([redacted]%) in the ITT population: [redacted] deaths ([redacted]%) in the abemaciclib + ET arm, and [redacted] deaths ([redacted]%) in the ET alone arm, representing an absolute difference of [redacted] deaths between the two arms. Among patients who received at least 1 dose of study treatment, there were fewer deaths due to study disease in the abemaciclib + ET arm ([redacted] deaths) compared to the ET alone arm ([redacted] deaths). However, the OS data is still immature.

The global COVID-19 pandemic impacted patient safety at AFU1 to a greater degree than at prior analyses due to the longer length of time since the onset of the pandemic. The impact of this on patient safety should be taken into consideration. There were [redacted] deaths with investigator

reported terms of infections confirmed or suspected due to COVID-19: [redacted] in the abemaciclib + ET arm and [redacted] in the ET alone arm. A COVID-19 sensitivity analysis was performed for OS by censoring the patients who died due to confirmed or suspected COVID-19 on the day prior to their deaths. The results of the sensitivity analysis are displayed in Table 19. After censoring for COVID-19 related deaths, the number of OS events was [redacted] in the abemaciclib + ET arm and [redacted] in the ET alone arm, reducing the absolute difference to only [redacted] events, and the estimated OS hazard ratio was [redacted]).[23]

K–M curves of OS in the ITT population at AFU1 are displayed in Figure 7.

Table 18: Summary of overall survival in the ITT population (AFU1 analysis)

	Abemaciclib + ET (N=2,808)	ET alone (N=2,829)	Treatment Effect/Difference 2-sided p-Value (nominal)[e]
Number of events, n (%)	[redacted]	[redacted]	
Deaths	[redacted]	[redacted]	
Number of patients censored, n (%)	[redacted]	[redacted]	
Alive	[redacted]	[redacted]	
Lost to follow-up	[redacted]	[redacted]	
Withdrawal by subject	[redacted]	[redacted]	
p-value (2-sided) log-rank, stratified[b]	[redacted]		
HR (95% CI)	[redacted]		
Overall survival rate, % (95% CI)[c]			
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
30 months	[redacted]	[redacted]	[redacted]

Footnotes: [a] Restriction time is defined by the latest time where the standard error of the survival estimates are ≤0.075; [b] Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [c] 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation; [d] 2-sided p-value based on normal approximation; [e] Treatment Effect/Difference/p-values are computed based on comparator ET.
Abbreviations: CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; IDFS: invasive disease-free survival; ITT: intent-to-treat; N: number of patients in the ITT population.
Source: Lilly Data on File. Clinical Study Report: monarchE.[23] Data cut-off: 01 April 2021 (AFU1 analysis).

Table 19: Summary of overall survival in the ITT population (including a COVID-19 sensitivity analysis) (AFU1 analysis)

Events, n (%)		ET alone (N=2,829)	Treatment Effect[a]

	Abemaciclib + ET (N=2,808)		Stratified HR (95% CI)[b]	2-sided p-value (nominal)[b]
OS	[redacted]	[redacted]	[redacted]	[redacted]
OS: COVID-19 sensitivity analysis[c]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a]Treatment effect in terms of HR estimates and p-values are computed based on comparator ET; [b] Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [c] patients who died due to suspected or reported COVID-19 were censored on the day prior to their deaths.
Abbreviations: CI: confidence interval; COVID-19: coronavirus, SARS-CoV-2; ET: endocrine therapy; HR: hazard ratio; ITT: intent-to-treat; N: number of patients in the ITT population; OS: overall survival.
Source: Lilly Data on File. Clinical Study Report: monarchE.[23] Data cut-off: 01 April 2021 (AFU1 analysis).

Figure 7: Summary of the OS results in monarchE (AFU1 analysis)

Abbreviations: #: number; CI: confidence interval; ET: endocrine therapy; HR: hazard ratio.
Source: Lilly Data on File. Clinical Study Report: monarchE.[23] Data cut-off: 01 April 2021 (AFU1 analysis).

B.2.6.3 Secondary IDFS analyses for patients with high Ki-67

There were two prespecified secondary IDFS analyses in monarchE:

- IDFS for patients with high (≥20%) Ki-67 (Cohort 1 or 2)
- IDFS for patients with high (≥20%) Ki-67 (Cohort 1)

IDFS endpoints for patients with high Ki-67 are not relevant for routine NHS clinical practice, because Ki-67 is not routinely tested for in the UK. These endpoints were included in the global monarchE trial as an exploratory analysis for predictive power and because they are potentially relevant for other countries worldwide. As these were included as secondary endpoints in monarchE, the results are presented for reference below.

IDFS for patients with high Ki-67 (Cohort 1 or 2)

Ki-67 is a protein biomarker that is used as a measure for proliferation rate of breast cancer cells, can be used to predict patients at high risk and was used as one inclusion criterion in the monarchE trial. IDFS in patients with Ki-67 index ≥20% in either Cohort 1 and Cohort 2 (Ki67H

population) was evaluated to test the superiority of abemaciclib + ET versus ET alone for patients with high Ki-67 index. To control the overall type-I error at 0.05 (2-sided), a gate-keeping strategy was used so that IDFS in Ki67H population was tested only if IDFS in ITT population was statistically significant. When IDFS in the ITT population was declared positive at IA2, statistical significance for IDFS in Ki67H population was not achieved and thus was re-evaluated at the PO IDFS analysis.

The secondary efficacy objective of IDFS in the Ki67H population was met at the PO IDFS analysis, demonstrating a statistically significant and clinically meaningful improvement in IDFS with abemaciclib + ET compared to ET alone (2-sided p=0.0111). This improvement continued with the longer follow-up at the AFU1. At the time of the AFU1, among the 2,498 patients in the Ki67H population, 290 IDFS events were observed, with 118 events in the abemaciclib + ET arm and 172 events in the ET alone arm. Abemaciclib + ET reduced the risk of developing invasive disease in patients with high Ki-67 tumours by [redacted]% (stratified HR=0.663, 95% CI: 0.524, 0.839), together with a clinically meaningful improvement in the 2-year IDFS rate (91.9% versus 87.9%) and the 3-year IDFS rate (86.8% versus 80.8%).[23] The full summary of IDFS in the Ki67H population at AFU1 is presented in Table 20.

Table 20: Summary of investigator-assessed IDFS in the Ki-67 high population (AFU1 analysis)

	Abemaciclib + ET (N=1,262)	ET (N=1,236)	Treatment Effect/Difference 2-sided p-Value (nominal)[e]
Number of events, n (%)	118 (9.4)	172 (13.9)	
Deaths without invasive disease	[redacted]	[redacted]	
Invasive disease	[redacted]	[redacted]	
Number of patients censored, n (%)	[redacted]	[redacted]	
Invasive disease prior to randomisation	[redacted]	[redacted]	
No post-baseline assessment	[redacted]	[redacted]	
No documented invasive disease	[redacted]	[redacted]	
p-value (2-sided) log-rank	Stratified[b]: p=0.00057 Unstratified: [redacted]		
HR (95% CI)	Stratified[b]: 0.663 (0.524, 0.839) Unstratified: [redacted]		
IDFS rate, % (95% CI)[c]			
12 months	[redacted]	[redacted]	[redacted]
24 months	91.9 [redacted]	87.9 [redacted]	4.0 [redacted]
36 months	86.8 [redacted]	80.8 [redacted]	6.0 [redacted]

Footnotes: [a] Restriction time is defined by the latest time where the standard error of the survival estimates is ≤0.075; [b] Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [c] 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation; [d] 2-sided p-value based on normal approximation; [e] Treatment Effect/Difference/p-values are computed based on comparator ET.
Abbreviations: CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; IDFS: invasive disease-free survival; ITT: intent-to-treat; IWRS: interactive web-response system; N: number of patients in the ITT population with high Ki-67 index; n: number of patients in specific population.
Source: Lilly Data on File. Clinical Study Report: monarchE.[23] Data cut-off: 01 April 2021 (AFU1 analysis).

IDFS for patients with high Ki-67 (Cohort 1)

Another secondary endpoint in the gated analysis is to evaluate IDFS for patients with Ki-67 index ≥20% in Cohort 1 (C1-Ki67H population). To control the overall type-I error at 0.05 (2-sided), this endpoint was gated after IDFS in the ITT and Ki67H populations. IDFS in C1-Ki67H population was to be tested only if IDFS in both the ITT and Ki67H populations were statistically significant.

The secondary endpoint of IDFS in the C1-Ki67H population was met for this study at the PO IDFS analysis (2-sided p=0.0042), demonstrating a statistically significant and clinically meaningful improvement in IDFS with abemaciclib + ET compared to ET alone. At the AFU1, the C1-Ki67H population continued to a demonstrate substantial treatment benefit in terms of IDFS. At the time of the AFU1, among the 2,003 patients in C1-Ki67H population, 262 IDFS events were observed, with 104 events in the abemaciclib + ET arm and 158 events in ET alone arm. Abemaciclib + ET reduced the risk of developing invasive disease in Cohort 1 patients with high Ki-67 tumours by [redacted]% (stratified HR=0.631, 95% CI: 0.493, 0.809), together with a clinically meaningful improvement in the 2-year IDFS rate (91.5% versus 86.4%) and the 3-year IDFS rate (86.1% versus 79.0%). The full summary of IDFS in the C1-Ki67H population at AFU1 is presented in Table 21.

Nevertheless, Ki-67 is not currently routinely tested for in the UK. Given the statistically significant and clinically meaningful benefit in IDFS observed across the ITT population of monarchE, Lilly is proposing abemaciclib, in combination with ET, as a treatment option for patients in the UK with HR+, HER2−, node-positive early breast cancer at a high risk of recurrence. Lilly proposes that breast cancer at high risk of recurrence should be defined as pathological tumour involvement in ≥4 ipsilateral axial lymph nodes (ALNs), or pathological tumour involvement in 1–3 ALNs as well as at least one of the following indicators of high disease recurrence risk; Grade 3 disease or primary tumour size ≥5 cm, irrespective of Ki-67 status.

Table 21: Summary of investigator-assessed IDFS in the Ki-67 high population of Cohort 1 (AFU1 analysis)

	Abemaciclib + ET (N=1,262)	ET (N=1,236)	Treatment Effect/Difference 2-sided nominal p-Value (nominal)[e]
Number of events, n (%)	104 (10.2)	158 (16.0)	
Deaths without invasive disease	[redacted]	[redacted]	
Invasive disease	[redacted]	[redacted]	
Number of patients censored, n (%)	[redacted]	[redacted]	

	Abemaciclib + ET (N=1,262)	ET (N=1,236)	Treatment Effect/Difference 2-sided nominal p-Value (nominal)[e]
Invasive disease prior to randomisation	[redacted]	[redacted]	
No post-baseline assessment	[redacted]	[redacted]	
No documented invasive disease	[redacted]	[redacted]	
p-value (2-sided) log-rank	Stratified[b]: p = 0.00020 [redacted]		
HR (95% CI)	Stratified[b]: 0.626 (0.488, 0.803) [redacted]		
IDFS rate, % (95% CI)[c]			
12 months	[redacted]	[redacted]	[redacted]
24 months	91.5 [redacted]	86.4 [redacted]	5.1 [redacted]
36 months	86.1 [redacted]	79.0 [redacted]	7.1 [redacted]

Footnotes: [a] Restriction time is defined by the latest time where the standard error of the survival estimates is ≤0.075; [b] Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [c] 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation; [d] 2-sided p-value based on normal approximation; [e] Treatment Effect/Difference/p-values are computed based on comparator ET.
Abbreviations: CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; IDFS: invasive disease-free survival; ITT: intent-to-treat; IWRS: interactive web-response system; N: number of patients in the Cohort 1 with high Ki-67 index; n: number of patients in specific population.
Source: Lilly Data on File. Clinical Study Report: monarchE.[23] Data cut-off: 01 April 2021 (AFU1 analysis).

B.2.6.4 Patient-reported outcomes

PRO endpoints were not analysed at the AFU1, so the results in the following section are from the PO analysis.

FACT-B, FACT-ES and FACIT-F summary scores

The mean scores for the FACT-B, FACT-ES and FACIT-F subscales are shown in Table 22, Table 23 and Table 24 respectively. The mean scores and changes from baseline scores were [redacted] in both arms for all measures. Changes in the Well-being scores, Breast Cancer Subscale, Trial Outcome Index, and FACT-B Total Score were [redacted] the minimally important difference (MID) of [redacted] of the baseline SD. Changes in FACT-ES and FACIT-F Total Score were [redacted] than the MID of [redacted] of the baseline SD.

In terms of Item HI7, “I feel fatigue”, mean scores within both arms remained around [redacted] for subsequent visits, indicating patients in both arms felt fatigue [redacted]. For bladder items BL1, “I have trouble controlling urine” BL2, “I urinate more frequently than usual”, and P8, “My problems with urinating limit my usual activities” mean scores in both arms were around [redacted] for all post-baseline visits, indicating most patients reported [redacted] when asked to describe any

urination issues. The cognitive items HI9, “I have trouble remembering things” and M9, “I have difficulty thinking clearly (remembering, concentrating)” were evaluated as a measure of cognitive symptoms. The baseline and all post-baseline scores for HI9 and M9 indicated cognitive symptoms were numerically [redacted] between arms, being around [redacted], indicating patients experience these cognitive symptoms [redacted].

These data support that the overall health status of patients was maintained throughout the study in both treatment arms, and therefore that the addition of abemaciclib may maintain patient HRQoL compared to ET alone.

Table 22: FACT-B summary scores (PO analysis)

FACT-B Total Score	Abemaciclib + ET (N=2,791)			ET alone (N=2,800)		Abemaciclib + ET *versus* ET alone	
	n	Mean (SD)	CfB, LSM (SE)	n	Mean (SD)	CfB, LSM (SE)	LSM Change Difference (SE)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 6 (3 months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 9 (6 months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 15 (12 months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 21 (18 months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All post-baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CfB: change from baseline; ET: endocrine therapy; FACT-B: Functional Assessment of Cancer Therapy – Breast; LSM: least-squares mean; N: number of patients in the safety population; NA: not applicable; NE: not evaluated; SD: standard deviation; SE: standard error.
Source: Lilly Data on File. Clinical Study Report: monarchE.[23] Data cut-off: 08 July 2020 (PO analysis).

Table 23 FACT-ES summary scores (PO analysis)

FACT-ES Total Score	Abemaciclib + ET (N=2,791)			ET alone (N=2,800)		Abemaciclib + ET *versus* ET alone	
	n	Mean (SD)	CfB, LSM (SE)	n	Mean (SD)	CfB, LSM (SE)	LSM Change Difference (SE)
ESS-19[a]							
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 6 (3 months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 9 (6 months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 15 (12 months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 21 (18 months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All post-baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ESS-23[b]							
Baseline	[redacted]						
Visit 6 (3 months)	[redacted]						
Visit 9 (6 months)	[redacted]						
Visit 15 (12 months)	[redacted]						
Visit 21 (18 months)	[redacted]						
All post-baseline	[redacted]						

Footnotes: [a] 19-item Endocrine Symptom Subscale; [b]23-item Endocrine Symptom Subscale, based on the same items as the ESS-19 plus the following 4 items of Physical Well-Being in FACT-B: i) item GP1 "I have lack of energy", ii) item GP2, "I have nausea", iii) item GP4, "I have pain", and iv) item GP5, "I am bothered by side effects of treatment"
Abbreviations: CfB: change from baseline; ET: endocrine therapy; FACT-B: Functional Assessment of Cancer Therapy – Breast; FACT-ES: Functional Assessment of Cancer Therapy – Endocrine Subscale; LSM: least-squares mean; N: number of patients in the safety population; NA: not applicable; NE: not evaluated; SD: standard deviation; SE: standard error.
Source: Lilly Data on File. Clinical Study Report: monarchE.[23] Data cut-off: 08 July 2020 (PO analysis)

Table 24: FACIT-F summary scores (PO analysis)

FACIT-F Total Score	Abemaciclib + ET (N=2,791)			ET alone (N=2,800)		Abemaciclib + ET *versus* ET alone	
	n	Mean (SD)	CfB, LSM (SE)	n	Mean (SD)	CfB, LSM (SE)	LSM Change Difference (SE)
Baseline	[redacted]						
Visit 6 (3 months)	[redacted]						
Visit 9 (6 months)	[redacted]						
Visit 15 (12 months)	[redacted]						
Visit 21 (18 months)	[redacted]						
All post-baseline	[redacted]						

Abbreviations: CfB: change from baseline ET: endocrine therapy; FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue; LSM: least-squares mean; N: number of patients in the safety population; NA: not applicable; NE: not evaluated; SD: standard deviation; SE: standard error.
Source: Lilly Data on File. Clinical Study Report: monarchE.[23] Data cut-off: 08 July 2020 (PO analysis).

EQ-5D-5L

The method of administration of the EQ-5D-5L instrument is summarised in Section B.2.3.1 and full details of the collection protocol, instrument scoring, and compliance are available in Appendix L. In accordance with the NICE position statement on the use of the EQ-5D-5L, the EQ-5D-5L data presented below were then cross-walked to the EQ-5D-3L prior to their inclusion in the economic model, using the Van Hout et al. (2012) approach, as detailed in Section

B.3.4.[65, 66] The EQ-5D-3L data were then valued using Dolan et al (1997), which provides the standard UK EQ-5D-3L weights.

The full EQ-5D-5L subscale scores for monarchE are presented in Appendix L.4. EQ-5D-5L index values were very similar between arms for all baseline and post-baseline assessments (Table 25). Overall, index values in most post-baseline assessments were stable and similar to baseline values for both treatment arms. The VAS demonstrated similar results as the index value; scores were similar between the two treatment arms for all baseline and post-baseline visits.

These data support that the overall health status of patients was maintained throughout the study in both treatment arms, and therefore that the addition of abemaciclib may be tolerable and maintain patient HRQoL compared to ET alone.

Table 25. Summary of EQ-5D-5L Index and Visual Analogue Scale in monarchE, safety population (PO analysis)

	Baseline Score Mean (SD)		Within-treatment Group Change from Baseline[a] LSM (SE)		Between- treatment Group Change Difference (Abemaciclib + ET vs ET alone)[a,b]		
	Abemaciclib + ET	ET Alone	Abemaciclib + ET	ET Alone	LS M (SE)	95% CI	p-Value[c]
EQ-5D-5L Health State Index	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visual analogue scale	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D 5L: EuroQol 5-Dimension 5-Level; LSM: least squares mean; SE: standard error; SD: standard deviation.
Footnotes: [a]Across all post-baseline visits; [b]A positive between treatment difference favours abemaciclib + ET; [c]p-Values are from Type 3 sums of squares mixed models repeated measures model: Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.
Source: Lilly Data on File. Clinical Study Report: monarchE.[1] Data cut-off: 08 July 2020 (PO analysis).

B.2.7 *Subgroup analysis*

Subgroup analysis of final invasive disease-free survival

No statistically significant interactions were observed, supporting a consistent treatment benefit across all pre-specified subgroups within the ITT population. See Figure 8 for a subgroup forest plot of IDFS – ITT population. This suggests that the addition of abemaciclib to ET translates to a reduction in the risk of disease recurrence in all the subgroups analysed, including patients from different regions and pre- and post- menopausal women. There were a few subgroups with hazard ratio point estimates greater than 1 and wide confidence intervals, primarily driven by the small number of events observed within those subgroups. Of note, sex was not a pre-specified subgroup due to the small sample size of male patients enrolled in this study.

Figure 8: Subgroup forest plot of IDFS – ITT population (AFU1)

Abbreviations: CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ET: endocrine therapy; IDFS: invasive disease-free survival; ITT: intent-to-treat; IWRS: interactive web-response system; NA: North America; n: number of patients in the specific population.
Source: Lilly Data on File. Clinical Study Report: monarchE.[23] Data cut-off: 01 April 2021 (AFU1 analysis).

Subgroup analysis of distant relapse-free survival

The majority of prespecified subgroups analysed showed consistent DRFS effects favouring abemaciclib + ET, with two exceptions. Consistent with what was observed in the subgroup analysis of IDFS, the addition of abemaciclib to ET translates to a reduction in the risk of developing DRFS events in all subgroups analysed, including patients from different regions and pre- and post- menopausal women. The two subgroups with hazard ratio point estimates greater than one, had wide confidence intervals and a limited number of observed events. No statistically significant interactions were observed, supporting a consistent treatment benefit with the ITT population. See Figure 9 for a subgroup forest plot of DRFS in the ITT population.

Figure 9: Subgroup Forest plot of DRFS – ITT Population (AFU1)

Abbreviations: CI: confidence interval; DRFS: distant relapse-free survival; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ET: endocrine therapy; ITT: intent-to-treat; IWRS: interactive web-response system; NA: North America; n: number of patients in the specific population.
Source: Lilly Data on File. Clinical Study Report: monarchE.[23] Data cut-off: 01 April 2021 (AFU1 analysis).

B.2.8 *Meta-analysis*

This section is not applicable as no pooling of trials will be undertaken.

B.2.9 *Indirect and mixed treatment comparisons*

This section is not applicable, as no indirect or mixed treatment comparisons are being conducted.

B.2.10 *Adverse reactions*

Summary of the safety evidence

- In the safety population, 98.4% of patients in the abemaciclib + ET arm (N=2,791) had ≥1 TEAE during the study, as well as 88.8% of patients in the ET alone arm (N=2,800).
- While TEAEs in both arms were predominantly of low grade, the incidence of grade ≥3 TEAEs was greater in the abemaciclib + ET arm (46.0% grade 3, [redacted]% grade 4) than in the ET alone arm (15.5% grade 3, [redacted]% grade 4).
- The most frequent TEAEs of any grade reported by the investigator in the abemaciclib + ET arm (versus the ET arm) were diarrhoea (83.5%, versus 8.6% in the ET arm), infections/infestations ([redacted]%, versus [redacted]% in the ET arm), neutropenia (45.8%, versus 5.6% in the ET arm) and fatigue (40.6%, versus 17.8% in the ET arm).
- The most frequent TEAEs in the ET arm (versus the abemaciclib + ET arm) were musculoskeletal and connective tissue disorders ([redacted]%, versus [redacted]% in the abemaciclib + ET arm) and infections and infestations ([redacted]%, versus [redacted]% in the abemaciclib + ET arm).
- The majority of diarrhoea events in the abemaciclib + ET arm were grade 1 or 2 in severity ([redacted]%). In the abemaciclib + ET arm, 146 patients (5.2%) discontinued abemaciclib or all study treatment (abemaciclib and ET) because of diarrhoea, suggesting that this TEAE was manageable and acceptable for the majority of patients.
- Neutropenia was experienced as a TEAE by 1,278 patients (45.8%) treated with abemaciclib + ET and 157 patients (5.6%) treated with ET alone. Of the patients in the abemaciclib + ET arm [redacted] ([redacted]%) reported Grade ≥3 neutropenia and [redacted] ([redacted]%) required dose modification due to neutropenia. However, only [redacted] patients ([redacted]%) discontinued abemaciclib or all treatment due to neutropenia, indicating that as a TEAE, neutropenia was manageable.
- The incidence of SAEs was higher in the abemaciclib + ET arm (15.2%) as compared with the ET alone arm (8.8%). Venous thrombolytic events (VTE) and pneumonia were the most commonly reported SAEs by patients treated with abemaciclib + ET ([redacted]% and [redacted]% of patients experienced VTE and pneumonia, respectively). Patients treated with ET alone reported pneumonia ([redacted]% [[redacted]/2,800]), cellulitis ([redacted]% [[redacted]/2,800]) and VTE ([redacted]% [[redacted]/2,800]) most commonly.
- In the abemaciclib + ET arm, [redacted] patients ([redacted]%) discontinued abemaciclib alone or abemaciclib + ET due to AEs, and 181 patients (6.5%) discontinued both abemaciclib + ET due to an AE. In comparison, 30 patients (1.1%) receiving ET alone discontinued ET due to AEs.
- Deaths due to AEs while on the study or within 30 days of treatment discontinuation at AFU1 were reported for [redacted] patients ([redacted]%) in the abemaciclib + ET, and [redacted] patients ([redacted]%) in the ET alone arm. The cause of death was generally considered to be confounded by multiple comorbid factors.
- Overall, abemaciclib + ET had a treatment-emergent adverse event (TEAE) profile in line with previous studies of abemaciclib in advanced breast cancer where it is part of routine NHS clinical practice.

B.2.10.1 Safety results informing the decision problem

The safety of abemaciclib + ET in men and women with HR+/HER2− early breast cancer at high risk of recurrence was evaluated in the monarchE trial. All 5,591 randomised and treated patients who received at least one dose of study treatment were included in the safety analyses as the safety population: 2,791 received abemaciclib + ET, and 2,800 received ET alone. With 90% of patients having completed or discontinued early from the study treatment period by the time of the AFU1, the safety data is considered mature. The overall safety profile of abemaciclib + ET at

the AFU1 was comparable to that reported at the PO analysis. There were minimal incremental increases in the incidences of any grade TEAEs, Grade ≥3 TEAEs, SAEs and discontinuation due to AEs.

The safety data reported in the following section is from the most recent data cut, AFU1. Safety results from the PO analysis are reported in Appendix L.2.4.

At the AFU1, the median duration of exposure to study treatment was similar across both arms of the study. In the abemaciclib + ET arm, the median duration of abemaciclib treatment was approximately [redacted] months (with a mean of approximately [redacted] months), while the median duration of ET was approximately [redacted] months (with a mean of approximately [redacted] months. In the ET alone arm the median duration of treatment was approximately and [redacted] months (with a mean of approximately [redacted] months). At the time of the data cut-off for the AFU1 analysis (01 April 2021), [redacted] patients ([redacted]%) in the abemaciclib + ET arm and [redacted] patients ([redacted]%) in the ET alone arm remained on study treatment. Overall, [redacted]% of total patients had completed two years on study treatment.

The safety of abemaciclib + ET was evaluated through the assessment of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), TEAEs leading to discontinuation, TEAEs leading to deaths and adverse events of special interest (AESIs). Physical assessments were conducted and clinical laboratory results, vital signs, AEs and ECOG PS were monitored routinely to assess safety. Electrocardiograms (ECGs) were performed at screening and then as clinically indicated at subsequent study visits.

TEAEs were classified and graded for severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

B.2.10.2 Summary of treatment-emergent adverse events

A summary of TEAEs reported in the safety population during the study at AFU1 is presented in Table 26. During the study period, a total of 5,231 patients (93.6%) experienced at least one TEAE, including 2,745 patients (98.4%) in the abemaciclib + ET arm and 2,486 patients (88.8%) of patients in the ET alone arm.

The incidence of treatment-related Grade ≥3 TEAEs (as judged by the investigator) was greater in the abemaciclib + ET arm than in the ET alone arm (Table 26).

Table 26: Summary of adverse events reported in monarchE (AFU1 analysis)

n (%)[a]	Abemaciclib + ET (N=2,791)	ET alone (N=2,800)
Patients with ≥1 TEAE	2,745 (98.4)	2,486 (88.8)
Patients with ≥1 CTCAE ≥ Grade 3 TEAE	[redacted]	[redacted]
Related to study treatment[b]	[redacted]	[redacted]
Patients with ≥1 TE-SAE	424 (15.2)	247 (8.8)
Patients who discontinued all study treatment due to an AE	181 (6.5)	30 (1.1)
Patients who discontinued all study treatment due to a SAE	[redacted]	[redacted]
Patients who died due to an AE on study treatment[c]	[redacted]	[redacted]
Patients who died due to an AE ≤30 days from discontinuation of study treatment[c]	[redacted]	[redacted]
Patients who died due to an AE >30 days after discontinuation from study treatment	[redacted]	[redacted]

Footnotes: [a] Patients may be counted in more than 1 category; [b] Includes events that were considered related to study treatment as judged by the investigator; [c] Deaths were also included as SAEs and discontinuations due to AEs
Abbreviations: AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; ET: endocrine therapy; N: number of patients in the safety population; n: number of patients in the specific category; SAE: serious adverse event; TE: treatment-emergent; TEAE: treatment-emergent adverse event.
Source: Lilly Data on File. Clinical Study Report: monarchE.[23] Data cut-off: 01 April 2021 (AFU1 analysis).

B.2.10.3 Treatment-emergent adverse events

A summary of system organ classes (SOC) most commonly affected by TEAEs at the AFU1 in the monarchE trial (experienced by ≥1% of patients in either arm) is presented in Table 27, ordered by decreasing frequency in the abemaciclib + ET arm. In the abemaciclib + ET arm, the most frequently reported class of TEAEs of any grade were gastrointestinal disorders represented ([redacted]%) and blood and lymphatic system disorders ([redacted]%). In the ET alone arm, musculoskeletal and connective tissue disorders ([redacted]%) and infections and infestations ([redacted]%) were the most frequently reported TEAE classes.

TEAEs by CTCAE Grade experienced by ≥10% of patients in either arm of the monarchE trial are presented in Table 28. Diarrhoea was the most commonly report TEAE for patients in the abemaciclib + ET arm, and was predominantly low grade, experienced by [redacted] patients ([redacted]%) at Grade ≥3. While data on diarrhoea management are not available from the AFU1, the results at the time of the PO analysis showed that in patients receiving abemaciclib + ET, diarrhoea was manageable with anti-diarrhoeal medications: [redacted] patients ([redacted]%) with Grade 1, [redacted] patients ([redacted]%) with Grade 2, and [redacted] patients ([redacted]%) with Grade 3 diarrhoea reported anti-diarrhoeal medication use, most commonly loperamide ([redacted]%). In addition to anti-diarrhoeal medication, higher-grade diarrhoea was managed with dose omissions of abemaciclib, although the majority of patients ([redacted]%) with diarrhoea did not require any treatment modification. It is reasonable to assume that similar results would be observed at the time of the AFU1 analysis, particularly when also considering the established safety profile of abemaciclib and timing of AEs Table 29.

In the abemaciclib + ET arm, [redacted] patients ([redacted]%) discontinued abemaciclib or all study treatment (abemaciclib and ET) because of diarrhoea, suggesting that this TEAE was manageable.[23] In the ET alone arm, [redacted]([redacted]%) of patients experienced diarrhoea, with only [redacted] patients ([redacted]%)

experiencing Grade 3 diarrhoea (Table 28). Neutropenia was experienced as a TEAE by 1,278 patients (45.8%) treated with abemaciclib + ET and 157 patients (5.6%) treated with ET alone. Of the patients in the abemaciclib + ET arm, [redacted] ([redacted]%) reported Grade ≥3 neutropenia and [redacted] ([redacted]%) required dose modification due to neutropenia while only [redacted] patients ([redacted]%) discontinued abemaciclib or all treatment due to neutropenia. It should be noted that clinical expert opinion sought by Lilly indicated that neutropenia caused by CDK4/6 inhibitors is rarely associated with infection. In the ET alone arm, neutropenia of any grade was reported in 157 patients (5.6%), of whom [redacted] ([redacted]%) experienced Grade ≥3. [redacted] patients in the ET alone arm discontinued treatment due to neutropenia. While treatment discontinuation data by month were not available from the AFU1 analysis, the total number of treatment discontinuations by month, due to diarrhoea, fatigue and neutropenia, at the PO analysis are presented in Table 29. This shows that treatment discontinuations were more frequent in early cycles of treatment.

At the time of the AFU1, infections of any grade and Grade ≥3 were reported in [redacted]% and [redacted]% of patients, respectively, in the abemaciclib + ET arm. In comparison, [redacted]% of patients in the ET alone arm reported infections of any grade, while [redacted]% reported infections of Grade ≥3. The most frequent (>5%) infections by patient in the abemaciclib + ET arm and the ET alone arm, respectively, were upper respiratory tract infection (URTI) (10.8% versus 8.5%), urinary tract infection (UTI) (12.0% versus 7.5%) and nasopharyngitis ([redacted]% versus [redacted]%).

Table 27: TEAEs by SOC in ≥1% patients (all grades) in the safety population (AFU1 analysis)

n (%)	Abemaciclib + ET (N=2,791)	ET alone (N=2,800)
Patients with ≥1 TEAE	**2,745 (98.4)**	**2,486 (88.8)**
Gastrointestinal disorders	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Respiratory, thoracic, and mediastinal disorders	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]
Injury, poisoning, and procedural complications	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]
Reproductive system and breast disorders	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Surgical and medical procedures	[redacted]	[redacted]

n (%)	Abemaciclib + ET (N=2,791)	ET alone (N=2,800)
Ear and labyrinth disorders	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified[a]	[redacted]	[redacted]
Endocrine disorders	[redacted]	[redacted]

Footnotes: [a] Including cysts and polyps.
Abbreviations: ET: endocrine therapy; MedDRA: Medical Dictionary for Regulatory Activities; N: number of patients in the safety population; n: number of patients in the specific category.
Source: Lilly Data on File. Clinical Study Report: monarchE.[23] Data cutoff: 01 April 2021 (AFU1 analysis).

Table 28: Treatment-emergent adverse events by maximum CTCAE grade experienced by ≥10% of population of either arm of monarchE, safety population (AFU1 analysis)

TEAE, n (%)	Abemaciclib + ET (n=2,791)						ET alone (N=2,800)					
	CTCAE Grade											
	1	2	3	4	5	Any	1	2	3	4	5	Any
Patients with ≥1 TEAE	[redacted]	[redacted]	**1,284 (46.0)**	**89 (3.2)**	[redacted]	**2,745 (98.4)**	[redacted]	[redacted]	**424 (15.1)**	**22 (0.8)**	[redacted]	**2,486 (88.8)**
Diarrhoea	[redacted]	[redacted]	218 (7.8)	0 (0.0)	[redacted]	2,331 (83.5)	[redacted]	[redacted]	6 (0.2)	0 (0.0)	[redacted]	242 (8.6)
Neutropenia	[redacted]	[redacted]	527 (18.9)	19 (0.7)	[redacted]	1278 (45.8)	[redacted]	[redacted]	19 (0.7)	4(0.1)	[redacted]	157 (5.6)
Fatigue	[redacted]	[redacted]	80 (2.9)	0 (0.0)	[redacted]	1133 (40.6)	[redacted]	[redacted]	4 (0.1)	0 (0.0)	[redacted]	499 (17.8)
Leukopenia	[redacted]	[redacted]	313 (11.2)	4 (0.1)	[redacted]	1049 (37.6)	[redacted]	[redacted]	11 (0.4)	0 (0.0)	[redacted]	186 (6.6)
Abdominal pain	[redacted]	[redacted]	39 (1.4)	0 (0.0)	[redacted]	992 (35.5)	[redacted]	[redacted]	9 (0.3)	0 (0.0)	[redacted]	275 (9.8)
Nausea	[redacted]	[redacted]	14 (0.5)	0 (0.0)	[redacted]	824 (29.5)	[redacted]	[redacted]	2 (0.1)	0 (0.0)	[redacted]	252 (9.0)
Anaemia	[redacted]	[redacted]	56 (2.0)	1 (0.0)	[redacted]	681 (24.4)	[redacted]	[redacted]	9 (0.3)	1 (0.0)	[redacted]	104 (3.7)
Arthralgia	[redacted]	[redacted]	9 (0.3)	0 (0.0)	[redacted]	742 (26.6)	[redacted]	[redacted]	29 (1.0)	0 (0.0)	[redacted]	1060 (37.9)
Headache	[redacted]	[redacted]	8 (0.3)	0 (0.0)	[redacted]	546 (19.6)	[redacted]	[redacted]	5 (0.2)	0 (0.0)	[redacted]	421 (15.0)
Vomiting	[redacted]	[redacted]	15 (0.5)	0 (0.0)	[redacted]	491 (17.6)	[redacted]	[redacted]	3 (0.1)	0 (0.0)	[redacted]	130 (4.6)
Hot flush	[redacted]	[redacted]	4 (0.1)	0 (0.0)	[redacted]	427 (15.3)	[redacted]	[redacted]	10 (0.4)	0 (0.0)	[redacted]	643 (23.0)
Lymphopenia	[redacted]	[redacted]	148 (5.3)	3 (0.1)	[redacted]	395 (14.2)	[redacted]	[redacted]	13 (0.5)	0 (0.0)	[redacted]	96 (3.4)

TEAE, n (%)	Abemaciclib + ET (n=2,791)						ET alone (N=2,800)					
	CTCAE Grade											
	1	2	3	4	5	Any	1	2	3	4	5	Any
Stomatitis[a]	[redacted]	[redacted]	4 (0.1)	0 (0.0)	[redacted]	385 (13.8)	[redacted]	[redacted]	0 (0.0)	0 (0.0)	[redacted]	151 (5.4)
Cough	[redacted]	[redacted]	1 (0.0)	0 (0.0)	[redacted]	391 (14.0)	[redacted]	[redacted]	0 (0.0)	0 (0.0)	[redacted]	222 (7.9)
Thrombocytopenia	[redacted]	[redacted]	28 (1.0)	8 (0.3)	[redacted]	373 (13.4)	[redacted]	[redacted]	2 (0.1)	2 (0.1)	[redacted]	52 (1.9)
Decreased appetite	[redacted]	[redacted]	16 (0.6)	0 (0.0)	[redacted]	329 (11.8)	[redacted]	[redacted]	2 (0.1)	0 (0.0)	[redacted]	68 (2.4)
Lymphoedema	[redacted]	[redacted]	5 (0.2)	0 (0.0)	[redacted]	347 (12.4)	[redacted]	[redacted]	1 (0.0)	0 (0.0)	[redacted]	250 (8.9)
Urinary tract infection	[redacted]	[redacted]	16 (0.6)	0 (0.0)	[redacted]	336 (12.0)	[redacted]	[redacted]	6 (0.2)	0 (0.0)	[redacted]	211 (7.5)
Constipation	[redacted]	[redacted]	2 (0.1)	0 (0.0)	[redacted]	333 (11.9)	[redacted]	[redacted]	1 (0.0)	0 (0.0)	[redacted]	168 (6.0)
URTI	[redacted]	[redacted]	6 (0.2)	0 (0.0)	[redacted]	301 (10.8)	[redacted]	[redacted]	0 (0.0)	0 (0.0)	[redacted]	238 (8.5)
ALT increased	[redacted]	[redacted]	72 (2.6)	5 (0.2)	[redacted]	343 (12.3)	[redacted]	[redacted]	19 (0.7)	0 (0.0)	[redacted]	157 (5.6)
Dizziness	[redacted]	[redacted]	4 (0.1)	0 (0.0)	[redacted]	304 (10.9)	[redacted]	[redacted]	1 (0.0)	0 (0.0)	[redacted]	188 (6.7)
Rash	[redacted]	[redacted]	11 (0.4)	0 (0.0)	[redacted]	312 (11.2)	[redacted]	[redacted]	0 (0.0)	0 (0.0)	[redacted]	127 (4.5)
AST increased	[redacted]	[redacted]	49 (1.8)	3 (0.1)	[redacted]	330 (11.8)	[redacted]	[redacted]	15 (0.5)	0 (0.0)	[redacted]	137 (4.9)
Alopecia	[redacted]	[redacted]	0 (0.0)	0 (0.0)	[redacted]	313 (11.2)	[redacted]	[redacted]	0 (0.0)	0 (0.0)	[redacted]	75 (2.7)
Pain in extremity	[redacted]	[redacted]	3 (0.1)	0 (0.0)	[redacted]	286 (10.2)	[redacted]	[redacted]	4 (0.1)	0 (0.0)	[redacted]	325 (11.6)

TEAE, n (%)	Abemaciclib + ET (n=2,791)						ET alone (N=2,800)					
	CTCAE Grade											
	1	2	3	4	5	Any	1	2	3	4	5	Any
Back pain	[redacted]	[redacted]	10 (0.4)	0 (0.0)	[redacted]	283 (10.1)	[redacted]	[redacted]	9 (0.3)	0 (0.0)	[redacted]	347 (12.4)
Pyrexia	[redacted]	[redacted]	2 (0.1)	0 (0.0)	[redacted]	279 (0.1)	[redacted]	[redacted]	0 (0.0)	0 (0.0)	[redacted]	127 (4.5)

Footnotes: [a] Includes mouth ulceration, mucosal inflammation, oropharyngeal pain, stomatitis.
Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; CTCAE: Common Terminology Criteria for Adverse Events; ET: endocrine therapy; MedDRA: Medical Dictionary for Regulatory Activities; N: number of patients in the safety population; n: number of patients in the specific category; TEAE: treatment-emergent adverse event; URTI: upper respiratory tract infection.

Table 29: Summary of abemaciclib or all treatment discontinuation due to AE by months – reported within selected months (AFU1 analysis)

n (%)	Arm A Abemaciclib + ET N=2791								
Months	TOTAL	1	2	3	6	9	12	18	24
Nx	2791	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation due to any AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade ≥3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade ≥3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade ≥3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade ≥3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: Percentages per month calculated using Nx as denominator.
[a] Two patients discontinued abemaciclib first due to AEs other than diarrhoea and then discontinued ET due to diarrhoea (adding up to 141 diarrhoea events leading to discontinuation of abemaciclib or all study treatment) [b] One patient discontinued abemaciclib first due to AEs other than fatigue and then discontinued ET due to fatigue (adding up to 53 fatigue events leading to discontinuation of abemaciclib or all study treatment).
Abbreviations: AE: adverse event; ET: endocrine therapy; N: number of patients in the safety population; n: number of patients within category; Nx = number of patients exposed to study treatment per month; NR: not reported.

B.2.10.4 Serious adverse events

The incidence of SAEs was higher in the abemaciclib + ET arm ([redacted]%) as compared with the ET alone arm ([redacted]%; Table 30). Venous thrombolytic events (VTE) and pneumonia were the most commonly reported SAEs by patients treated with abemaciclib + ET ([redacted]% [[redacted]2,791] and [redacted]% [[redacted]2,791], respectively). Patients treated with ET alone reported pneumonia ([redacted]% [[redacted]2,800]), cellulitis ([redacted]% [[redacted]2,800]) and VTE ([redacted]% [[redacted]2,800]) most commonly.

Table 30: SAEs in ≥5 patients in either arm of the safety population (AFU1 analysis)

n (%)	Abemaciclib + ET (N=2,791)	ET alone (N=2,800)
Patients with ≥1 serious adverse event	424 (15.2)	247 (8.8)
Infections and infestations	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Influenza	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Breast cellulitis	[redacted]	[redacted]
Erysipelas	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Pancreatitis	[redacted]	[redacted]
Colitis	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]
Lymphoedema	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]
Cholecystitis	[redacted]	[redacted]
Blood and lymphatic disorders	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Dehydration	[redacted]	[redacted]
Composite terms[a]		
Venous thromboembolic event[b]	[redacted]	[redacted]

Interstitial lung disease/pneumonitis[c]	[redacted]	[redacted]
ALT or AST increased	[redacted]	[redacted]

Footnotes: [a] Composite terms are defined as a grouping of terms from one or more PTs that are treatment-emergent events and related to a defined medical condition or area of interest; [b] VTE events included pulmonary embolism and deep vein thrombosis. See section 5.2.1.4.5 of the CSR for more information; [c] Interstitial lung disease/pneumonitis events were defined by SMQ of "interstitial lung disease".
Abbreviations: ET: endocrine therapy; N: number of patients in the safety population; n: number of patients within category; SAE: serious adverse event; SMQ: standardised MedDRA queries.
Source: Lilly Data on File. Clinical Study Report: monarchE.[23] Data cutoff: 01 April 2021 (AFU1 analysis).

B.2.10.5 Adverse events leading to discontinuation of study treatment

In the abemaciclib + ET arm, [redacted] patients ([redacted]%) discontinued abemaciclib due to AEs. Of these patients, 181 (6.5%) discontinued all study treatment due to an AE, as compared with 30 patients (1.1%) in the ET alone arm. The TEAEs that led to discontinuation of all study treatment are presented in Table 31. In the abemaciclib + ET arm, the most common TEAEs leading to all treatment discontinuation were diarrhoea ([redacted] patients, [redacted]%) and fatigue ([redacted] patients, [redacted]%). Dizziness ([redacted]%) led to discontinuation in the ET alone arm. The TEAEs that led to discontinuation of abemaciclib by SOC are presented in Table 32. In the abemaciclib + ET arm, the most common TEAEs leading to abemaciclib discontinuation were diarrhoea ([redacted] patients, [redacted]%) and fatigue ([redacted] patients, [redacted]%).

Table 31: AEs reported as reason for study treatment discontinuation (end of treatment) by ≥2 patients in either arm of the safety population (AFU1 analysis)

n (%)	Abemaciclib + ET (N=2,791)	ET alone (N=2,800)
Patients discontinued all study treatment due to AE[a]	181 (6.5)	30 (1.1)
Diarrhoea	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Depression	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]
Cardiac arrest	[redacted]	[redacted]
Dry eye	[redacted]	[redacted]
General physical health deterioration	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Hot flush	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Composite terms[b]		
Infections and infestations SOC	[redacted]	[redacted]
Venous thromboembolic event[c]	[redacted]	[redacted]
Interstitial lung disease/pneumonitis[d]	[redacted]	[redacted]
ALT or AST increased	[redacted]	[redacted]

Footnotes: [a] Includes patients who died due to AE during study treatment: PT cardiac arrest and PT general physical health deterioration ([redacted]). [b] Composite terms are defined as a grouping of terms from one or more PT or SOC that are related to a defined medical condition or area of interest; [c] VTE events included pulmonary embolism and deep vein thrombosis. See section 5.2.1.4.5 of the CSR for more information; [d] Interstitial lung disease/pneumonitis events were defined by SMQ of "interstitial lung disease".
Abbreviations: AE: adverse event; ET: endocrine therapy; N: number of patients in the safety population; n: number of patients within category; SAE: serious adverse event; SMQ: standardised MedDRA queries.
Source: Lilly Data on File. Clinical Study Report: monarchE.[23] Data cutoff: 01 April 2021 (AFU1 analysis).

Table 32: AEs reported as reason for abemaciclib or all treatment discontinuation (end of treatment) by system organ class ≥0.1% patients in the abemaciclib + ET arm of the safety population (AFU1 analysis)

n (%)	Abemaciclib + ET (N=2791)	ET alone (N=2800)
Patients discontinued abemaciclib or all treatments due to AE	[redacted]	**30 (1.1)**
Gastrointestinal disorders	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Flatulence	[redacted]	[redacted]
Gastritis	[redacted]	[redacted]
Haemorrhoids	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Malaise	[redacted]	[redacted]
General physical health deterioration	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]
Gamma-glutamyl transferase increased	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]

n (%)	Abemaciclib + ET (N=2791)	ET alone (N=2800)
Dyspnoea	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Influenza	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Alopecia	[redacted]	[redacted]
Psoriasis	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]
Depression	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]
Hot flush	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Neuropathy	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Cardiac arrest	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Bone pain	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]
Hepatic cirrhosis	[redacted]	[redacted]
Hepatic function abnormal	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]
Dry eye	[redacted]	[redacted]

n (%)	Abemaciclib + ET (N=2791)	ET alone (N=2800)
Composite terms[a]		
VTE[b]	[redacted]	[redacted]
ILD/pneumonitis[c]	[redacted]	[redacted]
Elevated transaminases	[redacted]	[redacted]

Footnotes: [a] Composite terms are defined as a grouping of terms from one or more PTs or SOC that are related to a defined medical condition or area of interest. [b] VTE events included pulmonary embolism and deep vein thrombosis. See section 5.2.1.4.5 of the CSR for more information; [c] Interstitial lung disease/pneumonitis events were defined by SMQ of "interstitial lung disease".
Abbreviations: AE: adverse event; ET: endocrine therapy; N: number of patients in the safety population; n: number of patients within category; SAE: serious adverse event; SMQ: standardised MedDRA queries.
Source: Lilly Data on File. Clinical Study Report: monarchE.[23] Data cut off: 01 April 2021 (AFU1 analysis).

B.2.10.6 Patient deaths

Overall, there were [redacted] deaths ([redacted]%) in the abemaciclib + ET arm, and [redacted] deaths ([redacted]%) in the ET alone arm. [redacted] deaths in the abemaciclib + ET arm occurred ≤30 days from discontinuation of study treatment, of which [redacted] were reported to be due to TEAEs; in the ET alone arm, [redacted] patients died within this timeframe, of which [redacted] were reported to be due to TEAEs. Of these, cardiac disorders ([redacted]%) and infections and infestations ([redacted]%) were the most commonly reported TEAEs leading to patient death in the abemaciclib + ET arm and ET alone arm, respectively. For deaths occurring >30 days after study treatment discontinuation, [redacted] of the [redacted] deaths in the abemaciclib + ET arm were considered to be due to TEAEs, as compared with [redacted] of the [redacted] deaths in the ET alone arm.

Table 33: Summary of deaths in the safety population (AFU1 analysis)

n (%)	Abemaciclib + ET (N=2,791)	ET alone (N=2,800)
All deaths	[redacted]	[redacted]
Deaths on therapy or ≤30 days from discontinuation of study treatment	[redacted]	[redacted]
Death due to adverse events	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
General disorders and administrative site conditions	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Death due to study disease	[redacted]	[redacted]
Deaths occurring >30 days from study treatment discontinuation	[redacted]	[redacted]
Death due to adverse events	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	[redacted]	[redacted]

n (%)	Abemaciclib + ET (N=2,791)	ET alone (N=2,800)
Gastrointestinal disorders	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]
General disorders and administrative site conditions	[redacted]	[redacted]
Death due to study disease	[redacted]	[redacted]

Abbreviations: ET: endocrine therapy; N: number of patients in the safety population; n: number of patients in the specific category.
Source: Lilly Data on File. Clinical Study Report: monarchE.[23] Data cutoff: 01 April 2021 (AFU1 analysis).

B.2.11 *Ongoing studies*

The pivotal trial for abemaciclib in this indication, monarchE, is ongoing and a further data cut is expected in [redacted].

B.2.12 *Innovation*

Abemaciclib would be the first licensed CDK4/6 inhibitor, and first licensed targeted therapy, available for the treatment of HR+, HER2−, node positive early breast cancer with a high risk of recurrence. Abemaciclib would represent an important step forward in the treatment paradigm of this disease.

There has been an historical lack of innovation for patients with HR+, HER2− early breast cancer, when compared to other breast cancer subtypes. In 2006, trastuzumab was recommended by NICE as a targeted biological treatment for patients with HER2+ early breast cancer[44], while more recently neratinib,[45] pertuzumab[46] and trastuzumab emtansine[67] have also been recommended in this indication. In comparison, currently there are no targeted therapies recommended for HR+, HER2− early breast cancer, where cytotoxic chemotherapy and/or ET have remained the standard of care for many years, except for the recent guideline recommendation that some postmenopausal patients may receive concomitant treatment with bisphosphonates.[13]

This historical lack of innovation means that patients face a clear unmet need at a critical stage of their disease treatment. It is of paramount importance to employ effective treatment options as early in the disease as possible, in order to increase the chances of disease cure and therefore reduce the likelihood of developing incurable advanced disease, and the associated substantial reduction in quality of life and inevitable early death.

With a novel, first in class, mechanism of action, abemaciclib is a targeted CDK4/6 inhibitor that would represent an important paradigm shift in the management of HR+, HER2− early breast cancer with a high risk of recurrence, allowing patients to access to a targeted treatment option earlier in the treatment pathway. The mechanism of action of abemaciclib has previously demonstrated an improved PFS versus the standard of care for the treatment of advanced breast cancer in the MONARCH-3 trial, and in combination with fulvestrant in the MONARCH-2 trial. Abemaciclib is now recommended by NICE as a treatment option for advanced breast cancer in combination with an aromatase inhibitor, as well as in combination with fulvestrant.[7, 32]

The introduction of abemaciclib in the early breast cancer setting would represent a more important step change, with the potential to prevent the disease from ever progressing to more advanced stages of breast cancer, where treatment is no longer provided with curative intent. In the monarchE trial, abemaciclib + ET resulted in a significant and meaningfully improved IDFS compared to ET alone for patients with HR+, HER2− early breast cancer with a high risk of recurrence. The margin of benefit demonstrated (reduction in the risk of developing invasive disease by 30.4% [stratified HR=0.696, 95% CI: 0.588, 0.823]) is clinically meaningful. Similarly, abemaciclib reduced the risk of distant relapse or death by 31.3%, resulting in a 2.5% and 4.2% increase in patients who were free of distant relapse at two years and three years respectively, versus ET alone.

As such, it is clear that abemaciclib would represent a valuable addition to the treatment armamentarium for clinicians to support patients in managing the risk of breast cancer recurrence, addressing the unmet need in this patient population for new, effective treatments that can protect from patients from advanced breast cancer, and the associated devastating prognosis and burden to HRQoL.

B.2.13 *Interpretation of clinical effectiveness and safety evidence*

B.2.13.1 Principal findings from the clinical evidence base

Abemaciclib + ET provided clinically meaningful improvements in IDFS and DRFS compared to ET alone.

The monarchE trial enrolled 5,637 patients across 38 countries, with a median follow-up time of [redacted] months in the abemaciclib + ET arm and [redacted] months in the ET alone arm at the AFU1. Results from the monarchE study demonstrated that treatment with abemaciclib + ET was associated with a significant and clinically meaningful improvement in IDFS, as well as a clinically meaningful improvement in DRFS, when compared to ET alone.

The monarchE study achieved its primary endpoint by demonstrating a statistically significant improvement in IDFS for abemaciclib + ET, compared to ET alone at the time of IA2 analysis. In the IA2 analysis, abemaciclib + ET reduced the risk of developing invasive disease by 25.3% compared to ET alone, with a clinically meaningful improvement in the two-year IDFS rate (92.2% versus 88.7% for abemaciclib + ET compared to ET alone).

This benefit was sustained over an increased duration of follow-up at the time of the pre-specified PO analysis and the AFU1. At the time of the AFU1, abemaciclib + ET reduced the risk of disease recurrence or death by 30.4% (stratified HR=0.696, 95% CI: 0.588, 0.823), together with a clinical meaningful improvement in the 2-year and 3-year IDFS rate: 92.7% vs 90.0% and 88.8% vs 83.4%, respectively. A consistent benefit in IDFS was also demonstrated across all pre-specified subgroups.

At the AFU1, the benefit of abemaciclib + ET in reducing the risk of developing a distant relapse was maintained with the longer follow-up time. Abemaciclib + ET reduced the risk of developing distant relapse by 31.3%, reflecting a 2.5% difference in 2-year DRFS rates (94.1% versus 91.6%) for patients treated with abemaciclib + ET for their disease, compared to patients treated with ET alone for their disease. Additionally, there was a 4.2% difference in 3-year DRFS rates between abemaciclib + ET and ET alone (90.3% versus 86.1%). For patients with early breast cancer at high risk of recurrence, this is clinically meaningful – distant relapse-free survival

means that a patient is free from metastatic disease. For patients with metastatic breast cancer, their disease cannot be cured and they face a poor prognosis, so preventing disease progression to incurable advanced breast cancer is a critical aim of treatment for early breast cancer.[13, 68]

It is reasonable to expect that these improvements in IDFS and DRFS will translate to improvements in OS in the long-term. However, establishing evidence for such anticipated improvements will require much longer follow up and OS data will not be mature during the timeframe of this appraisal. According to the panel of breast cancer experts who developed the STEEP system, distant recurrence is a life-threatening disease and is strongly associated with OS.[56] Thus, the effect in preventing the development of distant recurrence events is expected to translate to the survival benefit, after longer term follow-up. At the time of the AFU1, there were [redacted] deaths ([redacted]%) in the ITT population: [redacted] deaths ([redacted]%) in the abemaciclib + ET arm, and [redacted] deaths ([redacted]%) in the ET alone arm, representing an absolute difference of [redacted] deaths between the two arms. When the impact of the COVID-19 pandemic was considered in a sensitivity analysis, this difference was reduced to only [redacted].

Abemaciclib + ET is associated with a manageable safety profile

The evidence base for abemaciclib in combination with an ET demonstrates a tolerable safety profile in early breast cancer, in line with its established use in advanced breast cancer in NHS clinical practice and in prior clinical trials.

The most common TEAEs in the abemaciclib + ET arm were diarrhoea (83.5%), neutropenia (45.8%), and fatigue (40.6%) though they were rarely of high severity ([redacted]%, [redacted]%, [redacted]%, respectively, at grade ≥3). Clinical expert opinion sought by Lilly indicated that CDK4/6 inhibitor-induced neutropenia rarely progresses to serious infection and can be handled via dose modification. The most frequent TEAEs in the ET arm were musculoskeletal and connective tissue disorders ([redacted]%) and infections and infestations ([redacted]%).

While data on diarrhoea management were not available at AFU1, at the PO analysis, diarrhoea was managed with anti-diarrhoeal medications, most commonly loperamide ([redacted]%). In addition to anti-diarrhoeal medication, higher-grade diarrhoea was managed with dose omissions of abemaciclib, although the majority of patients ([redacted]%) with diarrhoea did not require any treatment modification. It is reasonable to assume that similar results would be observed at the time of the AFU1.

In the abemaciclib + ET arm 146 patients (5.2%) discontinued abemaciclib or all study treatment (abemaciclib and ET) because of diarrhoea, suggesting that this TEAE was manageable and acceptable.[23] Similarly, neutropenia was manageable with dose modifications, and only [redacted] patients ([redacted]%) discontinued study treatment due to neutropenia.

The safety results of monarchE were in line with previous studies of abemaciclib, including the MONARCH 2 and MONARCH 3 studies; where the most frequent AEs of any grade were also diarrhoea and neutropenia, of predominately grade 1 or 2 severity, which clinical experts have told Lilly is manageable in clinical practice.[57, 58]

The addition of abemaciclib to ET did not adversely affect HRQoL relative to the ET alone arm, with no differences larger than the minimally important difference in the FACT-B, FACT-ES and FACIT-F subscale scores and no significant differences in EQ-5D-5L index or Visual Analogue Score, between treatment arms, demonstrating that the addition of abemaciclib to ET was tolerable and did not adversely impact HRQoL.

B.2.13.2 Strengths and limitations of the clinical evidence base

Internal validity

The clinical evidence presented as part of the submission has been derived from a SLR that was conducted according to the principles of systematic reviewing published in the Cochrane handbook. The clinical SLR identified the pivotal monarchE trial as the only relevant clinical trial for abemaciclib + ET in this indication. As described in Section B.2.5, the SLR found that monarchE was a methodologically robust and well-reported RCT, considered to be at low risk of bias.

- Participants were appropriately randomised using an IWRS.
- The open-label nature of the trial was a necessary limitation because of the distinct toxicities and laboratory abnormalities related to abemaciclib. Eli Lilly remained blind to the treatment group assignments and study results throughout the duration of the study, and an independent data monitoring committee was responsible for reviewing unblinded data, minimising any impact of this limitation.[53]
- The sample size was sufficient to detect a difference in the primary objective of IDFS between the two treatment groups, yielding approximately 85% statistical power.[53]
- Participant flow through the study was well reported, and all treatment discontinuations and loss-to-follow up events were accounted for.
- The concomitant care given to enrolled patients was similar between arms.
- All randomised patients were included in the efficacy analyses, thereby maintaining the principle of ITT analysis, and preserving randomisation and the causality model.

External validity

The key evidence for the efficacy of abemaciclib in combination with ET in early breast cancer is based on the pivotal monarchE phase III trial. The results of the monarchE study are relevant to the decision problem specified by the NICE scope, which proposes the use of abemaciclib + ET in adults with hormone receptor-positive, HER2-negative, node-positive early breast cancer after definitive surgery of the primary breast tumour at high risk of recurrence.

- **Population** – The results of the monarchE trial provide evidence for abemaciclib + ET in a population of patients with HR+, HER2−, early breast cancer at high risk of recurrence, with baseline characteristics generalisable to patients in UK clinical practice. The population of patients included in monarchE is in line with the proposed marketing authorisation for abemaciclib in this indication and the population listed in the final scope, and reflects the population of patients where abemaciclib will be used in this indication in UK clinical practice.
- **Intervention** – Abemaciclib was directly evaluated in combination with ET as a treatment option for patients with HR+/HER2− early breast cancer at a high risk of disease recurrence, defined as pathological tumour involvement in ≥4 ipsilateral axial lymph nodes (ALNs), or pathological tumour involvement in 1–3 ALNs as well as either Grade 3 disease or primary tumour size ≥5 cm, as it would be used in NHS clinical practice.
- **Comparator** – The efficacy and safety of abemaciclib + ET was directly compared with that of ET alone in the monarchE trial.[53] In total, [redacted] of patients started on AIs and [redacted] of patients started on anti-oestrogen therapy, primarily tamoxifen. The split of AIs/tamoxifen

was well balanced and both AIs/tamoxifen are extensively used in the UK. The choice of AI was consistent with NICE guidelines.

- **Outcomes** – The efficacy and safety profile of abemaciclib + ET in HR+/HER2− node positive, early breast cancer at high risk of recurrence was demonstrated in a well-defined, homogenous population. A range of endpoints were evaluated, including all endpoints outlined in the scope that are relevant to clinicians and to patients (IDFS, DRFS, OS [although OS data are currently immature], AEs and HRQoL). IDFS is considered to be a particularly relevant endpoint for comparing treatment regimens for the management of early breast cancer, where maintaining a disease-free state, i.e. a functional cure, is the primary goal of treatment. DRFS is also clinically meaningful, as avoidance of metastatic recurrence is of particular importance, given the poor prognosis associated with advanced breast cancer, which is considered incurable.

Limitations

- While it is reasonable to suggest that the improvements in IDFS and DRFS for abemaciclib + ET versus ET alone will translate to improvements in OS in the long-term, it is not currently possible to determine the impact of abemaciclib + ET on OS, because the data were immature at the time of the data cut-off. However, IDFS and DRFS are clinically meaningful outcomes in early breast cancer, and therefore the absence of mature OS data does not represent a major limitation when assessing the benefits of abemaciclib in this indication and this situation is common in early breast cancer appraisals.[69]
- The open-label nature of the trial represents a necessary limitation of monarchE because the distinct toxicities and laboratory abnormalities related to abemaciclib (included diarrhoea, neutropenia and creatinine increase) mean that a study blind would be unlikely to be maintained. In order to maintain the study integrity, Eli Lilly remained blind to the treatment group assignments and study results throughout the duration of the study. An independent data monitoring committee was responsible for reviewing the unblinded safety and efficacy analyses, minimising the impact of the open-label nature of the study.

Conclusion

The results of the monarchE study demonstrated that abemaciclib + ET significantly improved IDFS, and demonstrated clinically meaningful improvements in DRFS, with a tolerable safety profile, whilst maintaining HRQoL. This benefit deepened with increased follow-up.

The quality of the evidence provided by the monarchE study is supported by robust and well-reported methodology. The results of monarchE highlight the key benefits of treatment with abemaciclib + ET for patients with HR+/HER2− early breast cancer at high risk of recurrence. The provision of a safe and tolerable treatment option for patients at high risk of recurrence means that the risk of developing incurable advanced or metastatic disease, or death, and the substantial associated humanistic and economic burden is reduced. With a novel, first in class mechanism of action, abemaciclib would represent an important paradigm shift in the management of HR+, HER2− early breast cancer, allowing access to a targeted treatment option earlier in the treatment pathway.

End-of-life-criteria

Abemaciclib in combination with ET does not meet the end-of-life criteria, as defined by NICE.

B.3 Cost effectiveness

Summary of cost-effectiveness analysis

De novo cost-effectiveness model

- A *de novo* cost-utility analysis of abemaciclib + ET versus ET relevant to the decision problem for this submission was performed
- The analysis was conducted from the perspective of the NHS and Personal Social Services (PSS) over a lifetime time horizon with a 28-day cycle length
  - In the model, lifetime corresponds to 49 years, as this is the time point by which survival in both arms fell to <0.1% for the base case extrapolations
- In line with the decision problem the analysis was conducted in the population with HR+, HER2−, node-positive early breast cancer at high risk of recurrence
- The model structure was based on previous early breast cancer models in the HER2+ patient population, the treatment pathway of patients with HR+/HER2− early breast cancer and data availability from the monarchE trial
  - The model consisted of a cohort state transition model with five health states: IDFS, non-metastatic recurrence, remission, metastatic recurrence, and death. Death and metastatic recurrence were modelled as absorbing health states
  - The metastatic recurrence health state was divided into two substates; endocrine resistant and endocrine sensitive. Transition into these substates was dependent on how long it took patients to experience disease recurrence after completing adjuvant ET
- Efficacy data for abemaciclib + ET and ET alone were derived from the monarchE trial for the IDFS health state. Efficacy data for the remaining health states were obtained from the literature, full details of which are presented in Section B.3.3.1
- IDFS, TTD, and OS (without distant recurrence) data from the monarchE trial was used to parameterise transitions for the abemaciclib + ET and ET treatment arms
- A utility analysis was conducted using EQ-5D-5L data collected during the monarchE trial for the IDFS health state, which was cross-walked to the 3L scale using the Van Hout *et al.* (2021) approach, to which the UK tariffs were applied.[66] As the data showed no significant difference between treatment arms, overall utilities were applied to both treatment arms instead of treatment-specific utilities in the base-case. Published utility values were used for post-IDFS health states
- Resource use and costs included in the model were based on previous technology appraisals expert opinion and appropriate published sources including the British National Formulary (BNF), electronic market information tool (eMIT), National Schedule of NHS Costs (2019/20), and Personal Social Services Research Unit (PSSRU 2020)
- In alignment with best practice, validation of the economic model structure was conducted by an independent health economist prior to the submission who carried out a technical cell by cell verification of formulae, functions and coding. The functionality of the sensitivity and scenario analyses were also reviewed

Base case cost-effectiveness results

- Abemaciclib + ET was found to result in an incremental gain of [redacted] undiscounted LYs and [redacted] QALYs compared to ET alone. Abemaciclib (at PAS price) + ET was associated with a higher total cost (£[redacted]) compared to ET alone. This was predominantly driven by the higher drug-related costs for abemaciclib + ET in the invasive disease free setting, compared to ET alone
- The base case analysis produced a pairwise ICER for abemaciclib + ET versus ET alone of £3,786 per QALY gained. The probability that abemaciclib + ET is cost-effective at the with-PAS price at a £30,000 ICER threshold is [redacted]%.

Sensitivity and scenario analyses

- Both probabilistic and deterministic sensitivity analyses were conducted to assess uncertainty in the base-case model parameters included in the economic analysis
- The DSA results identified the model was robust to uncertainty in the majority of parameters considered. The only parameter resulting in significant variation was the proportion of both abemaciclib and ET patients moving to the non-metastatic recurrence health state; this probability was robustly derived from the previous NICE appraisal of trastuzumab (TA632)[67]
- A number of scenario analyses were conducted to explore the impact of key assumptions and alternative input choices within the base case economic analysis including varying the curve choices and treatment waning assumptions. Whilst there was slight variations in the ICER, the cost-effectiveness conclusions remained the same across all scenarios and the ICERs are considered cost-effective at a willingness-to-pay threshold of £30,000 per QALY

Conclusions

- For patients with HR+, HER2− early breast cancer at high risk of recurrence, the addition of abemaciclib to ET would represent an important paradigm shift in the management of early breast cancer, providing patients with an increased chance of a potential disease cure, thereby avoiding progression to incurable advanced breast cancer and the associated substantial reduction in quality of life and inevitable early death
- This analysis demonstrates that abemaciclib would represent a cost-effective use of NHS resources for these patients

B.3.1 *Published cost-effectiveness studies*

In line with the final scope, this submission addresses the cost-effectiveness of abemaciclib in combination with endocrine therapy (ET) for patients with hormone receptor-positive (HR+), HER2-negative (HER2−), node-positive early breast cancer.

A systematic literature review was conducted to identify published cost-effectiveness studies in the HR+, HER2−, node-positive, high risk early breast cancer population. Due to the limited economic data pertaining to patients with node-positive, HR+ early breast cancer, the SLR included all published cost-effectiveness studies in early breast cancer, irrespective of node and HR status. Full details of the SLR are provided in Appendix G. In the past five years, clinical research has focused on HR+, HER2+, early breast cancer. No studies were identified which were representative of the monarchE patient population. The SLR concluded that there is a lack of economic evidence evaluating and comparing treatment options for the monarchE patient population.

To supplement the results of the economic SLR, a further targeted review (TLR) was conducted to identify all previous technology appraisals published by NICE in early breast cancer over the past five years.

The TLR identified four HTA submissions which have been summarised in Table 34. Three of the submissions modelled a HER2+ patient population and one modelled patients with early operable breast cancer with INTRABEAM radiotherapy. Of the three HER2+ HTA submissions, trastuzumab emtansine (TA632) was the most recent submission, followed by neratinib (TA612) and adjuvant pertuzumab in combination with trastuzumab and chemotherapy (TA569).[45, 46, 67]

All models identified from the TLR were consistent with the Markovian model structures identified in the SLR. Two of the submissions (TA632[67] and TA569[46]) followed a similar structure with seven health states included in the model and the IDFS health state split by ‘on treatment’ or ‘off

treatment'. In these submissions the first and second-line metastatic settings were modelled separately. A cycle length of one month was common across these three submissions while the submission modelling INTRABEAM radiotherapy (TA501, 2018)[70] followed a cycle length of one year, as the utility benefit from the intervention was deemed 'one-off' and 'very small'. The discount rate for costs and effects were consistent across all submissions. A lifetime horizon (40-55 years) was used as the base case across all submissions and was in line with the NICE reference case. Full details of the TLR are presented in Appendix H.

Table 34: Summary of previous NICE HTA submissions in early breast cancer model designs in HER2+ patient population

Author, year	Population	Intervention	Comparator	Model method	Health states	Time horizon	Cycle length	Discount rate for cost and effects
TA632, 2020[67]	HER2+ EBC	Trastuzumab emtansine	Standard adjuvant therapies including trastuzumab	Markov model	7 health states: 'IDFS – on treatment', 'IDFS – off treatment', 'Non-metastatic recurrence', 'Remission', 'First-line treatment for MBC (First-line MBC)', 'Subsequent treatment lines for MBC (Second+ line MBC)', and 'Death'	51 years (lifetime)	1 month	3.5%
TA612, 2019[45]	Early HR+, HER2+ BC	Neratinib	Standard treatment with no further HER2-directed therapy	Markov model	5 health states: 'IDFS', 'Local recurrence', 'Remission', 'Distant recurrence' and 'Death'	55 years (lifetime)	1 month	3.5%
TA569, 2019[46]	HER2+ EBC	Adjuvant pertuzumab in combination with trastuzumab & chemotherapy	Standard adjuvant therapy without pertuzumab	Markov model	7 health states: 'IDFS – on treatment', 'IDFS – off treatment', 'Non-metastatic recurrence', 'Remission', 'First-line treatment for MBC (First-line MBC)', 'Subsequent treatment lines for MBC (Second+ line MBC)', and 'Death'	52 years (lifetime)	1 month	3.5%
TA501, 2018[70]	Early operable BC	INTRABEAM radiotherapy	External beam	Markov model	6 health states: 'recurrence free', 'local recurrence', 'disease-free after local recurrence', 'any other recurrence', 'death from breast cancer', 'death from other causes'	40 years (lifetime)	1 year	3.5%

Abbreviations: BC: breast cancer; EBC: early breast cancer; HER2: human epidermal receptor 2; HER2+: human epidermal receptor 2 positive; HR+: hormone receptor positive; HTA: health technology assessment; IDFS: invasive disease-free survival; MBC: metastatic breast cancer; NICE: National Institute for Clinical Excellence; TA: technology appraisal.

B.3.2 *Economic analysis*

The objective of this economic analysis was to assess the cost-effectiveness of abemaciclib given for up to two years in combination with ET (administered for a minimum of five years) as a new treatment option versus ET alone in the NHS. The base case population is considered to be relevant to clinical practice within the NHS, reflecting the anticipated positioning of abemaciclib in the treatment pathway and those patients with high clinical unmet need.

A *de novo* cost-utility analysis of abemaciclib + ET versus ET relevant to the decision problem for this submission was performed. The analysis was conducted from the perspective of the NHS and Personal Social Services (PSS) over a lifetime time horizon. Sections B.3.2.1, B.3.2.2 and B.3.2.3 present the patient population, the model structure and the included interventions and comparators, respectively.

B.3.2.1 Patient population

The analyses evaluated the cost-effectiveness of abemaciclib + ET in patients with HR+, HER2−, node-positive early breast cancer at high risk of recurrence using data from the monarchE trial, in line with the final scope.

B.3.2.2 Model structure

The model structure was based on previous early breast cancer models in the HER2+ patient population, the treatment pathway of patients with HR+/HER2− early breast cancer, data availability from the monarchE trial, and feedback from clinical experts.[23]

A cohort state transition model with five health states was developed. The health states were IDFS, non-metastatic recurrence, remission, metastatic recurrence, and death. Death and metastatic recurrence were modelled as absorbing health states.

Figure 10 illustrates the top-line model structure. All patients enter the model in the IDFS health state and receive ET. Patients in the abemaciclib treatment arm additionally receive abemaciclib treatment for a maximum of two years. From the IDFS health state patients can either, i) die, ii) experience a disease recurrence and transition to the metastatic or iii) the non-metastatic recurrence health state, or iv) remain in the IDFS health state.

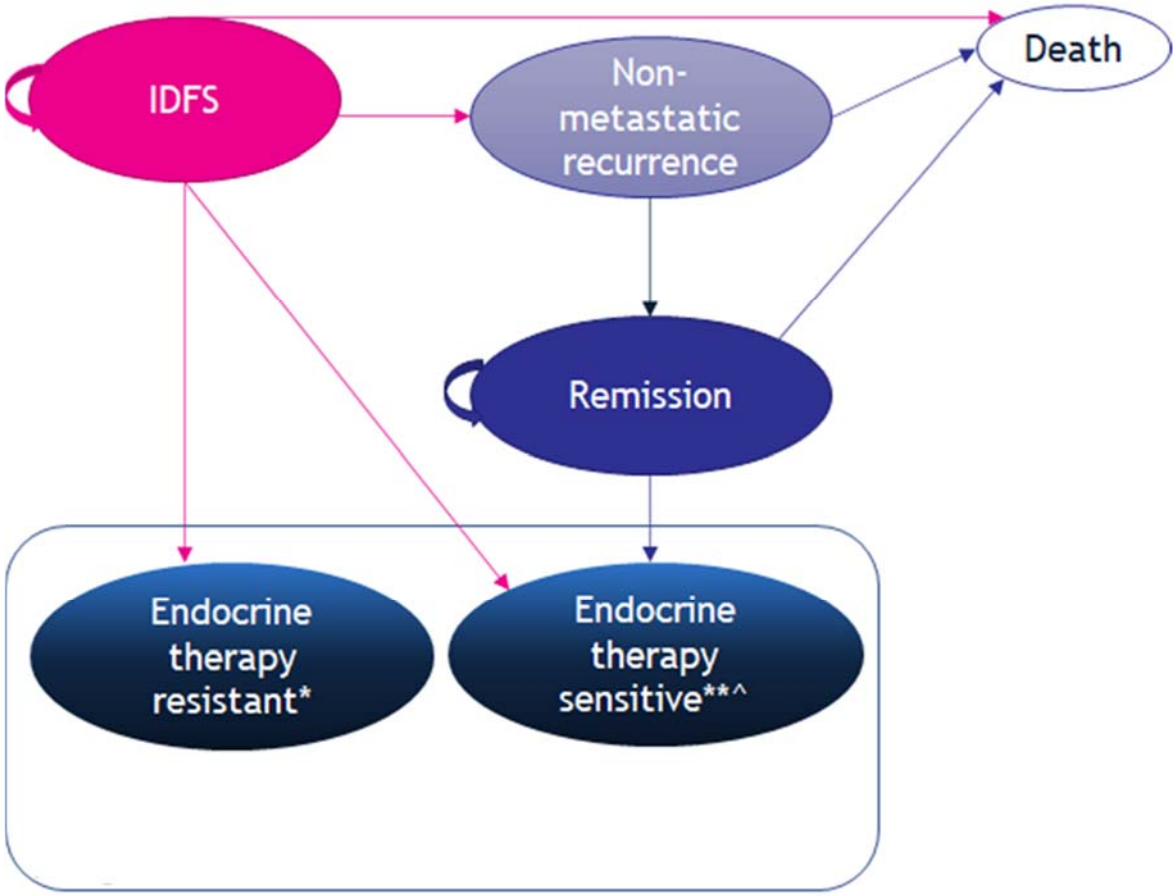
The non-metastatic recurrence state is split into two sub-states, second primary neoplasm and locoregional/contralateral. Second primary neoplasm was modelled as an absorbing state with patients only being allocated the cost of diagnosis following which they leave the model. This assumption is a necessary distinction from previous NICE appraisals in early breast cancer, which used *invasive breast cancer free survival* rather than IDFS, and therefore did not consider second primary neoplasm. Locoregional/contralateral recurrence was modelled as a tunnel state with patients receiving treatments dictated by the type/location of the disease recurrence experienced. Patients can die at any point from non-metastatic recurrence. Those who do not die are assumed, in the base case, to receive 12 months of treatment before transitioning to the remission health state. Once in remission, patients remain there unless they experience another recurrence. Such a further recurrence is assumed to be non-curative (i.e., either locally advanced or metastatic). From the remission health state, the model also allows patients to die from any cause.

Due to limited follow up in the latest monarchE data cut it was not possible to estimate transition probabilities for patients after experiencing a metastatic recurrence. Patients who experienced either a locally advanced (with non-curative intent) or a metastatic recurrent event were instead modelled as entering an absorbing health state with fixed payoffs for costs, LYs and QALYs.

Abemaciclib has previously been assessed in the advanced breast cancer setting, using the MONARCH 2 (ET-resistant) or MONARCH 3 (ET-sensitive) trials to inform clinical efficacy. From the IDFS health state patients followed either the ET-resistant pathway (based on the cost-effectiveness analysis in TA725) or the ET-sensitive pathway (based on the cost-effectiveness analysis in TA563) depending on their duration of the disease-free interval (DFI).

- **Endocrine -resistant:** Patients in IDFS who experience a disease recurrence while receiving adjuvant ET or within 12 months of completing adjuvant ET.
- **Endocrine-sensitive:** Patients in IDFS who experience a disease recurrence more than 12 months after completing their adjuvant ET.

Figure 10: Structure of the model used in the economic analysis



Abbreviations: IDFS: invasive disease free survival.

Health State Specific Assumptions

Non-metastatic recurrence

From the monarchE trial, a regional invasive breast cancer recurrence, and a contralateral invasive breast cancer are all assumed to be a non-metastatic recurrence event. This was in line

with the standardised definitions for efficacy end points criteria from the STEEP system developed by Hudis et al. (2007).[71]

Patients experiencing non-metastatic recurrence were assumed to have a negligible risk of experiencing metastases during the 12-month treatment period. Alternative evidence was not identified from literature or during consultations with clinical experts. The transition from non-metastatic recurrence to metastatic recurrence was not considered in the model.

Secondary primary neoplasm

The monarchE trial includes a 'second primary non-breast invasive cancer' or a 'second primary neoplasm' as an IDFS event. The CSR (PO data) states that it is not considered as a recurrence event of 'this' breast cancer.[23] Clinical experts agreed that these events should not be considered a NMR event as their treatment pathways are different. Furthermore, all recent HER2+ early breast cancer NICE TAs excluded second primary neoplasms from the definition of IDFS used in their cost-effectiveness models, an assumption which was accepted by the Committee.

Feedback from clinical experts indicated that neither abemaciclib + ET or ET alone results in any additional risk of a secondary primary neoplasm in clinical practice. The results of the AFU1 data cut validate this assumption, as the first occurrence of a secondary primary neoplasm was [redacted]% in both the abemaciclib + ET arm and the ET alone arm. Accordingly, it is assumed that the risk of a second primary neoplasm is equal across both treatment arms in the model. Feedback from clinical experts confirmed that this is an appropriate assumption.

To maintain a simple model structure, the full pathway of a second primary neoplasm is not modelled. For those patients who experience a second primary neoplasm they incur the cost of diagnosis of the event and exit the model after entering the non-metastatic recurrence health state. Further information on the costs associated with secondary primary neoplasm are presented in Section B.3.5.2.

Features of the economic analysis

A 28-day cycle length has been used in the model, which was deemed sufficient to accurately capture the clinical and cost outcomes for patients from the monarchE trial. Half cycle correction has been applied to account for events not occurring at beginning or end of every cycle. Based on the reference case, a 3.5% discount rate has been applied to the cost and effects.

The analyses were undertaken from a UK National Health Service (NHS) and Personal Social Services (PSS) perspective.

In line with the reference case, the cost and outcomes in the analyses were calculated over a lifetime horizon. In the model, lifetime corresponds to 49 years as this is the time point by which survival in both arms fell to <0.1% for the base case extrapolations.

The analyses calculate benefit in terms of life years (LYs) and quality-adjusted life years (QALYs). Base case results were generated using QALYs as the measure of benefit and the primary outcome was the incremental cost per QALY.

The key features of the model are outlined in Table 35. For the metastatic pay-off approach adopted, undiscounted LYs are taken from the ET-resistant metastatic setting and ET-sensitive

metastatic setting, aligning with the cost-effectiveness analyses for previous abemaciclib appraisals, TA725 and TA563, as much as possible.[7, 32] The costs applied from these models are discounted in the monarchE model, life years are undiscounted.

Table 35: Features of the economic analysis

	Previous appraisals		Current appraisal	
Factor	**TA632[67]**	**TA612[45]**	**Chosen values**	**Justification**
Model design	Markov model	Markov model	Markov model	In early breast cancer there are inherently insufficient long term follow up data to populate a partitioned survival model. In line with similar appraisals in HER2+ early breast cancer, a Markov structure was considered appropriate
Time horizon	51 years (lifetime)	55 years (lifetime)	49 years (lifetime)	NICE reference case[72]
Perspective	UK NHS and PSS	UK NHS and PSS	UK NHS and PSS	NICE reference case[72]
Cycle length	1 month	1 month	28 day	Deemed sufficient to accurately capture the clinical and cost outcomes for patients from the monarchE trial
Annual Discount rate	3.5%	3.5%	3.5%	NICE reference case[72]
Source of utilities	KATHERINE trial	ExteNET trial and published literature	• monarchE trial for IDFS utility • Published utility values for post-IDFS health states • Committee preferred utility values from TA725 and TA563 for metastatic health states	Abemaciclib trial data used where possible in both EBC and advanced BC, supplemented by literature values where required and aligned with committee preferred utility values from previous appraisals where possible.
Source of costs and resource use	• Published literature • Expert opinion	• NHS Reference Costs • BNF • Published literature	• National Schedule of NHS Costs 2019/20 • PSSRU 2020 • eMIT	NICE reference case[72]

		• Expert opinion	• BNF • monarchE trial • Expert opinion	
Health effects measure	QALYs	QALYs	QALYs	NICE reference case[72]

Abbreviations: BC: breast cancer; BNF: British National Formulary; EBC: early breast cancer; eMIT: electronic market information tool; HER2+: human epidermal receptor 2 positive; IDFS: invasive disease-free survival; NHS: National Health Service; NICE: National Institute for Clinical Excellence; PSS: Personal Social Services; PSSRU: Personal Social Services Research Unit; TA: technology appraisal; UK: United Kingdom; QALYs: quality-adjusted life years.
Source:

B.3.2.3 Intervention technology and comparators

The intervention of interest is abemaciclib 150 mg twice daily for up to 2 years in combination with ET (which is given for up to 5 or 10 years). This is in line with the regimen used in the monarchE trial informing the submission as well as the licence for abemaciclib.[4]

In the monarchE trial, abemaciclib + ET was compared to ET. ET comprised physician's choice of standard ET used in routine clinical practice and was confirmed to be relevant to NHS clinical practice in the UK by clinical experts, in line with the decision problem of this submission. The full list is presented in the monarchE CSR and includes:

- Aromatase inhibitors (AIs)
    - Anastrozole
    - Exemestane
    - Letrozole
- Anti-oestrogens
    - Tamoxifen

In the model, ET is costed as a weighted average of these treatments, based on the proportions of patients receiving each treatment in the monarchE trial, as detailed in Table 36. Information on the costs of ET included in the cost-effectiveness model are provided in Section B.3.5.

Table 36: Proportion of patients receiving each endocrine therapy in the model

Endocrine therapy	Proportion of patients receiving treatment in the model
Letrozole	[redacted]
Anastrozole	[redacted]
Tamoxifen	[redacted]
Exemestane	[redacted]

B.3.3 *Clinical parameters and variables*

The model structure uses IDFS, TTD, and OS (without distant recurrence) data from the monarchE trial to parameterise transitions for the abemaciclib + ET and ET treatment arms. Section B.3.3.1 discusses all the data sources used across all health states to inform the clinical

outcomes in the model. The methods of estimating long term IDFS, TTD, and OS (without distant recurrence) are discussed in Section B.3.3.2.

B.3.3.1 Data sources

A summary of the clinical effectiveness data sources and methods of parametrisation is presented in Table 37.

Table 37: Summary of clinical effectiveness data sources and methods of parameterisation

	Abemaciclib + ET	ET	Assumptions
IDFS	monarchE[23]	monarchE[23]	Based on the piecewise analysis from the monarchE trial, the HRs for Year 2+ (by which time most patients have discontinued treatment) suggest that a lasting treatment effect beyond discontinuation does exist for abemaciclib. However, the exact duration of the treatment effect is uncertain. As such, waning of the treatment effect was assumed beyond clinical trial data, based on long term treatment effect observed for ET from historical trial data. Historical ET data indicated that treatment waning starting from Year 8 was a reasonable assumption.[39] In the absence of additional evidence, it was assumed that the treatment effect waning starts from Year 8 and wanes until Year 27, the time point in the model where IDFS rates equal background mortality (See Section B.3.3.2).[39] This is in line with the approach used in TA612.[45]
NMR	monarchE[23] Literature: TA632,[67] TA612[45] and TA569[46] Clinical expert feedback	monarchE[23] Literature: TA632,[67] TA612[45] and TA569[46] Clinical expert feedback	Clinical outcomes within the NMR health state assumed the same for both treatment arms.

Remission	Literature: Hamilton et al. (2015)[73] TA632,[67] TA612[45] and TA569[46] Clinical expert feedback	Literature: Hamilton et al. (2015)[73] TA632,[67] TA612[45] and TA569[46] Clinical expert feedback	Clinical outcomes within the remission health state assumed same for both treatment arms.
OS (without distant recurrence)	monarchE[23]	monarchE[23]	Death rates from NMR and remission health states assumed same as the death rate from IDFS health state. Background mortality acts as a lower bound for the OS curve. Waning of treatment effect assumed beyond clinical trial data. Similar justification to IDFS.
Metastatic setting (ET-resistant and ET-sensitive)	ET-resistant (based on MONARCH 2) and ET-sensitive (based on MONARCH 3) [7, 32]	MONARCH 2 and MONARCH 3	Patients who do not experience a recurrent event for 12 months are considered to have endocrine-sensitive metastatic breast cancer, and will be modelled based on a previous cost-effectiveness analysis for patients in the MONARCH 3 indication (patients with previously untreated, hormone receptor-positive, HER2−, locally advanced or metastatic breast cancer), using the Committee's preferred assumptions from TA563 as far as possible.[32] Patients who do experience a recurrent event within 12 months are considered to have endocrine-resistant metastatic breast cancer, and will be modelled based on a previous cost-effectiveness analysis for patients in the MONARCH 2

			indication (patients with previously untreated, hormone receptor-positive, HER2−, locally advanced or metastatic breast cancer) using the Committee's preferred assumptions from TA725 as far as possible. [7]

Abbreviations: ET: endocrine therapy; HER2: human epidermal receptor 2; HR: hazard ratio; IDFS: invasive disease-free survival; NMR: non-metastatic recurrence; OS: overall survival; TA: technology appraisal.

B.3.3.2 Time to event analyses and efficacy outcomes

The IPD from the monarchE trial was used to generate the IDFS, TTD, and OS (without distant recurrence) outcomes for both abemaciclib + ET and ET. The parametrised curves for IDFS, TTD, and OS were utilised in the model. The parametrisation of the IDFS, TTD, and OS curves for abemaciclib + ET and ET aids in estimating long term outcomes for patients beyond the trial period and subsequently allows for modelling over a longer time period. At the time of the most recent data cut-off, the median treatment duration of abemaciclib was [redacted] months and the median duration of ET was balanced between the arms ([redacted] months in the abemaciclib arm and the ET alone arm). The analyses were carried out using SAS (traditional parametric models) and R (cubic spline models). More information on treatment exposure is presented in Section B.2.10.1.

Parametric models were fitted to the KM data of the monarchE trial. The parametric model fitting for IDFS, TTD and OS without distant recurrence was conducted according to the following steps recommended in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14:[74]

1) Tests for the proportional hazards (PH) assumption between treatment arms were conducted, which inferred the choice of fitting independent or dependent models. If the PH assumption held, a single dependent model for each survival curve was estimated, with treatment modelled as a single covariate. If violated, the same distribution was selected for both arms and fitted independently.
2) The parametric survival models were fitted to the survival data of monarchE
3) An initial selection of extrapolation models was based on visual inspection and statistical fit of the models to the trial data, based on Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC), as well as visual inspection of the survival and hazard curves
4) The models were further evaluated against additional evidence from data in the published literature. For outcomes where no additional evidence was available, model selection was based on the outcomes of step 3

Methodology

Proportional hazards assumption

The PH assumption was investigated using both qualitative assessment and quantitative assessment, as listed below:

1. **Log-cumulative hazard plots:** Log-cumulative hazard plots can be constructed to illustrate the hazards observed in the trial. A hazard plot of the log(cumulative hazard) against log(time) was used to assess proportionality of hazards over time and identify potential important changing points, with parallel curves of the different treatment arms indicating that the PH assumption was not violated. It is important to note that assessing parallelism is rather subjective, and non-crossing of the hazards does not conclude that the PH assumption is met. Additional graphical and statistical tests are needed to assess this assumption.

2. **Schoenfeld residuals test:** Testing for time dependency of the hazard ratio is equivalent to testing for a non-zero slope in a generalised linear regression of the scaled Schoenfeld

residuals over time. A non-zero slope is an indication of a violation of the PH assumption. In case the log(HR) does not fall within the 95% confidence interval (CI) bands, it could be a strong indicator for violation of proportionality between the two curves.

3. **Grambsch and Therneau test:** In addition to graphical assessments, statistical goodness of fit tests were used to assess whether the slope in a generalised linear regression of the scaled Schoenfeld residuals over time is zero. The Grambsch and Therneau test was used for this purpose. The test outcome is a measure of the correlation between the covariate specific residual and event times. If the p-value is significant (<0.05), it can be viewed as a violation of the null hypothesis of PH.

Survival extrapolation approaches

In accordance with NICE DSU TSD 14,[74] the range of parametric distributions fitted to the monarchE trial were: exponential, Weibull, Gompertz, log-normal, log-logistic, gamma and generalised gamma. In addition to the standard parametric distributions, Weibull spline models (from now on, referred to as hazard splines) with one and two intermediate knots were examined. Spline models with more intermediate knots were not considered, as these are deemed clinically implausible and associated with the risk of "overfitting" the data.

Model selection

A selection of extrapolation models was based on statistical fit of the models to the trial data, based on AIC and the BIC, as well as visual inspection of the survival curves and hazard plots. Consideration was given to the following, as per the recommendations provided in NICE DSU TSD 14.[74]

- Statistical fit criteria
- Visual inspection of extrapolation curves
- Visual inspection of smoothed hazard curves
- Consideration of data in the published literature

Analysis outcomes

Invasive disease free survival

The PH assumption between treatment arms was tested. The log-cumulative plot in Figure 11 shows the treatment arms are crossing during the first four months, after which they appear to move in parallel. The Grambsch and Therneau test could not be labelled as statistically significant (p-value = 0.227). This is consistent with the Schoenfeld residuals visualisation Figure 12 in which no clear time trend can be observed, suggesting no violation of the PH assumption. As such, a single model, including an adjustment factor for treatment effect (HR), could be fitted to the IDFS curve of the monarchE data.

Figure 11. IDFS log-cumulative hazard plot

Abbreviations: ET: endocrine therapy; SDF: survival distribution function; IDFS: invasive disease-free survival.

Figure 12: IDFS Schoenfeld residual plot

Footnotes: The red line indicates no treatment effect.
Abbreviations: IDFS: invasive disease-free survival.

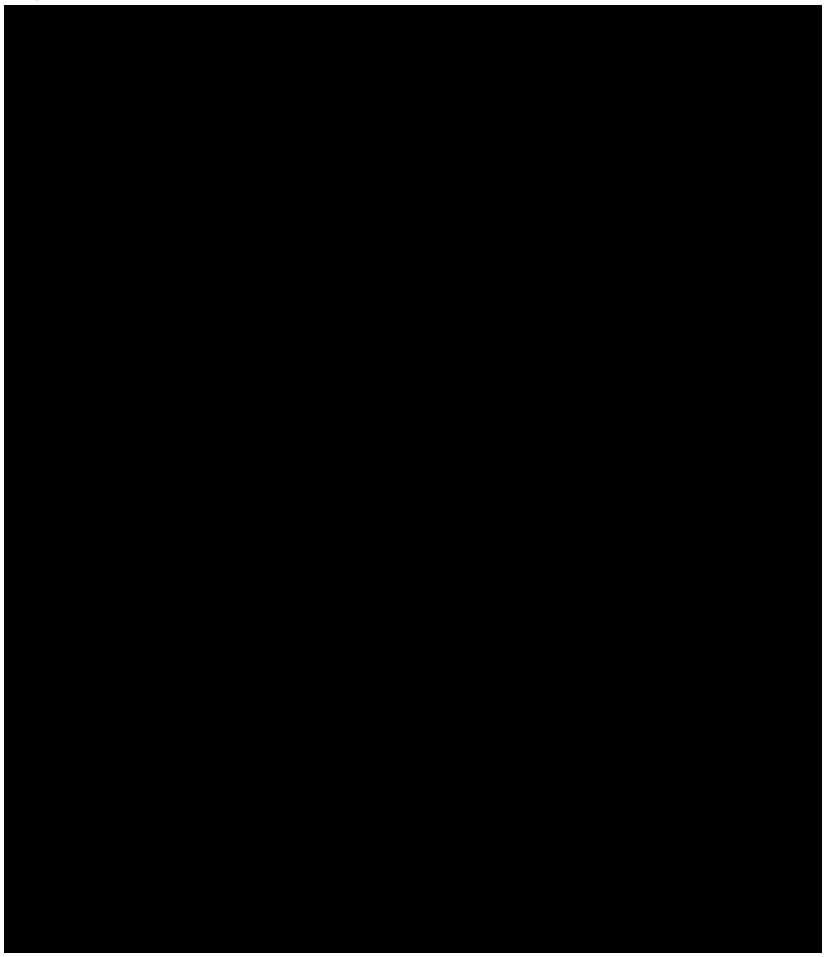
Seven parametric distributions and two spline models were fitted to the IDFS KM data and were evaluated based on AIC and BIC of the dependent models. A summary of all the AIC and BIC values is presented in Table 38.

Table 38: AIC and BIC values for IDFS extrapolations

Dependent distributions			
Distributions	**AIC**	**Distributions**	**BIC**
Weibull	[redacted]	Weibull	[redacted]
Log-logistic	[redacted]	Log-logistic	[redacted]
Hazard spline 1 knot	[redacted]	Gompertz	[redacted]
Generalised gamma	[redacted]	Hazard spline 1 knot	[redacted]
Gamma	[redacted]	Generalised gamma	[redacted]
Hazard spline 2 knots	[redacted]	Gamma	[redacted]
Gompertz	[redacted]	Exponential	[redacted]
Log-normal	[redacted]	Hazard spline 2 knots	[redacted]
Exponential	[redacted]	Log-normal	[redacted]

Note: the curves are in descending order according to how well they fit. The best fitting curve is in **bold**
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; IDFS: invasive disease-free survival.

Figure 13: AIC/BIC values for IDFS extrapolations



Footnotes: A lower AIC/BIC value indicates a better fitting curve.
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; IDFS: invasive disease-free survival.

The best statistical fit is provided by the Weibull distribution as it presents both the lowest AIC and BIC values. The Weibull distribution is followed by the log-logistic distribution, which deviates less than 2.0 points from the Weibull distribution in both AIC and BIC, indicating no significant difference between the two distributions in terms of statistical fit.

External validation

As well as statistical fit, the choice of extrapolation to model IDFS was informed by comparing the landmark IDFS estimates for abemaciclib + ET and ET alone predicted by the model to external data sources.

As described in Appendix D, a clinical SLR was conducted to identify relevant RCTs evaluating ET-regimens in patients with HR+, HER2− early breast cancer. An overview of the studies identified and the IDFS rates predicted has been provided in Table 39.

While the efficacy of different CDK4/6 inhibitors has historically been considered to be similar in the advanced setting, the PENELOPE and PALLAS trials both assessed palbociclib and found there to be no evidence to suggest that the addition of palbociclib to ET had any benefits in the early breast cancer setting. As such, palbociclib outcomes in the early breast cancer setting

should not be considered to be directly comparable to those of abemaciclib, and cannot be used to validate the choice of extrapolation.

Out of the six trials assessing ET regimes only, two trials did not include patients who were offered pre-treatment with neoadjuvant and adjuvant therapies. One trial only reported safety data. FATA-GIM3[30] and FACE[31] were the remaining trials which were comparable to monarchE, although additional event types were included in their disease-free survival (DFS) definition. The five-year DFS rates reported in these trials were used for external validation of extrapolations for the ET arm in the model.

Table 39. Comparison of HR+ HER2− early breast cancer trials identified from the clinical SLR reporting relevant survival outcomes

Trial name	Treatment	Timepoint for rate (Years)	IDFS/DFS rate (%) [95% CI]
monarchE[32]	ET + CDK4&6 inhibitors	~ 3	Abemaciclib + ET: 88.8 [87.0, 90.3][a] ET: 83.4 [81.3, 85.3][a]
HOBOE[35]	Tamoxifen vs. AI	~ 5	Tamoxifen: 85.4 [80.9, 88.9] Letrozole: 93.2 [89.7, 95.5]
FATA-GIM3[30]	**Tamoxifen to AI vs. AI**	**~ 5**	**Anastrozole pooled** **Letrozole pooled** **Exemestane pooled**
FACE[31]	**AI vs AI**	**~ 5**	**Letrozole: 84.9 [83.2-86.2]** **Anastrozole: 82.9 [81.2-84.5]**
SOFT[37]	Tamoxifen + OFS vs. AI + OFS	~8	Tamoxifen: 78.9 Exemestane + OFS: 85.9
TEXT[38]		N/A	Total events:[b] Tamoxifen + triptorelin: 12.59 Exemestane + triptorelin: 16.25

Footnotes: [a] 3-year IDFS rates from the AFU1. [b] The TEXT trial reported the total events, rather than the IDFS/DFS rate.
Abbreviations: AI: aromatase inhibitor; CDK: cyclin-dependent kinase; DFS: disease-free survival; ET: endocrine therapy; HER2−: human epidermal receptor 2 negative; HR+: hormone receptor positive; IDFS: invasive disease-free survival; N/A, Not applicable; OFS: ovarian function suppression; SLR: systematic literature review.

The landmark IDFS rates for abemaciclib + ET and ET alone for the seven parametric distributions and the two spline models are presented in Table 40.

The comparisons of the ET arm from monarchE and the external trials, should be approached cautiously as the populations and endpoints used in the external trials are not directly comparable with monarchE. External trials incorporated a mixture of patients, including those at lower risk of disease recurrence and hence had slightly better outcomes in the ET alone arms. For example, the FACT-GIM3 trial included patients with any pathological tumour size and

axillary lymph nodal status. However, this this was considered to be the most plausible method for validation of the extrapolations by UK clinical experts. When comparing the monarchE trial data with the five-year IDFS/DFS estimates for ET from the FACE trial (letrozole: 84.9% [95% CI: 83.2%, 86.2%] and anastrozole: 82.9% [95% CI: 81.2%, 84.5%]), all the extrapolations appear to estimate pessimistic outcomes for the ET arm as the monarchE trial only included patients at high risk of disease recurrence and therefore with worse disease prognosis.[31]

Table 40. Landmark IDFS rates for abemaciclib + ET and ET alone arms

	Five-year rates		Ten-year rates	
	Abemaciclib + ET	**ET**	**Abemaciclib + ET**	**ET**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Hazard spline 1 knot	[redacted]	[redacted]	[redacted]	[redacted]
Hazard spline 2 knots	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ET: endocrine therapy; IDFS: invasive disease-free survival.

The highest five-year IDFS rates for the ET arm were predicted by the log-normal ([redacted]%), exponential ([redacted]%) and log-logistic ([redacted]%) extrapolations. Considering the five-year IDFS rates predicted for the abemaciclib + ET arm by these extrapolations, the log-logistic extrapolation provided the most realistic estimate of [redacted]%, which appears plausible when considering the three-year IDFS rates estimated by the monarchE trial data ([redacted]%).

When considering the two best statistically fitting curves, the Weibull and the log-logistic, both appeared to underestimate outcomes for the ET arm. Given the log-logistic extrapolation predicts the higher IDFS rates for the ET arm, it was chosen as the most plausible for the base case economic analysis.

This approach, and the five and 10-year extrapolation results, were validated by UK clinical experts. Other extrapolations for IDFS were explored as scenario analyses (Section B.3.8.3).

Treatment waning

A piecewise analysis for IDFS in monarchE was performed at the most recent data cut-off. The results showed that the HRs over Year 0–1, Year 1–2 and Year 2+ were [redacted], [redacted] and [redacted], respectively (Table 15). The HRs, covering the period by which time most patients will have discontinued treatment, continue to deepen between Year 1–2 and Year 2+, which suggests that a lasting treatment effect beyond discontinuation does exist for abemaciclib. This is aligned with the evidence for other early breast cancer therapies and as such, a treatment effect beyond discontinuation was assumed for abemaciclib.

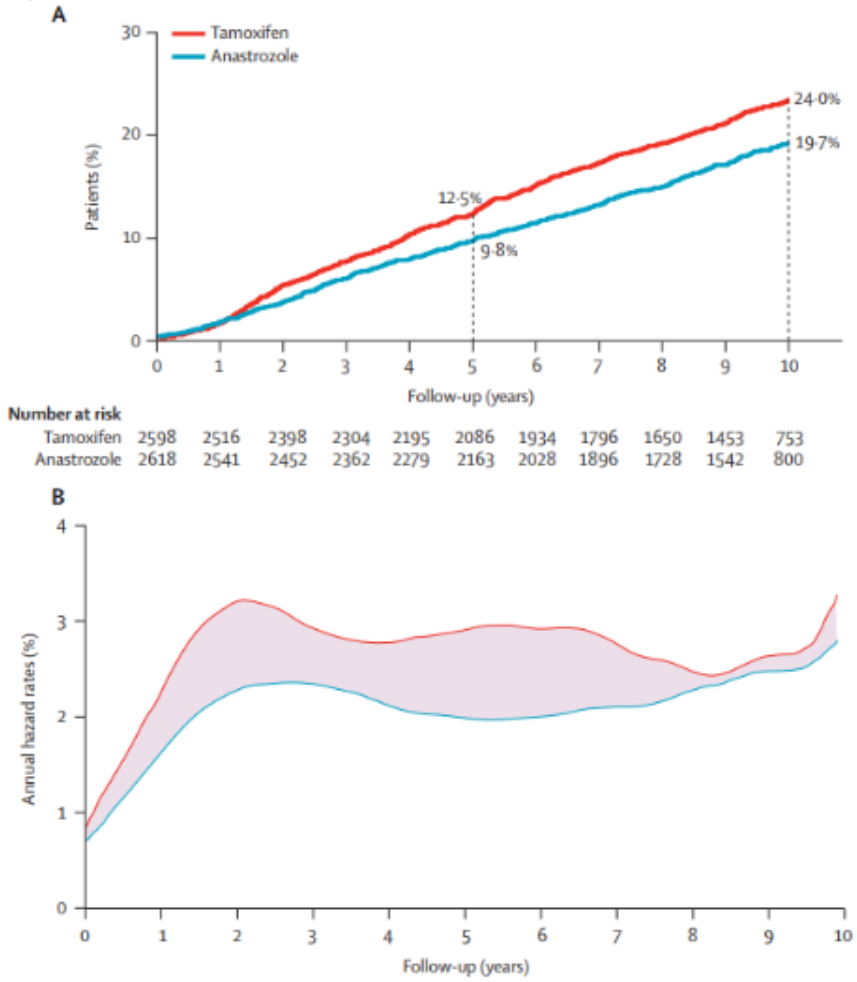
The existence of a lasting treatment effect is evident from monarchE, but due to the limited follow-up nature of the monarchE trial, the exact duration of the treatment effect associated with abemaciclib + ET is uncertain.

The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial was one of the few trials reporting on long term follow up data for anastrazole and tamoxifen for up to 10 years and clinical experts noted that the ATAC trial was the most relevant to inform treatment waning assumptions. The trial does not however report data on HER2 status. The authors of the paper demonstrate the falling recurrence rates for HR+ patients on anastrazole versus tamoxifen over time with 'carryover benefit' lasting up to 8 years following which the treatment effect begins to wane.[75] In an earlier publication 'carryover' effect was also discussed (see Figure 14).[40] Based on the results of Early Breast Cancer Trialists' Collaborative Group, 2005 and ATAC Trialists' Group, 2005 it was highlighted that effect of tamoxifen and AIs on recurrence rates were maintained for at least five and six years respectively after stopping treatment. In the absence of additional evidence, it was assumed that the treatment effect waning starts from Year 8.

In the absence of longer follow up data from other trials reporting specifically on HER2− status, the cost-effectiveness analysis assumes that the treatment effect difference between abemaciclib + ET versus ET alone would be similar to the treatment effect differences observed in the ATAC trial. It is assumed that treatment effect lasts for at least eight years from initiation of treatment with abemaciclib following which treatment effect starts to wane. Treatment effect wanes until Year 27, following which no treatment benefit was assumed. Year 27 was chosen because this was the point in the model where IDFS rates equal background mortality (Figure 15). The long-term extrapolations for abemaciclib + ET and ET using the loglogistic model and including the treatment waning assumptions are presented in Figure 16.The impact of the timing and duration of the treatment waning effect has been explored in scenario analyses (See Section B.3.8.3).

A lasting treatment effect has been assumed and accepted in a variety of previous NICE appraisals in the early breast cancer setting, including TA612 in which waning the treatment effect until the point in the model where IDFS rates equal background mortality was also adopted and accepted.[45]

Figure 14: Curves for time to recurrence in HR+ patients in the ATAC trial



Footnotes: A) KM prevalence curves and B) smoothed hazard rate curves. Numbers at risk differ in some cases from those provided in the 100-month analysis because of additional follow-up data.
Abbreviations: ATAC: Arimidex, Tamoxifen, Alone or in Combination; HR+: hormone receptor positive.
Source: Cuzick *et al.* (2010)[75]

Figure 15: Crossing of the hazard rate with general population morality[a]

Footnotes: [a] Hazard rate for the general populations mortality is in line with the DRFS ET hazard rate and therefore lies behind the green line. The rates can be assumed to be equal.
Abbreviations: ABE: abemaciclib; DRFS: distant relapse-free survival; ET: endocrine therapy

Figure 16: Long-term IDFS extrapolations for abemaciclib + ET and ET alone in the base case economic analysis

Footnotes: These extrapolations include treatment waning.
Abbreviations: ET: endocrine therapy; IDFS: invasive disease-free survival; KM: Kaplan-Meier.

Time to treatment discontinuation

The duration of treatment is determined by the TTD curves of the abemaciclib + ET and ET only treatment arms from the monarchE trial. In the monarchE trial, patients remained on treatment until they 1) reached a limit defined by a clinical stopping rule, 2) discontinued treatment due to toxicity, or 3) withdrew from study or experienced disease recurrence.

The PH assumption was tested between ET in the intervention arm and ET in the comparator arm. The log-cumulative plot in Figure 17 shows that there is convergence of the trial arms at several points in the plot, most noticeably during the first month and after 20 months. The Grambsch and Thernau test should be interpreted as statistically significant (p-value = [redacted]). This is consistent with the Schoenfeld residuals visualisation (Figure 18), in which clear time trends can be observed, suggesting violation of the PH assumption.

As such, three independent models were used in the base case cost-effectiveness analysis: one model fitted to the trial data for abemaciclib, one to the trial data for ET (for patients receiving abemaciclib) and one for ET (for patients receiving ET alone).

Figure 17. TTD log-cumulative hazard plot

Abbreviations: ET: endocrine therapy; SDF: survival distribution function; TTD: time to treatment discontinuation.

Figure 18. TTD Schoenfeld residual plot

Footnotes: The red line indicates no treatment effect.
Abbreviations: TTD: time to treatment discontinuation.

The seven parametric distributions and two spline models were fitted independently to the TTD KM data and were evaluated based on AIC and BIC, as presented in Table 41 to Table 43 and Figure 19 to Figure 21 below.

Table 41: AIC and BIC values for TTD extrapolations – abemaciclib

Abemaciclib – Independent distributions			
Distributions	**AIC**	**Distributions**	**BIC**
Hazard spline 2 knots	[redacted]	Hazard spline 2 knots	[redacted]
Log-normal	[redacted]	Log-normal	[redacted]
Hazard spline 1 knot	[redacted]	Hazard spline 1 knot	[redacted]
Generalised gamma	[redacted]	Generalised gamma	[redacted]
Log-logistic	[redacted]	Log-logistic	[redacted]
Weibull	[redacted]	Weibull	[redacted]
Gamma	[redacted]	Gamma	[redacted]
Exponential	[redacted]	Exponential	[redacted]
Gompertz	[redacted]	Gompertz	[redacted]

Note: the curves are in descending order according to how well they fit.
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; TTD: time to treatment discontinuation.

Table 42: AIC and BIC values for TTD extrapolations – ET intervention arm

ET intervention arm – Independent distributions			
Distributions	**AIC**	**Distributions**	**BIC**
Hazard spline 2 knots	[redacted]	Hazard spline 2 knots	[redacted]
Gamma	[redacted]	Weibull	[redacted]
Generalised gamma	[redacted]	Gamma	[redacted]

Weibull	[redacted]	Generalised gamma	[redacted]
Hazard spline 1 knot	[redacted]	Log-logistic	[redacted]
Log-logistic	[redacted]	Hazard spline 1 knot	[redacted]
Log-normal	[redacted]	Log-normal	[redacted]
Exponential	[redacted]	Exponential	[redacted]
Gompertz	[redacted]	Gompertz	[redacted]

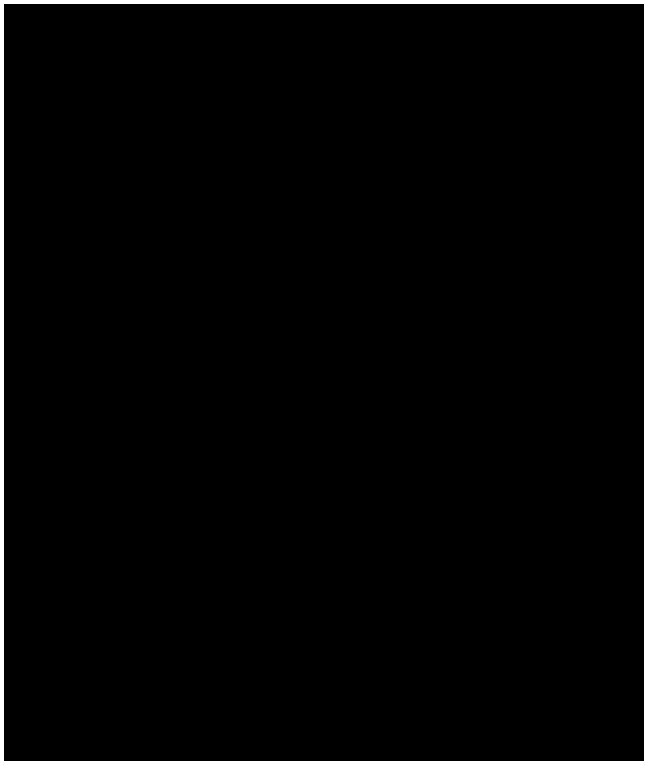
Note: the curves are in descending order according to how well they fit
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion. ET: endocrine therapy; TTD: time to treatment discontinuation.

Table 43: AIC and BIC values for TTD extrapolations – ET comparator arm

ET comparator arm – Independent distributions			
Distributions	**AIC**	**Distributions**	**BIC**
Hazard spline 2 knots	[redacted]	Hazard spline 2 knots	[redacted]
Hazard spline 1 knot	[redacted]	Hazard spline 1 knot	[redacted]
Gamma	[redacted]	Gamma	[redacted]
Generalised gamma	[redacted]	Generalised gamma	[redacted]
Weibull	[redacted]	Weibull	[redacted]
Log-logistic	[redacted]	Log-logistic	[redacted]
Exponential	[redacted]	Exponential	[redacted]
Gompertz	[redacted]	Gompertz	[redacted]
Log-normal	[redacted]	Log-normal	[redacted]

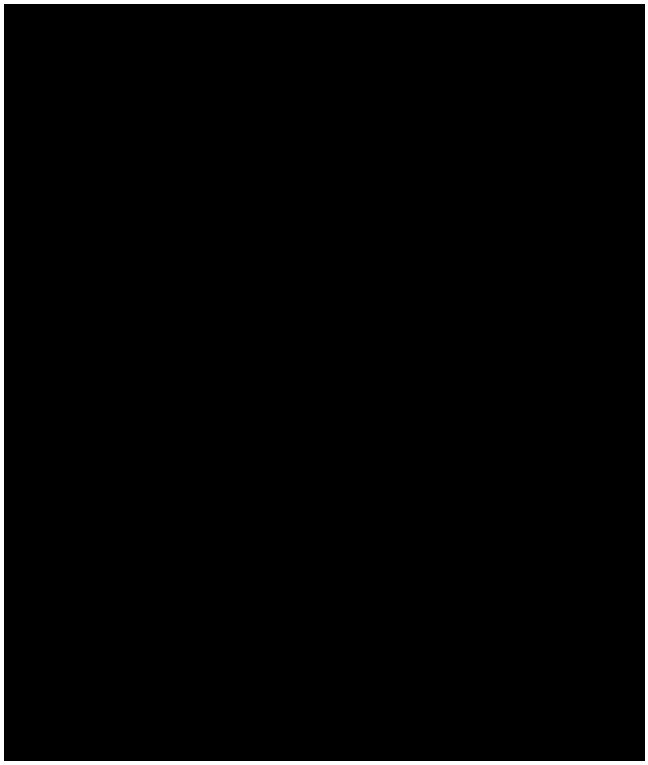
Note: the curves are in descending order according to how well they fit
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion. ET: endocrine therapy; TTD: time to treatment discontinuation.

Figure 19: AIC and BIC values for TTD extrapolation – abemaciclib



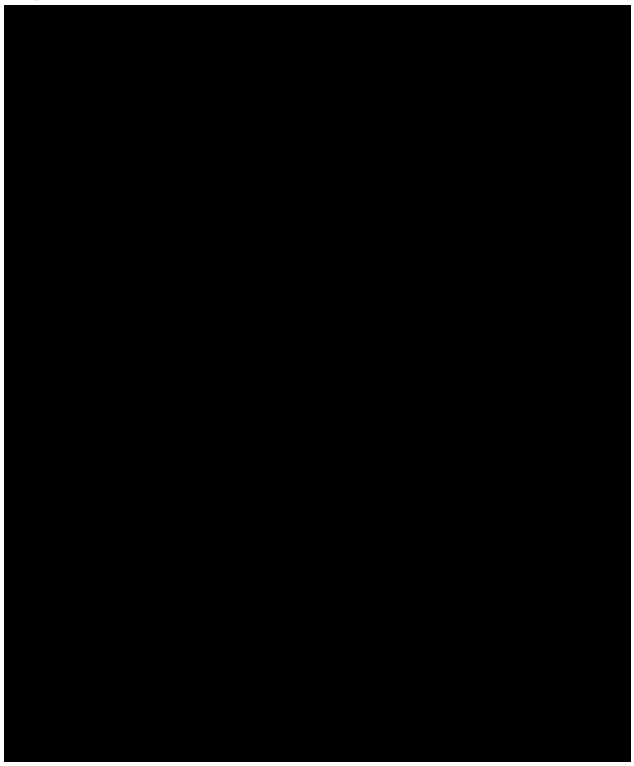
Footnotes: A lower AIC/BIC value indicates a better fitting curve
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; TTD: time to treatment discontinuation.

Figure 20: AIC and BIC values for TTD extrapolations – ET intervention



Footnotes: A lower AIC/BIC value indicates a better fitting curve
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; ET: endocrine therapy; TTD: time to treatment discontinuation.

Figure 21: AIC and BIC values for TTD extrapolation – ET comparator



Footnotes: A lower AIC/BIC value indicates a better fitting curve
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; ET: endocrine therapy; TTD: time to treatment discontinuation.

The best statistical fit was provided by the hazard spline 2 knots based on AIC and BIC for the intervention and comparator arms. Evidence from the monarchE trial was deemed the most recent and relevant for the validation of the TTD extrapolations. Since a clinical and economic stopping rule of 5 years was also applied for the ET arm in the base case analysis, there is limited risk of bias being introduced into the model. As such, the distribution with the best statistical fit, a hazard spline 2 knots distribution, was chosen for the TTD base case. A 10-year stopping rule for the ET arm has been explored in a scenario analysis and other extrapolations for TTD were also explored as scenario analyses (Section B.3.8.3). The long-term extrapolations for TTD for abemaciclib + ET and ET alone using the models selected for the base case economic analysis ***(before the base case stopping rules are applied)*** are presented in Figure 22.

Figure 22: Long-term TTD extrapolations for abemaciclib + ET and ET alone in the base case economic analysis *(before the base case stopping rules for abemaciclib and ET are applied)*

Abbreviations: ET: endocrine therapy; KM: Kaplan-Meier; TTD: time to treatment discontinuation

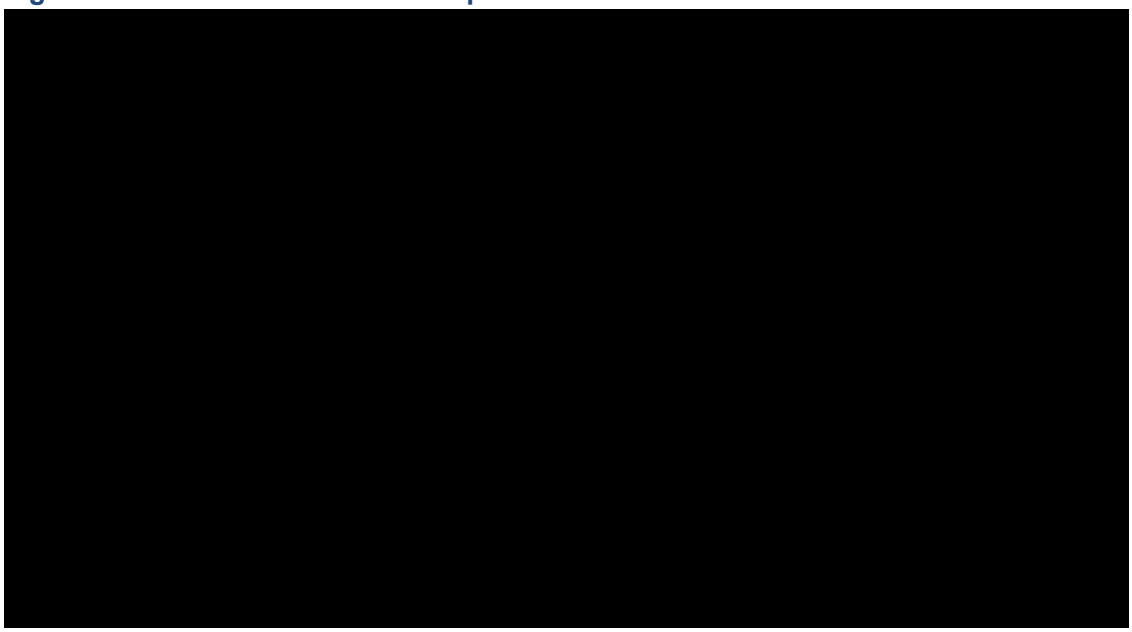
Overall survival

The log-cumulative hazard plot is displayed in Figure 23. The log-cumulative hazard plot does not suggest PH due to the crossing of the abemaciclib + ET and the ET curves. The Grambsch and Thernau test could not be labelled as statistically significant (p-value = [redacted]), which means that the PH assumption cannot be rejected based on this test. The Schoenfeld residuals plot (Figure 24) does seem to suggest a slightly increasing trend. However, it should be noted that these results should be considered volatile, as few OS without distant recurrence events were observed in the trial. As such, the base case cost-effectiveness model uses a single model fitted, using an adjustment factor for treatment effect (HR), to the monarchE trial data.

Figure 23. OS log-cumulative hazard plot

Abbreviations: ET: endocrine therapy; OS: overall survival; SDF: survival distribution function.

Figure 24. OS Schoenfeld residual plot



Footnotes: The red line indicates no treatment effect.
Abbreviations: OS: overall survival.

The seven parametric distributions and two spline models were fitted independently to the TTD KM data and were evaluated based on AIC and BIC, as presented in Table 44 and Figure 25.

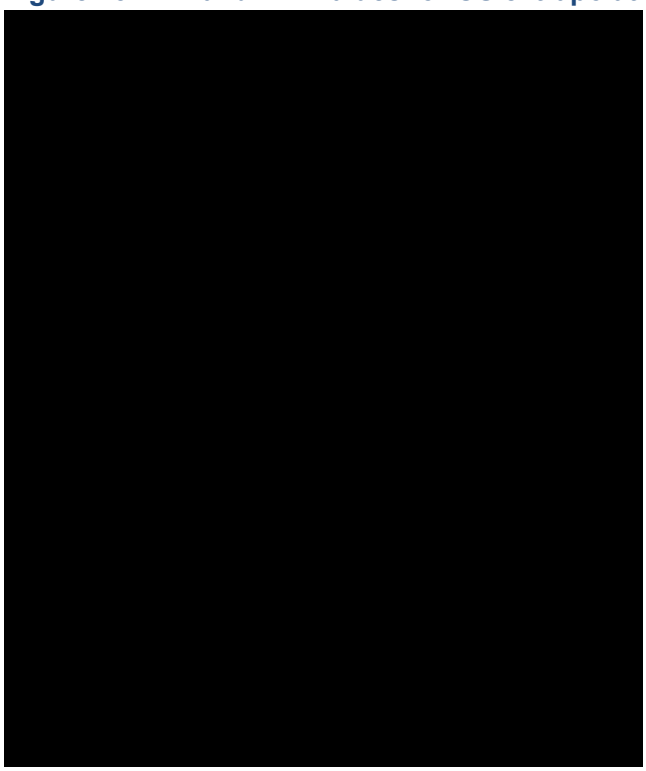
Table 44: AIC and BIC values for OS extrapolations

Dependent models			
Distributions	**AIC**	**Distributions**	**BIC**
Exponential	[redacted]	Exponential	[redacted]
Log-normal	[redacted]	Log-normal	[redacted]
Weibull	[redacted]	Weibull	[redacted]

Log-logistic	[redacted]	Log-logistic	[redacted]
Gompertz	[redacted]	Gompertz	[redacted]
Hazard spline 1 knot	[redacted]	Hazard spline 1 knot	[redacted]
Hazard spline 2 knots	[redacted]	Hazard spline 2 knots	[redacted]
Generalised gamma	[redacted]	Generalised gamma	[redacted]
Gamma[a]	[redacted]	Gamma	[redacted]

Note: The curves are in descending order according to how well they fit. [a] The Gamma distribution did not converge; hence the statistical fit of this model is not assessed.
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; N/A*: not applicable; OS: overall survival.

Figure 25: AIC and BIC values for OS extrapolations



Footnotes: A lower AIC/BIC value indicates a better fitting curve
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; OS: overall survival.

The exponential curve provided the best statistical fit based on both AIC and BIC. This was followed by the log-normal, Weibull, log-logistic and Gompertz models which were all within 2 points of the exponential curve. Evidence from the monarchE trial was deemed the most recent and relevant for the validation of OS without distant recurrence extrapolations. Therefore, based on internal validation, the exponential model was used in the base case to model OS. Other extrapolations for OS have been explored as scenario analyses (Section B.3.8.3).The long-term OS extrapolations for abemaciclib + ET and ET alone using the exponential model are presented in Figure 26.

Figure 26: Long-term OS extrapolations for abemaciclib + ET and ET alone in the base case economic analysis

Footnotes: These extrapolations include the treatment waning assumptions.
Abbreviations: ET: endocrine therapy; OS: overall survival; KM: Kaplan-Meier.

Within the framework of the model, the OS extrapolations are close to the background mortality rate. Given risk of death from a non-metastatic recurrence is limited, the risk of any bias is low, as the OS curve is bound by background mortality.

Summary

A summary of the base case extrapolations for IDFS, OS and TTD for abemaciclib + ET and ET alone is provided in Table 45.

Table 45: Summary of the base case extrapolations for IDFS, OS and ToT for abemaciclib + ET and ET alone

	Abemaciclib + ET		ET alone
Base case IDFS extrapolation	Log-logistic		Log-logistic
Base case OS extrapolation	Exponential		Exponential
	Abemaciclib	**ET (for patients receiving abemaciclib)**	**ET alone**
Base case TTD extrapolation	Hazard spline 2 knots	Hazard spline 2 knots	Hazard spline 2 knots

Abbreviations: ET: endocrine therapy; IDFS: invasive disease-free survival; OS: overall survival; ToT: time on treatment; TTD: time to treatment discontinuation.

B.3.3.3 Remission health state

The clinical, observational and economic SLRs identified a lack of data surrounding the non-metastatic recurrence and onwards pathway for the monarchE patient population. Following consultation with clinical experts, assumptions previously made in early breast cancer models, specifically for the HER2+ patient population, were considered the most appropriate data source. The most recent NICE TA for trastuzumab was used to inform the transition probability of patients moving from remission to the metastatic health state.[67] TA632 used a study (Hamilton et al. (2015) of 12,836 patients with early breast cancer which estimated the risk of incurring a second malignancy following adjuvant therapy.[73] The study reported a mean time until progression of 7.6 years (91.2 months). The mean time to progression was converted into a monthly transition probability of 0.00760. In line with TA632 and clinical expert feedback, recurrence rate from the remission health state was assumed to remain constant over time.

B.3.3.4 Metastatic health state

At the time of the most recent data cut the monarchE trial had limited follow up data. The data on post-recurrence events was immature and it was deemed unsuitable to fit statistical distributions and extrapolate beyond the trial data. The clinical and observational SLRs were also unable to identify suitable data to model the metastatic setting in greater detail.

In the absence of clinical data for the monarchE distant recurrent population, data from a broader advanced breast cancer population which included patients at a high-risk were considered. As such, inputs and assumptions from previous abemaciclib cost-effectiveness analyses in the metastatic settings (TA563 and TA725) were used to inform outcomes for patients in the metastatic setting, aligning with the Committee's preferred assumptions in these appraisals where possible. The ET-resistant and ET-sensitive metastatic patient pathway in this model is based on cost-effectiveness analyses based on the MONARCH 2 and 3 trials respectively, and past appraisals of abemaciclib in these indications. The MONARCH 2 trial included HR+, HER2− locally advanced or metastatic breast cancer patients. The MONARCH 3 trial included postmenopausal women with HR+, HER2− locoregionally recurrent or metastatic breast cancer patients with no prior systemic therapy in the current disease setting.

Clinical outcomes from the cost-effectiveness analyses in TA563 and TA725, aligning with the Committee's preferences where possible, were deemed the most recent and relevant data sources to inform the metastatic health state in this submission.

It was not possible to directly align with the Committee's preferences for all inputs, due to the need to accurately represent the full range of treatments a patient might receive in the metastatic setting in UK clinical practice, including treatments which were not relevant comparators in TA563 and TA725. Full details of the clinical inputs used in the metastatic setting are presented in Appendix M and Appendix N.

While this does introduce uncertainty, scenario analyses presented in Section B.3.8.3 demonstrate that variation in the pay-offs in the metastatic setting only result in minor changes to the ICER, illustrating that variation in the costs and outcomes experienced in the metastatic setting does not have a major impact on results.

Metastatic health state 'pay-off' approach

A metastatic health state 'pay-off' approach was used to inform the metastatic health state in the cost-effectiveness model in this submission, whereby survival outcomes following progression to the metastatic health state from either the IDFS or the remission health states at point of recurrence were attributed a 'fixed pay-off' of LYs from previous cost-effectiveness analyses in the advanced breast cancer setting, based on assumptions from TA563 and TA725 as far as possible.[7, 32] The costs and utilities associated with each health state within the respective metastatic pathways were combined with the LYs to determine the estimated total costs and QALY outcomes for the metastatic setting in the monarchE model.

The relevant treatment received in the metastatic setting was dictated by advanced breast cancer guidelines, data from the monarchE trial, clinical expert opinion and market share information from NICE resource impact statements and budget impact analyses from TA563 and TA725. There is currently no evidence regarding the efficacy associated with the use of a CDK4/6 inhibitor following disease recurrence either while on, or after, a prior CDK4/6 inhibitor treatment. Therefore, as stated by UK clinical experts, it was assumed that patients who received abemaciclib in the adjuvant setting were not permitted to receive a CDK4/6 inhibitor treatment in the metastatic setting. Within a scenario analysis, CDK4/6 inhibitor re-treatment has been assessed.

The treatment options included within the model for the two metastatic pathways are presented in Table 46. The second and third-line treatment assumptions are based on TA563, TA725, as well as Lilly's current understanding of clinical practice in the UK.

Table 46: Treatments received in each metastatic pathway

Endocrine treatment resistant	Endocrine treatment sensitive

• CDK 4/6 inhibitors
  o Abemaciclib + Fulvestrant
  o Palbociclib + Fulvestrant
  o Ribociclib + Fulvestrant
• Exemestane
• Exemestane + Everolimus
• Fulvestrant
• Capecitabine
	• CDK 4/6 inhibitors
	  o Abemaciclib + Non-steroidal aromatase inhibitor
	  o Palbociclib + Non-steroidal aromatase inhibitor
	  o Ribociclib + Non-steroidal aromatase inhibitor
	• Non-steroidal aromatase inhibitor
	• Exemestane
	• Tamoxifen
	• Fulvestrant

Abbreviations: CDK 4/6: cyclin-dependent kinase 4 and 6.
Source: Lilly Data on File

Modelling of the ET-resistant metastatic setting

Abemaciclib has previously been assessed in the ET-resistant metastatic breast cancer setting, for which the key clinical evidence comes from the MONARCH 2 trial. As such, the inputs and assumptions used to inform the clinical outcomes for the ET-resistant metastatic setting are based on those used in TA725. Where possible, the Committee's preferred assumptions from TA725 are used.

In TA725, the ET-resistant metastatic setting was modelled using a partitioned survival approach to model three health states progression free survival (PFS), post-progression survival (PPS),

and death. PFS and OS curves were modelled using the MONARCH 2 trial data. The PPS health state was estimated by taking the difference with the OS and PFS curves. LYs were accrued according to the proportion of patients in the PFS and PPS health states over time.

In the monarchE model in this submission, patients moving directly from the IDFS health state to the metastatic setting after experiencing an event while they are on adjuvant ET or within the 12 months after completing one line of adjuvant ET, were assumed to follow the ET-resistant metastatic pathway, based on TA725. For each of the possible treatment options, patients received a pay-off of LYs. To enable adjustment for utilities, these LYs were split according to PFS or PPS.

The treatment options modelled per monarchE treatment arm, based on current market share from NICE resource impact statements and company budget impact analyses from TA725, are provided in Table 47. The clinical outcomes used in the ET-resistant metastatic setting are provided in Table 48. Although these could not be aligned with those used in TA725, it should be noted that many of these outcomes should be considered conservative.

For example, the median time on treatment for abemaciclib in the base case analysis is assumed to be [redacted] months, compared with the Committee's preferred assumption of approximately [redacted] months in TA725.[7] However, in the metastatic setting, abemaciclib (along with palbociclib/ribociclib) are only received by patients in the comparator arm. It is reasonable to assume that patients receiving ET alone who then receive CDK 4/6 inhibitors in the metastatic setting are therefore modelled to incur reduced costs compared to those that they would incur in UK clinical practice.

Regardless, the scenarios presented in Section B.3.8.3 indicate that the specific outcomes modelled for patients in the metastatic setting should not be considered a major source of uncertainty.

To calculate the combined LYs for the CDK4/6 inhibitors + fulvestrant treatments, a weighted average of the ABE + FUL, PAL + FUL, and RIBO + FUL LYs were used. The undiscounted LYs were used for the MONARCH 2 model, the respective health state specific utility values were applied to calculate the total QALYs. Then a discounting formula was applied to calculate the appropriate discounted LYs in the monarchE model. The financial discounting formula is commonly used to calculate the present and future value of annuities and the concept has also been applied in the model:

$$\begin{aligned} Discounted\ QALY &= Undiscounted\ QALY \\ &\times \left(\left(1-(1+discount\ rate)^{-(number\ of\ cycles\ QALY\ is\ applied\ for)}\right) \div discount\ rate\right) \\ &\times (1+discount\ rate) \end{aligned}$$

LYs have not been discounted in addition to QALY and cost discounts to avoid double discounting. Further details of the ET-resistant metastatic pathway are presented in Appendix N.

Table 47. Proportion of patients whose early breast cancer is ET-resistant receiving each MONARCH 2 treatment

	Abemaciclib + ET	ET
ABE + FUL	[redacted]	[redacted][a]

RIBO + FUL	[redacted]	[redacted][a]
PAL + FUL	[redacted]	[redacted][a]
EXE + EVE	[redacted]	[redacted]
FUL	[redacted]	[redacted]
CAP	[redacted]	[redacted]
EXE	[redacted]	[redacted]

Footnotes: [a] It is assumed that 15% of patients receive CDK4/6 inhibitors in the ET-resistant metastatic setting. Based on NICE resource impact template 92354918701 (TA725), it is assumed that 30% of patients receive abemaciclib, 20% of patients receive ribociclib and 50% of patients receive palbociclib.[76]
Abbreviations: ABE+FUL: abemaciclib + fulvestrant; CAP: capecitabine; ET: endocrine therapy; EXE: exemestane; EXE+EVE: exemestane + everolimus; FUL: fulvestrant; PAL+FUL: palbociclib + fulvestrant; RIB+FUL: ribociclib + fulvestrant.

Table 48. Undiscounted LYs and mean time on treatment from the MONARCH 2 model

Comparator	LYs		Time on treatment
Treatment options	**PFS**	**PPS**	**Mean**
ABE + FUL	[redacted]	[redacted]	[redacted]
RIBO + FUL	[redacted]	[redacted]	[redacted]
PAL + FUL	[redacted]	[redacted]	[redacted]
CAP	[redacted]	[redacted]	[redacted]
EXE	[redacted]	[redacted]	[redacted]
EXE+EVE	[redacted]	[redacted]	[redacted]
FUL	[redacted]	[redacted]	[redacted]

Abbreviations: ABE+FUL: abemaciclib + fulvestrant; CAP: capecitabine; EXE: exemestane; EXE+EVE: exemestane + everolimus; FUL: fulvestrant; LYs: life years; PAL+FUL: palbociclib + fulvestrant; PFS: progression free survival; PPS: post-progression survival; RIBO+FUL: ribociclib + fulvestrant.
Source: Lilly Data on File.

Modelling ET-sensitive metastatic setting

Abemaciclib has previously been assessed in the ET-sensitive metastatic setting, for which the key clinical evidence comes from the MONARCH 3 trial. As such, the inputs and assumptions used to inform clinical outcomes for the ET-sensitive metastatic setting are based on those used in TA563. Where possible, the Committee's preferred assumptions from TA563 are used.[32]

The ET-sensitive metastatic setting was modelled using a cohort state transition model with three health states which were PFS for 1st line, PPS and death. The PFS health state was modelled as a Markov state. Following progression on their first advanced breast cancer ET treatment, patients were allocated a fixed pay-off for PPS using costs and outcomes from the MONARCH 2 model. More details of the modelling of the ET-sensitive metastatic setting are provided in Appendix M.

In the monarchE model, when a metastatic event occurs after being in IDFS for longer than 12 months or after being in remission, patients are assumed to be ET-sensitive and are assumed to follow the ET-sensitive metastatic pathway, based on TA563. For each of the possible treatment

options, these patients received a pay-off of LYs. To enable adjustment for utilities, these LYs were split according to 1st line advanced PFS, 2nd line advanced PFS or PPS.

An overview of the treatment options modelled per monarchE treatment arm, based on current market share date from NICE resource impact statements and company budget impact analyses from TA563, is provided in Table 49.

The clinical outcomes used in the ET-sensitive metastatic setting are provided in Table 50. Although these could not be aligned with those used in TA563, as outlined above, the clinical outcomes used are conservative. To calculate the combined LYs for the CDK4/6 inhibitors + non-steroidal aromatase inhibitor (NSAI) treatments, a weighted average of the ABE-NSAI, PAL-NSAI, and RIBO-NSAI LYs were used. Further details of the ET-sensitive metastatic pathway are presented in Appendix M.

Table 49. Weighted average proportion of patients receiving each MONARCH 3 treatment

	Abemaciclib + ET	ET
ABE + NSAI	[redacted]	[redacted][a]
RIB + NSAI	[redacted]	[redacted][a]
PAL + NSAI	[redacted]	[redacted][a]
NSAI	[redacted]	[redacted]
EXE	[redacted]	[redacted]
TMX	[redacted]	[redacted]
FUL	[redacted]	[redacted]

Footnotes: [a] It is assumed that 60% of patients receive CDK4/6 inhibitors in the ET-sensitive metastatic setting. Based on NICE resource impact template 6715479277 (TA563), it is assumed that 40% of patients receive abemaciclib, 40% of patients receive ribociclib and 20% of patients receive palbociclib.[76]
Abbreviations: ABE-NSAI: bemaciclib – non-steroidal aromatase inhibitor; ET: endocrine therapy; EXE,: exemestane; FUL: fulvestrant; LYs,: life years; NSAI: non-steroidal aromatase inhibitor (letrozole + anastrazole); PAL-NSAI: palbociclib - non-steroidal aromatase inhibitor; PFS: progression-free survival; PPS: post-progression survival; RIB-NSAI: ribociclib - non-steroidal aromatase inhibitor; TMX: tamoxifen.

Table 50. Undiscounted LYs from the MONARCH 3 model

Treatment	1st line PFS	2nd line PFS	PPS
ABE + NSAI	[redacted]	[redacted]	[redacted]
RIB + NSAI	[redacted]	[redacted]	[redacted]
PAL + NSAI	[redacted]	[redacted]	[redacted]
NSAI	[redacted]	[redacted]	[redacted]
EXE	[redacted]	[redacted]	[redacted]
TMX	[redacted]	[redacted]	[redacted]
FUL	[redacted]	[redacted]	[redacted]

Abbreviations: ABE-NSAI: bemaciclib – non-steroidal aromatase inhibitor; EXE,: exemestane; FUL: fulvestrant; LYs,: life years; NSAI: non-steroidal aromatase inhibitor (letrozole + anastrazole); PAL-NSAI: palbociclib - non-steroidal aromatase inhibitor; PFS: progression-free survival; PPS: post-progression survival; RIBO-NSAI: ribociclib - non-steroidal aromatase inhibitor; TMX: tamoxifen.

B.3.3.5 Adverse events

Adverse event probabilities for abemaciclib + ET and ET are informed by the AFU1 data of the monarchE trial. The model base case includes Grade III/IV AEs reported in the AFU1 data cut of the monarchE trial, with an incidence of ≥ 1% in the respective treatment arms in the trial, as well as Grade I/II AEs with an incidence of ≥ 50% (only Grade I/II diarrhoea had an incidence ≥ 50%). A summary of the AE rates for each treatment and the related sources are shown in Table 51.

Table 51: Summary of Grade III/IV adverse events used in the base case

Adverse event type	Treatment Arms	
	Abemaciclib + ET	ET
Grade I/II		
Diarrhoea	[redacted]	[redacted]
Grade III/IV		
Neutropenia	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Aspartate aminotransferase increase	[redacted]	[redacted]
Alanine aminotransferase increase	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Venous thromboembolic event	[redacted]	[redacted]

Abbreviations: ET: endocrine therapy.
Source: Lilly Data on File AFU1 CSR[23]

B.3.4 *Measurement and valuation of health effects*

B.3.4.1 Health-related quality-of-life data from clinical trials

Utility values derived from the EQ-5D-5L data collected in the monarchE trial were used to evaluate patients' health status to inform decision modelling for health economic evaluation. EQ-5D-5L data were crosswalked to the 3L scale using the Van Hout et al. (2012) approach,[66] to which the UK tariffs were applied. As the data showed no significant difference between treatment arms, overall utilities were applied to both treatment arms instead of treatment-specific utilities. In addition, mean change from baseline in mean index scores were estimated using Mixed effect Model Repeat Measurement (MMRM) regression and included independent variables treatment, visit, treatment*visit, and baseline. These values were used for the base case. The overall IDFS utility used in the base case was [redacted] with a standard error of [redacted].

B.3.4.2 Mapping

No mapping was undertaken, other than the crosswalk of EQ-5D-5L to EQ-5D-3L described above.

B.3.4.3 Health-related quality-of-life studies

A targeted literature review (TLR) was carried out on HTA databases and HTA websites on the 31st August 2020 to elicit potential utility data for use in the model. Full details of the TLR search strategy, study selection process and results are presented in Appendix H.

In total, 22 reports were identified of which 4 HTAs satisfied the inclusion criteria. Three of the NICE HTAs identified by the TLR specifically modelled a HER2+ patient population. An overview of the health state utility values used across the four identified HTA submissions is provided in Table 52.

Table 52: Summary of health state utility values and AE disutility values used in the identified HTA submissions

Author, year	Health state specific utility	Adverse event specific disutility
TA632, 2020[67]	Non-metastatic recurrence: 0.775 Remission: 0.788 1L MBC: 0.765 2L MBC: 0.508	N/A
TA612, 2019[45]	IDFS: 0.837 Local recurrence: 0.696 Remission assumed same as IDFS Distant recurrence < 12 months: 0.521 Distant recurrence > 12 months assumed same as distant recurrence < 12 months	Specific disutility for Grade 3/4 AEs as well as a disutility value for Grade 1/2 diarrhoea
TA569, 2019[46]	IDFS on treatment: 0.756 IDFS on treatment: 0.785 IDFS off treatment: 0.822 Local or regional recurrence: 0.756 Remission: 0.822 1L MBC: 0.773 2L MBC: 0.52	Assumed that any disutility from treatment-related AEs is reflected in the EQ-5D responses from the APHINITY study
TA501, 2018[70]	Recurrence free in 1st year: 0.7728 Recurrence free after first year: 0.8112 Local recurrence: 0.8112 Disease-free after local recurrence: 0.8112 Any other recurrence: 0.685	N/A

Abbreviations: AE: adverse event; EQ-5D: euroQol-5 dimensions; HTA: health technology assessment; IDFS: invasive disease-free survival; MBC: metastatic breast cancer; N/A: not applicable; TA: technology appraisal; 1L: first-line; 2L: second-line.

The cross-walked utility data for IDFS collected during the monarchE trial were in alignment with the values used in TA569, however the value was slightly lower than those utilised in TA612. Utility data for other health states was not able to be obtained from the monarchE trial.

Adverse reactions

AE disutility values and duration estimates are used to assess the impact of AEs on QALYs. The disutility value per AE was multiplied with the duration of the AE to obtain a QALY decrement. The QALY decrements are applied during the first model cycle. Disutility values and duration of

AEs are informed by the economic SLR and NICE technology appraisals in early breast cancer (Section B.3.1 and Appendix G). Table 53 summarises the disutility value and duration for each AE.

Table 53: Disutility and mean duration of adverse events

Parameter	Disutility	Reference	Mean duration (days)	Reference
Neutropenia	0.007	MONARCH 3,[32] Hudgens et al. (2016),[77] TA306,[78] TA579[79]	15.09	MONARCH 3,[32] Nafees et al. (2008), TA306,[78] TA579[79]
Leukopenia	0.003	MONARCH 3,[32] Hudgens et al. (2016),[77] TA306,[78] TA579[79]	13.96	MONARCH 3,[32] Nafees et al. (2008), TA306,[78] TA579[79]
Diarrhoea	0.103	TA612[45]	8.00	TA612[45]
Lymphopenia	0.000	MONARCH 3,[32] TA306,[78]	34.00	MONARCH 3,[32] TA306,[78]
Fatigue	0.003	Hudgens et al. (2016)[77]	12.70	Hudgens et al. (2016)[77]
Aspartate aminotransferase increase	0.000	MONARCH 3,[32] TA503[80]	0.00	MONARCH 3,[32] TA503[80]
Alanine aminotransferase increase	0.005	MONARCH 3,[32] TA503[80]	28.00	MONARCH 3,[32] TA503[80]
Thrombocytopenia	0.000	Assumption	0.00	Assumption
Anaemia	0.119	TA579[79]	16.07	TA579[79]
Abdominal pain	0.048	TA612[45]	8.82	TA612[45]
Venous thromboembolic event	0.000	Assumption	0	Assumption

Abbreviations: TA: technology appraisal.

B.3.4.4 Age-related utility deterioration

NICE DSU Technical Support Document 12 recommends that utility values should be age-adjusted.[81] The recommendation was made to ensure that the negative effect on HRQoL directly associated with age is being captured due to the increasing prevalence of comorbidities in older aged cohorts. This relationship has been documented in analyses of large UK survey data.[82, 83] To account for this relationship over the model time horizon, an index utility adjustment was applied to the utility values for each disease category. The health state utility values in the model are adjusted for age-related deterioration as recommended by the NICE DSU TSD 12.[81] Depending on the starting age, the age-adjusted utility has been implemented in the model using the utility values provided in the Janssen and Szende (2014) publication.[84] Age-related utility deterioration is only applied for patients in the early breast cancer health states of this model; this assumption was taken given the short life expectancy for patients in the metastatic health state.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

An overview of the utilities that are used in the model are presented in Table 54.

Table 54: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean	Source	Justification
IDFS	[redacted] for both trial arms	monarchE MMRM (Section B.3.4.1)	In line with the NICE Reference Case, utility data derived from the pivotal clinical trial are preferred where available
NMR	[redacted] weighted average 0.696 for first 3 months and [redacted] for last 9 months for both trial arms	Calculated as a weighted average: First 3 months: Lidgren *et al.* 2007[35] Last 9 months: assumed equal to IDFS	Clinical expert opinion indicated patients would receive intensive treatment for loco-regional/contralateral recurrence for the first few months, which is expected to be associated with a detrimental impact on HRQoL. Following this, patients would return to their previous HRQoL. The use of Lidgren *et al.* (2007) is aligned with prior NICE appraisal TA612 in the absence of trial utility data from monarchE to inform this state.
Remission	[redacted] for both trial arms	Assumed to be equal to IDFS	In line with prior NICE appraisal TA632 in the absence of trial utility data form monarchE to inform this state, it is assumed that patient utility returns to IDFS baseline following second remission[67]
MR2 – PFS	[redacted] for all MR2 treatments	MONARCH 2 trial[79]	In line with prior NICE appraisal TA725 in advanced breast cancer[7]
MR2 – PPS	[redacted] for all MR2 treatments	MONARCH 2 trial[79]	In line with the Committee's preferred values in TA725 in advanced breast cancer[7]
MR3 – PFS1	[redacted] for all MR3 treatments	MONARCH 3 trial[32]	In line with the ERG's preferred values in prior TA563 in advanced breast cancer[32]
MR3 – PFS2	[redacted] for all MR3 treatments	Mitra *et al.* (2016)[85]	In line with the ERG's preferred values in prior TA563 in advanced breast cancer[32]
MR3 – PFS3	[redacted] for all MR3 treatments	MONARCH 3 trial[32]	In line with the ERG's preferred values in prior TA563 for PPS in advanced breast cancer[32]

Abbreviations: IDFS: invasive disease-free survival; ERG: evidence review group; MMRM: Mixed Effect Model Repeat Measurement; NICE: National Institute for Health and Care Excellence; NMR: non-metastatic recurrence; MR2: MONARCH 2; MR3: MONARCH 3; PFS: progression free survival; PFS1: progression free survival 1st line; PFS2: progression free survival 2nd line; PFS3: progression free survival 3rd line; PPS: post progression survival TA: technology appraisal.

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

A targeted literature review (TLR) was carried out on HTA databases and HTA websites on the 31st August 2020 to elicit potential cost and resource data for use in the model. Full details of the TLR search strategy and study selection process are presented in Appendix H. Full results with respect to cost and resource data are presented in Appendix I.

In total, 22 reports were identified of which 4 HTAs satisfied the inclusion criteria. An overview of the cost and resource use data used across the four identified HTA submissions is provided in Table 55.

Table 55: Summary of previous HTA submission model cost inputs

Author, year	Cost inputs	Resource use inputs
TA632, 2020[67]	Technology acquisition costs, drug administration costs, health state specific costs (cycle cost), AE management costs	Health state specific resource use costs including: Oncologist visit, mammogram, ECHO scan, MUGA scan, CT scan, GP visit, clinical nurse specialist, District nurse (home visit)
TA612, 2019[45]	Drug acquisition cost, drug administration costs, health state specific costs, AE costs	Health state specific resource use costs including: Oncologist visit, mammogram, ECHO scan, MUGA scan, CT scan, GP visit, clinical nurse specialist, District nurse (home visit), social worker
TA569, 2019[46]	Technology acquisition costs, drug administration costs, health state specific costs (cycle cost), AE management costs, subsequent therapy management costs	Health state specific resource use costs including: Oncologist visit, mammogram, ECHO scan, MUGA scan, CT scan, GP visit, clinical nurse specialist, District nurse (home visit), social worker
TA501, 2018[70]	INTRABEAM capita cost, technology maintenance and operating costs, consumable costs	Cost of medical procedures, staff unit costs and additional staff resources

Abbreviations: AE: adverse event; CT: computerised tomography; ECHO: echocardiogram; GP: General Practitioner; HTA: health technology assessment; MUGA; multigated acquisition; TA: technology appraisal.

B.3.5.1 Intervention and comparators' costs and resource use

Drug acquisition

Drug acquisition costs were calculated by combining dosing regimens with relative dose intensity adjustments derived from the monarchE trial data. Drug costs per treatment regimen were extracted from the England based eMIT database.[86] For the ET arm, to maintain a conservative approach, for tamoxifen the lowest cost per mg was chosen from all the options available. Table 56 provides a breakdown of the drug acquisition costs which are included in the model.

Table 57 provides the dosing schedule and dose intensities. As noted (Section B.3.3.2), the TTD curves capture discontinuation of treatment for any cause, as such these curves are used alongside acquisition costs and clinical stopping rules to determine treatment cost.

Even though the primary endpoint was met, the latest monarchE trial data cut provides results from a relatively short follow-up. Further, the treatment pathway of the disease in the monarchE trial is subject to some heterogeneity. Thus it is also challenging to differentiate between which patients might be ET-sensitive or not. Given the uncertainty in the treatment pathway and the short follow up, extrapolating the TTD curve long-term introduces some degree of uncertainty in the model.

To explore the impact of different assumptions around discontinuation a scenario was presented in addition to the base case results which assumed a 10 year stopping rule for ET. This was in line with the upper bound of adjuvant ET treatment in monarchE.

Table 56: Drug acquisition costs

Treatment	Dose per tablet or vial	Units per package	Cost per package	Source
ABE	150mg	56	List price: £2,950.00 PAS price, £[redacted]	Lilly
ET options:				
Anastrozole	1mg	28	£1.37	eMIT 2020[86]
Exemestane	25mg	30	£5.58	eMIT 2020[86]
Letrozole	2.5mg	28	£1.56	eMIT 2020[86]
Tamoxifen	20mg	30	£8.44	Lowest cost option chosen from eMIT 2020[86]

Abbreviations: ABE: abemaciclib; eMIT: electronic market information tool; ET: endocrine therapy; PAS: patient access scheme.

Table 57: Dosing regimens and dose intensity

Treatment	Dosing schedule	Relative dose intensity
ABE	150mg BID	100%
ET	-	100%
Anastrozole	1mg QD	100%
Exemestane	25mg QD	100%

Letrozole	2.5mg QD	100%
Tamoxifen	20 mg QD	100%

Abbreviations: ABE: abemaciclib; BID: twice (two times) a day; ET: endocrine therapy: QD: once daily.
Source: Dosing Schedule: SmPC[87]

Drug administration

Administration costs are not relevant in the adjuvant setting as the abemaciclib + ET and the ET arm are administered orally. For the non-metastatic recurrence setting and the metastatic setting administration costs were applicable for some treatments. These have been costed separately according to NICE guidelines, please see Section B.3.5.2 for further details.

B.3.5.2 Health-state unit costs and resource use

IDFS health state costs

Following TA632,[67] TA612[45] and TA569[46] and clinical expert advice, the model includes differential levels of resource use (i.e. outpatient visit and mammograms) based on time spent in IDFS. Table 58 provides a summary of the health states and associated resource use costs included in the economic model.

Table 58: List of costs in the economic model associated with the IDFS health state

Resource use	Unit cost (£)	Reference	Annual resource use frequency			Source
			Year 1	Year 2 –5	Year >5	
GP visit	39.00	PSSRU 2020	0.00	0.08	0.08	TA569[46]
Oncologist visit	200.20	National Schedule of NHS Costs 2019/20	0.15	0.00	0.00	TA569[46]
Mammogram	33.61	TA612	0.08	0.08	0.00	TA569[46]
Multidisciplinary team meeting	121.68	Simcock and Heaford (2012)	0.08	0.00	0.00	TA569[46]
On treatment costs: Abemaciclib + ET						
Oncologist visit	200.20	National Schedule of NHS Costs 2019/20	0.15			MonarchE
Hospitalisation	3,622.16	TA725	0.0052			MonarchE
On treatment costs: ET alone						
Hospitalisation	3,622.16	TA725	0.0013			MonarchE

Abbreviations: ET: endocrine therapy; GP: General Practitioner; IDFS: invasive disease-free survival; NHS: National Health Service; PSSRU: Personal Social Services Research Unit; TA: technology appraisal.

Best supportive care

Components of best supportive care (BSC) were identified based on the concomitant medications prescribed in the monarchE trial. Specifically, concomitant medications taken by ≥5% of the ITT population in either treatment arm due to prophylaxis and/or medical history, as defined in the monarchE CSR. Clinical expert opinion confirmed that treatments for specific medical history events unrelated to the study should not be included within BSC. For the base case, these treatments are not included as part of the total BSC costs. As adverse events are costed separately (Section B.3.5.3) to avoid double-counting, concomitant medications

prescribed specifically for adverse events have not been included (with the exception of loperamide for the treatment of diarrhoea). In the model, BSC costs are incurred during the pre-recurrence/IDFS health state.

Table 59 provides and overview of the type of concomitant medications being modelled per treatment arm. Table 60 lists the dosing and cost assumptions for each concomitant medication.

Table 59: Type of concomitant medication by treatment arm

Agent	Abemaciclib + ET %	ET %
Loperamide	[redacted]	[redacted]
Colecalciferol	[redacted]	[redacted]
Calcium carbonate; colecalciferol	[redacted]	[redacted]
Vitamin D	[redacted]	[redacted]
Ibuprofen	[redacted]	[redacted]
Co-amoxiclav	[redacted]	[redacted]
Amoxicillin	[redacted]	[redacted]
Zoledronic acid	[redacted]	[redacted]
GnRH analogues	[redacted]	[redacted]

Abbreviations: ET: endocrine therapy.
Source: MonarchE CSR Table JPCF.4.11 PO data[23]

Table 60: Drug cost and dosing options used

Concomitant treatment dosing & administration	Cost per package	Total package dose	Dose per admin	Number of administrations per cycle (N)	Administration route	Assumption on formulations
Loperamide	£0.36	60 mg	2 mg	28.00	Oral	2mg capsules
Ibuprofen	£0.68	19200 mg	400 mg	28.00	Oral	400 mg tablets
Amoxicillin	£0.40	10500mg	500 mg	28.00	Oral	500 mg capsules
Co-amoxiclav	£2.00	7875mg	375 mg	21.00	Oral	375 mg tablets
Colecalciferol	£3.02	24000 IU	800 IU	28.00	Oral	800 unit tablets
Calcium carbonate; colecalciferol	£6.49	100 tablets	1 tablet	28.00	Oral	Calcium carbonate 1.25gram; Colecalciferol 200 unit
Vitamin D	£3.02	24000	800 mg	28.00	Oral	Assumed to be the same as colecalciferol
Zoledronic acid	£2.93	400 mg	400 mg	0.15[a]	IV	4mg/100ml solution
GnRH analogues	£70.00	4 mg	4 mg	1.00	SC	3.6mg implant every 28 days

Footnotes: [a]The duration of administration of zoledronic acid is capped at 3-years to reflect clinical guidance for the length of treatment with adjuvant bisphosphonates.[88]
Abbreviations: IU: international units; SC: sub-cutaneous.
Source: eMIT [86]

Non-metastatic health state

Clinical experts were consulted to assess the adjuvant treatment offered to patients with HER2− early breast cancer experiencing a non-metastatic recurrence of differing types. They highlighted that a mix of surgery, radiotherapy chemotherapy, and adjuvant ET are commonly offered as treatment options to patients who experience a non-metastatic recurrent event.

NICE final guidance for early and locally advanced breast cancer diagnosis and management were consulted to estimate the treatment mix offered.[13] It should be noted that the NG101 guideline was predominantly relevant for patients with HER2+ early breast cancer since there have been no changes in treatment guidelines for HER2− early breast cancer in the last 10 years. Although apart from specific HER2+ targeted therapies, the treatment offered to treat a specific recurrence location would remain the same irrespective of HER2+ or HER2− status.[13] Therefore the HER2+ or HER2− status would not impact the type of treatment a patient is offered for that area of recurrence. It was assumed that the treatments specifically recommended for HER2+ early breast cancer such as trastuzumab and pertuzumab would not be prescribed for the monarchE HER2− patient population, instead ET prescribed during the IDFS health state would be prescribed again.

The NG101 guideline specified that people with locoregional, regional or contralateral disease recurrence would undergo a mastectomy if they originally had breast conserving surgery or a 'major breast procedure' if they originally had a mastectomy.[13] The guidelines also state that:

- Breast reconstruction would be performed (either delayed or at the time of mastectomy)
- Lymph node clearance would be performed for people with regional disease recurrence
- Radiotherapy would be administered to those who were naïve to radiotherapy
- All patients with HER2+ early breast cancer would receive adjuvant chemotherapy, trastuzumab and pertuzumab

To inform the cost associated with non-metastatic recurrence location, the same algorithm as published in the NG101 guideline was applied, with the exception that treatment with trastuzumab and pertuzumab: following consultation with clinical experts, The HER2+ targeted treatments were replaced with ET received in the IDFS health state.[13]

Table 61 provides a breakdown of the type of treatment mix allocated to each type of recurrence as indicated in the NG101 guidelines. The proportion of patients experiencing their first local/regional and contralateral disease recurrence based on the monarchE CSR.[23] An assessment of the IPD was conducted to determine the prior surgical and treatment history of those with specific tumour recurrence locations.

Table 13–16 from the NG101 guidelines were updated with the number of procedures and associated costs recorded in the most recently available National Schedule of NHS Costs 2019/20.[89] Table 62 provides the updated weighted average costs per treatment type using Table 13–16 from the NG101 guidelines and the latest National Schedule of NHS Costs. A breakdown of the costs used to derive the weighted averages is provided in Appendix O. To capture ET treatment during non-metastatic recurrence, the same cost as applied to ET in each cycle in the IDFS health state was applied to each cycle in the non-metastatic health state, irrespective of recurrence type. Clinical experts agreed that ET would be offered to patients who experienced a non-metastatic recurrence.

Table 61: Breakdown of treatment algorithm applied for non-metastatic recurrence pathway

Recurrence type	% (SE) receiving mastectomy with reconstruction (if originally had breast conserving surgery)	% (SE) receiving major breast procedure (if originally had mastectomy)	% (SE) receiving delayed breast reconstruction	% (SE) receiving radiotherapy (proportion not received prior radiotherapy)
Locoregional	100 (0.1)	Local cost: 65 (0.06) Regional cost: 35 (0.04)	100 (0.1)	89 (0.9)
Contralateral	100 (0.1)	100 (0.1)	100 (0.1)	89 (0.9)

Abbreviations: ET: endocrine therapy; SE: standard error.
Source: TA569[46]

Table 62: Costs for each treatment offered in the non-metastatic recurrent health state

Parameter	2019/20 costs	Reference
Locoregional and Contralateral		
Oncologist visit	£200.20	National Schedule of NHS Costs 2019/20 - OPROC, WF01A Non-admitted F2F attendance, First, Service Code 370 (Medical Oncology)
Mammogram	£33.61	National Schedule of NHS Cost 2019-20, IMAGOP, PF, Plain Film, Outpatient
Radiotherapy	£3,724.11	See Appendix O for derivation of cost from sources
Chemotherapy cost per cycle (Cycle 1)	£239.30	
Chemotherapy cost per cycle (Cycle 2–6)	£271.72	
Chemotherapy cost per cycle (subsequent cycles until disease progression)	£253.77	
Multidisciplinary team meeting	£121.68	Simcock and Heaford (2012)[90]
Locoregional only		
Major breast procedures (if patients originally had mastectomy)		
Local: Major breast procedures (if patients originally had mastectomy)	*£4,199.10*	

Regional: Major breast procedures with lymph node clearance (for regional recurrences in patients that originally had mastectomy)	*£5,085.65*	See Appendix O for derivation of cost from sources
Delayed breast reconstruction	£10,096.59	
Mastectomy with reconstruction (if patients originally had breast conserving surgery)	£9,498.66	
Contralateral only		
Major breast procedures (if patients originally had mastectomy)	£3,994.22	See Appendix O for derivation of cost from sources
Delayed breast reconstruction	£9,690.56	
Mastectomy with reconstruction (if patients originally had breast conserving surgery)	£8,981.85	

Abbreviations: NHS: National Health Service; TA: technology appraisal.
Source: Table 13–16 NG101 Guideline,[13] National Schedule of NHS Costs 2019/20[89]

Second primary neoplasm

As noted above, the model assumed patients who experience a second primary non-breast cancer event, receive the cost of detecting the second primary neoplasm (i.e., one oncology multidisciplinary team [MDT] meeting; £121.68) and exit the model.

Remission

Following TA632,[67] TA612[45] and TA569[46] and clinical expert advice, levels of resource use based on year 2–5 of the IDFS health state from these TAs (i.e. GP visit, mammograms,) based on time spent in remission were modelled.

Table 63: Cost and resource use for remission health state

Resource use	Unit cost (£)	Reference	Frequency	Unit	Source
GP visit	39.00	PSSRU 2020	0.08	28 days	TA569,[46] TA612[45]
Oncologist visit, follow-up	200.20	National Schedule of NHS Costs 2019/2020: WF01A Consultant Lead, Non-Admitted Face-to-Face Attendance, Follow-up	0.15	28 days	TA569,[46] TA612[45]
Mammogram	33.61	TA612	0.08	28 days	TA569,[46] TA612[45]

Abbreviations: GP: General Practitioner; PSSRU: Personal Social Service Research Unit; TA: technology appraisal.

Metastatic health state costs

ET-resistant

For the ET-resistant metastatic patient pathway, the following cost and resource use categories from the MONARCH 2 model were incorporated within the monarchE model:

- Drug acquisition
- Drug administration
- BSC
- Follow-up care
- AEs
- Hospitalisations
- Post-progression therapy

For the health state specific resource use costs, the per cycle cost of each resource use was multiplied with the applicable number of cycles. To inform the total cycles the mean PFS, PPS, and time on treatment (ToT) values specified in Table 48 was used.

Additional details on the costs and resource use associated with the ET-resistant metastatic patient pathway are provided in Appendix N.

ET-sensitive

For the ET-sensitive metastatic patient pathway the cost and resource use categories considered in the first and second- line metastatic health state were based of those considered in the MONARCH 3 trial and are summarised in Table 64.

Additional details on the costs and resource use associated with the ET-sensitive metastatic patient pathway are provided in Appendix M.

Table 64: MONARCH 3 cost and resource categories considered in the ET-sensitive metastatic patient pathway

First-line health state	Second-line health state	
PFS1	**PFS2**	**PPS**
• Drug acquisition • Drug administration • AEs • BSC • Follow-up care • Hospitalisation	• Treatment cost • BSC • Follow-up care • Hospitalisation	• Treatment cost • BSC • Follow-up care • Hospitalisation

Abbreviations: AEs: adverse events; BSC: best supportive care; ET: endocrine therapy; PFS1: progression-free survival first-line; PFS2: progression free survival first line; PPS: post-progression survival.

The second-line PFS treatment costs in the model were calculated using the same method as first-line PFS treatment costs. Drug acquisition costs were combined with the respective dosing regimens. The appropriate mean weight or BSA was applied along with the RDI. Third-line treatment costs were applied using a weighted average cost approach. The cost was calculated by combining monthly drug acquisition and administration costs with time on the treatment and the proportion of patients receiving that treatment.

To appropriately implement the costs from the ET-sensitive metastatic pathway, for the health state specific resource use costs, the per cycle cost of each resource use was multiplied with the number of cycles the resource use was applicable for. To inform the total cycles, the mean 1st line PFS, 2nd line PFS, PPS, and ToT values specified in Table 48 were used.

Terminal care

All patients who died in the model were assumed to incur a terminal care cost. The proportion of patients who would receive care in a hospital, hospice and/or at home with community support was informed by the MONARCH 2 and MONARCH 3 models, and the NICE CG81 guidelines.[22,23,49] The total terminal care cost applied was £4,637.20. Table 65 provides the detailed breakdown of the cost components used to inform the total terminal care cost.

Table 65. Breakdown of terminal care cost included in the model

Setting of care	Proportion (%)	Mean cost (£)	Source
Hospital	40	£5,925.08	NICE CG81 clinical guidelines[49] package 3[a]
Hospice	10	£7,386.83	
At home with community support	50	£3,056.97	

[a]Inflated to 2019/2020 prices

Abbreviations: NICE: National Institute for Health and Care Excellence.

B.3.5.3 Adverse reaction unit costs and resource use

As detailed in Section B.3.3.5, AE probabilities in the model were informed by the additional follow-up 1 (AFU1) data cut of the monarchE trial. A summary of the AE rates for each treatment and the related sources are shown in Table 51.

AEs are assumed to occur once within the first cycle of the model, for patients receiving treatment. AEs are associated with one-off costs and negative HRQoL impacts (utility decrements), which are then multiplied by the AEs incidence to obtain the total costs and disutility associated with AEs.

Table 66 lists the Grade III/IV AE costs and their relevant sources.

Table 66: Adverse reaction unit costs and resource use

Adverse reactions	2019/20 unit cost (£)	Source
Grade III/IV AEs		
Neutropenia	£200.20	National Schedule of NHS Costs 2019/20: HRGs: WF01A Medical oncology non-admitted face to face attendance follow up
Leukopenia	£200.20	National Schedule of NHS Costs 2019/20: HRGs: WF01A Medical oncology non-admitted face to face attendance follow up
Diarrhoea	£200.20	National Schedule of NHS Costs 2019/20: HRGs: WF01A Medical oncology non-admitted face to face attendance follow up
Lymphopenia	£200.20	National Schedule of NHS Costs 2019/20: HRGs: WF01A Medical oncology non-admitted face to face attendance follow up
Fatigue	£380.71	TA403 is for locally advanced or metastatic non-small-cell lung cancer and the year of input is 2015
Aspartate aminotransferase increase	£200.20	National Schedule of NHS Costs 2019/20: HRGs: WF01A Medical oncology non-admitted face to face attendance follow up
Alanine aminotransferase increase	£200.20	National Schedule of NHS Costs 2019/20: HRGs: WF01A Medical oncology non-admitted face to face attendance follow up
Thrombocytopenia	£367.76	National Schedule of NHS Costs 2019/20 used to determine cost: Weighted average of thrombocytopenia scores, SA12G, SA12H, SA12J, SA12K
Anaemia	£221.46	National Schedule of NHS Costs 2019/20: SA44A, Outpatient procedures: Single plasma exchange or other IV blood transfusion 19 & over
Abdominal pain	£173.10	National Schedule of NHS Costs 2019/2020 WF01A, Non-Admitted Face-to-Face Attendance, Follow-up, Non Consultant Led
Venous thromboembolic event	£472.68	National Schedule of NHS Costs 2019/20 used to determine cost: Total HRG's, Deep Vein

		Thrombosis weighted average of: YQ51A; YQ51B; YQ51C; YQ51D; YQ51E gives unit cost
Grade I/II AEs		
Diarrhoea	£1.62	BNF: Loperamide 2mg tablets

Abbreviations: BNF: British National Formulary; HRG: healthcare resource group; IV: intravenous; NHS: National Health Service.
Source: TA563,[32] TA403, National Schedule of NHS Costs 2019/20,[89] Inflation: NHSCII prices, Curtis & Burns (2020)[91]

Hospitalisations

The monarchE trial provides a summary of all hospitalisations (on therapy or within 30 days of Treatment Disposition) at the time of the PO data cut off. The hospitalisation rates collected are either due to treatment or non-treatment related AEs. The majority of patients were hospitalised due to System Organ Class infections and infestations (177 patients [3.2%]), specifically, due to the PT pneumonia (22 [0.8%] in abemaciclib + ET arm and 13 [0.5%] in ET arm only).[23] The median duration of hospitalisation was 5 days for both abemaciclib + ET and ET only arms.

Only Grade III/IV AEs with an incidence of ≥ 1% are being included in the base case of the model and these AEs are already being costed based on the type of event a patient would experience. The AEs are costed from a day case or outpatient perspective (see Table 67) resulting in limited scope for double counting. For the abemaciclib + ET arm hospitalisation costs were applied for two years and for the ET alone arm hospitalisation costs were applied for five years. It should be noted that two-year data from ET alone arm from the monarchE trial was applied to the full five years of the ET alone arm.

Table 67: Hospitalisation rates and costs

	Abemaciclib + ET	ET alone	Source
Cost of hospitalisation (£)	£3,622.16	£3,622.16	TA725[7]
Duration of resource use (years)	2	5	Assumed only for the duration of treatment
Probability of hospitalisation per cycle	0.0052	0.0013	MonarchE[23]

Abbreviations: AFU1: additional follow-up 1; ET: endocrine therapy; NHS: National Health Service.

B.3.5.4 Miscellaneous unit costs and resource use

No additional miscellaneous unit costs and resource use were included in the model, therefore this section is not relevant to this submission.

B.3.6 *Summary of base-case analysis inputs and assumptions*

B.3.6.1 Summary of base-case analysis inputs

A summary of the base case model inputs is provided in Table 68.

Table 68: Summary of variables applied in the economic model

Variable	Value/source	Reference to section in submission
Model settings		
Discount rate, %	3.5%	Section B.3.2.2
Time horizon	Lifetime	
Perspective	UK NHS and PSS	
Clinical parameters		
Clinical effectiveness		
IDFS	IDFS was modelled using a dependent log-logistic model including an adjustment factor for treatment effect. For patients receiving abemaciclib + ET, a treatment waning effect was applied to IDFS starting at Year 8, ending at Year 27.	Section B.3.3.1
TTD	Independent hazard spline 2 knot extrapolations were used to model TTD for abemaciclib, ET (for patients receiving abemaciclib) and ET alone.	
OS (without distant recurrence)	OS without distance recurrence was modelled using a dependent exponential model including an adjustment factor for treatment effect.	
Remission	A monthly transition probability of 0.00760 from remission to the metastatic health state was derived from TA632[67], based on clinical expert feedback	
Metastatic setting (ET-resistant and ET-sensitive)	Clinical effectiveness estimates for the metastatic setting were derived from the MONARCH 2[79] (ET resistant) and MONARCH 3[32] (ET sensitive) trials	
AEs	Various – the model base case includes Grade III/IV AEs reported in the AFU1 data cut of the monarchE trial. Probabilities of each AE occurring were derived from the monarchE trial	Section B.3.3.5
Utility inputs		
Health state		
IDFS	[redacted] for both trial arms	Section B.3.4.5
NMR	[redacted] for both trial arms (Calculated as a weighted average of 0.696 for first 3 months and [redacted] for last 9 months for both trial arms)	
Remission	[redacted] for both trial arms	
MR2 – PFS	[redacted] for all MR2 treatments	
MR2 – PPS	[redacted] for all MR2 treatments	
MR3 – PFS1	[redacted] for all MR3 treatments	
MR3 – PFS2	[redacted] for all MR3 treatments	
MR3 – PFS3	[redacted] for all MR3 treatments	
Cost inputs		
ABE	List price: £2,950.00 PAS price, £[redacted]	Section B.3.5.1

Anastrozole	£1.37	
Exemestane	£5.58	
Letrozole	£1.56	
Tamoxifen	£8.44	
Drug administration	Administration costs are not relevant in the adjuvant setting as both the abemaciclib + ET and the ET arm are administered orally. Various administration costs were used in the metastatic setting	Section B.3.5.1
Health state unit cost		
IDFS		Section B.3.5.2
GP visit	£39.00	
Oncology visit	£200.20	
Mammogram	£33.61	
Multidisciplinary team meeting	£121.68	
NMR	Various – resource use costs were split according to recurrence type; local/regional, local, regional and contralateral. Costs were sourced from the National Schedule of NHS Costs 2019/20[89] database where possible	Section B.3.5.2 and Appendix O
Secondary primary neoplasm	The model assumed patients receive the cost of detecting the second primary neoplasm (e.g. one oncology multidisciplinary team [MDT] meeting) and exited the model. The cost of a multidisciplinary meeting was assumed to be £121.68 (National Schedule of NHS Costs 2019/20[89])	Section B.3.5.2
Remission		
GP visit	£39.00	Section B.3.5.2
Oncologist follow up visit	£200.20	
Mammogram	£33.61	
Metastatic		Appendix M and Appendix N
ET-resistant	Various – Cost and resource use in the ET resistant metastatic state were based on TA725 as far as possible	
ET-sensitive	Various – Cost and resource use in the ET sensitive first and second-line metastatic state were based on TA563 as far as possible	
Terminal care		
Hospital	£5,925.08	Section B.3.5.2
Hospice	£7,386.83	
At home with community support	£3,056.97	
AEs	Various – Grade III/IV AEs reported during the MonarchE trial were included in the model. Unit costs were sourced from the National Schedule of NHS Costs 2019/20[89] and the BNF	Section B.3.5.3
Hospitalisation	£3,622.16	

Abbreviations: ABE: abemaciclib; AEs: adverse events; ET: endocrine therapy; GP: General Practitioner; IDFS: invasive disease-free survival; MDR: multidisciplinary team; MR2: MONARCH 2; MR3: MONARCH 3; NHS: National Health Service; NMR: non-metastatic recurrence; OS: overall survival; PFS: progression free survival; PFS1: progression free survival 1st line; PFS2: progression free survival 2nd line; PFS3: progression free survival 3rd line; PPS: post progression survival.

B.3.6.2 Assumptions

A list of the assumptions used in the base case analysis is provided in Table 69 alongside a list of scenarios conducted to explore the impact of these assumptions on the cost-effectiveness results.

Table 69: List of assumptions for the base case analysis model

Assumption	Description of assumption for the base case	Justification	Addressed in scenario analysis
IDFS curves	Dependent model (single model with treatment coefficient) assumed with a log-logistic distribution	As explained in Section B.3.3, the monarchE trial provides direct clinical evidence for abemaciclib + ET and ET alone, for a population that is reflective of UK clinical practice. Statistical fit and landmark IDFS rates from external trials identified by the clinical SLR were used to validate the chosen extrapolation.	To explore any uncertainty associated with the choice of extrapolation for IDFS, scenario analyses have been conducted using the next best fitting extrapolations. A scenario analysis using an independent log-logistic extrapolation has also been conducted.
TTD curves	Extrapolations based on within trial data were used to inform ET (hazard knot two splines used to model TTD for abemaciclib, ET (for patients receiving abemaciclib) and ET alone.	As explained in Section B.3.3, evidence from the monarchE trial was deemed to be the most recent and relevant for the validation of the TTD extrapolations. The choice of extrapolation for TTD was based on statistical fit.	To explore any uncertainty associated with the choice of extrapolation for TTD, scenario analyses have been conducted using the next best fitting extrapolations
	Two year stopping rule applied for abemaciclib	Abemaciclib is to be taken continuously for up to two years, according to the SmPC.	No scenario analyses have been conducted varying the stopping rule for abemaciclib, as this is defined in the SmPC.
	Five year stopping rule was applied for ET	The timing of the ET stopping rule is not expected to have a significant impact on the cost-effectiveness results or represent a significant source of uncertainty, as it is applied in both the abemaciclib + ET arm and the ET alone arm (see Section B.3.8.3 for scenario analysis results). As such, a five year stopping rule was chosen in the base case analysis.	A scenario analysis has been conducted where a 10-year stopping rule was applied for ET. This demonstrates that the timing of the stopping rule has a minimal impact on the cost-effectiveness analysis.

Assumption	Description of assumption for the base case	Justification	Addressed in scenario analysis
OS without distant recurrence curves	Dependent model (single model with treatment coefficient) assuming an exponential distribution following internal validity checks	As explained in Section B.3.3, evidence from the monarchE trial was deemed the most recent and relevant for the validation of OS without distant recurrence extrapolations.	In order to explore any uncertainty associated with the choice of extrapolation for OS, scenario analyses have been conducted varying the OS extrapolation to the next best fitting extrapolations.
	Hazard of dying in NMR and remission health states assumed same as hazard of dying in the IDFS health state	In the absence of robust data for the hazard of death in the NMR and remission health states, this was considered to represent a reasonable assumption.	No scenario analyses have been conducted to explore the impact of this assumption.
Long-term treatment effect	Waning of treatment effect was applied starting from 8 years	A long-term treatment effect has been observed in variety of trials in the early breast cancer setting and IDFS piecewise analysis for monarchE demonstrates that a treatment effect past discontinuation does exist for abemaciclib. As explained in Section B.3.3.2, the start of the treatment waning effect was informed by the treatment effect observed for ET in the ATAC trial.	Scenario analyses have been conducted varying the start time and duration of the treatment waning effect.
	Waning of treatment effect was applied until the crossing of the ET IDFS hazard rate with the general population mortality, 27 years	The duration of the waning of treatment effect was informed by the point in the model where the IDFS rates equal background mortality, by when the hazard equals the general population mortality, in line with the approach used in TA612.[45]	

Assumption	Description of assumption for the base case	Justification	Addressed in scenario analysis
NMR tunnel state	All patients who experience a non-metastatic recurrence are assumed to receive additional adjuvant therapy for 12 months. After 12 months, patients are assumed to either transition into the remission health state or die due to all-cause mortality.	The duration of the NMR tunnel state of 12 months was informed by assumptions made in the most recent NICE TA for trastuzumab (TA632), which were accepted by NICE.[67]	No scenario analyses have been conducted to explore the impact of this assumption.
Probability for type of non-metastatic recurrence	The proportion of patients having a second primary, (loco)regional or contralateral recurrence when a non-metastatic recurrence event takes place has been assumed to be constant over time.	No alternative evidence was identified from the literature or during consultations with clinical experts, so the risk was assumed to be constant	No scenario analyses have been conducted varying the probability for the type of non-metastatic recurrence
Probability of recurrence from remission health state	A constant monthly probability of transition from remission to the metastatic health is assumed.	As outlined in Section B.3.3.3, the transition probability of patients moving from remission to the metastatic health state was informed by assumptions made in the most recent NICE TA for trastuzumab (TA632), which was also in line with feedback from UK clinical experts.[67]	No scenario analyses have been explored varying the probability of recurrence from the remission health state as it was not considered to be a large source of uncertainty. The impact of the probability of recurrence from the remission health state on the cost-effectiveness results has been explored in the DSA and PSA.
Hospitalisation costs	Hospitalisation costs dictated by the monarchE trial were used in the base case.	The monarchE trial was deemed to provide the most relevant evidence on hospitalisation costs in the abemaciclib + ET and the ET alone arm.	No scenario analyses have been conducted varying the costs of hospitalisation.
Re-treatment with CDK 4/6 inhibitors in the metastatic setting	Patients who receive abemaciclib + ET are assumed to not receive re-treatment with CDK4/6 inhibitors in the metastatic breast cancer setting.	Due to a lack of available evidence on the efficacy of re-treating patients with CDK4/6 inhibitors, patients were receiving abemaciclib were assumed to not receive subsequent treatment with CDK4/6 inhibitors.	A scenario analysis has been conducted in which patients receiving abemaciclib can be re-treated with CDK4/6 inhibitors.

Assumption	Description of assumption for the base case	Justification	Addressed in scenario analysis
Clinical outcomes for patients in the metastatic setting	Clinical outcomes for patients in the metastatic setting are based on previous cost-effectiveness analyses in TA563 and TA725	As outlined in Section B.3.3.4, the cost-effectiveness analyses in TA563 and TA725, aligning with the Committee's preferences where possible, were deemed the most recent and relevant data sources	A range of scenario analyses were conducted to explore the impact of this uncertainty on the cost-effectiveness results
Utility value in the NMR health state	Patients have a utility value of [redacted] for first 3 months and [redacted] for last 9 months for both trial arms yielding a weight average of [redacted] in the base case	Clinical expert opinion indicated patients would receive intensive treatment for loco-regional/contralateral recurrence for the first few months, which is expected to be associated with a detrimental impact on HRQoL. Following this, patients would return to their previous HRQoL.	• No scenario analyses have been conducted varying the NMR health state utilities

Abbreviations: CDK4/6: cyclin-dependent kinase 4 and 6; DSA: deterministic sensitivity analysis; ET: endocrine therapy; IDFS: invasive disease-free survival; NICE: National Institute for Clinical Excellence; NMR: non-metastatic recurrence; OS: overall survival; PSA: probabilistic sensitivity analysis; SmPC: Summary of Product Characteristics; SLR: systematic literature review; TA: technology appraisal; TTD: time to treatment discontinuation.

B.3.7 *Base-case results*

B.3.7.1 Base-case incremental cost-effectiveness analysis results

The base case deterministic results are presented in Table 70. In the base case economic analysis, abemaciclib (at PAS price) was associated with an ICER of £3,786 per QALY gained.

Table 70: Base-case deterministic economic analysis results (abemaciclib PAS price)[a]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3,786
ET alone	[redacted]	[redacted]	[redacted]				

Footnotes: This table reports undiscounted LYG, and discounted costs and QALYs.
Abbreviations: ET: endocrine therapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life years.

B.3.8 *Sensitivity analyses*

B.3.8.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted to assess the simultaneous effect of uncertainty in the different model parameters on the results of the cost-effectiveness analysis. The PSA was run for 1,000 iterations and in each iteration, model inputs were randomly sampled from the specified probability distributions. Where a standard error or CI was not available for a selected parameter, 10% of the mean was assumed as the standard error. A table containing a list of the inputs used in PSA is presented in Appendix J.

The results of the PSA with 1,000 iterations are presented in Table 71 for abemaciclib at PAS price. The results show that abemaciclib was associated with a [redacted]% probability of being cost-effective at a £30,000 willingness-to-pay threshold at PAS price.

Table 71: Probabilistic results (abemaciclib PAS price)

Technologies	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Probability of cost-effectiveness[a]
Abemaciclib + ET	[redacted]	[redacted]	3,782	[redacted]
ET alone	[redacted]	[redacted]	-	[redacted]

Footnotes: [a] The probability of abemaciclib with ET being cost-effective versus ET at a cost-effectiveness threshold of £30,000/QALY.
Abbreviations: ET: endocrine therapy; ICER: incremental cost-effectiveness ratio ; QALYs: quality-adjusted life years.

Figure 27: Cost-effectiveness plane for abemaciclib + ET versus ET alone

Abbreviations: ET: endocrine therapy; QALYs: quality adjusted life years.

Figure 28: Cost-effectiveness acceptability curve for abemaciclib + ET versus ET alone

Abbreviations: ET: endocrine therapy; QALYs: quality adjusted life years.

B.3.8.2 Deterministic sensitivity analysis

To account for uncertainty around the input parameters used in the base case analysis, a deterministic sensitivity analysis (DSA) was conducted. Where available, each parameter was varied by 95% CIs. For parameters where CIs were not available the input was varied by ±10% of their mean value. Pease note the DSA does not include parameters which require assessment of joint uncertainty, these correlated parameters are assessed within the PSA.

Figure 29: DSA tornado plot for abemaciclib + ET versus ET alone

Abbreviations: ABE: abemaciclib; ET: endocrine therapy; NMR: non-metastatic recurrence.

B.3.8.3 Scenario analysis

A number of scenario analyses were conducted to explore the impact of certain assumptions and alternative inputs within the base case economic analysis. Each scenario analysis is described in turn below and full results of all scenario analyses are presented in Table 73.

Discount rate

- Base case: a discount rate of 3.5% was applied for both costs and effects in the model
    - Scenario: A discount rate of 1.5% was applied for both costs and effects in the model

IDFS extrapolation

- Base case: A dependent log-logistic extrapolation was used to model IDFS
    - Scenario: A dependent Weibull extrapolation was used to model IDFS
    - Scenario: A dependent Generalised gamma extrapolation was used to model IDFS
    - Scenario: A dependent Gamma extrapolation was used to model IDFS
    - Scenario: An independent log-logistic extrapolation was used to model IDFS in both the abemaciclib + ET and ET arms

TTD extrapolation – abemaciclib

- Base case: A dependent hazard spline 2-knot extrapolation was used to model TTD for abemaciclib
    - Scenario: A dependent log-logistic extrapolation was used to model TTD for abemaciclib
    - Scenario: A dependent lognormal extrapolation was used to model TTD for abemaciclib
    - Scenario: A dependent hazard spline 1-knot extrapolation was used to model TTD for abemaciclib

TTD extrapolation – ET (intervention and comparator arms)

- Base case: An independent hazard spline 2-knot extrapolation was used to model TTD for ET (intervention and comparator)
    - Scenario: a dependent hazard spline 2-knot extrapolation was used to model TTD for ET (intervention and comparator)
    - Scenario: An independent hazard spline-1 knot extrapolation was used to model TTD for ET (intervention and comparator)
    - Scenario: An independent Weibull extrapolation was used to model TTD for ET (intervention and comparator)
    - Scenario: An independent log-logistic extrapolation was used to model TTD for ET (intervention and comparator)

OS extrapolation

- Base case: A dependent exponential extrapolation was used to model OS
    - Scenario: A dependent lognormal extrapolation was used to model OS
    - Scenario: A dependent Weibull extrapolation was used to model OS
    - Scenario: A dependent log-logistic extrapolation was used to model OS

Stopping rule for ET

A stopping rule of five years was applied for ET, for both the intervention and comparator arms, in the base case economic analysis, in line with expected prescribing in UK clinical practice. In order to explore the impact of this assumption on the cost-effectiveness results, a scenario in which a 10-year stopping rule for ET was applied.

- Base case: A five-year stopping rule for ET was applied (intervention and comparator arms)
    - Scenario: A 10-year stopping rule for ET was applied (intervention and comparator arms)

Treatment waning

A long-term treatment effect has been observed in a number of trials in the early breast cancer setting. The IDFS piecewise analysis for monarchE demonstrates the existence of a treatment effect past discontinuation for abemaciclib. The start time and duration of the treatment waning effect are uncertain. In the base case economic analysis, the start of the treatment waning effect was informed by the ATAC trial and began at 8 years.[75] The duration of the treatment waning effect, 27 years, was informed by the point in the model where the IDFS rates equal background mortality, by when the hazard equals general population mortality, in line with the approach used in TA612.[45]

Due to the uncertainty in the start time and duration of the treatment waning effect, scenario analyses varying these assumptions have been conducted, in which the treatment waning effect is assumed to be half of that in the base case (start at four years, stop at 13.5 years) and the treatment waning effect is informed by the treatment duration of AIs and length of follow-up from the ATAC study (start at five years, stop at 10 years).

- Base case: The treatment waning effect was assumed to start at 8 years and stop at 27 years
    - Scenario: The treatment waning effect was assumed to start at four years and stop at 13.5 years
    - Scenario: The treatment waning effect was assumed to start at five years and stop at 10 years

Subsequent treatments in the metastatic setting

In the base case analysis, subsequent treatments in the metastatic setting were informed by market shared information adapted from TA563 and TA725, and as such re-treatment with CDK4/6 was not permitted. To explore the uncertainty associated with this assumption, scenario analyses were conducted where subsequent treatments in the metastatic setting in the abemaciclib + ET arm are set equal to the ET arm in both the ET-sensitive and ET-resistant pathways. This assumes CDK4/6 re-treatment which, as discussed in Section B.3.3.4, there is no evidence for this so these results should be interpreted with caution. A second scenario analysis has been conducted whereby patients receiving treatments in the ET-sensitive and ET-resistant health states are assumed to receive the same treatment mix as the treatments received in the ET-sensitive health state by patients in the ET alone arm in the base case analysis. The subsequent treatment mixes are presented in Table 72.

- Base case: Subsequent treatments in the metastatic setting are informed by market share information adapted from TA563 and TA725[7, 32]
    - Scenario: For subsequent treatments in the metastatic setting, it is assumed that patients in the abemaciclib + ET arms receive the same treatment mixes in the ET-sensitive and ET-resistant pathways as patients in the ET arms in the base case analysis.
    - Scenario: Patients receiving treatments in the ET-sensitive and ET-resistant health states are assumed to receive the same treatment mix as the treatments received in the ET-sensitive health state by patients in the ET alone arm in the base case analysis. These subsequent treatment mixes are presented in Table 72 below.

Table 72. Proportion of patients whose early breast cancer is ET-resistant or ET-sensitive receiving each treatment in a scenario analysis

	ET-resistant	ET-sensitive
CDK4&6 + FUL	[redacted]	[redacted]
EXE + EVE	[redacted]	[redacted]
FUL	[redacted]	[redacted]
CAP	[redacted]	[redacted]
EXE	[redacted]	[redacted]
CDK4&6 + NSAI	[redacted]	[redacted]
TMX	[redacted]	[redacted]
NSAI	[redacted]	[redacted]

Footnotes: [a] It is assumed that 60% of patients receive CDK4/6 inhibitors. Based on NICE resource impact template 6715479277 (TA563), it is assumed that 40% of patients receive abemaciclib, 40% of patients receive ribociclib and 20% of patients receive palbociclib.[76]
Abbreviations: ABE+FUL: abemaciclib + fulvestrant; CAP: capecitabine; ET: endocrine therapy; EXE: exemestane; EXE+EVE: exemestane + everolimus; FUL: fulvestrant; PAL+FUL: palbociclib + fulvestrant; RIB+FUL: ribociclib + fulvestrant.

LY 'pay-offs' for the metastatic setting

In the base case economic analysis, the LY 'pay-offs' in the metastatic setting are informed by previous cost-effectiveness analyses in the advanced breast cancer setting, based on assumptions from TA563 and TA725 as far as possible.[7, 32] To explore the impact of the uncertainty around these assumptions, a scenario analysis was conducted whereby LYs for all arms were equated to the abemaciclib arm (ET-resistant pathway, PFS: [redacted], PPS: [redacted]; ET-sensitive pathway, PFS1: [redacted], PFS2: [redacted], PPS: [redacted]).

- Base case: LYs for the metastatic setting were informed by assumptions in TA563 and TA725 as far as possible
    - Scenario: LYs for all treatments in both arms were equated to the abemaciclib arm (ET-resistant pathway, PFS: [redacted], PPS: [redacted]; ET-sensitive pathway, PFS1: [redacted], PFS2: [redacted], PPS: [redacted]).

TTD in metastatic setting

In the base case economic analysis, TTD in the metastatic setting was informed by previous cost-effectiveness analyses in the advanced breast cancer setting, based on TA563 and TA725 as far as possible.[32] A scenario analysis was conducted whereby TTD for all CDK4/6 inhibitors was set equal to TTD for abemaciclib + ET (ET-resistant: [redacted] months; ET-sensitive: [redacted] months) and a shorter TTD was set for everolimus + exemestane ([redacted] months) to reflect the possible earlier discontinuation expected with everolimus, in line with TA725.[7]

- Base case: TTD was informed by TA563 and TA725 as far as possible
    - Scenario: TTD for all CDK 4/6 inhibitors was set equal (ET-resistant: [redacted] months; ET-sensitive: [redacted] months) and a shorter TTD was set for everolimus + exemestane ([redacted] months).

Age-adjusted utility values

- Base case: Age-adjusted utility values provided by Janssen and Szende[84]
    - Scenario: Age-adjusted utility values provide by Ara and Brazier[82]

The results for all scenario analyses are presented in Table 73.

Table 73: Scenario analysis results[a]

Parameter	Base case	Scenario	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
Base case			[redacted]	[redacted]	3,786
Discount rate	3.5% (costs and effects)	1.5% (costs and effects)	[redacted]	[redacted]	Dominant
IDFS extrapolation	Dependant Loglogistic	Dependant Weibull	[redacted]	[redacted]	1,188
		Dependant Generalised Gamma	[redacted]	[redacted]	959
		Dependant Gamma	[redacted]	[redacted]	962
		Independent Loglogistic	[redacted]	[redacted]	530
TTD extrapolation – ABE+ET	Dependant hazard spline 2-knot	Dependant Loglogistic	[redacted]	[redacted]	3,903
		Dependant Lognormal	[redacted]	[redacted]	3,849
		Dependant Hazard spline 1-knot	[redacted]	[redacted]	5,750
TTD extrapolation – ET (intervention + comparator arm)	Independent hazard spline 2-knot	Dependant hazard spline 2-knot	[redacted]	[redacted]	4,912
		Independent Hazard spline 1-knot	[redacted]	[redacted]	9,307

		Independent Weibull	[redacted]	[redacted]	5,608
		Independent Loglogistic	[redacted]	[redacted]	5,464
OS extrapolation	Dependent Exponential	Dependant Lognormal	[redacted]	[redacted]	3,787
		Dependant Weibull	[redacted]	[redacted]	3,786
		Dependant Loglogistic	[redacted]	[redacted]	3,786
Stopping rule for ET	5-years	10-years	[redacted]	[redacted]	3,760
Treatment waning	Start at 8-years, stop at 27-years	Start at 4-years, stop at 13.5-years (half effect)	[redacted]	[redacted]	5,723
		Start at 5-years, stop at 10-years (Treatment duration of AIs and length of follow-up from ATAC study)	[redacted]	[redacted]	5,997
% receiving subsequent treatment, metastatic set ting	Market share information adapted from TA563 and TA725	M2 and M3 pathway: ABE + ET = ET arm	[redacted]	[redacted]	12,216
		M3 ET arm equal for all arms	[redacted]	[redacted]	12,715
LY 'pay-offs' for the metastatic setting	Assumption s based on TA563 and TA725	Equate LYs for all arms to ABE arms M2: [redacted] (PFS), [redacted] (PPS) M3: [redacted] (PFS1), [redacted] (PFS2), [redacted] (PPS)	[redacted]	[redacted]	4,996
TTD in metastatic setting	Assumption s based on TA563 and TA725	TTD for all CDK4/6i equal: ET-resistant = [redacted] ET-sensitive = [redacted] Shorter TTD for EVE + EXE = [redacted]	[redacted]	[redacted]	3,792
Age-adjusted utility values	Age-adjusted utility values provided by	Age-adjusted utility values provided by Ara	[redacted]	[redacted]	3,841

	Janssen and Szende (2014)	and Brazier (2011)			

Footnotes: [a] Discounted costs and QALYs.
Abbreviations: ABE: abemaciclib; AI; aromatase inhibitor; CDK: cyclin-dependent kinase; ET: endocrine therapy; HSUV: health state utility values; IDFS: invasive disease free survival; LY; life years; NMR: non-metastatic recurrence; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival; TA: technology appraisal; TTD : time to discontinuation.

B.3.8.4 Summary of sensitivity analyses results

The sensitivity analyses support the conclusion of the base case economic analysis that abemaciclib + ET is a cost-effective use of NHS resources. The PSA demonstrated that abemaciclib + ET is associated with a [redacted]% probability of being cost-effectiveness at a willingness-to-pay threshold of £30,000 per QALY gained. Furthermore, the probabilistic ICER of £3,782 per QALY gained is very similar to the deterministic ICER of £3,786 per QALY gained, which shows that the results are robust to variation in the parameters included in the model.

The DSA showed that the only parameter that resulted in significant variation in the ICER was the probability of transition to the NMR health state for the ET arm. However, this probability was robustly derived from the previous NICE appraisal of trastuzumab (TA632), which was accepted by NICE.[67]

Scenario analyses were conducted to explore the uncertainty relating to the assumptions used in the base case economic analysis. The results of all scenario analyses were comfortably under the £30,000 willingness-to-pay threshold, demonstrating that there is minimal uncertainty surrounding the cost-effectiveness of abemaciclib + ET. The scenario analysis varying the assumptions used to inform the LY 'pay-offs' in the metastatic health state demonstrate that this area of uncertainty has a minimal impact on the ICER, with the ICER increasing by under £1,500 compared to the base case.

B.3.9 *Subgroup analysis*

NA – No economic subgroup analyses were conducted in this appraisal.

B.3.10 *Validation*

B.3.10.1 Validation of cost-effectiveness analysis

Technical Validation

In alignment with best practice, validation of the economic model structure was conducted by an independent health economist prior to the submission. A technical cell by cell verification of formulae, functions and coding was performed as part of this process. A number of technical and 'sanity' checklists were completed to ensure that the model functioned as intended and generated accurate results which were consistent with input data and robust to extreme values. The functionality of the sensitivity and scenario analyses were also reviewed.

B.3.11 *Interpretation and conclusions of economic evidence*

Generalisability of the analysis

The economic evaluation is based on the patient population for the monarchE trial, which may be considered representative of patients with HR+, HER2− early breast cancer at high risk of recurrence in the UK. ET alone, which was costed as a mix of anastrozole, letrozole, tamoxifen and exemestane, is the only relevant comparator for patients in UK clinical practice. Subsequent treatment pathways were also based on clinical practice in the UK. As per the NICE reference case, the analysis was conducted from an NHS and PSS perspective.

Strengths of the economic evaluation

The model structure was deemed appropriate for this decision problem, as it aligned with the model structures adopted in the cost-effectiveness analysis captured in the SLR and consistent with prior relevant NICE appraisals. The treatment pathways included in the model were based on the treatments available for patients in UK clinical practice in both the early breast cancer and metastatic breast cancer settings.

A large number of model inputs were taken from the methodologically robust monarchE trial, and parameter uncertainty was thoroughly explored through a PSA and a range of DSAs. Recent external evidence from comparable EBC populations were used to assess the face validity of the extrapolations. Clinical assumptions not dictated by the monarchE trial were instead informed by previously published HER2+ EBC models. Since HER2+ EBC population have a higher risk of recurrence compared to HER2− EBC population, the model outcomes can be considered conservative.

Given the limited data for patients who experienced metastatic recurrence in the monarchE trial, it was necessary to use inputs and assumptions from previous abemaciclib cost-effectiveness analyses in the metastatic settings to inform outcomes for patients in the metastatic setting. Where possible, this aligns with the Committee's previously preferred assumptions in the metastatic settings, or conservative estimates where this is not possible. Sensitivity analyses have indicated that, as patients typically only enter the metastatic health state after a number of years, the costs and outcomes in this setting are subject to a high degree of discounting, and therefore any outstanding uncertainty around the inputs in this setting does not have a major impact on the model results.

Other strengths of the evaluation are that the analysis meets all aspects of the NICE reference case, including performance of a cost-utility analysis from an NHS/PSS perspective, assessment of HRQoL using the EQ-5D and discounting of costs and benefits at 3.5%. The analysis has similarly taken into account NICE's position statement regarding use of EQ-5D-5L data. The 5L data captured in MONARCH 2 was mapped to the EQ-5D-3L value set.

Limitations of the economic evaluation

While the monarchE trial demonstrates robust evidence for the benefits of abemaciclib + ET in the immediate future, the follow-up time for the trial data means that there is uncertainty associated with the extrapolation of lifetime outcomes. Literature reviews were unable to identify long term outcomes for a monarchE comparable population. Heterogenous patient populations and endpoints, trials such as ATAC39, FACE31 and FATA-GIM330 were used as the best possible proxy evidence to externally validate IDFS curve selection.

The OS without distant recurrence extrapolations were reliant on internal validation of the DRFS monarchE trial data which could introduce bias in the cost-utility analysis by under or overestimating the long-term survival outcomes of the monarchE population. Alternative IDFS and OS distributions were tested within scenario analysis. The outcomes from these analyses showed that the base case distribution still provided conservative ICERs compared to the alternative second and third best-fitting distributions for IDFS and OS.

Overall LYs dictated by the MONARCH 2 and MONARCH 3 models were incorporated in the monarchE models. The model currently does not assume re-treatment with CDK 4/6 inhibitors in the metastatic setting. Based on the current results from the monarchE trial in the ET alone arm, a higher proportion of patients are recurring at an earlier timepoint and therefore moving to the ET-resistant metastatic pathway where they are being treated by CDK 4/6 inhibitors. Therefore these 'faster' recurring patients can experience the immediate QALY gains from re-treatment with CDK 4/6 inhibitors. Even though, the metastatic method may introduce uncertainty, it aims to model the monarchE indication with the most recent evidence from HR+, HER2− trials. Previous HTA submitted EBC models in HER2+ indications were able to include evidence from long term HER2+ trial data which is not the case for the monarchE patient population. The monarchE long term data on post-distant recurrence events were limited. It was not possible to make any reasonable assumption and long-term extrapolation from such a low number of events and would lead to implausible outcomes. In the absence of alternative evidence which is closely representative of the monarchE population, the fixed pay-off approach is considered the most recent and relevant evidence source.

Summary of economic evidence for abemaciclib + ET

In this analysis, abemaciclib + ET was found to result in an incremental gain of [redacted] undiscounted LYs and [redacted] QALYs compared to ET alone. Abemaciclib (at PAS price) + ET was associated with a higher total cost (£[redacted]) compared to ET alone. This was predominantly driven by the higher drug-related costs for abemaciclib + ET in the invasive disease free setting, compared to ET alone.

The base case analysis produced a pairwise ICER for abemaciclib + ET versus ET alone of £3,786 per QALY gained. The probability that abemaciclib + ET is cost-effective at the with-PAS price at a £30,000 ICER threshold is [redacted]%.

For patients with HR+, HER2− early breast cancer at high risk of recurrence, the addition of abemaciclib to ET would represent an important paradigm shift in the management of early breast cancer, providing patients with an increased chance of a potential disease cure, thereby avoiding progression to incurable advanced breast cancer and the associated substantial reduction in quality of life and inevitable early death. This analysis demonstrates that abemaciclib would represent a cost-effective use of NHS resources for these patients.

References

1. Schettini F, De Santo I, Rea CG, et al. CDK 4/6 inhibitors as single agent in advanced solid tumors. Frontiers in oncology 2018;8:608.
2. Castrellon AB. Novel strategies to improve the endocrine therapy of breast cancer. Oncology reviews 2017;11.
3. Torres-Guzman R, Calsina B, Hermoso A, et al. Preclinical characterization of abemaciclib in hormone receptor positive breast cancer. Oncotarget 2017;8:69493-69507.
4. Lilly Data on File. Abemaciclib draft SmPC. 2021.
5. NICE. Abemaciclib monotherapy for treating advanced hormone-receptor positive, HER2-negative breast cancer after endocrine therapy and chemotherapy ID1347. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10264 (Accessed 09.03.18). 2018.
6. NICE. Abemaciclib with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer after endocrine therapy ID1339. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10263 (Accessed 09.03.18). 2018.
7. National Institute for Health and Care Excellence (NICE). Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy [TA725]. Available at: https://www.nice.org.uk/guidance/TA725 [last accessed 01 March 2021].
8. British National Formulary. BNF Abemaciclib. Available at https://bnf.nice.org.uk/medicinal-forms/abemaciclib.html. [accessed 12 February 2021].
9. American Cancer Society. Breast cancer facts & figures 2019-2020. 2019. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breastcancer-facts-and-figures/breast-cancer-facts-and-figures-2019-2020.pdf. [last accessed 15 May 2020].
10. Cancer Research UK: Breast Cancer Statistics. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer. [Accessed 21 January 2021].
11. Cancer Research UK. Breast Cancer Statistics. Breast cancer incidence (invasive) Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer#heading-Zero Accessed: 23.02.18. 2014.
12. International Agency for Research on Cancer WHO. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. Available at: http://globocan.iarc.fr/Pages/fact_sheets_population.aspx [Accessed 23 February 2020]. 2012.
13. NICE. Early and locally advanced breast cancer: diagnosis and management. Available at: https://www.nice.org.uk/guidance/ng101 [Accessed 01 October 2021]. 2018.
14. Verrill M. Metastatic disease of the breast and local recurrence. Surgery - Oxford International Edition 2016;34:47-51.
15. NICE. Resource Impact Template: Palbociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer (TA495) 2017.
16. Resource Impact Template: Ribociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer (TA496). .
17. Gerber B, Freund M, Reimer T. Recurrent breast cancer: treatment strategies for maintaining and prolonging good quality of life. Dtsch Arztebl Int 2010;107:85-91.
18. Cardoso F, Costa A, Senkus E, et al. 3rd ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3). Ann Oncol 2017;28:16-33.
19. Sledge GW, Jr., Toi M, Neven P, et al. The Effect of Abemaciclib Plus Fulvestrant on Overall Survival in Hormone Receptor-Positive, ERBB2-Negative Breast Cancer That Progressed on Endocrine Therapy-MONARCH 2: A Randomized Clinical Trial. JAMA Oncol 2019;6:116-24.
20. NICE. Palbociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer [TA495]. Available at: https://www.nice.org.uk/guidance/ta495 [Accessed 27 February 2018]. 2017.
21. Walker MS, Hasan M, Yim YM, et al. Retrospective study of the effect of disease progression on patient reported outcomes in HER-2 negative metastatic breast cancer patients. Health Qual Life Outcomes 2011;9:46.

22. Rastogi P, O'Shaughnessy J, Johnston S, et al. Primary Outcome Analysis of Invasive Disease-free Survival for monarchE: Abemaciclib Combined with Adjuvant Endocrine Therapy for High RiskEarly Breast Cancer, In San Antonio Breast Cancer Symposium®, 2020.
23. Lilly Data on File. Clinical Study Report [monarchE]. 2020.
24. Observatory GC. Estimated number of new cases in 2020, worldwide, both sexes, all ages. Available at https://gco.iarc.fr/today/online-analysis-pie?v=2020&mode=cancer&mode_population=continents&population=900&populations=900&key=total&sex=0&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=7&group_cancer=1&include_nmsc=1&include_nmsc_other=1&half_pie=0&donut=0. [Accessed 21 January 2021].
25. Office for National Statistics. Cancer Registration Statistics, England: first release. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancerregistrationstatisticsengland/firstrelease2015 [Accessed 01 October 2021]. 2015.
26. Cancer Research UK. Breast cancer in men. Available at: https://www.cancerresearchuk.org/about-cancer/breast-cancer/stages-types-grades/types/male-breast-cancer. [Last accessed: 24 February 2021]. 2020.
27. Breast Cancer Care. Facts and Statistics 2018. Available at: https://www.breastcancercare.org.uk/about-us/media/press-pack-breast-cancer-awareness-month/facts-statistics [Accessed 01 October 2021]. 2018.
28. Cancer Research UK. Breast cancer incidence (invasive) statistics. Available at: www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-invasive#heading-One accessed 06.03.18. 2018.
29. Finn RS, Aleshin A, Slamon DJ. Targeting the cyclin-dependent kinases (CDK) 4/6 in estrogen receptor-positive breast cancers. Breast Cancer Res 2016;18:17.
30. Fan W, Chang J, Fu P. Endocrine therapy resistance in breast cancer: current status, possible mechanisms and overcoming strategies. Future Med Chem 2015;7:1511-9.
31. Public Health England (PHE). Proportion Diagnosed by Stage (stacked chart). Available at: https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/ [Last accessed 26 October 2021].
32. NICE. Abemaciclib with an aromatase inhibitor for untreated advanced hormone-receptor positive, HER2-negative breast cancer ID1227 [TA563]. Available at: https://www.nice.org.uk/guidance/TA563 [Last accessed 5 February 2021], 2019.
33. Wang L, Shi JF, Zhu J, et al. Health-related quality of life and utility scores of patients with breast neoplasms in China: A multicenter cross-sectional survey. Breast 2018;39:53-62.
34. Yu J, Son WS, Lee SB, et al. Uneven recovery patterns of compromised health-related quality of life (EQ-5D-3 L) domains for breast Cancer survivors: a comparative study. Health Qual Life Outcomes 2018;16:143.
35. Lidgren M, Wilking N, Jönsson B, et al. Health related quality of life in different states of breast cancer. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 2007;16:1073-81.
36. van Londen GJ, Beckjord EB, Dew MA, et al. Associations between adjuvant endocrine therapy and onset of physical and emotional concerns among breast cancer survivors. Support Care Cancer 2014;22:937-45.
37. Reed E, Simmonds P, Haviland J, et al. Quality of life and experience of care in women with metastatic breast cancer: a cross-sectional survey. J Pain Symptom Manage 2012;43:747-58.
38. Girgis A, Lambert S, Johnson C, et al. Physical, Psychosocial, Relationship, and Economic Burden of Caring for People With Cancer: A Review. Journal of Oncology Practice 2012;9:197-202.
39. Goren A, Gilloteau I, Lees M, et al. Quantifying the burden of informal caregiving for patients with cancer in Europe. Support Care Cancer 2014;22:1637-46.
40. Wagner CD, Bigatti SM, Storniolo AM. Quality of life of husbands of women with breast cancer. Psycho-Oncology 2006;15:109-120.
41. Yin W, Horblyuk R, Perkins JJ, et al. Association Between Breast Cancer Disease Progression and Workplace Productivity in the United States. J Occup Environ Med 2017;59:198-204.
42. University of Oxford. Cancer costs the UK economy £15.8bn a year. Available at: http://www.ox.ac.uk/news/2012-11-07-cancer-costs-uk-economy-%C2%A3158bn-year. [Last accessed 09 February 2021].

43. O'Shaughnessy J. Extending survival with chemotherapy in metastatic breast cancer. Oncologist 2005;10 Suppl 3:20-9.
44. NICE. Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer. Technology appraisal guidance [TA107]. Published date: 23 August 2006. Available at: https://www.nice.org.uk/Guidance/TA107. [Last accessed 03 February 2021]. 2006.
45. NICE. Neratinib for extended adjuvant treatment of hormone receptor-positive, HER2-positive early stage breast cancer after adjuvant trastuzumab [TA612]. Published date: 20 November 2019. Available at: https://www.nice.org.uk/guidance/TA612. [Last accessed 09 February 2021]. 2019.
46. NICE. Pertuzumab for adjuvant treatment of HER2- positive early stage breast cancer. [TA569]. Published date: 20 March 2019. Available at https://www.nice.org.uk/guidance/TA569. [Last accessed 09 February 2021]. 2019.
47. Lilly Data on File. Clinical Study Report [MONARCH 2]. 2017.
48. Hamilton E, Infante JR. Targeting CDK4/6 in patients with cancer. Cancer Treat Rev 2016;45:129-38.
49. Dickson MA. Molecular pathways: CDK4 inhibitors for cancer therapy. Clin Cancer Res 2014;20:3379-83.
50. Malumbres M, Barbacid M. To cycle or not to cycle: a critical decision in cancer. Nat Rev Cancer 2001;1:222-31.
51. Lilly Data on File. Clinical Study Report [MONARCH 3]. 2017.
52. Lee KA, Shepherd ST, Johnston SR. Abemaciclib, a potent cyclin-dependent kinase 4 and 6 inhibitor, for treatment of ER-positive metastatic breast cancer. Future Oncol 2019;15:3309-3326.
53. Johnston SRD, Harbeck N, Hegg R, et al. Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2−, Node-Positive, High-Risk, Early Breast Cancer (monarchE). Journal of Clinical Oncology 2020;38:3987-3998.
54. NICE. Early breast cancer (preventing recurrence and improving survival): adjuvant bisphosphonates. Evidence summary [ES15]. Available at: https://www.nice.org.uk/advice/es15/chapter/Key-points. [Last accessed 12 February 2021].
55. Harbeck NJ, S. Fasching, P. Martin, M. Toi, M. Rastogi, M. Song, C. High Ki-67 as a Biomarker for Identifying Patients with High RiskEarly Breast Cancer Treated in monarchE, In San Antonio Breast Cancer Symposium®, 2020.
56. Hudis CA, Barlow WE, Costantino JP, et al. Proposal for Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials: The STEEP System. Journal of Clinical Oncology 2007;25:2127-2132.
57. Sledge GW, Jr., Toi M, Neven P, et al. MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. J Clin Oncol 2017;35:2875-2884.
58. Goetz MP, Toi M, Campone M, et al. MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer. J Clin Oncol 2017;35:3638-3646.
59. ClinicalTrials.gov. Endocrine Therapy With or Without Abemaciclib (LY2835219) Following Surgery in Participants With Breast Cancer (monarchE). Available at: https://clinicaltrials.gov/ct2/show/NCT03155997?term=JPCF&rank=1 [Accessed 01 May 2021].
60. Gluz O, Nitz UA, Christgen M, et al. West German Study Group Phase III PlanB Trial: First Prospective Outcome Data for the 21-Gene Recurrence Score Assay and Concordance of Prognostic Markers by Central and Local Pathology Assessment. Journal of Clinical Oncology 2016;34:2341-2349.
61. Marmé F, Lederer B, Blohmer JU, et al. Utility of the CPS+EG staging system in hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer treated with neoadjuvant chemotherapy. Eur J Cancer 2016;53:65-74.
62. Mamounas EP, Tang G, Paik S, et al. 21-Gene Recurrence Score for prognosis and prediction of taxane benefit after adjuvant chemotherapy plus endocrine therapy: results from NSABP B-28/NRG Oncology. Breast Cancer Res Treat 2018;168:69-77.
63. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. bmj 2019;366.
64. Deluche E, Antoine A, Bachelot T, et al. Contemporary outcomes of metastatic breast cancer among 22,000 women from the multicentre ESME cohort 2008-2016. Eur J Cancer 2020;129:60-70.

65. National Institute for Health and Care Excellence (NICE). Position statement on use of the EQ-5D-5L value set for England (updated October 2019). Available at https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l [Accessed 19 March 2021].
66. van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health 2012;15:708-15.
67. NICE. Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer [TA632]. Published date: 10 June 2020. Available at: https://www.nice.org.uk/guidance/ta632/resources/trastuzumab-emtansine-for-adjuvant-treatment-of-her2positive-early-breast-cancer-pdf-82609074363589. [Accessed 17 March 2021].
68. Cardoso F, Kyriakides S, Ohno S, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2019;30:1674.
69. NICE. Single Technology Appraisal Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer [ID1516] Committee Papers. Available at: https://www.nice.org.uk/guidance/ta632/documents/committee-papers. [Last accessed: 19 March 2021]. 2020.
70. National Institute for Health and Care Excellence (NICE). Intrabeam radiotherapy system for adjuvant treatment of early breast cancer [TA501]. Available at: https://www.nice.org.uk/guidance/ta501 [Accessed 29 April 2021].
71. Hudis CA, Barlow WE, Costantino JP, et al. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. Journal of Clinical Oncology 2007;25:2127-2132.
72. NICE. Guide to the methods of technology appraisal 2013: The reference case. Available at: https://www.nice.org.uk/process/pmg9/chapter/the-reference-case [Last accessed 29th April 2021]. 2013.
73. Hamilton SN, Tyldesley S, Li D, et al. Second malignancies after adjuvant radiation therapy for early stage breast cancer: is there increased risk with addition of regional radiation to local radiation? International Journal of Radiation Oncology* Biology* Physics 2015;91:977-985.
74. Latimer NR. NICE DSU Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. Available at: http://nicedsu.org.uk/wp-content/uploads/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf [Accessed 18 August 2021]. 2013.
75. Cuzick J, Sestak I, Baum M, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. The Lancet Oncology. 2010;11(12):1135-1141. doi:10.1016/S1470-2045(10)70257-6.
76. NICE Resource Impact Template: Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy [TA725]. Available at: https://www.nice.org.uk/guidance/ta725/resources [Accessed 29 October 2021].
77. Hudgens S. A Method of Deriving Estimates of Health State Utilities for Patients With Metastatic Breast Cancer. Journal of Clinical Pathways 2016;2:39-45.
78. NICE. Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma [TA306]. Available at https://www.nice.org.uk/guidance/ta306 [Last accessed 29th April 2021]. 2014.
79. National Institute for Health and Care Excellence (NICE). Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy [TA579]. Available at: https://www.nice.org.uk/guidance/ta579 [Accessed 29 April 2021]. 2019.
80. National Institute for Health and Care Excellence (NICE). Fulvestrant for untreated locally advanced or metastatic oestrogen-receptor positive breast cancer [TA503]. Available at: https://www.nice.org.uk/guidance/ta503 (Accessed 01 October 2021).
81. Ara R, Wailoo A. NICE DSU Technical Support Document 12: the use of health state utility values in decision models. Available at: http://nicedsu.org.uk/wp-content/uploads/2016/03/TSD12-Utilities-in-modelling-FINAL.pdf [Accessed 12 August 2021]. 2017.
82. Ara R, Brazier JE. Using health state utility values from the general population to approximate baselines in decision analytic models when condition-specific data are not available. Value in Health 2011;14:539-545.
83. Kind P, Hardman G, Macran S. UK population norms for EQ-5D, 1999.

84. Szende A, Janssen B, Cabases J. Self-reported population health: an international perspective based on EQ-5D: Springer Nature, 2014.
85. Mitra D, Wood R, De Courcy J, Iyer S. Patient Reported Health Utility in HR+/HER2-Advanced/Metastatic Breast Cancer. Value in Health 2016; A347 – A766.
86. Department of Health and Social Care. Drugs and pharmaceutical electronic market information tool (eMIT). Available at: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit, 2018.
87. European Medicines Agency. Summary of Product Characteristics (SmPC). Available at https://www.medicines.org.uk/emc#gref. [Accessed 29th April 2021].
88. Dhesy-Thind S, Fletcher GG, Blanchette PS, et al. Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: A Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline. Journal of Clinical Oncology 2017;35:2062-2081.
89. NHS improvement. National schedule of reference costs - year 2019/2020 - NHS trust and NHS foundation trusts. Published online 2019. 2019.
90. Simcock R, Heaford A. Costs of multidisciplinary teams in cancer are small in relation to benefits. BMJ 2012;344.
91. Curtis L, Burns A. Unit Costs of Health and Social Care 2017, Personal Social Services Research Unit, University of Kent, Canterbury. Available at: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2017/. 2017.

Appendices

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Abemaciclib in combination with endocrine therapy for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer [ID3857]

Clarification questions

November 2021

File name	Version	Contains confidential information	Date
[ID3857] Eli Lilly_Abemaciclib in EBC_clarifications response_09122021 [ACIC REDACTED]	FINAL	NO	09 December 2021

Section A: Clarification on effectiveness data

Literature Searches

A1. Please provide full details of the searches of conference proceedings referred to in Appendix D.1.2, including the specific resources searched, and the search strategies or search terms used.

As stated in the CS, Appendices, Appendix D.1.2, the following conference websites were searched to identify relevant conference abstracts:

- San Antonio Breast Cancer Symposium (2018–2021)
- American Society of Clinical Oncology (2018–2021)
- European Society for Medical Oncology (2018–2021)
- European Society for Medical Oncology Breast (2018–2021)
- American Association for Cancer Research (2018–2021)
- St. Gallen Consensus International Breast Cancer Conference (2020–2021, added to the protocol during the SLR updates).

The key search terms used were “early breast cancer” or “ebc” or “breast cancer” or “adjuvant”.

A2. Please provide full details of the searches of the health technology assessment websites referred to in Appendices G.2 and H.2, including the specific resources searched, and the search strategies or search terms used, date searched, and results.

As part of the economic SLR a grey literature search was conducted in HTA databases and HTA websites. Table 1 provides an overview of the searches conducted in the CRD data base and Table 2 provides an overview of the searches conducted across the HTA websites. A time limit of 2015 onwards was applied. The search date has been provided under the tables. The results of the economic SLR were presented in the CS, Appendices, Appendix G.4, which stated that no relevant HTAs were identified by the economic SLR.

Table 1: Search results CRD database – economic evidence

Topic	#	Terms	# results
Population	1 2	(breast cancer) OR (breast tumor) OR (breast tumour) OR (breast carcinoma) (early stage) OR (HER2) OR (node positive)	
Total		#1 AND #2 (in HTA and NHS EED)	16

Search date: July 27, 2020

Table 2 Search results for HTAs

Database	Website	Terms	# results
CADTH	https://www.cadth.ca/search?keywords=early+stage+breast+cancer	early stage breast cancer Restricted to Product line: Common Drug Review Health Technology assessment Health Technology Update Issues in Emerging Health Technologies Pan Canadian Oncology Drug Review Pharmaceutical Review Update Technology Review Therapeutic Review	82
HAS	https://www.has-sante.fr/jcms/r_1455134/en/about-has	early stage breast cancer	17
NICE	https://www.nice.org.uk/search?q=early+stage+breast+cancer	early stage breast cancer	56
PBAC	http://www.pbs.gov.au/pbs/home	early stage breast cancer	106
SMC	https://www.scottishmedicines.org.uk/	early stage breast cancer	8
Total			269

Search date: July 27, 2020

A3. Please provide full details of the searches of trials database referred to in Appendix D.1.2, including the search strategies or search terms used, date searched, and results.

As stated in the CS, Appendices, Appendix D.1.2, three trial databases were searched: Clinicaltrials.gov, International Clinical Trials Registry Platform Search Portal and Australian New Zealand Clinical Trial Registry. The date searched, search terms and results for the original SLR, update 1 and update 2 are presented in Table 3.

Table 3: Date searched, search terms and results for the trial databases searched in the clinical SLR

	Original SLR	Update 2	Update 3
Clinicaltrials.gov			
Date searched	9th November 2019	4th January 2021	June 2021
Keywords used	letrozole OR anastrazole OR exemestane OR abemaciclib OR palbocilcib OR ribociclib OR tamoxifen OR everolimus | Recruiting, Not yet recruiting, Available,	letrozole OR anastrazole OR exemestane OR abemaciclib OR palbocilcib OR ribociclib OR tamoxifen OR everolimus | Recruiting, Not yet recruiting, Available,	letrozole OR anastrazole OR exemestane OR abemaciclib OR palbocilcib OR ribociclib OR tamoxifen OR everolimus | Recruiting, Not yet recruiting, Available,

	Active, not recruiting, Completed, Enrolling by invitation Studies | Breast Cancer | Adult, Older Adult | Phase Early Phase 1, 1, 2, 3, 4, Not Applicable |	Active, not recruiting, Completed, Enrolling by invitation Studies | Breast Cancer | Adult, Older Adult | Phase Early Phase 1, 1, 2, 3, 4, Not Applicable |	Active, not recruiting, Completed, Enrolling by invitation Studies | Breast Cancer | Adult, Older Adult | Phase Early Phase 1, 1, 2, 3, 4, Not Applicable |
Number of hits	420	300	252
International Clinical Trials Registry Platform Search Portal			
Date searched	9th November 2019	4th January 2021	June 2021
Keywords used	Breast cancer or early breast cancer and letrozole OR anastrazole OR exemestane OR abemaciclib OR palbocilcib OR ribociclib OR tamoxifen OR everolimus | recruiting | Phase II and III	Breast cancer or early breast cancer and letrozole OR anastrazole OR exemestane OR abemaciclib OR palbocilcib OR ribociclib OR tamoxifen OR everolimus | recruiting | Phase II and III	Breast cancer or early breast cancer and letrozole OR anastrazole OR exemestane OR abemaciclib OR palbocilcib OR ribociclib OR tamoxifen OR everolimus | recruiting | Phase II and III
Number of hits	123	138	10
Australian New Zealand Clinical Trial Registry			
Date searched	9th November 2019	4th January 2021	June 2021
Keywords used	Registry- ANZCTR | Treatment: Drugs | Interventional | Randomised | recruiting, active, not recruiting, completed | cancer |breast |both males and females | Adult (18yrs and over)	Registry- ANZCTR | Treatment: Drugs | Interventional | Randomised | recruiting, active, not recruiting, completed | cancer |breast |both males and females | Adult (18yrs and over)	Registry- ANZCTR | Treatment: Drugs | Interventional | Randomised | recruiting, active, not recruiting, completed | cancer |breast |both males and females | Adult (18yrs and over)
Number of hits	0	0	10

Decision problem

A4. Priority question: The company submission (CS) states 'It is therefore anticipated that patients with early breast cancer at high risk of recurrence in the UK will be identified by the various routinely collected clinical and pathological features outlined above, such as the number of ALNs and tumour size, in line with the inclusion criteria used in the monarchE trial, the pivotal trial for abemaciclib in this indication' (page17)

a. **Please provide an operational definition of 'high risk of recurrence' i.e. the way that a patient will be identified in clinical practice as being in this category.**

Abemaciclib is anticipated to have a marketing authorisation in combination with endocrine therapy [redacted].[1]

In clinical practice, high risk of recurrence is defined based a combination of clinical and pathological features, such as the number of axillary lymph nodes that a breast cancer has spread to, tumours of T2 or greater (tumour size of 2 cm or greater), and high-grade disease.[2, 3] Studies have shown that node involvement is a predictive factor for risk of recurrence, and therefore mortality. In patients with HR+, HER2- early breast cancer, higher mortality rates are observed for patients with ≥4 positive lymph nodes, a Bloom-Richardson combined score grade 3 (well-differentiated), and greater tumour size. The effect on mortality may be compounded with a combination of these histopathologic characteristics.[4] These characteristics align with the definition for patients at high-risk of recurrence based on clinical and pathological risk factors (Cohort 1 in the monarchE trial).

In addition, there is similar evidence for the presence of Ki-67 at higher levels as a predictive factor for higher disease recurrence rates (and therefore mortality) while receiving adjuvant ET following surgery in HR+ early breast cancer patients. In the BIG 1-98 study, patients receiving letrozole with HR+ early breast cancer involving their ALNs and low (≤11%) Ki-67 levels at baseline had a 4-year disease-free survival of 93% compared to 85% for patients with higher Ki-67 values (>11%).[5] Currently, there is no consensus as to the precise baseline level of Ki-67 that would differentiate a patient for being of higher or lower risk of disease recurrence whilst on adjuvant ET. However, the majority of the panel of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015 was prepared to accept a threshold value of Ki-67 within the range of 20% to 29% as indicative of high-risk group appropriate to receive adjuvant chemotherapy.[6] Together with some node involvement (1-3 ALN), high-levels Ki-67 expression (≥20%) is believed to be a valid factor for high-risk patient selection (Cohort 2 in the monarchE trial).

In practice, clinicians will use validated risk prediction tools, such as the PREDICT breast cancer tool or the Nottingham Prognostic Index, as outlined in NICE Guideline NG101, to make an individualised assessment on a patient-by-patient basis about whether disease should be considered as high risk of recurrence.[3, 7, 8]

For example, the PREDICT breast cancer tool takes into account a range of clinical and pathological features, including:[7]

- Tumour size
- Age at diagnosis
- Menopausal status
- Oestrogen receptor status
- Human epidermal growth factor receptor 2 (HER2) status
- Tumour grade
- Number of positive ALNs

The PREDICT tool also includes Ki-67 biomarker status as an optional risk factor to be considered, allowing a clinician to specify whether a patient has a Ki-67 level of ≥10%, if biomarker data are available.

As stated above, it should be noted that abemaciclib is anticipated to be an option for patients with [redacted] early breast cancer, which already is defined as a patient population at higher risk of recurrence relative to the whole population of patients with early breast cancer. Beyond this, it is anticipated that patients with disease at high risk of recurrence in the UK eligible for treatment with abemaciclib will be readily identified by a combination of the routinely collected clinical and pathological features outlined above, which are defined in the monarchE trial inclusion criteria.

b. Which of the two cohorts of the monarchE trial is this definition most consistent with and can be considered generalisable to NHS clinical practice?

The Company considers the ITT population to be the most generalisable source of evidence with the definition of high risk of recurrence used in clinical practice, as outlined in response to Question A4a. While the Company maintains the ITT population is a readily identifiable cohort in the UK, the Company acknowledge that the exact wording of the license for abemaciclib in this indication is still uncertain at this stage of the regulatory process, with more detail expected to be available in [redacted].

In clinical practice, clinicians would judge risk of recurrence using a combination of factors defined in the monarchE inclusion criteria, which includes node involvement, tumour size, tumour grade and Ki-67-status (if available), using validated risk prediction tools, such as the PREDICT breast cancer tool. As such, the monarchE selection criteria may be interpreted to fall within the clinical definition of high-risk of recurrence when applied in these validated prediction tools (PREDICT or the Nottingham Prognostic Index) and the Company maintains that the ITT cohort represents the cohort that is the most generalisable to anticipated UK clinical practice at this time.

In monarchE, as outlined in the CS, Document B, Table 3, Page 27, patients were included into one of two cohorts, based on different inclusion and exclusion criteria relating to risk of recurrence. Inclusion in Cohort 1 was based on a high risk of recurrence defined by clinical and pathological features, specifically tumour involvement in ≥4 ipsilateral ALNs, or pathological tumour involvement in 1–3 ALNs as well as either Grade 3 disease or a primary tumour size of ≥5 cm.[9] Inclusion in Cohort 2 of monarchE was based on a high risk of recurrence defined by pathological tumour involvements in 1–3 ALNs and a high (≥20%) Ki-67 index (but only for patients without Grade 3 disease or a tumour size ≥5 cm).

In monarchE, 5,120 patients (91%) were enrolled in Cohort 1 and 517 patients (9%) were enrolled in Cohort 2. This split is anticipated to mimic UK clinical practice. As such, the vast majority of patients in monarchE were enrolled in Cohort 1, in which high risk of recurrence was defined by clinical and pathological features readily assessed in clinical practice, whilst the remaining 9% were recruited on the basis of Ki-67 index and the pathological tumour involvement of 1–3 ALNs. While Ki-67 may not be routinely assessed in all UK centres, the Company commissioned market research indicates that some major centres in the UK do routinely undertake Ki-67 testing and it is performed ‘on-demand’ in select major centres in the UK. Thus, selecting a minority of patients on the basis of Ki-67 status does represent a relevant risk factor for defining breast cancer at high risk of recurrence for some patients in the UK, and Ki-67 is included as a relevant factor in validated risk prediction tools used routinely in clinical practice.

Accordingly, by combining Cohorts 1 and 2, the ITT population of monarchE represents the population that is most generalisable to how high risk of recurrence is defined in UK clinical practice than selecting only one cohort, as well as maximising the available sample size. There is no evidence to indicate that either of the two cohorts in monarchE, when considered in isolation, would provide more generalisable evidence than the other for patients with breast cancer at high risk of recurrence in UK clinical practice.

c. Please discuss the implications of any difference between this definition and that used to define the inclusion criteria for the most relevant cohort in the monarchE trial.

As outlined in response to Question A4a and A4b, the Company believe that the ITT cohort represents the cohort most consistent with the definition of high risk of recurrence used in clinical practice.

d. Please present all clinical effectiveness results for the cohort that most closely aligns with the definition generalisable to NHS clinical practice.

The Company considers that the ITT cohort represents the population that is the most suitable proxy for the criteria that will be used to define high risk of recurrence used in clinical practice, as outlined in response to Question A4a and A4b.

For completeness, clinical effectiveness results for IDFS and DRFS for patients in Cohort 1 in monarchE are presented below, where patients were defined as high risk of recurrence defined by clinical and pathological features, are presented below. OS data are immature and therefore are not presented here. The majority of patients in UK clinical practice are expected to be identified at high risk of recurrence based on the clinical and pathological features that represent inclusion criteria for Cohort 1. However, for the reasons discussed previously, the consideration of either Cohort of monarchE in isolation cannot be considered representative of UK clinical practice, and the Company considers the ITT population to represent the most generalisable source of evidence.

Table 4: Summary of investigator-assessed IDFS Cohort 1

	Abemaciclib + ET	ET alone	Treatment Effect/Difference 2-sided p-Value (nominal)[b]
Number of events, n (%)	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		
IDFS rate, % (95% CI)[b]			
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]

Footnotes: [a] Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [b] Treatment Effect/Difference/p-values are computed based on comparator ET.
Abbreviations: CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; IDFS: invasive disease-free survival; ITT: intent-to-treat; N: number of patients in the ITT population

Table 5: Summary of investigator-assessed DRFS Cohort 1

	Abemaciclib + ET	ET alone	Treatment Effect/Difference 2-sided p-Value (nominal)[b]
Number of events, n (%)	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		
DRFS rate, % (95% CI)[b]			
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]

Footnotes: [a] Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [b] Treatment Effect/Difference/p-values are computed based on comparator ET.
Abbreviations: CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; DRFS: distant relapse-free survival; ITT: intent-to-treat; N: number of patients in the ITT population

e. Please present an economic analysis for the cohort that most closely aligns with the definition generalisable to NHS clinical practice.

The selection of extrapolation models for the economic analysis using Cohort 1 followed the same process as the base case economic analysis using the ITT cohort, as outlined in the CS, Document B, Section B.3.3.2. Selection of extrapolation models was based on statistical fit to the trial data, using Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC), as well as visual inspection of the survival curves and hazard plots. The assessment of proportional hazards (PH), as well as the AIC and BIC values, for IDFS, time to treatment discontinuation (TTD), and OS for the economic analysis using Cohort 1 are presented in Appendix 1.

The choice of parametric extrapolations for IDFS and OS for the Cohort 1 economic analysis remain unchanged from the base case economic analysis presented in the CS using the ITT cohort. The hazard spline functions with 2-knots was chosen to model TTD for abemaciclib + ET in this scenario analysis, and the exponential function was chosen to model ET TTD in this scenario analysis. More information can be found in Appendix 1.

A summary of the extrapolations for IDFS, OS and TTD for abemaciclib + ET and ET alone for the economic analysis using Cohort 1 is provided in Table 6.

Table 6: Summary of the extrapolations for IDFS, OS and ToT for abemaciclib + ET and ET alone for the Cohort 1 economic analysis

	Abemaciclib + ET		ET alone
Base case IDFS extrapolation	Log-logistic		Log-logistic
Base case OS extrapolation	Exponential		Exponential
	Abemaciclib	**ET (for patients receiving abemaciclib)**	**ET alone**
Base case TTD extrapolation	Hazard spline 2-knots	Exponential	Exponential

Abbreviations: ET: endocrine therapy; IDFS: invasive disease-free survival; OS: overall survival; ToT: time on treatment; TTD: time to treatment discontinuation.

The deterministic results for the Cohort 1 economic analysis are presented in Table 7. In the Cohort 1 economic analysis, abemaciclib (at PAS price) was associated with an ICER of £4,427 per QALY gained.

Table 7: Deterministic Cohort 1 economic analysis results (abemaciclib PAS price)[a]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4,427
ET alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-

Footnotes: This table reports undiscounted LYG, and discounted costs and QALYs.
Abbreviations: ET: endocrine therapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life years.

f. Please clarify which of the outcome measures commissioned in the CS addresses the outcome 'response rate' specified in the final scope issued by NICE

As discussed in the Company response to the draft scope, response rate is not relevant as an outcome to the adjuvant treatment setting in early breast cancer. This was stated in the Company's response to the draft scope, after which NICE noted this response and removed response rate as an outcome from the final scope.[10]

In the adjuvant treatment setting, it is hoped that the cancer has been removed previously (through surgery, radiotherapy and/or chemotherapy) and the focus of adjuvant treatment is on prevention of recurrence (measured by IDFS and DRFS).[3] As such, the concept of response is not relevant in this disease setting so it was not a trial outcome in monarchE. Therefore, no results for response rate are available from monarchE either for the whole population or by menopausal status.

Systematic review

A5. Please clarify how many reviewers were involved in the quality assessment process, and how disagreements were resolved. Please also clarify how any data extraction inconsistencies or disagreements were resolved.

Two reviewers independently assessed the methodological quality and potential bias of the included RCTs using the quality criteria described in Chapter 8 of the Cochrane handbook for systematic reviews of interventions. Discrepancies between reviewers were resolved by a third independent reviewer with consensus reached. The same process was used to resolve any data extraction inconsistencies or disagreements.

A6. Quality assessment was presented for the trial as a whole. Please demonstrate how risk of bias varies (if at all) depending on outcome.

The risk of bias assessment for each trial included in the SLR, including the risk of bias due to measurement of outcomes and missing outcomes, is presented in the CS, Appendices, Table 19, Page 87.

Clinical trial

A7. Priority question: Randomisation was stratified by menopausal status. Please replicate Tables 13 to 18 with separate results for participants who are premenopausal and participants who are postmenopausal.

Subgroup analyses for IDFS and DRFS showed no significant differences with respect to menopausal status (CS, Document B, Section B.2.7), demonstrating a consistent treatment benefit of abemaciclib + ET versus ET alone across pre- and post-menopausal women.

The ITT population is therefore generalisable to both groups of patients and represents the most robust source of evidence. As such, it is not appropriate to consider premenopausal women/men and postmenopausal women as separate subgroups.

For completeness, IDFS and DRFS results stratified by menopausal status are presented in Table 8 to Table 11. OS data are immature and therefore are not presented here.

Table 8: Summary of investigator-assessed IDFS ITT population (AFU1 analysis): Premenopausal

	Abemaciclib + ET (N=1,227)	ET alone (N=1,224)	Treatment Effect/Difference 2-sided p-Value (nominal)[c]
Number of events, n (%)	[redacted]	[redacted]	-
Deaths without invasive disease	[redacted]	[redacted]	
Invasive disease	[redacted]	[redacted]	
Number of patients censored, n (%)	[redacted]	[redacted]	
Invasive disease prior to randomisation	[redacted]	[redacted]	
No post-baseline assessment	[redacted]	[redacted]	
No documented invasive disease	[redacted]	[redacted]	
p-value (2-sided) log-rank, stratified[a]	[redacted]		
HR (95% CI)	[redacted]		
IDFS rate, % (95% CI)[b]			
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]

36 months	[redacted]	[redacted]	[redacted]

Footnotes: [a] Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [b] 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation; [c] Treatment Effect/Difference/p-values are computed based on comparator ET.
Abbreviations: CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; IDFS: invasive disease-free survival; ITT: intent-to-treat; N: number of patients in the ITT population.

Table 9: Summary of investigator-assessed IDFS ITT Population (AFU1 analysis): Postmenopausal

	Abemaciclib + ET (N=1,576)	ET alone (N=1,605)	Treatment Effect/Difference 2-sided p-Value (nominal)[c]
Number of events, n (%)	[redacted]	[redacted]	-
Deaths without invasive disease	[redacted]	[redacted]	
Invasive disease	[redacted]	[redacted]	
Number of patients censored, n (%)	[redacted]	[redacted]	
Invasive disease prior to randomisation	[redacted]	[redacted]	
No post-baseline assessment	[redacted]	[redacted]	
No documented invasive disease	[redacted]	[redacted]	
p-value (2-sided) log-rank, stratified[a]	[redacted]		
HR (95% CI)	[redacted]		
IDFS rate, % (95% CI)[b]			
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]

Footnotes: [a] Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [b] 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation; [c] Treatment Effect/Difference/p-values are computed based on comparator ET.
Abbreviations: CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; IDFS: invasive disease-free survival; ITT: intent-to-treat; N: number of patients in the ITT population.

Table 10: Summary of Investigator-Assessed DRFS ITT Population (AFU1 analysis): Premenopausal

	Abemaciclib + ET (N=1,227)	ET alone (N=1,224)	Treatment Effect/Difference 2-sided p-Value (nominal)[d]
Number of events, n (%)	[redacted]	[redacted]	-
Death without distant relapse	[redacted]	[redacted]	
Distant relapse	[redacted]	[redacted]	
Number of patients censored, n (%)	[redacted]	[redacted]	

Distant relapse prior to randomisation	[redacted]	[redacted]	
No post-baseline assessment	[redacted]	[redacted]	
No documented distant relapse with regular assessment	[redacted]	[redacted]	
Minimum, months[a]	[redacted]	[redacted]	
Maximum, months[a]	[redacted]	[redacted]	
p-value (2-sided) log-rank[b]	[redacted]		
HR (95% CI)	[redacted]		
DRFS rate, % (95% CI)[c]			
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]

Footnotes: [a] For minimum and maximum, + indicates a censored observation; [b] Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [c] 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation; [d] Treatment Effect/Difference/p-values are computed based on comparator ET.
Abbreviations: CI: confidence interval; DRFS: distant relapse-free survival; ET: endocrine therapy; ITT: intent-to-treat; IWRS: interactive web-response system; N: number of patients in the ITT population; n: number of patients in the specific population.

Table 11: Summary of Investigator-Assessed DRFS ITT Population (AFU1 analysis): Postmenopausal

	Abemaciclib + ET (N=1,576)	ET alone (N=1,605)	Treatment Effect/Difference 2-sided p-Value (nominal)[d]
Number of events, n (%)	[redacted]	[redacted]	
Death without distant relapse	[redacted]	[redacted]	
Distant relapse	[redacted]	[redacted]	
Number of patients censored, n (%)	[redacted]	[redacted]	
Distant relapse prior to randomisation	[redacted]	[redacted]	-
No post-baseline assessment	[redacted]	[redacted]	
No documented distant relapse with regular assessment	[redacted]	[redacted]	
Minimum, months[a]	[redacted]	[redacted]	
Maximum, months[a]	[redacted]	[redacted]	
p-value (2-sided) log-rank[b]	[redacted]		
HR (95% CI)	[redacted]		

DRFS rate, % (95% CI)[c]			
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]

Footnotes: [a] For minimum and maximum, + indicates a censored observation; [b] Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [c] 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation; [d] Treatment Effect/Difference/p-values are computed based on comparator ET.
Abbreviations: CI: confidence interval; DRFS: distant relapse-free survival; ET: endocrine therapy; ITT: intent-to-treat; IWRS: interactive web-response system; N: number of patients in the ITT population; n: number of patients in the specific population.

A8. For each outcome, please clarify what the stratification factors were.

The stratification factors for all three outcomes (IDFS, DRFS and OS) were interactive web-based response system (IWRS) geographical region, IRWS prior treatment and IRWS menopausal status.

A9. Priority question: Please provide evidence to indicate the degree of generalisability of the types of endocrine therapy administered in the monarchE trial to those administered in NHS clinical practice. Please discuss the implications in terms of clinical effectiveness and cost-effectiveness of any discrepancy.

In monarchE, patients received either an aromatase inhibitor, including anastrozole, letrozole or exemestane, or anti-oestrogen therapies, including tamoxifen, as adjuvant ET. The full list of types of ET that patients received in monarchE is presented in the CS, Document B, Table 9. The choice of ET to individual patients in monarchE was determined by physician's choice (PC). For patients in monarchE in the UK, the types and distribution of ET administered to patients via PC are expected to be generalisable to the treatments that patients would receive in standard UK NHS clinical practice.

For UK patients in monarchE, 88% of postmenopausal women received an aromatase inhibitor, with the remaining 12% receiving tamoxifen/toremifene. For premenopausal women and men, 66% received tamoxifen/toremifene, with the remaining 33% receiving an aromatase inhibitor.[11] This is consistent with NICE guidelines for early breast cancer (NG101) treatment for pre and post-menopausal patients which are outlined in the CS, Document B, Section B.1.3.3.[12] The Company acknowledge that toremifene is not readily available in the UK, but as shown in the CS, Document B, Table 9, it was only prescribed to a very small number of patients ([redacted]) in monarchE.[13]

The distribution of ET prescribed to patients in the UK in monarchE is consistent with those received by patients in the safety cohort of monarchE as a whole, as presented in Table 12. The safety population of monarchE includes all of the patients in the ITT population, as well as a small number of additional patients, and as such, the types and distribution of ET received by patients in the ITT cohort can be considered to be generalisable to NHS clinical practice.

Table 12: Type and distribution of ET received in the monarchE safety population and the monarchE UK patients

	Premenopausal women		Postmenopausal women	
	monarchE safety population) (N=2,431)	monarchE UK patients (N=103)	monarchE safety population (N=3,156)	monarchE UK patients (N=97)
Aromatase inhibitor	41%	33%	89%	88%
Tamoxifen/Toremifene	58%	67%	11%	12%

Abbreviations: UK: United Kingdom
Source: Paluch-Shimon *et al*. (2021)[11]

Further evidence of the generalisability of ET in monarchE is provided by a real-world evidence (RWE) study conducted by the Company which included patients with HR+, HER2- early breast cancer in the UK between June and November 2019. In this study, [redacted]% of patients received an aromatase inhibitor as their first adjuvant ET and the remaining [redacted]% of patients received tamoxifen.[14] This is consistent with prescribing in the ITT cohort of monarchE, in which [redacted]% of patients had received an aromatase inhibitor at the start of the study, whilst [redacted]% of patients had received tamoxifen at the start of the study.[11]

Although the types and distribution of ET administered in monarchE are largely generalisable to those administered in UK clinical practice overall, the Company acknowledge that some types of ET administered to patients in monarchE are not widely used in the UK, such as toremifene. However, these types of ET were administered in very small numbers, with toremifene being received by only [redacted] patients ([redacted]) in monarchE.[13]

As stated in NG101, ovarian function suppression with a gonadotropin-releasing hormone (GnRH) analogue in addition to ET for premenopausal women with ER+ invasive breast cancer may also be considered. In these cases, an aromatase inhibitor may be used for premenopausal women instead of tamoxifen.[3] Accordingly, around [redacted] of patients in monarchE received GnRH analogues in the abemaciclib + ET and ET alone arms. The Company acknowledge that a small percentage of premenopausal patients ([redacted]) in monarchE received an AI without ovarian suppression, but this is not expected to overtly impact the generalisability of the results of the ITT population to UK clinical practice.

Regardless, there is not expected to be any difference in terms of efficacy associated with different types of ET within the same class and the cost of different types of ET is universally low.[15-18] As such, any discrepancies in terms of the types of ET used in monarchE and those used in NHS clinical practice would have a minimal impact on the cost-effectiveness analysis.

The evidence for patients in the UK from monarchE, combined with RWE collected by the Company, indicates that the type and distribution of the types of ET used in monarchE are generalisable to those administered in UK clinical practice. This, in combination with the minimal differences in cost and efficacy associated with different types of ET, mean that the generalisability of the types of ET used in monarchE to those administered in UK clinical practice should not be considered to be a major cause of uncertainty.

A10. Please clarify how the blinding of the trial sponsor was achieved and the process by which the fidelity of this procedure was assessed.

The monarchE trial was an open-label study, due to toxicities and laboratory abnormalities associated with abemaciclib treatment having the potential to unblind investigators to treatment allocation. To maintain study integrity, the trial sponsor was blinded to treatment group assignments until the study reached a positive outcome. An independent data monitoring committee was then responsible for reviewing the unblinded safety and efficacy analyses. Additionally, access to the study data was strictly controlled prior to the study reaching a positive outcome and will continue to be controlled throughout the entire study.

A11. In the Final scope issued by NICE, 'response rate' is an outcome measure (Document B, Table 1, page 11). Please clarify how this is measured and provide results for the whole population and the cohort most relevant to NHS clinical practice (see question A4) and by menopause status (see question A4).

Response rate is not relevant as an outcome to the adjuvant treatment setting in early breast cancer. Please see response to Question A4f.

A12. Priority question: The CS states that 3.5% of patients in the monarchE trial were recruited from study sites in the UK, and that the trial population is expected to be generalisable to the UK population. Please provide evidence as to how generalisable the trial is to UK clinical practice.

As stated in response to Question A9, the monarchE ITT population is generalisable to the UK population in terms of the types and distribution of ET administered.

Furthermore, evidence of the generalisability of the baseline characteristics of patients in monarchE to UK clinical practice is demonstrated by a [redacted], which included patients with HR+, HER2− early breast cancer at high risk of recurrence. [redacted]

- [redacted]
  - [redacted]
  - [redacted]

These features reflect how high risk of recurrence is defined in UK clinical practice, as detailed in response to Question A4, and this is in line with the criteria used in the monarchE study.

A summary of the baseline characteristics of patients in monarchE and the RWE study are presented in Table 13, which demonstrates that the baseline characteristics of monarchE closely align to UK clinical practice.

The comparison of baseline characteristics between monarchE and the RWE study, presented in Table 13, provides further evidence for the generalisability of the ITT cohort in the monarchE trial to patients with HR+, HER2− breast cancer at high risk of recurrence in the UK. [redacted]

Table 13: Summary of baseline characteristics of patients in monarchE (ITT cohort) and the RWE study

Demographic Parameter	monarchE (ITT cohort) (N=[redacted])	RWE study (N=[redacted])
Sex, n (%)		
Female,	99.4	[redacted]
Male,	0.6	[redacted]
Age, years		
Mean	[redacted]	[redacted]
<65 (%)	84.9	[redacted]
Primary tumour size by pathology (%)*		
<20 mm	[redacted]	[redacted]
≥20 mm but <50 mm	[redacted]	[redacted]
≥50 mm	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Number of positive lymph nodes (%)*		
0	0.2	[redacted]
1-3	40.1	[redacted]
4-9	[redacted]	[redacted]
≥10	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Histopathological diagnosis grade (%)		
G1 – favourable	7.5	[redacted]
G2 – moderately favourable	49.2	[redacted]
G3 – unfavourable	38.1	[redacted]
GX – cannot be accessed	4.7	[redacted]
Missing	0.4	

Abbreviations: ITT: intention to treat; RWE: real-world evidence; NR: not reported.
Footnote: [redacted]

A13. The sample sizes in Table 21 of (n=1,262) and ET (n=1,236) appear to be incorrect (page 57) as they are the same as Table 20. Please supply a correction.

The sample sizes in Table 21 of the Company submission were incorrectly reported. The correct sample sizes for Table 21 are N=1,017 for abemaciclib + ET and N=986 for ET.

A14. Please clarify the choice of minimally important difference (MID) for FACT-ES and FACIT-F. What is the justification for this choice of MID?

No published data on minimally important differences (MID) for the FACT-ES and FACIT-F summary scores were identified for an early breast cancer population. It was therefore decided to apply an effect size of one-half of the baseline standard deviation (0.5 SD) to represent the minimally important difference (MID). This represents a conservative estimate of MID, based on a systematic literature review (SLR) of studies that had computed a MID, conducted by Norman *et al*. (2003).[19] The conclusion of the SLR was that 'In most circumstances, the threshold of discrimination for changes in health-related quality of life for chronic diseases appears to be approximately half a SD'. For the analysis of individual items, a change of one point was deemed meaningful, being equivalent of a change in one level of response, for example, from 'Not at all' to 'A little bit'.

A15. Priority question: In addition to Table 25 (page 61), please provide the EQ-5D utility scores broken down by arm and time-point e.g. every 3 months. Please report mean differences and 95% confidence intervals for differences at each time point for analyses unadjusted by stratification factors and an analysis adjusted by these factors.

The EQ-5D-5L utility scores by treatment arm and time point, as well as the mean differences and 95% confidence intervals (CI), unadjusted for stratification factors are presented in Table 14 for the Health State Index and Table 15 for the Visual Analog Scale (VAS).

The original MMRM model did not include stratification factors. These have subsequently been included in the model and the resulting EQ-5D-5L utility scores by treatment arm and time point with treatment effect adjusted by stratification factors are presented in Table 14 and Table 17.

Table 14: Unadjusted EQ-5D-5L Health State Index scores by treatment arm and time point

	Treatment	N	Mean score (SD)	LS mean change differenc e (SE)	95% CI	p-value
Baseline	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
Visit 6	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			

Visit 9	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
Visit 15	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
Visit 21	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
All post−baseline	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			

Abbreviations: EQ-5D-5L: EuroQol-5 dimensions- 5 levels; ET: endocrine therapy: NA: not applicable; SD: standard deviation.
Source: Lilly Data on File. Clinical Study Report: monarchE.[13] Data cut-off: 08 July 2020 (PO analysis).

Table 15: Unadjusted EQ-5D-5L Visual Analogue Scale scores by treatment arm and time point

	Treatment	N	Mean score (SD)	LS mean change difference (SE)	95% CI	Abemaciclib + ET vs ET p–value
Baseline	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
Visit 6	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
Visit 9	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
Visit 15	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
Visit 21	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
All post-baseline	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			

Abbreviations: EQ-5D-5L: EuroQol-5 dimensions- 5 levels; ET: endocrine therapy: NA: not applicable; SD: standard deviation.
Source: Lilly Data on File. Clinical Study Report: monarchE.[13] Data cut-off: 08 July 2020 (PO analysis).

Table 16: EQ-5D-5L Health State Index scores by treatment arm and time point (adjusted for stratification factors)

	Treatment	N	Mean score (SD)	LS mean change difference (SE)	95% CI	p-value

Baseline	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
Visit 6	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
Visit 9	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
Visit 15	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
Visit 21	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
All post-baseline	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			

Abbreviations: EQ-5D-5L: EuroQol-5 dimensions- 5 levels; ET: endocrine therapy: NA: not applicable; SD: standard deviation.

Table 17: EQ-5D-5L Visual Analogue Scale scores by treatment arm and time point (adjusted for stratification factors)

	Treatment	N	Mean score (SD)	LS mean change difference (SE)	95% CI	Abemaciclib + ET vs ET p-value
Baseline	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
Visit 6	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
Visit 9	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
Visit 15	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
Visit 21	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
All post-baseline	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			

Abbreviations: EQ-5D-5L: EuroQol-5 dimensions- 5 levels; ET: endocrine therapy: NA: not applicable; SD: standard deviation.

A16. Table 30 (page 75), please check number and percentage of infections and infestations reported [i.e.146 (15.2)]. The numbers do not appear consistent with the number of patients with at least 1 serious adverse event [i.e. 424 (15.2)].

The percentage for 'infections and infestations' for the abemaciclib + ET arm (N=2,791) was incorrectly reported in Table 30 of the Company Submission. The correct percentage is 5.2%, as opposed to 15.2%.

Section B: Clarification on cost-effectiveness data

General

B1. Priority question: In several sections (relating to both, clinical as well as cost effectiveness), the company submission refers to clinical expert opinion. Please report on the methods sought to gather the clinical experts' opinions, along with all details of the communication between the company and the clinical experts. Please also include anonymised information about the clinical experts, detailed minutes of the face-to-face meeting and/or teleconference, list of expert recommendations and justifications for clinical assumptions and inputs used in the model. In particular, please indicate the following:

a. **How many experts provided information for each of the following: model structure, identification of subsequent treatments and their estimated shares in clinical practice, health state resource use and costs, modelling of invasive disease-free survival (IDFS), recurrence and duration of treatment effect? In each case, please provide more detail of the clinical/working setting and experience of included experts.**

Three thought leader meetings took place to discuss the cost-utility model structure and input assumptions.

The first thought leader meeting included one external health economic expert (Key Opinion Leader [KOL]1); a UK based Professor of health economics with a background in breast cancer modelling), one external clinical expert (KOL2; a UK based medical oncologist with research interest in health economics) and two internal Lilly medical team members. The monarchE trial data and the cost-utility model structure was presented. The method of extrapolation was presented and the input assumptions were checked.

After the first draft of the model was developed, thought leaders were approached for a second round of validations. The same external health economic and clinical expert attended the meeting. One member of the Lilly medical team from the previous meeting attended the meeting and one new member of the Lilly medical team joined the meeting.

The model structure was discussed with particular focus on the resource use assumptions in the IDFS health state. The non-metastatic recurrence health state costing approach was discussed along with the validations of the extrapolations and duration of treatment effect assumptions were checked.

A final set of thought leader meetings were scheduled. The first meeting was with two internal Lilly Medical team. The second meeting was with the same clinical expert from the first and second thought leader meetings. The final model structure was presented, additional clarifications were made surrounding the non-metastatic recurrent health state. The initial economic and clinical results from the cost-utility model was sense checked. Finally, the assumptions, strengths and limitations underpinning the final model structure was discussed.

b. **Please provide further details of the opinions given by experts in relation to each of aspects of the model listed in part "a." of this question and provide details regarding the extent to which these opinions were included in the model or justification of why they were not included. e.g. "Clinical expert opinion indicated that patients would receive intensive treatment for loco-regional/contralateral recurrence in the first few months, which is expected to be associated with a detrimental impact on HRQoL. Following this the patients would return to their previous HRQoL". (Table 69, pages141-144).**

Details of the assumptions supported by clinical experts relating to the aspects of the model listed in B1a are presented in Table 18, with additional details about the expert elicitation process.

Table 18: Assumptions supported by clinical expert opinion in the CS

Assumptions supported by clinical expert opinion		Additional details about the expert elicitation process
Incorporation of clinical parameters into the model	The choice of the log-logistic model for IDFS, and the five and 10-year extrapolation results, were validated by UK clinical experts	The five- and 10-year IDFS extrapolation results for ET were presented to the thought leaders, alongside a comparison of the results with the BIG 1-98, FACE trial and HER2+ Katherine trial. The thought leaders agreed with the approach to compare versus external evidence for adjuvant endocrine therapy where possible. It was acknowledged that the trial population and the endpoints were not necessarily directly comparable although the approach was the most plausible method for external validation given the lack of evidence available outside of the monarchE trial. The thought leaders did not flag any key concerns from the extrapolation results.
	The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial were noted as the most relevant to inform treatment waning assumptions	A concern was raised with using the Katherine trial since the population is not representative of HER2- pathway. It was highlighted that the Katherine trial was the only trial with long follow up data and it was being used to sense check the results. The thought leaders suggested looking at the ATAC trial instead especially when making assumptions surrounding treatment waning assumptions. As a result, the trends being observed from the 10 year follow up of the ATAC trial have guided the final treatment effect waning decisions incorporated in the base case cost-effectiveness analysis.

Secondary primary neoplasms	'Second primary non-breast invasive cancer' or a 'second primary neoplasm' IDFS events should not be considered an NMR event. The risk of a secondary primary neoplasm was derived from the data from the monarchE trial and the numbers of patients experiencing a secondary primary neoplasm event in the abemaciclib + ET and ET alone arms at the time of the AFU1 data cut, which showed that the risk of secondary primary neoplasm was equal between treatment arms.	The list of events accounted for under 'non-metastatic recurrence' was presented to the thought leaders. These were: • Ipsilateral invasive breast tumour recurrence, • Local/regional invasive breast cancer recurrence, • Contralateral invasive breast cancer, • Second primary non-breast invasive cancer. In addition, the different types of second primary non-breast invasive cancers were verbally discussed with the thought leaders. Amongst the thought leaders the general message regarding second primary non-breast invasive cancer was that they would have a different treatment pathway to locoregional recurrences. Clinical experts indicated that they did not expect any differences in the risk of secondary neoplasm between abemaciclib + ET and ET alone.
NMR assumptions	Clinical outcomes within the NMR health state and the remission health state were assumed the same for both treatment arms. This assumption was supported by previous NICE TAs and clinical expert feedback.	The key clinical and cost assumptions for the NMR health state were discussed with thought leaders. There was no indication to suggest that patients in the abemaciclib + ET arm would have a different treatment / clinical pathway to patients in the ET alone arm.
	A mix of surgery, radiotherapy, chemotherapy and adjuvant ET are offered as treatment options to patients who experience an NMR event.	The NICE guideline (NG101) specific to people with locoregional, regional or contralateral recurrence was discussed in detail in the second thought leader meeting. Apart from HER2+ treatments (such as trastuzumab and pertuzumab) the thought leaders did not flag concerns with using the guideline to inform the NMR health state specific costs.
Recurrence rate in the remission health state	The recurrence rate from the remission health state to the metastatic setting was informed by TA632, which clinical experts confirmed was the most appropriate source to inform this assumption.	The input sources being used for the remission health state were discussed with the thought leaders. No additional data sources were flagged.

	The recurrence rate from the remission health state was also assumed to remain constant over time, which is also in line with TA632.	
Utility values in the NMR health state	In the NMR health state, the utility value was a weighted average of 0.696 for the first three months and [redacted] for the last nine months for both trial arms. This approach was supported by clinical experts, who indicated that patients would receive intensive treatment for loco-regional/contralateral recurrence for the first few months, which is expected to be associated with a detrimental impact on HRQoL. Following this, patients would return to their previous HRQoL.	As stated above the NMR assumptions were discussed with the thought leaders. It was flagged that during period of intense treatment e.g. chemotherapy or surgery a patient's quality of life would be poorer.
Treatment assumptions in metastatic setting	The relevant treatments received in the metastatic setting were validated by clinical experts	The post-discontinuation therapies from monarchE and the MONARCH 2 and 3 model treatments were discussed with the thought leaders. The assumptions were based on thought leader feedback and previous NICE resource impact assessments and budget impact assessments, which was reflective of UK real world setting.
	It was assumed that patients who received abemaciclib in the adjuvant setting were not permitted to receive a CDK4/6 inhibitor treatment in the metastatic setting	In the metastatic setting, it was agreed that if patient had been treated with abemaciclib then it was reasonable to assume they would not then be retreated with Palbociclib for example.
Resource use	Clinical experts validated the levels of resource use in the model (e.g. GP visit, mammograms) based on Year 2–5 of the IDFS health state (from various TAs: TA632, TA612, TA569) and on the time spent in remission. Different levels of resource use (e.g. outpatient visit and mammograms) were included in the model based on time spent in IDFS.	The IDFS and remission health state resource use assumptions which were taken from previous early breast cancer submission were presented to and discussed with thought leaders. Thought leaders stated that mammogram visits can be expected to last between five to ten years. Oncologist visit would be expected for a minimum of five years.

B2. Priority Question. The CS does not populate the subgroup analysis section (B.3.9). Please provide justification for not providing analyses given the heterogeneity in the study population. Most importantly, we note that the population could be analysed by menopausal status (Document B, Table 6, page 35). This has implications for the comparators [e.g. TMX in premenopausal women (and men)] in the proposed positioning of abemaciclib in the care pathway (Document B, Figure 3, page 23). Please provide relevant results for these sub-groups using the relevant comparators and adjuvant therapies.

As highlighted in response to Question A7, menopausal status was not considered to be an appropriate subgroup to include in the economic analyses, as subgroup analyses of IDFS and DRFS in monarchE demonstrated a consistent treatment benefit of abemaciclib + ET across pre- and post-menopausal women.

As the difference in outcomes was not significant, the only difference impacting the economic analysis between pre- and postmenopausal patients would be costs. However, the relatively low costs of different distributions of ET therapy in the pre- and postmenopausal pathways is not expected to have an overt impact on cost effectiveness compared to the ITT. Furthermore, during the scoping stage menopausal status was not considered to be a clinically distinct subgroup and as such, it was not specified in the final scope for ID3857. Therefore, menopausal status subgroups have not been considered in economic analyses.

Published Cost-Effectiveness studies

B3. Appendix H provided the details of the Targeted Literature Review (TLR) that was carried out to elicit the utility, cost and resource use for the CEM that could not be identified through the economic and observational SLRs. Please clarify what utility values were identified and why these were not used in the analyses presented.

The utility values identified by the TLR are presented in the CS, Document B, Table 52, Page 123 and the CS, Appendices, Table 42, Page 167. The utility values identified by the TLR were not used in the cost-effectiveness analyses, because, where possible, it was considered more appropriate to reflect the reference case by using utility data derived directly from the monarchE trial and where this was not possible, utility values were aligned to the committee's preferred assumptions from previous Technology Appraisals which were identified in the economic SLRs.

The utility value for remission was aligned to assumptions from TA632 where it was accepted that patient's utility returns to IDFS baseline following second remission.

The utility value for local recurrence from TA612, identified by the TLR, was used to inform the overall utility for the non-metastatic recurrence health state as part of a weighted average with the IDFS utility value (as described in the CS, Document B, Table 54, Page 125) in line with the approach taken and accepted by NICE in TA612.

The utility values identified by the TLR for metastatic breast cancer were not used, as the Company preferred to align the utility values for metastatic breast cancer with the Committee's previously preferred utility values in previous appraisals of HR+, HER2- metastatic breast cancer.

Model structure

B4. Priority question: The CS states that the model is a state transition model (STM). However, given that occupancy in the IDFS and OS states appear to be determined by rates estimated independently from parametric functions fitted to each of IDFS and OS data, the model actually appears to be a partitioned survival model (PSM).

a. Please confirm that this is the case. Please also describe precisely the measures taken in the model to prevent occupancy in IDFS exceeding OS.

The model does utilise parametric survival equations to estimate the transition between IDFS to other health states. However, it should be noted that these parameterisations are not used in isolation to determine whether patients transition to NMR or MR if they experience an invasive disease event. Information on probabilities of having a distance vs local recurrence were applied to the extrapolation curve in order to determine the proportion of the cohort going either to the MR or NMR health state.

Furthermore, there is an explicit structural relationship between the NMR and MR health states. When patients reach the NMR health state, they enter a tunnel state, in which they reside for 12 months before transitioning into remission. From here, transition probabilities are applied to determine the number of patients moving to the metastatic health state.

It is not possible for state occupancy in IDFS to be higher than OS as it is not an explicit area under the curve model. To check whether patients are moving correctly throughout the model, state occupancy can be checked in the "Patient distribution ABE/ABE+ET" sheets, where the cohort sum up to the total number of patients in the model, which is 1000. When it comes to the parametrization of the extrapolation curves, the model prevents the OS without distant recurrence curve to fall below the IDFS curve at any timepoint, hence it is not possible to have a higher survival rate for IDFS than for OS without distant recurrence. In addition, background mortality is applied to the OS without distant recurrence curve in the model.

It is also worthwhile to note that the OS without distant recurrence extrapolation is only applied to patients who have not entered the distant recurrence state, as survival in the metastatic health state is determined by an "add on" of LYs.

b. Please justify the adoption of the PSM as opposed to STM structure.

Please note that as described in response to Question B4a, the model uses a STM, rather than a PSM, structure.

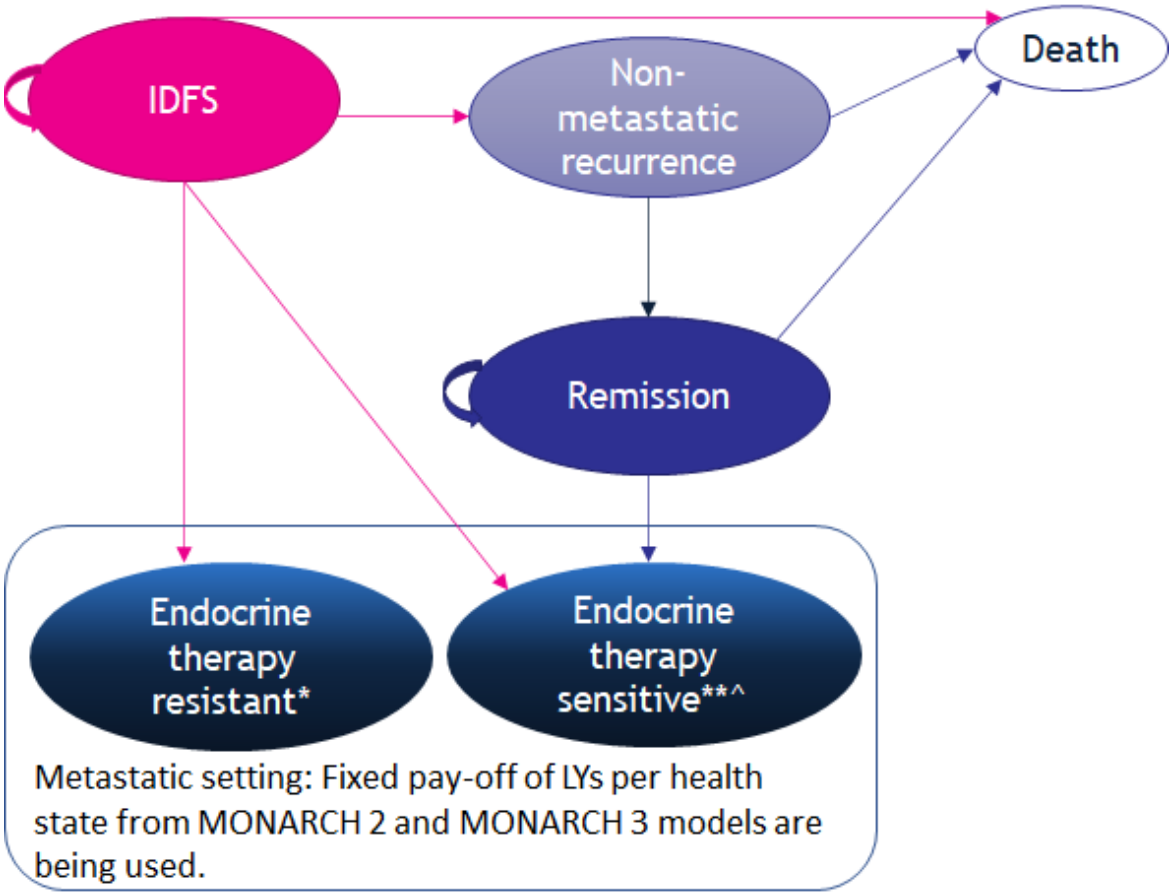
The monarchE model structure was based on the findings of previous EBC models specific to the HER2+ patient population, the treatment pathway of patients with EBC, data availability from the monarchE trial, and feedback from thought leaders. Both the structure and health states are in-line with the clinical pathway in early breast cancer and consistent with previous NICE technology appraisals in early breast cancer (TA107, TA424, TA569, TA612, TA632).[20-24] Furthermore, the monarchE model structure was discussed and validated by thought leaders, please see overview of thought leader meetings in response to B1(a).

B5. On viewing the model structure presented in Figure 10 (page 90), there are a couple of missing details:

a. Please insert label for 'metastatic recurrence' health state

Figure 1 from the CS, Document B, Page 90 is presented below, with the label for the metastatic recurrence health state included.

Figure 1: MonarchE top-line model structure



Footnotes: * Disease recurrence whilst receiving or within 12 months of completing prior adjuvant ET. ** Disease recurrence at least 12 months after completion of prior adjuvant ET. ^ Includes treatment with tamoxifen
Abbreviations: ET, Endocrine therapy; IDFS, Invasive disease-free survival; LYs, Life years

b. Please add the meaning of * and **^ in the footnotes.

Please see Figure 1 for the footnotes associated with * and **^.

B6. Please confirm whether the values in "Table 36 – Proportion of patients receiving each endocrine therapy in the model" (page 93) are generalisable to the UK setting.

The proportions of patients receiving each ET in the model is informed by data from monarchE. As outlined in response to question A9, the types of ET used in monarchE can be considered generalisable to UK clinical practice. Therefore, the proportions of patients receiving each ET in the model are generalisable to UK clinical practice.

Clinical effectiveness variables (Time to event, metastatic health states, etc.)

B7. Priority Question: Please provide further justification on how the 'carryover benefit' of tamoxifen is applicable for the abemaciclib setting. It is assumed that 'Treatment waning' starts at year 8. What evidence is there that abemaciclib behaves like aromatase inhibitors/tamoxifen? (page 105) Please perform a scenario analysis with no carryover benefit for abemaciclib.

As stated in the CS, Document B, Section B.2.6.1, a piecewise analysis for IDFS was performed, and the HRs for Year 2+ (by which time all patients had discontinued treatment) suggest that a lasting treatment effect beyond discontinuation does exist for abemaciclib.

As observed in the monarchE study, the benefit in terms of IDFS observed in the abemaciclib + ET arm, versus ET alone, in the ITT population at IA2 and PO cut-offs continued to deepen, with additional follow-up at the time of the AFU1 IDFS analysis. The magnitude of treatment benefit continued to increase over time in the follow-up period, as reflected by the further improvement in IDFS rates at 3 years and robust effect size beyond the 2-year study treatment period. This treatment benefit was observed over a large sample size, with a total of 565 IDFS events observed. As such, maintenance of the treatment effect was assumed beyond clinical trial data and it would be clinically implausible and inappropriate to provide a scenario analysis to assume that no lasting treatment effect exists for abemaciclib.

The Company acknowledge that the exact duration of the treatment effect is uncertain, and in the absence of longer-term clinical trial data for abemaciclib, assumptions informing the waning of the treatment effect were based on the long-term treatment effect for ET, from historical trial data. By doing so, the Company is not suggesting that abemaciclib behaves like aromatase inhibitors or tamoxifen (in terms of mechanism of action). Instead, the data for tamoxifen and aromatase inhibitors are used as the best available proxy to inform the plausible duration of treatment effect for abemaciclib, in the absence of data specific to abemaciclib. In addition to evidence from the ATAC study, a lasting treatment effect has also been observed and accepted in previous NICE appraisals for a range of treatments with different mechanisms of action in patients with HR+, HER2+ early breast cancer.[25-27] This indicates the existence of a lasting treatment effect in early breast cancer that is not derived from one specific mechanism of action and is independent of the specific treatment received.

In order to explore the uncertainty in the duration of the treatment effect, the Company has presented scenario analyses varying the treatment waning assumptions. These scenario analyses presented in the CS (Document B, Section B.3.8.3, Table 73, Page 149) are associated with ICERs of £5,723 per QALY (half effect) and £5,997 per QALY (treatment duration of AIs and length of follow-up from ATAC study) and still represent a cost-effective use of NHS resources. Considering the continuing deepening of the treatment effect for IDFS beyond 2-years of abemaciclib + ET compared to ET alone, the latter analysis represents an extremely conservative scenario where waning starts at 5-years and is halted abruptly at 10-years to align with the overserved period of follow-up from the ATAC study.

B8. Priority question. Please provide further justification for the assumption that "patients who received Abemaciclib in the adjuvant setting were not permitted to receive a CDK4/6 inhibitor treatment in the metastatic setting" (page118), and the impact this is likely to have in the pay-offs at the metastatic stage. What evidence is there for not using other CDK4/6 inhibitors in the metastatic setting given that it was used previously as an adjunct in early breast cancer setting?

As outlined in Section B.3.3.4 of the Company submission, there is currently no evidence regarding the efficacy associated with the use of a CDK4/6 inhibitor following disease recurrence either while on, or after, a prior CDK4/6 inhibitor treatment. This was further confirmed by UK clinical experts. As such, it was assumed that patients who received abemaciclib in the adjuvant setting were not permitted to receive a CDK4/6 inhibitor treatment in the metastatic setting.

The impact of this assumption was demonstrated through scenario analyses presented in the CS, Document B, Section B.3.8.3, in which subsequent treatments in the metastatic setting in the abemaciclib + ET arm are set equal to the ET arm in both the ET-sensitive and ET-resistant pathways. This assumes CDK4/6 re-treatment. The corresponding ICER is £12,216, which, demonstrates that even with CDK4/6 re-treatment, abemaciclib represents a cost-effective use of NHS resources. Seeing as there is no evidence to support CDK4/6 re-treatment, this represents a conservative scenario analysis.

B9. Priority question. The base-case cost-effectiveness model used a single model fitted, using an adjustment factor for treatment effect (HR), to the monarchE trial data (page 113). Please provide more detail regarding the adjustment factor used in this case.

The base-case cost-effectiveness model used a single model fitted to the monarchE trial data, and treatment effect was the only covariate used in the model. The Company can confirm that no further 'adjustment factors' were included.

B10. Priority question. Please comment further on the 'volatility' of the OS model (Figure 24, page 114) as mentioned in the text on page113. Given the evidence of the log cumulative hazard and Schoenfeld residual plot, please

provide a set of scenario analyses where separate parametric functions are chosen for each of the intervention and comparator.

Due to the limited number of death events in the monarchE trial (causing implausible survival estimations when extrapolated over a lifetime), background mortality quickly takes precedence over the OS without distant recurrence parametric curves in the model. Hence, the type of extrapolation that is being chosen has very limited impact on the results. Furthermore, the PH assessment did not suggest violation of the PH assumption (as detailed in the CS, Document B, Section B.3.3.2). Therefore, there is little evidence to suggest an independent model would provide a better fitting model. However, for completeness scenario analyses for independently fitted models are provided in Table 19 below for the best statistically fitting models. Fitting independent models has a negligible impact on the ICERs.

Table 19: Scenario analysis using independently fitted survival models

Parameter	Base case	Scenario	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
Base case			[redacted]	[redacted]	3,786
OS extrapolation	Dependent Exponential	Independent Exponential	[redacted]	[redacted]	3,786
		Independent lognormal	[redacted]	[redacted]	3,787
		Independent Weibull	[redacted]	[redacted]	3,788
		Independent Loglogistic	[redacted]	[redacted]	3,788

Abbreviations: ICER: incremental cost-effectiveness ratio; OS: overall survival; QALY: quality-adjusted life year

Health related quality of life

B11. Priority Question: Pooled utilities for both treatment arms have been used instead of treatment-specific utilities for the base case for the IDFS health state. However, the clinical effectiveness section only reports the EQ-5D results of change from baseline for the whole population and not by health state for each treatment arm. Please provide EQ-5D estimates from the trial data (as a function of both health state and treatment status). Please incorporate these into a scenario analysis.

Mature EQ-5D data from monarchE is only available for the IDFS health state. As such, treatment-specific utility values based on monarchE EQ-5D data are only available for the IDFS health state. The utility values for each treatment arm in the IDFS health state are presented in Table 20.

Although the Company acknowledge it is good practice to explore treatment-specific utilities when there is robust head-to-head data available, there was no meaningful difference between the EQ-5D results between each treatment arm. As such, the data from each treatment arm was pooled to maximise sample size, and equal utility for patients in the same health state,

irrespective of treatment received, was assumed. Any differences in HRQoL between treatments arms are accounted for by AE disutilities. This approach is in line with that taken in TA632.[27]

Table 20: Average EQ-5D-3L index score (UK) by follow-up period

	Abemaciclib + ET (N=2,791)			ET alone (N=2,800)		
Follow-up Period	**n**	**Mean**	**SD**	**N**	**Mean**	**SD**
Pre-Disease Recurrence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-Disease Recurrence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D-3L: European Quality of Life 5-Dimension 3-Level Version; SD: standard deviation

B12. Please comment further on the plausibility of the assumption that lymphopenia is not associated with any disutility (Table 53, page 124).

A suitable UK specific disutility value could not be identified for a Grade III/IV lymphopenia event from the economic SLR or the targeted literature searches. Therefore, an assumption of 0 disutility value for lymphopenia was also used in the monarchE early breast cancer setting.

B13. Please comment further on the plausibility of the assumptions that thrombocytopenia and venous thromboembolic events are not associated with any disutility (Table 53, page124).

Please note there is an inconsistency in reporting in Table 53, Page 124 of the CS Document B. A disutility for thrombocytopenia was applied in the model (See 'AE' sheet in the model) identified from Tolley et al 2013.[28]

A suitable UK specific disutility value could not be identified for Grade III/IV venous thromboembolic events from the economic SLR or the targeted literature searches. Clinical opinion sought did not provide any alternative suggestions for this input either.

B14. As shown in Table 54, page125, for the first 3 months of non-metastatic recurrence (NMR), a utility value of 0.696, gathered from a Swedish population by Lidgren et al (2007) was used in the model. From the Lidgreen et al. paper, it appears that the EQ-5D utility value of 0.696 refers to the health state 'First year after primary breast cancer (State P)', whereas for 'First year after recurrence (State R)' the EQ-5D utility value is 0.779. Please justify your use of the EQ-5D utility value for 'First year after primary breast cancer' rather than 'First year after recurrence' for NMR is your model.

All patients who experience a non-metastatic recurrence are assumed to receive additional adjuvant therapy for 12-months. After 12 months, patients are assumed to either transition into the remission health state or die due to all-cause mortality. Typically, patients receive intensive treatment for their breast cancer following recurrence, which has a substantial detrimental impact on HRQoL. Therefore, applying a value of 0.779 could be considered relatively high compared to

the utility values assumed in the IDFS health state. To account for this, the third KOL confirmed that applying an average utility value to the NMR health state was a reasonable assumption. The average takes account of three months of potential acute treatment, such as surgery, as discussed in the third thought leader meeting, which can be translated in the 0.696 value measured in Lidgren. The KOL confirmed that for the other 9 months of the tunnel state, it would be appropriate to assume quality of life to be equal to IDFS.

The Company acknowledge there is uncertainty over the choice of the utility applied for the first 3 months of NMR. It may be equally feasible that the 'First year after recurrence (State R)' EQ-5D utility value of 0.779 is appropriate to apply in the model. A scenario analysis is provided in Table 21 using the EQ5D utility value the 'First year after recurrence (State R)' for the first 3 months and IDFS utility value for the last 9 months which shows to have a negligible impact on the ICER.

Table 21: Scenario applying 'First year after recurrence (State R)' EQ-5D utility value of 0.779 for the first 3 months of NMR

Parameter	Base case	Scenario	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
NMR utility value	[redacted] average	[redacted] average	[redacted]	[redacted]	3,786

Abbreviations: ICER: incremental cost-effectiveness ratio;NMR: non-metastatic recurrence; QALY: quality-adjusted life year

Resource use and costs

B15. Please clarify the methods used to inflate the costs to a common cost year.

All costs in the model were sourced for the most recently available publications, when these costs were not available, they were inflated using the most recently published 2019/2020 PSSRU's NHS cost inflation index (NHSCII).[29] The NHSCII was used since it provides a more accurate measure of inflation than the previously accepted hospital and community health services pay and price inflation.

B16. Please present the cost weights used for each metastatic progression 'pay off'.

The resource use, and associated costs, for each of the health states in the ET-sensitive and ET-resistant metastatic pathways are presented in Table 22 and Table 23 below.

Table 22: Follow-up care resource use in the ET-sensitive metastatic pathway

	Resource use	Source	Cost	Source
PFS				
CT scan	0.42	MONARCH 3	£114.36	National Schedule of NHS Cost 2019-20, IMAGOP, PF, Plain Film, Outpatient
Electrocardio gram	0.33	MONARCH 3	£147.15	National Schedule of NHS Cost 2019-20,

				OPROC, 370, EY51Z, Electrocardiogram monitoring or stress testing
Complete blood count	1.00	MONARCH 3	£2.53	National Schedule of NHS Cost 2019-20, DAPS05, Haematology
Serum chemistry	1.00	MONARCH 3	£1.20	National Schedule of NHS Cost 2019-20, DAPS04, Clinical biochemistry
Oncologist visit, follow-up	1.00	MONARCH 3	£200.20	National Schedule of NHS Costs 2019/2020: WF01A Consultant Lead, Non-Admitted Face-to-Face Attendance, Follow-up
GP visit	0.23	NICE clinical guideline 81 (package 1 PFS, package 2 PPS)[30]	£39.00	PSSRU 2020
District nurse (home visit)	2.00	NICE clinical guideline 81 (package 1 PFS, package 2 PPS)[30]	£63.00	PSSRU 2020
Clinical nurse (specialist)	0.92	NICE clinical guideline 81 (package 1 PFS, package 2 PPS)[30]	£89.00	PSSRU 2020
Hospitalisation	0.01	MONARCH 3	£3,622.16	TA725
PFS2				
CT scan	0.50	MONARCH 3	£114.36	National Schedule of NHS Cost 2019-20, IMAGOP, PF, Plain Film, Outpatient
Electrocardio gram	0.50	MONARCH 3	£147.15	National Schedule of NHS Cost 2019-20, OPROC, 370, EY51Z, Electrocardiogram monitoring or stress testing
Complete blood count	1.00	MONARCH 3	£2.53	National Schedule of NHS Cost 2019-20,

				DAPS05, Haematology
Serum chemistry	1.00	MONARCH 3	£1.20	National Schedule of NHS Cost 2019-20, DAPS04, Clinical biochemistry
Oncologist visit, follow-up	1.00	MONARCH 3	£200.20	National Schedule of NHS Costs 2019/2020: WF01A Consultant Lead, Non-Admitted Face-to-Face Attendance, Follow-up
GP visit	0.23	NICE clinical guideline 81 (package 1 PFS, package 2 PPS)[30]	£39.00	PSSRU 2020
District nurse (home visit)	2.00	NICE clinical guideline 81 (package 1 PFS, package 2 PPS)[30]	£63.00	PSSRU 2020
Clinical nurse (specialist)	0.92	NICE clinical guideline 81 (package 1 PFS, package 2 PPS)[30]	£89.00	PSSRU 2020
Hospitalisation	0.01	MONARCH 3	£3,622.16	TA725
PPS				
CT scan	0.50	MONARCH 3	£114.36	National Schedule of NHS Cost 2019-20, IMAGOP, PF, Plain Film, Outpatient
Electrocardio gram	1.00	MONARCH 3	£147.15	National Schedule of NHS Cost 2019-20, OPROC, 370, EY51Z, Electrocardiogram monitoring or stress testing
Complete blood count	1.00	MONARCH 3	£2.53	National Schedule of NHS Cost 2019-20, DAPS05, Haematology
Serum chemistry	1.00	MONARCH 3	£1.20	National Schedule of NHS Cost 2019-20, DAPS04, Clinical biochemistry

Oncologist visit, follow-up	1.00	MONARCH 3	£200.20	National Schedule of NHS Costs 2019/2020: WF01A Consultant Lead, Non-Admitted Face-to-Face Attendance, Follow-up
GP visit	0.50	NICE clinical guideline 81 (package 1 PFS, package 2 PPS)[30]	£39.00	PSSRU 2020
District nurse (home visit)	4.00	NICE clinical guideline 81 (package 1 PFS, package 2 PPS)[30]	£63.00	PSSRU 2020
Clinical nurse (specialist)	4.00	NICE clinical guideline 81 (package 1 PFS, package 2 PPS)[30]	£89.00	PSSRU 2020
Therapist	4.00	NICE clinical guideline 81[30]	£69.00	PSSRU 2020
Hospitalisation	0.03	TA563[31]	£3,622.16	TA725

Abbreviations: CT: computerized tomography; ET: endocrine therapy; GP: general practice; NICE: National Institute for Health and Care Excellence; PFS: progression-free survival; PPS: post-progression survival

Table 23: Resource use in the ET-resistant metastatic pathway

	Resource use	Source	Cost	Source
PFS				
CT scan	[redacted]	MONARCH 2	£114.36	National Schedule of NHS Cost 2019-20, IMAGOP, PF, Plain Film, Outpatient
MRI scan	[redacted]	MONARCH 2	£182.34	National Schedule of NHS Cost 2019-20, RD05Z, MRI of 2 areas with contrast, outpt setting
PET scan	[redacted]	MONARCH 2	£727.29	National Schedule of NHS Cost 2019-20, RN 07A, PET, 19 years and over outpt setting
Electrocardiogram	[redacted]	MONARCH 2	£147.15	National Schedule of NHS Cost 2019-20,

				OPROC, 370, EY51Z, Electrocardiogram monitoring or stress testing
Complete blood count	[redacted]	MONARCH 2	£2.53	National Schedule of NHS Cost 2019-20, DAPS05, Haematology
Serum Chemistry	[redacted]	MONARCH 2	£1.20	National Schedule of NHS Cost 2019-20, DAPS04, Clinical biochemistry
Oncologist visit (follow-up)	[redacted]	MONARCH 2	£200.20	National Schedule of NHS Costs 2019/2020: WF01A Consultant Lead, Non-Admitted Face-to-Face Attendance, Follow-up
GP visit	1.09	NICE clinical guideline 81 (package 1)[30]	£39.00	PSSRU 2020
District nurse (home visit)	2.00	NICE clinical guideline 81 (package 1)[30]	£63.00	PSSRU 2020
Clinical nurse (specialist)	1.09	NICE clinical guideline 81 (package 1)[30]	£89.00	PSSRU 2020
Hospitalisation	0.01	MONARCH 2	£3,622.16	TA725
PPS				
CT scan	[redacted]	MONARCH 2	£114.36	National Schedule of NHS Cost 2019-20, IMAGOP, PF, Plain Film, Outpatient
MRI scan	[redacted]	MONARCH 2	£182.34	National Schedule of NHS Cost 2019-20, RD05Z, MRI of 2 areas with contrast, outpt setting
PET scan	[redacted]	MONARCH 2	£727.29	National Schedule of NHS Cost 2019-20, RN 07A, PET, 19 years and over outpt setting

Electrocardiogram	[redacted]	MONARCH 2	£147.15	National Schedule of NHS Cost 2019-20, OPROC, 370, EY51Z, Electrocardiogram monitoring or stress testing
Complete blood count	[redacted]	MONARCH 2	£2.53	National Schedule of NHS Cost 2019-20, DAPS05, Haematology
Serum Chemistry	[redacted]	MONARCH 2	£1.20	National Schedule of NHS Cost 2019-20, DAPS04, Clinical biochemistry
Oncologist visit, follow-up	[redacted]	MONARCH 2	£200.20	National Schedule of NHS Costs 2019/2020: WF01A Consultant Lead, Non-Admitted Face-to-Face Attendance, Follow-up
GP visit	2.00	NICE clinical guideline 81 (package 1)[30]	£39.00	PSSRU 2020
District nurse (home visit)	4.00	NICE clinical guideline 81 (package 1)[30]	£63.00	PSSRU 2020
Clinical nurse (specialist)	4.00	NICE clinical guideline 81 (package 1)[30]	£89.00	PSSRU 2020
Therapist	2.00	NICE clinical guideline 81 (package 1)[30]	£69.00	PSSRU 2020

Abbreviations: CT: computerized tomography; ET: endocrine therapy; GP: general practice; NICE: National Institute for Health and Care Excellence; PFS: progression-free survival; PPS: post-progression survival

Base case summary and assumptions

B17. Please report the probability that the treatment is cost effective at the £20,000 ICER threshold.

The results of the probabilistic sensitivity analysis (PSA) with 1,000 iterations show that abemaciclib was associated with a [redacted]% probability of being cost-effective at a £20,000 willingness-to-pay threshold at PAS price.

B18. Figure 29: 'DSA tornado plot for abemaciclib + ET versus ET alone' (page 147). The x-axis is labelled ICUR. Is this correct?

ICUR refers to incremental cost-utility ratio, and in this submission, the terms ICER and ICUR are used interchangeably. In the model, ICER is referred to as ICUR to make it clear that the 'effectiveness' measure is based on a health-related quality of life measure represented by a 'utility' score.

a. Please comment further on the impact of the proportion of patients moving to NMR (ET) on the ICER.

The probability of moving to either NMR or MR health states is interdependent. To avoid results in which the probability of going to either MR or NMR do not sum up to 1, only the probability of going to NMR is considered in the DSA. However, while the probability of transitioning to MR is not explicitly included in the DSA, it is automatically adjusted based on the proportion of patients transition to the NMR health state. Accordingly, the DSA results for the proportion of patients moving to NMR (ET) or NMR (ABE + ET) also account the uncertainty around the proportions of patients moving to MR (ET) or MR (ABE + ET).

Patients who transition to the NMR health state when experiencing an invasive disease event incur substantially greater QALYs and reduced costs, compared to patients who transition to the MR health state. As such, it is expected that increasing the probability of transition to the NMR health state for patients receiving ET worsens the ICER (due to less incremental effects gained and more costs incurred between ABE+ET vs ET), while increasing the probability of going to NMR for ABE+ET improves the ICER (more incremental effects gained and less costs incurred between ABE+ET vs ET).

As the probabilities of patients moving to NMR (ET) or NMR (ABE + ET) are robustly derived from the most appropriate data source in this submission (the monarchE trial), the uncertainty around these inputs should not be considered to represent a major source of uncertainty.

b. Please comment further on the impact of the proportion of patients moving to NMR (abemacicilb) on the ICER.

Please see the response above to Question B18a.

B19. Regarding the probability of the transition to the NMR state for the ET arm, the CS states that "the probability was robustly derived from the previous NICE appraisal of trastuzumab (TA632), which was accepted by NICE" (page153).

The Company would like to clarify that the CS incorrectly refers to the probability of patients moving to the non-metastatic recurrence health state being derived from TA632 on Page 86 and Page 153 of Document B.

The probability of patients moving to the NMR health state was derived from a combination of the IDFS extrapolations in the model, and the proportion of patients experiencing NMR versus MR based on the monarchE trial. The probability of moving to the NMR health state was not derived from TA632.

TA632 was used to derive the probability of experiencing recurrence and transitioning to MR health state from the remission health state, as detailed in the CS Document B, Section B.3.3.3.

a. Please comment on the uncertainty regarding the probability of the transition to the NMR state for the ET arm.

As detailed previously in response to Question B18a, the probabilities of patients moving to NMR (ET) or NMR (ABE + ET) were robustly derived from the most appropriate data source in this submission (the monarchE trial), and therefore these inputs should not be considered to represent a major source of uncertainty. The ICERs shown in the DSA, where the proportion of patients experiencing an invasive disease free event ([redacted]%) are varied by 10% either way, represent extreme bounds to the uncertainty, and the Company considers that the true uncertainty associated with this probability is likely to lie within a much narrower range

It should be noted that for the PSA, a Dirichlet distribution was applied based on the number of events that were observed to determine what type of NMR patients get, which makes the sensitivity analysis less extreme in terms of variability in for each type of NMR. This can be checked in the “Inputs” sheet of the CEM, in which the company has added an additional table presenting these calculations.

b. Please comment of the applicability of that estimate (which is originally derived from the KATHERINE trial) to this situation.

As previously noted, the transition probability of moving from IDFS to NMR was not derived from the KATHERINE trial. This transition is solely informed by the trial data in MonarchE (see question B10, where the IDFS curve is extrapolated and % of having NMR from the monarchE trial is applied to the extrapolation curve).

B20. Priority Question: Is medication adherence relevant to clinical practice and has it been captured within the MonarchE data? If relevant, then please factor adherence into the economic model.

Among the patients who completed the 2-year on study treatment period with abemaciclib + ET, the median dose compliance for abemaciclib was [redacted]% at the time of the additional follow-up 1 (AFU1). Compliance was calculated as a ratio of total dose taken to the total prescribed dose (minus any dose adjustments and dose omitted or withheld). Any implications of adherence are captured within the efficacy data from monarchE, and as such, these were included within the economic model. Any implications of adherence on the costs associated with abemaciclib were not included in the economic model. If the implications of adherence on the costs associated with abemaciclib were included, they would decrease the cost associated with abemaciclib. As such, not accounting for this within the economic model represents a conservative approach.

This being said, the implications of compliance on the costs associated with abemaciclib are likely to be minimal in reality, as whether patients comply with their treatment regime is unlikely to have an impact on the number of packs prescribed. As such, the cost of abemaciclib to the NHS is unlikely to be reduced due to patient compliance.

B21. Priority question: In estimating time to treatment discontinuation (TTD), please provide all of the reasons for discontinuation and the numbers of patients of who discontinued for each of these reasons for each arm of the MonarchE trial. If any discontinuations occurred for a reason that would not apply in clinical practice, then please re-estimate TTD censoring for those events and incorporate into the economic model.

The patient disposition in the monarchE trial at the time of the AFU1 data cut is detailed in Figure 2 below, alongside the reasons for discontinuation where applicable.

Figure 2: Flow of patients in the monarchE trial at the time of the AFU1 data cut

Footnotes: [a] At the time of data cut-off on 01 April 2021. [b] Includes patients who were off treatment as well as patients who were enrolled/randomly assigned, but never treated.
Abbreviations: ERB: ethical review board; ET: endocrine therapy; IRB: institutional review board; ITT: intention-to-treat.

As part of the TTD time-to-event analysis, patients in monarchE were censored if they were still receiving treatment at the time of the AFU1 cut-off, or if they discontinued treatment for reasons that were related to the design of the monarchE trial (i.e. reasons that would not apply in clinical

practice). Patients were only considered to experience a TTD event if they discontinue treatment for a reason that would be applicable in clinical practice.

As such, there is no need to re-estimate TTD censoring as per the ERG's request above.

Section C: Textual clarification and additional points

General Clarification/Comments

C1. Please note that: The standardized Definitions for Efficacy and End Points (STEEP) for adjunct breast cancer clinical trial end points criteria v1.0 2007 has been updated to v2.0 in 2021. Please state the differences between the versions and discuss any implications for the submission.

The key difference between STEEP v1.0 and v2.0 is the inclusion of an additional endpoint, invasive breast cancer-free survival, which includes all invasive disease-free survival events except second non-breast primary cancers. The authors recommended that invasive breast cancer-free survival could be considered in some trials. Other updates include endpoint recommendations for local therapy trials, low-risk populations, noninferiority trials and trials incorporating patient-reported outcomes.

The STEEP v2.0 was not published at the time of the monarchEtrial set up, so was not available for use. Regardless, the recommendations in STEEP v2.0 do not impact the outcomes considered in the monarchE trial, and so do not have any implications for this submission.

C2. Table 20 and 21 have the same numbers in the abemaciclib + ET arms (n=1262) and ET (n=1,236). Is this correct: if not then please supply the correction?

This question has been addressed in the answer to question A13.

C3. On page 105, the CS states: "In an earlier publication 'carryover' effect was also discussed (see Figure 14)." The reference 40 seems to be incorrect. Please clarify.

This statement was incorrectly referenced in the Company submission. The correct reference is Cuzick et al. (2006).[32]

C4. P. 31. The CS states: "PROs were collected on day 1 of the study treatment period, at Months 6, 9, 15, 21 and 27". However, Appendix L.3 Timing of assessment section states that Patient Reported Outcomes were also collected at 3 months (visit 6). Please clarify.

Table 4 on Page 31 of the Company Submission incorrectly states that patient-reported outcomes (PROs) were collected at *Months* 6, 9, 15, 21 and 27; this should read *Visits* 6, 9, 15, 21 and 27. The statement in Appendix L.3 is correct that (PROs) were also collected at Month 3.

References

1. Lilly Data on File. Abemaciclib draft SmPC. 2021.
2. Cancer Research UK. TNM staging. Available at: https://www.cancerresearchuk.org/about-cancer/breast-cancer/stages-types-grades/tnm-staging. [Accessed: 03 December 2021].
3. National Institute of Health and Care Excellence (NICE). Early and locally advanced breast cancer: diagnosis and management. Available at: https://www.nice.org.uk/guidance/ng101. [Accessed: 01 October 2021].
4. Brown J, Method MW, Nelson DR. Abstract P5-08-18: Mortality rates associated with clinical and pathological characteristics of hormone receptor positive human epidermal growth factor receptor 2 negative early breast cancer: An analysis of the 2010-2016 surveillance, epidemiology, and end results data. 2019 San Antonio Breast Cancer Symposium; December 10-14.
5. Viale G, Giobbie-Hurder A, Regan MM, et al. Prognostic and predictive value of centrally reviewed Ki-67 labeling index in postmenopausal women with endocrine-responsive breast cancer: results from Breast International Group Trial 1-98 comparing adjuvant tamoxifen with letrozole. J Clin Oncol 2008;26:5569-75.
6. Vasconcelos I, Hussainzada A, Berger S, et al. The St. Gallen surrogate classification for breast cancer subtypes successfully predicts tumor presenting features, nodal involvement, recurrence patterns and disease free survival. The Breast 2016;29:181-185.
7. National Health Service (NHS). PREDICT breast cancer. Available at: https://breast.predict.nhs.uk/tool. [Accessed: 08 December 2021].
8. National Institute for Health and Care Excellence (NICE). Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer. Available at: https://www.nice.org.uk/guidance/dg34/resources/tumour-profiling-tests-to-guide-adjuvant-chemotherapy-decisions-in-early-breast-cancer-pdf-1053750722245. [Accessed: 03 December 2021].
9. ClinicalTrials.gov. Endocrine therapy with or without abemaciclib (LY2835219) following surgery in participants with breast cancer (monarchE). Available at: https://clinicaltrials.gov/ct2/show/NCT03155997?term=JPCF&rank=1. [Accessed: 01 May 2021].
10. National Institute for Health and Care Excellence (NICE). Response to consultee and commentator comments on the draft remit and draft scope (pre-referral). Available at: https://www.nice.org.uk/guidance/gid-ta10749/documents/scope-consultation-comments-and-responses. [Accessed: 03 December 2021].
11. S. Paluch-Shimon HL, J. Beith, E. Tokunaga, J. Reyes Contreras, R.O. de Sant'Ana, T. Forrester, R. McNaughton, J. Wei, N. Harbeck. 153P - Adjuvant endocrine therapy combined with abemaciclib in monarchE patients with high-risk early breast cancer: Disease characteristics and endocrine therapy choice by menopausal status. Annals of Oncology (2021) 32 (supplementary 5): S407-S446.
12. National Institute for Health and Care Excellence (NICE). Early and locally advanced breast cancer: diagnosis and management [NG101]. Available at: https://www.nice.org.uk/guidance/ng101 [Accessed: 08 December 2021]. 2018.
13. Lilly Data on File. Clinical Study Report [monarchE]. 2020.
14. Adelphi Real World. HR+, HER2- Early Breast Cancer (EBC) DSP report: country level summaries v4.0.
15. Smith I, Yardley D, Burris H, et al. Comparative Efficacy and Safety of Adjuvant Letrozole Versus Anastrozole in Postmenopausal Patients With Hormone Receptor-Positive, Node-Positive Early Breast Cancer: Final Results of the Randomized Phase III Femara Versus Anastrozole Clinical Evaluation (FACE) Trial. J Clin Oncol 2017;35:1041-1048.
16. Goss PE, Ingle JN, Pritchard KI, et al. Exemestane versus anastrozole in postmenopausal women with early breast cancer: NCIC CTG MA.27--a randomized controlled phase III trial. J Clin Oncol 2013;31:1398-404.
17. Toremifene and tamoxifen are equally effective for early-stage breast cancer: first results of International Breast Cancer Study Group Trials 12-93 and 14-93. Annals of Oncology 2004;15:1749-1759.
18. Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. The Lancet 2007;369:1711-1723.

19. Norman G, Sloan J, Wyrwich K. Interpretation of changes in health-related quality of life: The remarkable universality of half a standard deviation. Medical Care. 2003;41:582-592.
20. National Institute for Health and Care Excellence (NICE). Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer. Technology appraisal guidance [TA107]. Available at: https://www.nice.org.uk/Guidance/TA107. [Accessed: 03 February 2021]. 2006.
21. NICE. Pertuzumab for adjuvant treatment of HER2- positive early stage breast cancer. [TA569]. Available at https://www.nice.org.uk/guidance/TA569. [Last accessed 09 February 2021]. 2019.
22. National Institute of Health and Care Excellence (NICE). Neratinib for extended adjuvant treatment of hormone receptor-positive, HER2- positive early stage breast cancer after adjuvant trastuzumab [TA612]. Available at: https://www.nice.org.uk/guidance/TA612. [Accessed: 09 February 2021]. 2019.
23. National Institute of Health and Care Excellence (NICE). Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer [TA632]. Available at: https://www.nice.org.uk/guidance/ta632/resources/trastuzumab-emtansine-for-adjuvant-treatment-of-her2positive-early-breast-cancer-pdf-82609074363589. [Accessed: 17 March 2021].
24. NICE. Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer [TA424]. Published date: 21 December 2016. Available at: https://www.nice.org.uk/guidance/ta424/resources/pertuzumab-for-the-neoadjuvant-treatment-of-her2positive-breast-cancer-pdf-82604663691973. [Accessed 03 December 2021].
25. National Institute for Health and Care Excellence. Neratinib for extended adjuvant treatment of hormone receptor-positive, HER2-positive early stage breast cancer after adjuvant trastuzumab [Technology appraisal guidance TA612], 2019.
26. National Institute for Health and Care Excellence. Pertuzumab for adjuvant treatment of HER2-positive early stage breast cancer [Technology appraisal guidance TA569], 2019.
27. National Institute for Health and Care Excellence. Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer [Technology appraisal guidance TA632], 2020.
28. Tolley K, Goad C, Yi Y, et al. Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia. The European Journal of Health Economics 2013;14:749-759.
29. Curtis L, Burns A. Unit Costs of Health and Social Care 2017, Personal Social Services Research Unit, University of Kent, Canterbury. Available at: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2017/. 2017.
30. National Institute of Health and Care Excellence (NICE). Advanced breast cancer: diagnosis and treatment. CG81. Available at: https://www.nice.org.uk/guidance/cg81 [Accessed: 09 March 2018]. 2009.
31. National Institute of Health and Care Excellence (NICE). Abemaciclib with an aromatase inhibitor for untreated advanced hormone-receptor positive, HER2-negative breast cancer ID1227 [TA563]. Available at: https://www.nice.org.uk/guidance/TA563 [Accessed: 05 February 2021].
32. Cuzick J, Sasieni P, Howell A. Should aromatase inhibitors be used as initial adjuvant treatment or sequenced after tamoxifen? British Journal of Cancer 2006;94:460-464.

Appendix 1

Clinical parameters to include the efficacy data from Cohort 1 in the cost-effectiveness model

Invasive disease-free survival

The PH assumption between treatment arms was tested. The log-cumulative plot in Figure 3 shows the treatment arms are crossing during the first four months, after which they appear to move in parallel. The Gramsch and Thernau test could not be labelled as statistically significant (p-value = [redacted]). This is consistent with the Schoenfeld residuals visualisation (Figure 4), in which no clear time trend can be observed, suggesting no violation of the PH assumption.

Accordingly, a single model, including treatment effect as a covariate, was fitted to the IDFS curve of the monarchE data in the Cohort 1 scenario presented in Question A4e, in line with the base case cost-effectiveness analysis.

Figure 3. IDFS log-cumulative hazard plot

Abbreviations: IDFS: invasive disease free survival ; TRTCDN = 0: ET+ABE, TRTCDN=1: ET

Figure 4. IDFS Schoenfeld residual plot

Footnotes: * The red line indicates no treatment effect

Seven parametric distributions and two spline models were fitted to the IDFS KM data and were evaluated based on AIC and BIC of the dependent models. A summary of all the AIC and BIC values is presented in Table 24. The best statistical fit is provided by the Weibull distribution as it presents the lowest AIC and BIC values. The Weibull distribution is followed by the log-logistic distribution, which deviates less than 2.0 points from the Weibull distribution in both AIC and BIC.

In line with the curve selection process described in Section B.3.3.2, the log-logistic extrapolation was chosen to model the efficacy data for Cohort 1 in the scenario presented in Question A4e, as the distributions produced similar landmark IDFS rates for ET which closely resembled IDFS estimates for ET in the published literature (Table 39, Company submission). The same treatment waning assumptions as the base case cost-effectiveness analysis were applied.

Table 24. AIC and BIC values

	Dependent distributions		
Distributions	**AIC**	**Distributions**	**BIC**
Weibull	[redacted]	Weibull	[redacted]
Log-logistic	[redacted]	Log-logistic	[redacted]
Hazard spline 1 knot	[redacted]	Exponential	[redacted]
Gamma	[redacted]	Hazard spline 1 knot	[redacted]
Generalised gamma	[redacted]	Gamma	[redacted]
Hazard spline 2 knots	[redacted]	Generalised gamma	[redacted]
Exponential	[redacted]	Log-normal	[redacted]
Log-normal	[redacted]	Hazard spline 2 knots	[redacted]

Footnotes: The best-fitting curve is marked in **bold**.
Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion.

Time to treatment discontinuation

The duration of treatment was determined by the TTD curves of the abemaciclib + ET (ABE + ET) and ET alone arms from the monarchE trial, in line with the approaches described in the CS, Document B, Section B.3.3.2.

The PH assumption was tested between ET in the intervention arm and ET in the comparator arm. The log-cumulative plot in Figure 5 shows that there is convergence of the trial arms at several points in the plot, most noticeably during the first month and after 20 months. Furthermore, the Grambsch and Thernau test could be labelled as statistically significant (p-value = [redacted]). This is consistent with the Schoenfeld residuals visualisation (Figure 6), in which a clear time trend can be observed, violation of the PH assumption. Accordingly, independent models were fitted to the trial data of ET, in line with the approaches taken in the base case cost-effectiveness analysis.

Figure 5. TTD log-cumulative hazard plot

Abbreviations : TRTCDN = 0: ET+ABE, TRTCDN=1: ET ;

Figure 6. TTD Schoenfeld residual plot

* The red line indicates no treatment effect

The seven parametric distributions and two spline models were fitted independently to the TTD KM data and were evaluated based on AIC and BIC, as presented in Table 25, Table 26 and Table 27.

The best statistical fit for abemaciclib was provided by the generalised gamma distribution as it provides both the lowest AIC and BIC values. However, the generalised gamma model did not produce clinically plausible TTD estimates for abemaciclib when compared with the monarchE data for the ITT population, and so the Hazard spline model with 2-knots was chosen to model abemaciclib TTD in this scenario analysis, which is around a 2 point difference of the generalised gamma, to ensure time on treatment was not overestimated for the abemaciclib arm. The clinical results for the cohort 1 subgroup are similar and consistent with the ITT population, therefore it was deemed unrealistic that TTD for abemaciclib arms would differ substantially for cohort 1 compared to ITT.

For ET in the intervention and ET in the comparator arm, the best fit was provided by the hazard spline 2 knots distribution, which performs best on AIC for the intervention arm and AIC and BIC for the comparator arm. However, the hazards knot 2 spline model did not produce clinically plausible TTD estimates for ET (intervention or comparator) when compared with the monarchE data for the ITT population, and so the Exponential was chosen to model ET TTD in this scenario analysis to ensure time on treatment was not overestimated for the ET comparator and intervention arm. The clinical results for the cohort 1 subgroup are similar and consistent with the ITT population, therefore it was deemed unrealistic that TTD for the ET arms would differ substantially for cohort 1 compared to ITT.

Table 25. AIC and BIC values for TTD extrapolations – abemaciclib

Abemaciclib – Independent distributions			
Distributions	**AIC**	**Distributions**	**BIC**
Generalised gamma	[redacted]	Generalised gamma	[redacted]
Hazard spline 2 knots	[redacted]	Log-normal	[redacted]
Hazard spline 1 knot	[redacted]	Hazard spline 1 knot	[redacted]

Log-normal	[redacted]	Hazard spline 2 knots	[redacted]
Log-logistic	[redacted]	Log-logistic	[redacted]
Weibull	[redacted]	Weibull	[redacted]
Exponential	[redacted]	Exponential	[redacted]
Gamma	[redacted]	Gamma	[redacted]

Footnotes: * Model did not converge. The first best-fitting curve is in **bold**
Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion

Table 26. AIC and BIC values for TTD extrapolations – ET intervention arm

ET intervention arm – Independent distributions			
Distributions	**AIC**	**Distributions**	**BIC**
Hazard spline 2 knots	[redacted]	Log-normal	[redacted]
Hazard spline 1 knot	[redacted]	Hazard spline 1 knot	[redacted]
Log-normal	[redacted]	Hazard spline 2 knots	[redacted]
Log-logistic	[redacted]	Log-logistic	[redacted]
Weibull	[redacted]	Weibull	[redacted]
Exponential	[redacted]	Exponential	[redacted]
Gamma	[redacted]	Gamma	[redacted]
Generalized Gamma	[redacted]	Generalized Gamma	[redacted]

Footnotes: * Models did not converge. The first best-fitting curve is in **bold**.
Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion

Table 27. AIC and BIC values for TTD extrapolations – ET comparator arm

ET comparator – Independent distributions			
Distributions	**AIC**	**Distributions**	**BIC**
Hazard spline 2 knots	[redacted]	Hazard spline 2 knots	[redacted]
Hazard spline 1 knot	[redacted]	Weibull	[redacted]
Gamma	[redacted]	Hazard spline 1 knot	[redacted]
Generalized Gamma	[redacted]	Log-logistic	[redacted]
Weibull	[redacted]	Gamma	[redacted]
Log-logistic	[redacted]	Generalized Gamma	[redacted]
Log-normal	[redacted]	Log-normal	[redacted]
Exponential	[redacted]	Exponential	[redacted]

Footnotes: The first best-fitting curve is in bold.
Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion.

Overall survival without distant relapse

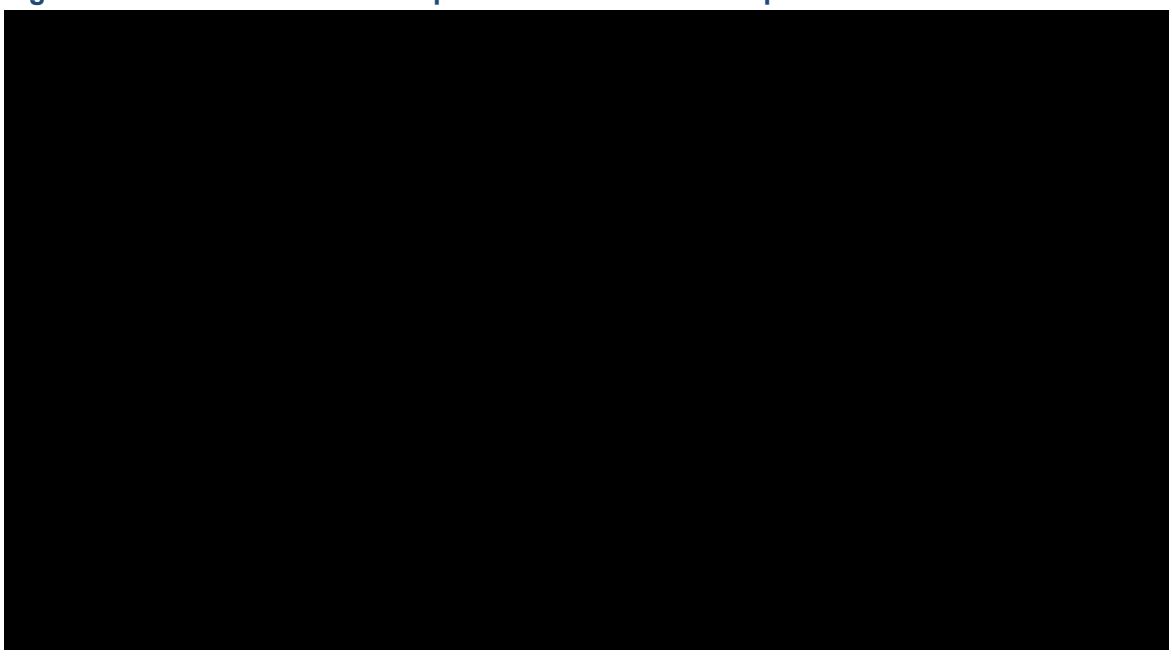
The log-cumulative hazard plot is displayed in Figure 7. The log-cumulative hazard plot moderately indicates PH violation due to the slight crossing of the ABE+ET and the ET curves. The Grambsch and Thernau test could not be labelled as statistically significant (p-value = [redacted]), which means that the proportional hazards assumption cannot be rejected based on this test. The Schoenfeld residuals plot (Figure 8) appears to suggest a slight increasing trend. It should be noted that these results can be considered volatile, as few OS without distant recurrence events were observed in the trial. Accordingly, a single model, including treatment effect as a

covariate, was fitted to the Cohort 1 data in the scenario analysis presented in response to Question A4e, in line with the approach taken in the base case cost-effectiveness analysis.

Figure 7. OS without distant relapse log-cumulative hazard plot

TRTCDN = 0: ET+ABE, TRTCDN=1: ET

Figure 8. OS without distant relapse Schoenfeld residual plot



* The red line indicates no treatment effect

A summary of all the AIC and BIC values is presented in Table 28. The best statistical fit is provided by the exponential distribution as it presents the lowest AIC and BIC values, meaning that the exponential distribution was used to model OS without distant recurrence in the scenario analysis presented in response to Question A4e.

Table 28. AIC and BIC values for OS without distant relapse extrapolations

	Dependent models		
Distributions	**AIC**	**Distributions**	**BIC**
Exponential	[redacted]	Exponential	[redacted]
Log-normal	[redacted]	Log-normal	[redacted]
Log-logistic	[redacted]	Log-logistic	[redacted]
Weibull	[redacted]	Weibull	[redacted]
Gompertz	[redacted]	Gompertz	[redacted]
Hazard spline 1 knot	[redacted]	Hazard spline 1 knot	[redacted]
Hazard spline 2 knots	[redacted]	Gamma	[redacted]
Generalised gamma	[redacted]	Generalised gamma	[redacted]

Footnotes: the first best-fitting curve is in **bold**. * The generalised gamma distribution did not converge; hence the statistical fit of this model is not assessed.
Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion

NICE National Institute for Health and Care Excellence

Patient organisation submission

Abemaciclib in combination with endocrine therapy for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer [ID3857]

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	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 Care and Breast Cancer Now merged on 1 April 2019 to create one charity – Breast Cancer Now. From research to care, our charity has people affected by breast cancer at its heart – providing support for today and hope for the future. United, we'll have the ability to carry out even more world-class research, provide even more life-changing support and campaign even more effectively for better services and care. We'll always be here for anyone affected by breast cancer. From our Moving Forward courses, Living With Secondary Breast Cancer groups, Helpline and more, we're that trusted friend you can turn to for support when you need it most. And by funding almost 360 of the brightest minds in breast cancer research, we're discovering how we can prevent, save lives and live well with breast cancer. All of our funding comes from the public and our partners.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant	In the last 12 months, Breast Cancer Now has received the following funding from manufacturers listed in the appraisal matrix. Please note, Breast Cancer Now does not receive any pharmaceutical funding for our Policy, Evidence and Influencing work. Our work on access to drugs is independent of any funding we may receive from the pharmaceutical industry and is based on the evidence of the clinical effectiveness of drugs. Lilly UK: £21,060 towards Breast Cancer Now's Living with Secondary Breast Cancer Service

manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	
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 utilise our various networks of those affected by breast cancer to gather information about patient experience.
Living with the condition	
6. What is it like to live with the condition? What do carers	A diagnosis of breast cancer will cause considerable anxiety to the patient as well as their family and friends. The initial diagnosis can be shocking, and in the longer-term the fear of breast cancer returning or spreading to other parts of the body (typically the bone, lungs, liver and brain) where it becomes incurable can cause considerable stress and fear for both patients and their loved ones.

experience when caring for someone with the condition?	Treatment for breast cancer can have a number of side effects which can have a significant impact on everyday activities, ability to work and relationships. A patient diagnosed with the type of breast cancer that this treatment is being assessed for told us: “My diagnosis came 2 months after losing my husband to lung cancer and with 2 teenage sons, it was devastating news. I am so pleased that already abemaciclib looks favourable, but the anxiety is only lessened slightly. I am currently waiting for counselling due to high recurrence anxiety”.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	In line with the NICE early and locally advanced guideline, men and premenopausal women will be offered tamoxifen as an adjuvant(following surgery) endocrine therapy. Premenopausal women could also be offered an aromatase inhibitor with ovarian suppression. An aromatase inhibitor (letrozole, anastrozole or exemestane) will be offered as the initial adjuvant endocrine therapy for postmenopausal women with ER positive breast cancer who are at medium or high risk of disease recurrence. Extended therapy (total duration of endocrine therapy of more than 5 years) with an aromatase inhibitor will be offered for postmenopausal women who are at medium of high risk of disease recurrence and who have been taking tamoxifen for 2 to 5 years. Extending the duration of tamoxifen for longer than 5 years for both pre-and post-menopausal women with ER positive invasive breast cancer is also considered. All treatments have side effects. Everyone reacts differently to drugs and some people have more side effects than others. Hormone therapy can have unpleasant menopausal side effects that can make it difficult for women to complete the recommended course of therapy.

8. Is there an unmet need for patients with this condition?	Hormone-receptor positive breast cancer is the most common type of breast cancer. A new adjuvant treatment that could further reduce the risk of cancer returning after surgery would be welcomed by this patient group. It is estimated that 15-20% of patients with hormone receptor positive cancer may experience a recurrence. The risk of recurrence is higher in those with node-positive, high risk primary breast cancer. New treatments which help reduce the chances of breast cancer returning are crucial.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The advantages of adding abemaciclib to adjuvant hormone therapy include: • Improved rates of invasive disease free survival. Latest data from monarchE at the time of writing this submission (median follow up of 27 months), showed an absolute improvement of 5.4% for 3 year invasive disease free survival rates (88.8% with abemaciclib compared with 83.4% for hormone therapy alone) • Improved distance relapse-free survival. The 3-year rate was 90.3% with the addition of abemaciclib compared with 86.1% for hormone therapy alone so an absolute improvement of 4.2%. Women with breast cancer and their families welcome improvements in these outcomes as the fear and anxiety of breast cancer returning can be particularly difficult for patients to cope with. • Abemaciclib is generally well tolerated. Adverse events from the monarchE trial were consistent for the known safety profile for abemaciclib. There is already experience of abemaciclib in secondary (metastatic patients) and patients tell us that whilst one of the most common side effects diarrhoea can in the worst cases disrupt their day-to-day activities, it can generally be managed through medication or treatment breaks.

	The addition of abemaciclib also does not add a significant burden on patients in terms of administration as it is a tablet they would take twice daily for two years along with their standard hormone therapy, which they would continue to receive for 5-10 years as recommended by their clinician. A patient who has received this treatment told us: "I am so pleased the results look like they can have a positive impact. As part of my breast cancer treatment for node positive, hormone positive receptor primary breast cancer, I was asked if I wanted to take part in the abemaciclib trial. I was fortunate to have been randomized onto the arm of the trial where I received the drug. It involves taking abemaciclib for 2 years and then being followed up. I finished taking the drug about 6 months ago. After losing my husband to lung cancer just a few months before my diagnosis and having 2 sons, I welcomed any opportunity to keep the cancer at bay. I know my positive experience of the drug might not be everyone's, but for me, the drug was very tolerable".
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	As with all breast cancer treatments, patients can experience side effects. Everyone reacts differently to drugs and some people have more side effects than others. Common side effects can include diarrhoea, fatigue and neutropenia. Patients' willingness to take 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 choice as to the level of risk they will be willing to take. A patient who received this treatment told us: "Whilst on the treatment, I fortunately didn't suffer any major side effects and those I had were really just a slight worsening of problems caused by aromatase inhibitor (AI) drugs. I think I had an episode of stomach upset which they gave me a 2 week break for. Other than that, I struggled with fatigue, but we think that may have been more induced by the AI. After trying all 3 AIs I have settled on anastrazole and realised that fatigue and joint aches are part of life now. I would take abemaciclib in a heartbeat again if offered it. I do know that not everyone is as lucky as I was in term of side effects".

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.	We note that the US Food and Drug Administration has approved abemaciclib as an adjuvant treatment for a subgroup of patients with hormone receptor positive, HER2 negative, node-positive early breast cancer specifically for those that have a Ki-67 score of 20% or greater. However, the benefit of abemaciclib with hormone therapy has been observed across the whole trial population, regardless of ki-67 index. As is often the case with adjuvant treatments, we are awaiting further results from the trial to understand the long-lasting effects of this treatment.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

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:

- A diagnosis of breast cancer can cause considerable anxiety to patients as well as their family and friends, including fear of recurrence or fear of it spreading to other parts of the body where it becomes incurable. This treatment option could be a significant advance in the treatment of certain patients with primary breast cancer.
- This treatment provides significant improvements in 3-year invasive disease-free survival, an outcome that is welcomed by patients with this type of breast cancer.
- There are several potential side effects, which can have a negative impact on patient's quality of life, however, we hear that the treatment is generally well tolerated and managed, with medication and treatment breaks where necessary. For many the potential benefits of the treatment will outweigh the risk of side effects.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Abemaciclib in combination with endocrine therapy for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer [ID3857]

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 the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	NCRI-ACP-RCP-RCR

3. Job title or position	RCP registrar
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 this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	NCRI-ACP-RCP-RCR
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	No

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Adjuvant to prevent breast cancer recurrence
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Clinically significant treatment response depends on the perspective and cannot be encapsulated with a single metric. Improvement of the PFS and/or OS when compared to standard treatment is a significant treatment response. A reduction in tumour size does not mean anything unless this reduction is maintained for reasonable time period.

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there is an unmet need for patients. While many patients with HR-positive early breast cancer will not experience recurrence on endocrine therapy alone, approximately 20 percent may experience disease recurrence in the first 10 years, in the form of incurable metastatic breast cancer. The risk of recurrence is higher among patients whose cancer has certain clinical and/or pathological risk factors such as a high number of positive lymph nodes, large tumour size, or a high cellular proliferation as measured by tumour grade or biomarkers.There is therefore a significant unmet need for this patient population and new treatment options to help prevent early breast cancer from returning for these patients should be carefully considered.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Endocrine monotherapy treatment alone
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	ESMO and NCCN suggest endocrine monotherapy
• Is the pathway of care well defined? Does it vary or are there differences of opinion	The pathway of care on the adjuvant setting for ER+ve HER2-ve early breast cancer involves endocrine treatment with Tamoxifen +/- ovarian suppression with GnRH analogues (for premenopausal women) or

between professionals across the NHS? (Please state if your experience is from outside England.)	Tamoxifen - Aromatase Inhibitors (for postmenopausal women) and the selection of endocrine treatment depends on the risk.
• What impact would the technology have on the current pathway of care?	Consideration should be given to the implications of the day-to-day practice, follow up appts, consultant time to review and manage toxicities, prescribe treatment, extra appts in clinic, extra visits to the hospitals and potentially higher chance of hospitalization compared to comparators (We do have an extensive experience now on using CDK4/6 and risk of hospitalization is very small) etc. So certainly, an impact on the clinic workload and on patient's day to day routine. However, the number of patients that will fulfil the criteria for adjuvant Abemaciclib will be limited to a small number of patients. The criteria for selecting the population eligible for Abemaciclib plus AI are at least four positive nodes or having one to three positive nodes in combination with either grade 3 disease, a tumour of at least 5 cm, or high Ki-67 status (where 'high' is defined as at least 20 percent positivity in tumour cells). Higher levels of Ki-67 protein are indicative of a fast-growing, aggressive tumour with increased probability of recurrence. However, the later criterion won't be used broadly and the reason is that very limited number of oncology centres have access to Ki67 and this due to lack of consensus for assessing Ki67. Of note FDA approved the Ki-67 IHC MIB-1 pharmDx (Dako Omnis) assay, submitted by Agilent, Inc., as a companion diagnostic for selecting patients for this indication. This is something that needs to be taken in consideration.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ	Usually, patients with early breast cancer on endocrine monotherapy will be discharged from oncology clinics and followed up by the surgeons on a yearly basis. The limited number of patients that will fulfil the

between the technology and current care?	criteria for Abemaciclib will remain under the care of the oncologists and attend monthly appointments for the first 3-6 months and then seen on a 3 monthly basis if no toxicities until completion of treatment.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Hospital, oncology specialist clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Additional time for oncologists, breast care nurses and pharmacists as well as Pathologists. As mentioned above based on MONARCHE trial data FDA approved the Ki-67 IHC MIB-1 pharmDx (Dako Omnis) assay, submitted by Agilent, Inc., as a companion diagnostic for selecting patients for this indication. This is something that needs to be taken in consideration. Is this going to be implemented in the current practice? Who will cover the cost? Do pathologists need training to qualify to run the test?
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes At a previous pre-planned interim analysis, monarchE met its primary endpoint when abemaciclib plus endocrine therapy demonstrated a statistically significant improvement in IDFS in the intent-to-treat (ITT) population compared with endocrine therapy alone. Recently the monarchE researchers presented updated results from the prespecified primary outcome analysis and an additional follow-up analysis with 27 months median follow-up and 90% of patients having completed or discontinued the 2-year study treatment period. . The study team reported that the magnitude of IDFS benefit deepened (hazard ratio [HR] 0.696, 95% confidence interval [CI] 0.588, 0.823; nominal p < 0.0001) and DRFS benefit was maintained (HR 0.687, 95% CI 0.571, 0.826; nominal p < 0.0001). At 3 years, absolute improvement in IDFS and DRFS rates were 5.4%

	and 4.2%, respectively. Abemaciclib benefit deepened during the treatment period and persisted after the 2 years treatment period.
• Do you expect the technology to increase length of life more than current care?	We do not have OS data yet. We have IDFS and DRFS data only, At 3 years, absolute improvement in IDFS and DRFS rates were 5.4% and 4.2%, respectively. Abemaciclib benefit deepened during the treatment period and persisted after the 2 years treatment period.
• Do you expect the technology to increase health-related quality of life more than current care?	The risk of recurrence is higher among patients whose cancer has certain clinical and/or pathological risk factors such as a high number of positive lymph nodes, large tumour size, or a high cellular proliferation as measured by tumour grade or biomarkers. Preventing or delaying recurrence has certainly a positive impact on health-related quality of life.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The group of patients that will benefit from the nee technology is the group of patients that fulfil the criteria below: at least four positive nodes or having one to three positive nodes in combination with either grade 3 disease, a tumour of at least 5 cm, or high Ki-67 status (where 'high' is defined as at least 20 percent positivity in tumour cells). Higher levels of Ki-67 protein are indicative of a fast-growing, aggressive tumour with increased probability of recurrence. However, the later criterion won't be used broadly and the reason is that very limited number of oncology centres have access to Ki67 and this due to lack of consensus for assessing Ki67.
The use of the technology	
13. Will the technology be easier or more difficult to use	As mentioned above patients with early breast cancer on endocrine monotherapy (current standard of care) will be discharged from oncology clinics and followed up by the surgeons on a yearly basis. The limited

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.)	number of patients that will fulfil the criteria for Abemaciclib will remain under the care of the oncologists and attend monthly appointments for the first 3-6 months and then seen on a 3 monthly basis if no toxicities until completion of treatment. Breast cancer nurses, pharmacists will also be involved in the care of these patients in the same way they are involved with MBC patients receiving CDK4/6in on the 1st or 2nd line of treatment. No restaging scans though will be required on the adjuvant setting. Bloods will be required on a monthly basis for the first 3-6 months and 3 monthly thereafter until completion of the 24 month period of treatment. As mentioned above based on MONARCHE trial data FDA approved the Ki-67 IHC MIB-1 pharmDx (Dako Omnis) assay, submitted by Agilent, Inc., as a companion diagnostic for selecting patients for this indication. This is something that needs to be taken in consideration. Is this going to be implemeneted in the current practice? Who will cover the cost? Do pathologists need training to qualify to run the test? Abemaciclib is a more demanding treatment compared to single endocrine monotherapy requiring monthly appointments with oncology, GP for blood tests and chemounit appts for tablet collection. So certainly, more difficult for patients compared to ET alone. Delays due to toxicities and subsequent burden on appointments with GP and Oncologists will also be considered. Risk of sepsis is less than 2% with CDK4/6i and 0% with ET. There is also a small risk of transaminitis and clots. Haematologican disorders are less common with Abemacicilb compared to other CDK4/6i.

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Eligibility criteria should be checked and only if fulfilled treatment to be offered to patient as per MONARCHE trial. These were mentioned above. Blood tests will be required on a monthly basis for the first few months. These will be performed at GP. Decision regarding Ki67 testing should be made. Who will cover the cost? Extra Pathology time will be required as potentially training.
15. 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?	No
16. 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	As above regarding reducing risk of recurrence iDFS and DFRS (please see above)

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes, it is. This is the first time ER+ HER2-ve early breast cancer patients with high-risk disease features will be offered an additional to AI treatment that will reduce/delay the risk of recurrence, Whether this will result in an improvement in OS this remains to be shown.
• Does the use of the technology address any particular unmet need of the patient population?	While many patients with HR-positive early breast cancer will not experience recurrence on endocrine therapy alone, approximately 20 percent may experience disease recurrence in the first 10 years, in the form of incurable metastatic breast cancer. The use of the new technology is relevant to this group of patients that until now they had no other option other than endocrine monotherapy.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	More difficult for both patients and healthcare professionals in terms of visits, additional blood tests, toxicities requiring appropriate management and clinic appts to review and manage the above. The role of CNSs and pharmacists should not be underestimated either as they will both impacted by the above due to their direct involvement with the patients. We should though keep in mind that we have now a log experience on using these drugs on the metastatic setting so managing this small group of patients will be manageable and will not require new skills from the HCP perspective but will certainly require additional clinic time. Abemaciclib is a more demanding treatment compared to single endocrine monotherapy requiring monthly appointments with oncology, GP for blood tests and chemounit appts for tablet collection. So certainly,

	more difficult for patients compared to ET alone. Delays due to toxicities and subsequent burden on appointments with GP and Oncologists will also be considered. Main side effect is diarrhoea Risk of sepsis is less than 2% with CDK4/6i and 0% with ET. There is also a small risk of transaminitis and clots. Haematological disorders are less common with Abemacicilb compared to other CDK4/6i. The most common adverse reactions (≥20%) were diarrhoea, infections, neutropenia, fatigue, leukopenia, nausea, anaemia, and headache.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	MONARCHE run in UK as well as US and Europe
• What, in your view, are the most important outcomes, and were they measured in the trials?	iDFS and no new safety signals
• If surrogate outcome measures were used, do they adequately predict	N/A

long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	Please see SABCS abstract 1478, 2019 San Antonio Breast Cancer Symposium®, December 10-14, 2019. Real world treatment sequencing patterns in secondary breast cancer (SBC): Pathway visualisation using national datasets by O. Oikonomidou et al.
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Given the broad use of CDK4/6 across the country our experts do not expect any equality issues. A consensus regarding Ki67 testing should be made.

21b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.

- The robust treatment benefit of abemaciclib extended beyond the 2-year treatment period and safety data were consistent with the known abemaciclib risk profile.
- Unmet need
- Very strict criteria for patient selection as per MONARCHE trial
- Impact on Clinicians and patients but statistically significant improvement in IDFS
- VP8-2021: O'Shaughnessy J, Rastogi P, Harbeck N, *et al.* Adjuvant abemaciclib combined with endocrine therapy (ET): Updated results from monarchE. *Annals of Oncology*. Published online 14 October 2021. DOI: https://doi.org/10.1016/j.annonc.2021.09.012
- Harbeck N, Rastogi P, Martin M, *et al.* Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. *Annals of Oncology*; Published online 14 October 2021. DOI: https://doi.org/10.1016/j.annonc.2021.09.015

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Newcastle University

Abemaciclib in combination with endocrine therapy for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer [ID3857]

Produced by Kleijnen Systematic Reviews (KSR) Ltd, in collaboration with Newcastle University

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Rider on responsibility for report

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Contributions of authors

Nigel Armstrong acted as project lead, health economist and systematic reviewer on this assessment, critiqued the clinical effectiveness and cost effectiveness methods and evidence and contributed to the writing of the report. Luke Vale acted as health economic project lead, critiqued the company's economic evaluation, and contributed to the writing of the report. Diarmuid Coughlan, Giovany Orozco, Tomos Robinson, and Charlotte Ahmadu acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Susan O'Meara and Kevin McDermott acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence, and contributed to the writing of the report. Steven Duffy critiqued the search methods in the submission and contributed to the writing of the report. Jos Kleijnen 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
AE	Adverse events
AI	Aromatase inhibitor
AIC	Akaike Information Criterion
ALT	Alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
BCS	Base-case scenario
BI	Budget impact
BIC	Bayesian information criterion
BMI	Body mass index
BNF	British National Formulary
CADTH	Canadian Agency for Drugs and Technologies in Health
CCTR	Cochrane Central Register of Controlled Clinical Trials
CDK	Cyclin-dependent kinase
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CEM	Company economic model
CHMP	Committee for Medicinal Products for Human Use
CfB	Change from baseline
CI	Confidence interval
CNS	Central nervous system
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
CT	Computerised tomography
CTR	Clinical trial results
DCIS	Ductal carcinoma in situ
DFS	Disease-free survival
DRFS	Distant relapse free survival
DSU	Decision Support Unit
eBC	Early breast cancer
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
eMIT	Electronic market information tool
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-5L	EuroQol-5 Dimensions-5 Levels
ER	Oestrogen receptor
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
ET	Endocrine therapy
EUR	Erasmus University Rotterdam
EVE	Everolimus
EXE	Exemestane
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue
FACT-B	Functional Assessment of Cancer Therapy – Breast
FACT-ES	Functional Assessment of Cancer Therapy-Endocrine Symptoms
FAS	Full analysis set
FAD	Final appraisal document

FDA	Food and Drug Administration
FE	Fixing errors
FV	Fixing violations
FUL	Fulvestrant
GHS	Global health status
GnRH	Gonadotropin-releasing hormone
HAS	Haute Autorité de santé
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health technology assessment
IC	Indirect comparison
ICD	International Statistical Classification of Diseases and Related Health Problems
ICER	Incremental cost effectiveness ratio
IDFS	Invasive disease-free survival
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITC	Indirect treatment comparison
ITT	Intention to treat
IU	International units
IV	Intravenous
IWRS	Interactive web-based randomisation scheme
KM	Kaplan-Meier curves
KSR	Kleijnen Systematic Reviews
LHRH	Luteinising hormone-releasing hormone
LILACS	Latin American and Caribbean Health Sciences Literature
LRRFS	Locoregional recurrence-free survival
LYs	Life years
LYG	Life years gained
M2	Monarch2 trial
M3	Monarch3 trial
MAIC	Match-adjusted indirect comparison
MBC	Metastatic breast cancer
MeSH	Medical subject headings
MHRA	Medicines and Healthcare Products Regulatory Agency
MJ	Matters of judgement
MMRM	Mixed effect Model Repeat Measurement
MOS SF-36	Medical Outcomes Study Short Form Survey
MR	Metastatic recurrence
MTA	Multiple technology appraisal
MTC	Mixed treatment comparison
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NCRI	National Cancer Research Institute
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Network meta-analysis
NMR	Non-metastatic recurrence
NR	Not reported
OFS	Ovarian function suppression
OS	Overall survival
PAS	Patient access scheme
PBAC	The Pharmaceutical Benefits Advisory Committee
PD	Pharmacodynamics

PFS	Progression-free survival
PH	Proportional hazards
PK	Pharmacokinetics
PR	Progesterone receptor
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q3W	Every three weeks
QALY	Quality adjusted life year
QLQ-BR23	Breast Cancer-Specific Quality of Life Questionnaire
QLQ-C30	Quality of Life Questionnaire
QoL	Quality of life
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RR	Relative risk; Risk ratio
SABCS	San Antonio Breast Cancer Symposium
SAE	Serious adverse events
SC	Subcutaneous
ScHARR	School of Health and Related Research
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SoC	Standard of care
STA	Single technology appraisal
STEEP	Standardised definitions for efficacy endpoints
TA	Technology assessment
TEAE	Treatment emergent adverse events
TMX	Tamoxifen
TSD	Technical support document
TTO	Time trade-off
TTD	Time to treatment discontinuation
UK	United Kingdom
UMC	University Medical Centre
USA	United States of America
VTE	Venous thromboembolism
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 Review Group (ERG) as being potentially important for decision making. If possible, it also includes the ERG'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. Other key issues are discussed in Section 1.6 while a summary is presented in Section 1.7.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main ERG report, see Section 2 (background), Section 3 (decision problem), Section 4 (clinical effectiveness) and Section 5 (cost effectiveness) for more details.

All issues identified represent the ERG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the ERG's key issues

Table 1.1: Summary of key issues

ID1457	Summary of issue	Report Sections
1	Potential lack of generalisability of the evidence to NHS clinical practice given ambiguity in the definition of high risk	2.1, 3.2
2	Lack of recognition that comparators depend on menopausal status leading to bias in effectiveness	2.1, 2.2, 2.3, 3.2
3	Lack of generalisability of monarchE to clinical practice in terms of endocrine therapy type	2.2, 2.3, 3.22
4	Lack of clarity around the model structure when aspects of partitioned survival model are used for transition probabilities	4.2.2
5	Lack of recognition that comparators depend on menopausal status leading to bias in cost effectiveness	4.2.3
6	Medication adherence not modelled	4.2.4
7	Potential bias from selection of survival curves for treatment and comparators, and lack of alternative scenarios	4.2.6
8	Discrepancy between overall survival in model and real-world evidence	4.2.6
9	Lack of long-term evidence for assumed 'carryover benefit' and justification for treatment waning trajectory	4.2.6
10	Same utility values applied to both treatment and control arms in the IDFS setting	4.2.8
11	Insufficient clarity in the probability of moving to non-metastatic and metastatic health states	5.1
12	Insufficient clarity of reporting of the cost effectiveness scenario results	5.2.3
13	Lack of detail in the model validation process in terms of verification of the formulae, functions, and coding.	5.2.4
IDFS = invasive disease-free survival; NHS = National Health Service		

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are a matter of judgement relating to the effectiveness of abemaciclib + endocrine therapy (ET) versus ET alone. This is with respect to invasive disease-free survival (IDFS) and overall survival (OS) as well as the assumption about how long treatment effects last and the impact of treatment on subsequent treatment.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (OS) and quality of life (QoL) 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:

- Length of invasive-free disease survival (IDFS) time
- Change in the chance of a metastatic recurrence

Overall, the technology is modelled to affect costs by:

- Change in the cost of the drug and treatment costs
- Change in the costs of managing adverse events (AEs)
- Change in chance of a metastatic recurrence

The modelling assumptions that have the greatest effect on the ICER are:

- The model that is used to extrapolate the IDFS curve beyond the treatment period
- Proportion of patients having a metastatic recurrence relative to the proportion who have a non-metastatic event in each intervention arm
- Treatment received when a metastatic recurrence occurs
- How long the effect of treatment lasts and how fast its effect reduces over time

1.3 The decision problem: summary of the ERG's key issues

Table 1.2: Key issue 1 Potential lack of generalisability of the evidence to NHS clinical practice given ambiguity in the definition of high risk

Report Section	2.1
Description of issue and why the ERG has identified it as important	The NICE scope and the company decision problem both use the term 'high risk of recurrence'. However, there is no clear definition and none in the NICE guideline NG101. This means that there might be a lack of generalisability of the evidence based on monarchE and NHS clinical practice.
What alternative approach has the ERG suggested?	The ERG would recommend greater clarity as to the NHS clinical practice criteria for determining high risk and ideally as close as possible alignment with the monarchE trial eligibility criteria.
What is the expected effect on the cost effectiveness estimates?	The ERG argued that Cohort 1 from monarchE would be of more relevance to the NHS. The adoption of this in the CS slightly increased the ICER. In the ERGs scenario analysis, the increase in the ICER is substantial. The company base-case ICER after clarification was £4,427. The ICER for the analogous ERG analysis was £13,339. However, due to coding errors in the model that could not be resolved PSA could not be performed..

Report Section	2.1
What additional evidence or analyses might help to resolve this key issue?	The ERG would recommend greater clarity as to the NHS clinical practice criteria for determining high risk and ideally as close as possible alignment with the monarchE trial eligibility criteria.
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSA = probabilistic sensitivity analysis	

Table 1.3: Key issue 3 Lack of recognition that comparators depend on menopausal status leading to bias in effectiveness and cost effectiveness estimates

Report Section	2.1, 2.2, 2.3, 3.2
Description of issue and why the ERG has identified it as important	Endocrine therapy (ET) type depends on menopausal status. The response to clarification also showed that outcomes in terms of IDFS and DRFS are better for premenopausal women. Therefore, if appraisal of the evidence is not by menopausal status a positive recommendation for the whole population might lead to an inefficient allocation of resources for those who are postmenopausal.
What alternative approach has the ERG suggested?	The company provided subgroup analyses for two of the three outcomes requested at clarification: IDFS and DRFS. OS was omitted. Also, no cost effectiveness analysis by subgroup was conducted.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	All outcomes including OS should be presented in a subgroup analysis by menopausal status. Separate cost effectiveness analyses should also be conducted.
DRFS = distant relapse free survival; IDFS = Invasive disease-free survival; OS = overall survival	

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

Table 1.4: Key issue 2 Lack of generalisability of monarchE to clinical practice in terms of endocrine therapy type

Report Section	2.2, 2.3, 3.22
Description of issue and why the ERG has identified it as important	Endocrine therapy (ET) was administered according to physician choice, which might not be aligned with NHS clinical practice. Indeed, in response to request for clarification, it was revealed that many premenopausal women received an aromatase inhibitor instead of tamoxifen, contrary to the NICE guideline NG101.
What alternative approach has the ERG suggested?	Subgroup analysis by menopausal status and ET type.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Subgroup analysis by menopausal status and ET type.

Report Section	2.2, 2.3, 3.22
ET = endocrine therapy; NHS = National Health Service; NICE = National Institute for Health and Care Excellence	

1.5 The cost effectiveness evidence: summary of the ERG's key issues

A full summary of the cost effectiveness evidence review conclusions can be found in Section 6.4 of this report. The company's cost effectiveness results are presented in Section 5, the ERG's summary and detailed critique in Section 4, and the ERG's amendments to the company's model and results are presented in Section 6. The main ERG results are reproduced using confidential Patient Access Schemes (PASs) in a confidential Appendix. The key issues in the cost effectiveness evidence are discussed in Tables 1.5 to 1.14.

Table 1.5: Key issue 4 Lack of clarity around the model structure when aspects of partitioned survival model is used for transition probabilities

Report Section	4.2.2
Description of issue and why the ERG has identified it as important	The company describe and maintain after clarification, that they are using a state transition model. The ERG considers the model structure to be more appropriately described as using partitioned survival model methodology. The rationale behind this is that the model utilises parametric survival equations to estimate the transition between IDFS to other health states. This is problematic as a set of survival curves describing state membership across non-mutually exclusive groups of health states are used.
What alternative approach has the ERG suggested?	The model is based on partitioned survival model methodology and limitations with such methodology ought to be acknowledged.
What is the expected effect on the cost effectiveness estimates?	The expected impact of using partitioned survival model methodology is unknown but could be substantial given that the vast proportion of outcomes are estimated to accumulate beyond the observed data.
What additional evidence or analyses might help to resolve this key issue?	The company could provide a justification for why they believe that their data inputs are valid and do not violate mutual exclusivity. They could also provide a state transition model as an alternative to the partitioned survival model.
ERG = Evidence Review Group; IDFS = Invasive disease-free survival	

Table 1.6: Key issue 5 Lack of recognition that comparators depend on menopausal status leading to bias in effectiveness and cost effectiveness estimates

Report Section	4.2.2
Description of issue and why the ERG has identified it as important	Although the comparators (ET) are in line with the NICE scope, a subgroup analysis by menopausal status is required as the precise types of ET recommended in the NICE guideline/clinical pathway differ by this status. A subgroup analyses by menopausal status would also affect mean age of population in the model with a likely divergence from the current mean age of [redacted] years.
What alternative approach has the ERG suggested?	Two separate economic analyses, one for each menopausal subgroup, each with the appropriate comparator and

Report Section	4.2.2
	effectiveness and cost estimates specific to those comparators and subgroups.
What is the expected effect on the cost effectiveness estimates?	If driven by effectiveness, then the ICER is likely to go down for the premenopausal subgroup and up for the postmenopausal subgroup.
What additional evidence or analyses might help to resolve this key issue?	The additional analyses by menopausal status.
ET = endocrine therapy; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; NICE = National Institute for Health and Care Excellence	

Table 1.7: Key issue 6 Medication adherence not modelled

Report Section	4.2.6
Description of issue and why the ERG has identified it as important	Medication adherence among ET users is a real-world issue that the company neglected to address in their submission.
What alternative approach has the ERG suggested?	It would have been helpful if there was a section on medication adherence in the company submission and scenario analyses in the model accounting for nonadherence in a real-world setting.
What is the expected effect on the cost effectiveness estimates?	If the issue with non-adherence is the same for both arms, then it is likely that the ICER would remain the same.
What additional evidence or analyses might help to resolve this key issue?	Scenario analyses in the model accounting for non-adherence in a real-world setting.
ET = endocrine therapy; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio	

Table 1.8: Key issue 7 Potential bias from selection of survival curves for treatment and comparators, and lack of alternative scenarios

Report Section	4.2.6
Description of issue and why the ERG has identified it as important	The company have selected extrapolation survival curves for IDFS and OS that may not reflect the real-world reality for NHS patients with HR+ HER2-, node-positive early breast cancer. Therefore, the results of the cost effectiveness analysis may be biased.
What alternative approach has the ERG suggested?	Log-normal extrapolation for IDFS in a scenario analysis may be a better predictor of real-world recurrence rates.
What is the expected effect on the cost effectiveness estimates?	If the treatment arm shows improved survival at 5-year and 10-year compared to the comparator, then this would likely result in the treatment being even more cost effective to the NHS. The ERG explored the use of a log-normal distribution as an alternative to the loglogistic regression used in the CS and in the ERG base-case. The ICER in the ERG base-case was £12,453 and £17,315 when a log-normal distribution was used.
What additional evidence or analyses might help to resolve this key issue?	Further longer-term data to allow the more accurate estimation of survival.

Report Section	4.2.6
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; IDFS = invasive disease-free survival; NICE = National Institute for Health and Care Excellence; OS = overall survival	

Table 1.9: Key issue 8 Discrepancy between overall survival in model and real-world evidence

Report Section	4.2.6
Description of issue and why the ERG has identified it as important	According to the company's long term extrapolations of OS without distant recurrence, ~97% of the monarchE Cohort will be alive at 5-years for both arms. According to NHS data, the 5-year survival is currently 85% for stage III HR+, HER2-, node-positive breast cancer patients.
What alternative approach has the ERG suggested?	Further explanation and analyses are required.
What is the expected effect on the cost effectiveness estimates?	The impact is unknown. It would depend on the treatment effect of the intervention.
What additional evidence or analyses might help to resolve this key issue?	Data from the trial and an analysis where OS (with and without distant recurrence) reflected the real-world evidence.
ERG = Evidence Review Group; NHS = National Health Service; OS = overall survival	

Table 1.10: Key issue 9 Lack of long-term evidence for assumed 'carryover benefit' and justification for treatment waning trajectory

Report Section	4.2.6
Description of issue and why the ERG has identified it as important	The 'carryover benefit' assumptions informing the waning of the treatment effect of abemaciclib were based on the long-term treatment effect for ET from historical trial data. Therefore, there is an absence of evidence to the carryover benefit of abemaciclib.
What alternative approach has the ERG suggested?	The alternative approach is a recommendation by the NICE DSU Document 14, which is to undertake scenario analysis with one of the three following assumptions: the treatment effect halts at the end of the trial; it declines over time; or it is maintained over the lifetime. Scenario analysis should assess the importance of duration of treatment effect assumptions.
What is the expected effect on the cost effectiveness estimates?	The ERG would expect the ICER to be higher than the current base-case. The ERG base-case took a constant treatment effect duration of three years and a waning effect from year 3 to year 8 with no treatment effect on IDFS beyond year 8. The company base-case ICER after errors were fixed was £5,309 and the ERG base-case was £12,453.
What additional evidence or analyses might help to resolve this key issue?	Further data specific to the decision problem that would allow waning effects to be more accurately estimated.
DSU = Decision Support Unit; ERG = Evidence Review Group; ET = endocrine therapy; ICER = incremental cost effectiveness ratio; IDFS = invasive disease-free survival; NICE = National Institute for Health and Care Excellence; OS = overall survival	

Table 1.11: Key issue 10 Same utility values applied to both treatment and control arms in the IDFS setting

Report Section	4.2.8
Description of issue and why the ERG has identified it as important	The company applied overall utilities to both treatment and control arms in the IDFS health state as there was no statistically significant difference between treatment and comparator arms. The ERG does not consider this to be best practice. This assumes that lack of evidence of a difference is the same as evidence of no difference.
What alternative approach has the ERG suggested?	The different utility values should be used for the different arms and the imprecision should be explored within the probabilistic sensitivity analyses.
What is the expected effect on the cost effectiveness estimates?	The impact on the ICER of using the utility values that are specific to each arm is small. The company base-case after fixing errors was £5,309 and the ERG analysis when treatment specific utilities was used was £5,216.
What additional evidence or analyses might help to resolve this key issue?	Nothing further.
ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; IDFS = invasive disease-free survival	

Table 1.12: Key issue 11 Insufficient clarity in the probability of moving to non-metastatic and metastatic health states

Report Section	5.1
Description of issue and why the ERG has identified it as important	The effect of the intervention on the proportion of non-metastatic recurrences (NMR) relative to metastatic recurrences (MR) beyond the trial data is not affected by treatment waning. Therefore, the model assumes a lifelong duration of the reduction in the proportion of NMR versus MR which is not supported by evidence and has an impact in the ICER for the long run.
What alternative approach has the ERG suggested?	As this difference in the proportion of NMR is based on trial data, the ERG considers that the same treatment waning assumption used for overall recurrences should apply to metastatic recurrences relative to non-metastatic. The ERG modified the probability of having an MR in the abemaciclib arm to converge to the probability of having an MR in the ET alone arm over the treatment waning effect period.
What is the expected effect on the cost effectiveness estimates?	There was a small increase in the ICER. The company base-case after fixing errors was £5,309. The ICER when the ERG modified the probability was £5,573.
What additional evidence or analyses might help to resolve this key issue?	Nothing further.
ERG = Evidence Review Group; ET = endocrine therapy; ICER = incremental cost effectiveness ratio; MR = metastatic recurrences; NMR = non-metastatic recurrences	

Table 1.13: Key issue 12 Insufficient clarity of reporting of the cost effectiveness scenario results

Report Section	5.1
Description of issue and why the ERG has identified it as important	The ERG considers that the scenario analyses conducted by the company were insufficient to draw reliable conclusions about the robustness of the model results. The ERG is concerned that alternative IDFS extrapolations with a large impact on the ICER were not part of the CS, which goes against guidance from TSD 14.[1] These included a log-normal model and scenarios eliminating the treatment waning assumption or with a treatment effect lasting only the duration of the current follow up.
What alternative approach has the ERG suggested?	A more complete set of scenario analyses in order to represent more accurately the impact of the assumptions tested in the final results as well as to inform the ERG base-case.
What is the expected effect on the cost effectiveness estimates?	The impact of more complete scenario analysis is variable, although many of them would most likely increase the ICERs as was the case with many of the ERG scenario analyses.
What additional evidence or analyses might help to resolve this key issue?	The ERG addressed several of the uncertainties in developing the ERG base-case and in the scenario analyses presented. However further evidence on the longer-term performance would provide more confidence in the results provided by both a base-case and associated scenario analysis.
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; IDFS = invasive disease-free survival; TSD = Technical Support Document	

Table 1.14: Key issue 13 Lack of detail in the model validation process in terms of verification of the formulae, functions, and coding.

Report Section	5.2.4
Description of issue and why the ERG has identified it as important	The lack of details the validation process of the model in terms of verification of the formulae, functions, and coding. The ERG has found several coding errors inside the model plus other basic mistakes (such as mixing rates with probabilities), with a varying impact on the ICER. Although the impact on the ICER in some of them may not be large, the company did not provide details on the validation process for functions and coding in the CS.
What alternative approach has the ERG suggested?	The ERG requested in the clarification letter for the company to provide further details on their communications with clinical and-mics experts to inform the model. By the information the company provided, clinical experts informed the model structure, parameter extrapolation and assumptions. No information about the cell-by-cell verification of the formulae was provided.
What is the expected effect on the cost effectiveness estimates?	The impact of correcting errors on the model results is not expected to be straightforward. Some of the errors found affect the ICER in favour and against the intervention and to different degrees. Overall, the cumulative effect of correcting the errors within the model was modest with the ICER increasing from £3,786 for the company base-case to £5,309 after fixing errors.

Report Section	5.2.4
What additional evidence or analyses might help to resolve this key issue?	It was not possible to correct all errors in the model. Remaining errors identified relate to the scenario analysis around Cohort 1, which the ERG believes is closer to NHS practice.
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; NHS = National Health Service	

1.6 Other key issues: summary of the ERG's view

There are no other key issues.

1.7 Summary of the ERG's view

The estimated ERG base-case ICER based on a probabilistic analysis and the ERG preferred assumptions was £12,233 per QALY gained for the comparison of abemaciclib + ET versus ET alone. The probabilistic ERG base-case analyses indicated cost effectiveness probabilities of 89% and 99% at willingness to pay thresholds of £20,000 and £30,000 per QALY gained respectively. The most influential adjustments were 1) decreasing the treatment effect duration on IDFS, 2) switching to Cohort 1 alone as the model population, and 3) decreasing the treatment effect duration on the probability of metastatic recurrences. It should be noted that ERG analyses are predicated on the company's CEM and this does not fully capture the set of unresolvable uncertainty around treatment duration and waning. Key uncertainties remain about the effectiveness and cost effectiveness of abemaciclib. As further data accrue from the monarchE study these will begin to be resolved. Other uncertainties relate to the applicability of the available data to the NHS and the analysis by menopausal status. For the former, further work could be performed to more clearly determine applicability and further analysis and modelling could begin to address whether there are meaningful differences in effectiveness and cost-effectiveness by menopausal status.

Table 1.15: Summary of ERG's preferred assumptions and ICER

Scenario	Incremental cost	Incremental QALYs	ICER
Company's base-case after clarification	£3,172	0.838	£3,786
Company's base-case after clarifications and including ERG corrections	£4,701	0.886	£5.309
Matters of judgement 3: shorter treatment effect duration on IDFS (Key issue 7)	£6,057	0.555	£10,904
Matters of judgement 4: treatment specific utilities (key issue 10)	£4,701	0.901	£5,216
Matters of judgement 5: shorter treatment effect on metastatic recurrences (Key issue 11)	£4,861	0.872	£5,573
ERG's preferred base-case (also includes matters of judgement 6-7: Kaplan-Meier curve for abemaciclib TTD and chemotherapy costs	£4,716	0.886	£5,326
ERG base-case probabilistic*	£6,526	0.533	£12,233
ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; IDFS = invasive disease-free survival; QALY = quality adjusted life year; TTD = time to discontinuation			

2. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	ERG Comment
Population	Adults with hormone receptor-positive, HER2-negative, node-positive early breast cancer after definitive surgery of the primary breast tumour at high risk of recurrence	Adults with hormone receptor-positive, HER2-negative, node-positive early breast cancer after definitive surgery of the primary breast tumour at high risk of recurrence	NA	Superficially there is no difference between the population in the decision problem and the scope, although there is a question regarding the definition of 'high risk of recurrence'
Intervention	Abemaciclib in combination with standard endocrine therapy (ET)	Abemaciclib in combination with standard ET	NA	The intervention is in line with the NICE scope
Comparator(s)	Standard ET	Standard ET	NA	Superficially, the comparators are in line with the NICE scope, although there is a question regarding the mix of types of ET in the monarchE trial. Also in the care pathway, reproduced from NICE guideline CG101, the CS indicates that type of ET depends on menopausal status
Outcomes	The outcome measures to be considered include: • overall survival (OS) • invasive disease-free survival (IDFS) • recurrence-free survival	• IDFS • Distant relapse free survival (DRFS) • OS (given the early disease stage, OS data will not be mature during the timeframe of the appraisal, which will	NA	The outcomes reported are in line with the NICE scope

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	ERG Comment
	• response rate • adverse effects of treatment • health-related quality of life (HRQoL)	focus of modelling disease recurrence) • Safety and tolerability (adverse effects of treatment) • PROs related to HRQoL: o FACT-B, FACT-ES, and FACIT-F o EQ-5D-5L and cross-walked to EQ-5D-3L using the van Hout 2012 methodology		
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 Personal Social Services (PSS) perspective The availability of any commercial arrangements for	As per NICE reference case, cost effectiveness is expressed in terms of incremental cost per QALY, and costs considered from the perspective of the NHS and PSS, with a life-time time horizon	NA	The analyses were conducted as per NICE reference case except that treatment-specific health utilities were not assigned in the IDFS health state. There was also uncertainty around transition probabilities within the model structure by using partitional survival methodology

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	ERG Comment
	the technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account			
Special considerations including issues related to equity or equality	The availability and cost of biosimilar and generic products should be taken into account Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator	Although breast cancer is predominantly a disease of women, it does occur in men; the trial included, and the anticipated licence will include, both men and women. Therefore, Lilly intend to submit evidence to support appraisal across both sexes. Inherently the evidence will be heavily weighted towards evidence in women, in line with the prevalent sexual distribution of the disease in the general population, but this is not anticipated to be a barrier to appraisal in the overall population of both sexes	NA	

Source: Table 1, CS[2]

ALN = axillary lymph nodes; CS = company submission; DRFS = distant relapse free survival; EQ-5D-5L = EuroQol-5 Dimensions-5 Levels; ERG = Evidence Review Group; ET = endocrine therapy; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-B = Functional Assessment of Cancer Therapy – Breast; FACT-ES = Functional Assessment Of Cancer Therapy-Endocrine Symptoms; HER2− = human epidermal growth factor receptor 2; HRQoL = health-related quality of life; IDFS = invasive disease-free survival; NA = not applicable; NICE = National Institute for Health and Care Excellence; OS = overall survival; PROs = patient-reported outcomes; PSS = Personal Social Services; QALY = quality adjusted life year

2.1 Population

The population defined in the scope is: adults with hormone receptor-positive, HER2-negative, node-positive early breast cancer after definitive surgery of the primary breast tumour at high risk of recurrence.[3] The population in the CS is described in the same way.[2]

ERG comment:

The CS states: '*It is therefore anticipated that patients with early breast cancer at high risk of recurrence in the UK will be identified by the various routinely collected clinical and pathological features outlined above, such as the number of ALNs and tumour size, in line with the inclusion criteria used in the monarchE trial, the pivotal trial for abemaciclib in this indication'* (page 17)[2] The ERG therefore asked:

a. Please provide an operational definition of 'high risk of recurrence' i.e., the way that a patient will be identified in clinical practice as being in this category.
b. With which of the two Cohorts of the monarchE trial is this definition most consistent with that is operational in UK clinical practice?
c. Please discuss the implications of any difference between this definition and that is used to define the inclusion criteria for the most relevant Cohort in the monarchE trial.
d. Please present all clinical effectiveness results for the Cohort that most closely aligns with the definition operational in UK clinical practice.
e. Please present an economic analysis for the Cohort that most closely aligns with the definition operational in UK clinical practice.
f. Please clarify which of the outcome measures commissioned in the CS addresses the outcome 'response rate' specified in the final scope issued by NICE

The company response was that 'high risk' will be defined in clinical practice according to a combination of clinical and pathological features, such as the number of axillary lymph nodes that a breast cancer has spread to, tumours of T2 or greater (tumour size of 2 cm or greater), and high-grade disease and that this was in line with Cohort 1 of the monarchE trial.[4] They also stated that ≥20% Ki-67 expression would be a *"valid factor for high-risk patient selection (Cohort 2 in the monarchE trial)."*[4] The NICE guideline NG101 is cited in support of the use of PREDICT as a tool for predicting risk. Indeed, NG101 does recommend this tool, but with no explicit threshold for determining high risk and that clinical expertise should also be employed (Section 1.7.3).[5] Also, it appears that the PREDICT tool does not identify risk level, but instead estimates OS.[6] The company also states that node positive indicates *"higher risk of recurrence"*, but the ERG would point out that this is not the same as 'high risk' and NG101 states that lymph node-positive status can be consistent with *"medium or high risk"*. (Section 1.7.6).[5] The company maintained that *"the ITT population to be the most generalisable source of evidence with the definition of high risk of recurrence used in clinical practice"* (page 6)[4] Nevertheless, the company did provide all efficacy analyses for Cohort 1 only (see Section 3.2.3) and a corresponding economic analysis as a response to request for the Cohort that most closely aligns with NHS clinical practice (see Section 6.1).[4]

No subgroup analysis was specified in the NICE scope.[3] However, the ERG noted in the clarification letter that the population could be analysed by menopausal status (men/pre- or post-). As indicated in Figure 3 of the CS, which was reproduced from the NICE Guideline NG101, this has implications for the comparators: tamoxifen is recommended for premenopausal women or men, but not for postmenopausal women in the population of this submission except if aromatase inhibitors are not tolerated or contraindicated.[5] In addition, ovarian ablation or suppression by a gonadotropin-releasing

hormone (GnRH) agonist is only recommended for premenopausal women and bisphosphonates only for postmenopausal women. Also, the monarchE trial randomisation was stratified by menopausal status, thus removing selection bias from any subgroup analysis by menopausal status. The company were therefore asked to provide analysis of IDFS, DRFS and OS from the monarchE trial and cost effectiveness analysis for these sub-groups using the relevant comparators and adjuvant therapies. In response, the company provided subgroup analyses for IDFS and DRFS, but not OS.[4] The company argued that the intention to treat (ITT) population analysis was applicable to both subgroups because there was no significant difference with respect to menopausal status for IDFS or DRFS with p values for interaction test of 0.082 and 0.137 respectively (Figures 8 and 9 of CS).[2] However, the hazard ratios (HRs) and 95% confidence intervals (CIs) appear to be clearly lower for those who are postmenopausal (see Table 3.13, 3.14, 3.19 and 3.20). Given this apparent difference in treatment effect and the lack of subgroup analysis of OS, this remains a Key Issue.

2.2 Intervention

The intervention (abemaciclib in combination with standard ET) appears superficially to be in line with the scope.

ERG comment:

Independent of menopausal status, ET might vary in clinical practice and did vary in the pivotal trial, monarchE according to physician choice (indirect comparison (IC)) (see Table 3.7). Therefore, in the clarification letter the ERG requested evidence to indicate the degree of correspondence between the types of ET administered in the monarchE trial and those that would be administered in actual UK clinical practice. The ERG also asked the company to discuss the implications in terms of clinical effectiveness and cost effectiveness of any discrepancy. The company responded by providing a table comparing UK patients with all patients in monarchE (see Table 3.8). As described in more detail below, there is reason to believe that fewer premenopausal patients received tamoxifen than the 100% that would be expected if NG101 was being followed.[5] It is also unclear whether the percentage of postmenopausal patients who received tamoxifen is as would be expected if contraindicated for or intolerant to aromatase inhibitors, as stipulated in NG101.[5] This is therefore a Key Issue.

Given that abemaciclib is added to the comparator therapy, the subgroup analysis by menopausal status mentioned in Section 2.1 has implications for the intervention as well as the comparator.

2.3 Comparators

The comparator (standard ET) appears superficially to be in line with the scope.

ERG comment:

See comments in Section 2.1 regarding subgroup analysis by menopausal status and Section 2.2 regarding the mix of ET.

2.4 Outcomes

The outcomes in the CS are at least as comprehensive as in the NICE scope.

2.5 Other relevant factors

The company claim that the evidence presented is relevant to both men and women.

ERG comment: It is unclear the extent to which the evidence is applicable to men given the very small number of male patients in the trial (21 (0.7%) and 15 (0.5%) in the intervention and comparator arms respectively). The CS also stated that there was no subgroup analysis because of those small numbers.

3. CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

Two systematic literature reviews (SLR) were conducted to identify relevant clinical evidence. Full details of the SLR search strategy, study selection process and results were reported in Appendix D.

3.1.1 Searches

Appendix D of the CS provided details of the literature searches conducted for the SLR of randomised controlled trials (RCTs) and the SLR of observational studies used to identify clinical efficacy and safety evidence.

Database searches for the SLR of RCTs were conducted in July 2019, then updated in October 2020 and December 2020. Summaries of the resources searched are provided in Table 3.1, Table 3.2, and Table 3.3. Searches for the SLR of observational studies were conducted in August 2020. A summary of the resources searched is provided in Table 3.4.

Table 3.1: Resources searched for the SLR of RCTs. July 2019.

Search strategy element	Resource	Host/Source	Date Range	Date searched
Databases	Embase	Ovid	NR	9 July 2019
	MEDLINE, MEDLINE In-Process	Ovid	NR	9 July 2019
	CCTR	Ovid	-	9 July 2019
	LILACS	NR	NR	9 July 2019
Conference Proceedings	SABCS	NR	NR	NR
	ASCO	NR	NR	NR
	ESMO	NR	NR	NR
	AACR	NR	NR	NR
	SG-BCC	NR	NR	NR
Clinical Trials Registries	ClinicalTrials.gov	https://clinicaltrials.gov/	-	NR
	WHO ICTRP	https://trialsearch.who.int/	-	NR
	ANZCTR	https://anzctr.org.au/TrialSearch.aspx	-	NR

CCTR = Cochrane Central Register of Controlled Clinical Trials; LILACS = Latin American and Caribbean Health Sciences Literature; NR = not reported; SABCS = San Antonio Breast Cancer Symposium; ASCO = American Society of Clinical Oncology; ESMO = European Society for Medical Oncology; AACR = American Association for Cancer Research; SG-BCC = St. Gallen Consensus International Breast Cancer Conference; ANZCTR = Australian New Zealand Clinical Trials Registry

Table 3.2: Resources searched for the SLR of RCTs. October 2020 update.

Search strategy element	Resource	Host/Source	Date Range	Date searched
Databases	Embase	Ovid	NR	22 Oct 2020
	MEDLINE, MEDLINE In-Process	Ovid	NR	22 Oct 2020
	CCTR	Ovid	-	22 Oct 2020
	LILACS	NR	NR	22 Oct 2020
Conference Proceedings	SABCS	NR	NR	NR
	ASCO	NR	NR	NR
	ESMO	NR	NR	NR
	AACR	NR	NR	NR
	SG-BCC	NR	NR	NR
Clinical Trials Registries	ClinicalTrials.gov	https://clinicaltrials.gov/	-	NR
	WHO ICTRP	https://trialsearch.who.int/	-	NR
	ANZCTR	https://anzctr.org.au/TrialSearch.aspx	-	NR

CCTR = Cochrane Central Register of Controlled Clinical Trials; LILACS = Latin American and Caribbean Health Sciences Literature; NR = not reported; SABCS = San Antonio Breast Cancer Symposium; ASCO = American Society of Clinical Oncology; ESMO = European Society for Medical Oncology; AACR = American Association for Cancer Research; SG-BCC = St. Gallen Consensus International Breast Cancer Conference; ANZCTR = Australian New Zealand Clinical Trials Registry

Table 3.3: Resources searched for the SLR of RCTs. December 2020 update.

Search strategy element	Resource	Host/Source	Date Range	Date searched
Databases	Embase	Ovid	NR	18 Dec 2020
	MEDLINE, MEDLINE In-Process	Ovid	NR	18 Dec 2020
	CCTR	Ovid	-	18 Dec 2020
	LILACS	NR	NR	18 Dec 2020
Conference Proceedings	SABCS	NR	NR	NR
	ASCO	NR	NR	NR
	ESMO	NR	NR	NR
	AACR	NR	NR	NR
	SG-BCC	NR	NR	NR
	ClinicalTrials.gov	https://clinicaltrials.gov/	-	NR

Clinical Trials Registries	WHO ICTRP	https://trialsearch.who.int/	-	NR
	ANZCTR	https://anzctr.org.au/TrialSearch.aspx	-	NR
CCTR = Cochrane Central Register of Controlled Clinical Trials; LILACS = Latin American and Caribbean Health Sciences Literature; NR = not reported; SABCS = San Antonio Breast Cancer Symposium; ASCO = American Society of Clinical Oncology; ESMO = European Society for Medical Oncology; AACR = American Association for Cancer Research; SG-BCC = St. Gallen Consensus International Breast Cancer Conference; ANZCTR = Australian New Zealand Clinical Trials Registry				

ERG comment:

- The selection of databases searched was comprehensive. Full details of the database searches, including the database name, host platform and date searched, were provided.
- Trials registers were searched, but details of the search strategies or search terms used, dates of searches, and results were not reported in the CS. Full details of the search strategies used were provided in response to the ERG clarification letter.
- Conference proceedings were searched. The search strategies or search terms used, date of searches, and results, were not reported in the CS. In response to the ERG clarification letter details of the search terms used were provided.
- The search strategies included truncation, proximity operators, synonyms, and subject headings (MeSH and EMTREE). There were no language or date limits.
- The facet of search terms used for 'early stage' could have been improved by including more search terms and synonyms, for instance, HER2 negative, recurrence, locally advanced, non-metastatic, etc.
- The facet of search terms for drug interventions did not include all of the drugs used in standard endocrine therapy in the UK, listed as the comparator in the NICE scope. For example, everolimus was not included in either SLR search strategy. Nor did the facet include generic terms for endocrine therapy (endocrine treatment, endocrinotherapy, hormone therapy, etc.) or for combination drugs (CDK 4/6 inhibitors).
- The drug interventions facet would have benefited from the inclusion of Subject Indexing terms (MeSH and EMTREE), synonyms and registry numbers.
- The drug interventions included in the SLR of RCTs search strategies did not match those included in the SLR of observational studies search strategies.
- Study design search filters for RCTs were included in the search strategies. The RCT filters used were acknowledged (Cochrane RCT filters), though full citation details were not provided.[7]
- An RCT filter was included in the CCTR search. As this is a database of controlled clinical trials, the ERG believes it was not necessary to include this filter, as it may have unnecessarily restricted the results retrieved.
- Separate searches for safety data were not conducted. It is unlikely that efficacy searches that include study design filters for RCTs and observational studies will be sensitive enough to identify safety data. Ideally, searches for AEs should be carried out alongside the searches for efficacy.[8]
- Boolean operators were incorrectly used in the first line of the LILACS search strategy.
- The second update searches were conducted in December 2020. An update of the searches immediately prior to submission to NICE would have been appropriate and could have identified potentially relevant studies published since December 2020.

- The two update searches used the 'date created' field to limit the search so that only studies added since the previous search were identified. This field is not static; it changes when there are database updates. It would have been better to have used the 'entry date' field. Best practice would be to run searches without any date limits and deduplicate against the previous search results.
- The short time frame between the two update searches (October 2020 and December 2020) was explained in appendix D. Key data were disclosed shortly after the October update searches had been conducted, so a further update search was conducted to capture those data.

As the CS SLR for RCTs did not identify relevant evidence, the company conducted an additional SLR to identify observational studies. Database searches for this SLR of observational studies were conducted in August 2020.

Table 3.4: Resources searched for the SLR of observational studies. August 2020.

Search strategy element	Resource	Host/Source	Date Range	Date searched
Databases	Embase	ProQuest	NR	28 Aug 2020
	MEDLINE	ProQuest	NR	28 Aug 2020
Conference Proceedings	ASCO	Embase via ProQuest	NR	28 Aug 2020
	ESMO	Embase via ProQuest	NR	28 Aug 2020
	EBCC	NR	NR	28 Aug 2020

ASCO = American Society of Clinical Oncology; ESMO = European Society for Medical Oncology; EBCC = European Breast Cancer Congress; NR = not reported

ERG comment:

- Systematic searches should be as extensive as possible, but only two databases were searched for the SLR of observational studies.
- Full details of the database searches, including the database name, host platform and date searched, were provided.
- Conference proceedings were searched via Embase. The main Embase search for observational studies omitted conference abstracts, and an additional search was conducted to identify abstracts from named conferences of interest. This search did not include the drug interventions facet, so was more sensitive. The methods section (D.2.2) listed three conferences, but the Embase search strategy only included two (ASCO and ESMO). It was not clear if the missing conference (EBCC) was searched elsewhere.
- The search facet for drug interventions did not include all of the drugs included in standard ET in the UK, listed as the comparator in the NICE scope.
- The drug interventions included in the SLR of observational studies search strategies did not match with those included in the SLR of RCTs search strategies.
- Study design search filters for observational studies produced by Scottish Intercollegiate Guidelines Network (SIGN) were included in the search strategies, and cited in detail, as good practice recommends.[7]
- The searches were conducted in August 2020. An update of the searches immediately prior to submission to NICE would have been appropriate and could have identified potentially relevant studies published since August 2020.

3.1.2 Inclusion criteria

The eligibility criteria used in the search strategy for RCTs and non-RCTs is presented in Table 3.5.

Table 3.5: Eligibility criteria used in search strategy for RCT and non-RCT evidence

Study Characteristic	Inclusion	Exclusion
Patient population	Patients: aged ≥18 years HR+ (i.e. ER+/PR−, ER−/PR+, and ER+/PR+) HER2− (if reported) or unknown HER2 status[a] non-metastatic (early–locally advanced) and invasive breast cancer any menopausal status	Patients with: evidence of distant metastases DCIS only inflammatory breast cancer and recurrent locally advanced breast cancer For mixed populations (HR/HER2 status): Exclude if <50% of population HR+ Exclude if >20% of population HER2+
Intervention	Tamoxifen Letrozole Anastrozole Exemestane Abemaciclib + ET Palbociclib + ET Ribociclib + ET Everolimus + ET Combination of above treatments with LHRH or GnRH agonists will be included	Any other treatment
Comparators	Any of the above-listed interventions Placebo No treatment	Any other treatment
Outcomes	Efficacy Invasive disease-free survival (IDFS)[b] Disease-free survival (DFS) Distant relapse-free survival (DRFS) Locoregional recurrence-free survival (LRRFS) Overall survival (OS) Safety Overall (any cause) discontinuation Discontinuation due to adverse events (AEs) Discontinuation due to serious AEs (SAEs) Treatment-related death Death The overall incidence of Grade 3-5 (CTCAE) Anaemia Constipation Diarrhoea	NA

Study Characteristic	Inclusion	Exclusion
	Fatigue/asthenia Febrile neutropenia Infections Leukopenia Nausea/vomiting Neutropenia Pulmonary embolism (PE, including VTE) Thrombocytopenia Interstitial lung disease SAE Health-related quality of life (HRQoL)[c] EQ-5D[d] FACT-B FACT-ES FACIT - fatigue, cognitive items, bladder symptoms	
Study design	RCTs	Non-randomised study PK/PD studies Case reports/series Commentaries, letters, editorials, opinions Guidelines/consensus statements Observational study design
Language	All languages Non-English language papers will have an additional screening before the full translation	NA

Source: Table 1, Appendix D.[9]

Footnotes: a HER2 is often not reported in older studies as this may not have been the standard procedure and such studies were not excluded. b Components of IDFS: Distant events/locoregional events were not extracted. The scope of SLR was expanded to include DFS outcome irrespective of the definition to check for the similarity in definitions across the studies. c Instruments reporting HRQoL were not limited to those listed in the table. These were noted in data extraction for future reference, full extraction of these data was not required as per agreed protocol. d Both EQ-5D-5L and EQ-5D-3L were included; 3L and/or 5L were specified in data extraction.

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; DCIS = ductal carcinoma in-situ; DFS = disease-free survival; DRFS = distant relapse-free survival EQ-5D = EuroQol-5D; ER = oestrogen receptor; ET = endocrine therapy; FACIT = Functional Assessment of Chronic Illness Therapy; FACT-B = Functional Assessment of Cancer Therapy-Breast Cancer; FACT-ES = Functional Assessment of Cancer Therapy-Endocrine Subscale; GnRH = gonadotropin-releasing hormone; HER2 = human epidermal growth factor receptor 2; HER2- = human epidermal growth factor receptor 2 negative; HER2+ = human epidermal growth factor receptor 2 positive; HR = hormone receptor; HR+ = hormone receptor positive; HRQoL = health-related quality of life; IDFS = invasive disease-free survival; LHRH = luteinising hormone-releasing hormone; LRRFS = locoregional recurrence-free survival; NA = not applicable; OS = overall survival; PD = pharmacodynamics; PE = pulmonary embolism; PK = pharmacokinetics; PR = progesterone receptor; RCTs = randomised controlled trials; SAE = serious adverse event; VTE = venous thromboembolism

ERG comment: The inclusion criteria are consistent with the scope.

3.1.3 Critique of data extraction

It was reported that this conducted by "two independent reviewers".[9]

ERG comment: This was conducted appropriately.

3.1.4 Quality assessment

It was reported that this conducted by "two independent reviewers".[9]

ERG comment: This was conducted appropriately.

3.1.5 Evidence synthesis

Overall, 164 publications presenting data on 37 RCTs evaluating adjuvant ET-based regimens were included in the SLR.[9]

ERG comment: Examining Table 17, Appendix D, apart from two trials of palbociclib, it appears that the other 35 RCTs compared treatments that are included in the scope in the form of ET.[9] However, the ERG accepts that monarchE RCT already provides a comparison with ET. Of course, if that had been a single form of ET then potentially an indirect comparison could have been possible with another form of ET via one of the other RCTs. However, the comparator in monarchE was investigator choice of ET (tamoxifen, toremifene, letrozole, anastrozole or exemestane). Therefore, the ERG considers that such an indirect comparison is not feasible because the investigator choice comparator is not common to any of the other RCTs.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The SLR identified one RCT for abemaciclib for which published literature was available, monarchE. The CS also reported that Lilly holds further unpublished data on file which is presented in the appraisal.

3.2.1 monarchE design and quality assessment

Summaries of the design and quality assessment of monarchE are presented in Tables 3.6 and 3.7.

Table 3.6: monarchE design

Category of design	Details
Study design	Parallel group, active controlled, open-label, global, randomised, phase III trial
Population	Patients with HR+, HER2−, node-positive eBC at high risk of recurrence (N=5,637) The ITT population in monarchE includes two Cohorts: **Cohort 1** Which enrolled 5,120 patients who were considered to be at high risk of recurrence based on clinical and pathological features defined as pathological tumour involvement in ≥4 ipsilateral ALNs, or pathological tumour involvement in 1–3 ALNs as well as either: Grade 3 disease (defined as at least 8 points on the Bloom Richardson grading system) Primary tumour size ≥5 cm **Cohort 2** Which enrolled 517 patients who were considered high risk based on pathological tumour involvements in 1–3 ALNs and a high (≥20%) Ki-67 index. This submission focusses on the ITT population of monarchE as this is generalisable to UK clinical practice and aligned to the monarchE statistical analysis plan.
Intervention(s)	Abemaciclib (150 mg twice daily on a continuous dosing schedule) for up to 2 years + ET (tamoxifen, toremifene, letrozole anastrozole or exemestane, with or without ovarian suppression) for 5 to 10 years
Comparator(s)	ET (tamoxifen, toremifene, letrozole anastrozole or exemestane; with or without ovarian suppression) for 5 to 10 years
Location	monarchE was an international, multicentre trial conducted in 611 centres across 38 countries: Argentina, Australia, Austria, Belgium, Brazil, Canada, China, Czech Republic, Denmark, Finland, France, Germany, Greece, Hong Kong, Hungary, India, Israel, Italy, Japan, Republic of Korea, Mexico, Netherlands, New Zealand, Poland, Portugal, Puerto Rico, Romania, Russia, Saudi Arabia, Singapore, South Africa, Spain, Sweden, Taiwan, Turkey, Ukraine, **United Kingdom** and United States of America.
Trial design	Phase III, randomised, open-label study of abemaciclib with standard adjuvant ET (abemaciclib + ET) versus standard adjuvant ET alone in patients with high risk, node-positive, early-stage HR+/HER2− breast cancer.

Category of design	Details
Duration of study	The trial included a 2-year on-study treatment period (study years 1 and 2), in which patients in the abemaciclib + ET arm could receive abemaciclib for up to 2 years, or until meeting a discontinuation criterion, and all patients received ET. After this on-study treatment period, all patients entered a long-term follow-up period of up to 8 years (overall study year 10), in which they received ET for at least 3 years (overall study year 5) if medically appropriate, and for up to 8 years (overall study year 10) as medically indicated.
Method of randomisation	Patients were randomly assigned to receive abemaciclib with ET or ET alone in a 1:1 ratio. Randomisation was performed using an interactive, web-based randomisation scheme (IWRS) and was stratified according to: Prior treatment (neoadjuvant chemotherapy versus adjuvant chemotherapy versus no chemotherapy) Menopausal status (premenopausal versus postmenopausal, as determined by investigator and based on patient's status at the time of diagnosis) Region (North America and Europe versus Asia versus Other)
Method of blinding	This was an open-label study. Toxicities and laboratory abnormalities related to abemaciclib treatment, such as diarrhoea, neutropenia, and creatinine increase, have the potential to unblind investigators to treatment allocation, justifying an open-label design. In order to maintain the study integrity, the sponsor was blinded to treatment group assignments until the study reached a positive outcome. An independent data monitoring committee was responsible for reviewing the unblinded safety and efficacy analyses. In addition, access to the study data was strictly controlled prior to the study reaching a positive outcome and will continue to be controlled throughout the entire study.
Primary endpoints (including scoring methods and timings of assessments)	The primary efficacy measure was IDFS, as defined by the STEEP system. IDFS time was measured from the date of randomisation to the date of first occurrence of: Ipsilateral invasive breast tumour recurrence Regional invasive breast cancer recurrence Distant recurrence Death attributable to any cause Contralateral invasive breast cancer Second primary non-breast invasive cancer IDFS was assessed at every visit and as clinically indicated until distant disease recurrence or death Patients for whom no event was observed were censored on the day of their last assessment for recurrence, or date of randomisation if no post-baseline clinic visit occurred.

Category of design	Details
	Assessments were also performed for patients who discontinued treatment without an IDFS event per STEEP criteria or who were randomised but never received study treatment.
Secondary endpoints (including scoring methods and timings of assessments)	**Efficacy:** IDFS, as defined by the STEEP system, for two prespecified groups with high Ki-67: Patients in the ITT population with pre-treated Ki-67 index ≥20% by a central laboratory In patients in Cohort 1 with pre-treated Ki-67 ≥20% by a central laboratory DRFS, defined as the time from randomisation to distant recurrence or death from any cause, whichever occurred first. For patients who experienced an IDFS event other than distant recurrence or death, assessments continued to be performed until an event of distant recurrence, death, or study completion, whichever occurred first. OS, defined as the time from randomisation until death from any cause PK/PD assessments **Safety:** During the study, all AEs were recorded and graded at every visit according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Any AEs resulting in dose reduction or discontinuation of treatment was reported and noted. AEs were assessed at all clinical visits and over the phone between clinical visits TEAEs, SAEs and hospitalisations. SAEs were defined as any AE that resulted in one of the following outcomes: Death Initial or prolonged inpatient hospitalisation A life-threatening experience (that is, immediate risk of dying) Persistent or significant disability/incapacity Congenital anomaly/birth defect Considered significant by the investigator for any other reason: important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered serious, based upon appropriate medical judgment Laboratory measurements Vital signs: Signs including blood pressure (systolic and diastolic), pulse rate, respiratory rate, temperature, BMI, and weight were collected at regular intervals during the study.

Category of design	Details
	Physical examinations PK/PD assessments **Patient-reported outcomes:** Patients completed paper versions of the PROs questionnaires at the planned visits for administration. The self-reported questionnaires were administered in countries where the questionnaires were translated into the native language of the region and linguistically validated. PROs were collected on day 1 of the study treatment period, at months 6, 9, 15, 21 and 27, 30 days post treatment discontinuation and during the first and second long-term follow-up visit FACT-B 37-item questionnaire Endocrine therapy-specific symptoms: FACT-ES 19-item subscale 2 FACIT-sourced items of cognitive symptoms 3 FACIT-sourced items for bladder symptoms Fatigue during abemaciclib, ET, or both via FACIT-F 13-item subscale EQ-5D-5L
Source: Tables 3 and 4 from CS[2] AE: adverse event; CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; CYP3A4: cytochrome P450 3A4; ET: endocrine therapy; EQ-5D-5L: EuroQol-5 Dimensions-5 Levels FACIT: Functional Assessment of Chronic Illness Therapy; FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-B: Functional Assessment of Cancer Therapy – Breast; FACTES: Functional Assessment of Cancer Therapy – Endocrine Subscale; GnRH: gonadotropin-releasing hormone; HER2−: human epidermal growth factor receptor-2 negative; HR+: hormone receptor positive; IDFS: invasive disease-free survival; IWRS: interactive, web-based randomisation scheme; PD: pharmacodynamics; PK: pharmacokinetics; PRO: patient reported outcome; SAE: serious adverse event; STEEP: standardised definitions for efficacy end points in adjuvant breast cancer trials; TEAE: treatment-emergent adverse event	

Table 3.7: Quality assessment of the monarchE trial

	monarchE
	Risk of bias
Bias arising from randomisation process	Low
Random allocation sequence	Yes

Allocation sequence concealed	Yes
Baseline differences	Probably no
Bias due to deviations from intended interventions – effect of assignment to intervention	Some concerns
Participant awareness	Yes
Delivery awareness	Yes
Deviations due to context	No information
Deviation balancing	NA
Affected outcomes	NA
Appropriate analysis	Yes
Substantial impact	NA
Bias due to deviations from intended interventions – effect of adhering to intervention	Low
Adherence participant awareness	Yes
Adherence delivery awareness	Yes
Adherence balancing	NA
Adherence affected outcome	NA
Non-adherence affected outcome	NA
Appropriate analysis	NA
Risk of bias due to missing outcome data	Low
Data randomised	Yes
No bias from missing data	NA
Missingness dependency	NA
Missingness likelihood	NA
Bias in measurement of the outcome	Low
Inappropriate method	No
Outcome difference	No
Assessor awareness	Yes

Assessment influence	Probably no
Influence likelihood	NA
Bias in selection of the reported result	Low
Appropriate analysis	Probably yes
Multiple outcomes	Probably no
Multiple analyses	Probably no
Overall bias	Some concerns

ERG comment: The monarchE study is useful to decision making in being randomised, relatively large and comparing the intervention in the NICE scope to comparators largely in line with NHS clinical practice. Lack of blinding does imply some concern regarding risk of bias.

3.2.2 monarchE eligibility criteria, baseline characteristics and treatments received

Summaries of the eligibility criteria, baseline characteristics and treatments received pertaining to monarchE are presented in Tables 3.8 to 3.11.

Table 3.8: Key eligibility criteria for monarchE

Key inclusion criteria	Key exclusion criteria
Male or female aged 18 years or older Confirmed HR+, HER2−, resected invasive EBC without metastases Undergone definitive surgery of primary breast tumour and randomised within 16 months of surgery ECOG PS ≤1 Adequate organ function Appropriate washout period for any adjuvant chemotherapy and/or radiotherapy and recovered from acute side effects prior to randomisation If on standard adjuvant ET at study entry, may receive up to 12 weeks of ET until randomisation following the previous non-ET (surgery, chemotherapy, or radiation), whichever is last Fulfil one of the following criteria: **Cohort** 1: Pathological tumour involvement in ≥4 ipsilateral axillary lymph nodes, or pathological tumour involvement in 1 to 3 ipsilateral axillary lymph node(s) *and at least one of the following indicating higher risk of recurrence:* Grade 3 disease or primary tumour size ≥5 cm **Cohort 2:** Pathological tumour involvement in 1 to 3 ipsilateral axillary lymph node(s) *and* Ki-67 index of ≥20%[b]	Metastatic disease, node-negative BC, inflammatory BC Previous history of BC with the exception of ipsilateral ductal carcinoma in situ treated by locoregional therapy alone ≥5 years ago Pregnant or lactating Concurrent exogenous reproductive hormone therapy (that is, birth control, hormone replacement therapy, or megestrol acetate) Previous exposure to CDK4 and CDK6 inhibitors Prior ET for BC prevention or raloxifene History of any other cancer[a] Any previous history of venous thromboembolic event Active systemic infections or viral load
Source: Table 5, CS[2] BC: breast cancer; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ET: endocrine therapy; HER2−: human epidermal growth factor receptor-2 negative; HR+: hormone receptor positive [a]Exception: nonmelanoma skin cancer or carcinoma in situ of the cervix, unless in complete remission with no therapy for ≥5 years; [b]Ki67 index was measured by a central laboratory	

ERG comment: As discussed in Section 2.1, there is ambiguity in what constitutes high risk and the extent to which the criteria applied in NHS clinical practice will match those of the monarchE trial as well as each of the Cohorts. Table 3.8 indicates a threshold in terms of lymph node involvement, depending on Grade (histology) and tumour size. However, NG101 states no lymph node threshold, and suggests that lymph node involvement can be consistent with medium as opposed to high risk (Section 1.7.6).[5] Given the ambiguity of those criteria, it is difficult to assess the generalisability of the monarchE trial to NHS clinical practice, which implies that this is a Key Issue.

Table 3.9: monarchE baseline characteristics

Characteristic[a]	Abemaciclib + ET (N=2,808)	ET alone (N=2,829)
Sex, n (%)	**n=2,808**	**n=2,829**
Female, n (%)	2,787 (99.3)	2,814 (99.5)
Male, n (%)	21 (0.7)	15 (0.5)
Age, years	**n=2,808**	**n=2,829**
Mean (SD)	[redacted]	[redacted]
Median (min, max)	51.0 (23, 89)	51.0 (22, 86)
Race, n (%)	**n=**[redacted]	**n=**[redacted]
American Indian or Alaska Native	[redacted]	[redacted]
Asian	675 (24.4)	669 (24.0)
Black or African American	[redacted]	[redacted]
Native Hawaiian or Other Pacific Islander	[redacted]	[redacted]
White	1,947 (70.3)	1,978 (71.0)
Multiple	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Region, n (%)	**n=2,808**	**n=2,829**
North America/Europe	1,470 (52.4)	1,479 (52.3)
Asia	574 (20.4)	582 (20.6)
Other	764 (27.2)	768 (27.1)
Ethnicity, n (%)[b]	**n=**[redacted]	**n=**[redacted]
Hispanic or Latino	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Menopausal status, n (%)	**n=2,803**	**n=2,829**
Premenopausal	1,221 (43.5)	1,232 (43.5)
Postmenopausal	1,587 (56.5)	1,597 (56.5)
Baseline ECOG PS, n (%)	**n=**[redacted]	**n=**[redacted]
0	2,405 (85.7)	2,369 (83.8)
1	401 (14.3)	455 (16.1)
2	[redacted]	[redacted]
3	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Weight (kg)	**n=**[redacted]	**n=**[redacted]
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
BMI (kg/m^2)	**n=**[redacted]	**n=**[redacted]
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]

Characteristic[a]	**Abemaciclib + ET (N=2,808)**	**ET alone (N=2,829)**
Missing	[redacted]	[redacted]
Country, n (%)	**n=**[redacted]	**n=**[redacted]
United Kingdom	[redacted]	[redacted]
Initial pathological diagnosis		
Invasive ductal breast carcinoma	[redacted]	[redacted]
Breast cancer, not otherwise specified	[redacted]	[redacted]
Invasive lobular breast carcinoma	[redacted]	[redacted]
Mucinous breast carcinoma	[redacted]	[redacted]
Invasive papillary breast carcinoma	[redacted]	[redacted]
Inflammatory carcinoma of the breast	[redacted]	[redacted]
Medullary carcinoma of the breast	[redacted]	[redacted]
Tubular breast carcinoma	[redacted]	[redacted]
Paget's disease of nipple	[redacted]	[redacted]
Metastatic breast carcinoma	[redacted]	[redacted]a
Missing	[redacted]	[redacted]
Primary tumour size by radiology prior to any systemic treatment, n	n=[redacted]	n=[redacted]
<20 mm	[redacted]	[redacted]
≥20 mm but <50 mm	[redacted]	[redacted]
≥50 mm	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Primary tumour size by pathology after definitive surgery	n=2,760	n=2,796
<20 mm	781 (27.8)	767 (27.1)
≥20 mm but <50 mm	1,372 (48.9)	1,419 (50.2)
≥50 mm	607 (21.6)	610 (21.6)
Missing	48 (1.7)	33 (1.2)
Involvement of ipsilateral supraclavicular, ipsilateral infraclavicular, or ipsilateral internal mammary nodes at initial diagnosis		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Axillary lymph node evaluation		
Positive	2,800 (99.7)	2,822 (99.8)
Negative	7 (0.2)	7 (0.2)
Missing	[redacted]	0
Number of positive lymph nodes		
0	7 (0.2)	7 (0.2)
1-3	1,118 (39.8)	1,142 (40.4)

4-9	[redacted]	[redacted]
≥10	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Histopathological diagnosis grade		
G1 – favourable	209 (7.4)	216 (7.6)
G2 – moderately favourable	1,377 (49.0)	1,395 (49.3)
G3 – unfavourable	1,086 (38.7)	1,064 (37.6)
GX – cannot be accessed	126 (4.5)	141 (5.0)
Missing	10 (0.4)	13 (0.5)
Disease stage at initial diagnosis		
Stage IA	2 (0.1)	1 (0.0)
Stage IIA	324 (11.5)	353 (12.5)
Stage IIB	392 (14.0)	387 (13.7)
Stage IIIA	1,029 (36.6)	1,026 (36.3)
Stage IIIB	99 (3.5)	88 (3.1)
Stage IIIC	950 (33.8)	963 (34.0)
Missing	[redacted]	[redacted]
Oestrogen receptor status		
Positive	2,786 (99.2)	2,810 (99.3)
Negative	16 (0.6)	17 (0.6)
Unknown	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Progesterone receptor status		
Positive	2,426 (86.4)	2,456 (86.8)
Negative	298 (10.6)	295 (10.4)
Unknown	[redacted]	[redacted]
Missing	[redacted]	[redacted]
HER2 status at initial diagnosis		
Positive	[redacted]	[redacted]
Negative	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Central lab Ki-67 results from untreated tumour (%)		
<20%	953 (33.9)	974 (34.4)
≥20%	1,262 (44.9)	[redacted]
Missing	[redacted]	[redacted]
Not applicable[b]	[redacted]	[redacted]
Not evaluable[c]	[redacted]	[redacted]

Source: Table 6, CS[2]
BMI: body mass index; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ET: endocrine therapy; ITT: intent-to-treat; max: maximum; min: minimum; N: number of patients in the ITT population; n: number of patients within category; SD: standard deviation; % = percentage

[a]Number of patients with non-missing data, used as denominator; [b]Only includes responses from US sites, n is the number of subjects with a value of "HISPANIC OR LATINO" or "NOT HISPANIC OR LATINO".

Table 3.10: Prior therapy and surgery for breast cancer monarchE ITT population

Prior Therapy, n (%)	Abemaciclib + ET (N=2,808)	ET alone (N=2,829)	Total (N=5,637)
Prior anticancer therapy			
Surgical procedure	[redacted]	[redacted]	[redacted]
Radiotherapy	2680 (95.4)	2700 (95.4)	5380 (95.4)
Systemic therapy	[redacted]	[redacted]	[redacted]
Surgical procedure: intent			
Curative intent	[redacted]	[redacted]	[redacted]
Radiotherapy: reason			
Neoadjuvant	71 (2.5)	82 (2.9)	153 (2.7)
Adjuvant	2,620 (93.3)	2,628 (92.9)	5,248 (93.1)
Systemic therapy: reason and type			
Neoadjuvant	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]
ET[a]	[redacted]	[redacted]	[redacted]
Other[b]	[redacted]	[redacted]	[redacted]
Target[c]	[redacted]	[redacted]	[redacted]
Adjuvant	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]
ET[a]	[redacted]	[redacted]	[redacted]
Other[b]	[redacted]	[redacted]	[redacted]
Target[c]	[redacted]	[redacted]	[redacted]
Term to be coded	[redacted]	[redacted]	[redacted]

ET: endocrine therapy; N: number of patients in the ITT population; n: number of patients within category; % = percentage

Table 3.11: Summary of endocrine treatments in the monarchE safety population

n, (%)	Abemaciclib + ET (N=2,791)		ET (N=2,800)	
	At start of study	Any time	At start of study	Any time
Aromatase inhibitors	[redacted]	[redacted]	[redacted]	[redacted]
Anastrozole	[redacted]	[redacted]	[redacted]	[redacted]
Exemestane	[redacted]	[redacted]	[redacted]	[redacted]
Letrozole	[redacted]	[redacted]	[redacted]	[redacted]
Anti-oestrogens	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	[redacted]	[redacted]	[redacted]	[redacted]
Toremifene	[redacted]	[redacted]	[redacted]	[redacted]
GnRH Analogues	[redacted]	[redacted]	[redacted]	[redacted]
Goserelin	[redacted]	[redacted]	[redacted]	[redacted]
Leuprorelin	[redacted]	[redacted]	[redacted]	[redacted]
Triptorelin	[redacted]	[redacted]	[redacted]	[redacted]

ET: endocrine therapy; N: number of patients in the ITT population; n: number of patients within category; % = percentage

ERG comment: In response to request for clarification the company provided a comparison between UK and all patients in the trial (See Table 3.12).

Table 3.12: Type and distribution of ET received in the monarchE safety population and the monarchE UK patients

	Premenopausal women		Postmenopausal women	
	monarchE safety population (N=2,431)	monarchE UK patients (N=103)	monarchE safety population (N=3,156)	monarchE UK patients (N=97)
Aromatase inhibitor	41%	33%	89%	88%
Tamoxifen/Toremifene	58%	67%	11%	12%

Source: company response to clarification, Table 12.[4]
N: number of patients in the ITT population; UK: United Kingdom

Given that the percentages of aromatase inhibitor or tamoxifen/toremifene sum almost precisely to 100%, it looks like patients either received an aromatase inhibitor or tamoxifen/toremifene. Although the percentage who received tamoxifen is higher, it seems strange to the ERG that such a high proportion of patients in the UK received an aromatase inhibitor instead of tamoxifen given that NG101 specifies only the latter.[5] For postmenopausal women the UK and all patients' percentages are almost identical. What is unclear is whether the percentage receiving tamoxifen/toremifene is consistent with intolerance or contraindication as stated in NG101. Therefore, this remains a Key Issue. The ERG recommends a subgroup analysis by ET within each of the menopausal status subgroups e.g. to estimate all efficacy outcomes for patients who are both premenopausal and received tamoxifen separately to patients who are both premenopausal and received an aromatase inhibitor.

3.2.3 monarchE efficacy

Results for the primary endpoint (IDFS), secondary endpoints (DRFS) and OS and patient-reported outcomes (e.g., functional assessment of cancer therapy and HRQoL) were provided in the CS. Results from three data cuts were reported, including: the interim analysis (IA) 2 (16th March 2020); primary outcome (PO) analysis (8th July 2020); and additional follow-up (AFU) 1 analysis (1st April 2021). The proportions of patients completing the 2-year study period at IA2, PO analysis and AFU1 were 12.5%, 25.5% and 72.2% respectively.[2]

A summary of results across the three data cut points were presented for IDFS in the CS documentation overall. Otherwise, Document B of the CS (and this report) focus mainly on results from the most recent data cut for each endpoint[2] whilst details of results from earlier data cuts are provided in Appendix L.2 of the CS.[9]

3.2.3.1 monarchE: invasive disease-free survival

A summary of results across the three data cut points are presented for IDFS in Table 3.13.[9]

The hazard ratio (HR) estimates derived from both stratified (for geographical region, prior treatment and menopausal status) and unstratified analyses in Table 3.13 suggest a more favourable outcome in terms of IDFS for patients receiving abemaciclib + ET compared with ET alone at all three data cut points (IA2, PO and AFU1).[2]

In terms of the IDFS rate, no between-group differences were observed at 12 months for any cut point however, more favourable outcomes were apparent for patients receiving abemaciclib + ET compared with ET alone at 24 months for all three data cut points. At 36 months, the only evaluable data were at AFU1 where the between-group difference was in favour of abemaciclib + ET.[2]

Further details of estimates for IDFS in the ITT population at AFU1 is presented in Table 3.14. Events were presented as deaths without invasive disease and invasive disease only.[2]

In order to assess the effect of abemaciclib over time, a piecewise analysis was undertaken (Table 3.15). HR estimates for three time periods (up to 1 year, 1 to 2 years and over 2 years, i.e., beyond the study period) all suggested more favourable IDFS outcomes for abemaciclib + ET compared with ET alone. The analysis of Kaplan-Meier survival curves in Figure 3.1 also suggests a result in favour of abemaciclib + ET over time (all patients censored at 45 months).[2]

A secondary analysis of IDFS at AFU1 for patients with high levels of the protein biomarker Ki-67 is reported in Section B.2.6.3 of the CS[2] but is not presented here given that it is not part of the NICE scope and does not appear to affect choice of comparator.

Table 3.13: Summary of investigator assessed IDFS in the monarchE ITT population at IA1, PO and AFU1

	IA2			PO			AFU1		
	Abemaciclib + ET (N=2,808)	ET alone (N=2,829)	Treatment Effect/Difference 2-sided p-value[c]	Abemaciclib + ET (N=2,808)	ET alone (N=2,829)	Treatment Effect/Difference 2-sided p-value[c]	Abemaciclib + ET (N=2,808)	ET alone (N=2,829)	Treatment Effect/Difference 2-sided p-value (nominal)[c]
Median follow up (months)	[redacted]	[redacted]	NA	19.1	19.2	NA	[redacted]	[redacted]	NA
p-value (2-sided) log-rank, stratified[a]	Stratified: p=.00957 [redacted]			Stratified: p=0.00089 [redacted]			[redacted]		
HR (95% CI)	Stratified: 0.747 (0.598, 0.932) [redacted]			Stratified: 0.713 (0.583, 0.871)[b] [redacted]			Stratified: 0.696 (0.588, 0.823) [redacted]		
IDFS rate, % (95% CI)[b]									
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	92.3 (90.9, 93.5)	89.3 (87.7, 90.7)	3.0 [redacted]	92.7 (91.6, 93.6)	90.0 (88.8, 91.1)	2.7 [redacted]
36 months	NE	NE	NE	NE	NE	NE	88.8 (87.0, 90.3)	83.4 (81.3, 85.3)	5.4 [redacted]

Source: Table 12, CS[2]

CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; IDFS: invasive disease-free survival; ITT: intent-to-treat; IWRS: interactive web-based randomisation scheme; N: number of patients in the ITT population; NA: not applicable; NE: not evaluable

[a]Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [b]95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation; [c]Treatment Effect/Difference/p-values are computed based on comparator ET

Table 3.14: Summary of investigator assessed IDFS ITT population (AFU1 analysis)

	Abemaciclib + ET (N=2,808)	ET alone (N=2,829)	Treatment Effect/Difference 2-sided p-value (nominal)[e]
Median follow up (months)	[redacted]	[redacted]	
Number of events, n (%)	232 (8.3)	333 (11.8)	
Deaths without invasive disease	[redacted]	[redacted]	
Invasive disease	[redacted]	[redacted]	
Number of patients censored n (%)	[redacted]	[redacted]	
Invasive disease prior to randomisation	[redacted]	[redacted]	
No post-baseline assessment	[redacted]	[redacted]	
No documented invasive disease	[redacted]	[redacted]	
p-value (2-sided) log-rank, stratified[b]	[redacted]		
HR (95% CI)	Stratified: 0.696 (0.588, 0.823) [redacted]		
IDFS rate, % (95% CI)[c]			
12 months	[redacted]	[redacted]	[redacted]
24 months	92.7 (91.6, 93.6)	90.0 (88.8, 91.1)	2.7 [redacted]
36 months	88.8 (87.0, 90.3)	83.4 (81.3, 85.3)	5.4 [redacted]

Source: Table 13, CS[2]

CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; IDFS: invasive disease-free survival; ITT: intent-to-treat; IWRS: interactive web-based randomisation scheme; N: number of patients in the ITT population

[a]Restriction time is defined by the latest time where the standard error of the survival estimates are ≤0.075; [b]Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [c]95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation; [d]2-sided p-value based on normal approximation; [e]Treatment Effect/Difference/p-values are computed based on comparator ET

Table 3.15: Piecewise analysis of IDFS ITT population (AFU1 analysis)

Analysis landmark	Number of events		Piecewise HR[a] (95% CI)[b]
	Abemaciclib + ET	ET alone	
Year 0–1	[redacted]	[redacted]	[redacted]
Year 1–2	[redacted]	[redacted]	[redacted]
Year 2+	[redacted]	[redacted]	[redacted]

Source: Table 14, CS[2]

CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; IDFS: invasive disease-free survival; ITT: intent-to-treat; OS: overall survival

[a]Piecewise HR was estimated using Bayesian piecewise exponential model for the yearly hazard rate within each treatment arm; [b]95% CIs were calculated by equal tails in the posterior samples of Bayesian exponential models

Figure 3.1: Summary of the IDFS results in monarchE (AFU1 analysis)

Source: Figure 5, CS[2]
ET = endocrine therapy; HR = hazard ratio; IDFS = invasive disease-free survival; ITT = intent-to-treat

ERG comment: The ERG asked the company to provide IDFS results for the monarchE Cohort that most closely aligns with the definition generalisable to NHS clinical practice. In response, the company provided results for Cohort 1 of monarchE that included patients at high risk of recurrence, defined by clinical and pathological features (Table 3.16). The company went on to suggest that the majority of patients in UK clinical practice are expected to be identified at high risk of recurrence based on the clinical and pathological features that represent inclusion criteria for Cohort 1. However, overall the company considered the ITT population to represent the most generalisable source of evidence.[4] Scrutiny of the data in Tables 3.13 and 3.16 indicates similar findings between the ITT population and Cohort 1 with the exception that the 12-month IDFS rate is more favourable for patients treated with abemaciclib + ET versus ET alone in Cohort 1 (Table 3.16) whereas no between-group difference was apparent in the ITT population (Table 3.13).

Table 3.16: Summary of investigator assessed IDFS for Cohort 1 of monarchE

	Abemaciclib + ET	**ET alone**	**Treatment Effect/Difference 2-sided p-Value (nominal)[b]**
Number of events, n (%)	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		
IDFS rate, % (95% CI)[b]			

12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]

Source: Table 4, company's response to clarification letter.[4]

CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; IDFS: invasive disease-free survival; ITT: intent-to-treat; IWRS: interactive, web-based randomisation scheme; N: number of patients in the ITT population

[a]Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [b]Treatment Effect/Difference/p-values are computed based on comparator ET

In response to the ERG's request, the company provided IDFS data for the ITT population at AFU1 stratified by menopausal status (premenopausal and postmenopausal) (Tables 3.17 and 3.18). The HR results were consistent with the analysis of the overall population. However, although the 95% CIs overlap, the HR for premenopausal women is [redacted] than that for postmenopausal women. Also, whilst IDFS rates were [redacted] favourable for the abemaciclib + ET-treated group versus ET alone in premenopausal patients across all time points (12, 24 and 36 months), this result was only seen at later time-points for the overall ITT population (24 and 36 months) and the postmenopausal subgroup (36 months) with no between-group differences apparent at earlier time points for these populations.[4] This therefore remains a Key Issue.

Table 3.17: Summary of investigator assessed IDFS ITT population (AFU1 analysis): Premenopausal

	Abemaciclib + ET (N=1,227)	**ET alone (N=1,224)**	**Treatment Effect/Difference 2-sided p-Value (nominal)[c]**
Number of events, n (%)	[redacted]	[redacted]	
Deaths without invasive disease	[redacted]	[redacted]	
Invasive disease	[redacted]	[redacted]	
Number of patients censored, n (%)	[redacted]	[redacted]	-
Invasive disease prior to randomisation	[redacted]	[redacted]	
No post-baseline assessment	[redacted]	[redacted]	
No documented invasive disease	[redacted]	[redacted]	
p-value (2-sided) log-rank, stratified[a]	[redacted]		
HR (95% CI)	[redacted]		
IDFS rate, % (95% CI)[b]			
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]

Source: Table 8, company's response to clarification letter.[4]

CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; IDFS: invasive disease-free survival; ITT: intent-to-treat; IWRS: interactive web-based randomised scheme; N: number of patients in the ITT population [a]Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [b]95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation; [c]Treatment Effect/Difference/p-values are computed based on comparator ET

Table 3.18: Summary of investigator assessed IDFS ITT population (AFU1 analysis): Postmenopausal

	Abemaciclib + ET (N=1,576)	ET alone (N=1,605)	Treatment Effect/Difference 2-sided p-Value (nominal)[c]
Number of events, n (%)	[redacted]	[redacted]	
Deaths without invasive disease	[redacted]	[redacted]	
Invasive disease	[redacted]	[redacted]	
Number of patients censored, n (%)	[redacted]	[redacted]	
Invasive disease prior to randomisation	[redacted]	[redacted]	
No post-baseline assessment	[redacted]	[redacted]	
No documented invasive disease	[redacted]	[redacted]	
p-value (2-sided) log-rank, stratified[a]	[redacted]		
HR (95% CI)	[redacted]		
IDFS rate, % (95% CI)[b]			
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]

Source: Table 9, company's response to clarification letter.[4]
CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; IDFS: invasive disease-free survival; ITT: intent-to-treat; IWRS: interactive web-based randomised scheme; N: number of patients in the ITT population [a]Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [b]95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation; [c]Treatment Effect/Difference/p-values are computed based on comparator ET

3.2.3.2 monarchE: distant relapse-free survival

The outcome of DRFS relates to survival without metastatic recurrence of disease. Results for DRFS at PO analysis and AFU1 are summarised in Table 3.19. Stratified and unstratified HR estimates derived from both PO and AFU1 analyses suggested results in favour of abemaciclib + ET compared with ET alone. The DRFS rate did not suggest a between-group difference for either analysis at 12 months however, both estimates suggested better outcomes for those receiving abemaciclib + ET at 24 months. Estimates from the PO analysis were not evaluable at 36 months whilst the result was in favour of abemaciclib + ET at AFU1. Further detail of the analysis of DRFS at AFU1 is shown in Table 3.20.

Piecewise analysis of DRFS suggested more favourable outcomes for abemaciclib + ET compared with ET alone in terms of HR estimates covering the time periods up to 1 year and 1 to 2 years however, no between-group difference was observed for over 2 years (Table 3.21). Figure 3.2 suggests a result in favour of abemaciclib + ET over time (all patients censored at 45 months).[2]

Table 3.19: Summary of investigator assessed DRFS in the monarchE ITT population (PO and AFU1 analysis)

	PO			AFU1		
	Abemaciclib + ET (N=2,808)	ET alone (N=2,829)	Treatment Effect/Difference 2-sided p-Value[f]	Abemaciclib + ET (N=2,808)	ET alone (N=2,829)	Treatment Effect/Difference 2-sided p-value (nominal)[f]
Number of events, n (%)	131 (4.7)	193 (6.8)	NA	191 (6.8)	278 (9.8)	NA
p-value (2-sided) log-rank	Stratified p=0.00088 [redacted]			[redacted]		
HR (95% CI)	Stratified: 0.687 (0.551, 0.858) [redacted]			Stratified: 0.687 (0.571, 0.826) [redacted]		
DRFS rate, % (95% CI)[d]						
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	93.8 (92.6, 94.9)	90.8 (89.3, 92.1)	3.0 [redacted]	94.1 (93.2, 95.0)	91.6 (90.5, 92.6)	2.5 [redacted]
36 months	NE	NE	NE	90.3 (88.6, 91.8)	86.1 (84.2, 87.9)	4.2 ([redacted]

Source: Table 15, CS[2]

CI: confidence interval; DRFS: distant relapse-free survival; ET: endocrine therapy; ITT: intent-to-treat; IWRS: interactive web-response system; N: number of patients in the ITT population; n: number of patients in the specific population; NE: not evaluable

[a]For minimum and maximum, + indicates a censored observation; [b]Restriction time is defined by the latest time where the standard error of the survival estimates is ≤0.075; [c]Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [d]95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation; [e]2-sided p-value based on normal approximation; [f]Treatment Effect/Difference/p-values are computed based on comparator ET

Table 3.20: Summary of investigator assessed DRFS in the monarchE ITT population (AFU1)

	Abemaciclib + ET (N=2,808)	ET alone (N=2,829)	Treatment Effect/Difference 2-sided p-Value (nominal)[f]
Number of events, n (%)	191 (6.8)	278 (9.8)	

Death without distant relapse	[redacted]	[redacted]	
Distant relapse	[redacted]	[redacted]	
Number of patients censored, n (%)	[redacted]	[redacted]	
Distant relapse prior to randomisation	[redacted]	[redacted]	
No post-baseline assessment	[redacted]	[redacted]	
No documented distant relapse with regular assessment	[redacted]	[redacted]	
Minimum, months[a]	[redacted]	[redacted]	
25th percentile (95% CI)	[redacted]	[redacted]	
Median (95% CI) months	[redacted]	[redacted]	
75% percentile (95% CI)	[redacted]	[redacted]	
Maximum, months[a]	[redacted]	[redacted]	
p-value (2-sided) log-rank	[redacted]		
HR (95% CI)	Stratified: 0.687 (0.571, 0.826) [redacted]		
DRFS rate, % (95% CI)[d]			
12 months	[redacted]	[redacted]	[redacted]
24 months	94.1 (93.2, 95.0)	91.6 (90.5, 92.6)	2.5 [redacted]
36 months	90.3 (88.6, 91.8)	86.1 (84.2, 87.9)	4.2 [redacted]

Source: Table 16, CS[2]
CI: confidence interval; DRFS: distant relapse-free survival; ET: endocrine therapy; ITT: intent-to-treat; IWRS: interactive web-response system; N: number of patients in the ITT population; n: number of patients in the specific population
[a]For minimum and maximum, + indicates a censored observation; [b]Restriction time is defined by the latest time where the standard error of the survival estimates is ≤0.075; [c]Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [d]95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation; [e]2-sided p-value based on normal approximation; [f]Treatment Effect/Difference/p-values are computed based on comparator ET

Table 3.21: Piecewise analysis of DRFS ITT population (AFU1 analysis)

Analysis landmark	Number of events		Piecewise HR[a] (95% CI)[b]
	Abemaciclib + ET	ET alone	

Year 0–1	[redacted]	[redacted]	[redacted]
Year 1–2	[redacted]	[redacted]	[redacted]
Year 2+	[redacted]	[redacted]	[redacted]

Source: Table 17, CS[2]
CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; DRFS: distant relapse-free survival; ITT: intent-to-treat; OS: overall survival
[a]Piecewise HR was estimated using Bayesian piecewise exponential model for the yearly hazard rate within each treatment arm.; [b]95% CIs were calculated by equal tails in the posterior samples of Bayesian exponential models

Figure 3.2: Summary of the DRFS results in monarchE (AFU1 analysis)

[redacted]

Source: Figure 6, CS[2]
DRFS: distant relapse-free survival; ET: endocrine therapy; HR: hazard ratio; ITT: intent-to-treat

ERG comment: The ERG asked the company to provide DRFS results for the monarchE Cohort that most closely aligns with the definition generalisable to NHS clinical practice. In response, the company provided results for Cohort 1 of monarchE that included patients at high risk of recurrence, defined by clinical and pathological features (Table 3.22). The company went on to suggest that the majority of patients in UK clinical practice are expected to be identified at high risk of recurrence based on the clinical and pathological features that represent inclusion criteria for Cohort 1. However, overall the company considered the ITT population to represent the most generalisable source of evidence.[4] The data in Tables 3.19 and 3.22 suggest similar results for the ITT population and Cohort 1 with the exception that the 12-month DRFS rate is more favourable for patients treated with abemaciclib + ET

versus ET alone in Cohort 1 (Table 3.22) whereas no between-group difference was apparent in the ITT population (Table 3.19).

Table 3.22: Summary of investigator assessed DRFS for Cohort 1 of monarchE

	Abemaciclib + ET	ET alone	Treatment Effect/Difference 2-sided p-Value (nominal)[b]
Number of events, n (%)	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		
DRFS rate, % (95% CI)[b]			
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]

Source: Table 5, company's response to clarification letter.[4]
CI: confidence interval; DRFS: distant relapse-free survival; ET: endocrine therapy; HR: hazard ratio; ITT: intent-to-treat; IWRS: interactive, web-based randomisation scheme; N: number of patients in the ITT population
[a]Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [b]Treatment Effect/Difference/p-values are computed based on comparator ET

ERG comment: In response to the ERG's request, the company provided DRFS data for the ITT population at AFU1 stratified by menopausal status (premenopausal and postmenopausal) (Tables 3.23and 3.24). The results were consistent with the analysis of the overall population.[4] The pattern of results in terms of populations and time points was similar to that seen for IDFS. HR results for DRFS in menopausal status subgroups were consistent with those seen in the ITT overall population. However, although the 95% CIs overlap, the HR for premenopausal women is [redacted] than that for postmenopausal women. DRFS rates were [redacted] favourable for the abemaciclib + ET-treated group versus ET alone in premenopausal patients across all time points (12, 24 and 36 months) but this result was observed only at later time-points for the overall ITT population (24 and 36 months) and the postmenopausal subgroup (36 months) with no between-group differences apparent at earlier time points for these populations.[4] This therefore remains a Key Issue.

Table 3.23: Summary of Investigator-Assessed DRFS ITT Population (AFU1 analysis): Premenopausal

	Abemaciclib + ET (N=1,227)	ET alone (N=1,224)	Treatment Effect/Difference 2-sided p-Value (nominal)[d]
Number of events, n (%)	[redacted]	[redacted]	
Death without distant relapse	[redacted]	[redacted]	-
Distant relapse	[redacted]	[redacted]	
Number of patients	[redacted]	[redacted]	

censored, n (%)			
Distant relapse prior to randomisation	[redacted]	[redacted]	
No post-baseline assessment	[redacted]	[redacted]	
No documented distant relapse with regular assessment	[redacted]	[redacted]	
Minimum, months[a]	[redacted]	[redacted]	
Maximum, months[a]	[redacted]	[redacted]	
p-value (2-sided) log-rank[b]	[redacted]		
HR (95% CI)	[redacted]		
DRFS rate, % (95% CI)[c]			
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]

Source: Table 10, company's response to clarification letter.[4]
CI: confidence interval; DRFS: distant relapse-free survival; ET: endocrine therapy; HR: hazard ratio; ITT: intent-to-treat; IWRS: interactive web-based randomised scheme; N: number of patients in the ITT population; n: number of patients in the specific population.
[a]For minimum and maximum, + indicates a censored observation; [b]Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [c]95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation; [d]Treatment Effect/Difference/p-values are computed based on comparator ET.

Table 3.24: Summary of Investigator-Assessed DRFS ITT Population (AFU1 analysis): Postmenopausal

	Abemaciclib + ET (N=1,576)	**ET alone (N=1,605)**	**Treatment Effect/Difference 2-sided p-Value (nominal)[d]**
Number of events, n (%)	[redacted]	[redacted]	
Death without distant relapse	[redacted]	[redacted]	-
Distant relapse	[redacted]	[redacted]	

Number of patients censored, n (%)	[redacted]	[redacted]	
Distant relapse prior to randomisation	[redacted]	[redacted]	
No post-baseline assessment	[redacted]	[redacted]	
No documented distant relapse with regular assessment	[redacted]	[redacted]	
Minimum, months[a]	[redacted]	[redacted]	
Maximum, months[a]	[redacted]	[redacted]	
p-value (2-sided) log-rank[b]	[redacted]		
HR (95% CI)	[redacted]		
DRFS rate, % (95% CI)[c]			
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]

Source: Table 10, company's response to clarification letter.[4]
CI: confidence interval; DRFS: distant relapse-free survival; ET: endocrine therapy; HR: hazard ratio; ITT: intent-to-treat; IWRS: interactive web-based randomised scheme; N: number of patients in the ITT population; n: number of patients in the specific population
[a]For minimum and maximum, + indicates a censored observation; [b]Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [c]95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation; [d]Treatment Effect/Difference/p-values are computed based on comparator ET

3.2.3.3 monarchE: overall survival

Neither stratified nor unstratified HR estimates suggested a between-group difference in terms of OS in the ITT population at AFU1 analysis and this result is also reflected in the accompanying Kaplan-Meier survival curves (Table 3.25 and Figure 3.3). Similarly, no between-group differences were apparent for the OS rate at 12, 24 or 30 months (Table 3.25). The results of a sensitivity analysis of OS in the ITT population at AFU1 that censored patients who died due to confirmed or suspected COVID-19 on the day prior to their deaths also suggested no between-group difference for abemaciclib + ET when compared with ET alone (Table 3.26).

Table 3.25: Summary of overall survival in the ITT population (AFU1 analysis)

	Abemaciclib + ET (N=2,808)	ET alone (N=2,829)	Treatment Effect/Difference 2-sided p-Value (nominal)[e]
Number of events, n (%)	[redacted]	[redacted]	
Deaths	[redacted]	[redacted]	
Number of patients censored, n (%)	[redacted]	[redacted]	
Alive	[redacted]	[redacted]	
Lost to follow-up	[redacted]	[redacted]	
Withdrawal by subject	[redacted]	[redacted]	
p-value (2-sided) log-rank, stratified[b]	[redacted]		
HR (95% CI)	[redacted]		
OS rate, % (95% CI)[c]			
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
30 months	[redacted]	[redacted]	[redacted]

Source: Table 18, CS[2]
CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; IDFS: invasive disease-free survival; ITT: intent-to-treat; N: number of patients in the ITT population OS= overall survival
[a]Restriction time is defined by the latest time where the standard error of the survival estimates are ≤0.075; [b]Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [c]95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation; [d]2-sided p-value based on normal approximation; [e]Treatment Effect/Difference/p-values are computed based on comparator ET

Table 3.26: Summary of overall survival in the ITT population (including a COVID-19 sensitivity analysis) (AFU1 analysis)

Events, n (%)	Abemaciclib + ET (N=2,808)	ET alone (N=2,829)	Treatment Effect[a]	
			Stratified HR (95% CI)[b]	2-sided p-value (nominal)[b]
OS	[redacted]	[redacted]	[redacted]	[redacted]
OS: COVID-19 sensitivity analysis[c]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 19, CS[2]
CI: confidence interval; COVID-19: coronavirus, SARS-CoV-2; ET: endocrine therapy; HR: hazard ratio; ITT: intent-to-treat; N: number of patients in the ITT population; OS: overall survival
[a]Treatment effect in terms of HR estimates and p-values are computed based on comparator ET; [b]Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [c]Patients who died due to suspected or reported COVID-19 were censored on the day prior to their deaths

Figure 3.3: Summary of the overall survival results in monarchE (AFU1 analysis)

Source: Figure 7, CS[2]
= number; CI = confidence interval; ET = endocrine therapy; HR = hazard ratio

ERG comment: No between-group differences are apparent in any analysis of OS. Despite a request by the ERG, the company did not provide separate data tables for premenopausal and postmenopausal participants, their rationale being that the OS data were not yet mature.[4] Therefore, given the findings for IDFS and DRFS, this remains a Key Issue.

3.2.3.4 monarchE: patient-reported outcomes

Patient-reported outcomes for the monarchE trial included several HRQoL assessments using the following scales/subscales: Functional Assessment of Cancer Therapy – Breast (FACT-B); Functional Assessment of Cancer Therapy – Endocrine Subscale (FACT-ES); Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F); and the EuroQol-five dimensions-five levels (EQ-5D-5L). All measures were reported at PO analysis since they were not analysed at AFU1.[2]

3.2.3.4.1 Functional Assessment of Cancer Therapy – Breast (FACT-B)

The FACT-B tool includes 37 items measuring five domains of HRQoL in patients with breast cancer (physical, social, emotional, functional well-being and a breast cancer subscale). The score ranges from zero to 148 with higher summary scores representing better QoL.[9]

Statistics for the comparison between abemaciclib + ET and ET alone suggested small between-group differences in summary scores at all follow-up times however, confidence intervals and p-values were not provided (Table 3.27).[2]

Table 3.27: Summary scores (PO analysis) for Functional Assessment of Cancer Therapy – Breast

FACT-B Total Score	Abemaciclib + ET (N=2,791)			ET alone (N=2,800)			Abemaciclib + ET versus ET alone
	n	Mean (SD)	CfB, LSM (SE)	n	Mean (SD)	CfB, LSM (SE)	LSM Change Difference (SE)
Baseline	[redacted]						
Visit 6 (3 months)							
Visit 9 (6 months)							
Visit 15 (12 months)							
Visit 21 (18 months)							
All post-baseline							

Source: Table 22, CS[2]
CfB: change from baseline; ET: endocrine therapy; FACT-B: Functional Assessment of Cancer Therapy – Breast; LSM: least-squares mean; N: number of patients in the safety population; NA: not applicable; NE: not evaluated; SD: standard deviation; SE: standard error

3.2.3.4.2 Functional Assessment of Cancer Therapy – Endocrine subscale (FACT-ES)

There was limited information about the FACT-ES tool within the CS aside from stating that higher summary scores represented more favourable HRQoL.[9] Other information suggests that the instrument includes 46 items measuring five domains (physical, social/family, emotional, functional well-being and additional concerns relating to possible symptoms arising from endocrine therapy) with scores ranging from zero to 184.[10]

The CS presented data for two endocrine symptom subscales (ESSs), covering 19 and 23 items respectively. Results from both subscales suggested small differences in summary scores at all follow-

up points between abemaciclib + ET and ET alone but confidence intervals and p-values for the comparisons were not provided (Table 3.28).[2]

Table 3.28: Summary scores (PO analysis) for Functional Assessment of Cancer Therapy – Endocrine subscale

FACT-ES Total Score	Abemaciclib + ET (N=2,791)			ET alone (N=2,800)			Abemaciclib + ET versus ET alone
	n	Mean (SD)	CfB, LSM (SE)	n	Mean (SD)	CfB, LSM (SE)	LSM Change Difference (SE)
ESS-19[a]							
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 6 (3 months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 9 (6 months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 15 (12 months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 21 (18 months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All post-baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ESS-23[b]							
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 6 (3 months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 9 (6 months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Visit 15 (12 months)	[redacted]						
Visit 21 (18 months)	[redacted]						
All post-baseline	[redacted]						

Source: Table 23, CS[2]
CS: company submission; CfB: change from baseline; ET: endocrine therapy; FACT-B: Functional Assessment of Cancer Therapy – Breast; FACT-ES: Functional Assessment of Cancer Therapy – Endocrine Subscale; LSM: least-squares mean; N: number of patients in the safety population; NA: not applicable; NE: not evaluated; SD: standard deviation; SE: standard error
[a]19-item Endocrine Symptom Subscale; [b]23-item Endocrine Symptom Subscale, based on the same items as the ESS-19 plus the following 4 items of Physical Well-Being in FACT-B: i) item GP1 "I have lack of energy", ii) item GP2, "I have nausea", iii) item GP4, "I have pain", and iv) item GP5, "I am bothered by side effects of treatment"

ERG comment: The ERG asked the company to define the minimally important difference (MID) for FACT-ES. The company replied that they had not identified FACT-ES summary scores for an early breast cancer population.[4] Source: findings from an SLR exploring changes in HRQoL scores,[11] the company applied an effect size of 0.5 of the baseline standard deviation to represent the MID, describing this as a '*conservative estimate of MID*'.[4]

3.2.3.4.3 Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) subscale

Similar to the above outcome, information in the CS indicated that higher summary scores represented more favourable HRQoL for FACIT-F[9] whilst separate sources describe the instrument as including 40 items that measure five domains (physical, social/family, emotional, functional well-being and additional concerns in relation to fatigue) with scores ranging from zero to 160.[12]

As for the previous two outcomes, the summary scores for the between-group differences appeared to be small but the data were not substantiated by CIs or p-values (Table 3.29).[2]

Table 3.29: Summary scores (PO analysis) for Functional Assessment of Chronic Illness Therapy – Fatigue subscale

FACIT-F Total Score	Abemaciclib + ET (N=2,791)			ET alone (N=2,800)			Abemaciclib + ET versus ET alone
	n	Mean (SD)	CfB, LSM (SE)	n	Mean (SD)	CfB, LSM (SE)	LSM Change Difference (SE)
Baseline	[redacted]						

FACIT-F Total Score	Abemaciclib + ET (N=2,791)			ET alone (N=2,800)			Abemaciclib + ET versus ET alone
	n	Mean (SD)	CfB, LSM (SE)	n	Mean (SD)	CfB, LSM (SE)	LSM Change Difference (SE)
Visit 6 (3 months)	[redacted]						
Visit 9 (6 months)	[redacted]						
Visit 15 (12 months)	[redacted]						
Visit 21 (18 months)	[redacted]						
All post-baseline	[redacted]						

Source: Table 24, CS[2]
CS: company submission; CfB: change from baseline ET: endocrine therapy; FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue; LSM: least-squares mean; N: number of patients in the safety population; NA: not applicable; NE: not evaluated; SD: standard deviation; SE: standard error.

ERG comment: The ERG asked the company to define the MID for FACIT-F. The company replied that they had not identified FACIT-F summary scores for an early breast cancer population.[4] Based on findings from an SLR exploring changes in HRQoL scores,[11] the company applied an effect size of 0.5 of the baseline standard deviation to represent the MID, describing this as a '*conservative estimate of MID*'.[4]

3.2.3.4.4 EQ-5D-5L

The EQ-5D-5L is a generic instrument, designed to assess HRQoL across different types of disease. It includes five dimensions: mobility; self-care; usual activities; pain or discomfort; and anxiety or depression. Respondents can choose from five levels within each domain: no problems/symptoms; slight problems/symptoms; moderate problems/symptoms; severe problems/symptoms; and unable to walk/self-care/perform usual activities or have severe pain/discomfort or anxiety/depression.[13] EQ-5D-5L can be administered in several ways and results relating to two methods were provided in the CS: health state index scores and visual analogue scales (VAS).[2] The summary health state index score has

a maximum value of one, indicating best possible HRQoL. The range for the VAS is zero to 100, with higher values representing more favourable HRQoL.[13]

Scores from the EQ-5D-5L were used to inform HRQoL status for the economic model in this submission. The company provided a brief summary of EQ-5D-5L outcomes in the CS, with data cross-tabulated by treatment arm and method of administration of the instrument for the PO analysis of the safety population. The data suggested no between-group difference for health state index scores and a small, statistically significant difference in favour of ET alone for VAS-derived values (Table 3.30).[2] Details of subscale scores are shown in Section L.4 of the CS appendices.[9]

Table 3.30: Summary of EQ-5D-5L Health State Index and Visual Analogue scores in monarchE safety population (PO analysis)

		Baseline Score Mean (SD)		Within-treatment Group Change from Baseline[a] LSM (SE)		Between- treatment Group Change Difference (Abemaciclib + ET versus ET alone)[a,b]		
		Abemaciclib + ET	ET Alone	Abemaciclib + ET	ET Alone	LS M (SE)	95% CI	p-Value[c]
EQ-5D-5L Health State Index		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visual analogue scale		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 25, CS[2]
CS: company submission; EQ-5D 5L: EuroQol 5-Dimension 5-Level; LSM: least squares mean; SE: standard error; SD: standard deviation
[a]Across all post-baseline visits; [b]A positive between treatment difference favours abemaciclib + ET; [c]p-Values are from Type 3 sums of squares mixed models repeated measures model: Change from baseline = Treatment + Visit + Treatment*Visit + Baseline. Denominators shown in Appendix L.4 are abemaciclib + ET n=2791 and ET alone n=2800.[9]

ERG comment: In response to the clarification letter (Question A15), the company provided more detailed information on EQ-5D-5L scores including tabulation of estimates for between-group differences by follow-up time (every 3 months) for both unadjusted and adjusted (by stratification factors) analyses.[4] The company provided separate tables for health state index and VAS scores (Tables 3.31 to 3.34). Results differed according to methods of administration of EQ-5D-5L. When assessed with health state index scores, those receiving ET alone had higher scores than patients on abemaciclib + ET at visit 21 but between-group differences were not apparent for other follow-up times or for post-baseline overall. However, VAS scores differed between groups for all follow-up times (including post-baseline overall) in favour of ET alone. Results were similar for unadjusted and adjusted analyses for both methods of EQ-5D-5L administration.[4]

Table 3.31: Unadjusted EQ-5D-5L Health State Index scores by treatment arm and time point

	Treatment	N	Mean score (SD)	LS mean change difference (SE)	95% CI	p-value
Baseline	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
Visit 6	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
Visit 9	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
Visit 15	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
Visit 21	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
All post−baseline	Abemaciclib + ET/ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 14, response to clarification letter.[4]
CI = confidence interval; EQ-5D-5L = EuroQol-5 dimensions- 5 levels; ET = endocrine therapy; N = number of patients; NA = not applicable; SD = standard deviation; SE = standard error

Table 3.32: Unadjusted EQ-5D-5L Visual Analogue Scale scores by treatment arm and time point

	Treatment	N	Mean score (SD)	LS mean change difference (SE)	95% CI	Abemaciclib + ET versus ET p–value
Baseline	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
Visit 6	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
Visit 9	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
Visit 15	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
Visit 21	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
All post-baseline	Abemaciclib + ET/ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 15, response to clarification letter.[4]
CI = confidence interval; EQ-5D-5L = EuroQol-5 dimensions- 5 levels; ET = endocrine therapy; N = number of patients ; NA = not applicable; SD = standard deviation ; SE = standard error

Table 3.33: EQ-5D-5L Health State Index scores by treatment arm and time point (adjusted for stratification factors)

	Treatment	N	Mean score (SD)	LS mean change difference (SE)	95% CI	p-value
Baseline	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
Visit 6	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
Visit 9	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
Visit 15	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
Visit 21	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
All post-baseline	Abemaciclib + ET/ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 16, response to clarification letter.[4]

CI = confidence interval; EQ-5D-5L = EuroQol-5 dimensions- 5 levels; ET = endocrine therapy: N = number of patients; NA = not applicable; SD = standard deviation ; SE = standard error

Table 3.34: EQ-5D-5L Visual Analogue Scale scores by treatment arm and time point (adjusted for stratification factors)

	Treatment	N	Mean score (SD)	LS mean change difference (SE)	95% CI	Abemaciclib + ET versus ET p-value
Baseline	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
Visit 6	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			

Visit 9	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
Visit 15	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
Visit 21	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ET	[redacted]	[redacted]			
All post-baseline	Abemaciclib + ET/ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 17, response to clarification letter.[4]
CI = confidence interval; EQ-5D-5L = EuroQol-5 dimensions- 5 levels; ET = endocrine therapy; N = number of patients; NA = not applicable; SD = standard deviation; SE = standard error

ERG comment: Interpretation of between-group differences for FACT-B, FACT-ES (both subscales) and FACIT-F were hindered by absence of CIs and p-values. EQ-5D-5L findings were not consistent across different methods of administering the instrument with health state index scores not differing between groups (apart from at visit 21 where a difference was observed in favour of ET alone) whereas VAS scores indicated better HRQoL for ET alone across all time periods. EQ-5D-5L health state index scores were used to inform the economic model, providing the most favourable HRQoL profile for the intervention, abemaciclib + ET.

3.2.4 monarchE safety

The safety population consisted of all 5,591 randomised and treated patients who received at least one dose of study treatment.[2] This resulted in 2,791 patients receiving abemaciclib + ET, and 2,800 receiving ET alone. The authors stated in the CS that the safety data is mature and recent, up to the latest data analysis, the AFU1 point (1st April 2021), emphasising that 90% of patients had completed or discontinued early from the study treatment period by the time of the AFU1. For clarity, by this point both arms had experienced a broadly similar treatment duration with those in in the abemaciclib + ET arm, experiencing a median duration of abemaciclib treatment of approximately 23.7 months (with a mean of approximately 19 months), while the median duration of ET was approximately 23.8 months (with a mean of approximately 21 months). Those in the ET alone arm experienced a median duration of treatment of approximately 23.8 months (with a mean of approximately 21 months).

Table 3.35 summarises the data on AEs up to AFU1 and highlights differences between the arms. More patients experienced ≥1 TEAE of any Grade in the abemaciclib + ET arm than in the ET alone arm (98.4% versus 88.8%). Investigators judged that 39.5% of ≥1 CTCAE ≥ Grade 3 TEAEs in the abemaciclib + ET arm, and 3% in the ET alone arm were related to the study treatment. Patients reported ≥1 TE-SAE in the abemaciclib + ET arm than in the ET alone arm (15.2% versus 8.8%) and discontinuation was more common in the abemaciclib + ET arm (6.5% versus 1.1%).

Closer inspection of this TEAE data experienced by ≥1% of patients in either arm by system organ class (Table 3.36) shows that the most frequently reported class of TEAEs in the experimental arm were

gastrointestinal disorders (90.2%), blood and lymphatic disorders (60.1%), General disorders and administration site conditions (57.3%), infections and infestations (51.2%), and musculoskeletal and connective tissue disorders (50.1%). In the ET alone arm, frequency, and distribution of TEAEs by SOC was different with musculoskeletal and connective tissue disorders being the most reported (59.8%), followed by infections and infestations (39.4%), general disorders and administration site conditions (34.9%), vascular disorders (34.9%), and gastrointestinal disorders (34.1%).

The CS reported data on TEAEs by CTCAE Grade experienced by ≥10% of patients in the experimental and control arms. These data are provided in Table 3.37. TEAEs in both arms were generally of lower grade (<3), however the incidence of any grade ≥3 TEAEs was greater in the abemaciclib + ET arm (46.0% Grade 3, 3.2% Grade 4) than in the ET alone arm (15.5% Grade 3, 0.8% Grade 4). Review of the data demonstrates that diarrhoea of any Grade was the most frequently reported TEAE in the abemaciclib + ET arm (83.5%), compared with the ET alone arm (8.6%). 7.8% patients in the abemaciclib + ET arm reported severe diarrhoea at Grade ≥3 compared to 0.2% in the ET alone arm. However, 75.7% of diarrhoea in the abemaciclib + ET arm was of lower Grade severity (<3). Neutropenia was reported by 45.8% of patients in the abemaciclib + ET arm compared to 5.6% of patients in the ET alone arm, with the incidence of Grade ≥3 TEAEs being greater (18.9% Grade 3, 0.7% Grade 4) than in the ET alone arm (0.7% Grade 3, 0.1% Grade 4). Fatigue was reported more frequently in the abemaciclib + ET arm (40.6%) than in the ET alone arm (17.8%) however these differences were predominately observed in the lower Grades of TEAE (<3) with 37.7% of fatigue events being reported in Grades 1or 2 in the abemaciclib + ET arm.

SAEs occurred more frequently in the abemaciclib + ET arm than in the ET alone arm (15.2% versus 8.8%). Closer examination reveals that the most reported SAEs in the abemaciclib + ET arm were venous thrombolytic events (VTE) (1.2%, 34/2791) and pneumonia (1.0%, 28/2791), while patients who were treated with ET alone reported pneumonia (0.6% [17/2,800]), cellulitis (0.4% [10/2,800]) and VTE (0.3% [8/2,800]). Table 3.38).

The CS presents data on study treatment discontinuation (end of treatment) by ≥2 patients in either arm of the safety population due to AEs (Table 3.39), and by AEs reported as reason for abemaciclib or all treatment discontinuation (end of treatment) by system organ class in ≥0.1% patients in the abemaciclib + ET arm of the safety population (Table 32, CS). Discontinuation due to AEs was higher in the abemaciclib + ET arm than the ET alone arm. The data shows that 18.5% of patients in the abemaciclib + ET arm discontinued abemaciclib or all treatments due to the consequences of an AE. From this 18.5%, 6.5% of patients discontinued both abemaciclib + ET due to an AE. The ET alone arm by contrast reported 1.1% of patients who discontinued because of AE's.

The most reported TEAEs leading to discontinuation are reported below in Table 3.39. In the abemaciclib + ET arm, the most frequently reported TEAEs leading to all treatment discontinuation were diarrhoea (2.5%) and fatigue (1.0%). In the abemaciclib + ET arm, the most common TEAEs leading to abemaciclib discontinuation were diarrhoea (147 patients, 5.3%) and fatigue (56 patients, 2.0%). The CS (page 76/160) emphasises that in the ET alone arm, dizziness (0.1%) led to discontinuation in the ET alone arm. However, the data presented in table 31 of the CS, and included below in Table 3.39 suggests that depression and hot flush (both 0.1%) had an equal occurrence leading to discontinuation to that of dizziness, However, arthralgia had a higher occurrence (0.2%). This does not appear to have been commented on and given that 59.8% of patients in the ET alone arm reported musculoskeletal and connective tissue disorders, it would be appropriate for this data to have been briefly remarked upon.

Deaths (see Table 3.40) were broadly similar in both treatment arms with [redacted] occurring in the abemaciclib + ET arm, compared with [redacted] in the ET alone arm. Deaths occurring while enrolled in the study or within 30 days of discontinuation, were also comparable, with [redacted] occurring in the abemaciclib + ET arm, and [redacted] occurring in the ET alone arm. Deaths related to AE's included [redacted] in the abemaciclib + ET arm, and [redacted] in the ET alone arm. Deaths that occurred >30 days of treatment discontinuation included [redacted] in the abemaciclib + ET arm, and [redacted] in the ET alone arm, of which, nine of the [redacted] in the abemaciclib + ET arm were considered to be due to TEAEs, as compared with four of the [redacted] in the ET alone arm. The CS states that cause of death was generally considered to be confounded by multiple comorbid factors, and review of the data presented in Table 33 of the CS (79/160) demonstrates that cardiac disorders ([redacted] were the most reported TEAE leading to death in the abemaciclib + ET arm, while and infections and infestations ([redacted] were the most reported TEAEs leading to patient death in the ET alone arm. The CS provides minor inconsistency data by stating in the commentary (page 9/160) that 0.1% of deaths in the ET alone arm are due to infections and infestations.

Table 3.35: Summary of adverse events reported in the safety population to AFU1 analysis

n (%)	Abemaciclib + ET (N=2,791)	ET alone (N=2,800)
Patients with ≥1 TEAE	2,745 (98.4)	2,486 (88.8)
Patients with ≥1 CTCAE ≥ Grade 3 TEAE	[redacted]	[redacted]
Related to study treatment[b]	[redacted]	[redacted]
Patients with ≥1 TE-SAE	424 (15.2)	247 (8.8)
Patients who discontinued all study treatment due to an AE	181 (6.5)	30 (1.1)
Patients who discontinued all study treatment due to a SAE	[redacted]	[redacted]
Patients who died due to an AE on study treatment[c]	[redacted]	[redacted]
Patients who died due to an AE ≤30 days from discontinuation of study treatment[c]	[redacted]	[redacted]
Patients who died due to an AE >30 days after discontinuation from study treatment	[redacted]	[redacted]

Source: Table 26[2]
Footnotes: [a]Patients may be counted in more than 1 category; [b]Includes events that were considered related to study treatment as judged by the investigator; [c]Deaths were also included as SAEs and discontinuations due to AEs
AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; ET = endocrine therapy; N = number of patients in the safety population; n = number of patients in the specific category; SAE = serious adverse event; TE = treatment-emergent; TEAE = treatment-emergent adverse event

Source: Adapted from Table 26 of CS, Lilly Data on File. Clinical Study Report: monarchE.[14] Data cut-off: 1 April 2021 (AFU1 analysis)

Table 3.36: TEAEs by SOC in ≥1% patients (all grades) in the safety population (AFU1 analysis)

n (%)	Abemaciclib + ET (N=2,791)	ET alone (N=2,800)
Patients with ≥1 TEAE	2,745 (98.4)	2,486 (88.8)
Gastrointestinal disorders	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Respiratory, thoracic, and mediastinal disorders	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]
Injury, poisoning, and procedural complications	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]
Reproductive system and breast disorders	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Surgical and medical procedures	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified[a]	[redacted]	[redacted]
Endocrine disorders	[redacted]	[redacted]

Source: Table 27[2]
Adapted from CS, Lilly Data on File. Clinical Study Report: monarchE.[14] Data cut-off: 1st April 2021 (AFU1 analysis).
Footnotes: [a] Including cysts and polyps.
CS: company submission; ET: endocrine therapy; MedDRA: Medical Dictionary for Regulatory Activities; N: number of patients in the safety population; n: number of patients in the specific category.
Source: Lilly Data on File. Clinical Study Report: monarchE.[14] Data cut-off: 1st April 2021 (AFU1 analysis).

Table 3.37: Treatment-emergent adverse events by maximum CTCAE grade experienced by ≥10% of population of either arm (AFU1 analysis)

TEAE, n (%)	Abemaciclib + ET (n=2,791)						ET alone (N=2,800)					
	CTCAE Grade											
	1	2	3	4	5	Any	1	2	3	4	5	Any
Patients with ≥1 TEAE	[redacted]	[redacted]	1,284 (46.0)	89 (3.2)	[redacted]	2,745 (98.4)	[redacted]	[redacted]	424 (15.1)	22 (0.8)	[redacted]	2,486 (88.8)
Diarrhoea	[redacted]	[redacted]	218 (7.8)	0 (0.0)	[redacted]	2,331 (83.5)	[redacted]	[redacted]	6 (0.2)	0 (0.0)	[redacted]	242 (8.6)
Neutropenia	[redacted]	[redacted]	527 (18.9)	19 (0.7)	[redacted]	1278 (45.8)	[redacted]	[redacted]	19 (0.7)	4(0.1)	[redacted]	157 (5.6)
Fatigue	[redacted]	[redacted]	80 (2.9)	0 (0.0)	[redacted]	1133 (40.6)	[redacted]	[redacted]	4 (0.1)	0 (0.0)	[redacted]	499 (17.8)
Leukopenia	[redacted]	[redacted]	313 (11.2)	4 (0.1)	[redacted]	1049 (37.6)	[redacted]	[redacted]	11 (0.4)	0 (0.0)	[redacted]	186 (6.6)
Abdominal pain	[redacted]	[redacted]	39 (1.4)	0 (0.0)	[redacted]	992 (35.5)	[redacted]	[redacted]	9 (0.3)	0 (0.0)	[redacted]	275 (9.8)
Nausea	[redacted]	[redacted]	14 (0.5)	0 (0.0)	[redacted]	824 (29.5)	[redacted]	[redacted]	2 (0.1)	0 (0.0)	[redacted]	252 (9.0)
Anaemia	[redacted]	[redacted]	56 (2.0)	1 (0.0)	[redacted]	681 (24.4)	[redacted]	[redacted]	9 (0.3)	1 (0.0)	[redacted]	104 (3.7)
Arthralgia	[redacted]	[redacted]	9 (0.3)	0 (0.0)	[redacted]	742 (26.6)	[redacted]	[redacted]	29 (1.0)	0 (0.0)	[redacted]	1060 (37.9)
Headache	[redacted]	[redacted]	8 (0.3)	0 (0.0)	[redacted]	546 (19.6)	[redacted]	[redacted]	5 (0.2)	0 (0.0)	[redacted]	421 (15.0)
Vomiting	[redacted]	[redacted]	15 (0.5)	0 (0.0)	[redacted]	491 (17.6)	[redacted]	[redacted]	3 (0.1)	0 (0.0)	[redacted]	130 (4.6)
Hot flush	[redacted]	[redacted]	4 (0.1)	0 (0.0)	[redacted]	427 (15.3)	[redacted]	[redacted]	10 (0.4)	0 (0.0)	[redacted]	643 (23.0)
Lymphopenia	[redacted]	[redacted]	148 (5.3)	3 (0.1)	[redacted]	395 (14.2)	[redacted]	[redacted]	13 (0.5)	0 (0.0)	[redacted]	96 (3.4)
Stomatitis[a]	[redacted]	[redacted]	4 (0.1)	0 (0.0)	[redacted]	385 (13.8)	[redacted]	[redacted]	0 (0.0)	0 (0.0)	[redacted]	151 (5.4)

TEAE, n (%)	Abemaciclib + ET (n=2,791)						ET alone (N=2,800)					
	CTCAE Grade											
	1	2	3	4	5	Any	1	2	3	4	5	Any
Cough	[redacted]	[redacted]	1 (0.0)	0 (0.0)	[redacted]	391 (14.0)	[redacted]	[redacted]	0 (0.0)	0 (0.0)	[redacted]	222 (7.9)
Thrombocytopenia	[redacted]	[redacted]	28 (1.0)	8 (0.3)	[redacted]	373 (13.4)	[redacted]	[redacted]	2 (0.1)	2 (0.1)	[redacted]	52 (1.9)
Decreased appetite	[redacted]	[redacted]	16 (0.6)	0 (0.0)	[redacted]	329 (11.8)	[redacted]	[redacted]	2 (0.1)	0 (0.0)	[redacted]	68 (2.4)
Lymphoedema	[redacted]	[redacted]	5 (0.2)	0 (0.0)	[redacted]	347 (12.4)	[redacted]	[redacted]	1 (0.0)	0 (0.0)	[redacted]	250 (8.9)
Urinary tract infection	[redacted]	[redacted]	16 (0.6)	0 (0.0)	[redacted]	336 (12.0)	[redacted]	[redacted]	6 (0.2)	0 (0.0)	[redacted]	211 (7.5)
Constipation	[redacted]	[redacted]	2 (0.1)	0 (0.0)	[redacted]	333 (11.9)	[redacted]	[redacted]	1 (0.0)	0 (0.0)	[redacted]	168 (6.0)
URTI	[redacted]	[redacted]	6 (0.2)	0 (0.0)	[redacted]	301 (10.8)	[redacted]	[redacted]	0 (0.0)	0 (0.0)	[redacted]	238 (8.5)
ALT increased	[redacted]	[redacted]	72 (2.6)	5 (0.2)	[redacted]	343 (12.3)	[redacted]	[redacted]	19 (0.7)	0 (0.0)	[redacted]	157 (5.6)
Dizziness	[redacted]	[redacted]	4 (0.1)	0 (0.0)	[redacted]	304 (10.9)	[redacted]	[redacted]	1 (0.0)	0 (0.0)	[redacted]	188 (6.7)
Rash	[redacted]	[redacted]	11 (0.4)	0 (0.0)	[redacted]	312 (11.2)	[redacted]	[redacted]	0 (0.0)	0 (0.0)	[redacted]	127 (4.5)
AST increased	[redacted]	[redacted]	49 (1.8)	3 (0.1)	[redacted]	330 (11.8)	[redacted]	[redacted]	15 (0.5)	0 (0.0)	[redacted]	137 (4.9)
Alopecia	[redacted]	[redacted]	0 (0.0)	0 (0.0)	[redacted]	313 (11.2)	[redacted]	[redacted]	0 (0.0)	0 (0.0)	[redacted]	75 (2.7)
Pain in extremity	[redacted]	[redacted]	3 (0.1)	0 (0.0)	[redacted]	286 (10.2)	[redacted]	[redacted]	4 (0.1)	0 (0.0)	[redacted]	325 (11.6)
Back pain	[redacted]	[redacted]	10 (0.4)	0 (0.0)	[redacted]	283 (10.1)	[redacted]	[redacted]	9 (0.3)	0 (0.0)	[redacted]	347 (12.4)

TEAE, n (%)	Abemaciclib + ET (n=2,791)						ET alone (N=2,800)					
	CTCAE Grade											
	1	2	3	4	5	Any	1	2	3	4	5	Any
Pyrexia	[redacted]	[redacted]	2 (0.1)	0 (0.0)	[redacted]	279 (0.1)	[redacted]	[redacted]	0 (0.0)	0 (0.0)	[redacted]	127 (4.5)

Source: Table 28, CS[2]
Footnotes: [a] Includes mouth ulceration, mucosal inflammation, oropharyngeal pain, stomatitis.
ALT: alanine aminotransferase; AST: aspartate aminotransferase; CS: company submission; CTCAE: Common Terminology Criteria for Adverse Events; ET: endocrine therapy; MedDRA: Medical Dictionary for Regulatory Activities; N: number of patients in the safety population; n: number of patients in the specific category; TEAE: treatment-emergent adverse event; URTI: upper respiratory tract infection

Table 3.38: SAEs in ≥5 patients in either arm of the safety population (AFU1 analysis)

n (%)	Abemaciclib + ET (N=2,791)	ET alone (N=2,800)
Patients with ≥1 SAEs	424 (15.2)	247 (8.8)
Infections and infestations	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Influenza	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Breast cellulitis	[redacted]	[redacted]
Erysipelas	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Pancreatitis	[redacted]	[redacted]
Colitis	[redacted]	[redacted]
Respiratory, thoracic, and mediastinal disorders	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]
Lymphoedema	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]
Cholecystitis	[redacted]	[redacted]
Blood and lymphatic disorders	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Dehydration	[redacted]	[redacted]
Composite terms[a]		
Venous thromboembolic event[b]	[redacted]	[redacted]
Interstitial lung disease/pneumonitis[c]	[redacted]	[redacted]
ALT or AST increased	[redacted]	[redacted]

Source: Table 30, CS[2]
Footnotes: [a]Composite terms are defined as a grouping of terms from one or more PTs that are treatment-emergent events and related to a defined medical condition or area of interest; [b]VTE events included pulmonary embolism and deep vein thrombosis. See Section 5.2.1.4.5 of the CSR for more information; [c]Interstitial lung disease/pneumonitis events were defined by SMQ of "interstitial lung disease".
CS: company submission; ET: endocrine therapy; N: number of patients in the safety population; n: number of patients within category; SAE: serious adverse event; SMQ: standardised MedDRA queries.

Table 3.39: AEs reported as reason for study treatment discontinuation by ≥2 patients in either arm (AFU1 analysis)

n (%)	Abemaciclib + ET (N=2,791)	ET alone (N=2,800)
Patients discontinued all study treatment due to AE[a]	181 (6.5)	30 (1.1)
Diarrhoea	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Depression	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]
Cardiac arrest	[redacted]	[redacted]
Dry eye	[redacted]	[redacted]
General physical health deterioration	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Hot flush	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Composite terms[b]		
Infections and infestations SOC	[redacted]	[redacted]
Venous thromboembolic event[c]	[redacted]	[redacted]
Interstitial lung disease/pneumonitis[d]	[redacted]	[redacted]
ALT or AST increased	[redacted]	[redacted]

Source: Table 31, CS[2]
Footnotes: [a]Includes patients who died due to AE during study treatment: PT cardiac arrest and PT general physical health deterioration ([redacted]). [b]Composite terms are defined as a grouping of terms from one or more PT or SOC that are related to a defined medical condition or area of interest; [c]VTE events included pulmonary embolism and deep vein thrombosis. See Section 5.2.1.4.5 of the CSR for more information; [d] Interstitial lung disease/pneumonitis events were defined by SMQ of "interstitial lung disease"
AE: adverse event; ET: endocrine therapy; N: number of patients in the safety population; n: number of patients within category; SAE: serious adverse event; SMQ: standardised MedDRA queries

Table 3.40: Summary of deaths (AFU1 analysis)

n (%)	Abemaciclib + ET (N=2,791)	ET alone (N=2,800)
All deaths	[redacted]	[redacted]
Deaths on therapy or ≤30 days from discontinuation of study treatment	[redacted]	[redacted]
Death due to AEs	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
General disorders and administrative site conditions	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]

Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Respiratory, thoracic, and mediastinal disorders	[redacted]	[redacted]
Death due to study disease	[redacted]	[redacted]
Deaths occurring >30 days from study treatment discontinuation	[redacted]	[redacted]
Death due to AEs	[redacted]	[redacted]
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]
General disorders and administrative site conditions	[redacted]	[redacted]
Death due to study disease	[redacted]	[redacted]
Source: Table 33, CS[2] AEs = adverse events; ET: endocrine therapy; N: number of patients in the safety population; n: number of patients in the specific category		

ERG comment: The data relating to AEs were derived from the latest analysis point of the trial, namely the AFU1 point (1st April 2021) and the authors emphasise it is mature, the most recent, and by this point 90% of patients had completed or discontinued the study. The ERG notes the incidence of Grade ≥3 TEAEs was greater in the abemaciclib + ET arm (46.0% Grade 3, [redacted] Grade 4) than in the ET alone arm (15.5% Grade 3, [redacted] Grade 4) and that SAEs were more common in the abemaciclib + ET arm with more venous thrombolytic events (VTE) and pneumonia than in the ET alone group.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

No indirect comparison was performed.

ERG comment: The ERG would not expect an indirect comparison given the availability of the comparators as specified in the NICE scope in the monarchE trial.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

Not applicable.

3.5 Additional work on clinical effectiveness undertaken by the ERG

None undertaken.

3.6 Conclusions of the clinical effectiveness section

The SLR identified one RCT for abemaciclib for which published literature was available, monarchE. Patients were randomised to either placebo plus ET or abemaciclib plus ET. The monarchE study is useful to decision making in being randomised, relatively large and comparing the intervention in the NICE scope to comparators largely in line with NHS clinical practice. Lack of blinding does imply some concern regarding risk of bias. As discussed in Section 2.1, there is ambiguity in what constitutes high risk and the extent to which the criteria applied in NHS clinical practice will match those of the monarchE trial as well as each of the Cohorts of which there were two, differing by the nature of high risk. The company suggested that the majority of patients in UK clinical practice are expected to be identified at high risk of recurrence based on the clinical and pathological features that represent

inclusion criteria for Cohort 1. Given the ambiguity of those criteria, it is difficult to assess the generalisability of the monarchE trial to NHS clinical practice, which implies that this is a Key Issue. ET was prescribed according to IC, and it appears that patients either received an aromatase inhibitor or tamoxifen/toremifene in the comparator arm or as concomitant therapy in the intervention arm. Although the percentage who received tamoxifen is higher, it seems strange to the ERG that such a high proportion of patients in the UK received an aromatase inhibitor instead of tamoxifen given that NG101 specifies only the latter.[5] For postmenopausal women the UK and all patients' percentages are almost identical. What is unclear is whether the percentage receiving tamoxifen/toremifene is consistent with intolerance or contraindication as stated in NG101. Therefore, this remains a Key Issue. The ERG recommends a subgroup analysis by ET within each of the menopausal status subgroups e.g. to estimate all efficacy outcomes for patients who are both premenopausal and received tamoxifen separately to patients who are both premenopausal and received an aromatase inhibitor.

Results for the primary endpoint (IDFS), secondary endpoints (DRFS) and OS and patient-reported outcomes (e.g., functional assessment of cancer therapy and HRQoL) were provided in the CS. Results from three data cuts were reported, including: the interim analysis (IA) 2 (16th March 2020); primary outcome (PO) analysis (8th July 2020); and additional follow-up (AFU) 1 analysis (1st April 2021).

The HR estimates derived from both stratified (for geographical region, prior treatment and menopausal status) and unstratified analyses suggest a more favourable outcome in terms of IDFS and DRFS for patients receiving abemaciclib + ET compared with ET alone at all data cut points (IA2, PO and AFU1 for IDFS and PO and AFU1 for DRFS).[2] No between-group differences were observed at 12 months for either outcome at any cut point however, more favourable outcomes were apparent for patients receiving abemaciclib + ET compared with ET alone at 24 months for all data cut points. At 36 months, the only evaluable data for both outcomes were at AFU1 where the between-group difference was in favour of abemaciclib + ET.[2] However, overall the company considered the ITT population to represent the most generalisable source of evidence.[4] Scrutiny of the data indicates similar findings between the ITT population and Cohort 1 with the exception that the 12-month IDFS and DRFS rates are more favourable for patients treated with abemaciclib + ET versus ET alone in Cohort 1 (Table 3.16) whereas no between-group difference was apparent in the ITT population. The subgroup analysis for both outcomes by menopausal status HR results were consistent with the analysis of the overall population. However, although the 95% CIs overlap, the HR for premenopausal women is [redacted] than that for postmenopausal women. Also, whilst rates for both outcomes were more favourable for the abemaciclib + ET-treated group versus ET alone in premenopausal patients across all time points (12, 24 and 36 months), this result was only seen at later time-points for the overall ITT population (24 and 36 months) and the postmenopausal subgroup (36 months) with no between-group differences apparent at earlier time points for these populations.[4] This therefore remains a Key Issue.

Neither stratified nor unstratified HR estimates suggested a between-group difference in terms of OS in the ITT population at AFU1 analysis. No subgroup analysis by menopausal status was performed, according to the company because data were immature. Nevertheless, given that findings for IDFS and DRFS, the ERG considers this to be a Key Issue.

Interpretation of between-group differences for FACT-B, FACT-ES (both subscales) and FACIT-F were hindered by absence of confidence intervals and p-values. EQ-5D-5L findings were not consistent across different methods of administering the instrument with health state index scores not differing between groups (apart from at visit 21 where a difference was observed in favour of ET alone) whereas VAS scores indicated better HRQoL for ET alone across all time periods. EQ-5D-5L health state index

scores were used to inform the economic model, providing the most favourable HRQoL profile for the intervention, abemaciclib + ET.

The data relating to AEs were derived from the latest analysis point of the trial, namely the AFU1 point (01 April 2021) and the authors emphasise it is mature: by this point [redacted] of patients had completed or discontinued the study. The ERG notes the incidence of Grade ≥3 TEAEs was greater in the abemaciclib + ET arm (46.0% Grade 3, [redacted] Grade 4) than in the ET alone arm (15.5% Grade 3, [redacted] Grade 4) and that SAEs were more common in the abemaciclib + ET arm with more VTE and pneumonia than in the ET alone group.

4. COST EFFECTIVENESS

4.1 ERG 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 (3.1.1) also contains summaries and critiques of other searches related to cost effectiveness 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 company conducted searches for cost effectiveness studies. A good range of databases was searched. The CS provided sufficient detail for the ERG to be able to appraise the searches conducted. Systematic searches to identify HRQoL and healthcare resource use evidence data were not conducted. Instead, a targeted literature review (TLR) was conducted to identify UK specific data. The TLR comprised of searches of HTA websites, with an emphasis on the NICE website to retrieve relevant submissions.

Details of the literature searches used to identify cost effectiveness studies were reported in Appendix G. The searches were conducted in August 2020. A summary of resources searched is provided in Table 4.1. Details of the TLR were reported in appendix H and repeated in Appendix I. The TLR search of HTA websites was conducted in August 2020.

Table 4.1: Resources searched for the SLR of cost effectiveness studies. August 2020.

Search strategy element	Resource	Host/Source	Date Range	Date searched
Databases	Embase	ProQuest	NR	28 Aug 2020
	MEDLINE	ProQuest	NR	28 Aug 2020
	EconLit	ProQuest	NR	28 Aug 2020
	NHS EED	CRD website	NR	31 Aug 2020
	HTA database	CRD website	NR	31 Aug 2020
HTA websites	NICE	NR	2015 onwards	NR
	SMC	NR	2015 onwards	NR
	HAS	NR	2015 onwards	NR
	CADTH	NR	2015 onwards	NR
	PBAC	NR	2015 onwards	NR
Conferences	ISPOR	Embase via ProQuest	Not reported	Not reported

Source: CS[2] Adapted from Table 30, Appendix C
NHS EED = National Health Service Economic Evaluation Database; HTA database = Health Technology Assessment database; NICE = National Institute for Health and Care Excellence; SMC = Scottish Medicines

Consortium; HAS = Haute Autorité de santé; CADTH = Canadian Agency for Drugs and Technologies in Health; PBAC = The Pharmaceutical Benefits Advisory Committee; ISPOR = International Society for Pharmacoeconomics and Outcomes Research

ERG Comment:

- The selection of databases searched was comprehensive. Full details of the database searches, including the database name, host platform and date searched, were provided.
- ISPOR conference proceedings were searched via Embase rather than the ISPOR conferences website.
- HTA organisation websites were searched, but details of the search terms used, dates of searches, and results, were not reported in the CS. Full details of the search terms used, dates of searches and results were provided in response to the ERG clarification letter.
- MEDLINE, Embase and EconLit were searched concurrently using ProQuest. This approach is not recommended, as it is difficult to evaluate the effectiveness of the search strategy in each database. A simultaneous multi-file search such as this should include both MeSH and EMTREE subject headings to ensure that all subject indexing terms are searched, and in this case the CS search strategy did include both MeSH and EMTREE terms.
- The facet of search terms for 'early stage' could have been improved by including more search terms and synonyms, for instance, HER2 negative, recurrence, locally advanced, non-metastatic, etc.
- The search strategy included a number of redundant search terms.
- A 5-year date limit was included in the economic SLR searches. The CS justified this limit: '*The 5-year limit ensured that most recent economic data were identified, and relevant, and applicable costs were captured'.*
- Study design search filters for cost effectiveness studies produced by Scottish Intercollegiate Guidelines Network (SIGN) and the Canadian Agency for Drugs and Technologies in Health (CADTH) were included in the search strategies, and cited in detail.[7]
- There was no reason to search NHS EED with a 5-year date limit, as this database has not been updated since March 2015.
- The TLR searches of the HTA database and HTA websites reported in Appendix H and Appendix I appear to have been conducted as part of the SLR of cost effectiveness studies reported in Appendix G and summarised in Table 4.1.
- Full details of the HTA website searches were not provided, though details of the search approach and search date for the NICE website were reported in Appendix H.
- HRQoL and healthcare resource use data were derived from previous NICE technology appraisals, identified from the TLR, NHS reference costs and unit costs of health and social care.[15, 16]
- The searches were conducted in August 2020. An update of the searches immediately prior to submission to NICE would have been appropriate and could have identified potentially relevant studies published since August 2020.

4.1.2 Inclusion/exclusion criteria

In- and exclusion criteria for the review on cost effectiveness studies, utilities and costs and resource use are presented in Table 4.2.

Table 4.2: Eligibility criteria for the systematic literature reviews

	Inclusion criteria	Exclusion criteria
Patient population[a]	• Early-stage breast cancer (Stage I-IIIC)	• Advanced or metastatic breast cancer (Stage IV) • Hormone-receptor negative

	Inclusion criteria	Exclusion criteria
	• Hormone-receptor positive • Node-positive • Adults >18 years • Received definitive surgery of the primary breast tumour	• Node-negative
Intervention[b]	NA	NA
Comparator[b]	NA	NA
Outcomes(s) **(Published economic evaluations, utility studies and cost/resource use studies)**	• (Incremental) costs • (Incremental) (quality adjusted) life years • ICER	• Outcomes other than specified under inclusion criteria
Study design **(Published economic evaluations, utility studies and cost/resource use studies)**	• Cost effectiveness analysis • Cost utility analysis	• Study designs other than specified under inclusion criteria • Systematic reviews and meta-analyses[c]

Source: CS[2]
CS = company submission; ICER = Incremental cost effectiveness ratio; NA: not applicable
[a]No restriction was placed on HER2 status due to the lack of published economic models in HER2- patients
[b]The primary focus of the economic SLR was to capture data on treatment pathway, model design, economic inputs/outputs (not specific to the treatment effect). Therefore, no inclusion/exclusion criteria were applied for intervention and comparator
[C]Data from systematic reviews were not extracted into the data extraction from. The references from these publications were checked to ensure no relevant article was missed by the search strategy

ERG comment: The ERG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify cost effectiveness studies. However, again the search strategy could have been updated prior to submission and included other NICE TA of CDK 4/6 inhibitors such as ribociclib for postmenopausal women with HR+ HER2-, locally advanced or metastatic breast cancer as initial endocrine-based therapy.[17]

4.1.3 Conclusions of the cost effectiveness review

The CS provides an overview of the included cost effectiveness, utility and resource use and costs studies that could be used to inform the development of the CEM and elicit the utility, cost, and resource use for the CEM. The economic SLR identified 32 studies but concluded that there is a lack of evidence evaluating and comparing treatment options for the monarchE patient population. A supplement targeted review identified four studies of previous technology appraisals published by NICE in early breast cancer over the past 5 years which helped inform model structure, health state utility values, resource use and costs.

ERG comment: The ERG felt that the CS did cover what it set out to do in the economic SLR and TLR. However, the CS did not discuss the other CDK 4/6 inhibitors used in breast cancer which was an oversight.

4.2 Summary and critique of company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 4.3: NICE reference case checklist

Element of HTA	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Complied with reference case
Perspective on costs	NHS and PSS	The company used an NHS and PPS perspective
Type of economic evaluation	Cost utility analysis with fully incremental analysis	The company has provided a cost utility analysis. This is based upon a hybrid state transition model with partitioned survival analysis
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The company has provided results for a lifetime time horizon for base-case analysis
Synthesis of evidence on health effects	Based on systematic review	The company undertook a targeted review, and evidence from the monarchE study was the main source used to inform the model
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Yes. For IDFS state, QALY based on EQ-5D-5L data from monarchE study with a crosswalk to EQ-5D-3L. The other utility values utilised are from previous TAs and the literature
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	Yes. Reported by patients for IDFS. For other data the source of measurement varied between patients, the public and expert opinion
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
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	Yes (costs have been sourced using NHS reference costs, the PSSRU unit costs, eMIT and expert opinion (Table 35, CS) and are reported in pound

Element of HTA	Reference case	ERG comment on company's submission
		Sterling for a 2019/2020 cost year)
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes
EQ-5D = European Quality of Life-5 Dimensions; EQ-5D-5L = EuroQol-5 Dimensions-5 Levels; EQ-5D-3L = EuroQol-5 Dimensions-3 Levels; ERG = Evidence Review Group; HRQoL = health-related quality of life; HTA = Health Technology Assessment; IDFS = invasive disease-free survival; NHS = National Health Service; PSS = Personal Social Services; PSSRU = Personal Social Services Research Unit; QALY = quality adjusted life year; TAs = technology appraisals; UK = United Kingdom		

4.2.2 Model structure

Health states/events and transitions

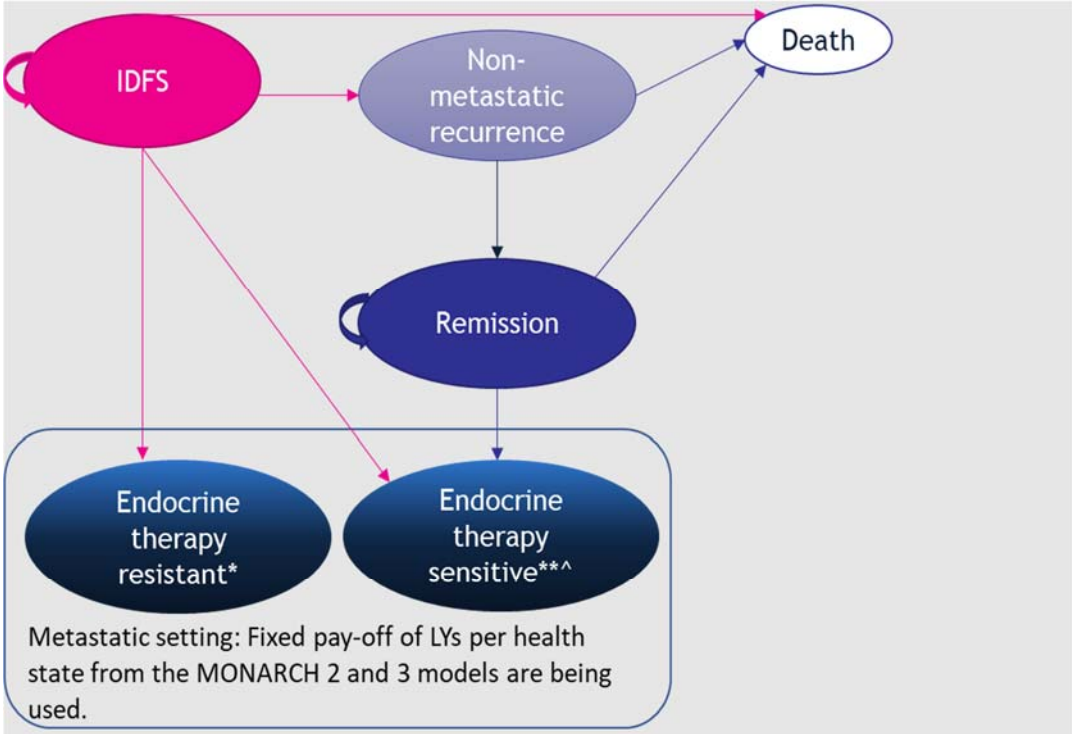
The company developed a de novo model in Microsoft Excel®. The 'top-line' model structure is presented in Figure 4.1. The model is described in the CS as a Cohort state transition model with five health states. The health states were invasive disease-free survival (IDFS), non-metastatic recurrence, remission, metastatic recurrence, and death. All patients enter the model in the IDFS progression-free state and receive ET for 5 years. Patients in the abemaciclib treatment arm receive additional abemaciclib treatment for a maximum of 2 years or until disease progression or toxicity. From the IDFS health state patients can either i) die; ii) experience a disease recurrence and transition to metastatic; iii) the non-metastatic recurrence health state; or iv) remain in the IDFS health state.

The non-metastatic recurrence state is split into two sub-states: second primary neoplasm; and locoregional/contralateral. Second primary neoplasm is modelled as an absorbing state with patients only being allocated a cost of diagnosis following which they leave the model. Locoregional/contralateral recurrence is modelled as a tunnel state, with patients receiving treatments dictated by the type/location of the disease recurrence experienced.

Patients can die at any point from non-metastatic recurrence. Those that do not die are assumed, in the base-case, to receive 12 months of treatment before transitioning to the remission health state. Once in remission, patients remain there unless they experience another recurrence. Such a further recurrence is assumed to be non-curative (i.e., either locally advanced or metastatic).

The metastatic recurrence health state is also divided into two sub-states: endocrine resistant; and endocrine sensitive. Transition into these sub-states was dependent on how long it took patients to experience disease recurrence after completing adjuvant ET. In these sub-states, based on previously TA submissions (TA563 and TA725)[18, 19] of abemaciclib for metastatic disease, patients entered a partitioned survival model (PSM), with three survival states: progression-free survival (PFS), post-progression survival (PPS) and death where patients started in the progression free state, and they could transition from PFS to PPS or death, and from PPS to death. Death and metastatic recurrence were modelling as absorbing health states.

Figure 4.1: Structure of the model used in the economic analysis



Source: Figure 10, CS,[2]

The monarchE trial provides the IDFS, TTD and OS (without distant recurrence) to parameterise transitions for the abemaciclib + ET and ET alone treatment arms. The parameterised curves for IDFS, TTD and OS curves aid in estimating long term outcomes for patients beyond the AFU-1 dataset. This was achieved by having parametric models fitted to the Kaplan-Meier data of the monarchE trial. Clinical outcomes within the NMR and remission health state assumed the same for both treatment arms. Patients who do not experience a recurrent event for 12 months are considered to have endocrine-sensitive metastatic breast cancer and inputs and assumptions are based on the Monarch3 trial. Patients who do experience a recurrent event within 12 months are considered to have endocrine-resistant metastatic breast cancer and inputs and assumptions are based on Monarch2 trial.

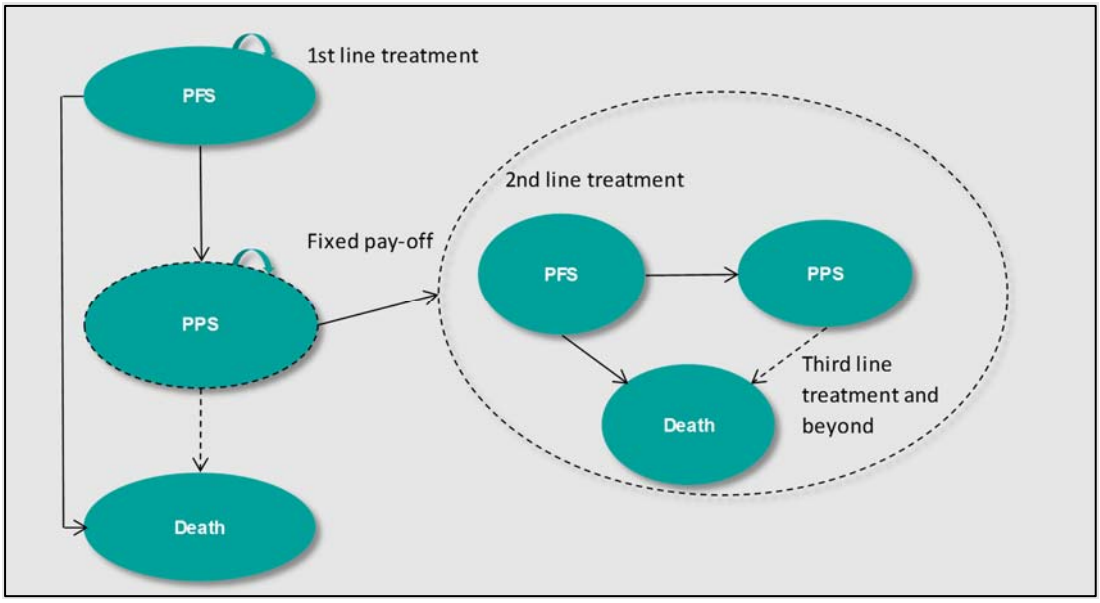
In TA725, the ET-resistant metastatic setting was modelled using a partitioned survival approach to model three health states PFS, PPS, and death (Figure 4.2).[19] PFS and OS curves were modelled using the Monarch2 trial data. The PPS health state was estimated by taking the difference with the OS and PFS curves. Life years (LYs) were accrued according to the proportion of patients in the PFS and PPS health states over time.

Figure 4.2: Model structure of ET-resistant metastatic setting

Source: Figure 20, Appendix N CS.[2]

In TA563, key clinical evidence comes from the Monarch3 trial. The ET-sensitive metastatic setting was modelled using a Cohort state transition with three health states which were PFS for 1st line, PPS and death (Figure 4.3).[18] The PFS health state was modelled as a Markov state. Following progression on their advanced breast cancer ET treatment, patients were allocated a fixed pay-off for PPS using costs and outcomes from the Monarch2 model.

Figure 4.3: Endocrine-sensitive metastatic breast cancer model diagram (Appendix M)



Source: Figure 9, Appendix M CS, [2]
PFS: progression-free survival; PPS = post-progression survival

The time period is a 28-day cycle. HRQoL varied across states. Costs varied across states due to different treatment distributions.

ERG Comment: The ERG considers the company's lifetime model to have captured all relevant health states. However, the ERG argues that the original 'top line' model is not a complete representation of the complexity of the model as presented in Microsoft Excel®. The ERG and company have debated whether the model is in fact a state transition modelling or a partitioned survival model (PSM). As acknowledged in the clarification letter, the CS model does utilise parametric survival equations to estimate the transition between IDFS to other health states.

The efficacy data is from the latest cut of the monarchE trial data. It is used to capture state transition probabilities from the IDFS health state to NMR or MR based on survival curves, akin to PSM. Within PSM, there is a survival curve for each health state. These describes time from model start (i.e., patient entry into the model) to transiting to any subsequent health state that is further along the sequence. This means that the survival curves do not represent mutually exclusive estimates of state membership.

The monarchE trial is due to end in 2029. At the time of the additional data cut (AFU1, 1st April 2021), the proportion who had completed 2-year study period was 72.2% (See Section 3.2.3).[2] This means that 27.8% of trial patients had not fully completed the planned study follow-up. Thereby, this seems premature, or at the very least, a very narrow timeframe to analyse the treatment effects of the intervention using the piecewise analysis method to assign IDFS status.

Disease stage at initial diagnosis for most patients in the monarchE trial (See Table 3.9) are stage IIIA (~36%) and stage IIIC (~34%). According to the most recent NCRAS data, the 5-year survival rates for ER+ HER2- in England with stage III initial diagnosis is 84.75%.[20] According to US statistics based on SEER database, the best survival pattern was observed among women with HR+/HER2- subtype (survival rate of 92.5% at 4 years) but show that stage III diagnosis had a 4-year survival of ~85%.[21] Estimating from Figure 26 of the CS (page 116), the 5-year (60 month) survival, excluding patients who have experienced a distant recurrence, is about ~97%. In the CEM, at cycle 60, less than one patient out of the Cohort of 1,000 was in the dead state. The ERG considers that this is an overestimation of the life expectancy of the monarchE patient group acknowledging that inclusion of death from metastatic/distant recurrence is not accounted for in the CEM.

A systematic review and meta-analysis on the risk of recurrence among this patient population (HR-positive, HER2-negative receiving adjunct endocrine therapy) reported that there was heterogeneity in outcome reporting but that the 5-year probability of breast cancer recurrence or death was 17.2% (95% credible interval: 14.6% – 20.3%).[22] Disease free survival (DFS) reported in three real-world evidence (RWE) studies ranged from 76.2% to 98.9% with follow-up periods ranging from 5 to 6 years.[23-25] In five RCT studies, the five-year DFS ranged from 79.7% (95% CI: 76.2% to 83.3%) to 91% (95% CI: 88.2% to 93.9%).[26-30] In the CS, in the abemaciclib arm, 80.7% remain in the IDFS health state compared with 74.1% in the ET only arm. Ten-year DFS was reported for patients with HR+/HER2- disease in the TEAM trial at approximately 67%.[31] In the CS, in the abemaciclib arm, 63.9% remain in the IDFS health state compared with 54.9% in the ET only arm. The ERG feels that the number of patients in the ET only arm maybe an underestimate compared to the literature.

The ERG also notes that partition survival models have been accepted predominately in metastatic/advanced disease submitted for NICE cancer appraisal. The use of PSMs for early-stage disease is relatively novel. A review of NICE cancer appraisals (between 2013 to 2016) found that when PSM models were used, 20 out of 22 were specifically for advanced disease.[32] The most commonly raised concerns found in that review related to the maturity of the data and the uncertainty around the modelled long-term OS projections. The ERG feels that concerns about trial data maturity and modelling projections also apply to this CS.

4.2.3 Population

An economic model with effectiveness evidence for a singular population was developed and the company did not provide subgroup analysis in their submission. The population in the base-case model was patients with hormone receptor positive, HER2-negative, node-positive early breast cancer. This was in line with proposed license, the final NICE scope, and population of monarchE trial (Table 4.4). Subgroup analysis by menopausal status for the economic model was asked for in the letter of clarification to the company but the company responded to the clarification letter by arguing that they did not consider menopausal status as an appropriate subgroup to include in the economic analyses. This was because subgroup analyses of IDFS and DRFS in monarchE demonstrated a consistent treatment benefit of abemaciclib + ET across pre- and post-menopausal women based on there being no statistically significant difference in the test for sub-group differences.

ERG Comment: The ERG agrees that the base-case population covers the population in the NICE scope for abemaciclib. However, the ERG argues that a subgroup analysis by menopausal status is necessary given the difference in treatment options for post-menopausal women compared with premenopausal women. That is the comparators would be different in a UK setting as outlined in Figure 2 (page 22) and Figure 3 (page 23) of the CS.[2] The standard adjunct ET in premenopausal women is tamoxifen under the current NICE guideline NG101.[5] In postmenopausal women, AIs would be given

to those with medium or high risk of recurrence. The age profile would also impact the life expectancy estimated in the model. The ERG would expect that premenopausal women would have a longer life expectancy compared to postmenopausal women and this may be an important factor in the CEA.

Another patient characteristic worthy of mention is the stage of initial diagnosis which is an important prognostic factor. According to the 2013 to 2017 cancer statistics from England, the 5-year age standardised survival is 97.9% (95% CI: 97.3 to 98.5%) for stage I, 89.6% (95% CI: 89.0% to 90.2%) for stage II and 72.0% (95% CI: 70.5 to 73.5%) for stage III. By molecular subtype, HR+/HER- has the best prognostic status of all molecular subtypes but staging still matters to OS.[21, 33] The 5-year survival rates for ER+ HER2- in England with stage III initial diagnosis is 84.75%.[20] Although the ERG did not ask for subgroup analyses by disease stage at initial diagnosis, it is important for estimates of OS and disease recurrence used in the CEA.

Table 4.4: Key baseline patient characteristics used in the economic model

Demographic parameter	Abemaciclib + ET (N=2,808) versus ET alone (N=2,829)	Source	ERG Comment
Age, years	**Mean (sd)** [redacted] versus. **Median (min, max)** 51.0 (22, 86)	monarchE	The age profile highlights the spread of patients in the monarchE trial.
Menopausal status **Premenopausal** **Postmenopausal**	**N (%)** 1,221 (43.5) versus. 1,232 (43.5) 1,587 (56.5) versus. 1,597 (56.5)	monarchE	According to the current pathway, the 43.5% of premenopausal women would be taking Tamoxifen in England. This is higher than the ~30-34% in the monarchE trial
Disease stage at initial diagnosis **Stage IA** **Stage IIA** **Stage IIB** **Stage IIIA** **Stage IIIB** **Stage IIIC** **Missing**	**N (%)** 2 (0.1) versus 1 (0.0) 324 (11.5) versus 353 (12.5) 392 (14.0) versus 387 (13.7) 1,029 (36.6) versus 1,026 (36.3) 99 (3.5) versus 88 (3.1) 950 (33.8) versus 963 (34.0) 12 (0.4) versus 11 (0.4)	monarchE	The overall survival of patients by disease stage at initial diagnosis is crucial. In England, the 5-year age standardised survival is 89.6% (95% CI: 89.0%-90.2%) for stage II and 72.0% (95% CI: 70.5-73.5%) for stage III.
Source: Table 6; Demographics of patients in the monarchE trial; Table 7: Summary of key baseline disease characteristics in monarchE. Table 9: Summary of endocrine treatments in the monarchE safety population [2]			

4.2.4 Interventions and comparators

The intervention is abemaciclib at 150 mg twice daily for a maximum of 2 years in combination with standard ET for up to 5 or 10 years. Patients would remain on abemaciclib until disease progression or toxicity in line with the proposed license and dose received in the monarchE trial. The comparators

were standard ET treatments for 5 years which consisted of aromatase inhibitors (i.e., anastrozole, exemestane, letrozole) or tamoxifen, an anti-oestrogen therapy.

In the monarchE trial, abemaciclib + ET was compared to ET. ET comprised physician's choice of standard ET used in routine clinical practice and reported in the CS to be confirmed to be relevant to NHS clinical practice in the UK by clinical experts. In the model, ET is costed as a weighted average of these treatments, based on the proportions of patients receiving each treatment in the monarchE trial (Table 36, page 93).[2] As outlined previously, menopausal status will determine comparators in England. Within the CS, there was no reference to issues with medication adherence outside the clinical trial setting and it was assumed that both arms followed therapeutic instructions.

ERG Comment: Several studies have highlighted the issue of non-adherence to adjuvant hormonal therapy in women with breast cancer.[34-37] Observational studies report rates of non-adherence from 27% to 69% over the 5- to 10-year span during which adjuvant ET is routinely prescribed.[38] This has led to many interventions to improve adherence to ET.[39] Within the CS, there was no mention of issue with ET nor was there mention of any adherence issues with abemaciclib.

As previously mentioned, proportion of ET comparators would differ by menopausal status.

4.2.5 Perspective, time horizon and discounting

The analysis was performed from the UK NHS and PSS perspective. The time horizon in the model was stated to be 49 years in the CS. The Excel model was programmed to run for 49 years from the starting age of [redacted] years. Discount rates of 3.5% are applied to both costs and benefits. A 28-day cycle length was implemented in the model and half-cycle correction was applied.

ERG Comment: The ERG notes that time horizon in the base-case analysis of the model was sufficiently long to capture the healthcare resources use and health outcomes affected by the interventions. This was considered to represent a lifetime time horizon. The approach is in concordance with the NICE reference case.

4.2.6 Treatment effectiveness and extrapolation

The process to derive the effectiveness data is summarised as follows:

- Individual Patient Data from the monarchE trial was used to build a lifetime model for a hypothetical Cohort of 1000 patients
- Kaplan-Meier curves were generated for each treatment for IDFS, TTD and OS
- To extrapolate survival beyond clinical follow-up, survival models (curves) were fitted to the data
- Several survival models (curves) were generated and compared to the Kaplan-Meier plots
- Tests for proportional hazards (PH) assumptions, alongside AIC and BIC statistics, visual inspection and consideration of published literature helped select the model adopted in the CS base-case
- A SLR was conducted to identify relevant RCTs evaluating ET-regimens in patients with HR+, HER2- early breast cancer for IDFS estimate comparison
- The relative effect of abemaciclib is the difference between abemaciclib + ET and ET only curves over time.

This Section is concerned with fitting and selecting the survival models for each treatment. To extrapolate IDFS and OS beyond the data collection period, the company followed the guidelines for survival models selection outlined in the NICE DSU TSDs 14 and 21.[1, 40] For this, Kaplan-Meier curves

from the monarchE trial data were produced. The company fitted different parametric survival models (PSMs), piecewise models and spline models to the individual patient data.

The model selection was as follows: A set of seven parametric survival curves (exponential, Weibull, Gompertz, log-normal, log-logistic, gamma and generalised gamma) and hazard splines with one or two intermediate knots were examined. Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) goodness of fit statistics; visual assessment of the survival curves and hazard plots and consideration of data in the published literature were used to determine appropriate model for the base-case economic model. The cost effectiveness results using alternative survival models were reported in scenario analyses (see Section B.3.8)

Invasive disease-free survival

The effectiveness data relevant to the model were the relative IDFS, TTD and OS (without distant recurrence) for abemaciclib + ET and the ET only comparators over time came from the monarchE. A piecemeal analysis for IDFS was performed (Table 3.15). According to the CS, the treatment benefit, based on the HRs of abemaciclib is maintained beyond the 2-year study period. Kaplan-Meier curves of IDFS for patients are displayed in Figure 3.1.

A piecewise analysis for DRFS was also performed to explore the impact of abemaciclib on DRFS over time and the results of this are presented in Table 3.21. The results, according to the CS is that the benefit of abemaciclib on DRFS is maintained beyond the 2-year study period. Kaplan-Meier curves of DRFS for patients in the ITT population receiving either abemaciclib + ER or ET alone are displayed in Figure 3.2. Despite the longer duration of follow-up at AFU1 (36 months), the OS data remained immature with a 3.3% event rate with minor difference between the trial arms (Figure 3.3).

The proportional hazard assumptions between treatment arms were tested using a log-cumulative plot, the Grambsch and Therneau test and Schoenfeld residuals visualisation. The company concluded that no violation of the proportional hazard assumption and that as such a single model, including an adjustment factor for treatment effect (HR), could be fitted to the IDFS curve of the monarchE data.

For comparison, the 5-year IDFS rates from comparative trials were used for external validation of extrapolations for the ET arm in the model (Table 4.5).

Table 4.5: Comparison of HR+ HER2− early breast cancer trials identified from the clinical SLR reporting relevant survival outcomes

Trial name	Treatment	Timepoint for rate (Years)	IDFS/DFS rate (%) [95% CI]
Monarch E	ET + CDK4&6 inhibitors	~3	Abemaciclib + ET: 88.8 [87.0, 90.3][a]
HOBOE	Tamoxifen versus. AI	~5	Tamoxifen: 85.4 [80.9, 88.9] Letrozole: 93.2 [89.7, 95.5]
FATA-GIM3	Tamoxifen to AI versus. AI	~5	Anastrozole pooled Letrozole pooled Exemestane pooled
FACE	AI versus AI	~5	Letrozole: 84.9 [83.2 - 86.2]

Trial name	Treatment	Timepoint for rate (Years)	IDFS/DFS rate (%) [95% CI]
			Anastrozole: 82.9 [81.2 - 84.5]
SOFT	Tamoxifen + OFS versus. AI + OFS	~8	Tamoxifen: 78.9 Exemestane + OFS: 85.9
TEXT		NA	Total events:[b] Tamoxifen + triptorelin: 12.59 Exemestane + triptorelin: 16.25

Source: Table 39, CS.[2]
[a]3-year IDFS rates from the AFU1
[b]The TEXT trial reported the total events, rather than the IDFS/DFS rate
AI = Aromatase inhibitor; CDK = cyclin-dependent kinase; CI = confidence interval; DFS = disease-free survival; ET = endocrine therapy; HER2- = human epidermal receptor 2 negative; HR+ = hormone receptor positive; IDFS = invasive disease-free survival; NA = not applicable; OFS = ovarian function suppression; SLR = systematic literature review

The company raises cautions about the direct comparison of data from other trials with the monarchE as the external trials incorporated a mixture of patients, including those at lower risk of disease recurrence. This would mean that patients would have had slightly better outcomes in the ET alone arms. The landmark IDFS rates for abemaciclib + ET and ET alone for the seven parametric distributions and the two spline models are presented in Table 4.6.

Table 4.6: Landmark IDFS rates for abemaciclib + ET and ET alone arms

	Five-year rates		Ten-year rates	
	Abemaciclib + ET	**ET**	**Abemaciclib + ET**	**ET**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Hazard spline 1 knot	[redacted]	[redacted]	[redacted]	[redacted]
Hazard spline 2 knots	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 40, CS.[2]
CS = company submission

An important consideration in treatment effect is that of 'treatment waning'. Based on their piecemeal analysis for IDFS HRs in monarchE, the company suggests that a lasting treatment effect beyond discontinuation does exist for abemaciclib. The Aromidex, Tamoxifen, Alone or in Combination (ATAC) trial was cited as the most relevant to inform treatment waning assumptions. The ATAC trial demonstrated the falling recurrence rates for HR+ patients with 'carryover benefit' lasting up to 8-years

following which treatment effects begins to wane.[41] The company assumed that treatment effects last for at least 8-years from initiation of treatment with abemaciclib following which treatment effect begins to wane. Treatment effect wanes until year 27 (where IDFS rates equal background mortality), following which no treatment benefit was assumed.

The long-term extrapolations for abemaciclib + ET and ET using the loglogistic model and including the treatment waning assumptions are presented in Figure 4.4. The impact of the timing and duration of the treatment waning effect are explored in scenario analyses.

Figure 4.4: Long-term IDFS extrapolations for abemaciclib + ET and ET alone in the base-case economic analysis

Source: Figure 16, CS.[2] These extrapolations include treatment waning.
ET: endocrine therapy; IDFS: invasive disease-free survival; KM: Kaplan-Meier.

The duration of treatment is determined by the TTD curves of both treatment arms from the monarchE trial where patients remained on treatment until they 1) reached a limit defined by a clinical stopping rule, 2) discontinued treatment due to toxicity, or 3) withdrew from study or experienced disease recurrence. Using the same statistical tests, violation of the proportional hazard assumption had occurred and that the hazard spline 2 knots was the best statistical fit for the intervention and comparator arms.

For OS, the same statistical tests and data visualisation were followed. According to the company, the base-case cost effectiveness model uses a single model fitted, using an adjustment factor for treatment effect (HR), to the monarchE trial data. The exponential curve provided the best statistical fit based on AIC and BIC (Figure 4.5). Other extrapolations for OS were explored as scenario analyses.

Figure 4.5: Long-term OS extrapolations for abemaciclib + ET and ET alone in the base-case economic analysis

Source: Figure 26, CS.[2]

A summary of the base-case extrapolations for IDFS, OS and TTD for abemaciclib + ET and ET alone are provided in Table 4.7.

Table 4.7: Summary of the base-case extrapolations for IDFS, OS and TTD for abemaciclib + ET and ET alone

	Abemaciclib + ET		**ET alone**
Base-case IDFS extrapolation	Log-logistic		Log-logistic
Base-case OS extrapolation	Exponential		Exponential
	Abemaciclib	**ET (for patients receiving abemaciclib)**	**ET alone**
Base-case TTD extrapolation	Hazard spline 2 knots	Hazard spline 2 knots	Hazard spline 2 knots
Source: Table 45 from the CS.[2] CS = company submission; ET = endocrine therapy; IDFS = invasive disease-free survival			

Remission health state

The most recent NICE TA for trastuzumab was used to inform the transition probability of patients moving from remission to the metastatic health state. TA632 used a study (Hamilton et al (2015) of 12,836 patients with early breast cancer which estimated a risk of incurring a second malignancy following adjunct therapy.[42] The study reported a mean time until progression of 7.6 years (91.2 months). The mean time to progression was converted into a monthly transition probability and assumed to remain constant over time based on clinical expert feedback.

Metastatic health state

In the absence of clinical data for the monarchE distant recurrent population, data from a broader advanced breast cancer population was used. Inputs and assumptions from previous abemaciclib cost effectiveness analyses in the metastatic settings (TA563 and TA725) were used to inform outcomes for patients in the metastatic setting.[18, 19]

The ET-resistant and ET-sensitive metastatic pathway in this model are based on the Monarch2 and Monarch3 trials respectively. These are populations that differ from monarchE patient population. The company state where possible they align with the Committee's preferences for all inputs, due to the need to accurately represent the full range of treatments a patient might receive in the metastatic setting in UK clinical practice, including treatments which were not relevant comparators in TA563 and TA725.[18, 19] Scenario analyses were conducted and the company state that variation in the costs and outcomes experienced in the metastatic setting did not have a major impact on result.

For this submission's cost effectiveness model, a metastatic health state 'pay off' approach was used. This is where survival outcomes following progression to the metastatic health state from either IDFS or the remission health state at point of recurrence were attributed a 'fixed pay off' of LYs from previous TA submissions as far as possible. Based on UK clinical experts, it was assumed that patients who received abemaciclib in the adjuvant setting were not permitted to receive a CDK4/6 inhibitor treatment in the metastatic setting. Within a scenario analysis, CDK4/6 re-treatment has been assessed.

ERG Comment: The ERG notes that there is considerable uncertainty in the long-term effectiveness of abemaciclib + ET compared with ET alone in extending IDFS and OS due to issues such as I) limited duration of follow-up periods, (II) patient heterogeneity, and (III) 'carryover benefit'.

I) In the clarification letter, the ERG has asked for the evidence of the suggested benefit beyond the trial be justified. The company responded by stating that: *a piecewise analysis for IDFS was performed, and the HRs for Year 2+ suggest that a lasting treatment effect beyond discontinuation does exist for abemaciclib*. The company also in the clarification letter state that it would be clinically implausible and inappropriate to provide a scenario analysis to assume that no lasting treatment effect exists for abemaciclib.

II) Patient heterogeneity -pre- and post-menopausal status may be important in determining the treatment effectiveness of abemaciclib.

III) The 'carryover benefit' - assumptions informing the waning of the treatment effect were based on the long-term treatment effect for ET, from historical trial data. Therefore, there is an absence of evidence to the carryover benefit of abemaciclib.

Uncertainty associated with these issues cannot be captured in the economic analysis results as provided without substantial re-working of the submission. For example, the functional form of treatment waning is assumed linear in the CEM but could take other forms. However, which functional form is most appropriate is currently an unresolvable uncertainty based upon the evidence submitted in the CS. the ERG notes that the CS follows recommendations in the TSDs 14 and 21 for the selection of the survival models to fit to the data, and for the selection of survival models to use in the economic analysis.[1, 40] For the TTD extrapolation for abemaciclib, a violation of proportional hazards assumption occurred and in the CEM, the company choose not to make use of the Kaplan-Meier-curve data which is questionable.

The scenario analyses do not report the impact of extrapolating IDFS with a log-normal distribution on the ICER. Section B.3.3.2 in the CS compares IDFS/DFS rates from the literature (see Table 39) with the IDFS rates extrapolated using different survival models (see Table 40), and notes that all the extrapolations estimate increasingly pessimistic outcomes for the comparator arm over time.[2] A log-logistic extrapolation was chosen as this parametric model presents a good statistical fit with the trial data, despite underpredicting IDFS rates at 5 and 10 years relative to the literature and alternative models such as a log-normal extrapolation.

The underprediction of IDFS rates is justified in the CS by the monarchE trial only including patients at high risk of disease recurrence; however, underpredicting IDFS in the long term can potentially benefit the intervention arm, as any improvements on IDFS are more meaningful if IDFS is low. Furthermore, the literature used reports DFS, which may underestimate IDFS as some DFS definitions are narrower, therefore the underestimation of IDFS in the model may be even more severe than reported by the CS.

4.2.7 Adverse events

AE probabilities for abemaciclib + ET and ET in the IDFS state were informed by the AFU1 data cut of the monarchE trial. These are presented in Table 4.8 and Table 4.9. The disutility values in the metastatic recurrence health state were informed by the Monarch2 and Monarch3 trials. These are presented in Tables 4.10 and 4.11.

It was reported in the CS that the model base-case included Grade III/IV AEs reported in the AFU1 data cut of the monarchE trial, with an incidence of ≥1% in the respective treatment arms in the trial, as well as Grade I/II AEs with an incidence of ≥ 50% (only Grade I/II diarrhoea had an incidence ≥ 50%).

Table 4.8: Summary of Grade I/II adverse events in IDFS

	Treatment Arms	
Health state	**Abemaciclib + ET**	**ET**
Diarrhoea	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Abdominal Pain	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Hot Flush	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]

Source: Table 51, CS.[2] and Economic Model
CS = company submission; ET = endocrine therapy

Table 4.9: Summary of Grade III/IV adverse events in IDFS

	Treatment Arms	
Health state	**Abemaciclib + ET**	**ET**
Neutropenia	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Aspartate aminotransferase increase	[redacted]	[redacted]
Alanine aminotransferase increase	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Venous thromboembolic event	[redacted]	[redacted]

Source: Table 51, CS.[2]
CS = company submission; ET = endocrine therapy

Table 4.10: Summary of Grade III/IV adverse events in Metastatic Recurrence Setting (Monarch3)

	Treatment Arms							
Health state	**ABE-NSAI**	**PAL-NSAI**	**RIBO-NSAI**	**CDK4&6i + NSAI**	**NSAI**	**EXE**	**TMX**	**FUL**
Grade III/IV								
Alanine aminotransferase increase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Source: Economic Model								

Table 4.11: Summary of Grade III/IV adverse events in Metastatic Recurrence Setting (Monarch2)

	Treatment Arms							
Health state	**ABE-FUL**	**RIBO-FUL**	**PAL-FUL**	**CDK4&6i + FUL**	**EXE-EVE**	**FUL**	**CAP**	**EXE**
Grade III/IV								
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma-glutamyl transferase (GGT) increase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Hyperglycaemia	[redacted]							
Leukopenia	[redacted]							
Neutropenia	[redacted]							
Stomatitis	[redacted]							
Source: Economic model								

Both the disutility values and costs of AEs were included in the economic model. AE disutility values and duration estimates were used to assess the overall impact of AEs on QALYs. These disutility values are discussed in Section 4.2.8. AEs were assumed to occur once within the first cycle of the model, for patients receiving treatment. AEs were associated with one-off costs and disutility values, which were then multiplied by the AEs incidence to obtain the total costs and disutility values associated with AEs.

ERG Comment: The ERG notes that the proportions of AEs for the comparators are taken from the monarchE trial, and that this is very likely to be the best available evidence at the time. The ERG considers the 1% inclusion threshold for the Grade III/IV AEs to be acceptable. The ERG considers the 50% inclusion threshold for the Grade I/II AEs to be acceptable. The proportion of patients with Grade I/II AEs (aside from diarrhoea) was not provided in either the main report or the Appendices but is included in the economic model. These data have been reproduced in Table 4.8.

It was assumed that AEs occur once within the first cycle of the model and were associated with one-off costs and disutility values which were multiplied by the incidence to calculate the total disutility. This is a typical assumption made in economic models of this nature and in previous TARs (for instance TA563 and TA612). However, the implication of this assumption is that all AEs are transitory, and that is there are no persisting impacts of AEs on individuals over time. Although this assumption may be justified for some AEs, for instance abdominal pain, it may not be for others, for instance fatigue. Consequently, it is possible that the disutility associated with some AEs has been underestimated in the economic model.

4.2.8 Health-related quality of life

Utility values for invasive disease-free survival (IDFS), non-metastatic recurrence (NMR), remission, progression-free survival (PFS) and disease progression (PPS) health states were included in the model. An economic systematic literature review (SLR) was carried out to identify cost effectiveness studies which could be used to inform the economic model. None of the identified cost effectiveness studies modelled a patient population consistent with the monarchE population. Therefore, to supplement the results from the SLR, a targeted literature review (TLR) was carried out on HTA databases and HTA websites to elicit potential utility data for use in the model. In total, 22 reports were identified, of which four HTAs satisfied the company's inclusion criteria (TA501, TA569, TA612, TA632). Eligible studies were economic evaluations (either cost effectiveness analysis or cost utility analysis) in the early-stage breast cancer population (Stage I - IIIC) since 2015. Three of the NICE HTAs identified by the TLR specifically modelled a HER2+ patient population (TA569, TA612, TA632) and were therefore seen to be appropriate for inclusion in the economic model. A summary of the health states utility values and AE disutility values used in the identified HTA submissions is shown in Table 4.12.

Table 4.12: Summary of health state utility value and AE disutility values used in the identified HTA submissions

Author, Year	Health state specific utility	Adverse event specific utility
TA632, 2020	Non-metastatic recurrence: 0.775	NA

	Remission: 0.788 1L MBC: 0.765 2L MBC: 0.508	
TA612, 2019	IDFS: 0.837 Local recurrence: 0.696 Remission assumed same as IDFS Distant recurrence <12 months: 0.521 Distant recurrence >12 months assumed same as distant recurrence <12 months l arms	Specific disutility for Grade 3/4 AEs as well as a disutility value for Grade 1/2 diarrhoea
TA569, 2019	IDFS on treatment: 0.756 IDFS on treatment: 0.785 IDFS off treatment: 0.822 Local or regional recurrence: 0.756 Remission: 0.822 1L MBC: 0.773 2L MBC: 0.52	Assumed that any disutility from treatment-related AEs is reflected in the EQ-5D responses from the APHINITY study[43]
TA501, 2018	Recurrence free in first year: 0.7728 Recurrence free after first year: 0.8112 Local recurrence: 0.8112 Disease-free after local recurrence: 0.8112 Any other recurrence: 0.685	NA
Source: Table 52, CS.[2] AEs = adverse events; CS = company submission; IDFS = invasive disease-free survival; NA = not applicable		

The company stated that utility decrements were also included for the proportion of patients who experienced a Grade III/IV AE, and for Grade I/II diarrhoea, which was experienced by >50% of those in the Abemaciclib + ET arm. The utility for each of the states was applied for the duration spent in each of the states. The utility decrement for an AE was included at the beginning of the model as a one-off decrement and multiplied with the duration of the AE to obtain a QALY decrement. The proportion of patients experiencing an AE was discussed in Section 4.2.7, and the proportions were reported in Tables 4.8 – Table 4.11.

Health state utility values

The utility value used in this model to represent the primary endpoint, IDFS, was sourced from the pivotal clinical trial, the monarchE trial. In line with the NICE reference case, utility for IDFS was measured using the EQ-5D-5L with responses cross-walked to the EQ-5D-3L value set. Participants in this trial completed the EQ-5D-5L at Baseline, visit 6 (3 months), visit 9 (6 months), visit 15 (12 months), visit 21 (18 months), visit 27 (30 days post treatment discontinuation) and during the first and second long-term follow-up visit. Thus, the timing of assessments did not capture the effects of any transitory AEs the patient might have experienced during the first 3 months (i.e., prior to visit 6). Nor would it have captured the impact of any AE that did not occur on or a few days before any of the data collection timepoints.

This EQ-5D-5L data was cross-walked to the existing EQ-5D-3L value set as currently recommended by NICE using the established mapping algorithm. As the data showed no significant difference between treatment arms, the CS made the assumption that overall utilities were appropriate to be applied to both treatment arms instead of treatment-specific utilities. In addition, mean change from baseline in mean index scores were estimated using a Mixed effect Model Repeat Measurement (MMRM) regression. This regression included independent variables for treatment, visit, an interaction term between treatment and visit (treatment*visit), and baseline. The cross-walked data for IDFS collected during the monarchE trial were in alignment with the values used in TA569. However, the value was slightly lower than those used in TA612. Utility data for the other health states was not able to be obtained from the monarchE trial.

In the absence of trial utility data form monarchE to inform the remission health state, it was assumed that patient's utility returned to IDFS baseline following second remission. For the NMR health state, clinical expert opinion was used as the basis of the assumption that patients would receive intensive treatment for loco-regional/contralateral recurrence for the first three months. This would be expected to be associated with a detrimental impact on HRQoL. Following this, patients would return to their previous HRQoL. The disutility for the first three months was taken from Lidgren et al (2007). The utilities for the various PFS health states and the PPS state were taken from the Monarch2 and Monarch3 clinical trials, except for the PFS2 health state (PFS 2nd line), which was taken from Mitra et al (2016). This is in line with the ERG's preferred values in TA563. A summary of all utility values used in the economic model is provided in Table 4.13.

Table 4.13: Health state utility values

Health state	Utility value	Source	Justification
IDFS	[redacted] for both trial arms	MMRM regression using data from monarchE trial	In line with the NICE reference case, utility data derived from the pivotal clinical trial are preferred where available
NMR	[redacted]Weighted average of 0.696 for first 3 months and [redacted] for last 9 months for both trial arms	Weighted average: First 3 months Lidgren et al (2007) Last 9months assumed to be equal to IDFS	Clinical expert opinion indicated patients would receive intensive treatment for loco-regional/contralateral recurrence for the first few months, which is expected to be associated with a detrimental impact on HRQoL. Following this, patients would return to their previous HRQoL. The use of Lidgren et al (2007) is aligned with prior NICE appraisal TA612 in the absence of trial utility data from monarchE to inform this state.
Remission	[redacted] for both trial arms	Assumed to be equal to IDFS	In line with prior NICE appraisal TA632 in the absence of trial utility data from monarchE to inform

			this state, it is assumed that patient utility returns to IDFS baseline following second remission
MR2 - PFS	[redacted] for all MR2 treatments	MONARCH 2 trial	In line with prior NICE appraisal TA725 in advanced breast cancer.
MR2 - PPS	[redacted] for all MR2 treatments	MONARCH 2 trial	In line with the Committee's preferred values in TA725 in advanced breast cancer.
MR3 - PFS1	[redacted] for all MR2 treatments	MONARCH 3 trial	In line with the ERG's preferred values in prior TA563 in advanced breast cancer.
MR3 - PFS2	[redacted] for all MR2 treatments	Mitra et al (2016)	In line with the ERG's preferred values in prior TA563 in advanced breast cancer.
MR3 - PFS3	[redacted] for all MR2 treatments	MONARCH 3 trial	In line with the ERG's preferred values in prior TA563 for PPS in advanced breast cancer.
Source: Table 54, CS.[2] CS = company submission; ERG = Evidence Review Group; HRQoL = health related quality of life; IDFS = invasive disease-free survival; MMRM = Mixed effect Model Repeat Measurement; NICE = National Institute for Health and Care Excellence			

The utility values for the early breast cancer states of the model were age adjusted using the values provided by Janssen and Szende in the base-case analysis. Given the short life expectancy for patients in the metastatic health state, age-related deterioration was not applied to these health states. A scenario analysis was conducted where the utility values were age-adjusted using the values provided by Ara and Brazier rather than Janssen and Szende. The ICER changed marginally, from £3,786 per QALY in the base-case to £3,841 per QALY. No other scenario analyses were conducted in relation to the utility values.

Disutility values

A number of AEs were included in the model. The disutility values for AEs in the IDFS health state are presented in Table 4.14.

Table 4.14: Disutility and mean duration of adverse events in IDFS health state

Parameter	Disutility	Reference	Mean duration (days)	Reference
Neutropenia	0.007	Monarch3, Hudgens et al (2016), TA306, TA579	15.09	Monarch3, Nafees et al (2008), TA306, TA579
Leukopenia	0.003	Monarch3, Hudgens et al (2016), TA306, TA579	13.96	Monarch3, Nafees et al (2008), TA306, TA579
Diarrhoea	0.103	TA612	8.00	TA612

Lymphopenia	0.000	Monarch3, TA306	34.00	Monarch3, TA306
Fatigue	0.003	Hudgens et al (2016)	12.70	Hudgens et al (2016)
Aspartate aminotransferase increase	0.000	Monarch3, TA503	0.00	Monarch3, TA503
Alanine aminotransferase increase	0.005	Monarch3, TA503	28.00	Monarch3, TA503
Thrombocytopenia	0.000	Assumption	0.00	Assumption
Anaemia	0.119	TA579	16.07	TA579
Abdominal pain	0.048	TA612	8.82	TA612
Venus thromboembolic event	0.000	Assumption	0.00	Assumption
Source: Table 53, CS.[2] CS = company submission				

The additional disutility values used in the Metastatic Recurrence health state are presented in Table 4.15. No scenario analyses were conducted in relation to the disutility values.

Table 4.15: Additional disutility and mean duration of adverse events used in the Metastatic Recurrence health state

Parameter	Disutility	Reference	Mean duration (days)	Reference
Dyspnoea	0.029	Hudgens et al (2016)	12.70	Hudgens et al (2016)
Gamma-glutamyl transferase (GGT) increase	0.000	Assumption	0.000	Assumption
Hyperglycaemia	0.119	Swinburn et al (2010) (Assumption: same as anaemia)	16.10	Swinburn et al (2010) (Assumption: same as anaemia)
Stomatitis	0.269	Swinburn et al (2010) (Assumption: disutility for mucositis only)	4.00	(Assumption: same as mucosal inflammation)
Source: Company Economic Model				

ERG Comment:

Utility Values

As noted above, the utility value used in the base-case analysis for the IDFS health state was based on the results from the ongoing monarchE trial, which is in line with the NICE base-case. As there was no statistically significant difference between treatment arms, overall utilities were applied to both treatment arms instead of treatment-specific utilities. The ERG does not consider this to be best practice. This assumes that lack of evidence of a difference is the same as evidence of no difference. Whilst the differences in utility values are small (see Table 3.33), the different utility values should be used for the different treatment arms and the imprecision should be explored within the probabilistic sensitivity

analysis (PSA). Furthermore, as the monarchE trial is currently ongoing, there may be missing follow-up data for the IDFS state (as measured by the EQ-5D-5L) from later data cuts. Further data from these later data cuts could improve the accuracy of the estimates for this parameter and would be informative.

The ERG considers the assumption that the utility of the remission health state would be equal to that of the IDFS state to be appropriate. This is consistent with previous TARs in this clinical area (TA569, TA612 and TA632).

For NMR state, it was assumed that patients would receive intensive treatment for loco-regional/contralateral recurrence for the first 3 months, which is expected to be associated with a detrimental impact on HRQoL. Following this, patients would return to their previous HRQoL (which was assumed to be equal to the IDFS state). These assumptions were gathered through expert opinion. During the clarification process, the company provided details of the clinical expert opinion used to support this assumption. Although expert opinion is not an optimal evidence source, the ERG accepts that there may be little alternative when no better data are available.

The utility value for the first 3 months was taken from Lidgren et al (2007), a well-established source of utility data which was also used in TAR612 for the 'local recurrence' state. The study results from a study of 361 patients with consecutive breast cancer attending the breast cancer outpatient clinic in Sweden. The EQ-5D-3L and time trade-off (TTO) were used to estimate the utility value of a range of breast cancer health states, including 'First year after primary breast cancer' (State P), 'First year after recurrence' (State R) and 'Second and following years after primary breast cancer/recurrence' (State S). The company used the utility values from the EQ-5D-3L rather than the TTO to populate the economic model. The company used State P as their utility value for loco-regional/contralateral recurrence (0.696). The ERG considers State R (0.779) to be a more appropriate utility value from the Lidgren et al (2007) study to use for the first 3 months of the NMR, as it is more closely aligned with the 'local recurrence' health state than State P. Taking a weighted average in the same manner as in the CS, using the utility value for the 'First year after recurrence' health state (State R) for the first 3 months rather than the utility value for 'First year after primary breast cancer' (State P) would increase the utility value of the NMR state from 0.760 to 0.781 for the full 12 months.

During the clarification process, the company acknowledged that there was uncertainty regarding the choice of utility applied for the first 3 months, and that it was equally feasible that 'First year after recurrence' (State R) was appropriate to apply in the economic model. A scenario analysis was provided by the company where 'First year after recurrence' (State R) was used in the place of 'First year after primary breast cancer' (State P) for the first 3 months in the economic model. There was no impact on the ICER (£3,786 per QALY).

For the PPS and PFS health states, the utility values are taken from the Monarch2 trial, and are consistent with TA725. The ERG considers these to be an appropriate utility values. For the PFS1 health state, the utility value is taken from the Monarch3 trial, and is consistent with TA563. The ERG considers this to be an appropriate utility value.

For the PFS2 health state, the utility value (0.690) is taken from Mitra et al (2016), which was reported as being the ERG preferred value in TA563. Mitra et al (2016) reports health utility (as measured by the EQ-5D-5L) for various metastatic breast cancer states, including PFS2. It should be noted that the study used patients from five major European Union countries and the United States (N=739), and therefore may not be transferable to the UK population. Furthermore, Mitra et al (2016) is a conference abstract, and therefore has not been through formal peer review. In TA563, the utility value used for PFS2 was 0.774, based on TA496 and Lloyd (2006). An alternative approach could be to assume that the utility for PFS1 would be expected to be at least as good as the utility for PFS2 for example 0.774 for both PFS1 and PFS2, but the ERG does not consider this a Key Issue. For the PFS3 health state, it

is assumed that the utility value is the same as the utility value for the PPS health state from the Monarch2 trial. No further justification was given by the company regarding this assumption.

Overall, the ERG considers the health state utility values used in the economic model to be appropriate and in line with previous TARs in this population. The main exception to this is the choice by the company to use overall utilities for the IDFS health state as opposed to treatment-specific utilities. This assumes that lack of evidence of a difference is the same as evidence of no difference and is not best practice. Treatment-specific utilities should be used, and the imprecision should be explored within a probabilistic sensitivity analysis. There is uncertainty regarding the choice of utility value for the first three months NMR health state, a scenario analysis provided by the company during the clarification process indicated that using a different (and equally feasible) utility value would have a negligible impact on the ICER.

Disutility Values

The ERG notes that the disutility values derived from the literature for AEs may not be representative of the study population and may not be the preferred measure of utility for the NICE reference case. However, the ERG also notes that these may be the best available estimates, and all of them have been used in previous NICE submissions. Specific issues related to the disutility values are discussed below.

The CS stated that utility decrements were included for the proportion of patients who experienced a Grade III/IV AE, and for Grade I/II diarrhoea, which was experienced by >50% of those in the abemaciclib + ET arm. TAR612 was used as the source of the utility decrement and duration of Grade III/IV diarrhoea, which uses data from Lloyd et al (2006). This study generated health state utilities for distinct stages of metastatic breast cancer using a nationally representative sample of the UK general public. The ERG considers this to be an appropriate data source for the utility value. However, it should be noted that several ERG reports have recognised some limitations of this study. The health states described in the Lloyd study were based on literature reviews, exploratory interviews with physicians, an oncology focus group made up of specialist nurses; and that the health states were gender neutral and did not mention cancer, the derived utility values for the general public may not be fully reflective of patients with breast cancer or even the true general population. The duration spent in the health state was not taken from Lloyd et al (2006) and was instead taken from data from the ExteNET trial on file from Puma Biotechnology. The ERG was therefore unable to scrutinise the source of the duration of diarrhoea used in the model.

A disutility value or duration was not provided for Grade I/II diarrhoea in the main submission or the appendices. Furthermore, upon inspection of the economic model, it was found that although the costs of Grade I/II diarrhoea had been included in the economic model, the disutility values for Grade I/II diarrhoea had not been. In TAR612 (the source of the utility decrement and duration for Grade III/IV Diarrhoea in the CS), the utility decrement for Grade I/II Diarrhoea is reported as 0.060. This utility decrement is originally sourced from Besuterien et al (2009),[44] in which utilities for AEs related to advanced melanoma were gathered from a representative sample of the UK population using the standard gamble method. In TAR612, the mean duration of Grade I/II diarrhoea was mean duration of 14.6 weeks (102 days) for those patients without prophylaxis and 9.9 weeks (69 days) for those with prophylaxis. Like the data for Grade III/IV diarrhoea, this duration data is taken from data from the ExteNET trial on file from Puma Biotechnology.

Hudgens et al (2016) was used as the source of the disutility values for ‘neutropenia’, ‘leukopenia’ and ‘dyspnoea’. This study derives health state utilities for patient with metastatic breast cancer, using data from a Phase III clinical trial in locally advanced metastatic breast cancer. The ERG considers these utility values to be appropriate. Hudgens et al (2016) is also used as the source for the duration for dyspnoea. It is unclear how the mean duration for dyspnoea has been calculated, as the durations of the different disutility values are not discussed in the Hudgens et al (2016) study. TAR306 and Nafees et

al (2008) were quoted as the sources for the durations for neutropenia and leukopenia. Although Nafees et al (2008) does generate a disutility value for neutropenia, it does not mention leukopenia or the duration of either AE. The source of the durations for neutropenia and leukopenia in TAR306 was the PIX301 trial, an RCT investigating pixantrone monotherapy for the treatment of relapsed or refractory aggressive non-Hodgkin's lymphoma. The durations used for neutropenia and leukopenia were 15.09 days and 13.96 days respectively. Although these durations were sourced from a different population, the ERG considers these durations to be the best available estimates, and therefore a reasonable assumption.

Hudgens et al (2016) was also used as the source for the disutility value for 'fatigue'. The utility decrement for fatigue in this study is 0.030 rather than the 0.003 value quoted in the CS. The correct value was used in the economic model. Although a larger utility decrement for fatigue has been reported in studies used for other utility decrements (Lloyd et al (2006)), the 0.030 utility decrement was used in TAR579, and the ERG consider this a reasonable assumption. It is unclear how the mean duration of Fatigue has been calculated, as the durations of the different disutility values are not discussed in the Hudgens et al (2016) study.

TAR563 is used as the source of the disutility value for lymphopenia. In TAR563, clinician opinion indicated that this health state was not associated with any disutility. The ERG considers this to be a strong assumption, as severe cases of lymphopenia can be life-threatening. During the clarification process, the company stated that as a suitable UK specific disutility value could not be identified from the economic SLR or targeted literature search, an assumption of zero disutility was used in the monarchE early breast cancer setting. It is worth noting that a disutility value for lymphopenia has been used in previous TARs. For instance, the disutility value for lymphopenia used in TAR306 was 0.371, as it was assumed to be equal to the maximum disutility of all other Grade III/IV AEs.[45] However, given the expected short duration of lymphopenia the ERG do not consider this a Key Issue. The duration of lymphopenia (34 days) is taken from TAR306. The ERG considers this duration to be a reasonable assumption.

TA579 is used as the source for the disutility value for 'anaemia' (0.119) and its duration (16.07 days). The original source of the utility decrement was Swinburn et al (2010),[45] a study which gathered health state utilities for several health states related to renal cell carcinoma from a representative UK population using the TTO method. The ERG considers this disutility value and duration to be the best available estimate, and therefore a reasonable assumption.

The Monarch3 trial (referenced as TAR563) and TA503 were used as the sources for the disutility values of 'Aspartate aminotransferase increase' (AST) and 'Alanine aminotransferase increase' (ALT). The utility decrement for ALT used in TA503 and TAR563 was 0.050 rather than the 0.005 value quoted in the CS. The correct value is used in the economic model. The duration length of 28 days for ALT is an assumption based on expert opinion originally made in TA347. The ERG considers this to be a reasonable assumption. No justification of the assumption of no disutility or duration for AST is given in TA503, and therefore the ERG was unable to scrutinise this value. Although data on disutility values for AST and ALT are scarce, it is worth noting that a previous economic evaluation in multiple sclerosis has assumed no disutility for both AST and ALT.[46]

Although in the CS it was stated that thrombocytopenia did not have a disutility value, in the economic model a disutility value of 0.108 and a duration of 23 days was included. These values were sourced from Tolley et al (2013) and TA359. Although the population for Tolley et al (2013) study was patients with late-stage chronic lymphocytic leukaemia, it should be noted that this disutility value has also been used in several other health economic models in different populations, including those related to Metastatic Merkel Cell Carcinoma and Midgut Neuroendocrine Tumours.[47, 48] The ERG considers the disutility value and duration to be reasonable assumptions.

Due to the lack of clinical evidence, the 'venous thromboembolic event' (VTE) health state was assumed to not be associated with any disutility. The ERG considers the assumption that a VTE (which may encompass conditions such as deep vein thrombosis or a pulmonary embolism) being associated with no disutility may be unrealistic given that this is an acute and potentially life-threatening condition. During the clarification process, the company stated that as a suitable UK specific disutility value could not be identified from the economic SLR or targeted literature search, an assumption of zero disutility was used in the monarchE early breast cancer setting. They also stated that clinical opinion sought did not provide any alternative suggestions for this input. Although data on disutility associated with thromboembolic events are scarce, previous health economic models have included a disutility for this event.[49-51] For instance, as part of a previous economic evaluation early-stage breast cancer (Hannouf et al (2020)[50]) it was assumed that thrombosis is associated with a disutility value of 0.160 (a value originally source from Enden et al (2013)[52] for the lifetime in the VTE state.

TAR612 is used as the source for the disutility value for abdominal pain (0.048) and its duration. It is assumed that abdominal pain is associated with the same disutility as nausea and vomiting. The ERG considers this to be a valid assumption. The utility values for nausea and vomiting are taken from Hafees et al (2008). The Nafees et al (2008) study utilises a Standard Gamble technique on a sample of the general population recruited from a local London newspapers and from an existing UBC database of willing survey participants. This study population is not fully representative of the UK population. The duration spent in the health state is taken from data from the ExteNET trial on file from Puma Biotechnology. The ERG was therefore unable to scrutinise the source of the duration of abdominal pain used in the model.

Gamma-glutamyl transferase (GGT) increase, hyperglycaemia and stomatitis were included as AEs in the Metastatic Recurrence Setting, using the data from Monarch2 trial (TA579). It was assumed that GGT would not be associated with any disutility. The ERG considers this to be a reasonable assumption. Swinburn et al (2010) was used as the source of the disutility value of hyperglycaemia and stomatitis. The ERG considers these disutility values to be the best available estimates, and therefore a reasonable assumption. It was assumed that the duration of hyperglycaemia would be the same as anaemia, and that the duration of stomatitis would be the same as mucosal inflammation. The ERG considers both assumptions to be reasonable.

Overall, the ERG considers the company's approach to including disutility values for AEs in the economic model to be consistent with previous TARs and economic models of this type. As noted in Section 4.2.7, by assuming that all AEs are transitory there is the possibility that disutility associated with AEs has been underestimated in the economic model. There are also several discrepancies and inconsistencies in the disutility values used in the economic model. However, the effect of most of these AEs on the ICER is likely to be negligible due to the low frequency of these AEs and relatively small disutility values.

4.2.9 Resources and costs

Resource use and costs data identified in the review

According to the CS, the SLR identified no studies reporting UK relevant resource use and cost information that was relevant to the monarchE patient population. For this reason, the targeted literature review of previous TAs published by NICE in early breast cancer was conducted.

The targeted search identified four relevant TAs. The previous TAs that were identified were TA632, TA612, TA569 & TA501.[42, 53-55] Resource use was derived from the monarchE trial and unit costs were derived from national published reference costs. The use of UK national reference costs aligns with NICE TA guidance. The CS also notes that clinical expert opinion has been sought for certain elements of the costing.

Drug Costs

Drug costs were calculated using published unit costs and the dose regiments based on data from the monarchE trial data. Unit costs were costed from the drugs and pharmaceutical electronic market information tool (eMIT) and from the British National Formulary (BNF).

Tables 4.16 and 4.17 displays the sources of drugs costed from the eMIT from the CS. Although the source is from the eMIT 2020, the accompanying reference is for the eMIT dated 2018.

Table 4.16: Costs from the CS for different drugs used in the model.

Treatment	Dose per tablet or vial	Units per package	Cost per package	Source
ABE	150 mg	56	List price: £2,950.00 PAS price, £[redacted]	Lilly
ET options:				
Anastrozole	1 mg	28	£1.37	eMIT 2020[56]
Exemestane	25 mg	30	£5.58	eMIT 2020[56]
Letrozole	2.5 mg	28	£1.56	eMIT 2020[56]
Tamoxifen	20 mg	30	£8.44	Lowest cost option chosen from eMIT 2020[56]
Source: Table 56, CS.[2] CS = company submission				

Table 4.17: Drug cost and dosing options used

Concomitant treatment dosing & administration	Cost per package	Total package dose	Dose per admin	Number of administrations per cycle (N)	Administration route	Assumption on formulations
Loperamide	£0.36	60 mg	2 mg	28.00	Oral	2 mg capsules
Ibuprofen	£0.68	19,200 mg	400 mg	28.00	Oral	400 mg tablets
Amoxicillin	£0.40	10,500mg	500 mg	28.00	Oral	500 mg capsules
Co-amoxiclav	£2.00	7,875mg	375 mg	21.00	Oral	375 mg tablets
Colecalciferol	£3.02	24000 IU	800 IU	28.00	Oral	800-unit tablets
Calcium carbonate; colecalciferol	£6.49	100 tablets	1 tablet	28.00	Oral	Calcium carbonate 1.25gram; Colecalciferol 200 unit
Vitamin D	£3.02	24,000	800 mg	28.00	Oral	Assumed to be the same as colecalciferol
Zoledronic acid	£2.93	400 mg	400 mg	0.15a	IV	4 mg/100 ml solution

Concomitant treatment dosing & administration	Cost per package	Total package dose	Dose per admin	Number of administrations per cycle (N)	Administration route	Assumption on formulations
GnRH analogues	£70.00	4 mg	4 mg	1.00	SC	3.6 mg implant every 28 days

Source: Table 60, CS.[2]
[a]The duration of administration of zoledronic acid is capped at 3-years to reflect clinical guidance for the length of treatment with adjuvant bisphosphonates.[57]
IU = international units; IV = intravenous; SC = sub-cutaneous
Source: eMIT[56]

Table 4.18 shows the values that the ERG identified for the drugs from both the eMIT 2018 (dated 01/07/2018–30/06/2019) and the eMIT 2021 (dated 01/07/20 to 30/06/21). Although the discrepancies are not large, a pattern could not be identified and there is a lack of clarity in CS as noted in the footnotes to Table 4.18**.**

Table 4.18: Comparison of costs to different eMIT values

Treatment	Dose	Source from submission	Company Value	eMIT 2021 Value	eMIT 2018 Value
Anastrozole	1mg – 28 units	eMIT 2020	£1.37	£0.98	£1.15
Exemestane	25mg – 30 units	eMIT 2020	£5.58	£4.76	£9.98
Letrozole	2.5mg – 28 units	eMIT 2020	£1.56	£1.63	£1.57
Tamoxifen	20mg – 30 units	eMIT 2020 – Lowest costs	£8.44	£4.20[1]	£1.74
Loperamide	2mg – 30 units	eMIT 2020	£0.36	£0.83	£0.37
Ibuprofen	400mg – 48 units	eMIT 2020	£0.68	£2.45	£1.11
Amoxicillin	500mg -21 units	eMIT 2020	£0.40	£0.92	£0.42
Co-amoxiclav[2]	375mg – 21 units	eMIT 2020	£2.00	£1.33	£1.23
Colecalciferol	800IU – 30 units	eMIT 2020	£3.02	£3.01	£2.99
Calcium carbonate; colecalciferol	1 tablet – 100 unts	eMIT 2020	£6.49	[3]	[3]
Vitamin D	800mg – 20 units	eMIT 2020	£3.02	[4]	[4]
Zoledronic acid	400mg – 1 unit	eMIT 2020	£2.93	£3.54	£2.94
GnRH analogues	4mg -1 unit	eMIT 2020	£70.00	[5]	[5]

- In the eMIT 2020 there was no value for the Tamoxifen 20mg in this version of the eMIT.
- No 375mg option available, *Co-amoxiclav 250mg/125mg tablets / Packsize 21* used.
- This dose and pack size cannot be identified on the eMIT
- Assumed same as Colecalciferol
- No cost available from eMIT, closest source identified by the ERG was the BNF 2020 value £75

Some costs are such as letrozole and loperamide do match the values when using the 2018 eMIT costing, others match the eMIT 2020 value such as colecalciferol. Although the magnitude of the cost differences is not large, there is inconsistency in the costing process for the drugs. In Appendix M, "Table 67 of the CS: BSC treatment dosing and acquisition cost" there are number of additional drugs

reported for best supportive care (Table 4.19). These drugs are costed from the BNF rather than the eMIT and do match up to the BNF 2021 (with the exception of erythropoietin).[58] It is unclear why some drug costs are sourced from the eMIT and others from the BNF.

Table 4.19: BSC treatment dosing and acquisition cost

Treatment	Dose per tablet/ Vial	Units per package	Cost per package	Dose per administration	Number of administrations per cycle	Route of administration	Drug cost per administration	Source
Oxycodone	5.00 mg	56	£6.86	200.00	28.00	Oral	£4.90	BNF43[58]
Loperamide	5.00 mg	30	£1.46	16.00	28.00	Oral	£0.39	BNF43[58]
Ondansetron	2.00 mg	10	£0.81	16.00	28.00	Oral	£0.32	BNF43[58]
Denosumab	4.00 mg	1	£183.00	60.00	0.15	SC	£183.00	BNF43[58]
Erythropoietin	60.00 mg	10	£18.00	32166	4.00	Oral	£5,789.88	BNF43[58]
Filgrastim	10.00 mg	5	£263.52	357	4.00	SC	£627.88	BNF43[58]
Alprazolam	30.00 mg	60	£3.18	16	28.00	Oral	£3.39	BNF43[58]
Rivaroxaban	0.25 mg	10	£18.00	15	0.75	Oral	£2.70	BNF43[58]

Source: Appendix M, Table 67, CS.[2]
Abbreviations: ABE: abemaciclib; BSC: best supportive care; BNF: British National Formulary; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; TMX: tamoxifen; SC: subcutaneous

Appointment Costs

In addition to drug costs, unit costs for health care appointments and imaging were derived from published unit costs (Table 4.20). The costs in this table were all reported to have come national reference costs or published sources.

Table 4.20: List of costs in the economic model associated with the IDFS health states

Resource use	Unit cost (£)	Reference	Annual resource use frequency			Source
			Year 1	Year 2 –5	Year >5	
GP visit	39.00	PSSRU 2020	0.00	0.08	0.08	TA569[55]
Oncologist visit	200.20	National Schedule of NHS Costs 2019/20	0.15	0.00	0.00	TA569[55]
Mammogram	33.61	National Schedule of NHS Costs 2019/20	0.08	0.08	0.00	TA569[55]
Multidisciplinary team meeting	121.68	Simcock and Heaford (2012)	0.08	0.00	0.00	TA569[55]
On treatment costs: Abemaciclib + ET						
Oncologist visit	200.20	National Schedule of NHS Costs 2019/20	0.15			monarchE

Hospitalisation	3,622.16	TA725	0.0052	monarchE
On treatment costs: ET alone				
Hospitalisation	3,622.16	TA725	0.0013	monarchE
Source: Table 58, CS.[2] Abbreviations: ET: endocrine therapy; GP: General Practitioner; IDFS: invasive disease-free survival; NHS: National Health Service; PSSRU: Personal Social Services Research Unit; TA: technology appraisal.				

The cost for the mammogram is costed as £33.61 which is sourced from National Schedule of NHS Cost 2019-20 (IMAGOP, PF, Plain Film, Outpatient). With regard to the cost of £121.68 for a multidisciplinary team meeting, the ERG is unclear how this cost is derived. The reference given is a letter to the editor in a journal and not primary research. The value in the letter given in is £85.62 and it is not clear where the value of £121.68 used in the model comes from.

In addition to the outpatient appointments mammograms and team meeting, hospitalisation costs were included. The costs were derived from a previous TA, specifically TA725.[19] The costing was based on a reference costing of "malignant breast disorders with/without interventions, non-elective long stay" which was inflated using "inflation adjusted cost based on user selected method" described in TA725. The value given in the CS is £3,622.16. It is unclear to the ERG as to which cost (or average of costs) and which inflation method is being used. On inspection of the national reference costs by the ERG the value for "malignant breast disorders without interventions, non-elective long stay" is £2,604 (JA12L) and the cost for "malignant breast disorders with interventions, non-elective long stay" is £4,447 (JA12L). It is unclear how the figure presented in the CS was reached.

Procedure Costs

A number of procedures were costed for individuals in the model which were based on NHS reference costs. Appendix O in the CS details the health state unit costs and resource use that was costed from eMIT and NHS reference costs 2020.[16] Some costs derived from the NHS reference costs 2019/20 differed from the costs derived by the ERG. The CS uses specific costs where the ERG uses the Total HRG cost as shown below. These deviations are described in Table 4.21 below. Of note the ERG were only able to identify one of these costs inside the model (Deliver Subsequent Elements of a Chemotherapy Cycle) for the others it is not clear or indeed if they were implemented in the model.

Table 4.21: Reference costs from Appendix O for which the ERG have derived different unit costs to those reported in the CS

Treatment	Code	Value from CS	ERG Value	Source
Deliver a Fraction of Complex Treatment on a Megavoltage Machine – Outpatient	SC23Z	£149	£158	NHS Reference Costs 2019/2020
Deliver Subsequent Elements of a Chemotherapy Cycle	SB15Z	£254	£341	NHS Reference Costs 2019/2020
Unilateral Major Breast Procedures with CC Score 3-5	JA20E	£4,031	£3,291	NHS Reference Costs 2019/2020
Unilateral Excision of Breast with Immediate Pedicled Myocutaneous Flap Reconstruction	JA32Z	£6,892	£6,352	NHS Reference Costs 2019/2020
CS = company submission				

Costs for each health state

The costs for each different health states were derived from previous TARs, expert clinical opinion, and relevant NICE guidelines. The specific NICE guideline which was utilised was NICE early and locally advanced breast cancer: diagnosis and management (NG101).

Non-metastatic health state

The non-metastatic health state has been costed based on previous data from TARs. Expert opinion was that a mix of surgery, radiotherapy chemotherapy, and adjuvant ET are commonly offered as treatment options to patients who experience a non-metastatic recurrent event. An assumption was made that treatments specifically recommended for HER2+ early breast cancer such as trastuzumab and pertuzumab would not be prescribed for the monarchE HER2 patient population, instead ET prescribed during the IDFS health state would be prescribed again.

Second primary neoplasm

The single cost included for the second primary neoplasm is the cost for a multidisciplinary meeting as the patient exits the model. There are no costs for the diagnostics involved with the secondary neoplasm.

Remission

The costs for the remission states are based on previous TAs (TA632,67 TA61245 and TA569) and expert clinical advice. The costs included were follow up GP visits (once per year), Oncology visits (twice per year) and mammograms (once per year) over a period of 2 to 5 years. These costs seem reasonable, though there is uncertainty regarding the mammogram unit costs as described above.

Metastatic health state costs - ET-resistant

The costs for the ET-Resistant Metastatic health state is described in Appendix N of the CS. This includes drug costs, procedure costs and follow up costs. What is included in these costs seems reasonable, though some of the unit costs which could not be reproduced are included (such as mammography). One point that is unclear from the ERGs perspective is the allocation of nursing costs. Two different nurses are costed within the model a District Nurse (£63) and a Band 6 Clinical Nurse Specialist (£89). Firstly, the use of a full hour of time for each visit is not justified within the CS, particularly as both can make visits four times a cycle in the PPS model state. It would be common for a nurse to visit multiple patients within an hour. Secondly the cost for the Clinical Nurse Specialist is based on a Community Nurse not a hospital-based Nurse. It is not clear why two distinct community-based nurses are included in this costing.

Metastatic health state costs - ET-sensitive

The costs for the ET-Sensitive Metastatic health state is described in Appendix M of the CS. This includes, drug costs, procedure costs and follow up costs. Like the values for the ET-resistant state described above the resources include seem to be appropriate but some of the sources for some of the individual unit costs are unclear as described above. The high cost of nursing care which is noted in the ET-resistant state is also included in ET-sensitive state.

Adverse Event Costings

The CS details describes the costs associated with AEs resulting from the treatment arms. These costs can be seen in Tables 4.22 and 4.23.

Table 4.22: Costs associated with adverse events

Adverse reactions	2019/20-unit cost (£)	Source
Grade III/IV AEs		
Neutropenia	£200.20	National Schedule of NHS Costs 2019/20: HRGs: WF01A Medical oncology non-admitted face to face attendance follow up
Leukopenia	£200.20	National Schedule of NHS Costs 2019/20: HRGs: WF01A Medical oncology non-admitted face to face attendance follow up
Diarrhoea	£200.20	National Schedule of NHS Costs 2019/20: HRGs: WF01A Medical oncology non-admitted face to face attendance follow up
Lymphopenia	£200.20	National Schedule of NHS Costs 2019/20: HRGs: WF01A Medical oncology non-admitted face to face attendance follow up
Fatigue	£380.71	TA403 is for locally advanced or metastatic non-small-cell lung cancer and the year of input is 2015
Aspartate aminotransferase increase	£200.20	National Schedule of NHS Costs 2019/20: HRGs: WF01A Medical oncology non-admitted face to face attendance follow up
Alanine aminotransferase increase	£200.20	National Schedule of NHS Costs 2019/20: HRGs: WF01A Medical oncology non-admitted face to face attendance follow up
Thrombocytopenia	£367.76	National Schedule of NHS Costs 2019/20 used to determine cost: Weighted average of thrombocytopenia scores, SA12G, SA12H, SA12J, SA12K
Anaemia	£221.46	National Schedule of NHS Costs 2019/20: SA44A, Outpatient procedures: Single plasma exchange or other IV blood transfusion 19 & over
Abdominal pain	£173.10	National Schedule of NHS Costs 2019/2020 WF01A, Non-Admitted Face-to-Face Attendance, Follow-up, Non-Consultant Led
Venous thromboembolic event	£472.68	National Schedule of NHS Costs 2019/20 used to determine cost: Total HRG's, Deep Vein Thrombosis weighted average of: YQ51A; YQ51B; YQ51C; YQ51D; YQ51E gives the unit cost
Grade I/II AEs		
Diarrhoea	£1.62	BNF: Loperamide 2mg tablets

Source: Table 66, CS.[2]
BNF: British National Formulary; CS = company submission; HRG: healthcare resource group; IV: intravenous; NHS: National Health Service. Source: TA563,[18] TA403,[59] National Schedule of NHS Costs 2019/20,[16] Inflation: NHSCII prices, Curtis & Burns (2020)[60]

Table 4.23: Costs associated with adverse events associated with the ET resistant metastatic state

Adverse reactions	2019/20-unit cost (£)	Source	Disutility	Source	Mean duration (days)	Source
Hypertension	£182.00	National Schedule of NHS Costs 2019/2020	0.153	Swinburn 2010	8.00	Swinburn 2010
Nausea	£182.00	National Schedule of NHS Costs 2019/2020	0.021	Hudgens 2016	6.00	TA306
Neutropenia	£200.20	National Schedule of NHS Costs FY 2019-20, 370, CL, WF01A, Non-Admitted Face-to-Face Attendance, Follow-up	0.007	Hudgens 2016	15.09	TA306

Source: Appendix M, Table 71, CS.[2]
CS = company submission; NHS = National Health Service

A number of AEs (neutropenia, leukopenia, lymphopenia, aspartate aminotransferase increase, alanine aminotransferase increase) were costed as a medical oncology consultant led outpatient appointment. However, the code included (WF01A) does not correlate with this kind of appointments in the NHS reference costs. The ERG is assuming this is a typing error. In addition, there are no costs included for any relevant drugs or management strategies for these AEs, it is unclear to the ERG why this is the case. The value for abdominal pain is based on a "non-admitted face-to-face attendance, follow-up". The value of £125 is used based on the "non-consultant led" value from the NHS reference costs rather than the £173.10 representing the total HRG costs.

The costs for thrombocytopenia are described as a weighted average of the thrombocytopenia CC Scores from the NHS reference costs 2019/2020 (SA12G, SA12H, SA12J, SA12K). The CS reports this weighted average to be £367.76, based on day case costs from NHS Reference Costs 2019/20. The ERG found these costs to range from £456 to £1913 with a weighted average of £771, based on the Total HRG costs from the NHS reference costs 2019/2020. The cost for a venous thromboembolic event was based on the weighted averages of CC scores across reference costs (YQ51A; YQ51B; YQ51C; YQ51D; YQ51E). The CS reports this weighted average as £472.68. The ERG found a range of costs to be £376 to £1451 with a weighted average of £681. The reason for the discrepancy between these costings is unclear.

Table 4.23 shows costs described as being the costs of managing adverse reaction in the ET-sensitive pathway. The cost for hypertension is referenced from NHS reference costs and "Swinburn 2010" with an estimate of £182. The study referenced related to the derivation of health states utilities and not unit costs, so this does not explain which precise NHS reference costs were used in this estimate. The cost estimate for nausea is also estimated as £182 and referenced from NHS Reference costs 2019/2020, the

reference for this value is TA306. The source of this cost is not seemingly available in the publicly available documents which relate to this TA and so the source of this value is also unclear.

ERG Comment: The ERG notes two issues with respect to the costing for this CS.

- .
- The assumptions regarding the frequency and times of certain health care professionals, particular those involved with nursing care are high. Appointments are assumed to be all be in the community and costed as such, rather than the hospital and all be an hour in length. This means that for certain states 8 hours of home nursing care per cycle (i.e., per month) are costed. The ERG is not clear on the basis of this assumption of care.

4.2.10 Summary of company base-case assumptions

A table containing a list of the assumptions used in the base-case analysis was provided alongside a list of scenarios conducted by the company to explore the impact of these assumptions in the cost effectiveness results (Table 4.24).

Table 4.24: Summary of company base-case assumptions

Base-case Assumption	Company	Justification*	Addressed in scenario analysis
IDFS curves	Dependent model (single model with treatment coefficient) assumed with a log-logistic distribution	As explained in Section B.3.3, the monarchE trial provides direct clinical evidence for abemaciclib + ET and ET alone, for a population that is reflective of UK clinical practice. Statistical fit and landmark IDFS rates from external trials identified by the clinical	To explore any uncertainty associated with the choice of extrapolation for IDFS, scenario analyses have been conducted using the next best fitting extrapolations. A scenario analysis using an independent log-logistic extrapolation has also been
TTD curves	Extrapolations based on within trial data were used to inform ET (hazard knot two splines used to model TTD for abemaciclib, ET (for patients receiving abemaciclib) and ET alone.	As explained in Section B.3.3, evidence from the monarchE trial was deemed to be the most recent and relevant for the validation of the TTD extrapolations. The choice of extrapolation for TTD was based on statistical fit.	To explore any uncertainty associated with the choice of extrapolation for TTD, scenario analyses have been conducted using the next best fitting extrapolations.
	2 year stopping rule applied for abemaciclib.	Abemaciclib is to be taken continuously for up to two years, according to the SmPC.	No scenario analyses have been conducted varying the stopping rule for abemaciclib, as this is defined in the SmPC.
	5 year stopping rule was applied for ET.	The timing of the ET stopping rule is not expected to have a significant impact on the cost effectiveness results or represent a significant source of uncertainty, as it is applied in both the abemaciclib + ET arm and the ET alone arm (see Section B.3.8.3 for scenario analysis results). As such, a five-year stopping rule was chosen in the base-case analysis.	A scenario analysis has been conducted where a 10-year stopping rule was applied for ET. This demonstrates that the timing of the stopping rule has a minimal impact on the CEA.

Base-case Assumption	Company	Justification*	Addressed in scenario analysis
OS without distant recurrence curves	Dependent model (single model with treatment coefficient) assuming an exponential distribution following internal validity checks.	As explained in Section B.3.3, evidence from the monarchE trial was deemed the most recent and relevant for the validation of OS without distant recurrence extrapolations.	In order to explore any uncertainty associated with the choice of extrapolation for OS, scenario analyses have been conducted varying the OS extrapolation to the next best fitting extrapolations.
	Hazard of dying in NMR and remission health states assumed same as hazard of dying in the IDFS health state.	In the absence of robust data for the hazard of death in the NMR and remission health states, this was considered to represent a reasonable assumption.	No scenario analyses have been conducted to explore the impact of this assumption.
Long-term treatment effect	Constant treatment effect duration of 6 years beyond the end of the treatment (8 years in total).	A long-term treatment effect has been observed in variety of trials in the early breast cancer setting and IDFS piecewise analysis for monarchE demonstrates that a treatment effect past discontinuation does exist for abemaciclib. As explained in Section B.3.3.2, the start of the treatment waning effect was informed by the treatment effect observed for ET in the ATAC trial.	Scenario analyses have been conducted varying the start time and duration of the treatment waning effect.
	Waning of treatment effect was applied until the crossing of the ET IDFS hazard rate with the general population mortality rate, (27 years in total).	The duration of the waning of treatment effect was informed by the point in the model where the IDFS rates equal background mortality, by when the hazard equals the general population mortality, in line with the approach used in TA612.	

Base-case Assumption	Company	Justification*	Addressed in scenario analysis
Probability for having either a metastatic recurrence (MR) or non-metastatic recurrence (NMR) at IDFS	When moving from IDFS to a recurrence state, patients in the abemaciclib arm have a lower probability of having a MR relative to an NMR. This probability is assumed to be constant over time.	The probability of patients moving to either the MR or NMR health state were derived from a combination of the IDFS extrapolations in the model, and the proportion of patients experiencing NMR versus MR based on the monarchE trial.	No scenario analyses have been conducted to explore the impact of this assumption.
NMR tunnel state	All patients who experience a non-metastatic recurrence are assumed to receive additional adjuvant therapy for 12 months. After 12 months, patients are assumed to either transition into the remission health state or die due to all-cause mortality.	The duration of the NMR tunnel state of 12 months was informed by assumptions made in the most recent NICE TA for trastuzumab (TA632), which were accepted by NICE.	No scenario analyses have been conducted to explore the impact of this assumption.
Probability for type of non-metastatic recurrence	The proportion of patients having a second primary, (loco) regional or contralateral recurrence when a non-metastatic recurrence event takes place has been assumed to be constant over time.	No alternative evidence was identified from the literature or during consultations with clinical experts, so the risk was assumed to be constant	No scenario analyses have been conducted varying the probability for the type of non-metastatic recurrence.
Probability of recurrence from remission health state	A constant monthly probability of transition from remission to the metastatic health is assumed.	As outlined in Section B.3.3.3, the transition probability of patients moving from remission to the metastatic health state was informed by assumptions made in the most recent NICE TA for trastuzumab (TA632), which was also in line with feedback from UK clinical experts.67	No scenario analyses have been explored varying the probability of recurrence from the remission health state as it was not considered to be a large source of uncertainty. The impact of the probability of recurrence from the remission health state on the cost effectiveness results has been explored in the DSA and PSA.

Base-case Assumption	Company	Justification*	Addressed in scenario analysis
Hospitalisation costs	Hospitalisation costs dictated by the monarchE trial were used in the base-case.	The monarchE trial was deemed to provide the most relevant evidence on hospitalisation costs in the abemaciclib + ET and the ET alone arm.	No scenario analyses have been conducted varying the costs of hospitalisation.
Re-treatment with CDK 4/6 inhibitors in the metastatic setting	Patients who receive abemaciclib + ET are assumed to not receive re-treatment with CDK4/6 inhibitors in the metastatic breast cancer setting.	Due to a lack of available evidence on the efficacy of re-treating patients with CDK4/6 inhibitors, patients were receiving abemaciclib were assumed to not receive subsequent treatment with CDK4/6 inhibitors.	A scenario analysis has been conducted in which patients receiving abemaciclib can be re-treated with CDK4/6 inhibitors.
Clinical outcomes for patients in the metastatic setting	Clinical outcomes for patients in the metastatic setting are based on previous cost effectiveness analyses in TA563 and TA725	As outlined in Section B.3.3.4, the CEAs in TA563 and TA725, aligning with the Committee's preferences where possible, were deemed the most recent and relevant data sources.	A range of scenario analyses were conducted to explore the impact of this uncertainty on the cost effectiveness results.
Utility values in the IDFS health state	Patients in both arms have an overall utility of 0.782 in the IDFS health state.	Although the company acknowledge it is good practice to explore treatment-specific utilities when there is robust head-to-head data available, there was no meaningful difference between the EQ-5D results between each treatment arm. As such, the data from each treatment arm was pooled to maximise sample size, and equal utility for patients in the same health state, irrespective of treatment received, was assumed.	No scenario analyses have been conducted to explore the impact of this assumption.

Base-case Assumption	Company	Justification*	Addressed in scenario analysis
Utility value in the NMR health state	Patients have a utility value of 0.696 for first 3 months and 0.782 for last 9 months for both trial arms yielding a weighted average of 0.760 in the base-case.	Clinical expert opinion indicated patients would receive intensive treatment for loco-regional/contralateral recurrence for the first few months, which is expected to be associated with a detrimental impact on HRQoL. Following this, patients would return to their previous HRQoL.	No scenario analyses have been conducted varying the NMR health state utilities.

Source: Table 69 of the CS

CEA = cost effectiveness analysis; CS = company submission; ERG: Expert Review Group; HRQoL = health related quality of life; IDFS: Invasive disease-free survival; ET: Endocrine therapy; TTD: time to discontinuation; KM: Kaplan-Meier curves; SLR = systematic literature review; SmPC: Summary of product characteristics; OS: Overall Survival; NMR: Non-metastatic recurrence; MR: Metastatic Recurrence; NICE: National Institute for Health and Care Excellence, TA: Technology Appraisal; UK = United Kingdom;

5. COST EFFECTIVENESS RESULTS

5.1. Company's cost effectiveness results

The discounted base-case deterministic results indicate that abemaciclib (at PAS price) + ET is more costly and more effective than ET alone, representing an undiscounted life year (LY) gain of [redacted], a discounted QALY gain of [redacted], and an incremental cost of [redacted]. Thus, the associated ICER was £3,786 per QALY gained. Base-case deterministic results are presented in Table 5.1.

Table 5.1: Base-case deterministic economic analysis results (Abemaciclib at PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,786.00
ET alone	[redacted]	[redacted]	[redacted]	-	-	-	

Source: Table 70 in the CS.[2]
This table reports undiscounted LYG, and discounted costs and QALYs.
ET: endocrine therapy; ICER: incremental cost effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life years; CS: company submission

Table 5.2 shows how the total costs reported in Table 5.1 accrue for each arm of the study. As the table shows the initial higher costs of medications for abemaciclib + ET are partially offset by lower costs incurred the metastatic recurrence states. AE costs were proportionately much higher in the abemaciclib + ET arm of the model but the total costs of these per patient are very low.

Table 5.2: Summary of costs disaggregated by health state

Health state	Costs intervention (Abemaciclib + ET)	Costs comparator (Endocrine therapy)	Increment	Absolute increment	% Absolute increment
Total drug-related costs pre-MR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Invasive disease-free survival	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-Metastatic Recurrence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic Recurrence-ET-Resistant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic Recurrence-ET-Sensitive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Terminal care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total discounted costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Appendix J Table 44.[2]
Abbreviations: MR: metastatic recurrence; ET: endocrine therapy

Corresponding to Table 5.2, Table 5.3 shows the contribution of each state to estimates of total QALYs. Of note here is that QALYs for metastatic disease states are proportionately much lower for the abemaciclib + ET arm but the overall quality adjusted survival in these states is small consequently the reduction in QALYs is more than compensated by the reduction in costs (see Table 5.2).

Table 5.3: Summary of QALYs disaggregated by health state

Health state	QALYs intervention (Abemaciclib + ET)	QALYs comparator (Endocrine therapy)	Increment	Absolute increment	% Absolute increment
Invasive disease-free survival	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-Metastatic Recurrence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic Recurrence-ET-Resistant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic Recurrence-ET-Sensitive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Appendix J Table 46.[2]
Abbreviations: ET: endocrine therapy; QALY: quality adjusted life year

ERG comment: The ERG requested in the clarification letter that sub-group analysis should be provided by menopausal status. The argument behind this was that the treatment pathways for menopausal women are different to those of pre-menopausal women. The response was that the data were equally applicable to both groups based on no evidence of a statistically significant difference between sub-groups. The ERG consider that it would be more appropriate to model the two groups separately in order to account for differences in treatments and explore imprecision probabilistically rather than make an assumption that they are the same.

The ERG note that the technology is modelled to affect QALYs by:

- An increase in invasive-free disease survival (IDFS) time
- A decrease in ET resistant and ET sensitive metastatic recurrences.

Similarly, the technology is modelled to affect costs by:

- An increase in drug acquisition and treatment specific costs
- An increase in costs related to AEs
- A reduction in ET resistant and ET sensitive metastatic recurrences.

Within the model the main assumptions that have a greater effect on the ICER are:

- The model used to extrapolate the IDFS curve beyond the treatment period
- Proportion of patients having a metastatic recurrence relative to a non-metastatic recurrence in each intervention arm
- Treatment costs in the metastatic recurrence state
- Treatment duration beyond 2 years and treatment waning.

The ERGs main concerns about the company cost effectiveness analysis relate to:

a) Lack of clarity around the model structure when aspects of partitioned survival model are used for transition probabilities
b) Lack of recognition that comparators depend on menopausal status leading to bias in cost effectiveness
c) Medication adherence not modelled
d) Potential bias from selection of survival curves for treatment and comparators, and lack of alternative scenarios
e) Discrepancy between OS survival in model and real-world evidence
f) Lack of long-term evidence for assumed 'carryover benefit' and justification for treatment waning trajectory
g) Same utility values applied to both treatment and control arms in the IDFS setting
h) Insufficient clarity in the probability of moving to non-metastatic and metastatic health states
i) Insufficient clarity of reporting of the cost effectiveness scenario results
j) Lack of detail in the model validation process in terms of verification of the formulae, functions, and coding.

5.2. Company's sensitivity analyses

5.2.1. Probabilistic sensitivity analysis

The company performed and presented the results of PSA, DSA as well as scenario analyses. The PSA for the CS base-case analysis was run for 1,000 iterations. A table containing a list of the inputs used in the PSA is reported in Appendix J of the CS, if standard errors (SEs) were not available for specific parameters, 10% of the mean estimate was assumed as the SE. Results are summarised in Table 5.4 for abemaciclib at PAS price.

Table 5.4: Probabilistic results (Abemaciclib at PAS price)

Technologies	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Probability of cost effectiveness (WTP: £20,000)	Probability of cost effectiveness (WTP: £30,000)
Abemaciclib + ET	[redacted]	[redacted]	£3,782.00	[redacted]	[redacted]
ET alone	[redacted]	[redacted]	-	[redacted]	[redacted]

Source: Table 71 in the CS, [2]
ET: endocrine therapy; ICER: incremental cost effectiveness ratio; WTP: willingness to pay threshold; PAS: patient access scheme; QALYs: quality-adjusted life years; CS: company submission

Results in the cost effectiveness plane and cost effectiveness curves are presented in Figure 5.1 and Figure 5.2 in the CS. Results indicated cost effectiveness probabilities of [redacted] and [redacted] at willingness to pay thresholds of £20,000 and £30,000 per QALY gained.

Figure 5.1: Cost effectiveness plane for Abemaciclib + ET versus ET alone

Source Figure 27, CS [2]

Figure 5.2: Cost effectiveness acceptability curve for Abemaciclib + ET versus ET alone

Source Figure 28, CS [2]

5.2.2. Deterministic sensitivity analysis

The company conducted a range of one-way DSA for upper and lower limits around the confidence interval for the parameters in Appendix J in the CS, results are summarised in Figure 5.3. The same 10% variation around the mean was applied for parameters without a confidence interval as in the PSA.

One-way sensitivity analyses with the greatest impact on the cost per QALY ICER for abemaciclib + ET versus ET alone (range varied in brackets):

- Proportion of patients moving to non-metastatic recurrence (relative to metastatic recurrence) in the ET alone arm (9%-48%)
- Proportion of patients moving to non-metastatic recurrence (relative to metastatic recurrence) in the abemaciclib + ET arm (ABE) (11%-50%)
- Proportion of patients receiving concomitant treatment based on GnRH analogues in the ET alone arm (19%-28%)

- Proportion of patients receiving concomitant treatment based on GnRH analogues in the Abemaciclib + ET arm (18%-27%)
- Intravenous (IV) treatment costs (£277-£411)
- Age-related utility by age group: 45 to 54-year-olds (0.65-0.97)
- Life years (LYs) in the PPS stage for ET sensitive metastatic recurrence patients receiving CDK4&6i + NSAI (Monarch3) (2.4-3.6)
- Administration cost of SC medications (£231.07-£342.30)
- Age-related utility by age group: 55 to 64-year-olds (0.62-0.93)
- LYs in the PPS stage for ET sensitive metastatic recurrence patients receiving NSAI (Monarch3) (1.38-2.04)
- Age-related utility by age group: 65 to 74-year-olds (0.61-0.91)
- Age-related utility by age group: 75+ year olds (0.57-0.86)
- LYs in the PFS1 stage for ET sensitive metastatic recurrence patients receiving ABE-NSAI (Monarch3) (2.42-3.59)
- LYs in the PFS1 stage for ET sensitive metastatic recurrence patients receiving PAL-NSAI (Monarch3) (2.42-3.58)
- Cost of a Clinical Nurse (specialist) (£72.41-£107.27)

Figure 5.3: DSA tornado plot for Abemaciclib + ET versus ET alone

Source Figure 29, CS [2]

ERG Comment: The tornado diagram indicated that the proportions of patients moving to a non-metastatic recurrence (relative to a metastatic recurrence) for the comparator and the intervention arm are the most influential parameters. This might be the case but using a 10% variation around the mean as the SE seems arbitrary and may not represent a plausible range of variation for these parameters, the company also acknowledges it in their response to the ERG points for clarification letter (Question B19.a (page 40))[4]. This also applies to all the LY "pay-offs" in the metastatic states, the uncertainty around which is not reported in the CS, and the model instead uses the 10% variation as SE, potentially

misrepresenting true uncertainty around these parameters. Whenever possible, the 95% CIs should be used to calculate the upper and lower bounds of the bars, especially for this parameter where trial data is available. Furthermore, as all the parameters presented in the diagram use the 10% variation from the mean as the SE, the ERG considers that this tornado diagram should be interpreted with caution.

5.2.3. Scenario analysis

The company conducted several scenario analyses to assess the impact of the following number of assumptions and alternative inputs:

- The discount rate
- The model used to extrapolate IDFS
- The models used to extrapolate TTD of abemaciclib
- The models used to extrapolate TTD of ET (intervention and comparator arms)
- The model used to extrapolate OS
- The duration of ET
- The duration of treatment effect and effect waning
- Treatments in the metastatic setting
- LY "pay-offs" for the metastatic setting
- TTD of CDK 4/6 inhibitors in the metastatic setting
- Age-adjusted utility values

The results showed ICERs ranging between absolute dominance of abemaciclib + ET over ET alone, to an ICER of £12,715. The three most influential scenarios in the CS that increased the ICER were: treatment in the metastatic setting being equal for both treatment arms, treatment for ET sensitive metastatic recurrence being equal for any metastatic recurrence and equal in both treatment arms and decreasing the discount rate to 1.5%, Table 5.5 reports the results for the CS scenario analysis.

Table 5.5: Scenario analysis results

Scenario	Base-case	Alternative input	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
Base-case			[redacted]	[redacted]	£3,786.00
1	Discount rate: 3.5% (costs and effects)	1.5% (costs and effects)	[redacted]	[redacted]	Dominant
2	IDFS extrapolation: Dependant Loglogistic	Dependant Weibull	[redacted]	[redacted]	£1,188.00
3		Dependant Generalised Gamma	[redacted]	[redacted]	£959.00
4		Dependant Gamma	[redacted]	[redacted]	£962.00
5		Independent Loglogistic	[redacted]	[redacted]	£530.00
6	TTD extrapolation – ABE+ET: Dependant hazard spline 2-knot	Dependant Loglogistic	[redacted]	[redacted]	£3,903.00
7		Dependant Lognormal	[redacted]	[redacted]	£3,849.00

Scenario	Base-case	Alternative input	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
8		Dependant Hazard spline 1-knot	[redacted]	[redacted]	£5,750.00
9	TTD extrapolation – ET (intervention + comparator arm): Independent hazard spline 2-knot	Dependant hazard spline 2-knot	[redacted]	[redacted]	£4,912.00
10		Independent Hazard spline 1-knot	[redacted]	[redacted]	£9,307.00
11		Independent Weibull	[redacted]	[redacted]	£5,608.00
12		Independent Loglogistic	[redacted]	[redacted]	£5,464.00
13	OS extrapolation: Dependent Exponential	Dependant Lognormal	[redacted]	[redacted]	£3,787.00
14		Dependant Weibull	[redacted]	[redacted]	£3,786.00
15		Dependant Loglogistic	[redacted]	[redacted]	£3,786.00
16	Stopping rule for ET: 5-years	10-years	[redacted]	[redacted]	£3,760.00
17	Start at 8-years, stop at 27-years	Start at 4-years, stop at 13.5-years (half effect)	[redacted]	[redacted]	£5,723.00
18		Start at 5-years, stop at 10-years (Treatment duration of AIs and length of follow-up from ATAC study)	[redacted]	[redacted]	£5,997.00
19	Percentage receiving subsequent treatment, metastatic setting: Market share information adapted from TA563 and TA725	M2 and M3 pathway: ABE + ET = ET arm	[redacted]	[redacted]	£12,216.00
20		M3 ET arm equal for all arms	[redacted]	[redacted]	£12,715.00

Scenario	Base-case	Alternative input	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
21	LY 'pay-offs' for the metastatic setting: Assumptions based on TA563 and TA725	Equate LYs for all arms to ABE arms: M2: 2.46 (PFS), 1.92 (PPS); M3: 2.98 (PFS1), 0.69 (PFS2), 1.69 (PPS)	[redacted]	[redacted]	£4,996.00
22	TTD in metastatic setting: Assumptions based on TA563 and TA725	TTD for all CDK4/6i equal: ET-resistant = 17.58; ET-sensitive = 32.11; Shorter TTD for EVE + EXE = 6.825	[redacted]	[redacted]	£3,792.00
23	Age-adjusted utility values: Age-adjusted utility values provided by Janssen and Szende et al (2014)	Age-adjusted utility values provided by Ara and Brazier et al (2011)	[redacted]	[redacted]	£3,841.00

Source: Table 73 in the CS, [2]
Abbreviations: ABE: abemaciclib; AI; aromatase inhibitor; CDK: cyclin-dependent kinase; ET: endocrine therapy; HSUV: health state utility values; IDFS: invasive disease-free survival; LY; life years; NMR: non-metastatic recurrence; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival; TA: technology appraisal; TTD : time to discontinuation; CS: Company submission.

ERG comment: The main concerns of the ERG relate to:

- Treatment costs for metastatic recurrences for each arm
- The function used to extrapolate IDFS
- The treatment waning assumption

All the scenario analyses conducted by the company had a small to moderate impact on the ICER. The largest difference relative to the base-case ICER was observed in scenarios where the percentages for patients receiving treatments for metastatic recurrence are equal for both arms but different for ET sensitive or ET resistant recurrences, and when the percentages of patients receiving treatments for metastatic recurrence were the same at all stages on both arms as an ET sensitive recurrence in the ET alone arm. As the ICERs in all scenarios were below the £20,000 per QALY threshold, the company concludes that there is little uncertainty around the cost effectiveness of the intervention, however, the ERG has identified several sources of uncertainty that could also have an impact in the model results. As many of these were not sufficiently explored by the company (like the selection of alternative models to extrapolate IDFS) or not explored at all, the ERG considers that the scenario analyses conducted by the company were insufficient to draw reliable conclusions over the robustness of the model results.

5.2.4. Validation

Technical validation

In the CS, the company states that validation of the model structure was conducted by an independent health economist prior to the submission. According to the CS, this validation process included a

technical cell by cell verification of the formulae, functions, and coding. However, the company also reports conducting a series of technical and sanity checklists to ensure consistency in the model results, the number, and details of which are not presented.

ERG comment: As requested by the ERG in Question B1 of the clarification letter, the company provided further details on their communications with the experts; according to their response, on three occasions members of the company met with a UK based professor of health economics and a medical oncologist to discuss the validation of extrapolations, treatment effect duration, inputs, and assumptions underpinning the model.[4] However, no further details were provided on the coding and verification of the formulae as the ERG has identified several coding errors with potentially meaningful results in the ICER. Cross validation of the model results was not possible since this is the first economic evaluation assessing the cost effectiveness of abemaciclib in combination with ET as an adjuvant treatment of adult patients with HR+, HER2−, node positive, early breast cancer at high risk of recurrence.

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

6.1.1. Explanation of the company adjustments after the clarification letter

Following the clarification questions from the ERG, the company made the following amendment to the original cost effectiveness model:

> Clarification Question A4e: the economic analysis for the Cohort that most closely aligns with the definition generalisable to NHS clinical practice. This resulted in an analysis based on Cohort 1 only from the monarchE trial dataset.[4]

6.1.2 ERG base-case

Table 6.1 summarises the key issues related to the cost effectiveness categorised according to the sources of uncertainty as defined by Grimm et al 2020kal:[61]

1. Transparency (e.g. lack of clarity in presentation, description, or justification)
2. Methods (e.g. violation of best research practices, existing guidelines, or the reference case)
3. Imprecision (e.g. particularly wide confidence intervals, small sample sizes, or immaturity of data)
4. Bias and 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)
5. 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 cost effectiveness, whether it is reflected in the ERG 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 ERG report, the ERG 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 ERG form the ERG base-case and were subdivided into three categories:[62]

- Fixing errors (FE) (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (FV) (correcting the model where the ERG considered that the NICE reference case, scope, or best practice had not been adhered to)
- Matters of judgement (MJ) (amending the model where the ERG considers that reasonable alternative assumptions are preferred)

The ERG found errors in the model but found no violations. Further adjustments were made based on MJ. After these changes were implemented in the company's model, additional scenario analyses were explored by the ERG in order to assess the impact of alternative assumptions on the cost effectiveness results.

Fixing errors

1. **Coding error:** Cells C1312:C1319 in the "Inputs" spreadsheet use Life Year pay-offs for PFS1 rather than the payoffs for PPS corresponding to that state. **Correction:** The column referenced in

the formula was changed from 'M; to 'Q' for the whole array, i.e. "=Survival!M143" to "=Survival!Q143".

2. **Coding error:** Cells AS80:AS86 in the "Calculations" spreadsheet multiply unit costs with QALYs rather than resource use. **Correction:** The 'AR' column was changed to a 'AN' column for all the formulas in the array; i.e. from "=AR80*Calculations!X67" to "=AN80*Calculations!X67".
3. **Coding error:** The model uses the probability of dying per cycle as the hazard rate for OS. **Correction:** on the 'Patient distribution ABE' and 'Patient distribution ET' sheets the values in the "BG mort." column were transformed from probabilities to hazard rates.
4. **Coding error:** The formula in the array of cells AI21:AI640 ("Hazard corr. For stop. Rule" column) from the "Patient distribution ABE" spreadsheet should be a weighted average of the intervention and control hazard rates for OS, rather than a weighted average of the intervention hazard rate for OS and the control OS survival curve. **Correction:** This coding error was solved by changing reference to column 'AD' in the formula to column 'AC', i.e. "=(AK21*AW21)+(AX21*'Patient distribution ET'!AD21)" to "=(AK21*AW21)+(AX21*'Patient distribution ET'!AC21)".

Matters of judgement

1. Choice of modelled Cohort. The company base-case population pools data from two Cohorts with different high-risk definitions (KEY ISSUE 1 Section 2.1 and Section 4.2.3).

   Cohort 1 was deemed by the ERG as the most appropriate representation of the UK population for the clinical context of this intervention. The ERG considered Cohort 1 as the most appropriate population for the base-case model; however, it was not possible to run a PSA on Cohort 1 alone due to an error in the model, therefore a sub-group analysis was presented for this population.

2. The use of a log-logistic extrapolation for both arms implying proportional hazards (Key Issue 7, Section 4.2.6).

   The ERG considered that the model choice used to extrapolate IDFS has an important impact on the results and remains a key source of uncertainty. The company presented the results for a base-case scenario using a log-logistic extrapolation for both arms implying proportional hazards; the model choice is justified by statistical fit and predictive quality. The ERG maintained the same extrapolation in its base-case but considered that a more careful discussion of predictive quality in the long term is necessary to justify the IDFS model choice. Alternative extrapolations were presented in the scenario analysis, including a scenario using a log-normal distribution.

3. The assumption that a treatment effect waning starts at year 8 and lasts until the hazard rate in the IDFS for ET is the same as the mortality rate for the general population (Key Issue 9, Section 4.2.6).

   The adoption of this assumption in the CS model implies a duration of 228 months (19 years) for the waning effect. The only source of evidence for this assumption presented in the CS was TA612, which the ERG considered inadequate. Therefore, the ERG preferred base-case presents a conservative scenario with a constant treatment effect duration of three years based on the follow up of the trial, and a waning effect from year 3 to year 8 with no treatment effect on IDFS beyond year 8. The impact of treatment waning on the ICER will be explored as a separate scenario analysis.

4. The use of a single utility value for IDFS rather than applying available treatment specific issues (Key Issue 10, Section 4.2.8).

   Treatment specific utilities for IDFS were applied to each arm instead of the single overall utility estimate used in both arms by the CS base-case.

5. Probability of having a recurrence, an MR, or an NMR, remains constant over time and is not affected by Abemaciclib treatment effect duration or waning (Key Issue 11, Section 5.1).

   The ERG modified the probability of having an MR in the abemaciclib arm to converge to the probability of having an MR in the ET alone arm over the treatment waning effect period on IDFS.

6. The non-use of the Kaplan-Meier curve to model TTD for abemaciclib (Section 4.2.6).

   The ERG considered it more appropriate to use the Kaplan-Meier curve directly to estimate treatment discontinuation for abemaciclib alone.

7. The cost of delivery of deliver subsequent elements of a chemotherapy cycle which deviated from the stated source of cost data (Section 4.2.9, Table 4.21)

   The ERG found a different value for the cost of "deliver subsequent elements of a chemotherapy cycle" than the value used in the company model. The ERG value for this cost was used instead.

6.1.2 ERG exploratory scenario analyses

The ERG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the ERG base-case. These scenarios explore aspects that were not explored in the CS, except for scenario 2 where the ERG expand upon what is presented in the CS.

Exploratory scenario analyses

1. IDFS extrapolation (Kay Issue 7, Section 4.2.6):
   a. ERG adjustment: dependent log-normal extrapolation (scenario 1)
   b. ERG adjustment: dependent Gompertz extrapolation (scenario 2)
2. Treatment duration and waning (Key Issue 9, Section 4.2.6):
   a. ERG adjustment: constant treatment effect over time (scenario 3)
   b. ERG adjustment: 8-year constant treatment effect duration, no effect beyond this point (scenario 4)
   c. ERG adjustment: 5-year constant treatment effect duration, waning effect between years 5-8 (scenario 5)
   d. ERG adjustment: 3-year constant treatment effect duration, no effect beyond this point (scenario 6)
   e. ERG adjustment: linear waning between years 3 to 27 (scenario 7)
3. Treatment effect on the probability of a recurrence being metastatic (MR) versus non metastatic (Key Issue 11, Section 5.1):
   a. ERG adjustment: no treatment effect on the probability of MR after 3 years (scenario 8)
   b. ERG adjustment: constant treatment effect on the probability of MR over time (scenario 9)
4. Scenarios from the CS (percentage receiving subsequent treatment, metastatic setting: Market share information adapted from TA563 and TA725):
   a. ERG Adjustment: metastatic recurrence treatment on both arms equivalent to the ET arm (scenario 10)

b. ERG adjustment: metastatic recurrence treatment on both arms equivalent to the ET sensitive treatment pathway (Monarch3 trial) (scenario 11)

Table 6.1: Overview of key issues related to the cost effectiveness

Key issue pertaining to cost effectiveness (See Section 1)	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in ERG base-case[b]
4) Lack of clarity around the model structure when aspects of partitioned survival model are used for transition probabilities	4.2.2	Transparency, methods	State transition probabilities	+/-	No
5) lack of recognition that comparators depend on menopausal status leading to bias in cost effectiveness	4.2.3	Bias and indirectness	Provide subgroup analysis by menopausal status	+/-	No
6) Medication adherence not modelled	4.2.4	Unavailability	Evidence from literature	+/-	No
7) Potential bias from selection of survival curves for treatment and comparators, and lack of alternative scenarios	4.2.4	(i) Imprecision (ii) Methods	Alternative extrapolation distribution for estimating IDFS from the literature	+	Partly, data immaturity cannot be currently resolved
8) Discrepancy between overall survival in model and real-world evidence	4.2.6	Methods	Incorporate external registry data	+	No
9) Lack of long-term evidence for assumed 'carryover benefit' and justification for treatment waning trajectory	4.2.6	Unavailability, Methods	Alternative scenario analyses based on assumptions on treatment duration and waning effect	+	Partly, data immaturity
10) Same utility values applied to both treatment and control arms in the IDFS health state	4.2.8	Methods	Use treatment-specific utilities	+	Yes
11) Insufficient clarity in the probability of moving to non-metastatic and metastatic health states	5.1	Transparency, Methods	External data and consider natural history models	+/-	No

Key issue pertaining to cost effectiveness (See Section 1)	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in ERG base-case[b]
12) Insufficient clarity of reporting of the cost effectiveness scenario results	5.2.3	Transparency	Subgroup analysis	+/-	Explored, ERG additional analysis
13) Lack of detail in the model validation process in terms of verification of the formulae, functions, and coding	5.2.4	Unavailability	More details about checklist used	+/-	Partly, errors picked up by ERG

[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 ERG and '+' indicates that the ERG believes this issue likely induces bias in favour of the intervention versus at least one comparator; [b] Explored
ERG = Evidence Review Group; IDFS = invasive disease-free survival; ICER = incremental cost effectiveness ratio

6.1.3 ERG subgroup analyses

The ERG considered that Cohort 1 from the monarchE trial was a more appropriate representation of the UK population in this clinical context. However, as PSA results could not be generated from the model using Cohort 1 alone, a subgroup analysis was presented populating the model with Cohort 1. Results from this subgroup analysis including scenario analyses are reported in the next section.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

In Section 6.1 the features of the ERG base-case was presented, which was based on various changes compared to the company base-case relating to both fixing of errors and matters of judgement (MJ). 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 ERG base-case. The analyses numbers in Tables 6.2 and 6.3 correspond to the numbers reported in Section 6.1. Finally, Tables 6.4 and 6.5 provide the results of the subgroup analysis and subsequent scenario analyses (as described in Section 6.1.3). The submitted model file contains technical details on the analyses performed by the ERG (e.g. the "ERG" sheet provides an overview of the cells that were altered for each adjustment).

Table 6.2: Deterministic ERG base-case results unless otherwise stated

Preferred Assumption	Key issues addressed	Sections	ABE + ET		ET Only		Inc. Costs (£)	Inc. QALYs	Cumulative ICER (£/QALY)
			Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
Company base-case			[redacted]	[redacted]	[redacted]	[redacted]	£3,172.46	0.838	£3,785.75
Fixing errors 1-4			[redacted]	[redacted]	[redacted]	[redacted]	£4,701.18	0.886	£5,308.74
Company base-case after fixing errors			[redacted]	[redacted]	[redacted]	[redacted]	£4,701.18	0.886	£5,308.74
Matters of judgement 3: Shorter treatment effect duration on IDFS	8	4.2.6	[redacted]	[redacted]	[redacted]	[redacted]	£6,057.12	0.555	£10,904.18
Matters of judgement 4: Treatment specific utilities	10	4.2.8	[redacted]	[redacted]	[redacted]	[redacted]	£4,701.18	0.901	£5,215.97
Matters of judgement 5: Shorter treatment effect on metastatic recurrences	11	5.1	[redacted]	[redacted]	[redacted]	[redacted]	£4,860.47	0.872	£5,572.96
Matters of judgement 6-7: KM curve for abemaciclib TTD and		4.2.6; 4.2.9	[redacted]	[redacted]	[redacted]	[redacted]	£4,716.33	0.886	£5,325.86

Preferred Assumption	Key issues addressed	Sections	ABE + ET		ET Only		Inc. Costs (£)	Inc. QALYs	Cumulative ICER (£/QALY)
			Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
chemotherapy costs									
ERG Base-case deterministic (ITT)			[redacted]	[redacted]	[redacted]	[redacted]	£6,498.74	0.522	£12,452.77
ERG Base-case probabilistic* (ITT)			[redacted]	[redacted]	[redacted]	[redacted]	£6,526.07	0.533	£12,232.98

QALY: Quality adjusted life year; ICER: Incremental cost effectiveness ratio; IDFS: Invasive disease-free survival; TTD: Time to treatment discontinuation; ERG: Evidence Review Group; ITT = intention to treat; KM = Kaplan-Meier. *1000 simulations run

Table 6.3: Deterministic scenario analyses (conditional on ERG base-case using the monarchE ITT population)

Scenario	ERG base-case inputs	Alternative input	Abe + ET		ET Only		Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
			Total costs (£)	Total QALYs	Total costs (£)	Total QALYs			
ERG Base-case (ITT)			[redacted]	[redacted]	[redacted]	[redacted]	£6,498.74	0.522	£12,452.77
1	IDFS extrapolation: dependent log-logistic model	Dependent log-normal model	[redacted]	[redacted]	[redacted]	[redacted]	£8,059.88	0.465	£17,314.95
2		Dependent Gompertz model	[redacted]	[redacted]	[redacted]	[redacted]	£4,568.20	0.341	£13,401.98
3	3 year constant treatment effect, waning from years 3-8	Constant life-long treatment effect duration	[redacted]	[redacted]	[redacted]	[redacted]	£4,538.98	0.975	£4,654.83
4		8 year constant treatment effect, followed by no effect	[redacted]	[redacted]	[redacted]	[redacted]	£5,443.25	0.680	£8,008.11
5		5 year constant treatment effect, waning from years 5-8	[redacted]	[redacted]	[redacted]	[redacted]	£5,774.20	0.596	£9,689.67

Scenario	ERG base-case inputs	Alternative input	Abe + ET		ET Only		Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
			Total costs (£)	Total QALYs	Total costs (£)	Total QALYs			
6		3 year constant treatment effect, followed by no effect	[redacted]	[redacted]	[redacted]	[redacted]	£8,610.26	0.320	£26,871.81
7	3 year constant treatment effect, linear waning from years 3-8	3 year constant treatment effect, linear waning from years 3-27	[redacted]	[redacted]	[redacted]	[redacted]	£5,214.43	0.810	£6,439.17
8	Treatment effect decreasing the probability of MR wanes from year 3-8	Treatment effect decreasing the probability of MR wanes completely after year 3	[redacted]	[redacted]	[redacted]	[redacted]	£6,740.02	0.504	£13,369.06
9		Treatment effect decreasing the probability of MR remains constant over time	[redacted]	[redacted]	[redacted]	[redacted]	£6,074.52	0.573	£10,593.98

Scenario	ERG base-case inputs	Alternative input	Abe + ET		ET Only		Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
			Total costs (£)	Total QALYs	Total costs (£)	Total QALYs			
10	Percentage receiving subsequent treatment, metastatic setting: Market share information adapted from TA563 and TA725	M2 and M3 pathway: ABE + ET = ET arm	[redacted]	[redacted]	[redacted]	[redacted]	£13,068.84	0.530	£24,651.27
11		M3 ET arm equal for all arms	[redacted]	[redacted]	[redacted]	[redacted]	£13,332.17	0.521	£25,608.49

Source: Table 73 in the CS, [2]

ERG: Evidence Review Group; QALY: quality adjusted life year; ICER: incremental cost effectiveness ratio; ITT: intention to treat; MR: metastatic recurrence; IDFS: invasive disease-free survival; TA: Technology Appraisal; TTD: time to discontinuation; CS: company submission

Table 6.4: Deterministic subgroup analysis (ERG base-case using the monarchE Cohort 1 population)

Preferred Assumption	Key issues addressed	Sections	ABE + ET		ET Only		Inc. Costs (£)	Inc. QALYs	Cumulative ICER (£/QALY)
			Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
Company base-case after fixing errors			[redacted]	[redacted]	[redacted]	[redacted]	£4,701.18	0.886	£5,308.74
Matters of judgement 1: Switching to	1	2.1; 4.2.3	[redacted]	[redacted]	[redacted]	[redacted]	£5,556.32	0.960	£5,785.42

Preferred Assumption	Key issues addressed	Sections	ABE + ET		ET Only		Inc. Costs (£)	Inc. QALYs	Cumulative ICER (£/QALY)
			Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
Cohort 1 alone									
ERG Base-case deterministic (Cohort 1)			[redacted]	[redacted]	[redacted]	[redacted]	£7,560.44	0.567	£13,339.17
ERG Base-case probabilistic (Cohort 1)			Not estimatable	Not estimatable	Not estimatable	Not estimatable	Not estimatable	Not estimatable	Not estimatable

ET = endocrine therapy; QALY = quality adjusted life year; ICER = incremental cost effectiveness ratio; TTD = time to treatment discontinuation; ERG = Evidence Review Group

Table 6.5: Deterministic subgroup scenario analysis (ERG base-case using the monarchE Cohort 1 population)

Scenario	ERG base-case inputs	Alternative input	Abe + ET		ET Only		Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
			Total costs (£)	Total QALYs	Total costs (£)	Total QALYs			
ERG Base-case (Cohort 1)			[redacted]	[redacted]	[redacted]	[redacted]	£7,560.44	0.567	£13,339.15
1	IDFS extrapolation: dependent log-logistic model	Dependent log-normal model	[redacted]	[redacted]	[redacted]	[redacted]	£9,054.74	0.519	£17,447.55

Scenario	ERG base-case inputs	Alternative input	Abe + ET		ET Only		Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
			Total costs (£)	Total QALYs	Total costs (£)	Total QALYs			
2		Dependent Gompertz model	Not estimatable	Not estimatable	Not estimatable	Not estimatable	Not estimatable	Not estimatable	Not estimatable
3	3 year constant treatment effect, waning from years 3-8	Constant life-long treatment effect duration	[redacted]	[redacted]	[redacted]	[redacted]	£5,413.81	1.052	£5,144.07
4		8 year constant treatment effect, followed by no effect	[redacted]	[redacted]	[redacted]	[redacted]	£6,418.27	0.736	£8,718.12
5		5 year constant treatment effect, waning from years 5-8	[redacted]	[redacted]	[redacted]	[redacted]	£6,776.31	0.646	£10,483.03
6		3 year constant treatment effect, followed by no effect	[redacted]	[redacted]	[redacted]	[redacted]	£9,861.82	0.349	£28,255.90
7	3 year constant treatment effect, linear waning from years 3-8	3 year constant treatment effect, linear	[redacted]	[redacted]	[redacted]	[redacted]	£6,164.45	0.875	£7,042.64

Scenario	ERG base-case inputs	Alternative input	Abe + ET		ET Only		Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
			Total costs (£)	Total QALYs	Total costs (£)	Total QALYs			
		waning from years 3-27							
8	Treatment effect decreasing the probability of MR wanes from year 3-8	Treatment effect decreasing the probability of MR wanes completely after year 3	[redacted]	[redacted]	[redacted]	[redacted]	£7,867.44	0.544	£14,450.24
9		Treatment effect decreasing the probability of MR remains constant over time	[redacted]	[redacted]	[redacted]	[redacted]	£7,025.37	0.631	£11,131.38
10	Percentage receiving subsequent treatment, metastatic setting: Market share information adapted from TA563 and TA725	M2 and M3 pathway: ABE + ET = ET arm	[redacted]	[redacted]	[redacted]	[redacted]	£14,114.30	0.575	£24,541.93

Scenario	ERG base-case inputs	Alternative input	Abe + ET		ET Only		Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
			Total costs (£)	Total QALYs	Total costs (£)	Total QALYs			
11		M3 ET arm equal for all arms	[redacted]	[redacted]	[redacted]	[redacted]	£14,402.77	0.565	£25,506.71

Source: Table 73 in the CS, [2]

ERG: Evidence Review Group; QALY: quality adjusted life year; ICER: incremental cost effectiveness ratio; ITT: intention to treat; MR: metastatic recurrence; IDFS: invasive disease-free survival; TA: Technology Assessment; M2: Monarch2 trial; M3: Monarch3 trial; ABE: abemaciclib; ET: endocrine therapy

6.3 ERG's preferred assumptions

The estimated ERG base-case ICER based on a probabilistic analysis and the ERG preferred assumptions described in Section 6.1, was £12,453 per QALY gained for the comparison of abemaciclib + ET versus ET alone. This is illustrated on a cost-effectiveness plane in Figure 6.3. The probabilistic ERG base-case analyses indicated cost effectiveness probabilities of 89% and 99% at willingness to pay thresholds of £20,000 and £30,000 per QALY gained respectively. Figure 6.4 illustrates this by presenting the cost effectiveness acceptability curve.

As Table 6.2 shows, the most influential adjustments were 1) decreasing the treatment effect duration on IDFS, 2) switching to Cohort 1 alone as the model population, and 3) decreasing the treatment effect duration on the probability of metastatic recurrences.

For the scenario analyses shown in Table 6.3, the ICER increased most in the scenario analysis with alternative assumptions regarding 1) the duration of the treatment effect period, 2) the percentage of patients receiving AIs as treatment for a metastatic recurrence in the intervention arm, 3) the model used to extrapolate IDFS, and 4) the duration of the waning effect period.

In addition to the scenario analysis described above the analyses described in Tables 6.2 and 6.3 were repeated for the ERGs preferred population Cohort: Cohort 1, as this was argued to be more applicable to the NHS. The pattern of results was the same as described above except that the ICERs increased further for all analyses presented (Tables 6.4 and 6.5).

To further explore uncertainty and provide comparison with the CS Figure 6.5 presents a one-way sensitivity analysis of the ERG base-case, caveats from Section 5.2.2 still apply to these results.

Figure 6.3: Cost effectiveness plane for Abemaciclib + ET versus ET alone

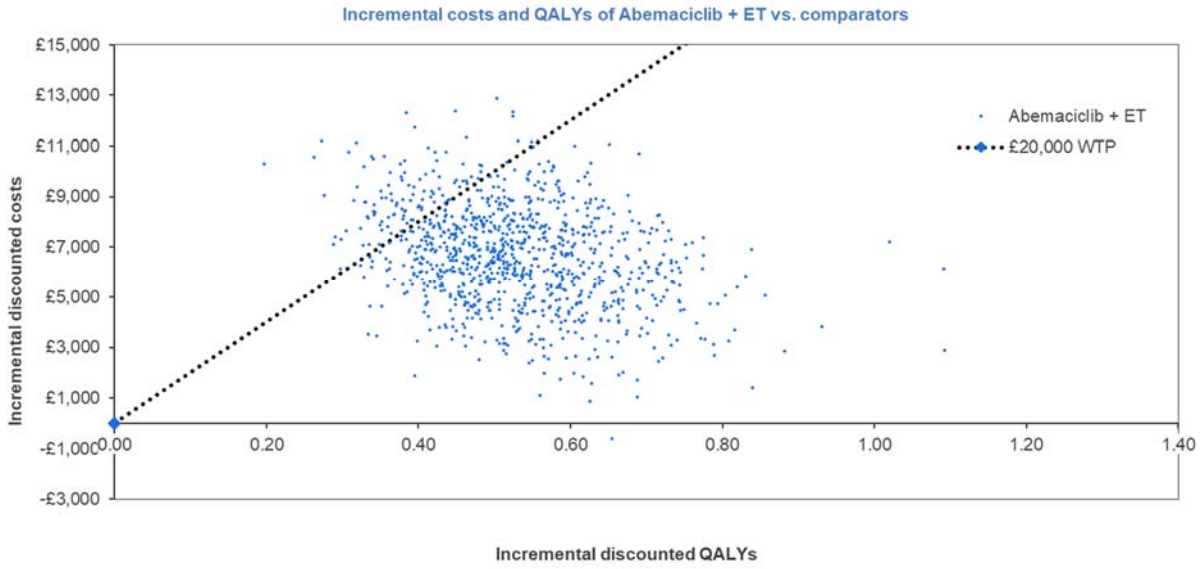
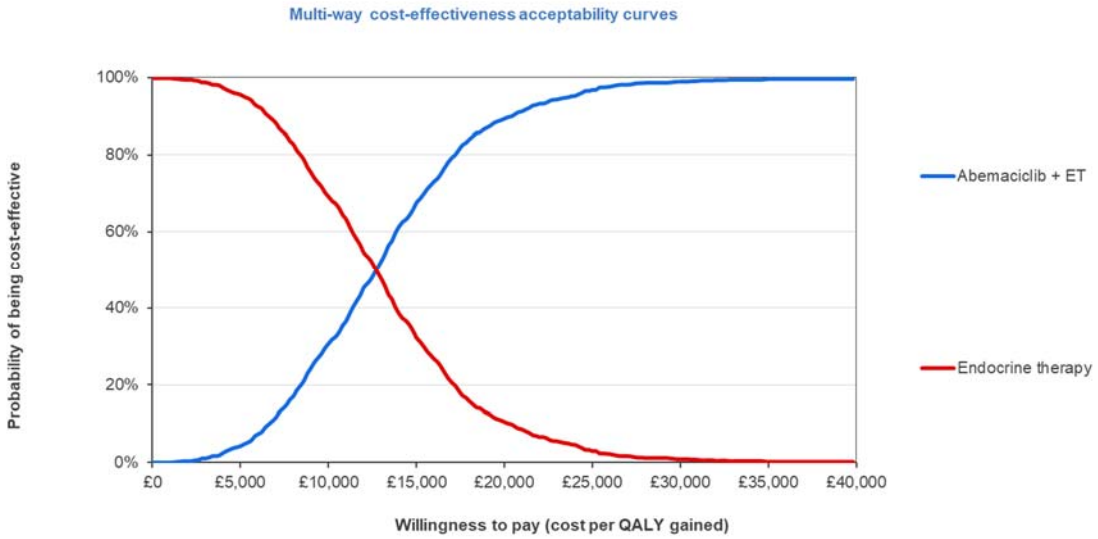
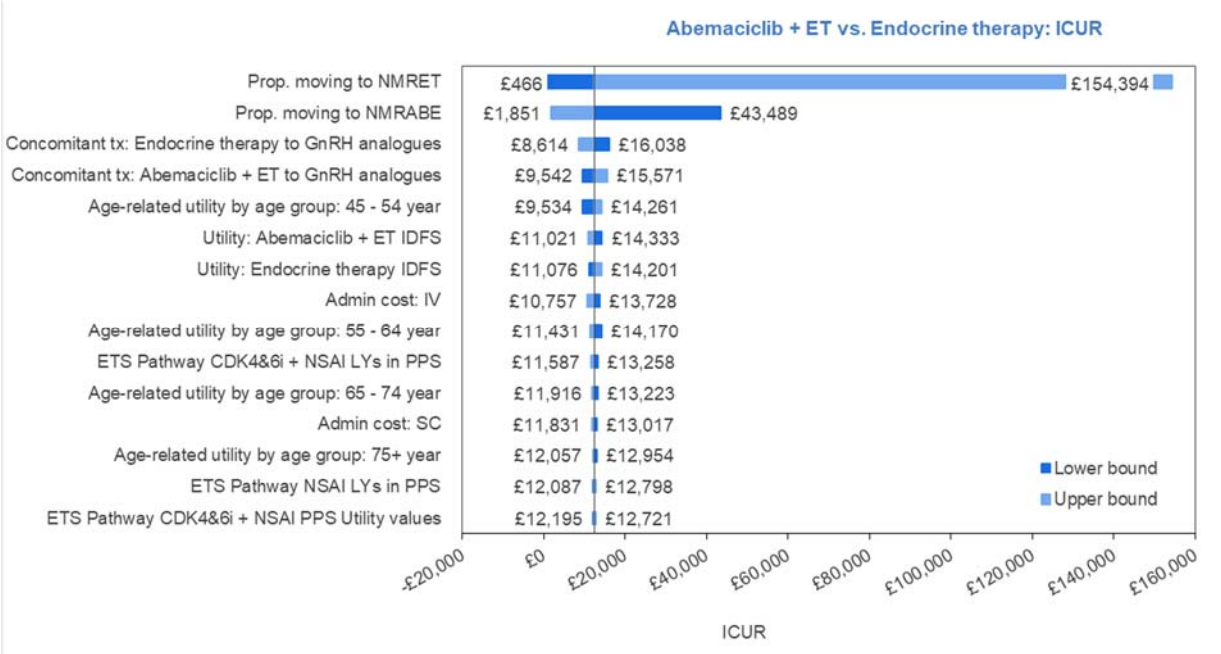


Figure 6.4: Cost effectiveness acceptability curve for Abemaciclib + ET versus ET alone



ET: endocrine therapy; QALY: quality adjusted life year.

Figure 6.5: DSA tornado plot for Abemaciclib + ET versus ET alone



6.4 Conclusions of the cost effectiveness section

The economic SLR reported in the CS identified 32 studies but concluded that there is a lack of evidence evaluating and comparing treatment options for the monarchE patient population. A supplementary targeted review identified four studies of previous TAs published by NICE in early breast cancer over the past 5 years which helped inform model structure, health state utility values, resource use and costs. The ERG felt that the CS did cover what it set out to do in the economic SLR and TLR. However, the CS did not discuss the other CDK 4/6 inhibitors used in breast cancer which was an oversight.

The ERG considers that the company appropriately complied with the majority of the elements present in the NICE reference case. The company developed a *de novo* model, described by the company as a state transition model consisting of five health states: invasive disease-free survival (IDFS), non-

metastatic recurrence (NMR), remission, metastatic recurrence (MR), and death. Patients start in the IDFS state and stay in this state or move to either having a recurrence or death following a partitioned survival structure, with independent survival curves for IDFS and OS. A proportion of patients having a recurrence moves to the NMR state and can stay there for 12 months or die, then they move to the remission state where they can remain in this state until they die or have a MR. The other proportion of patients that have a recurrence move to the MR state where they receive a payoff relative to whether the MR occurs within 12 months of completing ET (ET-resistant metastasis) or 12 months after receiving ET (ET-sensitive metastasis).

The ERG questioned the decision of the company to label the model structure as a state transition model considering that some of the central assumptions derive from the partitioned survival structure within the model. The NHS and PSS perspective and life-time time horizon of the model were considered appropriate by the ERG.

The population used in the CS base-case model was patients with hormone receptor positive, HER2-negative, node-positive early breast cancer based on the ITT population of the monarchE trial. The ERG agreed that the base-case population covers the population in the NICE scope but considered that a subgroup analysis by menopausal status is necessary, given the difference in treatment options for post-menopausal patients compared with premenopausal patients.

The intervention was abemaciclib at 150 mg twice daily for a maximum of 2 years in combination with standard ET for up to 5 years in the base-case versus standard ET alone for up to 5 years. ET was costed as a weighted average of the treatments used by the NHS in clinical practice. The impact of non-adherence on treatment effectiveness was the only issue raised by the ERG in this area.

The effectiveness of the intervention was derived primarily from its impact on IDFS and metastatic recurrences in proportion to non-metastatic recurrences. The ERG questioned the maturity of the data used to extrapolate the survival curves, and the lack of discussions on the accuracy of the predictions coming from those extrapolations. Furthermore, the ERG considered that the assumption of a constant 8-year treatment effect from the start of abemaciclib, and a 19-years linear waning period was a strong and optimistic assumption, that was not sufficiently supported by the evidence presented by the company. Furthermore, the model assumes a constant treatment effect on the proportion of metastatic recurrences, while a piecewise analysis of DRFS shows a non-statistically significant effect at years 2+. From an ERG analysis perspective, this set of uncertainties about the intervention is unable to be reconciled currently and it is with this fundamental caveat, that all subsequent analyses were undertaken.

The model assumes that AEs occur once within the first cycle with data taken from the monarchE trial. The ERG was concerned with the implication of this assumptions that all AEs only have a short transitory effect and that there are no longer term sequalae of any complication. It was felt that this can potentially underestimate their impact in the results.

Utility weights for the IDFS state were sourced from the monarchE trial. As the data showed no significant difference between treatment arms, the CS made the assumption that overall utilities were appropriate to be applied to both treatment arms instead of treatment-specific utilities. In addition, mean change from baseline in mean index scores were estimated using an MMRM regression. The ERG criticised the used of overall utilities in place of treatment specific values, and the timing of HRQoL assessments possibly missing the effect of adverse events occurring within the first 3 months after the intervention.

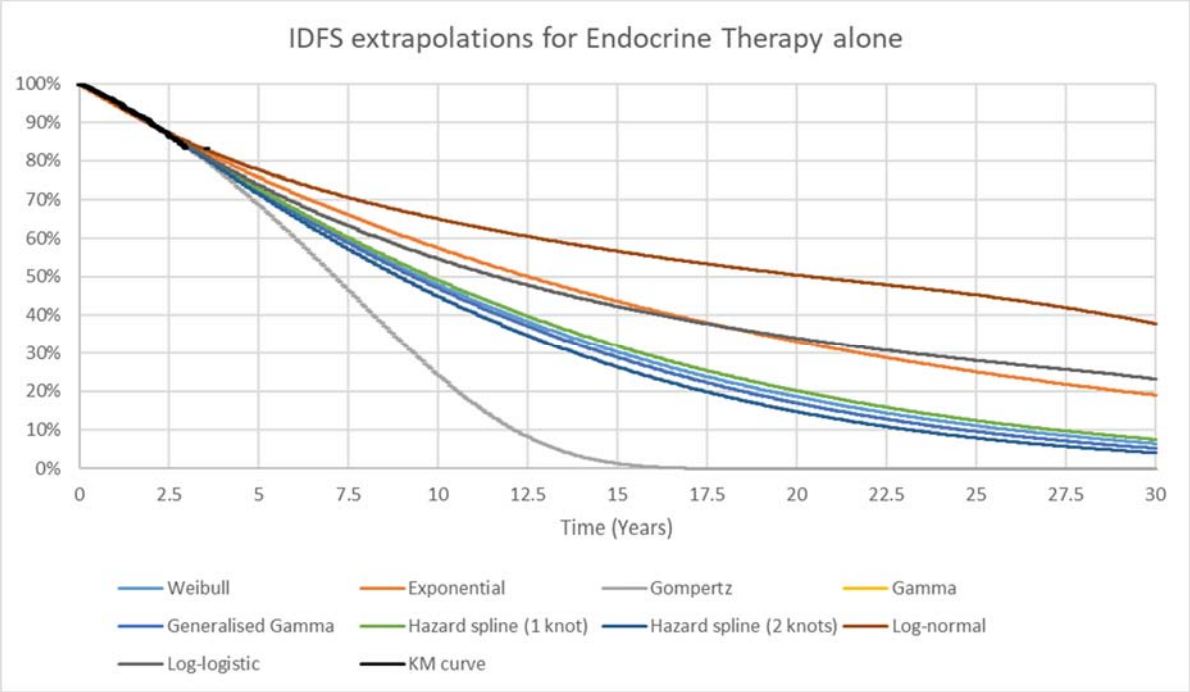
The costs for each different health states were derived from previous TARs, expert clinical opinion, and relevant NICE guidelines. For the ERG it was unclear where the sources of several of the procedure costs reported by the company were derived from, as they deviated from the NHS reference cost 2019/20, and there was a further lack of clarity on how they were implemented in the model.

The company's cost effectiveness model was built and complied with the NICE reference case. There were a number of coding errors. The main critique points are modelling choices and assumptions. The overarching challenge was the immaturity of the data from the monarchE trial, which results in the ICER being very uncertain. The company's base-case ICER was £3,782 compared to the ERG base-case of £12,453. This was primarily driven by the ERGs preferred assumptions around alternative assumptions around the treatment effect on IDFS.

A further area of contention was assembling the population that best resembled the high-risk HR+, HER2- population in the NHS in England, the company preference is for the ITT population from the monarchE trial. The ERG considers a population based on Cohort 1 to be more appropriate and presents results on this subgroup, in so far as was possible. Coding errors within the model provided by the company using the Cohort 1 population affecting some parameter extrapolation and the ability to use the PSA function, limit the ability of the ERG to perform certain analyses.

The company's approach of using a state-transition model was questioned, especially given that it relies heavily of PSM methodology. This methodology resulted in a large proportion of QALY gains being attributed to the time beyond available trial data. An influential issue was regarding the long-term IDFS extrapolation. The ERG accepts that this is a difficult task given the lack of long-term data on breast cancer recurrences in populations like monarchE trial characteristics (i.e., predominately Stage III with larger tumours and higher number of positive nodes). The ERG accepts that based on the more progressed disease end of the Cohort that the log-logistic prediction of ~35% in IDFS at 20-year (see Figure 6.6 which the ERG prepared from the company's model) is realistic and correspondences well with evidence for a general breast cancer population with similar advanced disease at diagnosis (Pan et al 2017).[63] An equally plausible prediction, not covered in the CS scenario, is that closer to a log-normal prediction where ~50% are in the IDFS health state at 20-years based on recent advances in surgery and therapeutics. The OS extrapolation in the CS is paradoxically likely to be overly optimistic for this population and the ERG questions the validity of these curves based on local national registry evidence.

Figure 6.6: IDFS extrapolations used by the company for Endocrine Therapy alone



ET: endocrine therapy; IDFS: invasive disease-free survival; KM: Kaplan-Meier.

The ERG does not accept the 8-year treatment effectiveness and up to 27-year waning assumptions of abemaciclib based on the monarchE trial. The ERG relaxed this assumption by implementing treatment waning from year 3 to year 8 in the ERG base-case, which had a substantial impact on the ICER. To explore the impact of this assumption on the ICER, the ERG conducted a series of scenarios where the treatment effect stops after the latest trial follow-up period, and with a life-long treatment duration, based on NICE DSU TSD 19 guidelines.[32] Furthermore, the ERG included the CS base-case assumption as one of the scenarios where the treatment effect has a total duration of 8 years and wanes completely after 8 years.[32] As further evidence found suggested a constant 3-year treatment effect duration post-treatment for AI therapy, this scenario was also explored.[64] Overall, the scenarios show a substantial impact of the treatment duration assumption in determining the cost effectiveness of the intervention.

An assumption in the CS/CEM was that the probability of having a MR in abemaciclib arm was different to the comparator over the treatment waning effect period. Parity was restored in the ERG base-case. The uncertainty around the probability of transitioning from IDFS to a metastatic recurrence was explored through the following two scenarios: a conservative scenario where the probability of having a MR type of recurrence is the same for both arms from the second year considering the piecewise analysis of DRFS in the CS [2] (see Table 17) where the HR is not statistically significant after 2+ years, and the impact of the CS base-case assumption of a constant probability of having and MR recurrence over time.

Given that IDFS extrapolation and treatment duration, are key issues driving the analyses. The ERG implemented the treatment-specific utilities in their base-case. Though not explored in the ERG analyses, AEs (e.g.., fatigue) may be misrepresented in the CEA model because of the company's applied selection criteria, which could result in underestimation of AE-related costs in the model. One scenario originally explored in the CS that was re-explored by the ERG was that, for MR treatment, both arms used a proportion of CDK4/6 inhibitors equivalent to the ET sensitive treatment pathway

(Monarch3 trial). The ERG considers the evidence used to justify differences in the proportion of patients receiving AI treatments in each arm was not strong enough and potentially would have an important impact on the ICER. Although the scenarios presented were conservative, the true impact of abemaciclib on the proportion of patients receiving CDK4/6 inhibitors to treat a metastatic recurrence is still unknown. Subsequent treatments and their treatment duration were also subject to uncertainty and may also warrant further investigation.

No subgroup analyses were provided, but the ERG considered that cost effectiveness may vary by subgroup. To demonstrate the effect of population difference, a subgroup ERG analyses on Cohort 1 was performed. Other subgroups could be based on menopausal status or AJCC staging status.

The ERG's replication of the corrected company base-case deterministic analysis resulted in an ICER of £5,309 per QALY gained. The estimated ERG base-case ICER (probabilistic), based on the ERG preferred assumptions highlighted in Section 6.1, was £12,233 per QALY gained. The most influential adjustment was implementing treatment duration and waning to 8 years. The ICER increased greatly in the scenario analysis using log-normal for the IDFS distribution and allowing for CDK4/6 inhibitors in subsequent metastatic setting. The probabilistic ERG base-case analyses indicated cost effectiveness probabilities of 89% and 99% at willingness to pay thresholds of £20,000 and £30,000 per QALY gained. In view of the immaturity of the monarchE study trial it was not possible for the ERG to adequately quantify uncertainty now. Further data cuts could potentially resolve this issue. r.

7. END-OF-LIFE

The company state that abemaciclib in combination with endocrine therapy (ET) does not meet the end-of-life criteria, as defined by the National Institute for Health and Care Excellence (NICE).

ERG comment: The Evidence Review Group (ERG) concurs with the company.

8. REFERENCES

[1] Latimer NR. *NICE DSU technical support document 14: survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. Last updated March 2013 [Internet]*. Sheffield: NICE Decision Support Unit, 2011 [accessed 4.11.21] Available from: http://nicedsu.org.uk

[2] Eli Lilly and Company Limited. *Abemaciclib for adjuvant treatment of hormone receptor positive, HER2-negative, node-positive early breast cancer [ID3857]. Document B. Company evidence submission. Single technology appraisal (STA)*: Eli Lilly and Company Limited, 2021

[3] National Institute for Health and Care Excellence. *Abemaciclib in combination with endocrine therapy for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer [ID3857]. Final scope [Internet]*. London: National Institute for Health and Care Excellence, 2021 [accessed 4.11.21] Available from: https://www.nice.org.uk/guidance/gid-ta10749/documents/final-scope-2

[4] Eli Lilly and Company Limited. *Abemaciclib in combination with endocrine therapy for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer [ID3857]. Clarification questions*: Eli Lilly and Company Limited, 2021

[5] National Institute for Health and Care Excellence. *Early and locally advanced breast cancer: diagnosis and management. NICE guideline 101 [Internet]*. London: National Institute for Health and Care Excellence, 2018 [accessed 4.11.21] Available from: https://www.nice.org.uk/guidance/ng101

[6] PREDICT Breast Cancer, NHS, University of Cambridge Winton Centre for Risk and Evidence Communication, Public Health England. PREDICT tool [Internet]. Cambridge: University of Cambridge, 2021 [accessed 20.12.21]. Available from: https://breast.predict.nhs.guk/tool

[7] Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al. PRISMA-S: an extension to the PRISMA statement for reporting literature searches in systematic reviews. *Syst Rev* 2021;10(1):39.

[8] Golder S, Peryer G, Loke YK. Overview: comprehensive and carefully constructed strategies are required when conducting searches for adverse effects data. *J Clin Epidemiol* 2019;113:36-43.

[9] Eli Lilly and Company Limited. *Abemaciclib for adjuvant treatment of hormone receptor positive, HER2-negative, node-positive early breast cancer [ID3857]. Company evidence submission. Appendices. Single technology appraisal (STA)*: Eli Lilly and Company Limited, 2021

[10] FACIT.org. FACT-ES: Functional Assessment of Cancer Therapy - Endocrine Symptoms. For patients with endocrine symptoms [Internet]. FACIT Group, [accessed 15.12.21]. Available from: https://www.facit.org/measures/FACT-ES

[11] Norman G, Sloan J, Wyrwich K. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care* 2003;41(5):582-92.

[12] FACIT.org. FACIT-F: Functional Assessment of Chronic Illness Therapy - Fatigue. A 13-item FACIT Fatigue Scale [Internet]. FACIT Group, [accessed 15.12.21]. Available from: https://www.facit.org/measures/FACIT-F

[13] EuroQol. EQ-5D-5L. About [Internet]. Rotterdam, The Netherlands: EuroQol Research Foundation, 2021 [accessed 20.12.21]. Available from: https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/

[14] Eli Lilly and Company. *monarchE: a randomized, open-label, phase 3 study of abemaciclib combined with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy alone in patients with high risk, node positive, early stage, hormone receptor positive,*

human epidermal receptor 2 negative, breast cancer. I3Y-MC-JPCF. Clinical Study Report. 01 April 2021 (date of interim data cut-off): Eli Lilly and Company, 2021

[15] Curtis L, Burns A. *Unit costs of health and social care 2017 [Internet]*. University of Kent, Canterbury: Personal Social Services Research Unit, 2017 [accessed 4.11.21] Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2017/

[16] NHS Improvement, NHS England. *National schedule of reference costs - year 2019/2020 - NHS trust and NHS foundation trusts [Internet]*: NHS England and NHS Improvement, 2019 [accessed 21.12.21] Available from: https://www.england.nhs.uk/national-cost-collection/

[17] National Institute for Health and Care Excellence. *Ribociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer. Technology appraisal guidance TA496. Resource impact template [Internet]*. London: National Institute for Health and Care Excellence, 2017 [accessed 21.12.21] Available from: https://www.nice.org.uk/guidance/ta496

[18] National Institute for Health and Care Excellence. *Abemaciclib with an aromatase inhibitor for untreated advanced hormone-receptor positive, HER2-negative breast cancer ID1227. Technology appraisal guidance TA563 [Internet]*. London: National Institute for Health and Care Excellence, 2019 [accessed 21.12.21] Available from: https://www.nice.org.uk/guidance/TA563

[19] National Institute for Health and Care Excellence. *Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy. Technology appraisal guidance 725 [Internet]*. London: National Institute for Health and Care Excellence, 2021 [accessed 21.12.21] Available from: https://www.nice.org.uk/guidance/TA725

[20] Sud A, Jones ME, Broggio J, Loveday C, Torr B, Garrett A, et al. Collateral damage: the impact on outcomes from cancer surgery of the COVID-19 pandemic. *Ann Oncol* 2020;31(8):1065-74.

[21] Howlader N, Cronin KA, Kurian AW, Andridge R. Differences in breast cancer survival by molecular subtypes in the United States. *Cancer Epidemiol Biomarkers Prev* 2018;27(6):619-26.

[22] Salvo EM, Ramirez AO, Cueto J, Law EH, Situ A, Cameron C, et al. Risk of recurrence among patients with HR-positive, HER2-negative, early breast cancer receiving adjuvant endocrine therapy: a systematic review and meta-analysis. *Breast* 2021;57:5-17.

[23] Alramadhan M, Ryu JM, Rayzah M, Nam SJ, Kim SW, Yu J, et al. Goserelin plus tamoxifen compared to chemotherapy followed by tamoxifen in premenopausal patients with early stage-, lymph node-negative breast cancer of luminal A subtype. *Breast* 2016;30:111-7.

[24] Kwak HY, Chae BJ, Eom YH, Hong YR, Seo JB, Bae JS, et al. Is adjuvant chemotherapy omissible in women with T1-2 stage, node-positive, luminal A type breast cancer? *J Chemother* 2015;27(5):290-6.

[25] Shimazu K, Miyake T, Okuno J, Naoi Y, Tanei T, Shimoda M, et al. One-step nucleic acid amplification can identify sentinel node-negative breast cancer patients with excellent prognosis. *Anticancer Res* 2019;39(3):1447-54.

[26] Colleoni M, Luo W, Karlsson P, Chirgwin J, Aebi S, Jerusalem G, et al. Extended adjuvant intermittent letrozole versus continuous letrozole in postmenopausal women with breast cancer (SOLE): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2018;19(1):127-38.

[27] Francis PA, Regan MM, Fleming GF, Láng I, Ciruelos E, Bellet M, et al. Adjuvant ovarian suppression in premenopausal breast cancer. *N Engl J Med* 2015;372(5):436-46.

[28] Ruíz-Borrego M, Guerrero-Zotano A, Bermejo B, Ramos M, Cruz J, Baena-Cañada JM, et al. Phase III evaluating the addition of fulvestrant (F) to anastrozole (A) as adjuvant therapy in postmenopausal women with hormone receptor-positive HER2-negative (HR+/HER2-) early breast cancer (EBC): results from the GEICAM/2006-10 study. *Breast Cancer Res Treat* 2019;177(1):115-25.

[29] Smith I, Yardley D, Burris H, De Boer R, Amadori D, McIntyre K, et al. Comparative efficacy and safety of adjuvant letrozole versus anastrozole in postmenopausal patients with hormone receptor-positive, node-positive early breast cancer: final results of the randomized phase III Femara versus Anastrozole Clinical Evaluation (FACE) trial. *J Clin Oncol* 2017;35(10):1041-8.

[30] Tjan-Heijnen VCG, van Hellemond IEG, Peer PGM, Swinkels ACP, Smorenburg CH, van der Sangen MJC, et al. Extended adjuvant aromatase inhibition after sequential endocrine therapy (DATA): a randomised, phase 3 trial. *Lancet Oncol* 2017;18(11):1502-11.

[31] Derks MGM, Blok EJ, Seynaeve C, Nortier JWR, Kranenbarg EM, Liefers GJ, et al. Adjuvant tamoxifen and exemestane in women with postmenopausal early breast cancer (TEAM): 10-year follow-up of a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2017;18(9):1211-20.

[32] Woods B, Sideris E, Palmer S, Latimer N, Soares M. *NICE DSU technical support document 19: partitioned survival analysis for decision modelling in health care: a critical review [Internet]*. Sheffield: NICE Decision Support Unit, 2017 [accessed 22.12.21] Available from: http://www.nicedsu.org.uk

[33] Cancer Research UK. *Breast cancer survival by stage at diagnosis [Internet]*: Cancer Research UK, [accessed 22.12.21] Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/survival#heading-Three

[34] Chirgwin JH, Giobbie-Hurder A, Coates AS, Price KN, Ejlertsen B, Debled M, et al. Treatment adherence and its impact on disease-free survival in the Breast International Group 1-98 trial of tamoxifen and letrozole, alone and in sequence. *J Clin Oncol* 2016;34(21):2452-9.

[35] Murphy CC, Bartholomew LK, Carpentier MY, Bluethmann SM, Vernon SW. Adherence to adjuvant hormonal therapy among breast cancer survivors in clinical practice: a systematic review. *Breast Cancer Res Treat* 2012;134(2):459-78.

[36] Neugut AI, Zhong X, Wright JD, Accordino M, Yang J, Hershman DL. Nonadherence to medications for chronic conditions and nonadherence to adjuvant hormonal therapy in women with breast cancer. *JAMA Oncol* 2016;2(10):1326-32.

[37] Neven P, Markopoulos C, Tanner M, Marty M, Kreienberg R, Atkins L, et al. The impact of educational materials on compliance and persistence rates with adjuvant aromatase inhibitor treatment: first-year results from the compliance of aromatase inhibitors assessment in daily practice through educational approach (CARIATIDE) study. *Breast* 2014;23(4):393-9.

[38] Finitsis DJ, Vose BA, Mahalak JG, Salner AL. Interventions to promote adherence to endocrine therapy among breast cancer survivors: a meta-analysis. *Psychooncology* 2019;28(2):255-63.

[39] Heiney SP, Parker PD, Felder TM, Adams SA, Omofuma OO, Hulett JM. A systematic review of interventions to improve adherence to endocrine therapy. *Breast Cancer Res Treat* 2019;173(3):499-510.

[40] Rutherford M, Lambert P, Sweeting M, Pennington B, Crowther M, Abrams K, et al. *NICE DSU technical support document 21: flexible methods for survival analysis [Internet]*. Sheffield: NICE Decision Support Unit, 2020 [accessed 17.12.21] Available from: http://www.nicedsu.org.uk

[41] Cuzick J, Sestak I, Baum M, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. *Lancet Oncol* 2010;11(12):1135-41.

[42] National Institute for Health and Care Excellence. *Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer. Technology appraisal guidance 632 [Internet]*. London: National Institute for Health and Care Excellence, 2020 [accessed 21.12.21] Available from: https://www.nice.org.uk/guidance/TA632

[43] von Minckwitz G, Procter M, de Azambuja E, Zardavas D, Benyunes M, Viale G, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N Engl J Med* 2017;377(2):122-31.

[44] Beusterien KM, Szabo SM, Kotapati S, Mukherjee J, Hoos A, Hersey P, et al. Societal preference values for advanced melanoma health states in the United Kingdom and Australia. *Br J Cancer* 2009;101(3):387-9.

[45] Swinburn P, Lloyd A, Nathan P, Choueiri TK, Cella D, Neary MP. Elicitation of health state utilities in metastatic renal cell carcinoma. *Curr Med Res Opin* 2010;26(5):1091-6.

[46] Chirikov V, Ma I, Joshi N, Patel D, Smith A, Giambrone C, et al. Cost-effectiveness of alemtuzumab in the treatment of relapsing forms of multiple sclerosis in the United States. *Value Health* 2019;22(2):168-76.

[47] Bullement A, Nathan P, Willis A, Amin A, Lilley C, Stapelkamp C, et al. Cost effectiveness of avelumab for metastatic merkel cell carcinoma. *Pharmacoecon Open* 2019;3(3):377-90.

[48] Leeuwenkamp O, Smith-Palmer J, Ortiz R, Werner A, Valentine W, Blachier M, et al. Cost-effectiveness of lutetium [(177)Lu] oxodotreotide versus best supportive care with octreotide in patients with midgut neuroendocrine tumors in France. *J Med Econ* 2020;23(12):1534-41.

[49] Borgström F, Ström O, Kleman M, McCloskey E, Johansson H, Odén A, et al. Cost-effectiveness of bazedoxifene incorporating the FRAX® algorithm in a European perspective. *Osteoporos Int* 2011;22(3):955-65.

[50] Hannouf MB, Zaric GS, Blanchette P, Brezden-Masley C, Paulden M, McCabe C, et al. Cost-effectiveness analysis of multigene expression profiling assays to guide adjuvant therapy decisions in women with invasive early-stage breast cancer. *Pharmacogenomics J* 2020;20(1):27-46.

[51] Zethraeus N, Borgström F, Jönsson B, Kanis J. Reassessment of the cost-effectiveness of hormone replacement therapy in Sweden: results based on the Women's Health Initiative randomized controlled trial. *Int J Technol Assess Health Care* 2005;21(4):433-41.

[52] Enden T, Wik HS, Kvam AK, Haig Y, Kløw NE, Sandset PM. Health-related quality of life after catheter-directed thrombolysis for deep vein thrombosis: secondary outcomes of the randomised, non-blinded, parallel-group CaVenT study. *BMJ Open* 2013;3(8):e002984.

[53] National Institute for Health and Care Excellence. *Intrabeam radiotherapy system for adjuvant treatment of early breast cancer. Technology appraisal guidance 501 [Internet]*. London: National Institute for Health and Care Excellence, 2018 [accessed 21.12.21] Available from: https://www.nice.org.uk/guidance/ta501

[54] National Institute for Health and Care Excellence. *Neratinib for extended adjuvant treatment of hormone receptor-positive, HER2- positive early stage breast cancer after adjuvant trastuzumab. Technology appraisal guidance 612 [Internet]*. London: National Institute for Health and Care Excellence, 2019 [accessed 21.12.21] Available from: https://www.nice.org.uk/guidance/TA612

[55] National Institute for Health and Care Excellence. *Pertuzumab for adjuvant treatment of HER2-positive early stage breast cancer. Technology appraisal guidance 569 [Internet]*. London:

National Institute for Health and Care Excellence, 2019 [accessed 21.12.21] Available from: https://www.nice.org.uk/guidance/TA569

[56] Department of Health and Social Care. *Drugs and pharmaceutical electronic market information tool (eMIT) [Internet]*: Department of Health and Social Care, 2018 [accessed 4.11.21] Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit

[57] Dhesy-Thind S, Fletcher GG, Blanchette PS, Clemons MJ, Dillmon MS, Frank ES, et al. Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer: a Cancer Care Ontario and American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2017;35(18):2062-81.

[58] Joint Formulary Committee. *British National Formulary [Internet]*. London: BMJ Group and Pharmaceutical Press, 2021 [accessed 4.11.21]. Available from: https://bnf.nice.org.uk/

[59] National Institute for Health and Care Excellence. *Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer. Technology appraisal guidance TA403 [Internet]*. London: National Institute for Health and Care Excellence, 2016 [accessed 17.1.22] Available from: https://www.nice.org.uk/guidance/TA403

[60] Curtis LA, Burns A. *Unit costs of health and social care 2020 [Internet]*. Canterbury: Personal Social Services Research Unit (PSSRU), University of Kent, 2020 [accessed 4.11.21] Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2020/

[61] Grimm SE, Pouwels X, Ramaekers BLT, Wijnen B, Knies S, Grutters J, et al. Development and Validation of the TRansparent Uncertainty ASsessmenT (TRUST) Tool for assessing uncertainties in health economic decision models. *Pharmacoeconomics* 2020;38(2):205-216.

[62] Kaltenthaler E, Carroll C, Hill-McManus D, Scope A, Holmes M, Rice S, et al. The use of exploratory analyses within the National Institute for Health and Care Excellence single technology appraisal process: an evaluation and qualitative analysis. *Health Technol Assess* 2016;20(26):1-48.

[63] Pan H, Gray R, Braybrooke J, Davies C, Taylor C, McGale P, et al. 20-year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. *N Engl J Med* 2017;377(19):1836-46.

[64] Dowsett M, Cuzick J, Ingle J, Coates A, Forbes J, Bliss J, et al. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. *J Clin Oncol* 2010;28(3):509-18.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Abemaciclib in combination with endocrine therapy for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer [ID3857]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG 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 28 January 2022** 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 separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Section 1: Factual inaccuracies

Major Inaccuracies

Issue 1 The ERG's Treatment Waning Correction (Error #5)

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG have incorporated a correction to the treatment waning approach in the Company model, which sets the ABE + ET IDFS curve equal to the ET curve after the period of treatment waning. **Page 126** states: **"Error** in the IDFS curve formula for abemaciclib. The formula used to derive IDFS in the abemaciclib arm maintained a treatment effect beyond the waning assumption (at 360 months) (see Figure 6.1). Once the effect of abemaciclib has completely waned, the IDFS curves in the treatment and control arms must be equivalent and have a hazard ratio of one. **Correction**: The formula was modified to have the treatment coefficient decrease to zero as the treatment effect wanes (instead of having treatment	Throughout the ERG report, references to the Company's modelling of the IDFS curve for abemaciclib are described as an "error" and the ERG's approach as a "correction". References to the ERG's "correction" and the Company's "error" should be amended to state that this represents the ERG's preferred methodology in response to a 'Matter of Judgement' or reviewed again by the ERG and removed entirely from its base case, given the Company rationale. • The text and figures on Line 15, Page 126 to Line 5, Page 127 should be moved to under 'Matters of judgement' rather than 'Fixing errors'. • The text on page 126 should be amended as follows: ~~**Error in the IDFS curve formula for abemaciclib.**~~ The formula used to derive IDFS in the abemaciclib arm maintained a treatment effect beyond the waning assumption (at 360 months) (see Figure 6.1). Once the effect of abemaciclib has completely waned, **the ERG's preferred assumption is that** the IDFS curves in the	As detailed on Page 125 of the ERG report, adjustments made for the purposes of fixing errors must represent situations "where the Company's submitted model was unequivocally wrong". The Company's treatment waning methodology does not represent an error, but a difference in opinion between the Company and the ERG. The substantial limitations with the ERG's approach, detailed below, mean that it is inappropriate to refer to the Company's approach as an unequivocal error, or the ERG's approach as an unequivocal correction of that error. The Company wish to clarify that the approach taken in the Company CEM already assumes that the hazards of experiencing invasive breast cancer in the abemaciclib + ET and ET alone arms are equal following	The ERG has revised its approach and decided to remove this error previously defined as "Coding error 5" entirely from the report, along with the figures and references to this error.

waning as a weighted average of the treatment and control hazard rates as it was originally implemented by the company). This way, the hazard rates in the IDFS function on both arms are the same beyond the complete waning point (See Figure 6.2), which led to more consistent results." **Page 127**, Figure 6.2 states: "Company base-case IDFS after correcting errors"	treatment and control arms must be equivalent and have a hazard ratio of one. **The ERG have incorporated their preferred waning methodology by modifying the formula** to have the treatment coefficient decrease to zero as the treatment effect wanes (instead of having treatment waning as a weighted average of the treatment and control hazard rates as it was originally implemented by the company). This way, the hazard rates in the IDFS function on both arms are the same beyond the complete waning point (See Figure 6.2), which led to more consistent results. • Please can the text on page, 127, Figure 6.2, be amended as follows: Company base-case IDFS **which has been amended in line with the ERG's preferred approach**	treatment waning, meaning that abemaciclib is associated with no treatment benefit on IDFS following the waning period. The Company CEM does this without setting the IDFS curves themselves equal to each other, and inherently cancelling out the prior treatment benefit of abemaciclib accumulated before the waning period. However, by equalising the IDFS curves for abemaciclib + ET and ET alone following the period of treatment waning, the ERG assumes that the addition of abemaciclib to ET <u>increases the risk of a patient experiencing invasive breast cancer recurrence</u> compared to patients who did not receive abemaciclib. The Company does not consider this to be clinically plausible. This can be observed visually in Figure 1 and 2, presented below this response. The hazard of recurrence in the ABE + ET arm fluctuates drastically over the treatment waning period, initially rising above the risk of IDFS in the ET alone arm, before declining sharply once treatment waning ends. In comparison, the hazard of recurrence in the ET alone arm remains largely	

		constant over the same time period. These differences are not clinically plausible, particularly when considering that over the treatment waning period (Year 3 to Year 8), all patients have discontinued ABE, and are receiving the same treatment (ET alone) in both arms. While the Company agrees that the hazard in both arms should be equivalent after the period of waning, this does not mean that the IDFS curves themselves should be set to be equal. Instead, the separation of the curves observed during the first years of the model, due to the treatment effect of abemaciclib reducing the risk of recurrence, means that the IDFS curves should remain separate once treatment waning is applied (until the curves are bounded by general population mortality), even though the HR between the curves equals 1 after treatment waning. It is also important to note that the Company approach to implementing treatment waning is consistent with previous early	

		breast cancer appraisals. The approach taken by the ERG, applying treatment waning by setting the IDFS curves to be equal in both arms, is inconsistent with the Committee's preferred treatment waning approaches in previously early breast cancer appraisals, including TA632 and TA612, as well as numerous other published NICE appraisals in other oncology indications.[1, 2] For example, the ERG's preferred approach to modelling IDFS (shown in Figure 3 below) in TA632 did not include a correction to set the IDFS curves equal when treatment waning was applied. Considering the potential limitations of the ERG's approach, and the inconsistency with previous NICE TAs, the Company does not agree with the ERG's proposed correction, and for the purposes of the Factual Accuracy Check, considers that it is inaccurate to refer to the Company's approach as an unequivocal error. We request the ERG to review its approach again for its validity and, if appropriate, to remove this correction entirely from its base case and amend the ERG report accordingly or update	

		the ERG report to denote this as a ‘Matter of Judgement’.	

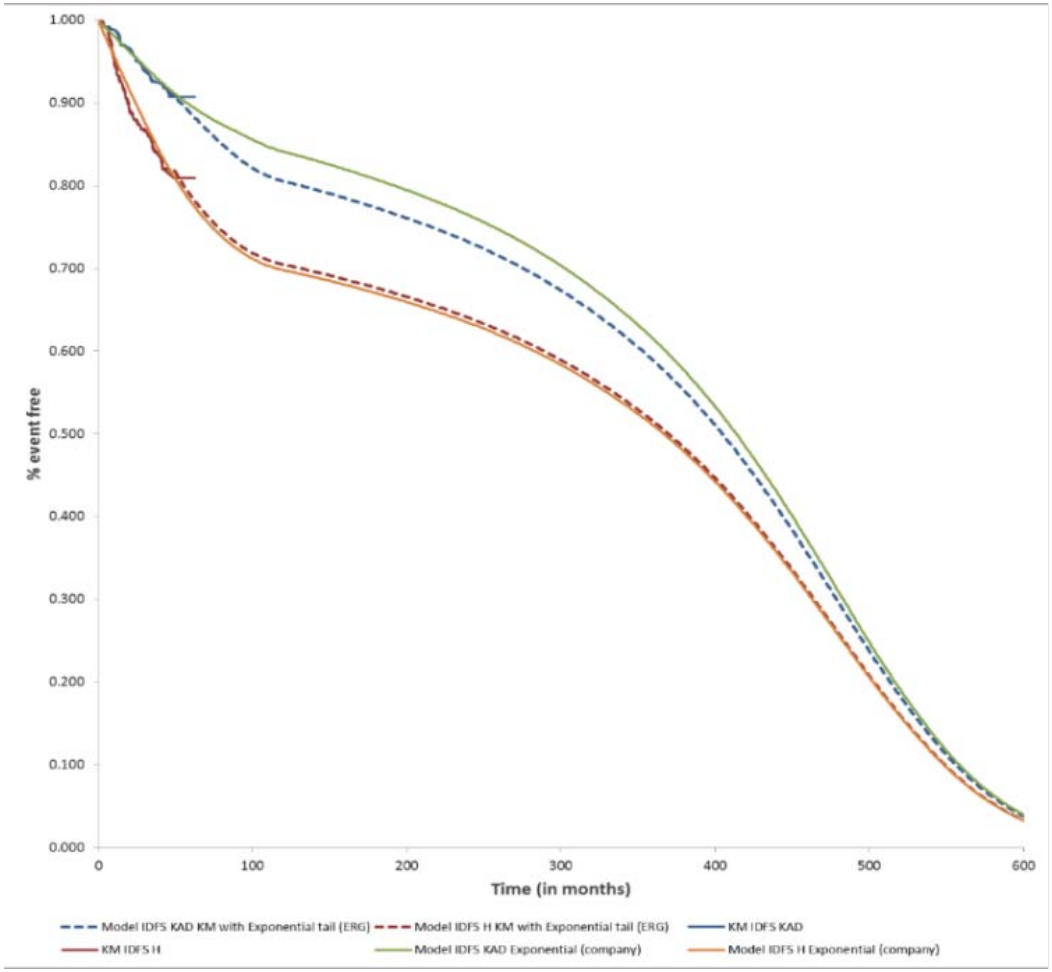
Figure 1: Comparison between the Company and ERG waning approaches (Waning begins at Year 8, and ends at Year 27)

Abbreviations: ABE: abemaciclib; ERG: Evidence Review Group; ET: endocrine therapy; IDFS: invasive disease free survival.

Figure 2: Comparison between the Company and ERG Waning Approaches (Waning Begins at Year 3, and Ends at Year 8)

Abbreviations: ABE: abemaciclib; ERG: Evidence Review Group; ET: endocrine therapy; IDFS: invasive disease free survival.

Figure 3: Company and ERG approaches to modelling IDFS in TA632 (TA632 Committee Papers, Page 579)



Abbreviations: ERG: Evidence Review Group; IDFS: Invasive disease free survival; TA: Technology Appraisal.

Issue 2 Distinction Between OS and OS Without Distant Recurrence

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG to refer to the OS extrapolations in the Company model without distinguishing between absolute OS estimates (e.g., those published in the literature) compared to **OS for patients without distant recurrence** (the endpoint included in the Company model). **Page 18: "**According to the company's long term OS extrapolations, ~97% of the monarchE Cohort will be alive at 5-years for both arms." **Page 84:** "Estimating from Figure 26 of the CS (page 116), the 5-year (60 month) survival is about ~97%. In the CEM at cycle 60, less than one patient out of the Cohort of 1,000 was in the dead state."	We request that any comparison to absolute OS to OS without distance recurrence in the ERG report should be amended. **Page 18: "**According to the company's long term **extrapolations of OS without distant recurrence** ~~OS extrapolations~~, ~97% of the monarchE Cohort **who have not experienced a distant recurrence** will be alive at 5-years for both arms." **Page 84:** "Estimating from Figure 26 of the CS (page 116), the 5-year (60 month) survival, **excluding patients who have experienced a distant recurrence**, is about 97%. In the CEM at cycle 60, less than one patient out of the Cohort of 1,000 **who had not experienced a distant recurrence** had died.	OS, and OS without distant recurrence, are two distinct endpoints, and should not be used interchangeably. It is inaccurate for the ERG to refer to the OS extrapolations in the Company model without indicating that these represent OS **for patients without distant recurrence**, or to compare **OS without distant recurrence** estimates in the model, to absolute OS estimates in the published literature. It is also inaccurate to suggest that the "dead" health state is the only absorbing health state in the model. As noted in the CS (Page 90), the metastatic recurrence health states are also absorbing health states. The dead health state only absorbs patients who die without experiencing distant recurrence. Patients who enter the metastatic recurrence health states will never transition to the dead health state, and are assigned fixed pay-	The ERG accepts the distinction between OS, and OS without distant recurrence made by the Company. However, the ERG feels that this clarity ought to be present throughout the company submission in every Figure and Table pertaining to 'OS'. It also presents a deficit in the company CEM and submission in terms of allowing the ERG to compare overall survival to registry data/literature.

		offs which consider the risk of death in the metastatic recurrence setting. For example, it should be noted that in the ERG's preferred base case, [redacted] patients ([redacted]%) are modelled to be in the MR-ET resistant health state at Cycle 60. Death in this health state is not explicitly recorded in the CEM, but it is likely that many of these patients would have died by Year 5, given the extremely poor prognosis in the metastatic health state.	

Issue 3 Inclusion of Treatment-Specific Utilities

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG report presents a scenario analysis which applies treatment-specific utilities to ABE + ET and ET alone (ERG Matter of Judgement #4), as reported in Table 1.15 (Page 21) and Table 6.2 (Page 133). This ICER is also referred to on Page 19: "The ICER when the ERG modified the probability was £9,228"	The IDFS treatment specific utilities used in this scenario should be updated to equal [redacted] (ABE + ET) and [redacted] (ET alone), as detailed in response to QB11, Table 20 of the Company's Response to the ERG Clarification Questions. The ICER for the resulting scenario analysis should be updated throughout the ERG report.	The treatment specific utilities used by the ERG in this scenario are inaccurate, and it is unclear how these have been derived. When used, the treatment specific utility values should be updated to align with those from monarchE, as presented in response to the ERG Clarification Questions (B11, Table 20).	The treatment specific utility values for IDFS initially applied by the ERG were those already included in the original model submission file. These have now been changed for the mean and standard deviation values reported in the Clarification Questions as proposed by the Company.

In the ERG's model, the ERG has applied IDFS treatment specific utilities of [redacted] for the ABE + ET arm, and [redacted] for the ET alone arm (Cells C58 and 59 of the "Input Conversion" tab of the ERG Base CEM).			

Issue 4 Modelling of Cohort 1 Scenario Analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG report presents a scenario analysis using the Cohort 1 population (Matter of Judgement #1), and presents the results of this scenario analysis in Table 6.4 (Page 137), and an ICER incorporating the Cohort 1 data in Table 1.2 (Page 14). However, the ERG report does not provide any details or justification regarding the choice of extrapolations used in this scenario, or any discussion regarding why the ERG have chosen different extrapolations compared to the Company's Cohort 1 scenario analysis	The ERG report should provide additional clarification and justification regarding the choice of clinical parameters for Cohort 1 in these scenario analyses. Alternatively, the ERG should amend the ERG base case for Cohort 1 to reflect the Company chosen TTD curves for the ET intervention and comparator arms in the Cohort 1 scenario analysis (Clarification Questions, QA4e).	The ERG report does not provide sufficient explanation of justification for the results of the ERG's Cohort 1 scenario analysis to be meaningfully interpreted. The Company provided details and justification for the choice of extrapolations used for IDFS, OS and ToT in the Cohort 1 cost-effectiveness estimates presented in response to the ERG's clarification questions. Notably, the Company used the exponential distributions for ET (intervention and comparator arms) in this scenario analysis, as the hazard spline 2 knots	The ERG is happy to amend the ERG base case for Cohort 1 to reflect the Company chosen TTD curves for the ET intervention and comparator arms in the Cohort 1 scenario analysis.

presented in response to the ERG's clarification questions. The Company's Cohort 1 scenario analysis uses the exponential extrapolation for ET alone (intervention and comparator arms), while the ERG's Cohort 1 scenario analysis uses the hazard spline 2 knots extrapolation. The ERG does not acknowledge this difference.		extrapolation was not considered to be clinically plausible. However, the ERG have instead chosen the hazard spline 2 knots extrapolation for their version of this scenario, but without providing any justification regarding this. The Company acknowledge that the ERG may prefer alternative extrapolations, but the Company would request that the ERG's preferred assumptions are clearly described and justified, so that this scenario analysis can be meaningful interpreted. Alternatively, the ERG should amend the ERG base case for Cohort 1 to reflect the Company chosen TTD curves for the ET intervention and comparator arms in the Cohort 1 scenario analysis, if this was the intention.	

Issue 5 Presentation of the Company's Corrected Base Case ICER

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG report presents a Company base-case after fixing errors of £8,991.73 in Table 1.15 (Page 21), Table 6.2 (Page 133) and Table 6.4 (Page 137).	All references to the Company corrected base case after fixing errors throughout the ERG report should be updated from £8,991.73 to £5,309. The ICER of £5,309 includes the fixes to Coding Error #1, Coding Error #2, Coding	As detailed in Issue 1 and Issue 2, it is inaccurate to refer to Coding Error #5 as an	The ERG accepts the amendment proposed by the company. Results and references to the Company corrected ICER have been updated in the report.

This ICER is also referenced throughout the ERG report: **Page 18:** "The company base-case ICER after errors were fixed was £8,992" **Page 19**: "The company base-case after fixing errors was £8,992" **Page 20: "**Overall, the cumulative effect of correcting the errors within the model was modest with the ICER increasing from £3,786 for the company base-case to £8,992 after fixing errors" **Page 145:** "The ERG's replication of the corrected company base-case probabilistic analysis resulted in an ICER of £8,992 per QALY gained" This ICER, denoted as the Company-corrected base case after fixing errors, includes the ERG's proposed fix to Coding Error #5 (Treatment Waning formula).	Error #3 and Coding Error #4, but excludes the ERG's proposed fixes to Coding Error #5. All scenarios presented throughout the ERG report which include the ERG's proposed fix to Coding Error #5 should be clearly marked as the ERG's preferred assumption regarding 'Matters of Judgement', rather than corrections to the Company base case, or this 'error' should be reviewed again by the ERG and removed entirely, given the Company rationale. After review of the Company's rationale of removing Coding Error #5, the ERG base case and scenario results should be updated throughout to reflect the removal of this correction.	unequivocal error in the Company model. As such, the Company request that the ERG report should be amended so that Coding Error #5 and the ERG's resulting fix is denoted as the ERG's preferred assumption regarding 'Matters of Judgement', rather than fixing an error which is unequivocally wrong. Alternatively, this should be reviewed again by the ERG and this correction removed entirely from its base case, and the ERG report amended accordingly, in line with the Company's rationale presented in Issue 1. Any reference to the Company-corrected ICERs should not include this fix.	

Other Inaccuracies

Issue 6 Cost source inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 106 states "The cost for the mammogram is costed as £33.61 which is sourced from TA612. When examining cost of a mammogram in TA612 the specific cost for a mammogram is £11.34 which is in turn costed from TA767. The cost for a mammogram in TA767 is £57.84 which is costed from TA569, which also cites a cost from £11.34 from TA767."	Please can this be amended as follows: The cost for the mammogram is costed as £33.61 which is sourced from **National Schedule of NHS Cost 2019-20 (IMAGOP, PF, Plain Film, Outpatient).** ~~**When examining cost of a mammogram in TA612 the specific cost for a mammogram is £11.34 which is in turn costed from TA767. The cost for a mammogram in TA767 is £57.84 which is costed from TA569, which also cites a cost from £11.34 from TA767.**~~	The Company have identified that this cost was incorrectly referenced in the CS, Document B. The Company would like to confirm that the cost for the mammogram was sourced from the National Schedule of NHS Cost 2019-20 (IMAGOP, PF, Plain Film, Outpatient), rather than TA612. Furthermore, the Company notes that the ERG refer to TA767, which appears to be a mistake. Based on the above correction, the sentence referring to TA767 is no longer relevant so can be removed.	The ERG have added the clarification in the text given the corrections that the company have provided.

Issue 7 Cost source inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 107 states "Some costs deviated from the NHS reference costs 2019/20". Table 4.21 contains the following information:	Please can this be amended as follows: ~~**Some costs deviated from the NHS reference costs 2019/20.**~~	The Company would like to highlight that each NHS reference cost code is associated with multiple different costs, depending on the setting, and so it is inaccurate for the ERG to state that there is only one	The ERG accepts the clarification to which individual costs were used. A clarification has been added to explain that costs deviate from the costs differ from the total

Treatment	Code	Value from CS	V
Deliver a Fraction of Complex Treatment on a Megavoltage Machine – Outpatient	SC23Z	£149	
Deliver Subsequent Elements of a Chemotherapy Cycle	SB12Z	£254	
Unilateral Major Breast Procedures with CC Score 3-5	JA20E	£4,031	£
Unilateral Excision of Breast with Immediate Pedicled Myocutaneous Flap Reconstruction	JA32Z	£6,892	£
Unilateral Excision of Breast with Immediate Free Perforator Flap Reconstruction	JA36Z	£12,620	£

Treatment	Code	Value from CS	E
Deliver a Fraction of Complex Treatment on a Megavoltage Machine – Outpatient	SC23Z	£149 **(Radiotherapy)**	
Deliver Subsequent Elements of a Chemotherapy Cycle	**SB15Z**	£254 **(Outpatient)**	
Unilateral Major Breast Procedures with CC Score 3-5	JA20E	£4,031 **(Elective inpatient)**	
Unilateral Excision of Breast with Immediate Pedicled Myocutaneous Flap Reconstruction	JA32Z	£6,892 **(Elective inpatient)**	
~~**Unilateral Excision of Breast with Immediate Free Perforator Flap Reconstruction**~~	~~**JA36Z**~~	~~**£12,620**~~	

reference cost associated with each cost code.

The Company note that the ERG have presented alternative costs from the NHS Reference Costs 2019/20, but it is inaccurate to state that some costs in the CS deviated from the NHS reference costs 2019/20. While the Company acknowledges that the ERG may prefer an alternative cost, it is inaccurate to state that the Company's values have not also been taken from the NHS reference costs. Further clarification should be added to Table 4.21 in the ERG report to indicate the exact source of the costs in the CS and the ERG values.

As stated in the CS, Appendix O, the costs were sourced from NHS Reference Costs 2019/20 as follows:

The cost used in the CS for 'Deliver a Fraction of Complex Treatment on a Megavoltage Machine – Outpatient' (£149) is the SC23Z cost for Radiotherapy, whereas the ERG have presented the corresponding cost for Total HRG.

HRG costs in favour of specific costs.

For The ERG is assuming that the cost for "Unilateral Excision of Breast with Immediate Pedicled Myocutaneous Flap Reconstruction' is based on JA32Z as HA32Z could not be identified.

The cost differential for "Unilateral Excision of Breast with Immediate Free Perforator Flap Reconstruction" has been removed.

		The cost used in the CS for 'Deliver Subsequent Elements of a Chemotherapy Cycle' (£254) is the SB15Z cost for outpatient whereas the ERG have presented the corresponding Total HRG cost. The Company notes that the code was incorrectly reported in the CS (as SB12Z, rather than SB15Z). The costs used in the CS for 'Unilateral Major Breast Procedures with CC Score 3-5' (£4,031) and Unilateral Excision of Breast with Immediate Pedicled Myocutaneous Flap Reconstruction' (£6,892) are the JA20E and HA32Z costs for elective inpatient, respectively. The ERG have presented the corresponding costs for Total HRG.	

Issue 8 Cost source inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Table 4.21 contains the following information:	Table 4.21 contains the following information:	The cost used in the CS for 'Unilateral Excision of Breast with Immediate Free Perforator Flap Reconstruction' is inaccurately	Line removed.

Treatment	Code	Value from CS	ERG Value
Unilateral Excision of Breast with Immediate Free Perforator Flap Reconstruction	JA36Z	£12,620	£14,610

Treatment	Code	Value from CS	ERG Value
~~Unilateral Excision of Breast with Immediate Free Perforator Flap Reconstruction~~	~~JA36Z~~	~~£12,620~~	~~£14,610~~

stated in the ERG report. The cost used is £14,610, as presented in CS, Appendix O, Table 82. Seeing as there is no difference between the value from the CS and the ERG value, this row can be removed

Issue 9 Cost source inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 110 states "The grouper code (WF01A) is associated with a value of £125 rather than £173.10. Again, the ERG is unclear why this is the case."	Please can this be amended as follows: ~~**The grouper code (WF01A) is associated with a value of £125 rather than £173.10. Again, the ERG is unclear why this is the case.**~~	It is inaccurate to state that the grouper code (WF01A) is associated with a value of £125 rather than £173.10, without any additionally clarity on the source of the costs. The Company notes that both £125 and £173.10 are costs associated with the code WF01A in the NHS Reference Costs 2019/2020. The value used in the CS (£173.10) refers to the Non-consultant led value, while the ERG's value (£125) refers to the total HRG costs.	Clarification accepted, this has been clarified in the text as such: "*The value of £125 is used based on the "non-consultant led" value from the NHS reference costs rather than the £173.10 representing the total HRG costs*."

Issue 10 Cost source inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 110 states "The CS reports this weighted average to	Please can this be amended as follows:	The costs reported in the CS for thrombocytopenia relate to the	Clarification accepted suggested amendment has been added.

be £367.76. These ERG found these costs to range from £456 to £1913 with a weighted average of £771 on the NHS reference costs 2019/2020."	The CS reports this weighted average to be £367.76, **based on day case costs from NHS Reference Costs 2019/20**. These ERG found these costs to range from £456 to £1913 with a weighted average of £771, **based on the Total HRG costs from** the NHS reference costs 2019/2020."	Day Case costs from NHS Reference Costs 2019/20, whereas the ERG have reported the Total HRG costs from the same source. It is inaccurate to refer to this as an error and further detail should be added to clarify why the discrepancy between the Company's costs and the ERG's costs exists.	

Issue 11 Incomplete presentation of data

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Table 3.30, Table 3.31, Table 3.32, Table 3.33 and Table 3.34, Page 63–65, all contain the following information: <table><tr><td>All post-baseline</td><td>Abemaciclib + ET</td><td>NA</td><td>NA</td></tr></table>	Please can this be amended as follows: <table><tr><td rowspan="2">All post-baseline</td><td>Abemaciclib + ET</td><td>NA</td><td>NA</td></tr><tr><td>ET</td><td>NA</td><td>NA</td></tr></table>	These tables are missing all post-baseline results for the ET alone arm, as presented in response to QA15 of the Company Clarification Questions.	Corrected.

Issue 12 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 86, Section 4.2.5 states "The Excel model was programmed to run for 49 years	Please can this be amended as follows:	Typographical error.	Corrected

from the starting age of [redacted] years”	The Excel model was programmed to run for 49 years from the starting age of [redacted] years	The correct data are reported in Document B, Table 6, page 35 of the CS.	

Issue 13 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The caption of Table 4.10 states “Summary of Grade III/IV adverse events in Metastatic Recurrence Setting (Monarch2)”	Please can this be amended as follows: Summary of Grade III/IV adverse events in Metastatic Recurrence Setting (**Monarch3**)’.	Typographical error. The data reported in Table 4.10 of the ERG report refer to Monarch3, rather than Monarch2. The data are reported on the ‘AE’ tab in the Company CEM.	Corrected

Issue 14 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The caption of Table 4.11 states “Summary of Grade III/IV adverse events in Metastatic Recurrence Setting (Monarch3)”	Please can this be amended as follows: Summary of Grade III/IV adverse events in Metastatic Recurrence Setting (**Monarch2**)’.	Typographical error. The data reported in Table 4.10 of the ERG report refer to Monarch2, rather than Monarch3. The data are reported on the ‘AE’ tab in the Company CEM.	Corrected

Issue 15 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 99 states "The utility value for the first 3 months was taken from Lidgreen et al (2007)"	Please can this be amended as follows: The utility value for the first 3 months was taken from **Lidgren et al (2007)**.	Typographical error.	Corrected

Issue 16 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 100 states "There was no impact on the ICER (£3,789 per QALY)."	Please can this be amended as follows: There was no impact on the ICER (**£3,786** per QALY).	Typographical error. The correct ICER is reported in the CS, Document B, Section B.3.7.1.	Corrected

Issue 17 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The column heading in Table 4.18, page 104, states "eMIT 2020 Value".	Please can this be amended as follows: eMIT **2021** Value	Typographical error. As stated in the text on page 104 above Table 4.18 of the ERG report, the costs presented are from eMIT 2021, rather than eMIT 2020.	Corrected

Issue 18 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 107, states "The single cost included for the second primary neoplasm is the cost for a multidisciplinary meeting as the patient exists the model."	Please can this be amended as follows The single cost included for the second primary neoplasm is the cost for a multidisciplinary meeting as the patient **exits** the model.	Typographical error.	Corrected

Issue 19 Typographical error

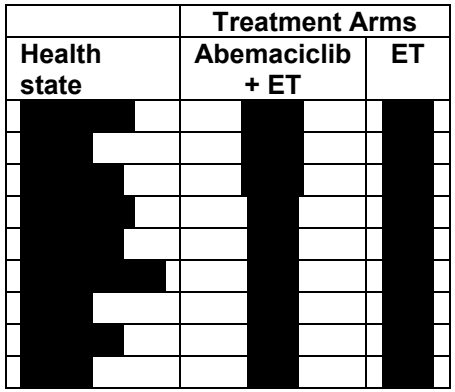
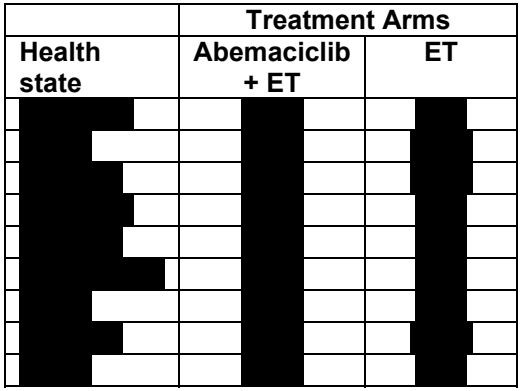
Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 117, Table 5.3 contains the following value for the % absolute increment for the metastatic recurrence-ET-sensitive health state: **Increment** | **Absolute increment** | **% Absolute increment** [redacted] | [redacted] | [redacted]	Please can this be amended as follows: **Increment** | **Absolute increment** | **% Absolute increment** [redacted] | [redacted] | [redacted]	Typographical error.	Amended by increasing the number of decimal places for the values reported in Table 5.3

Issue 20 Incomplete presentation of data

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG Response</th></tr>
<tr>
<td>Page 85, Table 4.4 contains the following information regarding the baseline patient characteristics included in the economic model:
<table>
<tr><th>Demographic parameter</th><th>Abemaciclib + ET (N=2,808) versus ET alone (N=2,829)</th></tr>
<tr><td>Age, years</td><td>Mean (sd)
[redacted]
versus.
[redacted]
Median (min, max)
51.0 (23, 89)</td></tr>
</table>
</td>
<td>Please amend the values in this table as follows:
<table>
<tr><th>Demographic parameter</th><th>Abemaciclib + ET (N=2,808) versus ET alone (N=2,829)</th></tr>
<tr><td>Age, years</td><td>Mean (sd)
[redacted] versus.
Median (min, max)
51.0 (23, 89) versus 51.0 (22, 86)</td></tr>
</table>
</td>
<td>The data presented in Table 4.4 of the ERG report only report the median (min, max) age for the abemaciclib + ET arm. The median (min, max) age of the ET alone arm should also be reported for completeness.

The data are reported in Document B, Table 6, page 35 of the CS.</td>
<td>Corrected</td>
</tr>
</table>

Issue 21 Data inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 92, Table 4.8 contains the following summary of Grade I/II adverse events in IDFS: 	Please amend the values in this table as follows: 	The summary of the frequency of grade I/II adverse events presented in the ERG report is incorrect. The correct values are presented on the 'AE' tab of the Company CEM.	Corrected

Issue 22 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 145 states "The ERG's replication of the corrected company base-case probabilistic analysis resulted in an ICER of £8,992 per QALY gained"	**Page 145** states "The ERG's replication of the corrected company base-case ~~probabilistic~~ **deterministic** analysis resulted in an ICER of £8,992 per QALY gained"	Typographic error	Corrected

Issue 23 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 110 states "A number of AEs (neutropenia, leukopenia, lymphopenia, aspartate aminotransferase increase, alanine aminotransferase increase) were costed as a medical outpatient consultant led outpatient appointment"	Please can this be amended as follows: A number of AEs (neutropenia, leukopenia, lymphopenia, aspartate aminotransferase increase, alanine aminotransferase increase) were costed as a medical **oncology** consultant led outpatient appointment"	Typographical error.	Corrected

Section 2: Confidentiality highlighting amendments

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG Response
Page 16, Page 85, Page 86	The mean starting age of the population used the model, based on the mean age in monarchE, should be AIC since these data are not publicly available	Please can the confidentiality highlighting be amended as follows: "A subgroup analyses by menopausal status would also affect mean age of population in the model with a likely divergence from the current mean age of [redacted] years." **Demographic parameter** / **Abemaciclib + ET (N=2,808) versus ET alone (N=2,829)** **Age, years** / **Mean (sd)** [redacted] versus. [redacted] **Median (min, max)** 51.0 (23, 89) versus 51.0 (22, 86)	Amended.

		"The Excel model was programmed to run for 49 years from the starting age of [redacted]"	
Page 50	Descriptions of the IDFS HR for the premenopausal and postmenopausal women subgroups should be marked as AIC as these data are not publicly available	Please can the confidentiality highlighting be amended as follows: "the HR for premenopausal women is [redacted] than that for postmenopausal women. Also, whilst IDFS rates were [redacted] favourable for the abemaciclib + ET-treated group versus ET alone"	Amended
Page 55	Descriptions of the DRFS HR for the premenopausal and postmenopausal women subgroups should be marked as AIC as these data are not publicly available	Please can the confidentiality highlighting amended as follows: "The HR for premenopausal women is [redacted] than that for postmenopausal women. DRFS rates were [redacted] favourable for the abemaciclib + ET-treated group versus ET alone	Amended
Page 62	The number of patients in the abemaciclib + ET and ET alone arms of monarchE are published on clinicaltrials.gov so do not need to be marked as AIC	Please can the confidentiality highlighting be amended as follows: "Denominators shown in Appendix L.4 are abemaciclib + ET **n=2791** and ET alone **n=2800**."	Amended
Page 66 and 67	Data relating to deaths in monarchE should be marked as AIC	Please can the confidentiality highlighting be amended as follows: "Deaths (see Table 3.40) were broadly similar in both treatment arms with [redacted] occurring in the abemaciclib + ET arm, compared with [redacted] in the ET alone arm."	Amended

<table>
<tr>
<td></td>
<td></td>
<td>“Deaths occurring while enrolled in the study or within 30 days of discontinuation, were also comparable, with [redacted] occurring in the abemaciclib + ET arm, and [redacted] occurring in the ET alone arm”

“Deaths related to AE’s included [redacted] in the abemaciclib + ET arm, and [redacted] in the ET alone arm.”

“Deaths that occurred >30 days of treatment discontinuation included [redacted] in the abemaciclib + ET arm, and [redacted] in the ET alone arm, of which, nine of the [redacted] in the abemaciclib + ET arm were considered to be due to TEAEs, as compared with four of the [redacted] in the ET alone arm.”

“The CS states that cause of death was generally considered to be confounded by multiple comorbid factors, and review of the data presented in Table 33 of the CS (79/160) demonstrates that cardiac disorders ([redacted] were the most reported TEAE leading to death in the abemaciclib + ET arm, while and infections and infestations [redacted] were the most reported TEAEs leading to patient death in the ET alone arm.”</td>
<td></td>
</tr>
<tr>
<td>Page 67, Table 3.35</td>
<td>Some results relating to adverse events in monarchE should be marked as AIC</td>
<td>Please can the confidentiality highlighting be amended as follows:

<table>
<tr><th>n (%)</th><th>Abemaciclib + ET (N=2,791)</th><th>ET alone (N=2,800)</th></tr>
<tr><td>Patients with ≥1 TEAE</td><td>2,745 (98.4)</td><td>2,486 (88.8)</td></tr>
</table>
</td>
<td>Amended</td>
</tr>
</table>

		<table><tr><td>Patients with ≥1 CTCAE ≥ Grade 3 TEAE</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Related to study treatment[b]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Patients with ≥1 TE-SAE</td><td>424 (15.2)</td><td>247 (8.8)</td></tr><tr><td>Patients who discontinued all study treatment due to an AE</td><td>181 (6.5)</td><td>30 (1.1)</td></tr><tr><td>Patients who discontinued all study treatment due to a SAE</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Patients who died due to an AE on study treatment[c]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Patients who died due to an AE ≤30 days from discontinuation of study treatment[c]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Patients who died due to an AE >30 days after discontinuation from study treatment</td><td>[redacted]</td><td>[redacted]</td></tr></table>	
Page 74	Data relating to Grade 4 TEAEs in monarchE should be AIC since these data are not publicly available	Please can the confidentiality highlighting be amended as follows: “The ERG notes the incidence of Grade ≥3 TEAEs was greater in the abemaciclib + ET arm (46.0% Grade 3, [redacted] Grade 4) than in the	Amended

		ET alone arm (15.5% Grade 3, [redacted] Grade 4) and that SAEs were more common in the abemaciclib + ET arm with more venous thrombolytic events (VTE) and pneumonia than in the ET alone group."	
Page 75	The description of the HR for premenopausal women should be AIC since these data are not publicly available	Please can the confidentiality highlighting be amended as follows: "However, although the 95% CIs overlap, the HR for premenopausal women is [redacted] than that for postmenopausal women."	Amended
Page 76	The percentage of patients who had completed or discontinued the study should be AIC since these data are not publicly available	Please can the confidentiality highlighting be amended as follows: "The data relating to AEs were derived from the latest analysis point of the trial, namely the AFU1 point (01 April 2021) and the authors emphasise it is mature: by this point [redacted] of patients had completed or discontinued the study."	Amended
Page 76	The Grade 4 TEAEs should be AIC since these data are not publicly available	Please can the confidentiality highlighting be amended as follows: "The ERG notes the incidence of Grade ≥3 TEAEs was greater in the abemaciclib + ET arm (46.0% Grade 3, [redacted] Grade 4) than in the ET alone arm (15.5% Grade 3, [redacted]Grade 4) and that SAEs were more common in the abemaciclib + ET arm with more VTE and pneumonia than in the ET alone group."	Amended
Page 88 and 89	The landmark IDFS rates for abemaciclib + ET and ET alone should be marked as AIC as these data are	Please can the confidentiality highlighted be amended as follows:	Amended

	not publicly available. These were mistakenly not underlined in the ERG report in Table 4.6.		**Five-year rates**		**Ten-year rates**		
			Abemaciclib + ET	**ET**	**Abemaciclib + ET**	**ET**	
		Exponential	[redacted]	[redacted]	[redacted]	[redacted]	
		Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	
		Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	
		Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	
		Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	
		Weibull	[redacted]	[redacted]	[redacted]	[redacted]	
		Hazard spline 1 knot	[redacted]	[redacted]	[redacted]	[redacted]	
		Hazard spline 2 knots	[redacted]	[redacted]	[redacted]	[redacted]	

References

1. National Institute of Health and Care Excellence (NICE). Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer [TA632]. Available at: https://www.nice.org.uk/guidance/ta632/resources/trastuzumab-emtansine-for-adjuvant-treatment-of-her2positive-early-breast-cancer-pdf-82609074363589. [Accessed: 17 March 2021].
2. National Institute of Health and Care Excellence (NICE). Neratinib for extended adjuvant treatment of hormone receptor-positive, HER2- positive early stage breast cancer after adjuvant trastuzumab [TA612]. Available at: https://www.nice.org.uk/guidance/TA612. [Accessed: 09 February 2021]. 2019.

NICE National Institute for Health and Care Excellence

Technical engagement response form

[ID3857] Abemaciclib in combination with endocrine therapy for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments: 5pm on 9 March 2022

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

- **Notes on completing this form**

  - Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
  - Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
  - If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
  - Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response 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.
  - Do not use abbreviations.
  - Do not include attachments such as journal articles, letters or leaflets. 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.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- 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 under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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

Comments received during engagement 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.

About you

Your name	Hamish Lunagaria
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Eli Lilly and Company
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Potential lack of generalisability of the evidence to NHS clinical practice given ambiguity in the definition of high risk	Yes	**Licensed population for abemaciclib** The ERG raised concerns that Cohort 1 of monarchE is more generalisable to UK clinical practice than the ITT cohort due to the definition of high risk of recurrence used to include patients in these cohorts. The Company can now confirm that abemaciclib has received a positive CHMP opinion for use in the early breast cancer indication, based on the Cohort 1 population from the monarchE trial.[1] That is, abemaciclib in combination with endocrine therapy is indicated for the adjuvant treatment of adult patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative, node positive early breast cancer at high risk of recurrence. In pre- or perimenopausal women, aromatase inhibitor endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist. MHRA approval for abemaciclib in this indication is anticipated to be received in [redacted]. Accordingly, the Company agree with the ERG that Cohort 1 represents the most generalisable cohort of monarchE to UK clinical practice. Full baseline characteristics and clinical effectiveness results for cohort 1 are presented in Appendix B and Appendix C, respectively.

		Generalisability of monarchE to UK clinical practice in terms of the definition of high risk of recurrence The ERG also state that there is no clear definition of high risk of recurrence in the NICE Guidelines on early and locally advanced breast cancer (NG101).[2] However, a lack of clear definition of high risk of recurrence in NG101 does not mean that these patients are not readily identified in clinical practice. As outlined in response to the Clarification Questions, QA4, clinicians judge risk of recurrence in clinical practice based on a combination of clinical and pathological features such as node involvement, tumour size, and tumour grade, using validated risk prediction tools, such as the PREDICT breast cancer tool or the Nottingham Prognostic Index, as outlined in NG101.[2] A similar set of features are used to define high risk of recurrence in the monarchE Cohort 1 inclusion criteria, including tumour involvement in ≥4 ipsilateral axillary lymph nodes (ALNs), or pathological tumour involvement in 1–3 ALNs, alongside Grade 3 disease and/or a primary tumour size of ≥5 cm. The monarchE Cohort 1 selection criteria are aligned with the overall continuum of factors used to identify high risk of recurrence in UK clinical practice and used within the validated tools discussed above. As such, the generalisability of monarchE to UK clinical practice in terms of the definition of high risk of recurrence should not be considered a major source of uncertainty in this appraisal. **Generalisability of monarchE Cohort 1 in terms of patient baseline characteristics** Further evidence for the generalisability of the monarchE population to UK clinical practice was provided in response to the Clarification Questions, QA12, where the baseline characteristics for the ITT population in monarchE were presented versus a [redacted] conducted by the Company. For completeness, the monarchE Cohort 1 baseline characteristics versus the [redacted] are now presented in Table 1. The resulting conclusions are aligned with those drawn in response to QA12 in the Clarification Questions, indicating that the patients in monarchE are generalisable to UK clinical practice.

[redacted]

Nevertheless, these baseline characteristics and associated conclusions provide further evidence for the generalisability of Cohort 1 to UK clinical practice.

Table 1: Summary of baseline characteristics of patients in monarchE (Cohort 1) and the [redacted]

Demographic Parameter	monarchE (Cohort 1) (N=[redacted])	[redacted] (N=[redacted])
Sex, %		
Female,	[redacted]	[redacted]
Male,	[redacted]	[redacted]
Age, years		
Mean	[redacted]	[redacted]
<65, %	[redacted]	[redacted]
Primary tumour size, %*		
<20 mm	[redacted]	[redacted]
≥20 mm but <50 mm	[redacted]	[redacted]
≥50 mm	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Number of positive lymph nodes, %*		
0	[redacted]	[redacted]
1-3	[redacted]	[redacted]
4-9	[redacted]	[redacted]
≥10	[redacted]	[redacted]
Missing	[redacted]	[redacted]

		Histopathological diagnosis grade, % G1 – favourable [redacted] [redacted] G2 – moderately favourable [redacted] [redacted] G3 – unfavourable [redacted] [redacted] GX – cannot be accessed [redacted] [redacted] Missing [redacted] **Abbreviations**: RWE: real-world evidence; NR: not reported. **Footnote:** [redacted] In monarchE, tumour size was assessed by radiology prior to any systemic treatment. The Company's updated deterministic and probabilistic base case results, including data from Cohort 1 of monarchE, are presented in Appendix A.
Key issue 2: Lack of recognition that comparators depend on menopausal status leading to bias in effectiveness	Yes	**Lack of statistically significant difference in treatment benefit of abemaciclib + ET versus ET alone with respect to menopausal status** Despite clarification from the Company in the response to the Clarification Questions, the ERG expressed concern about the potential impact of menopausal status on the efficacy results, and the bias this may introduce due to differences in comparators for pre and postmenopausal patients. Subgroup analyses of IDFS and DRFS in the ITT population show no significant differences with respect to menopausal status at diagnosis (Clarification Questions, QA7). The same analyses in Cohort 1, presented in Figure 1 and Figure 2, similarly demonstrate that there are no statistically significant differences with respect to menopausal status at diagnosis in Cohort 1 of monarchE. IDFS and DRFS data by menopausal status at diagnosis are presented in full in Appendix D for completeness; OS data are immature and cannot be meaningfully interpreted, and therefore have not been presented. These results demonstrate that abemaciclib + ET has a consistent treatment benefit versus ET alone for both pre- and postmenopausal women and demonstrates that the overall Cohort 1

		population should be considered generalisable to both subgroups of patients. As such, Cohort 1 should be considered to represent the most robust source of evidence for both subgroups, in order to preserve sample size, and it would not be appropriate to consider premenopausal women and postmenopausal women as separate subgroups. **Figure 1: Forest plot of investigator-assessed IDFS Cohort 1 Population (AFU1 analysis)**  **Abbreviations**: AFU1: additional follow-up one; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; EDT: endocrine therapy; HR: hazard ratio; IDFS: invasive disease-free survival; IWRS: interactive web response systems; NA: North America; PS: performance status.

Figure 2: Forest plot of investigator-assessed DRFS Cohort 1 Population (AFU1 analysis)

Abbreviations: AFU1: additional follow-up one; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; EDT: endocrine therapy; HR: hazard ratio; IDFS: invasive disease-free survival; IWRS: interactive web response systems; NA: North America; PS: performance status.

Distinction between menopausal status at diagnosis versus functional menopausal status

In addition to the lack of statistically significant difference in treatment effect between the subgroups, additional limitations (further discussed in Key Issue Three) mean that comparisons between pre and postmenopausal patients are challenging, and any observed conclusions be influenced by a number of additional factors.

		Primarily, it is important to consider the distinction between menopausal status at the time of diagnosis and 'functional' menopausal status, based on whether a patient receives ovarian suppression post-diagnosis. In monarchE, menopausal status **at diagnosis** was a stratification factor, and this definition of menopausal status is also the one from which the above menopausal subgroup analyses have been derived. Furthermore, the use of analyses by menopausal status at diagnosis is additionally problematic due to the time between diagnosis and study entry for many patients, due to factors such as surgery and prior treatment with radiotherapy and chemotherapy. Menopausal status after chemotherapy or at randomisation, or hormone levels, were not collected as study endpoints in the monarchE trial.[3] However, a patient's menopausal status at the time of diagnosis does not necessarily reflect their 'functional' menopausal status at the time of treatment – particularly, as ovarian function suppression may be considered for premenopausal women with HR+ early breast cancer.[2] For example, the current clinical pathway of care for patients with HR+, HER2- early breast cancer is presented in the CS (Document B, Section B.1.3.3, Figure 2). This pathway of care is based on 'functional' menopausal status, whereby, in line with NG101, premenopausal women can either be treated with tamoxifen (i.e. 'functionally premenopausal'), or considered for ovarian suppression in addition to endocrine therapy, at which point they can be considered as 'functionally postmenopausal'.[2] NG101 notes that "a specific drug has not been recommended for endocrine therapy [alongside ovarian function suppression] to allow clinical discretion to use AIs or tamoxifen as considered appropriate".[2] Feedback from clinical experts indicated that premenopausal patients treated with ovarian suppression, and therefore considered 'functionally postmenopausal', are typically treated the same as postmenopausal patients (which may include treatment with aromatase inhibitors), with similar treatment benefits observed.[2] In the monarchE safety population, [redacted]% of premenopausal women received aromatase inhibitors (Clarification Question, A9). Of these, [redacted]% also received GnRH agonists (i.e. ovarian suppression), and should be considered to be 'functionally postmenopausal'. This means that, at least [redacted] of

		the overall premenopausal subgroup in monarchE should be considered functionally postmenopausal at the time of treatment. Consequently, drawing any conclusions regarding the relative treatment efficacy for abemaciclib + ET versus ET alone by menopausal status, based on comparisons based on menopausal status at the time of diagnosis, should be interpreted with extreme caution. Furthermore, it is possible that this comparison could be influenced by the impact of additional factors; it is likely that patients who were premenopausal at the time of diagnosis are likely to be younger than patients who were postmenopausal at the time of diagnosis, which could impact the observed results. Considering the uncertainty associated with these comparisons, as well as the absence of statistically significant differences in treatment effect between pre and postmenopausal patients, it would not be appropriate to conduct cost-effectiveness analyses by menopausal subgroups. Furthermore, it is important to note that in previous NICE appraisals in HR+, HER2- breast cancer, such as TA632 and TA612, where the trial populations similarly included a split of pre- and postmenopausal patients, menopausal status was not highlighted as an issue, and cost-effectiveness analyses by menopausal status were not considered. Accordingly, the final recommendations in these appraisals were made irrespective of menopausal status.[4, 5]
Key issue 3: Lack of generalisability of monarchE to clinical practice in terms of endocrine therapy type	No	**Clinical pathway for patients with HR+, HER2- early breast cancer in the UK** The ERG expressed concerns that the treatments received by pre and postmenopausal women in monarchE are not aligned with NG101, in particular by highlighting that fewer than 100% of premenopausal patients in monarchE received tamoxifen.[2] However, as previously discussed in Key Issue 2, this does not take into consideration that a number of patients who were premenopausal at the time of diagnosis may not be 'functionally premenopausal' at the time of treatment. In line with NG101, premenopausal patients can either receive tamoxifen (as a 'functionally premenopausal patient') or ovarian suppression in addition to endocrine therapy, at which point, they could be considered as 'functionally postmenopausal', and

		could receive treatment with aromatase inhibitors, as per the recommendation NG101 detailed in Key Issue 2.[2] This is supported by ESMO guidelines on the treatment of early or locally advanced breast cancer, which state that premenopausal patients can receive an aromatase inhibitor in combination with ovarian suppression if considered to be high risk.[6] The treatment distributions in monarchE are broadly aligned with these guidelines. This clearly demonstrates that the fact that fewer than 100% of premenopausal patients in monarchE received tamoxifen is not a deviation from NICE guidelines and should not be considered a concern. In addition, it should also be noted that other factors, such as contraindications to tamoxifen, means that even aside from ovarian suppression, it would be unrealistic to expect 100% of premenopausal patients to receive tamoxifen. **Evidence supporting the generalisability of monarchE to clinical practice in terms of type of ET** As outlined in response to the Clarification Questions, QA9, the type and distribution of ET administered to individual patients in monarchE was determined by physician's choice (PC). Accordingly, for patients in monarchE in the UK, their ET is expected to be generalisable to the treatments that patients would receive in standard UK NHS clinical practice. The types of ET received by patients in the UK in monarchE were consistent with those received by patients in monarchE as a whole. Further evidence that the types and distribution of the types of ET used in monarchE are generalisable to those administered in UK clinical practice comes from a second real-world evidence (RWE) study conducted by the Company, which included patients with HR+, HER2- early breast cancer in the UK between June and November 2019, as presented in the response to the Clarification Questions, QA9. This generalisability also extends to Cohort 1 of monarchE, in which ~[redacted]% of patients in both arms had received an aromatase inhibitor at the start of the study and ~[redacted]% of patients in both arms had received tamoxifen at the start of the study. This is aligned

		with the RWE study in which [redacted]% of patients received an aromatase inhibitor as their first adjuvant ET and the remaining [redacted]% of patients received tamoxifen. Regardless, the cost of different types of ET is universally low, and there are not expected to be any differences in terms of efficacy associated with different types of ET within the same class.[7-10] Moreover, the distribution of different classes of ET used was balanced between the abemaciclib + ET arm and ET alone arm of the monarchE trial. If any differences were to exist between menopausal subgroups (as suggested by the ERG and discussed in more detail in Key Issue 2), they are likely to result from differences in baseline characteristics, such as age, rather than differences in efficacy between types of ET or menopausal status itself. As such, any discrepancies in terms of the types of ET used in monarchE and those used in NHS clinical practice would have a minimal impact on the cost-effectiveness analysis and this should not be considered to be a significant source of uncertainty in this appraisal. **Subgroup analyses of IDFS and DRFS by menopausal status and first type of ET received** As requested by the ERG, the subgroup analyses of IDFS and DRFS by menopausal status and first ET received (i.e. tamoxifen or aromatase inhibitor) are presented in Appendix D. Importantly, the data show that there are no statistically significant differences in terms of IDFS and DRFS between the subgroups. It should be noted that the number of events in each group is low (range: [redacted]) as the subgroup analyses split the cohort two-fold, firstly by menopausal status at diagnosis (pre- and postmenopausal) and secondly, by the first type of ET received (aromatase inhibitor and tamoxifen). Furthermore, it should be noted that Cohort 1 was not stratified by the first type of ET received. Additionally, the data do not give any indication of how long a patient was receiving each type of ET and it is possible that patients switched to a different type of ET shortly after initiation of treatment. As such, the results from the subgroup analyses should be interpreted with extreme caution. However, for the reasons discussed throughout Key Issues 2 and 3, the consideration of menopausal subgroups is not appropriate, and we believe there are no concerns with the

		generalisability of monarchE to UK clinical practice with regard to menopausal status or ET received.
Key issue 4: Lack of clarity around the model structure when aspects of partitioned survival model are used for transition probabilities	No	The ERG noted that there was a lack of clarity around the model structure and suggested it could be more appropriately described as using partitioned survival model (PSM) methodology. The Company maintains that the cost-effectiveness model uses a Markov model structure (a type of state transition model [STM] methodology) to model the early breast cancer pathway (CQ B4). Partitioned survival methodology has only been used to calculate fixed payoffs associated with the metastatic recurrence (MR) health states, based on the previously accepted PSM structures for these metastatic indications in TA563 and TA725.[11, 12] The model used in this appraisal is closely aligned with the Markov model structure previously used in the NICE STA for trastuzumab emtansine for the adjuvant treatment of HER2-positive early breast cancer (TA632).[4] Both the ERG and the committee considered that this model structure was appropriate for the early breast cancer pathway. Similar STM structures were also used and accepted in previous early breast cancer appraisals, including TA107, TA424, TA569, and TA612.[5, 13-15] Given the consistent use of STMs in previous NICE appraisals, the Company considered the use of a STM structure for the early breast cancer pathway was the most appropriate approach for this appraisal. Further details and clarity regarding the model structure and underlying transition probabilities are provided below. **Summary of the model structure and transition probabilities used in this appraisal**

		IDFS ***IDFS to NMR or MR (IDFS_NMR, IDFS_ETR and IDFS_ETS)*** Patients first enter the model in the IDFS health state. From the IDFS health state, patients can either remain there, or transition to the non-metastatic recurrence (NMR), MR or death health states. The Company uses parametric survival equations to extrapolate the monarchE IDFS data beyond the follow-up duration of the trial to model the occupancy of the IDFS health state for the duration of the modelled time horizon. Therefore, if $S(t)$ represents the IDFS function over time, the transition probability from the IDFS health state to either NMR, MR or death is $1 - S(t)$. The per cycle probability of death without distant recurrence was only applied to the proportion of invasive disease events experienced in each cycle, rather than to the IDFS extrapolated curve as the IDFS curve also includes death. Therefore, if the probability of death was applied directly to the IDFS curve the death events would be double counted. The OS curve in use is for patients who have not experienced a distance recurrence and therefore only applied to the IDFS events. This approach is aligned with the approaches taken, and accepted, in previous early breast cancer appraisals, including TA569, TA612 and TA632. The Company acknowledges some specific elements of the IDFS extrapolation in this appraisal might warrant separate, specific discussion (Key Issues 7 and 9). However, based on the approaches previously used and accepted in previous NICE appraisals for early breast cancer, the Company does not consider the use of parametric survival equations to extrapolate IDFS beyond the duration of the monarchE trial to represent a concern in this appraisal. Importantly, the use of an IDFS extrapolation does not mean that the model is a PSM. The ERG state *"within PSM, there is a survival curve for each health state".* This is not the case in the Company's model; the IDFS extrapolation is the only survival curve which directly defines the occupancy of a health state (IDFS). OS without distant recurrence extrapolations is not used to directly define the occupancy of the death health state. Further distinctions between a PSM, and the Company's STM, are discussed later in this section.

The proportion of patients moving to the NMR versus MR health states is determined by the proportion of NMR and MR in the monarchE trial. The proportions are assumed to be constant over time, except for the probabilities in the abemaciclib + ET arm waning to the probabilities in the ET alone arm (as detailed in Key Issue 11). Patients who move into the MR state up to Month 72 (i.e. 12 months after 5 years of ET) move into the endocrine-resistant MR state, otherwise, patients move into the endocrine-sensitive MR state.

If p_{NMR} denotes the constant proportion of NMR, then the transition probability to the NMR health state from the IDFS state is $p_{\mathrm{NMR}} \times (1 - S(t))$. The IDFS curve determines how many patients are actually leaving IDFS and how many remain in each cycle. To determine in which health state these patients who leave IDFS go to, constant probabilities are used to distribute the patients over the different health states. These constant probabilities are based on monarchE trial data (*see Key Issue for 11 for further details on the waning assumptions applied to these transition probabilities*). Table 2 summarises the transitions from the IDFS health state to the NMR and MR health states.

Table 2: Transition from IDFS health based on constant proportions of IDFS events

Starting state (from)	Proportion of destination state (to)	Transition probabilities or rates
IDFS	iDFS: $S(t)$	Remaining in IDFS: $S(t)$
	NMR: p_{NMR}	IDFS_NMR: $p_{\mathrm{NMR}} \times (1 - S(t))$
	MR: p_{MR}	IDFS_MR: $p_{\mathrm{MR}} \times (1 - S(t))$

Abbreviations: IDFS: invasive disease-free survival; MR: metastatic recurrence; NMR: non-metastatic recurrence.

IDFS to death (IDFS_D)

The transition probability from the IDFS (and the NMR and remission health states) to the death health state is derived from OS **without distant recurrence** data from the monarchE trial.

		This endpoint is distinct from the 'absolute' OS data presented in the CS, Document B. OS without distant recurrence was defined where patients experiencing MR were censored at the date of MR. The distinction between OS and OS without distant recurrence is further discussed in Key Issue 8. The OS without distant recurrence extrapolation is used to derive transition probabilities of moving to the death health state, which are applied to the IDFS, NMR and remission health states, if the probability of death is higher than background mortality at any given timepoint. It is important to note that the OS without distant recurrence extrapolation does not directly define the occupancy of the death health state. For example, if the OS without distant recurrence extrapolation is 95% at Year 5, this does not mean that the occupancy of the death health state is 5%. This is an important distinction from a PSM, where an OS extrapolation of 95% at Year 5 would correspond to 5% of patients in the death health state. ***NMR pathway*** ***Transition probability from NMR to remission (NMR_REM)*** If patients experience an NMR, they transition to the NMR health state, which is a 12-month tunnel state. After 12 months, all patients move to the remission health state, except for those patients who have died. ***Transition probability from NMR to death (NMR_D)*** Mortality in patients with NMR was assumed to be the same as patients in the IDFS or remission health states, using the OS without distant recurrence data from monarchE described previously ***Remission*** ***Transition probability from remission to metastatic recurrence 1L (REM_ETS)*** It will be assumed that patients who are in remission health state will remain in this state until they experience either MR or death. The monthly transition probability of experiencing MR was equal to 0.0076, based on the previously accepted estimate in TA632, derived from Hamilton et al. (2015), and assumed to remain constant over time (CS, Document B, Section B.3.3.3).[16, 17] Patients

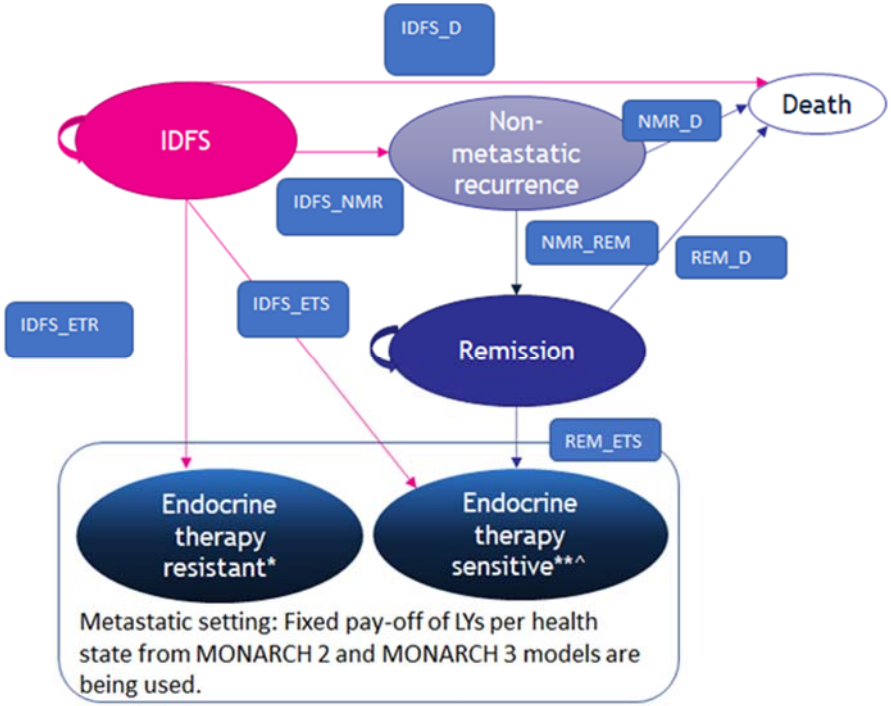
experiencing MR all move to the endocrine-sensitive MR health state, as these patients are modelled to have remained free of MR for at least 12 months following discontinuation of ET.

Transition probability from remission to death (REM_D)

Mortality in patients in the remission health state was assumed to be the same as patients in the IDFS or NMR health states, using the OS without distant recurrence data from monarchE described previously.

A summary of the transition probabilities used in the model is presented in the updated model structure diagram in Figure 3 below, alongside the corresponding sources of transition probabilities provided in Table 3.

Figure 3: Model structure diagram including transition probabilities



Footnotes: * Endocrine therapy resistant: disease recurrence whilst receiving or within 12 months of completing prior adjuvant ET. ** Endocrine therapy sensitive: disease recurrence at least 12 months after completion of prior adjuvant ET. ^ includes treatment with tamoxifen
Abbreviations: D: death health state; ETS: endocrine therapy sensitive health state; ETR: endocrine therapy resistant health state; IDFS: invasive disease free survival; LYs: life years; REM: remission; NMR: non-metastatic recurrence.

Table 3: Summary of transition probabilities used in the CEM

Starting state	Destination state	Transition name	Value	Source
IDFS	NMR	IDFS_NMR	NMR % from trial applied to adjusted IDFS curve[a]	monarchE
	MR (ET resistant)	IDFS_ETR	MR % from trial applied to adjusted IDFS curve[a] After 72 months, this decreases to 0, as all patients enter the MR (ET sensitive) health state	monarchE
	MR (ET sensitive)	IDFS_ETS	MR % from trial applied to adjusted IDFS curve[a] Patients only experience the IDFS_ETS transition if they have a recurrence at least 12 months after completion of prior adjuvant ET. In this case, the probability of moving to ETS instead of ETR is 100%	monarchE
	Death	IDFS_D	Maximum of background mortality or IDFS death rate (=OS without distance recurrence)	monarchE and UK lifetable
Non-metastatic recurrence	Remission	NMR_REM	1	After 12 months, all patients transition into the

					remission health state or die due to all cause mortality
		Death	NMR_D	Maximum of background mortality or IDFS death rate (=OS without distance recurrence)	monarchE and UK lifetable
	Remission	MR (ET sensitive)	REM_ETS	0.0076	Hamilton et al. (2015), in line with the approach accepted in TA632 [16, 17]
		Death	REM_D	Maximum of background mortality or IDFS death rate (=OS without distance recurrence)	monarchE and UK lifetable

Footnotes: a The IDFS curve was adjusted for mortality and treatment waning assumptions.
Abbreviations: CEM: cost-effectiveness model; ET: endocrine therapy; IDFS: invasive disease-free survival; MR: metastatic recurrence; NMR: non-metastatic recurrence; OS: overall survival; TA: Technology Appraisal.

Distinction Between STMs and PSMs

Considering the detailed overview of the Company's model and the underlying transition probabilities detailed above, the below section details some key differences between STMs and PSMs (based on a recent publication from the authors of NICE TSD 19)[18], and considers why the Company's model should be considered as a STM based on these:

1. "In STMs, movements between health states are referred to as transitions, and the speed at which these transitions occur as transition probabilities or rates."[18] "PSMs do not use transitions between states to determine the proportion of patients in each health state at each point (state membership)".[18]
    - Unlike a PSM, the Company's model includes transition probabilities between all health states in the model, as detailed in Figure 3 and Table 3 above.

		2. "In a PSM, the survival curves that inform the estimates of state membership (e.g, PFS and OS) are modelled completely independently. This is the fundamental difference from STMs, where clinical events are explicitly related."[18] o The Company's STM includes structural links between endpoints – clinical events (such as NMR, MR and death) are explicitly related, and patients have different probabilities of experiencing these events depending on which health state they are in. o For example, the probability of a patient experiencing metastatic recurrence varies between the IDFS, NMR and remission health states. Thus, NMR (and resulting remission) is an intermediate clinical event that is explicitly related to a subsequent clinical event (metastatic recurrence) – something which is not incorporated in a PSM model structure. 3. "[In a STM] The structural link between OS predictions and intermediate endpoints such as progression is the fundamental difference from PSMs, which consider OS to be independent of other clinical events."[18] o In the Company's STM, OS is not independent of other intermediate endpoints, such as metastatic recurrence; the probability of death in the model varies, depending on health state. For patients in the IDFS, NMR or REM health states, death is modelled based on extrapolations of the OS **without distant recurrence** data from the monarchE trial, as outlined above. o However, OS for patients in the metastatic recurrence health states is instead modelled using a fixed LY pay-off approach, based on the average PFS and PPS for patients in these metastatic health states derived from TA563 and TA725.[11, 12]
Key issue 5: Lack of recognition that comparators depend on menopausal status leading to bias in cost effectiveness	Yes	As outlined in response to Key Issue 2, subgroup analyses of IDFS and DRFS by menopausal status in Cohort 1 of monarchE demonstrate a consistent treatment benefit of abemaciclib + ET and ET alone across both subgroups. There are also substantial limitations associated with the consideration of menopausal subgroups; in particular, the discrepancy between menopausal

		status at diagnosis (which was a stratification factor in monarchE) compared to 'functional' menopausal status at the time of treatment, as discussed in more detail in Key Issues 2 and 3. Considering these substantial limitations, and for the reasons discussed in Key Issues 2 and 3, Cohort 1 represents the most appropriate source of evidence for the overall proposed patient population for abemaciclib in order to maximise sample size. It would be inappropriate and highly uncertain to consider premenopausal women/men and postmenopausal women in two separate economic analyses. As stated in response to the Clarification Questions, QB2, as there was no statistically significant difference between outcomes, the only difference impacting the economic analysis between pre- and postmenopausal patients would be costs. However, the relatively low costs of different distributions of ET therapy in the pre- and postmenopausal pathways is not expected to have an overt impact on cost effectiveness compared to the overall Cohort 1 population. The Company maintains that menopausal status should not be considered in the economic analysis, thus, cost-effectiveness results split by menopausal status have not been presented.
Key issue 6: Medication adherence not modelled	No	The ERG highlighted that non-adherence to adjuvant ET is a concern in UK clinical practice. However, this is already inherently captured in the cost-effectiveness analyses, and does not represent a source of uncertainty. The Company acknowledges that non-adherence to ET occurs, however the effect of this on efficacy is implicitly captured in the trial efficacy outcomes, and extrapolations based on monarchE trial data. The effect of non-adherence to ET on costs is reflected in the TTD extrapolations, which are based on monarchE trial data. The patterns of non-adherence to ET in monarchE are expected to be broadly reflective of real-world ET non-adherence despite some differences due to the clinical trial setting. As such, the monarchE trial data and cost-effectiveness analyses will broadly capture the implications of non-adherence to ET. A summary of the subject disposition for Cohort 1 of monarchE is presented in Table 4, which presents the reasons for discontinuation in the abemaciclib + ET and ET alone arms.

Table 4: Summary of subject disposition in Cohort 1 (AFU1)

	Abemaciclib + ET	ET alone
Enrolled/randomised, but never treated[a]	[redacted]	[redacted]
Treated[a]	[redacted]	[redacted]
On treatment	[redacted]	[redacted]
Off treatment	[redacted]	[redacted]
Reason for discontinuation of treatment		
Adverse event	[redacted]	[redacted]
Completed	[redacted]	[redacted]
Death	[redacted]	[redacted]
Disease relapse	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Non-compliance with study drug	[redacted]	[redacted]
Physician decision	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]
Study terminated by IRB/ERB	[redacted]	[redacted]
Withdrawal by subject	[redacted]	[redacted]

Footnotes: a At the time of the 01 April 2021 data cut-off.
Abbreviations: ERB: ethical review board; ET: endocrine therapy; IRB: institutional review board.

Additionally, the implication of adherence on the costs associated with ET are likely to be minimal. In UK clinical practice, whether patients comply with their treatment regime is unlikely to have an impact on the number of prescribed packs. As such, patient non-adherence to ET is unlikely to have a meaningful impact on the costs of ET to the NHS. Furthermore, any reduction in cost of ET is likely to have a small impact on the cost-effectiveness analysis, as the overall costs for ET are relatively low. While non-adherence to ET could reduce the efficacy associated with ET, this will similarly impact both the intervention and comparator arms, and there is no reason to suggest this

		would have a relatively larger impact on the abemaciclib + ET arm versus the ET alone arm. Therefore, as acknowledged by the ERG, any impact of ET non-adherence on the cost-effectiveness results will likely be insignificant. Moreover, conducting the above analyses would be associated with a number of practical difficulties, which would likely result in increased, rather than reduced, uncertainty in the resulting analyses. For example, it would be inappropriate to adjust the time on treatment for ET in the cost-effectiveness model without also accounting for the impact of this on clinical effectiveness, and it is unclear how the impact of non-adherence on effectiveness could be considered. Accordingly, the Company have not presented additional scenario analyses requested by the ERG accounting for non-adherence to ET in a real-world setting, and do not believe it would be appropriate to do so, particularly when considering the negligible impact any analyses would likely have on the cost-effectiveness results.
Key issue 7: Potential bias from selection of survival curves for treatment and comparators, and lack of alternative scenarios	Yes	**Evidence supporting the loglogistic model as the most appropriate extrapolation for IDFS for Cohort 1** ***NICE guidance for the selection of extrapolations*** The ERG expressed concerns over the Company's selected extrapolations chosen for IDFS and OS, suggesting that the results of the cost-effectiveness analysis may therefore be biased. The ERG proposed that a log-normal extrapolation for IDFS may be more appropriate. However, there are equal limitations associated with this extrapolation, as highlighted below. As stated in the CS (Document B, Section B.3.3.2), the selection of extrapolation for IDFS (and OS and TTD) was conducted in accordance with NICE DSU TSD 14, considering:[19] • Statistical fit criteria (e.g. Akaike Information Criterion [AIC] and Bayesian Information Criterion [BIC]) • Visual inspection of extrapolation curves • Visual inspection of smoothed hazard curves

		• Consideration of data in the published literature The log-logistic extrapolation provided the second best statistical fit for extrapolation of IDFS, and this differed by less than 2.0 points from the best statistically fitting extrapolation in terms of both AIC and BIC (Weibull), indicating that there is weak evidence of any difference between the two extrapolations in terms of statistical fit.[20, 21] ***Comparison of IDFS extrapolation versus external data sources for Cohort 1*** The Company acknowledge that statistical fit alone is not sufficient for choice of extrapolation, particularly where there is immature data. However, where there are a set of plausible extrapolation curves, statistical fit can be used to guide choice for the base case curve. Therefore, as well as statistical fit, the choice of extrapolation for IDFS was informed by comparing the landmark IDFS estimates for abemaciclib + ET and ET alone predicted by the model to external data sources. Of the studies identified in the clinical SLR for ET, TEXT was excluded due to presenting total events rather than IDFS rate, and HOBOE and SOFT were excluded as they did not include patients who were offered pre-treatment with neoadjuvant and adjuvant therapies.[22-24] As such, FACE and FATA-GIM were the remaining trials which reported IDFS/DFS estimates comparable to monarchE (CS, Document B, Section B.3.3.2).[7, 25] The FACE trial produced 5-year DFS estimates for ET of 84.9% (95% CI: 83.2%, 86.2%) for letrozole and 82.9% (95% CI: 81.2%, 84.5%) for anastrozole.[7] The FATA-GIM3 trial produced 5-year DFS estimates for ET of 90.0% (95% CI: 87.9, 91.7) for anastrozole, 88.0% (95% CI: 85.8, 89.9%) for exemestane and 89.4% (95% CI: 87.3, 91.1%) for letrozole. Compared to the published literature on ET, the extrapolations based on monarchE all appear to underestimate the 5-year IDFS rates for ET, but the log-normal ([redacted]%), exponential ([redacted]%), gompertz ([redacted]%) and log-logistic ([redacted]%) extrapolations for the ET alone arm based on monarchE provide the highest, and therefore most plausible, landmark 5-year IDFS estimates. However, the comparisons of the ET arm in monarchE and the external trials should be approached cautiously as the populations and endpoints used in the external trials are not directly comparable with monarchE. Both trials included DFS as the endpoint, rather than IDFS as in

		monarchE; while this is a limitation of the comparison, the two endpoints can be considered broadly comparable (CS, Document B, Section B.3.3.2).[7, 25] However, a more substantial limitation is that the FACE and FATA-GIM3 trials included patients with disease at lower risk of recurrence than those in monarchE Cohort 1. Of particular note, the majority of patients in FATA-GIM3 had zero positive axillary lymph nodes (ALNs), while the majority of patients in FACE had 1–3 positive lymph nodes (Table 28). In comparison, [redacted]% of patients in monarchE had 4–9 positive ALNs, and a further [redacted]% had ≥10 positive ALNs.[25] Additionally, only [redacted]% of patients in monarchE had a primary tumour size of ≤20mm, compared to 45.5% and 70% of patients in the anastrozole arm in FACE and the letrozole arm of FATA-GIM3, respectively (*the anastrozole and letrozole arms of FACE and FATA-GIM3, respectively, represent the treatment arms with baseline characteristics most similar to monarchE Cohort 1; similar percentages are observed in the other arms of these trials*). Additionally, both FACE and FATA-GIM3 included some patients with HER2+ breast cancer, whereas monarchE Cohort 1 included only patients with HER2− breast cancer. A detailed comparison of key baseline characteristics of monarchE Cohort 1 versus FACE and FATA-GIM3 is presented in Table 28 in Appendix F. As such, the rate of IDFS/DFS in the external trials would be expected to be considerably higher than compared to monarchE Cohort 1, because these trials included patients at a much lower risk of recurrence compared to monarchE. However, as the absolute magnitude of this difference is unknown, these external estimates cannot be used to precisely validate the exact predictions of the monarchE ET IDFS extrapolation, but instead should be used primarily to exclude clinically implausible extrapolations. ***Comparison of IDFS extrapolations versus RWE for Cohort 1*** Lower IDFS rates than the published literature are likely in the monarchE population and this is supported by a [redacted] conducted by the Company, which included patients with HR+, HER2- early breast cancer at high risk of recurrence, for which the definition was [redacted] (Clarification Question, A12). Moreover, [redacted] used IDFS as the primary endpoint which aligns with the definition of IDFS used in monarchE. As

		such, landmark IDFS rates in [redacted] should be more comparable to the extrapolations based on monarchE data, versus the published literature. In [redacted], the 5-year IDFS rate was [redacted]% which is more closely aligned with the extrapolations for the ET alone arm based on monarchE (i.e., [redacted]% to [redacted]% for the log-logistic and lognormal extrapolations, respectively) and provides further support that the IDFS/DFS estimates based on published literature for ET are substantially higher than would be expected for the monarchE Cohort 1 population. Based on comparisons to the published literature for ET, and considering that patients in monarchE are at a substantially higher risk of recurrence compared to the published literature, it is reasonable to conclude that the log-logistic, exponential, gompertz and lognormal models *could* all produce potentially plausible 5-year IDFS rate estimates. In order to differentiate between these plausible extrapolations, the Company aligned with NICE guidance on the selection of extrapolations and considered the statistical fit of each extrapolation. The log-logistic extrapolation was therefore chosen as the most appropriate for the base case economic analysis, as the lognormal, gompertz and exponential extrapolations provided a poorer statistical fit to the trial data than the log-logistic extrapolation. **Limitations associated with the lognormal IDFS extrapolation** As an alternative to the Company's chosen base case log-logistic extrapolation, the ERG state that the log-normal extrapolation for IDFS may be a better predictor of real-world recurrence rates. ***Statistical fit*** The lognormal extrapolation provides the worst statistical fit to the monarchE trial data in terms of AIC and the second-worst fit in terms of BIC. For both AIC and BIC, the absolute values differ by more than 10 points from the extrapolation with the lowest value, and the log-logistic extrapolation, which indicates very weak support for the statistical fit of the extrapolation to the trial data

compared to alternative extrapolations.[20, 21] The lognormal model therefore provides a worse fit to the first 3 years of KM data from monarchE than the log-logistic model; a substantial limitation.

Long-term extrapolations

As outlined above, estimates for IDFS for ET in the published literature are not directly comparable with monarchE, as the studies in the published literature included patients at lower risks of recurrences compared to monarchE therefore inferences need to be made on the IDFS rates for a higher risk population.

A more appropriate source of external validation for the IDFS extrapolation may be provided by the longer term [redacted] conducted by the Company in a more comparable high risk population. The 10-year IDFS rate was [redacted]%, which is considerably different to the 10-year IDFS rates for the ET alone arm predicted by the ERG's proposed lognormal or the Company's log-logistic extrapolation ([redacted]% or [redacted]%, respectively; both of these extrapolations demonstrate more than a ~[redacted] difference compared to the [redacted]). Instead, this may more closely align with either the exponential extrapolation ([redacted]%) or the gompertz extrapolation ([redacted]%), both a ~[redacted] difference, as presented in Table 5.

Table 5: Comparison of landmark IDFS rates for ET alone versus the RWE study

	5-year IDFS rates	10-year IDFS rates
	ET	ET
Exponential	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]

		<table><tr><td>Weibull</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Hazard spline (1 knot)</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Hazard spline (2 knots)</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>RWE study</td><td>[redacted]</td><td>[redacted]</td></tr></table> **Abbreviations**: ET: endocrine therapy; IDFS: invasive disease-free survival; RWE: real-world evidence. Accordingly, the Company disagree that the lognormal model might be a more appropriate extrapolation for IDFS than the log-logistic model. The Company acknowledge there is some uncertainty associated with the long-term extrapolations of IDFS in comparison to landmark estimates from RWE in a more comparable population, but note that the log-logistic extrapolation provides a significantly better statistical fit to the KM data from monarchE. Furthermore, the log-logistic extrapolation produced equally plausible long-term landmark IDFS estimates when the limitations of the published literature, including the inclusion of patients at lower risk of recurrence compared to monarchE, are taken into consideration. As such, the Company maintain its base case using the log-logistic curve for IDFS given a combination of internal and external validation factors but provide scenario analyses using a set of dependant (and independent) parametric survival curves which also show good external validity (lognormal, exponential and gompertz) in Appendix A. Ultimately, the limitations associated with the lognormal extrapolation are acknowledged by the ERG, as, in line with the CS, the ERG maintain the Company's chosen log-logistic extrapolation in their preferred base case. As such, the Company believe the choice of IDFS extrapolation should not be considered to be a significant source of uncertainty in this appraisal.
Key issue 8: Discrepancy between overall survival in model and real-world evidence	No	**OS without distant recurrence and OS are two distinct endpoints** The ERG expressed concerns that OS in the model does not align with real-world OS estimates for patients in the same population. However, as outlined in Issue Two of the ERG report factual accuracy check (FAC), OS extrapolations in the model represent OS for patients *without distant recurrence* (i.e. only including patients who die in the IDFS, remission or NMR health state). OS

		and OS without distant recurrence are two distinct endpoints and should not be used interchangeably. Since OS extrapolations in the Company model refer to patients without distant recurrence, the associated OS estimates are not comparable to the 84.75% OS estimate reported from NHS data in the ERG report, even before other uncertainties, such as differences in the patient population, are considered. Similarly, the dead health state in the model only absorbs patients who die without experiencing distant recurrence. The metastatic recurrence health states are also absorbing health states; patients who experience metastatic recurrence will never transition to the dead health state. Therefore, the number of patients in the dead state refers to patients who have died without experiencing metastatic recurrence of their disease. **Estimated OS predicted by the model** Accordingly, consideration of the number of patients in the metastatic recurrence health states will give a more realistic indication of the absolute OS of patients in the model. At Month 24, approximately [redacted]% ([redacted] patients out of the modelled cohort of 1,000) of patients in the ET alone arm are in the metastatic recurrence ET-resistant health state. As stated in Issue 2 of the ERG report FAC, death in this health state is not explicitly recorded in the CEM, but OS is recorded as a fixed life-year (LY) pay-off of approximately 3–4 years (depending on treatment regimen) in the metastatic health state, which represents an average of the expected LYs in this health state. Given the number of patients entering the metastatic health state and the extremely poor prognosis of these patients in clinical practice, it is likely that many of these patients would have died by Year 5 in the real-world. Moreover, by Month 60, approximately [redacted]% of patients in the ET alone arm are in the MR ET-resistant health state. A further proportion of these patients would also be expected to have died by Year 5. Consideration of the metastatic recurrence health state occupancy therefore indicates that OS predicted by the model is much closer to the ERG's stated figure of 84.75% than initially suggested.

		Furthermore, the 5-year survival figure of 84.75% stated by the ERG refers to patients with HR+, HER2- breast cancer *with an initial stage III diagnosis*. This population is not directly comparable to the monarchE trial population, as in the monarchE trial ITT population (used as proxy, in the absence of data for Cohort 1), only [redacted]% of patients were initially diagnosed with stage III breast cancer, whilst [redacted] of patients were initially diagnosed with less advanced disease (stage I or II breast cancer). The paucity of baseline characteristics for the real-world estimate introduces additional uncertainty as to whether this population is comparable to monarchE Cohort 1. As such, the 5-year OS of patients modelled to receive ET in the Company cost-effectiveness model would not be expected to equal 84.75%, and is expected to differ as a substantial proportion of patients in the monarchE trial are initially diagnosed with less advanced disease. Considering this, and the distinction between OS and OS without distant recurrence, there is no evidence to suggest any discrepancy between the OS predicted by the model with that expected in UK clinical practice.
Key issue 9: Lack of long-term evidence for assumed 'carryover benefit' and justification for treatment waning trajectory	Yes	**Evidence supporting the long-term treatment benefit for abemaciclib + ET** The ERG highlighted concerns with the evidence used to inform the Company's assumptions supporting the long-term treatment benefit of abemaciclib and the ERG state that "there is an absence of evidence to the carryover benefit for abemaciclib". The Company acknowledge the lack of long-term follow-up data on the lasting treatment benefit for abemaciclib, but would like to reiterate that the assumptions used in the Company base case were informed by the available data from monarchE and published literature as the best available proxy (CS, Document B, Section B.3.3.2). Data from monarchE demonstrates the existence of a treatment effect of abemaciclib + ET beyond discontinuation. A piecewise analysis for IDFS in monarchE was performed at the most recent data cut-off in the ITT population, demonstrating that the magnitude of the treatment benefit of abemaciclib, in terms of the reduced risk of an IDFS event, continued to increase over time in the follow-up period, and the HRs continue to deepen between Year 1–2 and Year 2+, by which time most patients will have discontinued treatment with abemaciclib (CS, Document B, Section

		B.2.6.1).[26]. A similar analysis for Cohort 1 of monarchE is not available, however seeing as Cohort 1 comprises 91% of the ITT population, the HRs based on the ITT population are a suitable proxy. The Company acknowledge that the exact duration of the long-term treatment effect is uncertain due to a lack of long-term clinical evidence on the treatment benefit of abemaciclib + ET. However, as highlighted in the CS (Document B, Section B.3.3.2), in the absence of longer-term clinical data for abemaciclib + ET, assumptions informing the duration of the abemaciclib treatment effect, and the waning of this effect, were based on long-term data for ET. The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial was one of the few trials reporting on long term follow up data for anastrozole and tamoxifen for up to 10 years and clinical experts noted that the ATAC trial was the most relevant to inform treatment waning assumptions.[27] The data for tamoxifen and aromatase inhibitors are used as the best available proxy to inform the plausible duration of treatment effect for abemaciclib, in the absence of data specific to abemaciclib; this data demonstrated a lasting treatment benefit of up to 8 years for one ET over the other (Clarification Question, B7). Based on this, the Company maintains the base case assumption that a full treatment effect of abemaciclib + ET versus ET alone is experienced until at least Year 8 (CS, Document B, Section B.3.3.2). Please note, the Company believe that applying assumptions that mimic ET based on the ATAC study is the most conservative assumption that remains plausible given that a significant and deepening treatment effect has been demonstrated over ET in the monarchE trial. **Evidence supporting the long-term treatment waning assumptions for abemaciclib + ET** A full treatment effect for abemaciclib + ET was assumed to last for 8 years, after which treatment effect wanes until Year 27, which represents the point in the model where IDFS rates equal background mortality (CS, Document B, Section B.3.3.2, Figure 15). Clinical trial data from Colleoni *et al.* (2016) further supports the long-term waning of the treatment effect by demonstrating that the highest risk of recurrence from early breast cancer occurs in the first 5 years following initiation of adjuvant therapy.[28] The hazards of IDFS recurrence in the ET alone arm and the abemaciclib + ET arm under the Company's base case treatment waning

		assumptions are consistent with this data. This can be observed visually in Figure 4 and Figure 5 which presents the hazard of recurrence of the abemaciclib + ET and ET alone arm over the model lifetime under the ERG's preferred treatment waning assumptions and the Company base case treatment waning assumptions, respectively. **Figure 4: Hazard of IDFS using the ERG's preferred treatment waning assumptions (waning begins at Year 3, and ends at Year 8)**  **Abbreviations:** ABE: abemaciclib; ERG: Evidence Review Group; ET: endocrine therapy; IDFS: invasive disease free survival.

Figure 5: Hazard of IDFS using the Company base case treatment waning assumptions (waning begins at Year 8, and ends at Year 27)

Abbreviations: ABE: abemaciclib; ERG: Evidence Review Group; ET: endocrine therapy; IDFS: invasive disease free survival.

When treatment waning is assumed to end at Year 8 (Figure 4) a continual increase in the hazard of IDFS in the abemaciclib + ET arm is observed over the first eight years of the model, until the peak IDFS hazard is reached at Year 8. In contrast, the hazard of IDFS for patients receiving ET alone reaches its peak at Year 4 and then decreases thereafter until background mortality is reached much later.

The comparison of the trends in the IDFS hazards between abemaciclib + ET versus ET alone from Year 3 to Year 8 does not appear to be clinically plausible, particularly when considering that

		over this time period, patients in both arms are receiving the same treatment regimen (i.e. ET alone). It therefore does not seem plausible for the hazard of IDFS to be steadily increasing for one group of patients and decreasing for another. Furthermore, the rising IDFS hazard in the abemaciclib + ET arm does not align with the available data from Colleoni *et al*. (2016), which indicates that the risk of recurrence for patients with early breast cancer decreases over time.[28] Table 2 of Colleoni et al. indicates that the hazards of recurrence (measured using either breast-cancer free interval [BCFI] or DFS) for patients with ER+ early breast cancer are markedly reduced in Years 5–10, compared to Years 0–5 (BCFI: 5.4% versus 9.9%; DFS: 6.6% versus 10.6%).[28] The ERG's preferred assumptions, where the risk of recurrence for patients receiving abemaciclib + ET is highest in Year 8, appears to be in stark contrast with these published data, and raises substantial clinical plausibility concerns. The turning point at Month [redacted] in the abemaciclib + ET arm also appears to be clinically implausible, whereby the hazard of IDFS in the abemaciclib + ET arm continually increases until Month [redacted] and then suddenly starts to decrease once the waning period ends. There does not appear to be any clinical rationale explaining why the hazard of IDFS would change so markedly at Year 8, or why the overall trend of the IDFS hazards (i.e. the gradient of the IDFS hazards curve) in the abemaciclib + ET arm would be so different to the ET alone arm between Year 3 and Year 8, during which time both groups of patients are receiving ET alone. In contrast, when treatment waning is assumed to occur over a longer period, such as Year 27 in the Company base case (Figure 5), the trend of the hazard of recurrence of the abemaciclib + ET arm is much more aligned with the trend of the hazard in the ET alone arm, without the peak IDFS hazard or marked turning point at Year 8 using the ERG's preferred assumptions, both of which raise considerable clinical plausibility concerns. Instead, it gradually wanes to the hazard of IDFS in the ET alone arm, following a more plausible pattern that is also consistent with Colleoni *et al.* (2016) where the risk of recurrence decreases over time.[28] Based on this evidence, the treatment benefit of abemaciclib + ET should be gradually waned until it reaches background population mortality, in line with the Company's base case assumptions.

		Evidence from monarchE for a treatment effect of abemaciclib + ET beyond Year 3 The Company acknowledge that there is a lack of long-term evidence available for the exact duration of the treatment effect associated with abemaciclib and the long-term IDFS risk for patients with HR+, HER2- early breast cancer, but there is no evidence supporting the ERG's preferred assumption that waning begins at Year 3. Considering the available evidence from monarchE, the piecewise IDFS analysis of the ITT population demonstrated that the magnitude of the treatment benefit of abemaciclib, in terms of the reduced risk of an IDFS event, continued to increase over time in the follow-up period, with HRs for Year 0–1, Year 1–2 and Year 2+ being [redacted], [redacted] and [redacted], respectively.[26] Importantly, the HRs continue to deepen between Year 1–2 and Year 2+, by which time most patients will have discontinued treatment with abemaciclib. This confirms the existence of a treatment benefit beyond discontinuation with abemaciclib, with no indications of a reduction in this treatment effect beyond Year 3. This is further demonstrated by the plot of the hazard of IDFS for abemaciclib + ET and ET alone, based on monarchE trial data for Cohort 1, presented in Figure 6. This clearly demonstrates a continued widening of the gap in treatment benefit between abemaciclib + ET and ET alone between Month 24 and Month 36, providing no indication that the treatment effect should wane after Month 36 (Year 3). Although there are limitations surrounding sample size at Month 30–Month 36 due to censoring, there is no evidence to support the ERG's preferred assumption that waning of the treatment effect associated with abemaciclib begins at Year 3 (or notably, any evidence of a waning treatment benefit for abemaciclib + ET versus ET alone). Given the lack of long-term data on the duration of the abemaciclib treatment effect, any assumptions should align with the limited data that is available. Accordingly, the Company

		maintains that waning of the treatment effect starting at Year 8 represents the most conservative assumption that remains plausible. **Figure 6: Smoothed hazard of IDFS events until Year 3 – Cohort 1**  **Abbreviations**: IDFS: invasive disease-free survival. **Evidence for treatment waning assumptions from past NICE appraisals** Finally, it should be noted that the preferred treatment waning assumptions proposed by the ERG are more pessimistic than those accepted in a number of past NICE appraisals for early breast cancer treatments, including TA424, TA569 and TA612 in which a full treatment effect was

		assumed for a minimum of 4 years.[5, 15, 29] Considering the data from monarchE, which does not provide any indication of the effect of abemaciclib waning, there is no evidence to support the use of more pessimistic assumptions than those previously accepted by NICE. The ERG's preferred treatment waning assumptions (waning begins at Year 3 and ends at Year 8) are in line with the Committee's preferred assumptions in TA632.[16] However, Year 3 and Year 8 were timepoints specifically calculated based on the annual HRs used in TA632, and should not be generalised to this appraisal. Moreover, the annualised HRs from the KATHERINE trial presented in TA632 (Figure 5.9 of the ERG report for TA632) show a reduction in the treatment benefit of trastuzumab emtansine versus trastuzumab from Year 1 to Year 4, providing clear evidence of waning from Year 2 onwards. In contrast, the annualised HRs from the monarchE IDFS piecewise analysis demonstrate an increasing magnitude of treatment benefit throughout the trial period, and importantly after Year 2, when most patients will have discontinued treatment with abemaciclib. Given that the monarchE data shows a stronger treatment effect over time versus the data used in TA632, it appears to be overly pessimistic to apply the same treatment waning assumptions from TA632 to this appraisal. The Company maintain that the original base case assumptions of waning beginning at Year 8 and lasting until Year 27 represent the most robust assumption, considering the totality of evidence in the published literature, however, acknowledge there is some uncertainty surrounding the exact duration of the abemaciclib + ET treatment benefit, particularly the period over which this treatment benefit declines or wanes. Applying the duration of treatment benefit observed for ET in the ATAC study as an assumption should be viewed as the most conservative option that is plausible given that a significant and deepening treatment effect has been demonstrated over ET in the monarchE trial. Therefore, the Company has provided a number of scenario analyses applying alternative durations for the waning period starting at year 8 in Appendix A.
Key issue 10: Same utility values applied to both	Yes	In the Company's original base case, the data from each treatment arm was pooled to maximise sample size, and equal utility for patients in the same health state, irrespective of treatment received, was assumed. For the monarchE ITT population, there was a very small (0.001) difference in IDFS utility between the treatment arms, but this was not considered meaningful and

treatment and control arms in the IDFS setting		any differences in health-related quality of life between treatments arms are accounted for by adverse event (AE) disutilities, in line with the approach taken in TA632.[4] However, for Cohort 1 there are no differences in the treatment specific IDFS utility values between the abemaciclib + ET and ET alone arms of Cohort 1 of monarchE ([redacted] for both arms). As such, the revised Company base case has been updated to reflect these pooled IDFS health state utility values for Cohort 1, but this will have no difference on the cost-effectiveness results compared to if treatment-specific IDFS utility values for Cohort 1 were used.
Key issue 11: Insufficient clarity in the probability of moving to non-metastatic and metastatic health states	No	The ERG noted that there was insufficient clarity in reporting the probability of moving to non-metastatic and metastatic health states. Additional details on these transition probabilities are now provided in Figure 3 and Table 3 in response to Key issue 4. The ERG also noted that the same waning assumptions used for overall recurrences should apply to metastatic recurrences relative to non-metastatic. The Company agrees with the ERG that this is a reasonable assumption. As such, waning of the metastatic recurrence/non-metastatic recurrence probabilities in line with the ERG's methodology, starting at Year 8 and ending at Year 27, has been incorporated in the Company's updated base case (in line with the Company's preferred waning assumptions detailed in response to Key Issue 9). The Company's updated base case results, including the waning of the recurrence probabilities, are presented in Appendix A.
Key issue 12: Insufficient clarity of reporting of the cost effectiveness scenario results	No	Updated scenario analyses, incorporating the changes to the Company's base case as part of technical engagement, are presented in Appendix A. Further scenario analyses regarding the choice of IDFS extrapolation and the treatment waning assumptions are discussed separately in Key Issue 7 and Key Issue 9.
Key issue 13: Lack of detail in the model validation process in terms of	No	The Company acknowledge the ERG's proposed corrections (Coding Errors 1–4) to the cost-effectiveness model and have included these within the updated Company base case following

verification of the formulae, functions, and coding.		technical engagement. As highlighted in the ERG report, incorporating these updates into the model has a minimal impact on the cost-effectiveness results. In response to the ERG's concerns regarding the validation process of the model, the Company has provided additional details on the internal validation of the cost-effectiveness model in the reference pack submitted with this response (Internal Validation of the Cost Effectiveness Model).

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER (cumulative)
Key issue 13: Lack of detail in the model validation process in terms of verification of the formulae, functions, and coding.	NA	The Company has included the ERG's proposed corrections for Coding Errors 1–4.	ICER (£/QALY) = £5,309 Change from original base case ICER = +40.2%
Key Issue 11: Insufficient clarity in the probability of moving to non-metastatic and metastatic health states	The probability of moving from IDFS health state to NMR and MR health states was fixed throughout the model time horizon.	The Company has included the ERG's preferred methodology that the same treatment waning assumptions used for overall recurrences should apply to the probability of transitioning to the NMR and MR health states. In the Company base case, waning is assumed to start at Year 8 and ends at Year 27.	ICER (£/QALY) = £5,572 Change from original base case ICER = +47.1%
Key issue 1: Potential lack of generalisability of the evidence to NHS clinical practice given ambiguity in the definition of high risk	The Company included the monarchE ITT population in the base case cost-effectiveness analysis.	The Company has included the monarchE Cohort 1 population in the updated base case cost-effectiveness analysis following technical engagement.	ICER (£/QALY) = £6,098 Change from original base case ICER = +61.1%

Key issue 10: Same utility values applied to both treatment and control arms in the IDFS setting	The Company applied pooled HSUVs for IDFS given lack of statistically significant EQ5D clinical results from monarchE	The Company has updated pooled HSUVs ([redacted]) to reflect Cohort 1 given there was no difference found between treatment arms	ICER (£/QALY) = £6,153 Change from original base case ICER = +62.5%
Matters of judgement 6: The non-use of the Kaplan-Meier curve to model TTD for abemaciclib	The Company did not utilize the KM curve to model TTD for abemaciclib alone	The Company utilized the KM curve to model TTD for abemaciclib alone	ICER (£/QALY) = £6,196 Change from original base case ICER = +63.7%
Matters of judgement 7: The cost of delivery of deliver subsequent elements of a chemotherapy cycle which deviated from the stated source of cost data	The Company applied a value of £253.77	The Company updated this cost to ERG preferred value of £341	ICER (£/QALY) = £6,195 Change from original base case ICER = +63.6%

Appendix A: Updated Company base case following technical engagement

The updated Company base case following technical engagement is presented in Table 6 (deterministic) and Table 7 (probabilistic).

Table 6: Updated Company base case following technical engagement (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Abemaciclib + ET	[redacted]	[redacted]	[redacted]	-	-	-	-
ET alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,195

Footnotes: This table reports undiscounted LYG, and discounted costs and QALYs.
Abbreviations: ET: endocrine therapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life years.

Probabilistic sensitivity analysis

The results of the PSA with 1,000 iterations are presented in Table 7 for abemaciclib at PAS price. The results show that abemaciclib was associated with a [redacted]% probability of being cost-effective at a £30,000 willingness-to-pay threshold at PAS price.

Table 7: Updated Company base case following technical engagement (probabilistic)

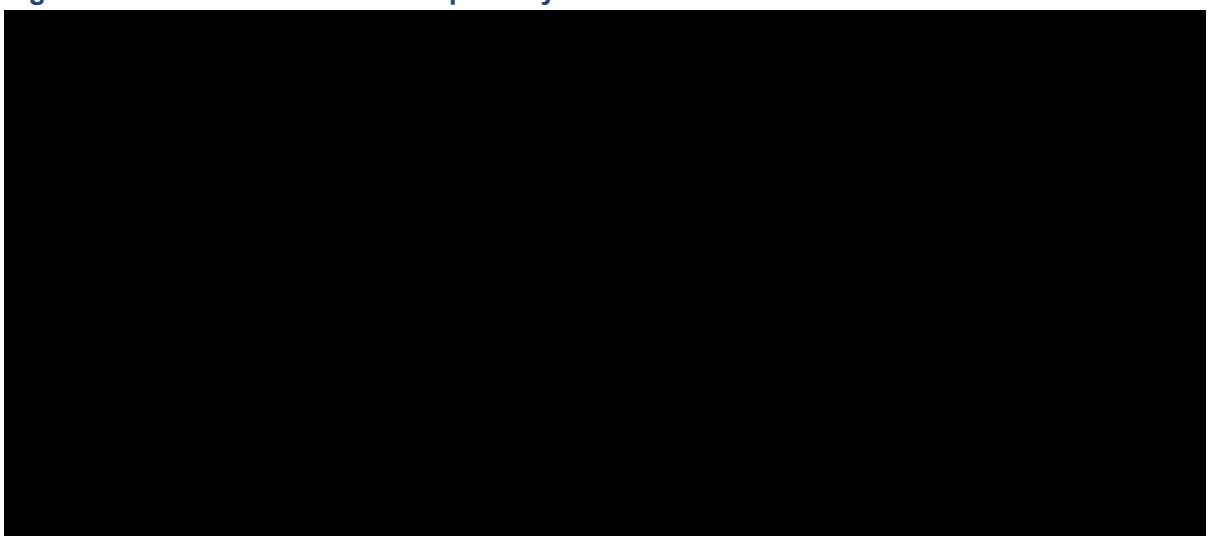
Technologies	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Probability of cost-effectiveness[a]
Abemaciclib + ET	[redacted]	[redacted]	5,897	[redacted]
ET alone	[redacted]	[redacted]	-	[redacted]

Footnotes: This table reports undiscounted LYG, and discounted costs and QALYs.
Abbreviations: ET: endocrine therapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life years.

Figure 7: Cost-effectiveness plane for abemaciclib + ET versus ET alone

Abbreviations: ET: endocrine therapy; QALYs: quality adjusted life years.

Figure 8: Cost-effectiveness acceptability curve for abemaciclib + ET versus ET alone



Abbreviations: ET: endocrine therapy; QALYs: quality adjusted life years.

Deterministic sensitivity analysis

To account for uncertainty around the input parameters used in the base case analysis, a deterministic sensitivity analysis (DSA) was conducted. Where available, each parameter was varied by 95% CIs. For parameters where CIs were not available the input was varied by ±10% of their mean value. Pease note the DSA does not include parameters which require assessment of joint uncertainty, these correlated parameters are assessed within the PSA.

Figure 9: DSA tornado plot for abemaciclib + ET versus ET alone

Abbreviations: ABE: abemaciclib; ET: endocrine therapy; NMR: non-metastatic recurrence.

Scenario analyses

Scenario analyses exploring alternative IDFS extrapolations and treatment waning assumptions are presented in Table 8.

Table 8: Updated scenario analyses

Parameter	Base case	Scenario		Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
Updated Base case				[redacted]	[redacted]	6,195
IDFS extrapolation	Dependant Loglogistic	Dependant lognormal		[redacted]	[redacted]	10,744
		Dependant gompertz		[redacted]	[redacted]	4,691
		Dependant Exponential		[redacted]	[redacted]	4,491
		Independent Loglogistic		[redacted]	[redacted]	3,249
		Independent lognormal		[redacted]	[redacted]	5,001
		Independent gompertz		[redacted]	[redacted]	Dominant
		Independent exponential		[redacted]	[redacted]	4,491
Treatment waning	Start at 8-years, stop at 27-years	Wane start	Wane ends			
		Year 8	Year 10	[redacted]	[redacted]	8,632
			Year 15	[redacted]	[redacted]	7,218

			Year 20	[redacted]	[redacted]	6,641

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

Appendix B: Baseline characteristics for Cohort 1

Table 9: Demographics of patients in the monarchE trial for Cohort 1

Demographic Parameter[a]	Abemaciclib + ET (N=[redacted])	ET alone (N=[redacted])
Sex, n (%)	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]
Male, n (%)	[redacted]	[redacted]
Age, years	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Race, n (%)	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]
Native Hawaiian or Other Pacific Islander	[redacted]	[redacted]
White	[redacted]	[redacted]
Multiple	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Region, n (%)	[redacted]	[redacted]
North America/Europe	[redacted]	[redacted]
Asia	[redacted]	[redacted]
Other	[redacted]	[redacted]
Ethnicity, n (%)[b]	[redacted]	[redacted]
Hispanic or Latino	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Menopausal status, n (%)	[redacted]	[redacted]
Premenopausal	[redacted]	[redacted]
Postmenopausal	[redacted]	[redacted]
Baseline ECOG PS, n (%)	[redacted]	[redacted]
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Weight (kg)	[redacted]	[redacted]

Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
BMI (kg/m^2)	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]

Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Status; ET: endocrine therapy; ITT: intent-to-treat; max: maximum; min: minimum; N: number of patients in the ITT population; n: number of patients within category; SD: standard deviation.
Footnotes: [a] Number of patients with non missing data, used as denominator; [b] Only includes responses from US sites, n is the number of subjects with a value of "HISPANIC OR LATINO" or "NOT HISPANIC OR LATINO".
Source: Lilly Data on File. Data cut-off: 08 July 2020 (PO analysis)

Table 10: Summary of key baseline disease characteristics in monarchE (Cohort 1)

Baseline Disease Characteristic, n (%) unless otherwise specified	**Abemaciclib + ET (N=[redacted])**	**ET alone (N=[redacted])**
Initial pathological diagnosis		
Invasive ductal breast carcinoma	[redacted]	[redacted]
Breast cancer, not otherwise specified	[redacted]	[redacted]
Invasive lobular breast carcinoma	[redacted]	[redacted]
Mucinous breast carcinoma	[redacted]	[redacted]
Invasive papillary breast carcinoma	[redacted]	[redacted]
Inflammatory carcinoma of the breast	[redacted]	[redacted]
Medullary carcinoma of the breast	[redacted]	[redacted]
Tubular breast carcinoma	[redacted]	[redacted]
Paget's disease of nipple	[redacted]	[redacted]
Metaplastic breast carcinoma	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Primary tumour size by radiology prior to any systemic treatment, n	[redacted]	[redacted]
<20 mm	[redacted]	[redacted]
≥20 mm but <50 mm	[redacted]	[redacted]
≥50 mm	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Primary tumour size by pathology after definitive surgery	[redacted]	[redacted]
<20 mm	[redacted]	[redacted]
≥20 mm but <50 mm	[redacted]	[redacted]
≥50 mm	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Involvement of ipsilateral supraclavicular, ipsilateral infraclavicular, or ipsilateral internal mammary nodes at initial diagnosis		

Baseline Disease Characteristic, n (%) unless otherwise specified	Abemaciclib + ET (N=[redacted])	ET alone (N=[redacted])
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Axillary lymph node evaluation		
Positive	[redacted]	[redacted]
Negative	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Number of positive lymph nodes		
0	[redacted]	[redacted]
1-3	[redacted]	[redacted]
4-9	[redacted]	[redacted]
≥10	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Histopathological diagnosis grade		
G1 – favourable	[redacted]	[redacted]
G2 – moderately favourable	[redacted]	[redacted]
G3 – unfavourable	[redacted]	[redacted]
GX – cannot be accessed	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Disease stage at initial diagnosis		
Stage IA	[redacted]	[redacted]
Stage IIA	[redacted]	[redacted]
Stage IIB	[redacted]	[redacted]
Stage IIIA	[redacted]	[redacted]
Stage IIIB	[redacted]	[redacted]
Stage IIIC	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Oestrogen receptor status		
Positive	[redacted]	[redacted]
Negative	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Progesterone receptor status		
Positive	[redacted]	[redacted]
Negative	[redacted]	[redacted]
Unknown	[redacted]	[redacted]

Baseline Disease Characteristic, n (%) unless otherwise specified	Abemaciclib + ET (N=[redacted])	ET alone (N=[redacted])
Missing	[redacted]	[redacted]
HER2 status at initial diagnosis		
Positive	[redacted]	[redacted]
Negative	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Central lab Ki-67 results from untreated tumour (%)		
<20%	[redacted]	[redacted]
≥20%	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Not applicable[b]	[redacted]	[redacted]
Not evaluable[c]	[redacted]	[redacted]

Abbreviations: ET: endocrine therapy; G1: low combined histologic grade (favourable); G2: intermediate combined histologic grade (moderately favourable); G3: high combined histologic grade (unfavourable); GX: grade cannot be assessed; HER2: human epidermal growth factor receptor 2; N: number of patients in the ITT population; n: number of patients within category.
Footnotes: [a] This patient was enrolled due to a protocol deviation, as detailed in the CSR. [b] Not applicable was defined as <200 viable tumour cells present, and therefore the test was not performed; [c] Not evaluable was defined as >200 viable tumour cells present, but expression cannot be determined due to issue with section that obscures or prevents an accurate evaluation, such as damage, artifact, or washing off.
Source: Lilly Data on File. Data cut-off: 08 July 2020 (PO analysis).

Table 11: Prior therapy and surgery for breast cancer monarchE (Cohort 1)

Prior Therapy, n (%)	Abemaciclib + ET (N=[redacted])	ET alone (N=[redacted])	Total (N=[redacted])
Prior anticancer therapy			
Surgical procedure	[redacted]	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]	[redacted]
Systemic therapy	[redacted]	[redacted]	[redacted]
Surgical procedure: intent			
Curative intent	[redacted]	[redacted]	[redacted]
Radiotherapy: reason			
Neoadjuvant	[redacted]	[redacted]	[redacted]
Adjuvant	[redacted]	[redacted]	[redacted]
Systemic therapy: reason and type			
Neoadjuvant	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]
ET[a]	[redacted]	[redacted]	[redacted]
Other[b]	[redacted]	[redacted]	[redacted]

Target[c]	[redacted]	[redacted]	[redacted]
Adjuvant	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]
ET[a]	[redacted]	[redacted]	[redacted]
Other[b]	[redacted]	[redacted]	[redacted]
Target[c]	[redacted]	[redacted]	[redacted]
Term to be coded	[redacted]	[redacted]	[redacted]

Footnotes: [a] ET included patients treated with endocrine treatment and/or GnRH analogues; [b] "Other" is any other type of prior therapy not listed above; [c] "Target" is any prior therapy that is target therapy based on compound-wise documentation on systemic drugs.
Abbreviations: ET: endocrine therapy; GnRH: gonadotropin-releasing hormone; ITT: intent-to-treat; N: number of patients in the ITT population; n: number of patients within category.
Source: Lilly Data on File. Data cut-off: 08 July 2020 (PO analysis).

Appendix C: Efficacy analyses for Cohort 1

Invasive disease-free survival

Table 12: Summary of IDFS in Cohort 1 (AFU1 analysis)

	Abemaciclib + ET (N=[redacted])	ET alone (N=[redacted])	Treatment Effect/Difference 2-sided p-Value (nominal)c
Number of events, n (%)	[redacted]	[redacted]	
Deaths without invasive disease	[redacted]	[redacted]	
Invasive disease	[redacted]	[redacted]	
Number of patients censored, n (%)	[redacted]	[redacted]	
Invasive disease prior to randomisation	[redacted]	[redacted]	
No post-baseline assessment	[redacted]	[redacted]	
No documented invasive disease	[redacted]	[redacted]	
p-value (2-sided) log-rank, stratified[a]	[redacted]		
HR (95% CI)[a]	[redacted]		
IDFS rate, % (95% CI)[b]			
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]

Footnotes: [a] Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [b] Treatment Effect/Difference/p-values are computed based on comparator ET.
Abbreviations: CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; IDFS: invasive disease-free survival; ITT: intent-to-treat; N: number of patients in the ITT population.
Source: Lilly Data on File. Clinical Study Report: monarchE.[26] Data cut-off: 01 April 2021 (AFU1 analysis).

Figure 10: Summary of the IDFS results in monarchE Cohort 1 (AFU1 analysis)

Abbreviations: ET: endocrine therapy; HR: hazard ratio; IDFS: invasive disease-free survival; ITT: intent-to-treat.
Source: Lilly Data on File. Clinical Study Report: monarchE.[26] Data cut-off: 01 April 2021 (AFU1 analysis).

Disease relapse-free survival

Table 13: Summary of DRFS in Cohort 1 (AFU1 analysis)

	Abemaciclib + ET (N=[redacted])	ET alone (N=[redacted])	Treatment Effect/Difference 2-sided p-Value (nominal)c
Number of events, n (%)	[redacted]	[redacted]	
Death without distant relapse	[redacted]	[redacted]	
Distant relapse	[redacted]	[redacted]	
Number of patients censored, n (%)	[redacted]	[redacted]	
Distant relapse prior to randomisation	[redacted]	[redacted]	
No post-baseline assessment	[redacted]	[redacted]	
No documented distant relapse with regular assessment	[redacted]	[redacted]	
p-value (2-sided) log-rank[a]	[redacted]		
HR (95% CI)[a]	[redacted]		

DRFS rate, % (95% CI)[b]			
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]

Footnotes: [a] Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [b] Treatment Effect/Difference/p-values are computed based on comparator ET.
Abbreviations: CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; DRFS: distant relapse-free survival; ITT: intent-to-treat; N: number of patients in the ITT population.
Source: Lilly Data on File. Clinical Study Report: monarchE.[26] Data cut-off: 01 April 2021 (AFU1 analysis).

Figure 11: Summary of the DRFS results in monarchE Cohort 1 (AFU1 analysis)

Abbreviations: DRFS: distant relapse-free survival; ET: endocrine therapy; HR: hazard ratio; ITT: intent-to-treat.
Source: Lilly Data on File. Clinical Study Report: monarchE.[26] Data cut-off: 01 April 2021 (AFU1 analysis).

Overall survival

Table 14: Summary of OS in Cohort 1 (AFU1 analysis)

	Abemaciclib + ET (N=[redacted])	ET alone (N=[redacted])	Treatment Effect/Difference 2-sided p-Value (nominal)c
Number of deaths, n (%)	[redacted]	[redacted]	
Number of patients censored, n (%)	[redacted]	[redacted]	

Alive	[redacted]	[redacted]	
Lost to follow-up	[redacted]	[redacted]	
Withdrawal by subject	[redacted]	[redacted]	
p-value (2-sided) log-rank, stratified[a]	[redacted]		
HR (95% CI)	[redacted]		
Overall survival rate, % (95% CI)[b]			
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
30 months	[redacted]	[redacted]	[redacted]

Footnotes: [a] Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [b] Treatment Effect/Difference/p-values are computed based on comparator ET.
Abbreviations: CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; ITT: intent-to-treat; N: number of patients in the ITT population; OS: overall survival.

Table 15: Summary of overall survival in Cohort 1 (including a COVID-19 sensitivity analysis) (AFU1 analysis)

Events, n (%)	Abemaciclib + ET (N=[redacted])	ET alone (N=[redacted])	Treatment Effecta	
			Stratified HR (95% CI)b	2-sided p-value (nominal)b
OS	[redacted]	[redacted]	[redacted]	[redacted]
OS: COVID-19 sensitivity analysis[c]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a]Treatment effect in terms of HR estimates and p-values are computed based on comparator ET; [b] Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [c] patients who died due to suspected or reported COVID-19 were censored on the day prior to their deaths.
Abbreviations: CI: confidence interval; COVID-19: coronavirus, SARS-CoV-2; ET: endocrine therapy; HR: hazard ratio; ITT: intent-to-treat; N: number of patients in the ITT population; OS: overall survival.
Source: Lilly Data on File. Clinical Study Report: monarchE.[26] Data cut-off: 01 April 2021 (AFU1 analysis).

Figure 12: Summary of the OS results in monarchE Cohort 1 (AFU1 analysis)

Abbreviations: #: number; CI: confidence interval; ET: endocrine therapy; HR: hazard ratio.
Source: Lilly Data on File. Clinical Study Report: monarchE.[26] Data cut-off: 01 April 2021 (AFU1 analysis).

Appendix D: Subgroup analyses of IDFS and DRFS by menopausal status

Subgroup analyses for IDFS – Cohort 1

Table 16: Summary of investigator-assessed IDFS Cohort 1 Population (AFU1 analysis): Postmenopausal

	Abemaciclib + ET (N=[redacted])	ET alone (N=[redacted])	Treatment Effect/Difference 2-sided p-Value (nominal)c
Number of events, n (%)	[redacted]	[redacted]	
Deaths without invasive disease	[redacted]	[redacted]	
Invasive disease	[redacted]	[redacted]	
Number of patients censored, n (%)	[redacted]	[redacted]	-
Invasive disease prior to randomisation	[redacted]	[redacted]	
No post-baseline assessment	[redacted]	[redacted]	
No documented invasive disease	[redacted]	[redacted]	
p-value (2-sided) log-rank, stratified[a]	[redacted]		

HR (95% CI)	[redacted]		
IDFS rate, % (95% CI)[b]			
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]

Footnotes: [a] Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [b] 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation; [c] Treatment Effect/Difference/p-values are computed based on comparator ET.
Abbreviations: CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; IDFS: invasive disease-free survival; N: number of patients in the Cohort 1 population.

Table 17: Summary of investigator-assessed IDFS Cohort 1 Population (AFU1 analysis): Premenopausal

	Abemaciclib + ET (N=[redacted])	ET alone (N=[redacted])	Treatment Effect/Difference 2-sided p-Value (nominal)[c]
Number of events, n (%)	[redacted]	[redacted]	
Deaths without invasive disease	[redacted]	[redacted]	
Invasive disease	[redacted]	[redacted]	
Number of patients censored, n (%)	[redacted]	[redacted]	-
Invasive disease prior to randomisation	[redacted]	[redacted]	
No post-baseline assessment	[redacted]	[redacted]	
No documented invasive disease	[redacted]	[redacted]	
p-value (2-sided) log-rank, stratified[a]	[redacted]		
HR (95% CI)	[redacted]		
IDFS rate, % (95% CI)[b]			
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]

Footnotes: [a] Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [b] 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation; [c] Treatment Effect/Difference/p-values are computed based on comparator ET.
Abbreviations: CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; IDFS: invasive disease-free survival; N: number of patients in the Cohort 1 population.

Subgroup analyses for DRFS – Cohort 1

Table 18: Summary of investigator-assessed DRFS Cohort 1 Population (AFU1 analysis): Postmenopausal

	Abemaciclib + ET (N=[redacted])	ET alone (N=[redacted])	Treatment Effect/Difference 2-sided p-Value (nominal)[c]
Number of events, n (%)	[redacted]	[redacted]	-
Deaths without distant relapse	[redacted]	[redacted]	
Distant relapse	[redacted]	[redacted]	
Number of patients censored, n (%)	[redacted]	[redacted]	
Distant relapse prior to randomisation	[redacted]	[redacted]	
No post-baseline assessment	[redacted]	[redacted]	
No documented distant relapse with regular assessment	[redacted]	[redacted]	
p-value (2-sided) log-rank, stratified[a]	[redacted]		
HR (95% CI)	[redacted]		
IDFS rate, % (95% CI)[b]			
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]

Footnotes: [a] Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [b] 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation; [c] Treatment Effect/Difference/p-values are computed based on comparator ET.
Abbreviations: CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; DRFS: distant relapse-free survival; N: number of patients in the Cohort 1 population.

Table 19: Summary of investigator-assessed DRFS Cohort 1 Population (AFU1 analysis): Premenopausal

	Abemaciclib + ET (N=[redacted])	ET alone (N=[redacted])	Treatment Effect/Difference 2-sided p-Value (nominal)[c]
Number of events, n (%)	[redacted]	[redacted]	-
Deaths without distant relapse	[redacted]	[redacted]	
Distant relapse	[redacted]	[redacted]	
Number of patients censored, n (%)	[redacted]	[redacted]	

Distant relapse prior to randomisation	[redacted]	[redacted]	
No post-baseline assessment	[redacted]	[redacted]	
No documented distant relapse with regular assessment	[redacted]	[redacted]	
p-value (2-sided) log-rank, stratified[a]	[redacted]		
HR (95% CI)	[redacted]		
IDFS rate, % (95% CI)[b]			
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]

Footnotes: [a] Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [b] 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation; [c] Treatment Effect/Difference/p-values are computed based on comparator ET.
Abbreviations: CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; DRFS: distant relapse-free survival; N: number of patients in the Cohort 1 population.

Appendix E: Subgroup analyses of IDFS and DRFS by menopausal status and first ET

Subgroup analyses for IDFS – Cohort 1

First ET: Aromatase inhibitor

Table 20: Summary of investigator-assessed IDFS Cohort 1 Population (AFU1 analysis): postmenopausal and aromatase inhibitor received as first ET

	Abemaciclib + ET (N=[redacted])	ET alone (N=[redacted])	Treatment Effect/Difference 2-sided p-Value (nominal)[c]
Number of events, n (%)	[redacted]	[redacted]	
Deaths without invasive disease	[redacted]	[redacted]	
Invasive disease	[redacted]	[redacted]	
Number of patients censored, n (%)	[redacted]	[redacted]	-
Invasive disease prior to randomisation	[redacted]	[redacted]	
No post-baseline assessment	[redacted]	[redacted]	
No documented invasive disease	[redacted]	[redacted]	
p-value (2-sided) log-rank, stratified[a]	[redacted]		

HR (95% CI)	[redacted]		
IDFS rate, % (95% CI)[b]			
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]

Footnotes: [a] Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [b] 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation; [c] Treatment Effect/Difference/p-values are computed based on comparator ET.
Abbreviations: CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; IDFS: invasive disease-free survival; N: number of patients in the Cohort 1 population.

Table 21: Summary investigator-assessed IDFS Cohort 1 Population (AFU1 analysis): premenopausal and aromatase inhibitor received as first ET

	Abemaciclib + ET (N=[redacted])	ET alone (N=[redacted])	Treatment Effect/Difference 2-sided p-Value (nominal)[c]
Number of events, n (%)	[redacted]	[redacted]	
Deaths without invasive disease	[redacted]	[redacted]	
Invasive disease	[redacted]	[redacted]	
Number of patients censored, n (%)	[redacted]	[redacted]	-
Invasive disease prior to randomisation	[redacted]	[redacted]	
No post-baseline assessment	[redacted]	[redacted]	
No documented invasive disease	[redacted]	[redacted]	
p-value (2-sided) log-rank, stratified[a]	[redacted]		
HR (95% CI)	[redacted]		
IDFS rate, % (95% CI)[b]			
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]

Footnotes: [a] Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [b] 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation; [c] Treatment Effect/Difference/p-values are computed based on comparator ET.
Abbreviations: CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; DRFS: distant relapse-free survival; N: number of patients in the Cohort 1 population.

First ET: tamoxifen

Table 22: Summary of investigator-assessed IDFS Cohort 1 Population (AFU1 analysis): postmenopausal and tamoxifen received as first ET

	Abemaciclib + ET (N=[redacted])	ET alone (N=[redacted])	Treatment Effect/Difference 2-sided p-Value (nominal)[c]
Number of events, n (%)	[redacted]	[redacted]	-
Deaths without invasive disease	[redacted]	[redacted]	
Invasive disease	[redacted]	[redacted]	
Number of patients censored, n (%)	[redacted]	[redacted]	
Invasive disease prior to randomisation	[redacted]	[redacted]	
No post-baseline assessment	[redacted]	[redacted]	
No documented invasive disease	[redacted]	[redacted]	
p-value (2-sided) log-rank, stratified[a]	[redacted]		
HR (95% CI)	[redacted]		
IDFS rate, % (95% CI)[b]			
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]

Footnotes: [a] Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [b] 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation; [c] Treatment Effect/Difference/p-values are computed based on comparator ET.
Abbreviations: CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; DRFS: distant relapse-free survival; N: number of patients in the Cohort 1 population.

Table 23: Summary of investigator-assessed IDFS Cohort 1 Population (AFU1 analysis): premenopausal and tamoxifen received as first ET

	Abemaciclib + ET (N=[redacted])	ET alone (N=[redacted])	Treatment Effect/Difference 2-sided p-Value (nominal)[c]
Number of events, n (%)	[redacted]	[redacted]	-
Invasive disease	[redacted]	[redacted]	
Number of patients censored, n (%)	[redacted]	[redacted]	
No post-baseline assessment	[redacted]	[redacted]	
No documented invasive disease	[redacted]	[redacted]	

p-value (2-sided) log-rank, stratified[a]	[redacted]		
HR (95% CI)	[redacted]		
IDFS rate, % (95% CI)[b]			
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]

Footnotes: [a] Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [b] 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation; [c] Treatment Effect/Difference/p-values are computed based on comparator ET.
Abbreviations: CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; IDFS: invasive disease-free survival; N: number of patients in the Cohort 1 population.

Subgroup analyses for DRFS – Cohort 1

First ET: aromatase inhibitor

Table 24: Summary of investigator-assessed DRFS Cohort 1 Population (AFU1 analysis): postmenopausal and aromatase inhibitor received as first ET

	Abemaciclib + ET (N=[redacted])	ET alone (N=[redacted])	Treatment Effect/Difference 2-sided p-Value (nominal)[c]
Number of events, n (%)	[redacted]	[redacted]	
Deaths without distant relapse	[redacted]	[redacted]	
Distant relapse	[redacted]	[redacted]	
Number of patients censored, n (%)	[redacted]	[redacted]	-
Distant relapse prior to randomisation	[redacted]	[redacted]	
No post-baseline assessment	[redacted]	[redacted]	
No documented distant relapse with regular assessment	[redacted]	[redacted]	
p-value (2-sided) log-rank, stratified[a]	[redacted]		
HR (95% CI)	[redacted]		
DRFS survival time survival rate, % (95% CI)[b]			
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]

Footnotes: [a] Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [b] 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation; [c] Treatment Effect/Difference/p-values are computed based on comparator ET.
Abbreviations: CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; DRFS: distant relapse-free survival; N: number of patients in the Cohort 1 population.

Table 25: Summary of investigator-assessed DRFS Cohort 1 Population (AFU1 analysis): premenopausal and aromatase inhibitor received as first ET

	Abemaciclib + ET (N=[redacted])	ET alone (N=[redacted])	Treatment Effect/Difference 2-sided p-Value (nominal)[c]
Number of events, n (%)	[redacted]	[redacted]	-
Deaths without distant relapse	[redacted]	[redacted]	
Distant relapse	[redacted]	[redacted]	
Number of patients censored, n (%)	[redacted]	[redacted]	
Distant relapse prior to randomisation	[redacted]	[redacted]	
No post-baseline assessment	[redacted]	[redacted]	
No documented distant relapse with regular assessment	[redacted]	[redacted]	
p-value (2-sided) log-rank, stratified[a]	[redacted]		
HR (95% CI)	[redacted]		
DRFS survival time survival rate, % (95% CI)[b]			
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]

Footnotes: [a] Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [b] 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation; [c] Treatment Effect/Difference/p-values are computed based on comparator ET.
Abbreviations: CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; DRFS: distant relapse-free survival; N: number of patients in the Cohort 1 population.

First ET: tamoxifen

Table 26: Summary of investigator-assessed DRFS Cohort 1 Population (AFU1 analysis): postmenopausal and tamoxifen received as first ET

	Abemaciclib + ET (N=[redacted])	ET alone (N=[redacted])	Treatment Effect/Difference 2-sided p-Value (nominal)[c]
Number of events, n (%)	[redacted]	[redacted]	-

Deaths without distant relapse	[redacted]	[redacted]	
Distant relapse	[redacted]	[redacted]	
Number of patients censored, n (%)	[redacted]	[redacted]	
Distant relapse prior to randomisation	[redacted]	[redacted]	
No post-baseline assessment	[redacted]	[redacted]	
No documented distant relapse with regular assessment	[redacted]	[redacted]	
p-value (2-sided) log-rank, stratified[a]	[redacted]		
HR (95% CI)	[redacted]		
DRFS survival time survival rate, % (95% CI)[b]			
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]

Footnotes: [a] Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [b] 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation; [c] Treatment Effect/Difference/p-values are computed based on comparator ET.
Abbreviations: CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; DRFS: distant relapse-free survival; N: number of patients in the Cohort 1 population.

Table 27: Summary of investigator-assessed DRFS Cohort 1 Population (AFU1 analysis): premenopausal and tamoxifen received as first ET

	Abemaciclib + ET (N=[redacted])	ET alone (N=[redacted])	Treatment Effect/Difference 2-sided p-Value (nominal)[c]
Number of events, n (%)	[redacted]	[redacted]	
Distant relapse	[redacted]	[redacted]	
Number of patients censored, n (%)	[redacted]	[redacted]	-
No post-baseline assessment	[redacted]	[redacted]	
No documented distant relapse with regular assessment	[redacted]	[redacted]	
p-value (2-sided) log-rank, stratified[a]	[redacted]		
HR (95% CI)	[redacted]		
DRFS survival time survival rate, % (95% CI)[b]			
12 months	[redacted]	[redacted]	[redacted]

24 months	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]

Footnotes: [a] Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [b] 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation; [c] Treatment Effect/Difference/p-values are computed based on comparator ET.
Abbreviations: CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; DRFS: distant relapse-free survival; N: number of patients in the Cohort 1 population.

Appendix F: Baseline characteristics for external ET trials

A summary of the baseline characteristics of monarchE Cohort 1 versus FACE and FATA-GIM3 is presented in Table 28. For FACE and FATA-GIM3, the arms demonstrating baseline characteristics most similar to Cohort 1 of monarchE, and therefore disease with the highest risk of recurrence, were selected for the purposes of this comparison.

Table 28: Baseline characteristics of monarchE Cohort 1 versus FACE and FATA-GIM

	monarchE, Cohort 1 (N=[redacted])	FACE, anastrozole arm (N=2,075)[7]	FATA-GIM3, letrozole arm (N=1,233)[25 a]
Number of positive lymph nodes, %			
0	[redacted]	NR	791 (64)[b]
1	[redacted]	NR	309 (25)[b]
1-3	[redacted]	1,477 (71.2)	133 (11)[b]
4-9	[redacted]	598 (28.8)	
≥10	[redacted]	NR	
Missing	[redacted]	NR	NR
Primary tumour size prior to systemic therapy, %			
≤20 mm, T0 or T1	[redacted]	945 (45.5)	867 (70)
>20 mm but ≤50 mm, T2	[redacted]	926 (44.6)	291 (24)
>50 mm, T3	[redacted]	196 (9.4)	34 (3)
Missing	[redacted]	NR	41 (3)

Footnotes: a FATA-GIM included patients who received either 5 years of aromatase inhibitor, or 2 years of tamoxifen followed by 5 years of aromatase inhibitor. b Number of axillary lymph nodes in FATA-GIM was assessed using pathological nodal status, whereby pN0 equates to 0 positive ALN, pN1 equates to 1–3 positive ALNs and pN2 equates to 4–9 positive ALNs and pN3 equates to ≥10 positive ALNs.
Abbreviations: NR: not reported.
Source: De Placido *et al*. (2018),[25] Smith *et al*. (2017)[7]

References

1. European Medicines Agency (EMA). Summary of opinion (post authorisation). Verzenios, abemaciclib. Available at: https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-opinion-verzenios-ii-13_en.pdf [Accessed: 25 February 2022].
2. National Institute for Health and Care Excellence (NICE). Early and locally advanced breast cancer: diagnosis and management [NG101]. Available at: https://www.nice.org.uk/guidance/ng101 [Accessed: 08 December 2021]. 2018.
3. S. Paluch-Shimon HL, J. Beith, E. Tokunaga, J. Reyes Contreras, R.O. de Sant'Ana, T. Forrester, R. McNaughton, J. Wei, N. Harbeck. 153P - Adjuvant endocrine therapy combined with abemaciclib in monarchE patients with high-risk early breast cancer: Disease characteristics and endocrine therapy choice by menopausal status. Annals of Oncology (2021) 32 (supplementary 5): S407-S446.
4. National Institute for Health and Care Excellence. Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer [Technology appraisal guidance TA632], 2020.
5. National Institute of Health and Care Excellence (NICE). Neratinib for extended adjuvant treatment of hormone receptor-positive, HER2- positive early stage breast cancer after adjuvant trastuzumab [TA612]. Available at: https://www.nice.org.uk/guidance/TA612. [Accessed: 09 February 2021]. 2019.
6. Cardoso F, Kyriakides S, Ohno S, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2019;30:1674.
7. Smith I, Yardley D, Burris H, et al. Comparative Efficacy and Safety of Adjuvant Letrozole Versus Anastrozole in Postmenopausal Patients With Hormone Receptor-Positive, Node-Positive Early Breast Cancer: Final Results of the Randomized Phase III Femara Versus Anastrozole Clinical Evaluation (FACE) Trial. J Clin Oncol 2017;35:1041-1048.
8. Goss PE, Ingle JN, Pritchard KI, et al. Exemestane versus anastrozole in postmenopausal women with early breast cancer: NCIC CTG MA.27--a randomized controlled phase III trial. J Clin Oncol 2013;31:1398-404.
9. Toremifene and tamoxifen are equally effective for early-stage breast cancer: first results of International Breast Cancer Study Group Trials 12-93 and 14-93. Annals of Oncology 2004;15:1749-1759.
10. Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. The Lancet 2007;369:1711-1723.
11. National Institute of Health and Care Excellence (NICE). Abemaciclib with an aromatase inhibitor for untreated advanced hormone-receptor positive, HER2-negative breast cancer ID1227 [TA563]. Available at: https://www.nice.org.uk/guidance/TA563 [Accessed: 05 February 2021].
12. National Institute for Health and Care Excellence (NICE). Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy [TA725]. Available at: https://www.nice.org.uk/guidance/TA725 [last accessed 01 March 2021].
13. National Institute for Health and Care Excellence (NICE). Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer. Technology appraisal guidance [TA107]. Available at: https://www.nice.org.uk/Guidance/TA107. [Accessed: 03 February 2021]. 2006.
14. National Institute for Health and Care Excellence. Pertuzumab for adjuvant treatment of HER2-positive early stage breast cancer [Technology appraisal guidance TA569], 2019.
15. NICE. Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer [TA424]. Published date: 21 December 2016. Available at: https://www.nice.org.uk/guidance/ta424/resources/pertuzumab-for-the-neoadjuvant-treatment-of-her2positive-breast-cancer-pdf-82604663691973. [Accessed 03 December 2021].
16. National Institute of Health and Care Excellence (NICE). Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer [TA632]. Available at: https://www.nice.org.uk/guidance/ta632/resources/trastuzumab-emtansine-for-adjuvant-treatment-of-her2positive-early-breast-cancer-pdf-82609074363589. [Accessed: 17 March 2021].
17. Hamilton SN, Tyldesley S, Li D, et al. Second malignancies after adjuvant radiation therapy for early stage breast cancer: is there increased risk with addition of regional radiation to local radiation? International Journal of Radiation Oncology* Biology* Physics 2015;91:977-985.
18. Woods BS, Sideris E, Palmer S, et al. Partitioned Survival and State Transition Models for Healthcare Decision Making in Oncology: Where Are We Now? Value in Health 2020;23:1613-1621.
19. Latimer NR. NICE DSU Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. Available at: http://nicedsu.org.uk/wp-content/uploads/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf [Accessed 18 August 2021]. 2013.
20. Burnham KP, Anderson DR. Multimodel Inference:Understanding AIC and BIC in Model Selection. Sociological Methods & Research 2004;33:261-304.
21. Raftery AE. Bayesian Model Selection in Social Research. Sociological Methodology 1995;25:111-163.

22. Francis PA, Regan MM, Fleming GF, et al. Adjuvant ovarian suppression in premenopausal breast cancer. N Engl J Med 2015;372:436-46.
23. Perrone F, De Laurentiis M, De Placido S, et al. Adjuvant zoledronic acid and letrozole plus ovarian function suppression in premenopausal breast cancer: HOBOE phase 3 randomised trial. Eur J Cancer 2019;118:178-186.
24. Pagani O, Regan MM, Walley BA, et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. N Engl J Med 2014;371:107-18.
25. De Placido S, Gallo C, De Laurentiis M, et al. Adjuvant anastrozole versus exemestane versus letrozole, upfront or after 2 years of tamoxifen, in endocrine-sensitive breast cancer (FATA-GIM3): a randomised, phase 3 trial. The Lancet Oncology 2018;19:474-485.
26. Lilly Data on File. Clinical Study Report [monarchE]. 2020.
27. Cuzick J, Sestak I, Baum M, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. The Lancet Oncology. 2010;11(12):1135-1141. doi:10.1016/S1470-2045(10)70257-6.
28. Colleoni M, Sun Z, Price KN, et al. Annual Hazard Rates of Recurrence for Breast Cancer During 24 Years of Follow-Up: Results From the International Breast Cancer Study Group Trials I to V. J Clin Oncol 2016;34:927-35.
29. NICE. Pertuzumab for adjuvant treatment of HER2- positive early stage breast cancer. [TA569]. Available at https://www.nice.org.uk/guidance/TA569. [Last accessed 09 February 2021]. 2019.

in collaboration with:

Newcastle University

Abemaciclib in combination with endocrine therapy for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer [ID3857]

Critique of company Technical Engagement Response

Produced by Kleijnen Systematic Reviews (KSR) Ltd, in collaboration with Newcastle University

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Contributions of authors

Nigel Armstrong acted as project lead, health economist and systematic reviewer on this assessment, critiqued the clinical effectiveness and cost effectiveness methods and evidence and contributed to the writing of the report. Luke Vale acted as health economic project lead, critiqued the company's economic evaluation, and contributed to the writing of the report. Diarmuid Coughlan, Giovany Orozco, Tomos Robinson, and Charlotte Ahmadu acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Susan O'Meara and Kevin McDermott acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence, and contributed to the writing of the report. Steven Duffy critiqued the search methods in the submission and contributed to the writing of the report. Jos Kleijnen 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
AE	Adverse events
AI	Aromatase inhibitor
AIC	Akaike Information Criterion
ALT	Alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
BCS	Base-case scenario
BI	Budget impact
BIC	Bayesian information criterion
BMI	Body mass index
BNF	British National Formulary
CADTH	Canadian Agency for Drugs and Technologies in Health
CCTR	Cochrane Central Register of Controlled Clinical Trials
CDK	Cyclin-dependent kinase
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CEM	Company economic model
CHMP	Committee for Medicinal Products for Human Use
CfB	Change from baseline
CI	Confidence interval
CNS	Central nervous system
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
CT	Computerised tomography
CTR	Clinical trial results
DCIS	Ductal carcinoma in situ
DFS	Disease-free survival
DRFS	Distant relapse free survival
DSU	Decision Support Unit
eBC	Early breast cancer
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
eMIT	Electronic market information tool
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-5L	EuroQol-5 Dimensions-5 Levels
ER	Oestrogen receptor
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
ET	Endocrine therapy
EUR	Erasmus University Rotterdam
EVE	Everolimus
EXE	Exemestane
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue
FACT-B	Functional Assessment of Cancer Therapy – Breast
FACT-ES	Functional Assessment of Cancer Therapy-Endocrine Symptoms
FAS	Full analysis set
FAD	Final appraisal document

FDA	Food and Drug Administration
FE	Fixing errors
FV	Fixing violations
FUL	Fulvestrant
GHS	Global health status
GnRH	Gonadotropin-releasing hormone
HAS	Haute Autorité de santé
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health technology assessment
IC	Indirect comparison
ICD	International Statistical Classification of Diseases and Related Health Problems
ICER	Incremental cost effectiveness ratio
IDFS	Invasive disease-free survival
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITC	Indirect treatment comparison
ITT	Intention to treat
IU	International units
IV	Intravenous
IWRS	Interactive web-based randomisation scheme
KM	Kaplan-Meier curves
KSR	Kleijnen Systematic Reviews
LHRH	Luteinising hormone-releasing hormone
LILACS	Latin American and Caribbean Health Sciences Literature
LRRFS	Locoregional recurrence-free survival
LYs	Life years
LYG	Life years gained
M2	Monarch2 trial
M3	Monarch3 trial
MAIC	Match-adjusted indirect comparison
MBC	Metastatic breast cancer
MeSH	Medical subject headings
MHRA	Medicines and Healthcare Products Regulatory Agency
MJ	Matters of judgement
MMRM	Mixed effect Model Repeat Measurement
MOS SF-36	Medical Outcomes Study Short Form Survey
MR	Metastatic recurrence
MTA	Multiple technology appraisal
MTC	Mixed treatment comparison
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NCRI	National Cancer Research Institute
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Network meta-analysis
NMR	Non-metastatic recurrence
NR	Not reported
OFS	Ovarian function suppression
OS	Overall survival
PAS	Patient access scheme
PBAC	The Pharmaceutical Benefits Advisory Committee
PD	Pharmacodynamics

PFS	Progression-free survival
PH	Proportional hazards
PK	Pharmacokinetics
PR	Progesterone receptor
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q3W	Every three weeks
QALY	Quality adjusted life year
QLQ-BR23	Breast Cancer-Specific Quality of Life Questionnaire
QLQ-C30	Quality of Life Questionnaire
QoL	Quality of life
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RR	Relative risk; Risk ratio
SABCS	San Antonio Breast Cancer Symposium
SAE	Serious adverse events
SC	Subcutaneous
ScHARR	School of Health and Related Research
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SoC	Standard of care
STA	Single technology appraisal
STEEP	Standardised definitions for efficacy endpoints
TA	Technology assessment
TEAE	Treatment emergent adverse events
TMX	Tamoxifen
TSD	Technical support document
TTO	Time trade-off
TTD	Time to treatment discontinuation
UK	United Kingdom
UMC	University Medical Centre
USA	United States of America
VTE	Venous thromboembolism
WHO	World Health Organization
WTP	Willingness-to-pay

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Key issue 1: Potential lack of generalisability of the evidence to NHS clinical practice given ambiguity in the definition of high risk

The company has now confirmed that abemaciclib has received a positive CHMP opinion for use in the early breast cancer indication, based on the Cohort 1 population from the monarchE trial i.e. adjuvant treatment of adult patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative, node positive early breast cancer at high risk of recurrence. In pre- or perimenopausal women, aromatase inhibitor endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist. MHRA approval is anticipated to be received in [redacted].

The company have also provided for Cohort 1 baseline characteristics and efficacy analyses (invasive disease-free survival (IDFS), distant relapse-free survival (DRFS) and overall survival (OS)) in Appendices B and C respectively. In addition, the company provided a comparison between Scottish real-world evidence (RWE) (data from 2005) and Cohort 1 baseline characteristics.

ERG comment: The ERG has presumed that the 'D' in DRFS was accidentally represented by the company as 'Disease'. Given that most of the ITT population were in Cohort 1 (91% calculated by the ERG), it is not surprising that there are generally no substantial differences between either the baseline characteristics or the outcomes between these two populations. It does appear that the severity of the condition, as indicated by percentage of patients in the more severe categories of number of positive lymph nodes, histopathological diagnosis grade, disease stage, is slightly greater for Cohort 1.

In comparison to the RWE, Cohort 1 has fewer older (at least 65) patients, patients with large primary tumours (≥50 mm) and with unfavourable histopathological grade (G3), but more patients with many lymph nodes (4-9 and ≥10). It is difficult to say how these differences will translate into differences in risk of recurrence and thus outcome and treatment effect on outcome. It is also the case that the RWE might be outdated given that it is over 15 years old.

In conclusion, there is still a potential lack of generalisability of the evidence to NHS clinical practice given lack the ambiguity in the definition of high risk of recurrence and lack of recent evidence of the characteristics of NHS patients.

Key issue 2: Lack of recognition that comparators depend on menopausal status leading to bias in effectiveness

The company argue that menopausal status should not be considered when appraising abemaciclib and on this basis have refused to perform cost-effectiveness analyses separately for pre- and post-menopausal subgroups. The basis for this argument is lack of statistically significant difference by subgroup, uncertainty due to lower patient numbers per subgroup, and the variation in the definition of menopause i.e. at diagnosis or following ovarian suppression (functionally postmenopausal). The company also refused to present OS data by menopausal status on the grounds of lack of maturity.

ERG comment: Although there is overlap in the 95% confidence intervals (CIs) for the hazard ratios for IDFS and DRFS and no evidence of a statistically significant difference between the two group, the point estimate for premenopausal is clearly lower than for postmenopausal group. The ERG would argue that drawing a conclusion that there is no difference because there is no statistically significant difference is incorrect. Furthermore, it does not matter at all that there is CI overlap between subgroups given that the appropriate form of cost-effectiveness analysis is one where a set of estimates for only one subgroup would be used as source of effectiveness and any difference, however uncertain, has the potential to lead to a difference in whether abemaciclib is judged cost-effective versus the comparator

appropriate to the subgroup. Also, the fact that some patients become functionally menopausal highlights the difference in care pathway and thus the comparator between those who are pre- or post-menopausal at diagnosis.

Key issue 3: Lack of generalisability of monarchE to clinical practice in terms of endocrine therapy type

The company argue that the prescription of aromatase inhibitors (AIs) instead of tamoxifen is not contrary to the NICE guideline NG101 because many premenopausal women become functionally postmenopausal due to ovarian suppression, as well as some being contraindicated for tamoxifen. The company also present evidence from a UK based RWE study of percentage use of AI vs. tamoxifen, which was [redacted] vs. [redacted] compared to approximately [redacted] vs. [redacted] for Cohort 1.

The company also presented IDFS and DRFS results by menopausal status and whether received an AI or tamoxifen.

ERG comment: It would make sense that the percentage receiving an AI in those who are premenopausal at diagnosis would be greater than zero if they subsequently become functionally postmenopausal because of ovarian suppression, which would be due to a GnRH Analogues. However, the percentage who receive GnRH Analogues is no more than about [redacted], whereas the percentage who receive an AI in the premenopausal group is 41% and no information is provided about whether patients in the trial were contraindicated or not. Also, the RWE is limited in that there is no information on menopausal status.

The ERG notes that abemaciclib performs a little better vs. endocrine therapy (ET) for both IDFS and DRFS in those treated with tamoxifen than with an AI, although there is overlap in the 95% CIs for the HRs and it is unclear from the evidence presented whether there is evidence of a difference or not.

Given the lack of NHS clinical practice evidence and the apparent difference in effectiveness between tamoxifen and AIs, the issue of potential lack of generalisability of the trial remains.

Key issue 4: Lack of clarity around the model structure when aspects of partitioned survival model are used for transition probabilities

The company provides a detailed overview of the transition probabilities used in the economic model to argue that the model structure cannot be categorised exclusively as a partitioned survival model (PSM), and instead it should be described as a Markov or state transition model (STM). Subsequently the company highlights the following 3 reasons that differentiate the model from a PSM: i) The use of transition probabilities between all health states; ii) the structural relationship between the non-metastatic recurrence and metastatic recurrence health states; and iii) having OS dependent on metastatic recurrence (an intermediate endpoint) and OS without distant recurrence.

ERG comment: The ERG agrees with the company's assertion that the model cannot be categorised exclusively as a PSM. However, it remains relevant to the ERG to highlight that important assumptions within the model follow a PSM structure, including the transitions between IDFS, non-metastatic recurrence and remission to a death (without distant recurrence) state. These all depend on the same OS without distant recurrence curve. Similarly, the transition between IDFS and any of the recurrence states depends on the shape of the IDFS curve. Acknowledging the arguments raised by the company and following the literature, the ERG suggests that this model structure can be best described as a hybrid or semi-Markov model.[1, 2]

Key issue 5: Lack of recognition that comparators depend on menopausal status leading to bias in cost effectiveness

The Company refers back to the response to Key issue 2 that it would be inappropriate and highly uncertain to consider premenopausal and post-menopausal patients in two separate economic analyses. The company reiterates that there is no statistically significant difference between outcomes, and while there is a difference in costs between both groups this is not expected to have an overt impact on cost-effectiveness.

ERG comment: While the company report there is evidence of no statistically significant difference between the subgroups the ERG argues that it would be incorrect to interpret this as evidence of no difference. The ERG would like to see a cost-utility analysis comparing Abemaciclib + Tamoxifen vs. Tamoxifen alone for premenopausal women & men and Abemaciclib + AIs vs AIs alone for postmenopausal women.

Key issue 6: Medication adherence not modelled

The ERG requested that the company model the impact of non-adherence to adjuvant ET. The company elected not to do this as it believes it would not be appropriate to do so. The effect of non-adherence to adjuvant ET, the company argues, is implicitly captured in the efficacy data and extrapolations from the MonarchE trial, which the company expects to be reflective of the real world. Furthermore, it is argued that the pattern of non-adherence observed in monarchE trial would be representative of that seen in practice.

ERG comment: The acknowledges the response by the company. The ERG notes that a judgement is needed as to the applicability of monarchE adherence data to UK practice. This is judgement is made difficult as alternative data on adherence from a UK source is not presented.

Key issue 7: Potential bias from selection of survival curves for treatment and comparators, and lack of alternative scenarios

The company provides an overview of the process used for selecting the extrapolation of IDFS in the original CS, particularly for their choice of a log-logistic model rather than any of the alternatives. In terms of statistical fit alone, the log-logistic extrapolation provided the best statistical fit to the data; however, when compared with the external sources originally referenced in the CS, all models used potentially underpredict IDFS at 5 years, including the log-logistic extrapolation.

The biggest limitations of the comparisons with external data were the differences in population and endpoints used by the external trials. The company stated that these studies used a different definition of IDFS and had populations with less severe disease. To address this limitation, the company provided data from its own [redacted], with a population inclusion criterion [redacted]. The RWE provided estimates of IDFS at 5 years ([redacted]) closer to those generated by extrapolating MonarchE data (i.e. [redacted] to [redacted] with the log-logistic and log-normal extrapolation). At 10-years, results from the [redacted] showed larger differences relative to extrapolation from MonarchE with an IDFS rate of [redacted] compared to [redacted] and [redacted] for the log-logistic and log-normal extrapolations respectively.

The company has argued that its choice of log-logistic model is the more appropriate method of extrapolation compared with the log-normal model considering both statistical fit (as it provided the second best fit to the MonarchE data in terms of AIC and BIC, second to the Weibull model) and comparisons with the RWE.

ERG comment: The ERG agrees that the log-logistic extrapolation had a statistically better fit that than a lognormal extrapolation for IDFS, and indeed the ERG base-case used a log-logistic IDFS extrapolation. The log-normal extrapolation was selected as an alternative scenario. As acknowledged by the company in the TE, all the extrapolations are based on immature data, hence, focusing on statistical fit alone may lead to overfitting issues. This means that external validation is also a crucial factor in selecting the best extrapolation.

As stated by the company, comparisons between the extrapolations and estimates from the literature suggested a possible underprediction of IDFS by all the models extrapolated from MonarchE data; however, differences between the trials reported in the literature and MonarchE made these comparisons difficult. The data from the [redacted] conducted by the company seem to confirm some of these concerns. As shown by Table 1 in the TE document comparing patient characteristics, [redacted] of patients in the [redacted] have a G3 'unfavourable' histopathological diagnosis grade relative to [redacted] of patients in Cohort 1 of the MonarchE trial. Despite having this relatively lower degree of severity, the log-logistic extrapolation continues to predict a lower IDFS rates at 5 and 10 years.

The ERG acknowledges that the log-normal extrapolation offers a comparatively worse level of statistical fit. It was for this reason that it was not chosen in the ERG's base-case analysis. Nevertheless, it still provides IDFS rate predictions closer to the [redacted] Indeed it is the only extrapolation that gives an overprediction. In light of this, the ERG believes that the extrapolation of long-term IDFS is still a substantial source of uncertainty where the company base-case presents a slightly pessimistic scenario for the duration of IDFS. The ERG sensitivity analysis illustrates the impact on the ICER of an alternative assumption (the more optimistic scenario, a log-normal extrapolations, increase the ICER).

Key issue 8: Discrepancy between overall survival in model and real-world evidence

The company provided further clarity on the distinction between overall survival (OS) and OS without distant recurrence, the latter being an endpoint of importance in the economic model. The company argues that, as they are different endpoints its inappropriate to compare them or use them interchangeably.

ERG comment: the ERG appreciates that further clarity is provided on the distinction between OS rates for this population and OS rates without distant recurrence. However, a concern remains about the difficulty in comparing both parameters, which makes it harder to validate the model predictions (of OS without distant recurrence) with external data.

Within the model, the hazard rates of OS without distant recurrence are extrapolated using MonarchE trial data and are capped by the hazard rates from the UK general population using life tables.[3] However, since the trial data is immature, the extrapolation of OS without distant recurrence starts using hazard rates from the general population. In short, after a few cycles have occurred the model assumes that the OS without distant recurrence at IDFS, non-metastatic recurrence and remission stage are equivalent to the general population survival. The ERG considers that more clarity around the use and implications of UK life tables within the model could have been provided by the company initially.

Key issue 9: Lack of long-term evidence for assumed 'carryover benefit' and justification for treatment waning trajectory

The company argues against the ERG base-case assumption of a full treatment effect stopping at year 3 and treatment waning down to year 8. The company refers back to the original submission showing a

decrease in the HR for Abemaciclib at year 2+ in the ITT population; although this analysis is not replicated for Cohort 1 as this comprises 91% of the ITT population. Therefore, the company maintains its position of a full treatment effect of 8 years based on results from the ATAC trial. The company presents a smoothed hazards plot of IDFS for Cohort 1, which suggest a widening gap in hazard rates between months 24-36.

For the long-term waning assumption, the company also maintains its base-case assumption of a waning duration from year 8 to year 27, which is the point where IDFS hazard rates equal background mortality. Using data from Colleoni et al. (2016) which shows that the highest risk of recurrence from early breast cancer occurs in the first 5 years following initiation of adjuvant therapy, the company argues that a shorter waning period between year 3 and year 8 causes the hazard rate in the Abemaciclib arm to peak at year 8, while the hazard rate for the ET arm peaks at year 4.[4]

Furthermore, the company argues this assumption causes the hazard rate of the Abemaciclib arm to increase while the hazard rate of ET alone is decreasing, particularly at a time where according to the Colleoni et al. (2016) study the hazard rate of recurrence should be steadily decreasing.[4] The company argues that a waning assumption from year 8 to year 27 generates a hazard rate pattern more aligned with Colleoni et al. (2016).[4]

ERG comment: The ERG recognises that the widening in the hazard rates of IDFS between the arms of the trial at year 2+ is a promising result which could suggest a treatment effect duration beyond the current follow up. However, as a consequence of the uncertainty in the duration of the full treatment effect and the lack of data beyond the current follow up point, the ERG sticks to its base-case while acknowledging that this is a conservative scenario. Further scenarios varying full treatment duration were explored in the ERG analysis.

For the long-term waning assumption, the ERG stills considers that a waning duration defined by the timepoint where the hazard rate of IDFS and OS are equivalent, which was originally used in TA612 in the context of an advanced stage disease where the OS hazard rate was high, is extremely optimistic in this context. The ERG considers that a less optimistic waning duration assumption still needs to be explored.

The ERG does not consider an increase in the hazard rate of IDFS to be clinically implausible from a waning effect of abemaciclib, as the IDFS hazard rate for the abemaciclib arm never increases above IDFS rate for the comparator ET alone.

Comparisons with Colleoni et al. (2016) should be taken with caution given the differences in population and output definitions (DFS vs IDFS).[4] Although this renders the comparison of trends in hazard rates between the abemaciclib arm in the model and the Colleoni et al. (2016) study difficult due to differences in the interventions, the results in the Colleoni et al. (2016) show a substantial decrease in recurrence risks after 10 years after adjuvant therapy, while the recurrence risk in the extrapolated ET arm remains high.[4] This ties with Key issue 7 where the ERG is concerned that the model presents a pessimistic prediction of IDFS.

Key issue 10: Same utility values applied to both

The company provides a pooled IDFS health state utility value for Cohort 1 of MonarchE ([redacted]) under the argument that there are no differences in this value across the treatment arms.

ERG comment: The ERG is still concerned that this is the approach taken by the company, as the specific utility values are not reported; neither are the standard deviations which makes it impossible to assess any differences in uncertainty across both arms. Nevertheless, given further data presented in the clarification response it is expected that difference in utility by arm for Cohort 1 would be small and may favour the abemaciclib arm.[5]

Key issue 11: Insufficient clarity in the probability of moving to non-metastatic and metastatic health states

The company provided further details on all the probabilities included in the model in their response to Key issue 4, including the transitions to non-metastatic and metastatic recurrence states. Furthermore, the company adopted the approach suggested in the ERG base-case to have the effect of Abemaciclib on non-metastatic recurrences wane following the treatment effect waning assumption on IDFS.

ERG comment: The ERG considers this issue to be appropriately addressed.

Key issue 12: Insufficient clarity of reporting of the cost effectiveness scenario results

The company has expanded the scenario analysis by adding the impact on results from choosing a log-normal IDFS extrapolation and from varying the waning effect duration.

ERG comment: The ERG appreciates the acknowledgement that both the duration of treatment effect waning and the functions chosen to extrapolate IDFS are included in the scenario as potential sources of uncertainty. However, one important factor of uncertainty which the ERG considers has been left out is the proportion of patients receiving CDK 4/6 inhibitors at the metastasis stage, particularly for ET sensitive recurrences in the Abemaciclib arm. Results from previous analyses has consistently shown that increasing this proportion from 0% at the base-case can have a significant impact on the ICER.

Key issue 13: Lack of detail in the model validation process in terms of verification of the formulae, functions, and coding.

The company acknowledged and implemented corrections to Coding errors 1-4 from the ERG report; furthermore, the company submitted additional details for the internal validation process used in the economic model. Furthermore, the company also provided and updated version of the model that solved an error when running a PSA on Cohort 1 and annexed the results from the changes made to the company base-case.

ERG comment: The ERG accepts the additional model validation documentation as evidence of internal validation. The ERG would also recommend the use of checklists like TECH-VER and AdViSHE to improve the internal validation process.[6, 7]

Results presented by the company from the updated base-case were successfully replicated by the ERG.

1. REFERENCES

[1] Woods B, Sideris E, Palmer S, Latimer N, Soares M. *NICE DSU technical support document 19: partitioned survival analysis for decision modelling in health care: a critical review [Internet]*. Sheffield: NICE Decision Support Unit, 2017 [accessed 22.12.21] Available from: http://www.nicedsu.org.uk

[2] Woods BS, Sideris E, Palmer S, Latimer N, Soares M. Partitioned survival and state transition models for healthcare decision making in oncology: where are we now? *Value Health* 2020;23(12):1613-21.

[3] Office for National Statistics. *National life tables: UK. Life expectancy in the UK, 2018 to 2020 [Internet]*. London: Office for National Statistics, 2021 [accessed 18.3.22] Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables

[4] Colleoni M, Luo W, Karlsson P, Chirgwin J, Aebi S, Jerusalem G, et al. Extended adjuvant intermittent letrozole versus continuous letrozole in postmenopausal women with breast cancer (SOLE): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2018;19(1):127-38.

[5] Eli Lilly and Company Limited. *Abemaciclib in combination with endocrine therapy for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer [ID3857]. Clarification questions*: Eli Lilly and Company Limited, 2021

[6] Buyukkaramikli NC, Rutten-van Molken M, Severens H, Al M. TECH-VER: a verification checklist to reduce errors in models and improve their credibility. *Pharmacoeconomics* 2019;37(11):1391-408.

[7] Vemer P, Corro Ramos I, Voorn GAK, Al M, Feenstra T. AdViSHE: a validation-assessment tool of health-economic models for decision makers and model users. *Pharmacoeconomics* 2016;34(4):349-61.