Medicinrådet

Bilag til Medicinrådets anbefaling vedr. abemaciclib i kombination med endokrin behandling som adjuverende behandling af tidlig ER+/HER2-neg brystkræft

Patienter med lymfeknudepositiv sygdom og høj risiko for recidiv

Vers. 2.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. adjuverende abemaciclib til ER+/HER2- brystkræft
2. Forhandlingsnotat fra Amgros vedr. adjuverende abemaciclib til ER+/HER2-brystkræft
3. Ansøgers endelige ansøgning vedr. adjuverende abemaciclib til ER+/HER2-brystkræft

Eli Lilly Danmark A/S
Lyskær 3E, 2. tv
DK-2730 Herlev
Tlf. (+45) 4526 6000
CVR-nr. 51 61 98 11

Den 31. januar 2025

Til: Medicinrådet
Dampfærgevej 21-23, 3. sal.
2100 København Ø

Lilly Danmark A/S (Lilly) har læst udkastet til rapporten vedr. abemaciclib til adjuverende behandling af tidlig østrogenreceptor-positiv (ER+)/human epidermal vækstfaktorreceptor 2-negativ (HER2-neg) brystkræft hos patienter, som har høj risiko for tilbagefald og takker for muligheden for at give kommentarer.

Vi ser det som positivt, at fagudvalget anderkender at endepunkerne er relevante i relation til adjuverende onkologisk behandling. Fagudvalget betragter IDFS som indikator for om den undersøgte behandling reducerer risikoen for invasivt tilbagefald. Særligt positivt ser vi det at fagudvalget betragter DRFS informativt til belysning af, hvor stor en andel af de observerede hændelser er kurable og dermed om sygdommen er helbredelig eller ej.

Vi er enige i fagudvalgets betragtning af, at der potentielt er forskel i effektiviteten af CDK4/6-hæmmere. Vi ser derudover forskelle som kan være relevante, herunder til eksempel at abemaciclib til adjuverende behandling gives i en behandlingslængde af 2 år. Der er god klinisk erfaring med håndtering af bivirkninger ved behandling med abemaciclib også til metastatisk bryskræft, de er behandlelige, reversible og man har mulighed for to gange dosisjustering i et behandlingsforløb uden at effekten af adjuverende behandling med abemaciclib kompromitteres [1].

Vi anerkender at det med den nuværende kliniske erfaring samt evidens vedrørende ET behandling fra kliniske studier i adjuverende setting vurderes klinisk plausibelt, at forskellen mellem behandlingsarmenene kan øges yderligere med tiden. Med den lange observationstid i MonarchE har vi set en fortsat øget forskel mellem behandlingsarmene ved 3 til 5 års opfølgning.

Lilly anser abemaciclib til patienter med tidlig brystkræft og høj risiko for tilbagefald, som defineret i MonarchE´s inklusionskriterier, som en vigtig behandlingsmulighed, der i lighed med de øvrige nordiske lande bør tilbydes den pågældende patientgruppe.

Vi takker sekretariatet for et godt samarbejde omkring denne re-evaluering.

Med venlig hilsen

Anders Troelsgaard Buchholt
Market Access Manager Denmark
Eli Lilly Danmark A/S

[1] M. P. Goetz, I. Cicin, L. Testa, S. M. Tolaney, J. Huober, V. Guarneri, S. R. Johnston, M. Martin, P. Rastogi, N. Harbeck, A. Shahir, R. Wei, V. André, H. Rugo and J. O'Shaughnessy, "Impact of dose reductions on adjuvant abemaciclib efficacy for patients with high-risk early breast cancer: analyses from the monarchE study," *npj Breast Cancer,* 2024.

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

23.01.2025
CAF/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	26.02.2025
Leverandør	Eli Lilly
Lægemiddel	Verzenios (abemaciclib)
Ansøgt indikation	Abemaciclib i kombination med endokrin behandling som adjuverende behandling af tidlig ER+/HER2- brystkræft
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har følgende aftalepris på Verzenios (abemaciclib)

Tabel 1: Aftalepris

Lægemiddel	Styrke (Paknings-størrelse)	AIP (DKK)	Nuværende SAIP, (DKK)	Nuværende rabat ift. AIP
Verzenios	100 mg (28 stk.)	9.199,20	[redacted]	[redacted]
Verzenios	100 mg (56 stk.)	18.076,73	[redacted]	[redacted]
Verzenios	150 mg (28 stk.)	9.199,20	[redacted]	[redacted]

Verzenios	150 mg (56 stk.)	18.076,73	[redacted]	[redacted]
Verzenios	50 mg (28 stk.)	9.199,20	[redacted]	[redacted]

Aftaleforhold

Verzenios er en del af et udbud med de øvrige CDK4/6-hæmmere. Amgros har en aftale med leverandøren, som gælder til den 30.09.2025. Aftalen kan forlænges med yderligere 6 måneder. Der skal publiceres et nyt udbud, når alle igangværende anmodninger er vurderet og behandlingsvejledningen vedr. CDK4/6-hæmmere til ER+/HER2-lokalt fremskreden eller metastatisk brystkræft er opdateret med den nye indikation og godkendt i Medicinrådet.

Konkurrencesituationen

Verzenios er den første CDK4/6-hæmmer, der har fået anbefalet indikationen adjuverende behandling af tidlig ER+/HER2- brystkræft. Kisqali (ribociclib) har anmodet Medicinrådet om vurdering til samme indikation og forventes vurderet i 3. kvartal 2025.

Tabel 2 viser lægemiddeludgifter i relation til andre lægemidler.

Tabel 1: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Verzenios	150 mg (56 stk.)	300 mg (2 x 150 mg) dagligt*	[redacted]	[redacted]
Kisqali	200 mg (63 stk.)	600 mg dagligt i 21 dage med en uges pause i cyklus a 28 dage.	[redacted]	[redacted]

*udregnet på fuld dosis (uden dosisjustering)

Status fra andre lande

Tabel 2: Status fra andre lande

Land	Status	Link
Norge	Anbefalet	Link til vurdering
England	Anbefalet	Link til vurdering
Sverige	Anbefalet	Link til vurdering

Opsummering

[redacted]

Application for the assessment of abemaciclib in combination with endocrine therapy for adjuvant treatment of patients with HR+/HER2-, node-positive early breast cancer at high risk of recurrence

Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
	Confidential information
[Other]	**[Definition of color-code]**

Contact information

Contact information	
Name	**Eli Lilly**
Title	Anders Buchholt
Phone number	Market Access Manager
E-mail	Health economics and negotiation
	+45 20962124
	anders.troelsgaardbuchholt@lilly.com
Name (External representation)	**NA**
Title	
Phone number	
E-mail	

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Tables and Figures

Abbreviations

Abbreviation term	Definition
1L	First-line
aBC	Advanced/metastatic breast cancer
ABE	Abemaciclib
AE	Adverse event
AFT	Accelerated failure time
AIC	Akaike information criterion
BC	Breast cancer

BCS	Breast cancer subscale
BIC	Bayesian information criterion
BID	Twice a day
CDK	Cyclin-dependent kinase
CEAC	Cost-effectiveness acceptability curve
CEAF	Cost-effectiveness acceptability frontier
CEM	Cost-effectiveness model
CSR	Clinical study report
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
DBCG	Danish Breast Cancer Group
DCO	Data cut-off
DFS	Disease-free survival
DMC	Danish Medicine Council
DNA	Deoxyribonucleic acid
DRFS	Distant relapse-free survival
DSA	Deterministic sensitivity analysis
DSU	Decision support unit
eBC	Early Breast Cancer
EMA	European Medicines Agency
ER	Estrogen Receptor
ESMO	Society of Medical Oncology
ET	Endocrine therapy
ETR	Endocrine therapy-resistant
ETS	Endocrine therapy-sensitive
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
HR	High risk
HR+	Hormone receptor
HRa	Hazard ratio
HRQoL	Health-related quality of life
ICUR / ICER	Incremental cost-utility ratio / incremental cost-effectiveness ratio
IDFS	Invasive disease-free survival
IPD	Individual patient data
ITC	indirect treatment comparisons
ITT	Intention to treat
IWRS	interactive, web-based randomisation scheme
KM	Kaplan-Meier
LHRH	Luteinizing hormone–releasing hormone
LY	Life-year
MDTM	Multidisciplinary team meeting
MID	Minimally important difference
MMRM	Mixed effects repeated measures
MR	Metastatic recurrence
NA	Not available or applicable
NE	Not evaluable
NICE	National Institute for Health and Clinical Excellence
NMB	Net monetary benefit
NMR	Non-metastatic recurrence
NR	Not reported
PH	Proportional hazards
PgR	Progesterone receptor
PPP	Pharmacy purchasing price
PRO	Patient-reported outcome

PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life-years
QD	Once a day
Rb	Retinoblastoma
RCT	Randomised controlled trial
RFA	Relapse-free survival
OFS	Ovarian function suppression
OS	Overall survival
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
STEEP	Safe, Timely, Effective, Efficient, Equitable and Patient-centered care
TA	Technology appraisal
TEAE	Treatment-emergent adverse events
TL	Thought leader
TLR	Targeted literature review
TNM	Tumour size, nodal status, and identification of distant metastasis
TTD	Time to treatment discontinuation
VAS	Visual analogue scale
WTP	Willingness to pay

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Verzenios®
Generic name	Abemaciclib
Therapeutic indication as defined by EMA	Abemaciclib in combination with endocrine therapy for adjuvant treatment of patients with hormone receptor (HR+)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive early breast cancer at high risk of recurrence
Marketing authorization holder in Denmark	Eli Lilly Denmark A/S
ATC code	L01EF03
Combination therapy and/or co-medication	Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR+, HER2-, node-positive, high-risk, early breast cancer.
(Expected) Date of EC approval	April 2022
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	Advanced or metastatic breast cancer
Other indications that have been evaluated by the DMC (yes/no)	Yes - advanced or metastatic breast cancer
Dispensing group	BEGR

Overview of the medicine	
Packaging – types, sizes/number of units and concentrations	Verzenios® 50mg, 28 pcs. coated tablets (blister) – Each tablet contains 50mg abemaciclib Verzenios® 100mg, 28 pcs. coated tablets (blister) – Each tablet contains 100mg abemaciclib Verzenios® 100mg, 56 pcs. coated tablets (blister) – Each tablet contains 100mg abemaciclib Verzenios® 150mg, 28 pcs. coated tablets (blister) – Each tablet contains 150mg abemaciclib Verzenios® 150mg, 56 pcs. coated tablets (blister) – Each tablet contains 150mg abemaciclib

Abbreviations: HR+= hormone receptor; HER2 = human epidermal growth factor receptor 2; pcs= packs

2. Summary table

Provide the summary in the table below, maximum 2 pages.

Summary	
Therapeutic indication relevant for the assessment	Abemaciclib in combination with endocrine therapy for adjuvant treatment of patients with hormone receptor (HR+)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive early breast cancer at high risk of recurrence
Dosage regiment and administration	300 mg daily (150 mg, 1 tablet BID). A 2-year stopping rule is applied.
Choice of comparator	Standard of Care (Soc) – endocrine therapy
Prognosis with current treatment (comparator)	Even though most early-stage HR+ patients receive adjuvant ET with curative intent, approximately 30% of them will eventually experience relapse with metastatic disease (1, 2). Especially in node-positive cases, the cumulative risk of HR+ and HER2- breast cancer distant recurrences remained steady for decades, and optimal adjuvant systemic therapy for these early-stage high-risk patients is still recognized as an unmet clinical need. Of note, the risk of recurrence and death from HR+ and HER2- breast cancer vary over time. There is a sharp peak at 2 years, which defines the intrinsic endocrine resistant cases, and then a gradually decreasing plateau follows thereafter for at least 20 years from diagnosis (2).
Type of evidence for the clinical evaluation	Head-to-head clinical study (MonarchE [NCT03155997])
Most important efficacy endpoints (Difference/gain compared to comparator)	Abemaciclib plus ET reduced the risk of developing invasive disease by [redacted] versus ET alone, together with a 5-year IDFS rate: [redacted] for abemaciclib plus ET versus ET alone, respectively The DRFS (stratified [redacted]), reflecting a [redacted] reduction in the risk of developing distant relapse, and a [redacted] difference in 5-year DRFS rates [redacted] for patients treated with abemaciclib in combination with ET, compared to patients treated with ET alone. The HRa estimate for overall survival (OS) was [redacted]). No significant differences in OS between the two treatment arms were observed. Despite the longer duration of follow-up at 54 months from the DCO in July 2023, the OS data remained immature.
Most important serious adverse events for the	The most important Grade III/IV AEs with an incidence of ≥ 1% included neutropenia [redacted] in the abemaciclib plus ET arm.

Summary	
intervention and comparator	In the ET alone arm those percentages were [redacted] respectively.
Impact on health-related quality of life	Clinical documentation: Based on data collected using the FACT-B, FACT-ES, FACIT-F, and EQ-5D-5L instruments, the overall health status of patients was maintained throughout the study in both treatment arms, and therefore that addition of abemaciclib may maintain patient HRQoL compared to ET alone. Health economic model: The results of the health economic model indicate that the addition of abemaciclib to ET generates more QALYs.
Type of economic analysis that is submitted	Cost-utility analysis, employing a Markov model
Data sources used to model the clinical effects	MonarchE clinical trial
Data sources used to model the health-related quality of life	MonarchE clinical trial
Life years gained	[redacted]
QALYs gained	[redacted]
Incremental costs	[redacted]
ICER (DKK/QALY)	[redacted]
Uncertainty associated with the ICER estimate	The parameters that had the greatest impact on changes in the ICUR were the proportion of patients moving to NMR, age related and post-progression CDK4&6 inhibitor utility value and LYs that patients obtain once they enter the ETR and ETS metastatic setting.
Number of eligible patients in Denmark	Incidence of patients with high-risk HR+/HER2- eBC eligible to treatment with abemaciclib the next 5 years: 2024: 402; 2025: 410; 2026: 419; 2027: 427; 2028: 436 Prevalence of diagnosed with HR+/HER2- breast cancer (not only high-risk patients): 2024: 49.091; 2025: 50.471; 2026: 51.883; 2027: 53.328; 2028: 54.807
Budget impact (in year 5)	[redacted]

Abbreviations: HR+= hormone receptor; HER2 = human epidermal growth factor receptor 2; BID=Twice a day ; ET= endocrine treatment; IDFS= Invasive disease-free survival; HRa= hazard ratio; OS= overall survival; DCO= data cut off; AE= adverse event; FACT-B=Functional Assessment of Cancer Therapy – Breast; FACT-ES=Functional Assessment of Cancer Therapy – Endocrine Symptoms; FACIT-F=Functional Assessment of Chronic Illness Therapy - Fatigue; EQ-5D-5L= EuroQol 5-dimensons 5-levels; HRQoL= health-related quality of life; QALY= quality adjusted life-years; NMR=Non-metastatic recurrence; ICER= incremental cost-effectiveness ratio; ETR= endocrine therapy-resistant; ETS= endocrine therapy-sensitive; LY= life-years; eBC= Early Breast Cancer; SoC= standard of care; CDK= Cyclin-dependent kinase

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

Breast cancer (BC) is the most common cancer amongst women in Denmark, with an estimated 4,900 new cases of invasive disease diagnosed each year (3). BC is responsible for 7%. of all cancer deaths in Denmark counting for approximately 1,100 BC deaths every year, meaning that BC is the third most common cause of cancer death overall and the most common in women (3, 4). The 5-year survival for patients with BC is approximately 90 % (3). Today 72,193 Danish women are living with the diagnosis of BC (5).

Breast cancer occurs to genomic instability caused by defects in deoxyribonucleic acid (DNA) damage repair, transcription, DNA replication, telomere maintenance, and mitotic chromosome segregation (6). Furthermore, BC is classified according to the cell type from which the tumour arises and is described in terms of 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 68% of all BCs, where around 30% of patients with HR+/HER2- BC will be at high-risk and develop distant metastasis (7, 8).

Early breast cancer (eBC) can be defined as not having spread beyond the breast tissue or nearby lymph nodes and generally includes ductal carcinoma in situ (Stage 0) and Stages I–IIIA, but may also be defined as invasive breast cancer Stages I–IIIC, excluding Stage 0 carcinoma (9). Anatomical staging of breast cancer is based on the size and extent of the breast tumour (T), the extent of regional lymph node involvement (N), and the presence/absence of distant metastases (M) (10-12). These features are assigned individual scores, which are then combined to identify the stage (Stage 0-IV) (13).

With an annual BC incidence of 0.08%, approximately 4,700 women in Denmark are diagnosed with BC each year. Whilst predominantly a disease affecting women, BC also occurs at a much lower incidence in men, with an estimated 45 men diagnosed each year in Denmark (14). Breast cancer incidence is strongly age-dependent, with more than 80% of cases occurring in women over the age of 50 (15). It is assumed that 20-30% of patients diagnosed with eBC will experience a relapse either locally or in other organs (distant metastasis). The distant metastatic survival among patients is around 2-3 years and 25% will have a 5-year survival (7). It has been shown that patients younger than the age of 60 years are at a higher risk of experiencing a relapse or dying of BC (16).

Most cases of BC are discovered through a nodule in the breast discovered by the patient or through screenings as mammography or ultrasound. Other symptoms of BC change in

the appearance of the breast or papillae mammae, swollen lymph node in the axilla, fluid or blood from the papillae mammae, and ulceration (17).

3.2 Patient population

The population of interest for this submission is patients with a high-risk (HR) for recurrence that are HR+/HER2−, node-positive eBC in an adjuvant setting. Approximately 15% of the Danish eBC population exhibits HR features, as included in the MonarchE-trial and thereby matching the trial population. The HR group has a higher risk of early recurrence, with 5-year risk of early recurrence is 20% for this group versus 10% for the non-HR group.

Currently, there is no difference in therapeutic treatment options between the HR vs non-HR groups in clinical practice. There has been no development in adjuvant treatment of HR+/HER2 negative eBC for many years, and therefore the long-term risk of relapse and death has outpaced the same risk of that of triple negative BC where progress in treatment have evolved. Hence, the population of MonarchE reflects the HR -population which has a high-risk of recurrence on current SoC (approx. three times more likely to experience recurrence than those with low-risk characteristics in general – with the majority being incurable metastatic disease).

Danish clinical experts have confirmed that the definition of high-risk eBC patients in Denmark (18) is in line with the definition in the MonarchE trial and the approved EMA indication (19). 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 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 Danish clinical practice and used within the validated tools discussed above. As such, the generalisability of MonarchE to Danish clinical practice in terms of the definition of high risk of recurrence should not be considered a major source of uncertainty in this appraisal.

The Intention to treat (ITT) cohort in MonarchE trial includes the use of ki67 to define high-risk which is not used in Danish clinical practice in the identification of high-risk patients. Which is also the case in the majority of European countries, hence the European Medicines Agency (EMA) have not included ki67 in the approved indication.

Based on the above estimations and on the Danish Health and Medicines Authority reports of the last few years (20-24)(please see Table 1), it is expected that around 3.600 patients per year will have HR+/HER2- BC. Moreover, based on Danish clinical experts (25) and on a Real World Evidence report from Norway (26), approximately 15% of these patients will be considered high-risk. Considering that Danish clinical experts expect 70% of ER+ HER2 negative patients at high risk of recurrence to be eligible to abemaciclib in combination with ET, the incident number of patients with high-risk HR+/HER2-, node-positive eBC, eligible for treatment is estimated to be approximately 300 in Denmark (25).

Table 1. Incidence and prevalence of the general population diagnosed with HR+/HER2- breast cancer in the past 5 years

Year	*2019 (23)*	*2020 (20)*	*2021(21)*	*2022(22)*	*2023(24)*
Incidence in Denmark	*3.471*	*3.540*	*3.611*	*3.683*	*3.757*
Prevalence in Denmark	*49.091*	*50.471*	*51.883*	*53.328*	*54.807*
Global prevalence *	*NA*	*NA*	*NA*	*NA*	*NA*

Note: The number of incidence and prevalence is based on the total number from the yearly cancer reports published by the Danish Health and Medicines Authority (20-24). The total numbers are multiplied by the percentage from SEER (68%) to get the number of the general patient population with HR + / HER2- breast cancer in Denmark (8). ; ** For small patient groups, also describe the worldwide prevalence.*

As no report was published yet by the Danish Health and Medicines Authority (20-24) for the following years, the expected number of patients diagnosed with high-risk for recurrence HR+/HER2−, node-positive eBC in the next 5 years, is built on the trend of the available data, extrapolated onto current and following 5 years. To estimate the number of incident patients in the next five years, we have applied an average percent increase calculated based on the increase observed over the years 2019-2023 presented in Table 1. The estimated number of incident patients in the next five years is presented in Table 2. Of these patients, 15% is expected to be high-risk patients (25, 26). Of the high-risk patients, 70% is estimated to be eligible for treatment with abemaciclib in combination with ET in the next five years, which was confirmed by Danish clinical experts, (please see Table 3).

Table 2. Incidence of high-risk HR+/HER2- in the next 5 years

Year	2024	2025	2026	2027	2028
Number of patients in Denmark who are eligible for treatment in the coming years (27)	3832	3909	3987	4067	4148

Table 3. Incidence of patients with high-risk HR+/HER2- eBC eligible to treatment with abemaciclib the next 5 years

Year	2024	2025	2026	2027	2028
Number of patients in Denmark who are eligible for treatment in the coming years	402	410	419	427	436

3.3 Current treatment options

Prognosis and treatment decisions for BC and eBC have historically been guided by the anatomic extent of disease as measured by tumour size, nodal status, and identification of distant metastasis (TNM) staging. TNM staging remains valuable, but biological factors (e.g., histologic tumour grade, cell proliferation rate, hormone receptor [HR](HR+) expression, HER2 expression, and gene expression prognostic panels [or multi-gene assays]) are now increasingly important in determining prognosis and response to treatment (12).

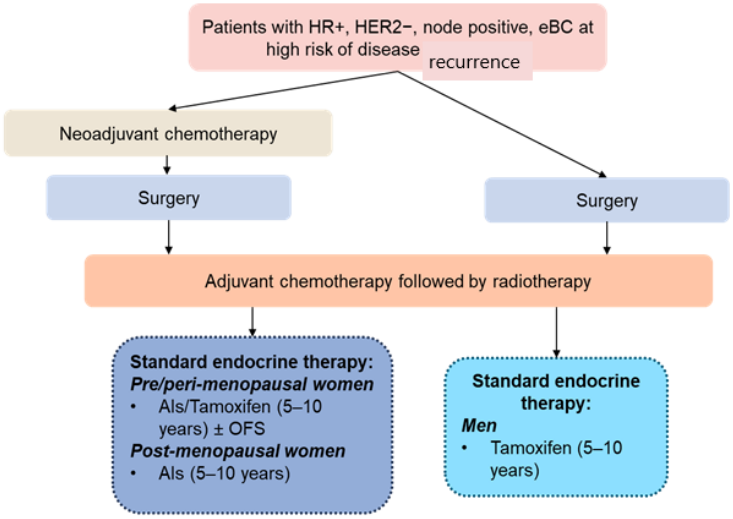
The Danish Medicines Council (DMC) does not have a guideline for the treatment of high-risk HR+/HER2-, node-positive eBC. The current treatment pathway for patients within this group follows the current guidelines developed by the Danish Breast Cancer Group (DBCG).

The DBCG recommends surgery and breast radiotherapy as standard treatment for patients with eBC (27). Patients with eBC should undergo breast-conserving surgery and appropriate (neo)adjuvant therapy as a treatment for their disease unless significant comorbidity precludes surgery. Prior to surgery, neoadjuvant chemotherapy may be considered as an option to shrink tumor size to allow surgery with curative intent, if chemotherapy is indicated (28).

Following surgery, adjuvant therapy is prescribed based on prognostic and predictive factors. For patients with BC that are considered to be at sufficient risk of recurrence with T1-2, N0-1, M0 disease, chemotherapy is indicated. Adjuvant chemotherapy should be offered as a regimen that contains six series both a taxane and an anthracycline or six series of docetaxel and cyclophosphamide (16).

All HR+ breast cancer patients are recommended to receive adjuvant ET as a treatment for their disease. Tamoxifen should be offered to men and premenopausal women, adjuvant ovarian suppression in combination with ET could also be considered for premenopausal women (16). Postmenopausal women should be offered aromatase inhibitor if they are at high-risk of disease recurrence, or tamoxifen. Patients at high-risk of recurrence should be offered extended adjuvant ET for at least five years and up to ten years (16). Additionally, bisphosphonates (zoledronic acid) may be offered as add-on adjuvant therapy for postmenopausal women with node-positive invasive breast cancer (16). See Figure 1 for a summary diagram of the treatment pathway according to these guidelines.

Figure 1. Current treatment pathway and proposed positioning of abemaciclib in Danish clinical practice for patients with HR+, HER2– node-positive eBC at high-risk of disease recurrence (29)



Abbreviations: AIs: aromatize inhibitors; HER2–: human epidermal growth factor receptor-2 negative; HR+: hormone receptor-positive; OFS: ovarian function suppression; eBC= early breast cancer; OFS= ovarian function suppression.
Source: St Gallen guidelines (29).

3.4 The intervention

Abemaciclib is an oral therapy administrated 150 mg film-coated tablets twice a day (BID). Currently, abemaciclib is recommended for treatment of HR+/HER2- advanced/metastatic

BC (aBC)(30). Abemaciclib has obtained marketing authorization in combination with endocrine therapy for the adjuvant treatment of adult patients with HR+/HER2−, node-positive, early breast cancer at high-risk of recurrence (19).

Table 4. Overview of abemaciclib (Verzenios®)

Overview of intervention	
Therapeutic indication relevant for the assessment	*Abemaciclib in combination with endocrine therapy for adjuvant treatment of patients with hormone receptor (HR+)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive early breast cancer at high risk of recurrence*
Method of administration	*Oral*
Dosing	*300 mg daily (150 mg, 1 tablet BID). A 2- year stopping rule is applied.*
Dosing in the health economic model (including relative dose intensity)	*Abemaciclib: 150mg BID; 100% relative dose intensity*
Should the medicine be administered with other medicines?	*Yes. Abemaciclib is administered in combination with endocrine therapy. Anastrozole: 1mg QD; exemestane: 25mg QD; letrozole: 2.5mg QD; tamoxifen: 20 mg QD*
Treatment duration / criteria for end of treatment	*2-years as adjuvant treatment or to progression, as metastatic treatment until unacceptable toxicity or progression. Dose reductions as per SmPC*
Necessary monitoring, both during administration and during the treatment period	*Prior to start of therapy complete monitoring of blood count (white blood cells, red blood cells, platelets) and liver function (ALT, AST) every two weeks for the first two months, monthly the next two months, and as clinically indicated (30).* *Before treatment initiation, absolute neutrophil count (30)*
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	*No*
Package size(s)	*Verzenios® 50mg, 28 pcs. coated tablets (blister) – Each tablet contains 50mg abemaciclib* *Verzenios® 100mg, 28 pcs. coated tablets (blister) – Each tablet contains 100mg abemaciclib* *Verzenios® 100mg, 56 pcs. coated tablets (blister) – Each tablet contains 100mg abemaciclib* *Verzenios® 150mg, 28 pcs. coated tablets (blister) – Each tablet contains 150mg abemaciclib* *Verzenios® 150mg, 56 pcs. coated tablets (blister) – Each tablet contains 150mg abemaciclib*

Abbreviations: ALT= Alanine aminotransferase; AST= Aspartate aminotransferase; BID= Twice (two times) a day QD= Once daily; SmPC= Summary of product characteristic; HER2–: human epidermal growth factor receptor-2 negative; HR+: hormone receptor-positive

3.4.1 The intervention in relation to Danish clinical practice

Please see section 3.3 for information on the intervention in relation to Danish clinical practice

3.5 Choice of comparator(s)

The comparator was selected based on the current treatment guidelines recommended by the DBCG (27) and validated by Danish clinical experts (25). DBCG guidelines recommend that following surgery, adjuvant treatment such as chemotherapy and

endocrine therapy is prescribed based on prognostic and predictive factors. All HR+ breast cancer patients are recommended to receive adjuvant ET. Endocrine treatment is offered to patients according to menopausal status. Premenopausal women and men are offered tamoxifen as SoC, with or without ovarian suppression. Postmenopausal women are offered in first hand aromatase inhibitor (letrozole, anastrozole or exemestane) in second hand tamoxifen. Patients at high-risk of recurrence should be offered extended adjuvant ET from five to ten years. Patients in Denmark diagnosed with HR+/HER2−, node-positive, eBC with high-risk of recurrence is offered adjuvant chemotherapy containing six series of a taxane and an anthracycline or six series of docetaxel and cyclophosphamide.

No DMC treatment recommendation for high-risk HR+/HER2-, node-positive eBC exists. For this reason, choice of comparators was selected based on the DBCG guidelines. Following the DBCG guidelines, the comparator would be considered SoC consisting of adjuvant ET (tamoxifen, letrozole, anastrozole, or exemestane). In the MonarchE trial different proportions of patients received the following ET:

- Tamoxifen: 1,755 of 5,591 ≈31%
- Toremifene: 17 of 5,591 ≈ 0.3%
- Letrozole: 2,138 of 5,591≈ 38%
- Anastrozole: 1,228 of 5,591 ≈ 22%
- Exemestane: 453 of 5,591 ≈ 8%

The proportion split of ET is overall representative for the proportion split used in Danish clinical practice, as estimated by a leading clinical expert, except for toremifene (0.3%) which is not used in Denmark. Clinical expert estimates revealed minor discrepancies in the proportion of patient treated with anastrozole and letrozole in MonarchE compared to Danish clinical practice. This was explained to the similarity between the treatments and preference from the Danish clinicians. The estimate from the Danish clinicians are as follows (25):

- Tamoxifen: ≈ 30%
- Letrozole: ≈ 50%
- Anastrozole: ≈ 10%
- Exemestane: ≈ 10%

Overall, the split of ET in the SoC-arm in MonarchE reflects the split of ET in Danish clinical practice.

The different types of ET treatments presented in Table 5, Table 6, Table 7, and Table 8 is approved in the EU and used in Denmark for the 1L adjuvant ET treatment of patients with high-risk HR+/HER2-, node-positive eBC (31-33). These four types of ET have been confirmed to be relevant in treatment of high-risk HR+/HER2-, node-positive eBC by Danish clinicians (25).

Table 5. Description of tamoxifen

Overview of comparator	
Generic name	*Tamoxifen*
ATC code	*L02BA01*
Mechanism of action	*Inhibits the stimulations of estrogen hormones involving in tumor growth.*

Overview of comparator	
Method of administration	*Oral*
Dosing	*20 mg orally QD*
Dosing in the health economic model (including relative dose intensity)	*20 mg QD, 100% relative dose intensity*
Should the medicine be administered with other medicines?	*No*
Treatment duration/ criteria for end of treatment	*5-10 years, if no progression or unacceptable toxicity*
Need for diagnostics or other tests (i.e. companion diagnostics)	*The presence of ER must be confirmed using validated examinations by a pathologist*
Package size(s)	• *Mylan® 20mg, 100 pcs. tablets – Each tablet contains 20mg tamoxifen* • *Sandoz® 20mg, 100 pcs. coated tablets (blister) – Each tablet contains 20mg tamoxifen*

Abbreviations: QD= Once a day.

Table 6. Description of letrozole

Overview of comparator	
Generic name	*Letrozole*
ATC code	*L02BG04*
Mechanism of action	*Inhibits the stimulations of estrogen hormones involving in tumor growth.*
Method of administration	*Oral*
Dosing	*2.5 mg orally QD*
Dosing in the health economic model (including relative dose intensity)	*2.5mg QD, 100% relative dose intensity*
Should the medicine be administered with other medicines?	*No*
Treatment duration/ criteria for end of treatment	*5 years, if no progression or unacceptable toxicity*
Need for diagnostics or other tests (i.e. companion diagnostics)	*The presence of ER must be confirmed using validated examinations by a pathologist*
Package size(s)	• *Femar® 2.5mg, 100 pcs. coated tablets (blister)* • *Letrozole "2care4" 2.5mg, 30 pcs. coated tablets (blister)* • *Letrozole" Abacus medicine" 2.5mg, 30 pcs. coated tablets (blister)* • *Letrozole "Accord" 2.5mg, 100 pcs. coated tablets (blister)* • *Letrozole "Medical Valley" 2.5mg, 30 pcs. and 100 pcs. coated tablets (blister)* • *Letrozole "Stada" 2.5mg, 100 pcs. coated tablets (blister)*

Abbreviations: QD= Once a day.

Table 7. Description of anastrozole

Overview of comparator	
Generic name	*Anastrozole*
ATC code	*L02BG03*

Overview of comparator	
Mechanism of action	*Inhibits the stimulations of estrogen hormones involving in tumor growth.*
Method of administration	*Oral*
Dosing	*1 mg orally QD*
Dosing in the health economic model (including relative dose intensity)	*1mg QD, 100% relative dose intensity*
Should the medicine be administered with other medicines?	*No*
Treatment duration/ criteria for end of treatment	*5 years, if no progression or unacceptable toxicity*
Need for diagnostics or other tests (i.e. companion diagnostics)	*The presence of ER must be confirmed using validated examinations by a pathologist*
Package size(s)	• *Armidex® 1mg, 98 pcs. coated tablets (blister)* • *Anastelb 1mg, 100 pcs. coated tablets (blister)* • *Anastrozole "Sandoz" 1mg, 100 pcs. coated tablets (blister)* • *Anastrozole "Accord" 1mg, 98 pcs. coated tablets (blister)* • *Anastrozole "Medical Valley" 1mg, 98 pcs. And 100 pcs. coated tablets (blister)*

Abbreviations: QD= Once a day; ER= estrogen receptor

Table 8. Description of exemestane

Overview of comparator	
Generic name	*Exemestane*
ATC code	*L02BG06*
Mechanism of action	*Inhibits the stimulations of estrogen hormones involving in tumor growth.*
Method of administration	*Oral*
Dosing	*25 mg orally QD*
Dosing in the health economic model (including relative dose intensity)	*25 mg QD, 100% relative dose intensity*
Should the medicine be administered with other medicines?	*No*
Treatment duration/ criteria for end of treatment	*5 years, if no progression or unacceptable toxicity*
Need for diagnostics or other tests (i.e. companion diagnostics)	*The presence of ER must be confirmed using validated examinations by a pathologist*
Package size(s)	• *Aromasin 25mg, 100 pcs. coated tablets (blister)* • *Exemestane "2care4" 25mg, 100 pcs. coated tablets (blister)* • *Exemestane "Accord" 25mg, 100 pcs. coated tablets (blister)* • *Exemestane "Stada" 25mg, 100 pcs. coated tablets (blister)*

Abbreviations: QD= Once a day; ER= estrogen receptor

3.6 Cost-effectiveness of the comparator(s)

In the MonarchE trial, abemaciclib in combination with endocrine therapy was compared to endocrine therapy alone. The ET included a combination of physician's choice therapies in both trial arms. Given that ET has been a longstanding and established treatment modality and that is considered the gold standard in clinical practice in Denmark, it is reasonable to assume that it is cost-effective as it has also been indicated in the past (34).

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Table 9. Efficacy outcome measures relevant for the application from MonarchE trial

Outcome measure	*Time point**	*Definition*	*How was the measure investigated/method of data collection*
Primary			
IDFS, defined by STEEP criteria	54 months	Measured from the date of randomization to the date of first occurrence of any of the following: • Ipsilateral invasive breast tumor recurrence • Regional invasive breast cancer recurrence • Distant recurrence • Death attributable to any cause Contralateral invasive breast cancer and second primary non-breast invasive cancer	All randomly assigned patients were followed for local/regional and distant recurrence and OS. At each visit, patients were assessed by medically qualified individual for AEs and any signs or symptoms of recurrence. At clinic visits, central chemistry and hematology laboratories were drawn, performance status was assessed, and physical examinations were conducted. Test to confirm recurrence after discretion of treating medically qualified individuals.
Key Secondary			
DRFS	54 months	Measured from the date of randomization to the first occurrence of distant recurrence or death due to any cause. Patients for whom no distant recurrence event observed were censored at the day of their last disease recurrence assessment or date of randomization.	See collection of primary outcome measure
OS	54 months	Time from the date of randomization to the date of death from any cause	See collection of primary outcome measure

**** Time point for data collection used in analysis (follow up time for time-to-event measures)***

Abbreviations: IDFS= Invasive disease-free survival; DRFS= Distant relapse-free survival; OS= Overall survival; STEEP= Standardized Definitions for Efficacy End Points; AE= adverse event

Validity of outcomes

Table 10. Validity of outcomes

Outcome measure	*Validity*
IDFS, defined by STEEP system	The STEEP criteria were developed in 2007, specifically for the adjuvant breast cancer setting by breast cancer leaders to provide consistency and standardization in evaluating the risk-benefit ratio of novel treatments compared to standard of care (35)
DRFS	Distant recurrence (the major component of DRFS) is a well-recognized predictor of breast cancer mortality and often occurs long before metastasis-related mortality for any cause. Distant recurrence (the major component of DRFS) is a well-recognized predictor of breast cancer mortality and often occurs long before metastasis-related mortality for any cause (36)
OS	The gold standard in cancer trials (FDA)(EMA) (37)

Abbreviations: IDFS= Invasive disease-free survival; DRFS= Distant relapse-free survival; OS= Overall survival; STEEP= Standardized Definitions for Efficacy End Points

IDFS and OS relationship

In 2016, Fetini and Bonnetain conducted a literature search to review surrogate end points for overall survival in breast cancer trials assessing surrogacy with the German institute of Quality and efficiency in Health Care's (IQWiG) framework and the Fleming hierarchy (38). For the adjuvant setting, the conclusion is based on one meta-analysis published by Ng et al. in 2008 including a total of 126 adjuvant breast cancer studies where both the 2-year disease-free survival (DFS) and 5-year overall survival (OS) were reported (39). The conclusion from Fetini and Bonnetain is that the 2-year DFS is not considered a valid surrogate for OS according to the IQWiG framework and Fleming hierarchy (38).

Interestingly, the 2-year DFS was assessed for surrogacy but not DFS itself. In the original review by Ng et al in 2008, the authors found a statistically significant study level correlation of moderate strength between 2-year disease free survival and 5-year OS despite the heterogeneity of the trials included in the analysis and the variability in the definitions for disease recurrence (39).

Of note, the year accrual ended for 126 trials included in this large meta-analysis ranged from 1970 to 2002, which precedes the publication of the standardisation of the definition of disease recurrence in early-stage adjuvant breast cancer clinical trials in 2007.

The positive association between recurrence and OS in adjuvant breast cancer trials is supported by several additional meta-analyses. Ciccarese et al. 2007 performed a literature based meta-analysis including 10 randomised controlled trials in which 27,653 patients were randomised to receive standard tamoxifen or Ais (40). They reported strong correlations between DFS and OS and concluded that the strong correlation between DFS and OS in AIs adjuvant endocrine treatment for eBC underlines the choice of DFS as a surrogate endpoint for OS. Although this meta-analysis also precedes the STEEP criteria, DFS is considered in a set of trials focusing specifically on AIs adjuvant endocrine treatment for eBC.

More recently, Savina et al. 2017 analysed data from 11,676 patients from 5 randomised controlled trials in the adjuvant breast cancer setting to evaluate 4 disease recurrence

endpoints (relapse-free survival [RFS], Invasive disease-free survival (IDFS), locoregional RFS and distant DFS) as potential surrogates for OS (41). The endpoints were highly associated with OS at the patient level. At the trial level, IDFS showed a high association with OS. In 2019, a meta-analysis including 8 trials and patient-level data in women with HER2+ eBC (n=21,480 patients) investigated disease-free survival as a surrogate endpoint for OS. Both patient-level and trial-level associations between disease free and overall survival were strong. The authors concluded that disease free survival was an appropriate surrogate for OS. (42) Along similar lines, a recent systematic review assessed DFS as a surrogate for OS in the adjuvant treatment of HR+/HER2− eBC. Both trial-level and patient-level analyses demonstrated a positive correlation between DFS and OS, supporting the use of DFS as a reliable surrogate endpoint for OS in HR+/HER2− eBC trials which in turn facilitates early access to innovative therapies. (43)

Overall, the evidence from these meta-analyses is consistent with the assessment made by the panel of breast cancer experts who developed the STEEP system (Hudis et al. 2007) (44). The authors strongly recommend the use of IDFS as the key endpoint to evaluate treatment effect in adjuvant breast cancer trials in a consistent and standardised way. While the authors acknowledge OS as the least ambiguous and most clinically relevant clinical end point in cancer trials, DFS is frequently employed as a surrogate to evaluate treatment effect in early breast cancer where all identifiable tumour has been resected. Given the strong correlation between distant recurrence and OS, DFS can serve as an early indicator of improved survival. For early breast cancer specifically, the use of an early endpoint is reasonable because of the relatively long expected survival time for patients, even those with metastatic recurrence. In this context, it is not practical to use OS as the primary end point of many adjuvant trials waiting for OS would slow the development of improved therapies. The recommendations from Hudis et al. are further reinforced by the DATECAN initiative set up with the objective to provide guidelines for standardised definitions of time-to events end points in randomised clinical trials for different cancer sites for breast cancer where IDFS is discussed and confirmed as an appropriate endpoint for the adjuvant setting.

Given the evolution of breast cancer clinical trials and improvements in outcomes, the standardised definitions for efficacy endpoints in adjuvant breast cancer trials were reviewed by a panel of experts to determine whether modifications were needed (Tolaney et al. 2021) (45). The authors conducted a systematic search for adjuvant breast cancer trials with the aim to investigate if the primary end points reported met STEEP criteria. Overall, the authors continue to support the use of iDFS and they recommended an additional endpoint, invasive breast cancer-free survival, which includes all invasive disease-free survival events except second non breast primary cancers, that can be considered for trials in which the toxicities are well known and where risk of second primary cancer is small.

In the clinical setting, five-year efficacy results from the prespecified OS interim analysis indicate that the addition of abemaciclib to standard-of-care ET in the adjuvant treatment of HR+, HER2–, high-risk eBC provided a persistent IDFS and DRFS benefit, with deepening of the absolute benefit in IDFS and DRFS rates at 5 years compared with that at previous years. (46) Previous studies in adjuvant treatment of HR+ breast cancer has shown that a

survival signal could emerge after 10 or more years of follow-up (SOFT/TEXT, EBCTCG meta-analysis). (47, 48) In this analysis of MonarchE, statistical significance was not reached for OS; however, a numerical difference in favor of abemaciclib was observed. The study continues until final OS with the majority of patients in active follow-up. With low and well-balanced permanent dropout rates across arms indicating no informative censoring, the assessment of OS is robust and reliable. These data, along with the distant relapse-free survival (DRFS) results in the ITT population and the substantially lower number of patients living with metastatic disease in the abemaciclib plus ET arm, provide potential insights into how OS data in the ITT population are likely to mature with additional follow-up. (46)

In the case of the high-risk patients enrolled in MonarchE, at the time of the OS IA1 interim analysis which correspond to the latest data cut, out of the 538 confirmed disease recurrences, there were only 40 second primary non-breast events, 20 in each arm. These events represent a small proportion of the total number of recurrence events and given the fact that they are balanced across arms, excluding these events to assess invasive breast cancer-free survival would lead to a consistent treatment benefit. Notably, most IDFS recurrences were distant metastatic events. Overall, evidence from the scientific literature including numerous meta-analyses support the use of disease-free survival as an endpoint to assess the efficacy of breast cancer therapies in the adjuvant setting. Specifically, IDFS has been developed by a panel of breast cancer experts to standardise the endpoint definition – which is now being used consistently in adjuvant breast cancer trials, in line with available regulatory guidance.

Lastly, it should be highlighted that both preclinical and clinical data substantiate that abemaciclib not only delays disease progression i.e., IDFS or DRFS events but also induces apoptosis and senescence, leading to sustained antitumor effects and result in an overall survival benefit. Using in vitro and in vivo breast cancer models Torres-Guzmán et al. showed that abemaciclib as a single agent reduces cell proliferation – notably, even after drug removal. and upon longer treatment can lead to sustained antitumor effects through the induction of senescence, apoptosis, and alteration of cellular metabolism (49). Clinically, the MONARCH 1 study further supports abemaciclib's efficacy as it exhibited clinical activity in a population of poor-prognosis, endocrine-resistant, heavily pre-treated patients with refractory HR+/HER2- metastatic breast cancer (50) .

4. Health economic analysis

4.1 Model structure

The MonarchE model structure was based on the findings of previous eBC models specific to the HER2+ patient population, and the treatment pathway of patients with eBC, data availability from the MonarchE trial.

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

Figure 2 illustrates the top-line model structure. All patients enter the model in the IDFS health state and receive adjuvant ET. Patients receiving Abemaciclib (ABE) + ET receive

ABE treatment for a maximum of two years. From the IDFS stage, patients can either progress to i) death (absorbing state), ii) metastatic recurrence (absorbing state), iii) non-metastatic recurrence, or they can complete 5 years of endocrine therapy and remain in the IDFS health state. Non-metastatic recurrence is divided into two categories: i) another primary neoplasm, which is absorbing. Second primary neoplasm was modelled as an absorbing state with patients only being allocated the cost of diagnosis following which they leave the model to receive treatment for that specific neoplasm., and ii) locoregional/contralateral recurrence. Locoregional/contralateral recurrence was modelled as a tunnel state with patients receiving treatment dictated by the type/location of the disease recurrence experienced. Patients can die at any point from the disease recurrence. Patients can also experience MR at any point. Patients who experienced either a locally advanced (with non-curative intent) or a metastatic disease recurrent event transitioned to the MR health state; modelled as an absorbing health state with fixed payoffs for costs, LYs and QALYs. Those who do not die or experience MR 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 until they experience another disease recurrence. The disease 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.

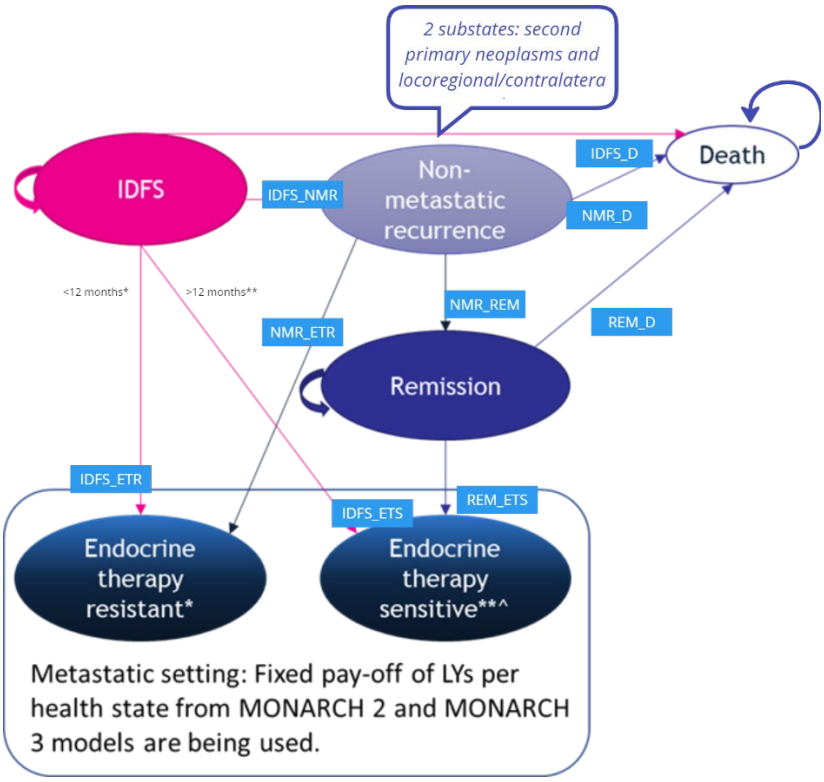
From the IDFS health state patients followed either the ET-resistant route or ET-sensitive pathway depending on the duration of their disease-free interval.

ET-resistant: Patients in IDFS who experience recurrence during adjuvant endocrine therapy or within 12 months after completing it (up to 5 years) are classified as endocrine-resistant, based on PFS and PPS from Monarch 2.

ET-sensitive: Patients in IDFS with recurrence more than 12 months after completing 5 years of adjuvant therapy, or those in remission, are classified as endocrine-sensitive, based on PFS1, PFS2, and PPS from Monarch 3.(51, 52).

From the NMR health state, patients follow the ET-resistant route, given that they experience disease recurrence within 12 months of entering the NMR state. From the remission health state, patient follow the ET-sensitive route, given that they experience disease recurrence after experiencing remission. For a detailed overview of transition probabilities, refer to 8.1.2.

Figure 2. MonarchE top-line model structure



Abbreviations: ET= Endocrine therapy; IDFS= Invasive disease-free survival; ETS= endocrine therapy sensitive; ETR = endocrine therapy resistant; NMR= non metastatic recurrence; MR= metastatic recurrence; D= death; LYs= Life years
*ET-resistant= Disease recurrence while receiving or within 12 months of completing prior adjuvant ET or within 12 months of entering the NMR health state.
**ET-sensitive= Disease recurrence at least 12 months after completion of prior adjuvant ET.
^Includes treatment with tamoxifen (51, 52).
Note: Metastatic recurrence is defined as either endocrine-resistant or endocrine-sensitive, based on the time of recurrence during treatment with endocrine therapy (before or after 12 months following completion of endocrine therapy).

4.2 Health State Specific Assumptions and descriptions

Refer to key assumptions presented in Section 8.4.

4.2.1 Invasive disease-free survival

From the IDFS health state patients can experience death, based on OS (without distant recurrence) curve. Patients who did not die, but experienced a non-metastatic or metastatic disease recurrence, transitioned from IDFS to the NMR or MR health states. Refer to 8.1.2 for transition probabilities.

4.2.2 Non-metastatic recurrence

From the monarchE trial, dictated by the standardised definitions (35) for efficacy end points criteria an ipsilateral invasive breast tumour recurrence, a regional invasive breast cancer recurrence, and a contralateral invasive breast cancer are all assumed to be a NMR event (53). Locoregional/contralateral disease recurrence events were modelled as a tunnel state with patients receiving treatment dictated by the type/location of the disease recurrence experienced. The frequency of recurrence events is treatment arm-specific, based on the OS IA3 data cut of monarchE, as presented in Table 21.

Patients can also die at any point from the disease recurrence. Patients who experienced either a locally advanced (with non-curative intent) or a metastatic disease recurrent event transitioned to the MR health state; modelled as an absorbing health state with fixed payoffs for costs, LYs and QALYs. Those who do not die or experience MR are assumed to receive 12 months of treatment before transitioning to the remission health state. Alternative evidence was not identified from literature or during consultations with thought leaders (TLs).

4.2.3 Secondary primary neoplasm

The monarchE trial includes a 'second primary non-breast invasive cancer' or a 'second primary neoplasm' as an IDFS event. The clinical study report (CSR) (primary outcome data) states that it is not considered as a recurrence event of 'this' breast cancer (53). TLs agreed that these events should not be considered an NMR event as their treatment pathways are different.

Based on the monarchE CSR (OS IA3 data, Table JPCF.5.4, first occurrence), 1.3% and 1.6% of patients in the ABE + ET and ET alone arms, respectively, were diagnosed with the first occurrence of a second primary neoplasm. The results of the OS IA3 data cut further validate the assumption from the final meeting with TLs during the original model development. Neither ABE + ET nor ET alone result in any additional risk of a second primary neoplasm.

To maintain a simple model structure, we do not model the full pathway of a second primary neoplasm. 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 NMR health state. Second primary neoplasm was therefore 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.

4.2.4 Remission health state

At this stage, the patients are in remission. Patients in remission can either remain in this condition, move to death, or experience MR.

4.2.5 Metastatic health state

At this stage, the patient has experienced MR. This stage was included as an absorbing stage, meaning that no patients move beyond MR. MR is defined as either endocrine-resistant or endocrine-sensitive, based on the timing of the relapse during endocrine therapy (before or after 12 months following the completion of ET).

4.3 Model features

Table 11. Features of the economic model

Model features	Description	*Justification*
Patient population	Patients with HR+, HER2-, node-positive, high risk eBC (Cohort 1)	This reflects the Danish patient population expected to be treated with abemaciclib + ET

Model features	Description	*Justification*
	Alternative populations are available: ITT population Cohort 1 Ki-67-High	
Perspective	Denmark Restricted Societal Perspective	According to DMC guidelines (54)
Time horizon	Lifetime - 49 years	In alignment with the DMC's guidelines (54). 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.
Cycle length	28 days	Sufficient to accurately capture the clinical and cost outcomes for patients from the MonarchE trial
Half-cycle correction	Yes	To account for events not occurring at beginning or end of every cycle.
Discount rate	3.5% Scenario with 1.5% discount rate for effects	As defined by the Danish Ministry of Finance and in the DMC guidelines (54).
Intervention	Abemaciclib in combination with endocrine therapy	In line with treatment regimen in SmPC and in MonarchE trial
Comparator(s)	Endocrine treatments of tamoxifen, letrozole, anastrozole, and exemestane	According to national treatment guidelines by the Danish Breast Cancer Group (DCBG).
Outcomes	• Costs by category, e.g., study drug, AEs • QALYs & LYs • Incremental costs, incremental QALYs, incremental LYs • Cost per QALY / LY gained • Net monetary benefits	

Abbreviations: AE= adverse events; DMC=Danish Medicine Council; eBC= early breast cancer; HR+= hormone receptor; HER2= human epidermal growth factor receptor; ET= endocrine treatment; ITT= intention to treat; SmPC= summary of product characteristics; LYs= life years; QALYs= quality-adjusted life years; DCBG= Danish Breast Cancer Group

5. Overview of literature

5.1 Literature used for the clinical assessment

In accordance with the DMC guidance, if a head-to-head study with a comparator relevant to Danish clinical practice exists, the literature search can be omitted (40).

Eli Lilly has conducted the MonarchE trial, a randomized control, phase III trial conducted to compare the safety and efficacy of abemaciclib in combination with ET versus ET alone in adjuvant treatment for HR+/HER2-, node-positive, high-risk eBC (33). The MonarchE trial was a head-to-head trial. For this reason, it was considered sufficient to demonstrate the efficacy and safety of abemaciclib plus ET for adjuvant treatment for eBC in comparison to ET alone.

A global clinical systematic literature review (SLR) was conducted to inform the health economic model and underlying assumptions. However, MonarchE provides the most relevant and suitable evidence representative of the Danish clinical practice, and therefore the SLR was not used to directly inform the clinical section of this submission, as in accordance with the DMC guidelines (23) (40)

Table 12. Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Full paper Priya Rastogi et al., Adjuvant Abemaciclib Plus Endocrine Therapy for Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative, High-Risk Early Breast Cancer: Results From a Preplanned MonarchE Overall Survival Interim Analysis, Including 5-Year Efficacy Outcomes. JCO. 2024 Jan; 42, 987-993(2024) (46) Rugo et al. (2021)*(55) / Toi et al. (2021)*(56) / Yap et al. (2021)*(57) / Martin et al. (2021)*(58) / Shao et al. (2021)*(59) / Jiang et al. (2020)*(60) / Johnston et al. (2020a)*(61) / Johnston et al. (2020b)(62) / Johnston et al. (2020c)*(63) / O'Shaughnessy et al. (2020)*(64) / Harbeck et al. (2020)*(65) / EUCTR2016-004362-26-NL(66) / Eli Lilly and Company (CSR at interim analysis)(67) / Rastogi et al. (2018)*(68) Rastogi et al. (2019)*(69)	MonarchE	NCT03155997	Start: 12/07/2017 Completion: 16/03/2020 Data cut-off 03/07/2023 Future data cut-offs Not defined	Abemaciclib combined with endocrine therapy vs. endocrine therapy in adjuvant treatment for HR+/HER2-, node-positive, high-risk eBC

* Conference abstracts

Abbreviations: HR+= hormone receptor positive; HER2= human epidermal receptor 2; eBC= early breast cancer;

5.2 Literature used for the assessment of health-related quality of life

Health-related quality of life data was obtained from the Monarch trial, where different patient-reported outcomes (PROs) were used to measure HRQoL: FACT-B, FACT-ES, FACIT-F, and EQ-5D-5L.

Table 13. Relevant literature included for (documentation of) health-related quality of life

Reference (Full citation incl. reference number)	*Input/estimate*	*Method of identification*	*Reference to where in the application the data is described/applied*
MonarchE	EQ-5D-5L. HSUVs for IDFS, NMR, REM, MR ETR and ETS PFS1.	From trial (MONARCH 2 and 3)	Section 10
Lidgren et at (2007)(70)	HSUV for NMR, first 3 months	N/A. For the metastatic setting, utilities from Lidgren et al. (2007) were deemed more appropriate as it was in line with the NICE reference case and was previously accepted by the committee for TA612	Section 10
NICE TA563(71)	HUSVs for *ETS – PFS2 and PPS*	Previous used and accepted by NICE and other HTA authorities.	Section 10

5.3 Literature used for inputs for the health economic model data sources and methods used to parameterise all events in the CE model

At the time of the last data cut (OS IA3) the monarchE trial had limited follow-up data (54 months). The data on post-recurrence events were immature and it was deemed unsuitable to fit statistical distributions and extrapolate beyond the trial data. The clinical SLRs were unable to identify suitable data to model the metastatic setting in greater detail.

In the absence of clinical data for the monarchE distant disease recurrent population, data from a broader advanced breast cancer population which included patients at high risk of disease recurrence were considered. The ET-resistant and ET-sensitive metastatic patient pathways were based on the clinical and economic evidence supporting the use of abemaciclib in combination with ET as a treatment for advanced breast cancer in these settings. The MONARCH 2 and MONARCH 3 trials, respectively, are the foundation of this evidence base. The MONARCH 2 trial included HR+, HER2- locally advanced or metastatic breast cancer patients who had disease recurrence on or immediately after prior (neo)adjuvant ET. The MONARCH 3 trial included postmenopausal women with HR+, HER2- locoregionally recurrent or metastatic breast cancer patients who had disease recurrence more than 12 months after completing prior adjuvant ET. It is acknowledged that the MONARCH 2 and MONARCH 3 trials did not exclusively include monarchE like patients. However, the cost-effectiveness model (CEM)s which used these trial data were deemed the most recent, robust and comprehensive, and relevant data sources to inform the metastatic health state.

The metastatic disease setting was modelled using the MONARCH 2 and MONARCH 3 models. The chosen approach for implementation in the model whereby survival outcomes following disease recurrence to the metastatic health state from either the IDFS or the remission health states at the point of disease recurrence were attributed a ‘fixed pay-off’ of LYs from these advanced breast cancer models. The costs and utilities associated with each health state within the respective metastatic disease pathways were combined with the LYs to determine the estimated total costs and QALY outcomes for the metastatic disease setting in the monarchE model. The limitations of this approach related to the including crude assumptions of uncertainty for the LYs in the model. The two key limitations, population heterogeneity and critique of input assumptions being transferred over to the monarchE model from the MONARCH 2 and MONARCH 3 models. There was an eight- and 11-year difference in age between the patients enrolled in the monarchE trial compared to MONARCH 2 and MONARCH 3, respectively. All assumptions surrounding the costs and utilities would be directly transferred from the MONARCH 2 and MONARCH 3 CEMs into the monarchE model.

Table 14. Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	*Input/estimate*	*Method of identification*	*Reference to where in the application the data is described/applied*
TA632[16], TA612[17] and TA569[18]	Non-metastatic remission (NMR); recurrence rates	Targeted literature review	Appendix J
Hamilton et al. (2015)[26] TA632[16], TA612[17] and TA569[18]	Remission (REM) transition probability to metastatic setting	Targeted literature review	Appendix J
MONARCH 2[27] and MONARCH 3[28]	Metastatic recurrence (MR)	Targeted literature review	Appendix J
MonarchE trial	Concomitant medication by treatment arm; Disease management resource use; Adverse events – costs	From trial data	Section 11
NICE guidelines (72)	Administration costs for NMR health state.	For the NMR health state, administration costs were included for chemotherapy, which was assumed to be administered for the treatment of certain types of disease recurrence. These have been costed separately according to NICE guidelines	Section 11
DBCG Quality Database for Breast Cancer National Annual Report 2020(27).	Ccomparison of Cohort 1 patients in the MonarchE trial compared to the characteristics of Danish HR+/HER2−, node-positive eBC patients according as derived from the DBCG annual report on breast cancer	Included in perevious submission	Table 16

Abbreviations: TA= technology appraisal; NMR= non-metastatic remission; REM= remission; MR= metastatic remission

6. Efficacy

Chapter 6 of this submission is structured around the Cohort 1 in the MonarchE study, as this cohort matches the EMA indication and Danish clinical practice. Given that Cohort 1 started enrolment 1 year earlier than Cohort 2 and included 91% of the ITT population, the evolution of follow-up time observed in the ITT population at each analysis time point is entirely driven by patients enrolled in Cohort 1. As mentioned above, the trial MonarchE is sufficient to inform the entire scope of the assessment, as it reflects the clinical practice in Denmark where ET is the SoC used in adjuvant treatment for HR+/HER2-, node-positive high-risk eBC patients.

In section 6.1.1 a description of the MonarchE trial will be provided. Followed by the section 6.1.4 where efficacy and safety data of the trials is presented.

6.1 Efficacy of abemacilib combined with endocrine therapy compared to endocrine therapy for HR+/HER2-, node-positive, early breast cancer with high risk of recurrence

6.1.1 MonarchE trial

MonarchE (NCT03155997) is an open-label, head-to-head, phase III study evaluating the clinical efficacy and safety of abemaciclib in combination with ET as adjuvant treatment for patients with HR+/HER2-, node-positive, high-risk eBC. All patients had surgery prior to the trial, and radiotherapy and/or adjuvant/neoadjuvant chemotherapy. Patients with four or more positive-nodes, or one to three nodes and either tumor size ≥5 cm, histologic grade 3, or central Ki-67 ≥20%, were eligible and randomly assigned (1:1) to SoC adjuvant ET with or without abemaciclib (150 mg twice daily for 2 years), see Figure 3.

Study design, main characteristics of the MonarchE trial, and the primary, secondary and exploratory endpoints are presented in Figure 3 and Table 15.

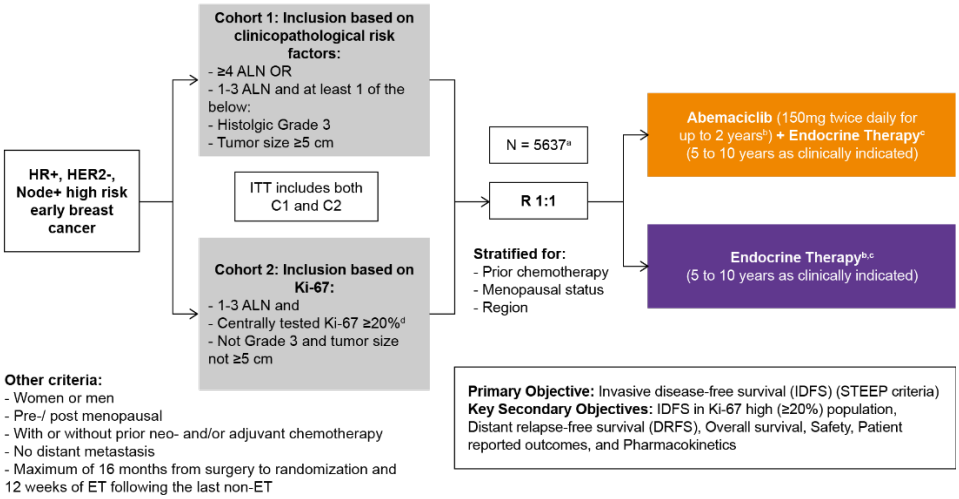
A total of 5,637 patients were randomized in a 1:1 ratio to receive 2 years of abemaciclib 150 mg twice daily plus physician's choice of standard endocrine therapy, or standard endocrine therapy alone in the ITT population. Randomization was stratified by prior chemotherapy, menopausal status, and region. Men were stratified as postmenopausal. Patients had completed definitive locoregional therapy (with or without neoadjuvant or adjuvant chemotherapy). Patients must have recovered from the acute side effects of any prior chemotherapy or radiotherapy. A washout period of 21 days after chemotherapy and 14 days after radiotherapy prior to randomization was required. Patients were allowed to receive up to 12 weeks of adjuvant endocrine therapy prior to randomization. Adjuvant treatment with fulvestrant was not allowed as standard endocrine therapy. Patients with ECOG Performance Status 0 or 1 were eligible. Patients with history of VTEs were excluded from the study. After the end of the study treatment period, in both treatment arms patients continued to receive adjuvant endocrine therapy for a cumulative duration of at least 5 years and up to 10 years, if medically appropriate. Luteinizing hormone–releasing hormone (LHRH) agonists were given when clinically indicated to pre- and perimenopausal women, and men.

Among the 5,637 randomized patients, 5,120 were enrolled in Cohort 1, representing 91 % of the ITT population. In Cohort 1, patient demographics and baseline tumor characteristics were balanced between treatment arms. The median age of patients enrolled was approximately 51 years (range, 22-89 years), 15 % of patients were 65 or

older, 99 % were women, 71 % were Caucasian, 24 % were Asian, and 5 % Other. Forty three percent of patients were pre- or perimenopausal. Most patients received prior chemotherapy (36 % neoadjuvant, 62 % adjuvant), and prior radiotherapy (96 %). Initial endocrine therapy received by patients included letrozole (39 %), tamoxifen (31 %), anastrozole (22 %), or exemestane (8 %).

Sixty-five percent of the patients had 4 or more positive lymph nodes, 41 % had Grade 3 tumor, and 24 % had pathological tumor size ≥ 5 cm at surgery.

Figure 3. MonarchE study design (73)



a Recruitment from July 2017 to August 2019 (cohort 2 recruited from August 2018)
b Treatment period = first 2 years on study treatment after randomisation
c Endocrine therapy of physician's choice (e.g., aromatase inhibitors, tamoxifen and LHRH agonist)
d Ki-67 expression assessed in all patients from both cohorts with suitable untreated breast tissue using Ki-67 immunohistochemistry assay by Dako/Agilent
Abbreviations: ALN= axillary lymph node; C1= Cohort 1; C2= Cohort 2; ET= endocrine therapy; HER2-= human epidermal growth factor receptor 2-negative; HR+= hormone receptor-positive; ITT = intent-to-treat; N= number of patients in ITT population; OR= odds ratio, R= randomisation; STEEP= standardised definitions for efficacy end points in adjuvant breast cancer trials

Table 15. Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	*Study design*	*Study duration*	*Patient population*	*Intervention*	*Comparator*	*Outcomes and follow-up period*
MonarchE, NCT03155997	Multicentre, open-label, randomised, Phase III trial	Open-label study with abemaciclib plus standard adjuvant endocrine therapy for up to 2 years. After the end of the study treatment period, in both treatment arms patients continued to receive adjuvant endocrine therapy for a cumulative duration of at least 5 years and up to 10 years.	Patients with HR+/HER2-, node-positive, high-risk eBC.	Abemaciclib plus standard adjuvant endocrine therapy, 150mg, twice daily, with at least 6-hour separating dose, for up to 2 years or until discontinuation criteria are met.	Standard adjuvant endocrine therapy of physician's choice, taken as prescribed	**Primary outcome measures** Invasive Disease-Free Survival (IDFS) (baseline to recurrence or death from any cause (up to 32 months)) **Secondary outcome measures** - IDFS for Participants with Ki-67 Index ≥20% (Baseline to Recurrence or Death from Any Cause (Approximately 10 Years) - Distant Relapse-Free Survival (DRFS) (Baseline to Distant Recurrence or Death from Any Cause (Up to 32 Months)) - Overall Survival (OS) (Baseline to Death from Any Cause (Approximately 10 Years)) - Pharmacokinetics (PK): Minimum Steady State Concentration (Cmin,ss) of Abemaciclib (Day 1 (2 hours post-dose), Days 30, 60, 90 post-dose) - Change From Baseline on the Functional Assessment of Cancer Therapy - Breast (FACT-B) (Baseline, Follow Up (Approximately 3 Years)) - Change From Baseline on the Functional Assessment of Cancer Therapy - Endocrine Symptoms (FACT-ES) (Baseline, Follow Up (Approximately 3 Years)) - Change From Baseline on the Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) (Baseline, Follow Up (Approximately 3 Years)) - Change From Baseline on the EuroQol Five-Dimension Five-Level Questionnaire (EQ-5D-5L) (Baseline, Follow Up (Approximately 3 Years))

Abbreviations: HR+= hormone receptor positive; HER2= human epidermal receptor 2; eBC= early breast cancer; IDFS=Invasive disease-free survival; DRFS=Distant Relapse-Free Survival; OS= overall survival; PK = pharmacokinetics; FACT-B= Functional Assessment of Cancer Therapy - Breast ; FACT-ES= Functional Assessment of Cancer Therapy – Endocrine Symptoms; FACIT-F= Functional Assessment of Chronic Illness Therapy - Fatigue; EQ-5D-5L= EuroQol 5-dimensions 5-levels

6.1.2 *Comparability of studies*

Not applicable

6.1.2.1 Comparability of patients across studies

Not applicable

6.1.3 *Comparability of the study population(s) with Danish patients eligible for treatment*

The population for this application is the Cohort 1 subgroup of the MonarchE trial, composed of HR+/HER2−, node-positive eBC patients with a high risk for recurrence presented in the clinical section of this application. Cohort 1 patients were specifically defined as patients presenting tumour involvement in ≥4 axillary lymph node (ALN)s, or pathological tumour involvement in 1–3 ALNs, alongside Grade 3 disease and/or a primary tumour size of ≥5 cm.

Danish clinical experts have confirmed that the definition of high-risk eBC patients in Denmark is in line with the definition in the MonarchE trial and the approved EMA indication (19). 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 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 Danish clinical practice and used within the validated tools discussed above. As such, the generalisability of MonarchE to Danish clinical practice in terms of the definition of high risk of recurrence should not be considered a major source of uncertainty in this appraisal.

Table 16 presents a comparison of Cohort 1 patients in the MonarchE trial compared to the characteristics of Danish HR+/HER2−, node-positive eBC patients according as derived from the DBCG annual report on breast cancer (27).

Table 16. Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference) MonarchE (NCT03155997) (27) /	Value used in health economic model (reference if relevant) MonarchE (NCT03155997)
Age, median (range)	51.0 (22, 89)	51.0 (22, 89)
Female, %	5088 (99.4)	5088 (99.4)
Race, n (%)		
White	Slightly higher	3575 (70.8)
Asian	Lower	1227 (24.3)
Menopausal status, n (%)		
Premenopausal	2220 (43.4)	2220 (43.4)
Postmenopausal	2896 (56.6)	2896 (56.6)
Number of Positive Lymph nodes, %		
0	2.113 (56,3)	12 (0.2)
1-3	765 (20,4)	1761 (34.4)
4-9	205 (5,5)*	2223 (43.4)
≥10	NA	1123 (21.9)
Missing	NA	1 (0.0)

Histopathological Diagnosis Grade		
G1 – Favourable	127 (23,6)	425 (7.5)
G2 – Moderately Favourable	382 (71,1)	2772 (49.2)
G3 – Unfavourable	28 (5,2)	2150 (38.1)
GX – Cannot be Accessed	NA	267 (4.7)
Missing	NA	23 (0.4)

Abbreviations: ET, endocrine therapy

*>= 4

Source: Cohort 1 patients in the MonarchE trial and Groups, D.B.C.C., DBCG Kvalitetsdatabase for Brystkræft National årsrapport 2020. 2020.

6.1.4 Efficacy – results per MonarchE

The MonarchE study investigated the efficacy and safety of abemaciclib in combination with ET which is the scope of submission to the DMC. Results reported in the following section relates to Cohort 1, as this cohort matches the EMA indication and Danish clinical practice. Given that Cohort 1 started enrolment 1 year earlier than Cohort 2 and included 91% of the ITT population, the evolution of follow-up time observed in the ITT population at each analysis time point is entirely driven by patients enrolled in Cohort 1.

The relevant efficacy outcomes presented are based on the latest data cut (July 2023), with a median follow-up time of 54 months. In cohort 1, IDFS, DRFS, and OS were consistent with the ITT population.

6.1.4.1 MonarchE - IDFS

A total of 935 patients experienced IDFS events, including 382 (14.9%) in the abemaciclib + ET arm and 533 (21.5%) in the ET alone arm. With the additional follow-up, abemaciclib plus ET reduced the risk of developing invasive disease by 33.0% (stratified HRa=0.67, 95% CI: 0.588, 0.764 [p=0.00001]) versus ET alone, together with a 5-year IDFS rate: 83.2% vs 75.3%, for abemaciclib plus ET versus ET alone respectively. Kaplan Meier (KM) curves of IDFS for patients in the Cohort 1 population of monarchE who received either abemaciclib plus ET or ET alone are displayed in Figure 4. In Table 17, result of IDFS from the latest DCO from July 2023 is presented. The data from the updated DCO showed a positive development in IDFS from the previous DCO with a hazard ratio (HRa) of 0.67 versus 0.68 (please see previous DMC application for full details on previous DCO results).

Figure 4. Kaplan Meier IDFS by investigator assessment - Cohort 1 population (DCO July 2023).

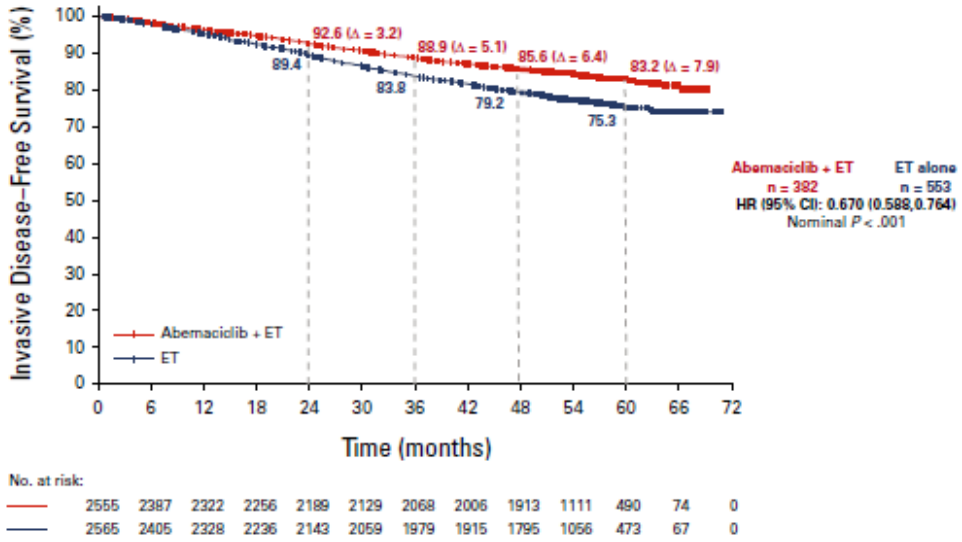


Table 17. Summary of investigator assessed IDFS in Cohort 1 (DCO July 2023).

	Abemaciclib + ET n=2,555 (46)	*ET alone (n=2,565)*
No. of events, n (%)	382 (15)	553 (21.6)
Five-year event rate, % (95% CI)	83.2 (81.5 to 84.7)	75.3 (73.4 to 77.2)
IDFS rate, % (95% CI)		
24 months	92.6 (91.5, 93.6)	89.4 (88.2, 90.6)
36 months	88.9 (87.5, 90.1)	83.8 (82.2, 85.2)
48 months	85.6 (84.1, 86.9)	79.2 (77.6, 80.8)
60 months	83.2 (81.5, 84.7)	75.3 (73.4, 77.2)
HRa (95% CI)	**0.670 (0.588 to 0.764)**	
Nominal *P*	<.001	

Abbreviations: ET= endocrine therapy; HRa= hazard ratio; IDFS= invasive disease-free survival.

Table 18 shows an overview of the recurrence locations of the ITT population (DCO July 2023).

Table 18. Summary of tumour recurrence locations- all occurrences of events, ITT population (DCO July 2023).

	Abemaciclib + ET n=2,808 (46)	*ET alone (n=2,829)*
Patients with any disease recurrence, n (%)	369 (13.1)	559 (19.8)
Local / regional recurrence	55 (2.0)	99 (3.5)
Distant recurrence	297 (10.6)	465 (16.4)
Contralateral recurrence	14 (0.5)	17 (0.6)
Second primary neoplasm	39 (1.4)	49 (1.7)

Abbreviations: ET= endocrine therapy; HRa= hazard ratio; IDFS= invasive disease-free survival

6.1.4.2 MonarchE - DRFS

A total number of 802 DRFS events were observed, including 325 in the abemaciclib + ET arm and 477 in the ET alone arm. The DRFS (stratified HRa=0.665, 95% CI: 0.577, 0.765), reflecting a 33.15 reduction in the risk of developing distant relapse, and a 7.1% difference

in 5-year DRFS rates (85.6% versus 78.5%) for patients treated with abemaciclib in combination with ET, compared to patients treated with ET alone. The data from the updated DCO showed a positive development in DRFS from the previous DCO with a HRa of 0.665 versus 0.669 (please see previous DMC application for full details on previous DCO results).

Figure 5. Kaplan-Meier plot of DRFS by investigator assessment – Cohort 1 population (DCO July 2023)

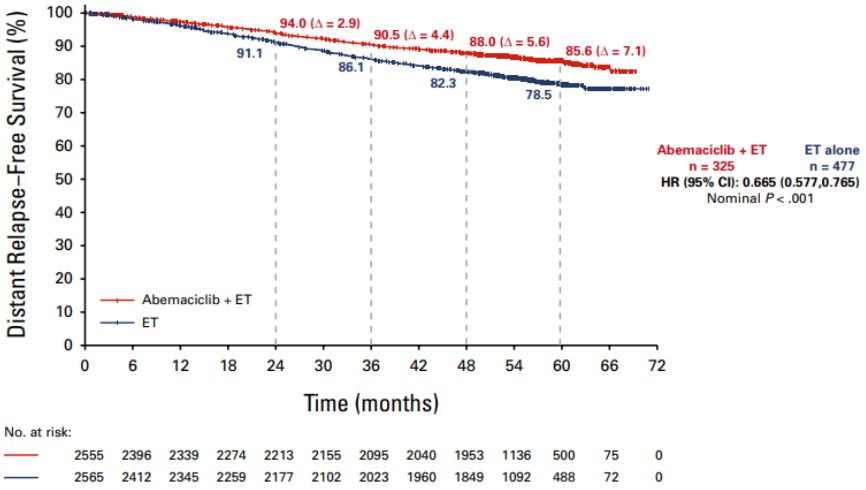


Table 19. Summary of investigator assessed DRFS in Cohort 1 (DCO July 2023)

	Abemaciclib + ET n=2,555 (46)	*ET alone (n=2,565)*
No. of events, n (%)	325 (12.7)	477 (18.6)
Five-year event rate, % (95% CI)	85.6 (84 to 87.1)	78.5 (76.6 to 80.3
HRa (95% CI)	**0.665 (0.577 to 0.765)**	
Nominal *P*	<.001	

Abbreviations: DRFS= distant relapse-free survival; ET= endocrine therapy; HRa= hazard ratio.

Overall, the data from the updated DCO showed a positive development, underlining a continued deepened benefit for IDFS and DRFS rates a 2-, 3- and 4-year follow up. Both IDFS and DRFS curves continue to separate, suggesting a carryover effect with a sustained impact of abemaciclib even after the 2-year treatment period.

6.1.4.3 MonarchE - OS

A total number of 420 deaths (8.2%) were observed, including 197 (7.7%) in the abemaciclib + ET arm and 223 (8.7%) in the ET alone arm. The HRa estimate for OS was 0.894 (95% CI: 0.737, 1.084), which shows a numerical advantage with abemaciclib and endocrine combination therapy compared with endocrine therapy alone and a clear trend towards a significant OS benefit, although OS data remained immature at this point in time. It should be noted that patients with HR+/HER2- metastatic BC have a median OS ranging between 3 to 5 years, based on real-world evidence and trials of CDK 4/6 inhibitors in the metastatic setting (74-76). 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 OS data in MonarchE to capture any

significant treatment effect of abemaciclib on OS. KM curves of OS are displayed in Figure 6. The data from the updated DCO showed a positive development in OS from the previous DCO with a HRa of 0.894 versus 1.044 (please see previous DMC application for full details on previous DCO results).

Figure 6. Kaplan-Meier plot of OS – Cohort 1 population first OS interim analysis (DCO July 2023)

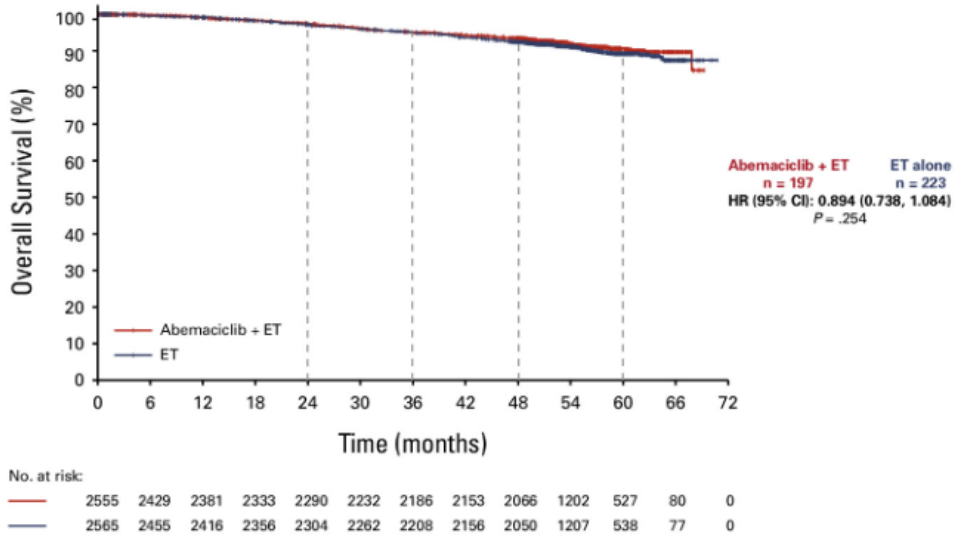


Table 20. Summary of OS in Cohort 1 (DCO July 2023)

	Abemaciclib + ET n=2,555 (46)	*ET alone (n=2,565)*
No. of events, n (%)	197 (7.7)	223 (8.7)
HRa (95% CI)	**0.894 (0.738 to 1.084)**	
Nominal *P*	0.254	

Abbreviations: ET= endocrine therapy; HRa= hazard ratio; OS= overall survival.

7. Comparative analyses of efficacy

MonarchE is a head-to-head study, for that reason no comparative analysis has been performed.

7.1.1 *Differences in definitions of outcomes between studies*

Not applicable.

7.1.2 *Method of synthesis*

Not applicable.

7.1.3 *Results from the comparative analysis*

Not applicable.

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

Clinical effectiveness data

Table 21 below presents an overview of the clinical data sources and the methods used to parameterise all events in the CE model.

Table 21. Summary of clinical effectiveness data sources and methods of parameterisation

Events	ABE + ET	ET alone	Assumptions
Disease recurrence	MonarchE (ITT – OIA3)	MonarchE (ITT – OIA3)	Local/regional recurrence, contralateral recurrence and second primary neoplasm are all types of NMR events. Distant recurrence is a MR event.
IDFS	MonarchE (ITT – OIA3) IDFS to NMR: 27.1% IDFS to MR: 72.9%	MonarchE (ITT – OIA3) IDFS to NMR: 25.3% IDFS to MR: 74.7%	Treatment effect waning starts from year eight and no treatment effect exists beyond 26 years
NMR	MonarchE (ITT – OIA3) TA632, TA612, TA569; TL feedback (Loco)regional: 54.8% Contralateral: 12.4% Second Primary: 32.8%	MonarchE (ITT – OIA3) TA632, TA612, TA569; TL feedback (Loco)regional: 56.6% Contralateral: 10.6% Second Primary: 32.8%	Clinical outcomes within the NMR health state are treatment arm-specific, based on the OS IA3 data cut of monarchE. Second primary neoplasms are considered in the NMR health state. At which time these patients exist the model
REM	Hamilton et al (2015) TA632, TA612, TA569; TL feedback REM to MR: 0.00757	Same as for ABE + ET	Clinical outcomes within the REM health state assumed same for both treatment arms.
OS (without distant recurrence)	MonarchE (ITT – OIA3)	MonarchE (ITT – OIA3)	Death from IDFS assumed equal to death from NMR and REM. Background mortality acts as a lower bound for the OS curve. Waning of treatment effect assumed beyond clinical trial data. Similar justification to IDFS.
MR	ET-resistant (MONARCH 2) and ET-sensitive (MONARCH 3)	ET-resistant (MONARCH 2) and ET-sensitive (MONARCH 3)	1. Assumed that patients enrolled in MONARCH 2 and MONARCH 3 are inclusive of patients enrolled in monarchE. In the absence of long-term data this approach was considered reasonable.

Events	ABE + ET	ET alone	Assumptions
			2. Patients who experience a disease recurrent event on or within 12 months of completing adjuvant ET either in IDFS or NMR follow the ET-resistant (MONARCH 2) pathway. Patients who experience a disease recurrent event more than 12 months after completing adjuvant ET (IDFS) or while in REM follow the ET-sensitive (MONARCH 3) pathway.

Abbreviations: IDFS= invasive disease-free survival; NMR= non-metastatic recurrence; MR= metastatic recurrence; OS= overall survival; ET= endocrine therapy; REM= remission.

Time to event analyses and efficacy outcomes

The individual patient data (IPD) from the MonarchE trial was used to generate the IDFS, time to treatment discontinuation (TTD), and OS (without distant recurrence) outcomes for both ABE + ET and ET-alone. The parametrised curves for IDFS, TTD, and OS were utilised in the CEM. The parametrisation of the IDFS, TTD, and OS curves for ABE + ET and ET-alone aids in estimating long-term outcomes for patients beyond the trial period and subsequently allows for modelling over a longer time. At the OS IA3 analysis, the median duration of follow-up was approximately 54 months in both trial arms. The median treatment duration of abemaciclib was 23.7 months. The analyses were carried out using SAS Software 9.4 (SAS Institute, Cary NC; traditional parametric models) and R 3.6.2 Software (cubic spline models). Please refer to the SAP for further details (77).

Parametric models were fitted to the KM data of the MonarchE trial. The models provided a more granular overview of the survival data and the approach enabled estimation of long-term outcomes to inform the lifetime horizon of the CEM. The parametric model fitting for IDFS, TTD and OS without distant recurrence were conducted according to the following steps recommended in the National Institute for Health and Clinical Excellence (NICE) Decision Support Unit (DSU) 14 (78):

- Proportional hazards (PH) assumption was tested between treatment arms, which inferred the choice of fitting independent or dependent models. If the PH assumption could not be rejected, a single dependent model for each survival curve was estimated, with treatment modelled as a single covariate. Otherwise, an independent model was fit.
- Following the PH test, parametric survival models were fit to the survival data of the pivotal trial (i.e., MonarchE in this case).
- An initial selection of extrapolation models was based on visual inspection and statistical fit of the models to the trial data, based on Akaike's Information Criterion (AIC) and the Bayesian Information Criterion (BIC), as well as visual inspection of the survival and hazard curves.
- The models were further evaluated against additional evidence from external sources (trials included in the clinical SLR report for IDFS) and further discussed with TLs for their opinion. For outcomes where no additional evidence was available, model selections were based on the outcomes of step 3.

Refer to Appendix D for further extrapolation description.

8.1.1 Extrapolation of efficacy data

Survival extrapolation approaches

The parametric distributions fitted to the MonarchE trial are 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.

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. In situations where there is a misalignment in AIC and BIC to select the best-fitting model, BIC will be chosen as the best model in terms of statistical fit. As the BIC is more stringent towards both type I and type II errors, it can potentially protect against overfitting (79).

Visual inspection of extrapolation curves

Models were also assessed based on the visual fit following the recommendations in the NICE DSU Technical Support Document 14 (78). It should be noted that this method needs to be used with caution and only complementary to the other model selection methods. Due to censoring and clustered data points in the KM curve, some parts of the extrapolated curve may fit the observed data very well, while in other parts it will not. This does not necessarily mean that the model is inappropriate. If the parametric curves closely follow the observed data, this does not necessarily mean that they are able to correctly predict the survival beyond the trial duration, especially at the tail of the curve.

Visual inspection of smoothed hazard curves

In addition to visual assessment of the extrapolation curves, a visual assessment of the smoothed hazard curves was performed. The smoothed hazard curve indicates whether observed hazards are likely to be constant, monotonic, or non-monotonic. In general, the hazards of the exponential models will provide the best fit when the observed hazard is approximately constant and non-zero. The Weibull and Gompertz models incorporate monotonic hazards, while the log-logistic and log-normal models can incorporate non-monotonic hazards. The generalised gamma and the spline models are generally more flexible in incorporating multiple turning points in hazards. Like with the visual inspection of extrapolation curves (and other validation criteria), the observed smoothed hazard curves do not always predict the hazards beyond trial period.

External validation

Evidence from the monarchE trial was deemed the most recent and relevant for the validation of the OS without distant recurrence extrapolations. The final choice of distribution was based on internal validations.

8.1.1.1 Extrapolation of IDFS

Table 22. Summary of assumptions associated with extrapolation of IDFS

Method/approach	Description/assumption
Data input	MonarchE
Model	Full parametrization

Method/approach	Description/assumption
Assumption of proportional hazards between intervention and comparator	Yes
Function with best AIC fit	[redacted]
Function with best BIC fit	[redacted]
Function with best visual fit	[redacted]
Function with best fit according to evaluation of smoothed hazard assumptions	[redacted]
Validation of selected extrapolated curves (external evidence)	No external validation has been performed in the cohort 1 population due to a lack of comparable studies
Function with the best fit according to external evidence	Intervention: NA Comparator: NA
Selected parametric function in base case analysis	[redacted]
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	Yes. Treatment effect is assumed to last for at least eight years at which point treatment effect starts to wane. Treatment effect waning continue until year 28 following which no treatment benefit was assumed. Year 28 was chosen as this was the point in the model where IDFS rates equal background mortality).
Assumptions of cure point	No.

Abbreviations: NA= not applicable

The PH assumption between treatment arms was tested. Although, the crossing of the treatment arms suggests a violation of the PH assumption, indicating that the HRa is not constant over time, it occurs only for a small part of the observed data. Over time the treatment arms start to move parallel, indicating a constant hazard over time. Furthermore, the Grambsch and Therneau test could not be labelled as statistically significant (p-value = 0.705) as it exceeded p = 0.05. This is consistent with the residuals visualisation in which no time trend can be observed, and the slope generally aligns the zero slope, suggesting no violation of the PH assumption. Therefore, a single model including an adjustment factor for treatment effect (hazard ratio - HRa), instead of independent models, was fitted to the IDFS data of the cohort 1 population of the MonarchE trial.

Seven parametric distributions and two spline models were fit to the IDFS KM data and were evaluated based on AIC and BIC values of the dependent models. It is not directly obvious which survival curve to select based on statistical fit. The best statistical fit based on BIC value is provided by the log-logistic distribution, which also provides a relatively low AIC value, approximately four points away from the lowest AIC value (Table 22). The next best statistical fit was found within the hazard spline knot 1 distribution, which

deviates five points for the log-logistic distribution in BIC value, and three points from the distribution with the lowest AIC value. When comparing the five-year landmark IDFS rates of the ET-alone arm of the MonarchE trial with the extrapolation curves at five year, the log-logistic shows a good fit with the OS IA3 data. The five-year extrapolations of all curves are close to each other (75.2-75.6), except for the log-normal (76.2). The log-logistic estimate for the ABE + ET arm is slightly lower than the five-year the OS IA3 data. However, all extrapolation curves estimate the five-year IDFS rate slightly under the observed five-year data of the MonarchE trial for ABE + ET. As can be seen in Table 10, the five-year extrapolations of all curves are close to each other (82.5-82.8). On visual inspection, all extrapolated curves seem to fit the MonarchE trial data for the observed time-period relatively well (Figure 7). Although the curves follow a similar pattern for the first five years, over time the curves show more variation in the extrapolated IDFS.

Figure 7. Long-term IDFS extrapolations – Cohort 1 population; left panel ABE+ET and right panel ET-alone

8.1.1.2 Extrapolation of TTD

Table 23. Summary of assumptions associated with extrapolation of TTD

Method/approach	Description/assumption
Data input	MonarchE
Model	Full parametrization
Assumption of proportional hazards between intervention and comparator	Yes
Function with best AIC fit	
Function with best BIC fit	
Function with best visual fit	

Method/approach	Description/assumption
Function with best fit according to evaluation of smoothed hazard assumptions	[redacted]
Validation of selected extrapolated curves (external evidence)	No. Evidence from the MonarchE trial was deemed the most recent and relevant for the validation of the TTD extrapolations of the ET-arms.
Function with the best fit according to external evidence	[redacted]
Selected parametric function in base case analysis	[redacted]
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

Abbreviations: NA= not applicable

The duration of treatment is determined by the TTD curves of the ABE + ET and ET-alone 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. Due to the maximum two-year treatment duration permitted for ABE, and the follow-up period of the OS IA3 2023 data cut, the full KM curve was used to estimate TTD for ABE in the base case.

The MonarchE trial was set up with a 2-year on-study treatment period for both treatment arms, after which patients could enter the study follow-up period and receive post-discontinuation therapies (including ET). This means that data on TTD were already considered final at the OS IA2 data cut and were not updated in the OS IA3 data cut. Therefore, OS IA2 data is used to inform TTD. However, ABE has been approved for EBC patients with node-positive HR+ / HER2- in combination with a minimum of five years of adjuvant ET. As such, TTD data of the MonarchE trial for the ET treatment arms should be extrapolated to reflect the full treatment period as approved. The ET data used for extrapolation was re-censored at month 20, to prevent that a drop in TTD towards the end of the 2-year on-study treatment period has an impact on the long-term extrapolation.

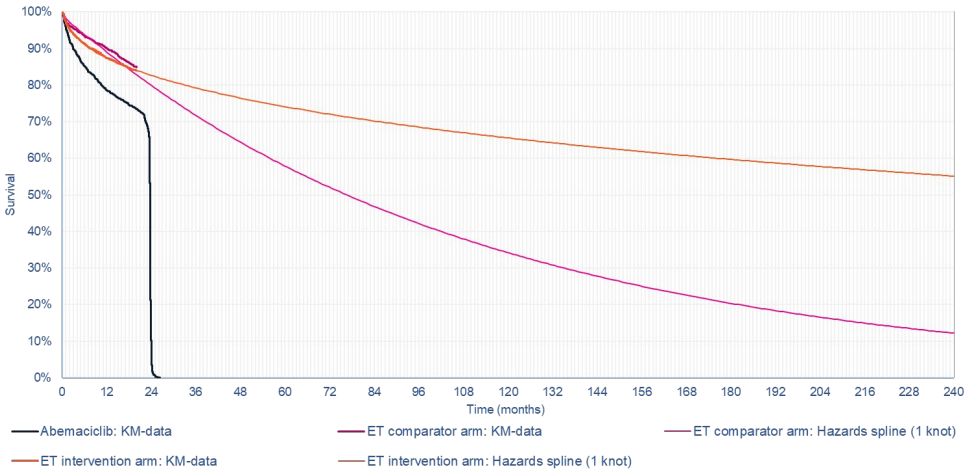


Figure 8 CEM extrapolation of TTD, including KM data for ABE

As adjuvant ET is assumed for a minimum of five years in the base case, parametric extrapolations are required to estimate the TTD beyond the 2-year on-study treatment period of the trial. The PH assumption was tested between ET in the intervention arm and ET in the comparator arm. The log-cumulative plot shows that there is convergence of the trial arms at several points in the plot, indicating that the PH assumption is violated. Therefore, two independent models were fitted to the ET data of the MonarchE trial.

The seven parametric distributions and two spline models were fitted independently to the TTD KM data and were evaluated based on AIC and BIC values. The best statistical fit, when considering both trial arms, is provided by the hazard spline knot 2 distribution, followed by the hazard spline knot 1 distribution. Figure 9 gives a visual presentation of the TTD curves. The selection of the hazard spline knot 2 distribution eventually leads to a crossing of the TTD curves in the model. This can be considered as an unrealistic estimation, as it would be expected that ET in both trial arms follows the same pattern. Therefore, the hazard spline knot 1 distribution is recommended as the base case, as no crossing of curves can be seen when this curve is selected. Based on the AIC and BIC values for the ET intervention arm, the log-normal could be selected as an alternative distribution, although it is a poor fit for the ET comparator arm.

Figure 9. Long-term extrapolations – Cohort 1 population; left panel ET intervention arm and right panel ET comparator arm

Evidence from the MonarchE trial was deemed the most recent and relevant for the validation of the TTD extrapolations of the ET-arms. For the ABE treatment, the KM curve was used, which falls to zero at two years, in accordance with the 2-year on-study treatment period. For the ET-arms, clinical and economic stopping rules were applied at five years, which means that there is limited risk of bias being introduced into the model by selection of the TTD extrapolation curves

8.1.1.3 Extrapolation of OS without distant recurrence

Table 24. Summary of assumptions associated with extrapolation of OS

Method/approach	Description/assumption
Data input	MonarchE
Model	Full parametrization
Assumption of proportional hazards between intervention and comparator	No, although the data are too immature to assume a PH violation
Function with best AIC fit	
Function with best BIC fit	
Function with best visual fit	
Function with best fit according to evaluation of smoothed hazard assumptions	
Validation of selected extrapolated curves (external evidence)	
Function with the best fit according to external evidence	

Method/approach	Description/assumption
Selected parametric function in base case analysis	[redacted]
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	Yes. Waning of treatment effect assumed beyond clinical trial data. Similar justification to IDFS.
Assumptions of waning effect	Waning of treatment effect assumed after eight years with no treatment effect assumed after 18 years (ITT population).
Assumptions of cure point	No

Abbreviations: OS= overall survival; PH= proportional hazard; HRa= hazard ratio; NA= not applicable

The PH assumption between treatment arms was tested. The log-cumulative hazard plot shows the treatment arms are crossing at two time points, indicating a violation of the PH assumption. Therefore, the PH assumption cannot be rejected. These results can be considered volatile due to the small number of OS without distant recurrence events observed in the trial. The data are too immature to assume a PH violation. A single model, including an adjustment factor for treatment effect (hazard ratio - HRa), was fitted to the OS (without distant recurrence) data of the MonarchE trial.

Seven parametric distributions and two spline models were fit to the IDFS KM data and were evaluated based on AIC and BIC of the dependent models. The best statistical fit is provided by the exponential distribution as it presents the lowest BIC value and is less than 2 points away from the lowest AIC value. Therefore, the exponential distribution was used in the base case analysis. Despite the Weibull distribution presenting the lowest AIC value, the BIC value is around six points from the exponential distribution. A second alternative distribution is the log-logistic, being the second and third best-fit on AIC and BIC, respectively. The Weibull and log-logistic distributions were explored through scenario analyses. Figure 10 gives a visual presentation of the OS without distant relapse curves.

Figure 10. Long-term OS without distant relapse extrapolations – Cohort 1 population; left panel ABE + ET and right panel ET-alone

Evidence from the MonarchE trial was deemed the most recent and relevant for the validation of the OS without distant recurrence extrapolations. The final choice of the distribution was based on internal validations.

Within the framework of the model, the selected OS extrapolations for base case and scenarios provide a hazard rate which is just below the hazard rate of age and gender corrected background mortality for the first few years. After which, the OS curve is bound by background mortality in the model. Considering the risk of death is low from a NMR, the likelihood of any bias is minimal.

8.1.2 Calculation of transition probabilities

The frequency of recurrence events is treatment arm-specific, based on the OS IA3 data cut of monarchE, as presented in Table 21.

8.1.2.1 IDFS

Patients enter the model in the IDFS state. From IDFS, patients can remain in IDFS, or transition to NMR, MR, or death. Using parametric survival equations, the monarchE IDFS data was extrapolated beyond the follow-up period. The probability that a patient will leave the IDFS state at any given time is calculated as 1 – S(t), where S(t) represents the survival function for remaining in IDFS. This transition probability is used to estimate the likelihood of moving to NMR, MR, or death. However, since death is already included within the IDFS survival curve, the probability of death without a distant recurrence is applied separately to avoid double-counting death events.

The model does not use a separate survival curve for the death state, distinguishing it from a partitioned survival model (PSM), where each health state would have its own survival curve. Instead, the IDFS curve is the only one that directly defines the proportion of patients staying in or leaving the IDFS state. OS is applied only to patients who have not experienced a distant recurrence, aligning with approaches in previous early breast cancer appraisals (e.g., TA569, TA612, TA632). (Refer to *Table 25*).

8.1.2.2 NMR

Patients experiencing non-metastatic disease recurrence were assumed to have a low risk of experiencing disease metastases during the 12-month treatment period. At the time of the last data cut (OS IA3) the monarchE trial had follow-up data of 54 months, allowing data to be used to estimate a transition to MR from NMR. Due to the limited data, and uncertainty, an exponential distribution was fit based on a single constant hazard over time. The assumption of a constant hazard was deemed the most suitable. An independent exponential model was the only model which converted when fit to the OS IA3 data of the ITT population of monarchE. Consequently, the independent exponential model for the ITT population was used for all populations in the model. Patients can also die at any point from the disease recurrence. Those who do not die or experience MR are assumed to receive 12 months of treatment before transitioning to the remission health state.

8.1.2.3 Remission

The clinical observational and economic SLRs identified a lack of data surrounding the remission health state and subsequent pathway for the monarchE patient population. Following consultation with TLs, assumptions previously made in EBC 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. TA632 used a study (Hamilton et al. (2015)) (80).

8.1.2.4 MR

At the time of the last data cut (OS IA3) the monarchE trial had limited follow-up data (54 months). Due to the study design of monarchE, the data on post-recurrence events are not suitable for modelling these advanced health states. The clinical observational SLRs were unable to identify suitable data to model the metastatic setting in greater detail.

In the absence of clinical data for the monarchE distant disease recurrent population, data from a broader advanced breast cancer population which included patients at high risk of disease recurrence were considered. The ET-resistant and ET-sensitive metastatic patient pathways were based on the clinical and economic evidence supporting the use of ABE in combination with ET as a treatment for advanced breast cancer in these settings.

The metastatic disease setting could in theory be modelled in three different ways using the MONARCH 2 and MONARCH 3 models. A further description of the mentioned approaches can be found in Appendix M. An assessment of the three methods of implementation concluded that the first 'fixed pay-off' method was the most appropriate. The approach incorporates a suitable level of complexity by allowing the model cohort to move to the metastatic disease setting via both faster and slower pathways (i.e., ET-resistant [MONARCH 2] and ET-sensitive pathways [MONARCH 3]). The method allows crucial survival, utility, and cost data from both CMs to be incorporated into the monarchE model while maintaining the computational power of the Excel model.

8.1.2.4.1 Metastatic recurrence chosen approach

An assessment of the three methods of implementation concluded that the first 'fixed pay-off' method in Table 15 was the most appropriate. The approach incorporates a suitable level of complexity by allowing the model cohort to move to the metastatic disease setting via both faster and slower pathways (i.e., ET-resistant [MONARCH 2] and ET-sensitive pathways [MONARCH 3]). The metastatic health state is further described in Appendix M.

8.1.2.4.2 Previous discussions regarding the similarities to Partitioned Survival modelling (PSM)

In prior discussions, the DMC suggested that a partitioned survival model (PSM) might better describe the approach. However, a Markov model for the early breast cancer pathway is maintained for this submission, incorporating only select elements of the PSM framework. In Markov models, 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). Unlike a PSM, the submitted model includes transition probabilities between all health states in the model.

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. In the submitted model, the model 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. 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.

Lastly, in a Markov model, the structural link OS predictions and intermediate endpoints such as progression is the fundamental difference from PSMs, which consider OS to be independent of other clinical events. In the submitted model, 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.

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.

8.1.2.5 Transition probabilities

Table 25. Transition from IDFS

Health state (from)	*Health state (to)*	*Transition probabilities or rates*
IDFS	IDFS: S(t)	Remaining in IDFS: S(t)
	NMR: Pnmr	IDFS_NMR: Pnmr x (1-S(t))
	MR: Pmr	IDFS_MR: Pmr x (1-S(t))

Note: *IDFS(t)* represents the IDFS function over time, the transition probability from IDFS health state to any health state is 1 – *IDFS(t)*. Applying mortality among patients in the IDFS health state (i.e. OS without distant recurrence [OSM]) the patients still alive with a recurrence event 1 – *IDFS(t)* – Prb $_{death}$ (t). If $p_{NMR} = p$ denotes the constant proportion of non-metastatic recurrence, then the transition probability to non-metastatic recurrence health state from IDFS state is $p \times (1 - IDFS(t) - Prb_{death}(t)) = Prb_{NMR}$. This formula was also applied for $p_{MR} = 1 - p$.

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, refer to *Table 26*. The proportion of patients transitioning to NMR or MR is based on constant values derived from the monarchE trial. In the abemaciclib + ET arm, these probabilities decline over time, eventually matching those in the ET-only arm after 5 years of treatment. If patients transition to the MR state within 72 months (i.e., 12 months after the 5-year treatment window), they are considered endocrine-resistant. After this period, patients are classified as endocrine-sensitive.

The remaining IDFS events are either NMR or MR. The proportion between the number of NMR and MR is considered constant overtime. The split of the total number of IDFS events

(excluding death) is 1 – *IDFS(t)* – $Prb_{death}(t) = Prb_{NMR}(t) + Prb_{MR}(t)$. Therefore: p × (1 – *IDFS(t)* – *OSM(t))* = P_{NMR}

N_{NMR}: number of non-metastatic recurrence, N_{MR}: number of metastatic recurrence, $N_{any\ recurrence}$: total number of IDFS events (excluding death). Therefore, the constant proportion of NMR is p= N_{NMR} / N_{any} $r_{ecurrence.}$

Table 26 below presents the transition probabilities used in the model (Refer to Appendix L for further description).

Table 26. Transitions in the health economic model

Health state (from)	*Health state (to)*	*Transition name*	*Value / Description of method*	*Reference*
NMR	Remission	NMR_REM	1	*After 12 months all patients transition into the remission health state or die due to all cause mortality*
	MR (ET resistant)	NMR_ETS	At the time of the last data cut (OS IA3) the monarchE trial had follow-up data of 54 months, allowing data to be used to estimate a transition to MR from NMR.	*Patients who experience a disease recurrent event on or within 12 months of completing adjuvant ET either in IDFS or NMR follow the ET-resistant (MONARCH 2) pathway.*
	Death	NMR_D	Maximum of background mortality or IDFS death rate (= OS without distance recurrence)	*MonarchE and life tables*
Remission	MR (ET sensitive)	REM_ETS	0.0076	*Hamilton et al (2015)*
	Death	REM_D	Maximum of background mortality or IDFS death rate (= OS without distance recurrence)	*MonarchE and life tables*
IDFS	NMR	IDFS_NMR	NMR % from trial applied to adjusted IDFS curve.	*MonarchE. The model applies constant probabilities from trial data to*
	MR (ET resistant)	IDFS_ETR	MR % from trial applied to adjusted IDFS curve. After 72 months, this decreases to 0, as all patients enter the MR (ET sensitive) health state	

MR (ET sensitive)	IDFS_ETS	MR % from trial applied to adjusted IDFS curve. 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%.	*distribute patients leaving IDFS into NMR or MR states. The IDFS curve determines how many patients leave IDFS in each cycle, while the transition probabilities assign those patients to the respective health states (NMR, MR).*
Death	IDFS_D	Maximum of background mortality or IDFS death rate (= OS without distance recurrence)	

Abbreviations: NMR= non-metastatic recurrence; IDFS= Invasive disease-free survival; MR= metastatic recurrence

Note: OS without distant recurrence is defined by censoring patients who experience metastatic recurrence (MR) at the time of their MR event. 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.

8.2 Presentation of efficacy data from [additional documentation]

Not applicable

8.3 Modelling effects of subsequent treatments

Clinical guidelines informed the treatments included in the NMR setting. Subsequent treatment for ET-resistant and ET-sensitive MR health states have also been included, however, based on the ABE CMs for ABC (MONARCH 2 and MONARCH 3, respectively).

As described in 5.3 the metastatic disease setting was modelled using the MONARCH 2 and MONARCH 3 models. The chosen approach for implementation in the model whereby survival outcomes following disease recurrence to the metastatic health state from either the IDFS or the remission health states at the point of disease recurrence were attributed a 'fixed pay-off' of LYs from these advanced breast cancer models. The costs and utilities associated with each health state within the respective metastatic disease pathways were combined with the LYs to determine the estimated total costs and QALY outcomes for the metastatic disease setting in the MonarchE model.

Refer to Section 11.6 for description of the subsequent treatment costs.

8.4 Other assumptions regarding efficacy in the model

Treatment waning effect

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 (Cuzick et al. (2010) (81)) However, the ATAC trial does not report data on HER2 status.

The authors of the paper demonstrate the falling recurrence rates for HR+ patients on anastrozole versus tamoxifen over time with 'carryover benefit' lasting up to eight years following which the treatment effect begins to wane (Figure 32).

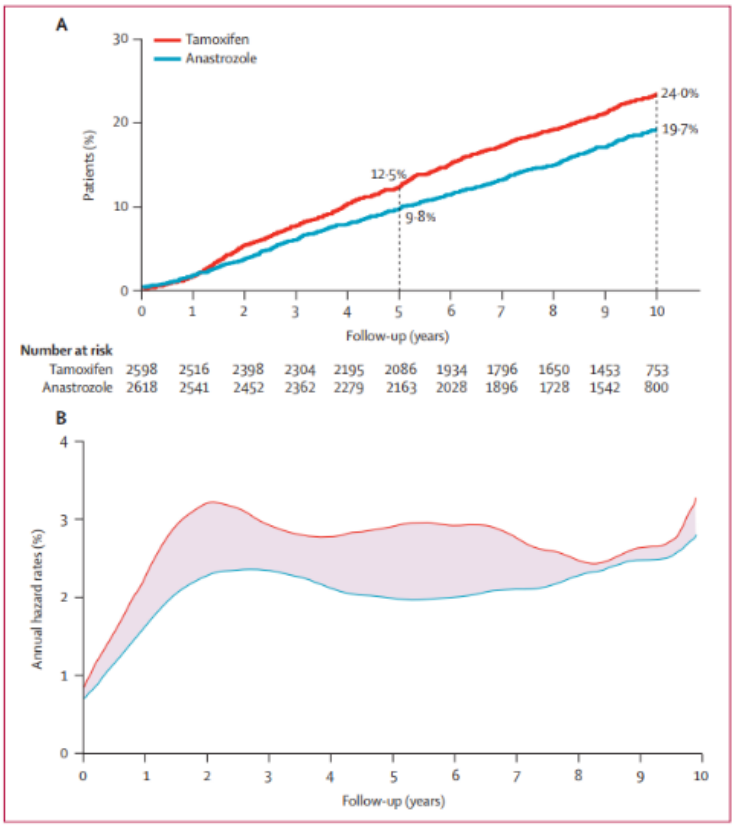


Figure 1: **Curves for time to recurrence in hormone-receptor-positive patients**
(A) Kaplan-Meier prevalence curves and (B) smoothed hazard rate curves.[6] Numbers at risk differ in some cases from those provided in the 100-month analysis[3] because of additional follow-up data.

Abbreviations: HR+, hormone receptor positive
Source: Figure 1a and 1b, Cuzick et al. (2010)

Although the population of the Cuzick et al. (2010 (81)) paper is not directly comparable to monarchE, it was assumed that the treatment effect between ABE + ET and ET alone would follow a similar trend to what was observed beyond more effective ET treatments. We have assumed that treatment effect lasts for at least eight years but starts to wane afterward. By year 26, the model assumed no further treatment benefit remains. Year 26 was the point in the model where the IDFS hazard rate equals the hazard rate of background mortality (Figure 11), aligned with the approach from TA612 in the HER2+ space (82).

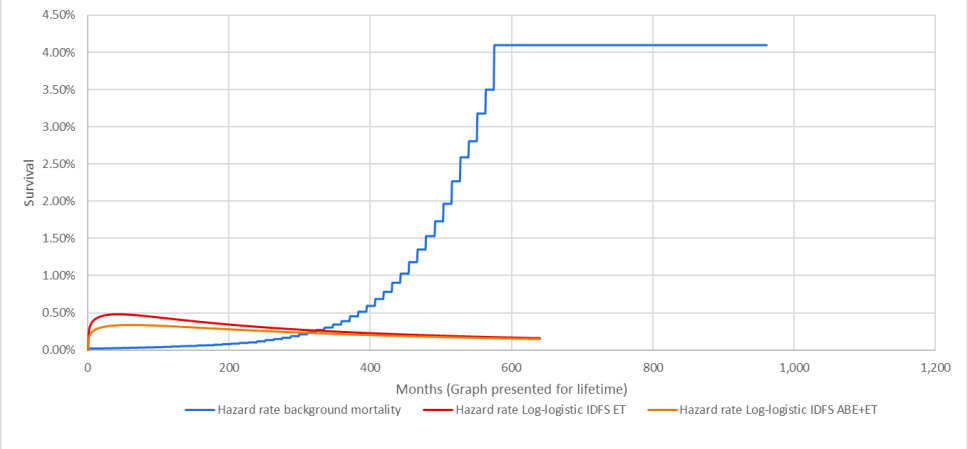


Figure 11 IDFS - crossing of the hazard rate with general population mortality
Abbreviations: ABE, Abemaciclib; ET, Endocrine therapy; IDFS, Invasive disease-free survival

The observed IDFS OS IA3 data of the monarchE trial did not indicate a treatment waning effect, although ABE treatment stopped at two years. Figure 12 illustrates the IDFS hazard rates of the ABE + ET (in black) and ET alone (in pink) arms at six monthly intervals over 60 months. The curves show the second order polynomial trendline of the individual six-monthly hazard rates (presented in dots). The curves show that after approximately 36 months the IDFS hazard rates start to decline for both treatment arms. Based on visual inspection, the relative effect between the treatment arms is not narrowing as the two curves are not converging, suggesting a continued treatment effect from ABE. It cannot be ruled out that over time the IDFS hazard rates of ABE + ET and ET alone will converge.

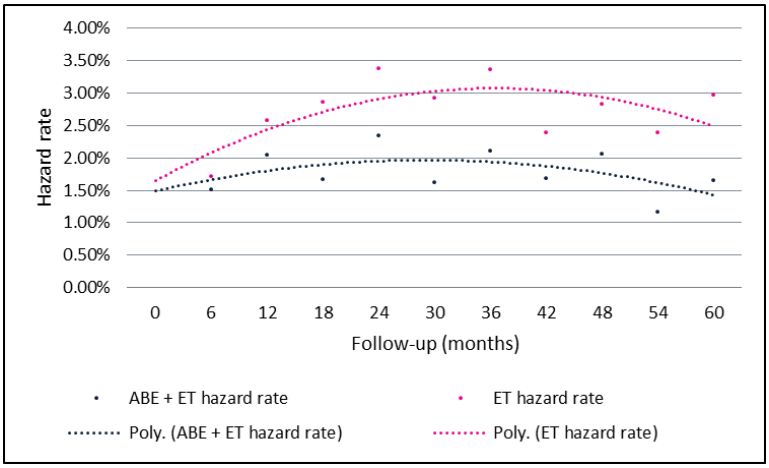


Figure 12 Curves of IDFS hazard rates of ABE + ET and ET alone arms - OS IA3 2023 ITT population

Figure 13 Curves for time to recurrence in HR+ patients

Table 27 Assumptions regarding waning effect

Model input	Base case	Assumption
Waning effect	For the ABE + ET arm, treatment effect waning assumption from eight years with no treatment effect	Waning of treatment effect assumed beyond clinical trial data. Based on long-term treatment effect observed for ET from historical trial data and in the absence of additional evidence we

Model input	Base case	Assumption
	beyond year 26 (resulting in a total waning period of 18 years).	assume the treatment effect waning starts from year eight and no treatment effect exists beyond 26 years. At 26 years, the risk of disease recurrence from IDFS was equal to or less than background mortality.

Also, refer to Table 22, Table 23, and Table 24.

Key model assumptions

Table 28 provides an overview of several clinical assumptions.

Table 28 Key clinical assumptions

Model input	Assumption
IDFS curves	• Dependent model (single model with treatment coefficient) assumed with a log-logistic distribution following internal validity checks and assessment of external evidence for OS IA3 data cut. • Constant proportions between IDFS events have been assumed.
TTD curves	• Extrapolations based on within trial data were used to inform the ET arms. Independent models assumed with Hazard spline knot 2 distribution following internal validity checks. • KM curve was used to inform ABE TTD. • Two-year stopping rule applied for abemaciclib (24 months). • Five-year stopping rule applied for ET (60 months).
ET regimens	• The first ET regimen administered in monarchE was used for the ET cost estimate. • The proportion of ET received used the % given any time during the study.
OS without distant recurrence	• Dependent model (single model with treatment coefficient) assuming an exponential distribution following internal validity checks. • Hazard of dying in IDFS health state assumed the same as the hazard of dying in the NMR and REM health states.
Long-term treatment effect	• Waning of treatment effect was applied from year eight and no treatment effect exists beyond year 26, lasting for 18 years. At 26 years, the risk of disease recurrence from IDFS was equal to or less than background mortality.
NMR health state • **Duration of tunnel state** • **Utility estimate**	• All patients who experience an NMR were assumed to receive additional adjuvant therapy for up to 12-months. • Patients could experience MR or die due to all-cause mortality at any point. Patients who remained in the NMR health state at 12 months were assumed to transition into the REM health state. • An average utility value was applied to the NMR health state. The average takes account of three months of potential acute

Model input	Assumption
	treatment as discussed in third TL meeting. The method could lead to not assigning discount rates proportionately.
Probability for type of NMR from IDFS state	• The proportion of patients having a second primary, (loco)regional or contralateral disease recurrence when an NMR event takes place was assumed to be constant over time.
Probability of disease recurrence from REM health state	• A constant monthly probability of transition from remission to the metastatic disease health state.
Mean LYs for the ET-resistant & ET-sensitive pathways from the MONARCH 2 & MONARCH 3 CMs	• As the monarchE CM used mean LYs from the MONARCH 2 and MONARCH 3 CMs, it was assumed that all patients are alive until the mean LY point. This assumption may lead to under or overestimating the survival outcomes of the population. As we do not use individual survival curves from the MONARCH 2 and 3 CMs this is a limitation.
Cost of hospitalisation	• Cost of hospitalisation for treatment related and non-treatment related AEs was applied.

Abbreviations: IDFS: invasive disease-free survival; OS= overall survival; TTD = Time to treatment discontinuation, ET= endocrine therapy; NMR= non-metastatic recurrence; MR= metastatic recurrence; REM= remission; LY= life years;KM = kaplan-meier; ABE= abemaciclib;

8.5 Overview of modelled average treatment length and time in model health state

Table 29. Estimates in the model, half-cycle corrected

	Modelled average IDFS ("Outcomes" row 82-85)	Modelled median IDFS ("Outcomes" row 82-85)	Observed median from relevant study
ABE + ET	[redacted]	[redacted]	[redacted]
ET-alone	[redacted]	[redacted]	[redacted]

Abbreviations: ABE= Abemaciclib: ET= endocrine treatment; NA= not applicable; IDFS= Invasive disease-free survival

The model does not specifically report the average length of treatment as this is not particularly informative, considering the stopping rules in both arms. The model has a 5-year stopping rule for ET and a two-year stopping rule for abemaciclib. The TTD curve is used to extrapolate until the 5-year stopping rule but following that point, it is not used to inform anything in the model anymore.

The duration of treatment is determined by the TTD curves for ABE+ET and ET alone 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 monarchE trial was designed with a two-year on-study treatment period for both treatment arms, after which patients could enter the study follow-up period and receive post-discontinuation therapies (including ET). The TTD data were considered final at the previous cut-off. No new assumptions were made regarding TTD for this re-evaluation.

Table 30. Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length [months]	IDFS years	NMR years	Remission	Metastatic Recurrence-ET-Resistant	Metastatic Recurrence-ET-Sensitive
ABE + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ET-alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABE= Abemaciclib: ET= endocrine treatment; NA= not applicable; IDFS= Invasive disease-free survival; NMR= non-metastatic recurrence

9. Safety

9.1 Safety data from the clinical documentation

The safety of abemaciclib plus ET in men and women with HR+/HER2− early breast cancer at high-risk of recurrence was evaluated in the MonarchE trial. With all patients having completed or discontinued early from the two-year on-study treatment period at the previous data cut the cumulative safety data of abemaciclib plus ET at OS IA3 were comparable to that reported at OS IA2. There were no new adverse drug reactions identified at the time of OS IA3. Overall, there were minimal changes in the incidences of any-grade treatment-emergent adverse events (TEAEs), Grade ≥3 TEAEs, serious adverse events (SAEs) at OS IA3 compared to OS IA2.

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 plus ET, and 2,800 received ET alone.

The median duration of exposure to study treatment was similar across both arms of the study. In the abemaciclib plus ET arm, the median duration of abemaciclib treatment was approximately 23.7 months (with a mean of approximately 19 months), while in the ET alone arm the median duration treatment was approximately 23.8 months (with a mean of approximately 21 months).

The safety of abemaciclib in combination with ET was evaluated through the assessment of TEAEs, SAEs, TEAEs leading to discontinuation, and TEAEs leading to deaths.

Table 31. Overview of safety events. Safety population (DCO 03 July 2023) (83)

	Abemaciclib + ET (n=2,791)	ET alone (N=2,800)	*Difference, % (95 % CI)*
Number of adverse events, n	*2746*	*2488*	*258 (9.4) (NA)*
Number and proportion of patients with ≥1 adverse events, n (%)	*2746 (98.4)*	*2488 (88.9)*	*258 (9.4) (NA)*
Number of serious adverse events*, n	*435*	*435*	*0 (0) (NA)*

	Abemaciclib + ET (n=2,791)	ET alone (N=2,800)	*Difference, % (95 % CI)*
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	*435 (15.6)*	*258 (9.2)*	*117 (40.7) (NA)*
Number of CTCAE grade ≥ 3 events, n	*1395*	*474*	*NA 921 (66.0) (NA)*
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	*1395 (50.0)*	*474 (16.9)*	*NA 921 (66.0) (NA)*
Number of adverse reactions, n	*NA*	*NA*	*NA*
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	*NA*	*NA*	*NA*
Number and proportion of patients who had a dose reduction, n (%)	*1221 (43.7)*	*NA*	*NA*
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	*NA*	*NA*	*NA*
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	*180 (6.4)*	*30 (1.1)*	*150 (83.3) (NA)*

** A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).*
§ CTCAE v. 5.0 must be used if available.
NA= no statistical analysis was performed, thus a comparison is not provided.
Abbreviations: ET= endocrine treatment; CI= confidence interval; CTCAE= National Cancer Institute Common Terminology Criteria for Adverse Events

The incidence of SAEs was higher in the abemaciclib plus ET arm as compared with the ET alone arm. Injury, poisoning and procedural complications and pneumonia were the most commonly reported SAEs by patients treated with abemaciclib + ET (1.3% [37/2,791] and 1.0% [28/2,791], respectively). Patients treated with ET alone reported injury, poisoning and procedural complications (1.0% [29/2,800]) and pneumonia (0.6% [17/2,800]) most commonly.

Table 32. SAEs in ≥5 patients in either arm of the safety population, July 2023 DCO

Adverse events	**Abemaciclib + ET (N=2,791)**		**ET alone (N=2,800)**	
	Number of patients with adverse events	***Number of adverse events***	***Number of patients with adverse events***	***Number of adverse events***
Infections and infestations	149 (5.3)	NA	82 (2.9)	NA
Pneumonia	28 (1.0)	NA	17 (0.6)	NA
Cellulitis	14 (0.5)	NA	10 (0.4)	NA
Urinary tract infection	14 (0.5)	NA	4 (0.1)	NA
COVID-19 pneumonia	9 (0.3)	NA	1 (0.0)	NA
Influenza	7 (0.3)	NA	4 (0.1)	NA
Mastitis	6 (0.2)	NA	7 (0.3)	NA
Appendicitis	6 (0.2)	NA	2 (0.1)	NA
Sepsis	6 (0.2)	NA	3 (0.1)	NA
Upper respiratory tract infection	6 (0.2)	NA	0 (0.0)	NA
Breast cellulitis	5 (0.2)	NA	5 (0.2)	NA
Erysipelas	6 (0.2)	NA	0 (0.0)	NA
COVID-19	5 (0.2)	NA	1 (0.0)	NA
Diverticulitis	3 (0.1)	NA	5 (0.2)	NA
Gastrointestinal disorders	59 (2.1)	NA	17 (0.6)	NA
Diarrhoea	15 (0.5)	NA	0 (0.0)	NA
Abdominal pain	6 (0.2)	NA	1 (0.0)	NA
Pancreatitis	6 (0.2)	NA	2 (0.1)	NA
Colitis	5 (0.2)	NA	3 (0.1)	NA
Respiratory, thoracic and mediastinal disorders	38 (1.4)	NA	10 (0.4)	NA
Pneumonitis	8 (0.3)	NA	0	NA
Pulmonary embolism	18 (0.6)	NA	4 (0.1)	NA
Vascular disorders	31 (1.1)	NA	12 (0.4)	NA
Lymphoedema	7 (0.3)	NA	3 (0.1)	NA
Nervous system disorders	29 (1.0)	NA	20 (0.7	NA
Syncope	5 (0.2)	NA	2 (0.1)	NA
Cardiac disorders	26 (0.9)	NA	15 (0.5)	NA
Atrial fibrillation	8 (0.3)	NA	1 (0.0)	NA
General disorders and administration site conditions	27 (1.0)	NA	10 (0.4)	NA
Pyrexia	10 (0.4)	NA	0 (0.0)	NA
Cardiac disorders	25 (0.9)	NA	15 (0.5)	NA
Atrial fibrillation	8 (0.3)	NA	1 (0.0)	NA
Hepatobiliary disorders	24 (0.9)	NA	9 (0.3)	NA
Cholecystitis	10 (0.4)	NA	4 (0.1)	NA
Cholecystitis acute	5 (0.2)	NA	0 (0.0)	NA
Blood and lymphatic disorders	24 (0.9)	NA	4 (0.1)	NA
Anaemia	9 (0.3)	NA	2 (0.1)	NA
Thrombocytopenia	6 (0.2)	NA	1 (0.0)	NA
Febrile neutropenia	5 (0.2)	NA	1 (0.0)	NA
Metabolism and nutrition disorders	16 (0.6)	NA	8 (0.3)	NA
Dehydration	7 (0.3)	NA	0 (0.0)	NA
Hypokalemia	5 (0.2)	NA	1 (0.0)	NA
Renal and urinary disorders	15 (0.5)	NA	5 (0.2)	NA
Acute kidney injury	7 (0.3)	NA	1 (0.0)	NA

Adverse events	**Abemaciclib + ET (N=2,791)**		**ET alone (N=2,800)**	
Nephrolithiasis	5 (0.2)	NA	2 (0.1)	NA
Reproductive system and breast disorders	14 (0.5)	NA	25 (0.9)	NA
Uterine polyp	4 (0.1)	NA	5 (0.2)	NA
Injury, poisoning and procedural complications	37 (1.3)	NA	29 (1.0)	NA
Wound dehiscence	0 (0.0)	NA	5 (0.2)	NA

Abbreviations: ET= endocrine therapy; N= number of patients in the safety population; n= number of patients within category; SAE= serious adverse event; NA= not available
Source: Lilly Data on File. Clinical Study Report Addendum: MonarchE. Data cutoff: 03 July 2023

The model base case includes Grade III/IV AEs with an incidence of ≥ 1% observed in the respective treatment arms of MonarchE. Grade I/II AEs with an incidence of ≥ 1% observed in the respective treatment arms of MonarchE could be included in the model in case of interest to the model user. The inclusion of side effects has two functions in the health economic model. Side effects incur costs related to the treatment/management of the side effect, as well as a utility loss associated with experiencing the respective side effect. A summary of the Grade III/IV AE rates used in the model for each treatment and the related sources are shown in Table 33**Error! Reference source not found.**. A full list of all Grade III AEs is provided in Appendix K.

Table 33. Adverse events used in the health economic model

Adverse events	***Intervention***	***Comparator***	
	Frequency used in economic model for intervention	***Frequency used in economic model for comparator***	***Source & Justification***
Neutropenia	19.60%	0.90%	*Based on the MonarchE trial. Grade, Grade III/IV AEs*
Leukopenia	11.40%	0.40%	
Diarrhoea	7.80%	0.20%	
Lymphopenia	5.40%	0.50%	
Fatigue	2.90%	0.10%	
Aspartate aminotransferase increase	1.50%	0.90%	
Alanine aminotransferase increase	2.50%	1.20%	
Thrombocytopenia	1.30%	0.10%	
Anaemia	2.10%	0.40%	
Abdominal pain	1.40%	0.30%	
Venous thromboembolic event	1.40%	0.30%	

Abbreviations: AE= adverse event

9.2 Safety data from external literature applied in the health economic model

Not applicable

Table 34. Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	NA	NA	NA	NA	NA	NA	NA	NA

Abbreviations: NA= not applicable

10. Documentation of health-related quality of life (HRQoL)

Utility values were derived from the utility analyses carried out using the IPD from the monarchE trial 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 values. Descriptive utility tariff was used for the base case.

It should be noted that the included HSUVs in this submission were also submitted to the DMC and assessed in the previous assessment of abemaciclib (refer to the assessment report in Table 41 in the previous report).

Table *35. Overview of included HRQoL instruments*

Measuring instrument	Source	Utilization
FACT-B (Functional Assessment of Cancer Therapy-Breast)	MonarchE	Its purpose was to measure 5 domains of HRQOL in breast cancer patients: physical, social, emotional, functional well-being as well as a breast-cancer subscale (BCS). Presented in Appendix F.
FACT-ES (Functional Assessment of Cancer Therapy - Endocrine Symptoms)	MonarchE	To describe endocrine therapy-related symptoms with 5 domains of: physical, social, emotional, functional, and endocrine symptom subscale. Presented in Appendix F.
FACIT-F (Functional Assessment of Chronic Illness Therapy – Fatigue)	MonarchE	Assess self-reported fatigue and its impact upon daily activities and function. Presented in Appendix F.
EQ-5D-5L	MonarchE	Measure HRQOL with 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problem, slight problems, moderate problems, severe problems, and extreme problems.

Abbreviations: FACT-B= Functional Assessment of Cancer Therapy-Breast; FACT-ES= Functional Assessment of Cancer Therapy - Endocrine Symptoms; FACIT-F= Functional Assessment of Chronic Illness Therapy – Fatigue; EQ-5D-5L= EuroQol 5-dimensions 5-levels; HRQoL= health-related quality of life; BCS= breast cancer subscale

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instrument

In the MonarchE trial, utility data was collected on therapy or up to "Short Term Follow-Up" or Q12M (one year after discontinuation). The MonarchE trial was set up with a 2-year on-study treatment period for both treatment arms, after which patients could enter the study follow-up period. This means that all patients were off the study treatment for at least a year at the OS IA2 data cut and as such, utility data was considered final at the OS IA2 data cut. Therefore, utility data was not updated with the OS IA3 data cut and OS IA2 data is used to inform the utility analysis (DCO 2021).

Different PROs were used to measure HRQoL: FACT-B, FACT-ES, FACIT-F, and EQ-5D-3L. After the baseline assessment, FACT-B, FACT-ES, 2 FACIT-sourced items of cognitive symptoms, 3 FACIT-sourced items for bladder symptoms, EQ-5D-5L questionnaires were next administered to patients at visit 6, visit 9, visit 15, and visit 21 (approximate timepoints of visits, 3, 6, 12 and 18 months respectively). Questionnaires were given at

visit 27 (end of on study treatment period) and follow-up visits are not included in IA2 due to <25% of patients having an assessment at those visits.

For this submission, EQ-5D-5L is used to inform HSUVs. It should be noted that EQ-5D-5L index is reported from the 2021 data cutoff (the same data cutoff that was submitted in the previous abemaciclib submission to the DMC). For EQ-5D-5L by VAS score, FACT-B, FACT-ES, and FACIT-F, the available data cutoff(s) is July 2020. Only data collection and results for EQ-5D-5L index is reported in the following section. For the other PRO analyses and results, please refer to Appendix F.1.

The analyses on PROs were based on the safety population (DCO 2021) (results reported in 10.1.3). A mixed effects repeated measures (MMRM) model was applied to compare treatment arms by assessment with respect to each of the summary scores and select items. The summary scores were calculated as per the FACIT guidance. An effect size of one-half standard deviation (0.5 SD) was used. This represents a conservative estimate of a minimally important difference (MID) (Norman 2003). For the analysis of individual items, a change of one point was deemed meaningful.

As a result of the large sample size necessary to support other efficacy endpoints, all statistical comparisons of PRO data are overpowered and it is likely that any numerical differences between arms will be deemed statistically significant regardless of clinical significance. Because patients are disease-free at enrolment and the majority of patients in either arm do not experience disease recurrence, the majority of changes in patient-felt symptoms or impacts are assumed to be treatment-related. Therefore, differences across treatment arms were evaluated based on numerical estimates and the interpretation should be viewed as exploratory.

10.1.2 *Data collection*

Tables below shows the pattern of missing EQ-5D data and completion, for ABE + ET and for ET alone, respectively. The collection data in the table below is from the 2021 data cut-off. Compliance rates and reason for noncompliance can also be found in Appendix F.3.

Table *36. Pattern of missing data and completion – ABE + ET (DCO: 2021)*

Time point	*HRQoL population N*	*Missing N (%)*	*Expected to complete N*	*Completion N (%)*
	Number of patients at randomization	*Number of patients for whom data is missing (% of patients at randomization)*	*Number of patients "at risk" at time point X*	*Number of patients who completed (% of patients expected to complete)*
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Visit 6	[redacted]	[redacted]	[redacted]	[redacted]
Visit 9	[redacted]	[redacted]	[redacted]	[redacted]
Visit 15	[redacted]	[redacted]	[redacted]	[redacted]
Visit 21	[redacted]	[redacted]	[redacted]	[redacted]
Visit 27	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up	[redacted]	[redacted]	[redacted]	[redacted]

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Add. Follow-up 1	[redacted]	[redacted]	[redacted]	[redacted]
Add. Follow-up 2	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HRQoL= health-related quality of life; N=number of patients

Table *37. Pattern of missing data and completion – ET alone (DCO: 2021)*

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	*Number of patients for whom data is missing (% of patients at randomization)*	*Number of patients "at risk" at time point X*	*Number of patients who completed (% of patients expected to complete)*
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Visit 6	[redacted]	[redacted]	[redacted]	[redacted]
Visit 9	[redacted]	[redacted]	[redacted]	[redacted]
Visit 15	[redacted]	[redacted]	[redacted]	[redacted]
Visit 21	[redacted]	[redacted]	[redacted]	[redacted]
Visit 27	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up	[redacted]	[redacted]	[redacted]	[redacted]
Add. Follow-up 1	[redacted]	[redacted]	[redacted]	[redacted]
Add. Follow-up 2	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HRQoL= health-related quality of life; N=number of patients

10.1.3 HRQoL results

The mean scores for the EQ-5D-5L VAS score, FACT-B and FACT-ES subscales are shown in Table 80, Table 78 and Table 79 in Appendix F, respectively. For the base case analysis, EQ-5D-5L has been used to inform HSUVs. EQ-5D-5L results are provided in the following subsection.

EQ-5D-5L

EQ-5D-5L index values were very similar between arms for all baseline and post-baseline assessments. Overall, index values in most post-baseline assessments were stable and similar to baseline values for both treatment arms, see Table 38.

The 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.

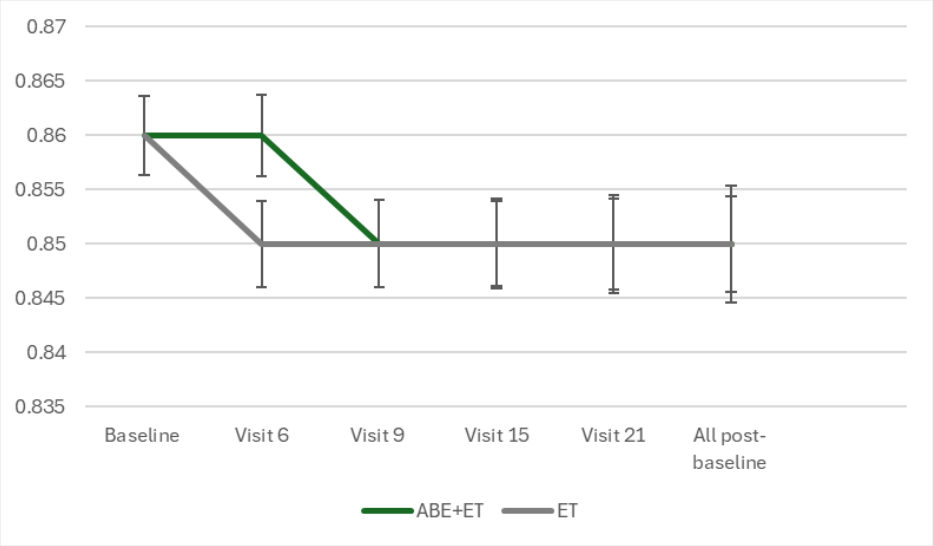


Figure 14 Mean change from baseline, ABE + ET and ET - EQ-5D (DCO 2021)

Table 38. Summary of EQ-5D-5L Index in MonarchE, safety population, DCO 2021, DK weighted

	Abemaciclib + ET DCO 2021			ET alone DCO 2021			Abemaciclib + ET versus ET alone
	n	Mean (SD)	CfB, LSM (SE)	n	Mean (SD)	CfB, LSM (SE)	LSM Change Difference (SE)
EQ-5D-5L Health State Index							
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: EQ-5D 5L= EuroQol 5-Dimension 5-Level; LSM= least squares mean; SE= standard error; SD= standard deviation; CfB= change from baseline; ET= endocrine therapy.
Source: Lilly Data on File. Clinical Study Report: MonarchE. Data cut-off: 08 July 2020.

10.2 Health state utility values (HSUVs) used in the health economic model

10.2.1 HSUV calculation

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. 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 MMRM regression and included independent variables treatment, visit, treatment*visit, and baseline. These values were used for the base case.

Danish preference weights

In accordance to the DMC guidelines for the assessment of pharmaceuticals, derived from the MonarchE trial, were weighted based on the general Danish population preferences (85) based on the suggested method (86) (87).

Age-related utility deterioration

Utility values of the model pre-metastatic health state utilities (IDFS, non-metastatic recurrence and remission) health states are adjusted to account for the natural decrease in QoL associated with age. Adjusting utilities for age can prevent the overestimation of benefits associated with treatment that can occur if otherwise a baseline of perfect health is assumed. HSUVs are age-adjusted according to the methods described in the Appendiks: Aldersjustering for sundhedsrelateret livskvalitet of the DMC guidelines.

10.2.1.1 Mapping

Not applicable

10.2.2 *Disutility calculation*

Not applicable

10.2.3 *HSUV results*

An overview of the utilities that are used in the model are presented in Table 39. The iDFS utility value was weighted based on the general Danish population preferences and adjusted for age-related utilities, as described above. In regard to utility values for the other health states, as they were derived from the literature or the metastatic setting monarch 2 and monarch 3 models, no adjustment was applied to the values.

Table 39. Overview of health state utility values used in the model

	Results [95% CI]	*Instrument*	*Tariff (value set) used*	*Comments / source*
HSUVs				
IDFS	[redacted]	*EQ-5D-5L*	*DK*	*Estimate is based on mean of both trial arms. MonarchE (ITT), Lilly statistics team (MMRM) DCO 2021*
NMR	*0,696* [redacted]	*EQ-5D-5L*	*UK / DK*	*0,696 for first 3 months and* [redacted] *for last 9 months for both trial arms; Last 3 months: assumed equal to IDFS* First 3 months: Lidgren *et al.* 2007 (70). Last 9 months: assumed equal to IDFS (therefore, DK weighted) = applied as an average for NMR utility = [redacted]
REM	[redacted]	*EQ-5D-5L*	*UK*	*For both trial arms; equal to IDFS (TA632 assumption)* (therefore, DK weighted)
ETR-PFS	*0,747*	*EQ-5D-5L*	*UK*	*MONARCH 2 and NOMA assessment (ID2021_038, Table 13)*
ETR-PPS	*0,505*	*EQ-5D-5L*	*UK*	*Utilizing the utility value applied for ETS-PPS, can be found in NOMA assessment (ID2021_038, Table 13)*
ETS – PFS1	*0,724*	*EQ-5D-5L*	*UK*	*For all ETS treatments, MONARCH 3 and NOMA assessment (ID2021_038, Table 13)*
ETS – PFS2	*0,690*	*EQ-5D-5L*	*UK*	*For all ETS treatments, TA563, ACD committee papers, section 4.3.5 – ERG preferred (71)*

	Results [95% CI]	Instrument	Tariff (value set) used	Comments / source
ETS-PPS	*0,505*	*EQ-5D-5L*	*UK*	*For all ETS treatments, TA563, ACD committee papers, section 4.3.5 – ERG preferred and NICE submission (TA239) (Lloyd et al) (71). Also found in NOMA assessment (ID2021_038, Table 13)*

Abbreviations: ETR= Endocrine therapy resistant (MONARCH 2); ETS= Endocrine therapy sensitive MONARCH 3; IDFS= Invasive disease-free survival; NMR= Non-metastatic recurrence; OS= overall survival; PFS= Progression free survival; PFS1= Progression free survival advanced breast cancer 1st line; PFS2= Progression free survival advanced breast cancer 2nd line; PPS= Post progression survival; REM= remission; EQ-5D= EuroQol 5-dimensions; CI= confidence interval

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

Not applicable

11. Resource use and associated costs

The costs included in this section are categorised as medicine costs (including co-administration costs), monitoring and administration costs, disease management costs, AE costs, as well as transport costs and time spent on treatment by patients, consistent with the restricted societal perspective as described in the DMC guidelines (54). Drug costs are sourced from Medicinpriser.dk and applied as pharmacy purchasing prices (PPP) (apotekernes indkøbspris, AIP) (88). Disease management, administration costs, and AE costs are based on Danish diagnosis related groups (DRG) tariffs from 2024 (89) and DMC catalogue for unit costs (2023) (90). Patient and transportation costs are based on the DMC catalogue for unit costs and are presented in a separate section covering all patient- and transportation costs for all health states (90).

11.1 Medicine costs - intervention and comparator

Medicine costs were calculated by combining dosing regimens with relative dose intensity adjustments derived from the MonarchE trial data (84). All PPP have been extracted from the Danish Medicines Agency database Medicinpriser.dk (88). For the ET regimens, to maintain a conservative approach, the lowest cost per mg was chosen from all the options available. An overview of the medicines used in the model is presented in Table 49 below, along with relevant dosages, frequency and relative dose intensity.

The TTD curves capture discontinuation of treatment for any cause, as such these curves are used alongside drug acquisition costs to determine treatment cost. Despite the primary endpoint being met, the follow-up period for MonarchE is relatively short. The treatment pathway of EBC is heterogenous. Internal research has been conducted by the Lilly team to assess adherence rates of patients with EBC to their adjuvant ET regimen. The study identified that adherence rates to adjuvant ET decline with each refill, with adherence expected to drop to 60% after two years (91). Given the short follow-up, extrapolating the TTD curve long-term may introduce moderate uncertainty in the CEM.

Drug wastage was not included in the base case analysis.

Table 40. Medicine costs used in the model for adjuvant setting

Medicine	*Dose*	*Relative dose intensity*	*Frequency*	*Vial sharing*	*Strength/unit (mg)*	*Units/pack*	*Pack cost (DKK)*
Abemaciclib	150mg	100%	Twice daily	NA	150	56 28	18,843 9,406
Letrozole	2.5mg	100%	Once daily	NA	2.5	100	135
Anastrozole	1mg	100%	Once daily	NA	1	100	38
Tamoxifen	20mg	100%	Once daily	NA	20	100	154
Exemestane	25mg	100%	Once daily	NA	25	100	3,650

Abbreviations: NA= not applicable

Please refer to Appendix M.4.1.1 and Appendix M.4.2.1 for description of drug costs in the metastatic setting.

11.2 Medicine costs – co-administration

Best supportive care

Components of best supportive care (BSC) were identified based on the concomitant medications prescribed in the MonarchE trial (84). 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. Table 39. provides an overview of the type of concomitant medications being modelled per treatment arm. Table 42 lists the dosing and cost assumptions for each concomitant medication.

Table 41. Type of concomitant medication by treatment arm

Agent	ABE + ET	ET-alone
Loperamide	66.6%	1.9%
Ibuprofen	9.1%	9.7%
Amoxicillin; Clavulanic	7.8%	5.4%
Amoxicillin	5.6%	4.8%
Colecalciferol	7.3%	8.4%
Calcium carbonate; colecalciferol	6.2%	7.3%
Vitamin D Nos	5.6%	5.4%
Zolederonic acid	9.9%	10.9%
Paracetamol	24.6%	21.0%
Levothyroxine	9.3%	8.6%
Metformin	5.8%	5.5%

Abbreviations: ABE= Abemaciclib; ET= Endocrine therapy
Source: Table JPCF.4.11 PO data cut 08JULY2020

Table 42. Drug cost and dosing options used in the model

Concomitant treatment dosing & administration	Cost/ package (DKK)	Total package dose (mg)	Dose per admin (mg)	Vial sharing	Number of administrations per cycle (N)	Admin route
Loperamide	182.15	200	2	N/A	28.00	Oral
Ibuprofen	55	100000	400	N/A	28.00	Oral
Amoxicillin; Glavulanic acid	65.75	18750	625	N/A	21.00	Oral
Amoxicillin	7.00	7500	750	N/A	28.00	Oral
Colecalciferol	63.38	4	0	N/A	28.00	Oral
Calcium carbonate; colecalciferol	110.00	96000	400	N/A	28.00	Oral
Vitamin D Nos	63.38	4	0	N/A	28.00	Oral
Zolederonic acid	70.06	4	4	N/A	0.15*	IV
Paracetamol	12.03	55000	500	N/A	28.00	Oral
Levothyroxine						
Metformin	39.00	200000	500	N/A	28.00	Oral

Abbreviations: IV= Intravenous; mg= Milligram; N= Number; N/A= not applicable
*Only administered in first 3 years
Source: Medicinpriser.dk

11.3 Administration costs

Administration costs were not considered to be relevant as all comparator treatments received in the adjuvant setting are administered orally. For the NMR health state, administration costs were included for chemotherapy, which was assumed to be administered for the treatment of certain types of recurrence. These have been costed separately according to NICE guidelines. Please refer to Appendix M.4 for further information regarding costing in the metastatic setting.

Table 43. Administration costs used in the model

Administration type	*Frequency*	*Unit cost [DKK]*	*DRG code*	*Reference*
IV	For first attendance & Subsequent cycles	1.625 kr.	Kvinde, 51 År (DC509) Brystkræft UNS, 09MA98 - MDC09 1-dagsgruppe, pat. mindst 7 år	DRG 2024 (89)
Oral		0 kr.	-	Assumption
SC		1.625 kr.	Kvinde, 51 År (DC509) Brystkræft UNS, 09MA98 - MDC09 1-dagsgruppe, pat. mindst 7 år	DRG 2024 (89)

Abbreviations: IV= Intravenous; SC= Subcutaneous; DRG= diagnosis-related groups

11.4 Disease management costs

The model attributes different types and levels of resource use to each health state. For each health state, resource use was based on clinical experts feedback (25) and on the MonarchE trial (84). For the metastatic recurrence health state, resource use was informed by global expert's feedback and the DMC submissions for aBC previously mentioned in section

11.4.1 Health state specific costs

11.4.1.1 IDFS

Based on Danish clinical expert (25) opinion, Table 44 provides a summary of the resources and associated resource use costs included in the economic model for the IDFS health state (92).

Table 44. Disease management costs used in the model for the IDFS health state

Activity	*Frequency*	*Unit cost [DKK]*	*DRG code*	*Reference*
Oncologist visit	Year 0-1.5: 0.31 visits per year Year >1.5: 0.15 visits per year	1,625	-09MA98 - MDC09 1-dagsgruppe, pat. mindst 7 år	DRG 2024 (89)
Mammogram	Year 0-1.5: 0.05 visits per year Year >1.5: 0.05 visits per year	4,248	(DC509) Brystkræft UNS, 30PR13 - Mammografi, kompliceret	DRG 2024 (89)

Abbreviations: DRG= diagnosis-related groups

11.4.1.1.1 Best supportive care

Please refer to Section 11.2.

11.4.1.2 Non-metastatic health state

Resource use and the treatment offered to patients with HER2− early breast cancer experiencing a non-metastatic recurrence of differing types was based on the NICE NG10 guideline for early and locally advanced breast cancer diagnosis (93). Danish clinical experts were then consulted to assess the relevance of these inputs in the Danish system (25). Both these sources 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 guidance for early and locally advanced breast cancer diagnosis and management were closely consulted to estimate the treatment mix offered (94). It should be noted that the NG101 guideline was predominantly relevant for patients with HER2+ EBC as there have been no changes in treatment guidelines for HER2- EBC in the last 10 years. Except for specific HER2+ targeted therapy, the treatment administered for a specific disease recurrence location would remain the same irrespective of HER2 status. It was assumed that HER2+ or HER2- status would not impact the type of treatment a patient is offered for that type of recurrence. Consequently, the CEM excludes HER2+ targeted treatment, but includes the rechallenge with ET prescribed during the IDFS health state, for the treatment

of an NMR event. During the second TL meeting Dr Hall agreed that ET may be offered to patients who experience an NMR.

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 (94). 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+ EBC would receive adjuvant chemotherapy, trastuzumab and pertuzumab.

Table 45 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 was based on the MonarchE CSR (53). An assessment of the IPD was conducted to determine the prior surgical and treatment history of those with specific tumour recurrence locations. Table 46 provides the costs per treatment type and associated costs were sourced from DRG tariffs 2024 (89). To capture ET for an NMR event, the same cost of ET in each cycle in the IDFS health state was applied to each cycle in the NMR health state, irrespective of recurrence type.

Table 45. Breakdown of Resource use for non-metastatic recurrence pathway

Recurrence type	*N (% receiving Mastectomy) [if originally had breast conserving surgery]*	*N (% receiving Major breast procedure)*
Oncologist visit, follow-up	N/28 days (per cycle)	0.153
Mammogram	N/28 days (per cycle)	0.051
Local: Major breast procedures (if patients originally had mastectomy)	% patients (one-off)	75%
Local/Regional: Delayed breast reconstruction	% patients (one-off)	10%
Local/Regional: Mastectomy with reconstruction (if patients orginaly had breast conserving surgery)	% patients (one-off)	30%
Contralateral: Major breast procedures (if patients originally had mastectomy)	% patients (one-off)	95%
Contralateral: Delayed breast reconstruction	% patients (one-off)	10%
Contralateral: Mastectomy with reconstruction (if patients originally had breast conserving surgery)	% patients (one-off)	30%
Radiotherapy	% patients (one-off)	100%
Chemotherapy (cycle 1)	% patients (one-off)	5%

Chemotherapy (cycle 2-6)	N/28 days (per cycle)	5%
Chemotherapy (subsequent cycles)	N/28 days (per cycle)	5%
Complete blood count	N/28 days (per cycle)	5%
Multidisciplinary team meeting	% patients (one-off)	100%

Abbreviations: ET= Endocrine therapy; N= Number

Note: The patient level data does not split surgical procedure into 'Mastectomy' or 'Major breast procedure', these proportions have been assumed the same. To ensure a simpler implementation of the resource use in the model.

Source: Danish clinical expert validation (25) (7)

Table 46. Costs for each treatment offered in the non-metastatic recurrent health state

Parameter	Costs	Reference (89)
Locoregional		
Major breast procedures (if patients originally had mastectomy)	DKK 38,816	DRG 2024 - 09MP03
Delayed breast reconstruction	DKK 70,086	DRG 2024 - 09MP07
Mastectomy with reconstruction (if patients originally had breast conserving surgery)	DKK 145,581	DRG 2024 - 09MP01
Radiotherapy	DKK 15,847	DRG 2024 - 27MP13
Chemotherapy: Total cost per cycle (Cycle 1)	DKK 19,511	DRG 2024 - 27MP21
Chemotherapy: Total cost per cycle (Cycle 2-6)	DKK 19,511	DRG 2024 - 27MP21
Chemotherapy: Total cost per cycle (subsequent cycles until disease progression)	DKK 19,511	DRG 2024 - 27MP21
Regional		
Delayed breast reconstruction	DKK 70,086	DRG 2024 - 09MP07
Mastectomy with reconstruction (if patients originally had breast conserving surgery)	DKK 145,581	DRG 2024 - 09MP01
Radiotherapy	DKK 15,847	DRG 2024 - 27MP13
Chemotherapy: Total cost per cycle (Cycle 1)	DKK 19,511	DRG 2024 - 27MP21
Chemotherapy: Total cost per cycle (Cycle 2-6)	DKK 19,511	DRG 2024 - 27MP21
Chemotherapy: Total cost per cycle (subsequent cycles until disease progression)	DKK 19,511	DRG 2024 - 27MP21
Contralateral		
Major breast procedures (if patients originally had mastectomy)	DKK 38,767	DRG 2024 - 09MP03
Delayed breast reconstruction	DKK 70,086	DRG 2024 - 09MP07
Mastectomy with reconstruction (if patients originally had breast conserving surgery)	DKK 145,581	DRG 2024 - 09MP01
Radiotherapy	DKK 15,847	DRG 2024 - 27MP13
Chemotherapy: Total cost per cycle (Cycle 1)	DKK 19,511	DRG 2024 - 27MP21
Chemotherapy: Total cost per cycle (Cycle 2-6)	DKK 19,511	DRG 2024 - 27MP21

Chemotherapy: Total cost per cycle (subsequent cycles until disease progression)	DKK 19,511	DRG 2024 - 27MP21

Abbreviations: DRG= diagnosis-related groups
Source: DRG 2024 (89)

11.4.1.3 Second primary neoplasm

As noted above, the CEM assumed patients who experience a second primary non-breast cancer event, receive the cost of diagnosing the second primary neoplasm (e.g., one oncology multidisciplinary team meeting (MDTM)) and exit the model.

Table 47. Base case multidisciplinary team meeting cost

	Cost per patient	Source (89)
Multidisciplinary team meeting Cost	DKK 1,625	DRG 2024 - 09MA98: MDC09 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DC509: Brystkræft UNS Procedure: (ZZ0190D1)Multidisciplinær team (MDT) konf., behandlingsbesluttende

Abbreviations: DRG= diagnosis-related groups

11.4.1.4 Remission

Following Danish clinical expert validation; Table 48 provides a breakdown of the resource use and cost assumptions for the remission health state.

Table 48. Cost and resource use for remission health state

Resource use	*Unit cost*	*Reference*	*% patients*	*Annual frequency*
GP visit	DKK 153.63	DMC Værdisætning af enhedsomkostninger (90)	100	1
Oncologist visit, follow-up	DKK 1,625.00	DRG 2024 - 09MA98 - MDC09 1-dagsgruppe, pat. mindst 7 år (89)	100	1

Abbreviations: GP= General practitioner; DMC= Danish Medicines Council; DRG= diagnosis-related groups

11.4.1.5 Metastatic health state costs

ET-resistant pathway
For the ET-resistant distant recurrence patient pathway, the following cost and resource use categories from the MONARCH 2 CEM were incorporated within the MonarchE CEM:

- Drug acquisition
- Drug administration
- BSC
- Follow-up care
- AE
- 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.

A detailed breakdown for metastatic health state costs is provided in Appendix M.4

ET-sensitive pathway

For the ET-sensitive distant recurrence patient pathway, cost categories considered in the from the MONARCH 3 CEM were incorporated within the MonarchE CEM (see Figure 15).

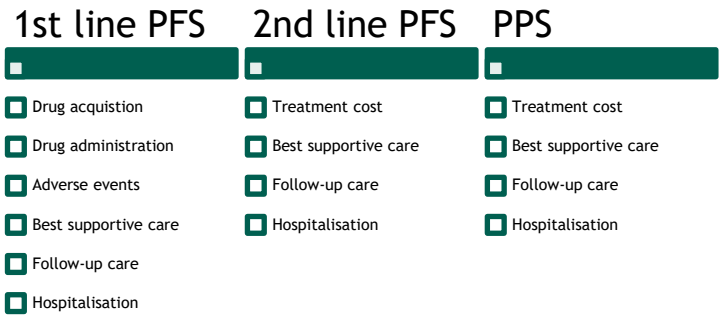


Figure 15 MONARCH 3 CM cost and resource categories
Abbreviations: CM, Cost-utility model; PFS, Progression-free survival; PPS, Post-progression survival
Please note: The second-line advanced PFS treatment costs were calculated using the same method as first-line advanced PFS treatment costs. Drug acquisition costs were combined with the respective dosing regimens. The appropriate mean weight or BSA was applied along with the RDI. The third-line of treatment costs were applied in the model 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 distant recurrence 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 first-line advanced PFS, second-line advanced PFS, PPS, and ToT values (specified in Appendix M.3)

Hospitalisation

The MonarchE trial provides a summary of all hospitalisations (on therapy or within 30 days of Treatment Disposition) for the study treatment period (i.e., two years). The hospitalisation probability collected were due to treatment or non-treatment related AEs. The median duration of hospitalisation was five days for both ABE + ET and ET-alone arms for the ITT population.

The number of hospitalisations were collected on therapy or within 30 days of Treatment Disposition. The MonarchE trial was set up with a 2-year on-study treatment period for both treatment arms, after which patients could enter the study follow-up period. This means that data on hospitalisation events were considered final at the OS IA2 data cut and were not updated of the OS IA3 data cut. Therefore, OS IA2 data is used to inform the probability of hospitalisation per treatment arm.

Table 49 shows that for those receiving ABE + ET the model applied the probability of hospitalisation from MonarchE associated with ABE + ET for the first two years or for the duration on ABE treatment, whichever of the two is shorter. For the remaining duration on ET treatment (most likely three years), the hospitalisation probability related to ET-alone was applied, starting from year three. So, for the first two years, to patients receiving ABE + ET a higher hospitalisation probability is applied and for the remaining ToT, patients

were assumed to have the same probability of hospitalisation as per those in the ET-alone arm. For those on ET-alone, the probability of hospitalisation for the ET-alone arm of MonarchE was applied for the duration of ToT (most likely five years).

Refer to Appendix M.4 for further information on hospitalisations in metastatic settings, ET-sensitive.

Table 49. Hospitalisation probability (Cohort 1) and costs

	ABE + ET	ET	Source
Cost of hospitalisation	DKK 38,767	DKK 38,767	DRG 2024 - (DC509)Brystkræft UNS DRG gruppe 09MA08 – mammacancer (89)
Duration of resource use*	2 years	5 years	OS IA3 data cut
Probability of hospitalization per cycle	=427 hospitalisations / 2539 patients / 2 years (26 cycles) = 0.00248 per cycle Probability set to 0.01	=262 hospitalisations / 2539 patients / 5 years (65 cycles) = 0.00392 per cycle Probability set to 0.01	OS IA3 data cut Refer to CEM sheet "Calculations"
Probability in MR ETR, PFS per cycle	0.01	0.01	
Probability in MR ETR, PFS per cycle	0.01	0.01	
Probability in MR ETS, PFS1	0.0085	0.0085	Appendix M.4
Probability in MR ETS, PFS2	0.0085	0.0085	Appendix M.4
Probability in MR ETS, PPS	0.0288	0.0288	Appendix M.4

*__Note__: Assumed only for the duration of treatment.
Abbreviations: ABE= Abemaciclib ; ET= endocrine treatment; DRG= diagnosis-related groups; OS= overall survival

Please refer to Appendix M.4.1.3, Appendix M.4.1.5, Appendix M.4.2.3, and Appendix M.4.2.4 for disease management costing and hospitalisations costs for the metastatic setting.

11.5 Costs associated with management of adverse events

With all patients having completed or discontinued early from the on-study treatment period of 2 years at the OS IA2 data cut, data on treatment exposure and safety were considered final at the OS IA2 data cut and were not updated at the OS IA3 data cut. Therefore, adverse event probabilities for ABE + ET and ET-alone were informed by the OS IA2 data cut of the MonarchE trial for the Cohort 1 population. The model base case includes Grade III/IV AEs with an incidence of ≥ 1% observed in the respective treatment arms of MonarchE. Grade I/II AEs with an incidence of ≥ 1% observed in the respective treatment arms of MonarchE could be included in the model in case of interest to the

model user. A summary of the Grade III/IV AE rates for each treatment and the related sources are shown in Table 50.

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

The costs for managing side effects during the treatment of metastatic recurrence are also included in the model. Table 129 and Table 130 in Appendix M show the grade 3 and 4 AEs that has been included for endocrine-resistant and endocrine-sensitive recurrence.

Table 50. Cost associated with management of adverse events

	DRG code (89)	*Unit cost/DRG tariff*
Abdominal pain	DRG 2024 - Kvinde, 51 År (DC509)Brystkræft UNS, DRG gruppe 09MA08 - mammacancer, (DI829)Emboli eller trombose i vene UNS	DKK 7,818
Alanine aminotransferase increase	DRG 2024 - Kvinde, 51 År (DC509)Brystkræft UNS, DRG gruppe 09MA08 - mammacancer, (DR740)Transaminase- og	DKK 1,828
Anaemia	DRG 2024 - Kvinde, 51 År (DC509)Brystkræft UNS, DRG gruppe 09MA08 - mammacancer,(DD696)Trombocytopeni UNS	DKK 2,111
Aspartate aminotransferase increase	DRG 2024 - Kvinde, 51 År (DC509)Brystkræft UNS, DRG gruppe 09MA08 - mammacancer, (DR740)Transaminase- og laktatdehydrogenaseforhøjelse	DKK 1,828
Diarrhoea	DRG 2024 - Kvinde, 51 År (DC509)Brystkræft UNS, DRG gruppe 09MA08 - mammacancer, (DK529B)Ikke-infektiøs diaré UNS	DKK 7,818
Fatigue	DRG 2024 - Kvinde, 51 År (DC509)Brystkræft UNS, DRG gruppe 09MA08 - mammacancer, (DT983D5)Følgetilstand med træthed efter kræftbehandling	DKK 5,103
Leukopenia	DRG 2024 - Kvinde, 51 År (DC509)Brystkræft UNS, DRG gruppe 09MA08 - mammacancer, (DD709)Neutropeni UNS	DKK 2,111
Lymphopenia	DRG 2024 - Kvinde, 51 År (DC509)Brystkræft UNS, DRG gruppe 09MA08 - mammacancer, (DD728H)Leukopeni	DKK 1,989
Neutropenia	DRG 2024 - Kvinde, 51 År (DC509)Brystkræft UNS, DRG gruppe 16MA98	DKK 2,111
Thrombocytopenia	DRG 2024 - Kvinde, 51 År (DC509)Brystkræft UNS, DRG gruppe 09MA08 - mammacancer, (DD696)Trombocytopeni UNS	DKK 2,111
Venous thromboembolic event	DRG 2024 - Kvinde, 51 År (DC509)Brystkræft UNS, DRG gruppe 09MA08 - mammacancer,(DR100)Akutte mavesmerter	DKK 25,233

Abbreviations: DRG= diagnosis-related groups

Please refer to Appendix M.4.1.4 Appendix M.4.2.4 for adverse events costs applied in metastatic settings.

11.6 Subsequent treatment costs

Metastatic recurrence

it was assumed that patients receive treatment based on their designated treatment arm (ET-sensitive or ET-resistant). Eli Lilly has estimated total costs by calculating drug costs adjusted for the average duration of treatment.

ET-resistant

For ET-resistant patients, the distribution of treatments administered during the endocrine therapy (ET)-resistant progression-free survival (PFS) phase is informed by insights from medical experts consulted by Eli Lilly, as detailed in Appendix M.2 Table 93 and Table 94 (informed by MONARCH 2 CM). No re-treatment using the same medication after disease progression) was assumed. The distribution of subsequent treatments administered after progression (PPS) is presented in 51. The pricing for each drug per package/unit utilized during endocrine-resistant PFS is provided in Table 53.

Table 51. Distribution of post-progression therapy regimens

Regimen	*Therapy*						
	ABE-FUL	**RIBO-FUL**	**PAL-FUL**	**EXE-EVE**	**FUL**	**CAP**	**EXE**
CAP	17.59%	17.59%	17.59%	32.23%	16.03%	0.00%	34.5%
PAC	17.59%	17.59%	17.59%	0.00%	16.03%	19.50%	0.0%
VNB	4.61%	4.61%	4.61%	9.40%	5.83%	7.09%	16.0%
ERI	5.48%	5.48%	5.48%	0.00%	4.37%	5.32%	0.0%
FUL	0.00%	0.00%	0.00%	30.89%	0.00%	0.00%	22.2%
LTZ	6.34%	6.34%	6.34%	0.00%	8.01%	9.75%	0.0%
EXE	14.71%	14.71%	14.71%	0.00%	17.85%	21.72%	0.0%
EVE	11.54%	11.54%	11.54%	0.00%	13.11%	15.96%	0.0%
CYC	4.04%	4.04%	4.04%	12.09%	2.55%	3.10%	11.1%
GEM	2.31%	2.31%	2.31%	5.37%	2.55%	3.10%	6.2%
BEV	5.77%	5.77%	5.77%	0.00%	3.64%	4.43%	0.0%

Abbreviations: ABE= Abemaciclib; BEV= Bevacizumab; CAP= Capecitabine; CYC= Cyclophosphamide; ERI= Eribulin; EVE= Everolimus; EXE= Exemestane; EXE-EVE= Exemestane + everolimus; FUL= Fulvestrant; GEM= Gemcitabine; LTZ= Letrozole; PAC= Paclitaxel; PAL-FUL= Palbociclib + fulvestrant; PFS= Progression-free survival; RIBO-FUL= Ribociclib + fulvestrant; VNB= Vinorelbine

Source: ABE-FUL, MONARCH 2; CAP, BOLERO 6; FUL, MONARCH 2; EXE and EXE-EVE, BOLERO-2; PAL-FUL & RIBO-FUL, assumed same as ABE-FUL

Post-progression therapy costs comprised drug acquisition and drug administration. These were assigned to the proportion of patients experiencing disease progression in each cycle. This was based on the PFS curve for each comparator adjusted by the proportion of PFS events which were progressive disease rather than death. The proportion of PFS events which were progressive disease for ABE was estimated based on the MONARCH 2 trial. Data were unavailable from the primary publications for the comparators. This proportion was assumed to be equivalent across all comparators.

Table 52. Costs post-progression therapy regimens

Treatment	Study	Dose (mg)	Admins per cycle	Cycle length	RDI	Comments
ABE-FUL	MONARCH 2	ABE: 150mg FUL: 500mg	ABE: 56	ABE-FUL	MONARCH 2	ABE: 150mg FUL: 500mg
RIBO-FUL	MONALEESA-3	RIBO: 600	RIBO-FUL	MONALEESA-3	RIBO: 600	RIBO-FUL
FUL	MONARCH 2	500mg	1 (2 in cycle 1	FUL	MONARCH 2	500mg
EXE	BOLERO 2	25mg	28	28	100%	RDI assumed to be 100% for oral treatment
EXE-EVE	BOLERO 2	EXE: 25mg EVE: 10mg	EXE: 28	EXE-EVE	BOLERO 2	EXE: 25mg EVE: 10mg
PAL-FUL	PALOMA 3	PAL: 125mg FUL: 500mg	PAL: 21	PAL-FUL	PALOMA 3	PAL: 125mg FUL: 500mg

Abbreviations: ABE= Abemaciclib; BEV= Bevacizumab; CAP= Capecitabine; CYC= Cyclophosphamide; ERI= Eribulin; EVE= Everolimus; EXE= Exemestane; EXE-EVE= Exemestane + everolimus; FUL= Fulvestrant; GEM= Gemcitabine; LTZ= Letrozole; PAC= Paclitaxel; PAL-FUL= Palbociclib + fulvestrant; PFS= Progression-free survival; RIBO-FUL= Ribociclib + fulvestrant; VNB= Vinorelbine

Table 53 Medicine costs of subsequent treatments, ETR setting

Medicine	Strength	Package size	Pharmacy purchase price [DKK]	Relative dose intensity	Average duration of treatment
Abemaciclib	150 mg	56 pcs	18,077	Please see Appendix M.4.1.6	Please see Appendix M.4.1.6
	150 mg	28 pcs	9,199	Please see Appendix M.4.1.6	Please see Appendix M.4.1.6
Exemestane	25 mg	100 pcs	3,650	Please see Appendix M.4.1.6	Please see Appendix M.4.1.6
Fulvestrant	250 mg	2 vials	462	Please see Appendix M.4.1.6	Please see Appendix M.4.1.6
Ribociclib	200 mg	63 pcs	22,797	Please see Appendix M.4.1.6	Please see Appendix M.4.1.6
Palbociclib	125 mg	21 pcs	22,854	Please see Appendix M.4.1.6	Please see Appendix M.4.1.6
Everolimus	10 mg	30 pcs	19,500	Please see Appendix M.4.1.6	Please see Appendix M.4.1.6

ET-sensitive

For ET-sensitive patients, the distribution of treatments provided as first-line therapy during endocrine-sensitive PFS1 is based on expert consultations and is outlined in

Appendix M.3 (Table 95 and Table 96). No re-treatment using the same medication after disease progression) was assumed.

Second-line advanced treatment (PFS2)
Therapies received for second-line advanced disease were modelled in the same way as treatments received for first-line advanced disease. The proportions of patients in each arm of the model receiving each therapy were based on the proportions suggested by the ERG in TA503. An assumption was made that patients would not be re-treated with the same treatment following progression (i.e., those receiving first-line advanced NSAI-based combination would not receive NSAI after progression). Consequently, distributions (where applicable) were subsequently rescaled to sum to 100%; these data are presented in Table 54.

PPS
Treatments received following disease progression on second-line advanced therapy were included in the analysis as a weighted cost. This was thought to be reasonable as differences in long-term outcomes associated with these therapies were unlikely to differ between comparators sufficiently to impact on cost-effectiveness estimates.

A fixed cost of post-progression therapy was assigned to the proportion of patients who progressed in each cycle (per month) for each first-line advanced treatment. The fixed cost of post-progression therapy was calculated by combining:

- Monthly costs of acquisition and administration for each post-progression therapy,
- Time on post-progression therapy in months,
- Proportion of patients who receive each post-progression therapy.

The proportion of patients who receive each post-progression therapy was informed by the proportions used in the manufacturer's submission in TA503. Fifty-four percent of patients were assumed to receive systemic therapy following progression from second-line advanced disease. An assumption was made that patients would not be re-treated with the same treatment in post-progression (i.e., those receiving TMX in the first-line advanced setting would not receive TMX following progression). Consequently, the distributions (where applicable) were subsequently rescaled to sum to 100%. These data are presented in Table 55.

The distribution of subsequent treatments administered in PFS2 and PPS are illustrated in Table 54 and Table 55.

Table 54. Distribution of PFS2 (ETS) therapy regimens

Regimen	*Therapy*						
	ABE+NSAI	PAL-NSAI	RIBO-NSAI	NSAI	RIBO-FUL	TMX	FUL
FUL	10.9%	10.9%	10.9%	10.9%	12.7%	9.0%	0.0%
ANAS	0.0%	0.0%	0.0%	0.0%	20.2%	14.3%	13.5%
LTZ	0.0%	0.0%	0.0%	0.0%	17.7%	12.5%	12.0%
EXE	37.0%	37.0%	37.0%	37.0%	0.0%	30.5%	26.6%
TMX	18.5%	18.5%	18.5%	18.5%	21.5%	0.0%	14.2%
EXE-EVE	8.0%	8.0%	8.0%	8.0%	0.0%	8.0%	8.0%
CAP	12.3%	12.3%	12.3%	12.3%	13.4%	12.3%	12.3%
PAC	6.2%	6.2%	6.2%	6.2%	6.7%	6.2%	6.2%
DOC	7.2%	7.2%	7.2%	7.2%	7.8%	7.2%	7.2%
FUL	10.9%	10.9%	10.9%	10.9%	12.7%	9.0%	0.0%

Abbreviations: ABE= Abemaciclib; BEV= Bevacizumab; CAP= Capecitabine; CYC= Cyclophosphamide; ERI= Eribulin; EVE= Everolimus; EXE= Exemestane; EXE-EVE= Exemestane + everolimus; FUL= Fulvestrant; GEM= Gemcitabine; LTZ= Letrozole; PAC= Paclitaxel; PAL-FUL= Palbociclib + fulvestrant

Table 55. Distribution of PPS (ETS) therapy regimens

Regimen	*Therapy*						
	ABE-NSAI	PAL-NSAI	RIBO-NSAI	NSAI	RIBO-FUL	TMX	FUL
CAP	24.8%	24.8%	24.8%	24.8%	24.8%	24.8%	24.8%
ERI	5.6%	5.6%	5.6%	5.6%	5.6%	5.6%	5.6%
FUL	11.2%	12.0%	0.0%	10.1%	11.2%	12.0%	0.0%
ANAS	4.3%	4.6%	6.2%	0.0%	4.3%	4.6%	6.2%
EXE	0.0%	7.4%	8.2%	6.2%	0.0%	7.4%	8.2%
TMX	8.6%	0.0%	9.6%	7.7%	8.6%	0.0%	9.6%

Abbreviations: ABE= Abemaciclib; BEV= Bevacizumab; CAP= Capecitabine; CYC= Cyclophosphamide; ERI= Eribulin; EVE= Everolimus; EXE= Exemestane; EXE-EVE= Exemestane + everolimus; FUL= Fulvestrant; GEM= Gemcitabine; LTZ= Letrozole; PAC= Paclitaxel; PAL-FUL= Palbociclib + fulvestrant

Please refer to Appendix M.4.1.6 and 0 for subsequent treatment costs applied in the metastatic setting.

11.7 Patient costs

Patient and transportation costs are included in the model. The unit cost per patient hour is assumed to be DKK 203, the transportation cost per visit was assumed to be DKK 3.73 per km and the average distance to health care provider was 40 km round trip. Patient hours and mean number of visits per cycle were confirmed with Danish clinical experts and presented in Table 56 (25).

Table 56. Patient costs used in the model

Activity	*Value*
Caregiver costs	
Hourly wage caregiver cost	DKK 203.00
Hours per cycle in IDFS	0.25
Hours per cycle in NMR	0.25
Hours per cycle in REM	0.25
Travel costs	
Average distance to health care provider (round trip, km)	DKK 40.00
Travel costs per km	DKK 3.73
Mean number of visits per cycle in IDFS	0.15
Mean number of visits per cycle in NMR	0.15

Activity	*Value*
Mean number of visits per cycle in REM	0.15

Abbreviations: IDFS= invasive disease-free survival; NMR= Non-metastatic recurrence ; REM= remission;

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Not applicable

12. Results

12.1 Base case overview

Table 57. Base case overview

Feature	Description
Comparator	ET
Type of model	Markov model
Time horizon	49 years (lifetime)
Treatment line	1st line
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in MonarchE. Danish population weights were used to estimate health-state utility values
Costs included	Medicine costs Hospital costs Costs of adverse events Patient costs
Dosage of medicine	Based on weight
Average time on treatment	[redacted]
Parametric function for IDFS	[redacted]
Parametric function for OS	[redacted]
Inclusion of waste	[redacted]
Average time in model health state IDFS NMR Remission Metastatic Recurrence-ET-Resistant Metastatic Recurrence-ET-Sensitive	[redacted]

Abbreviations: ET= endorcrine treatment; EQ-5D-5L= EuroQol 5-dimensions 5-levels; TTD= time to treatment discontinuation; RDI= relative dose intensitiy; NA= not applicable; ABE= Abemaciclib; IDFS= invasive disease-free survival; NMR= Non-metastatic recurrence

12.1.1 Base case results

Discounted (3.5%) disaggregated LYs and QALYs, disaggregated costs by resource category and the base case cost-effectiveness results are presented in Table 58. ABE + ET was

associated with the highest estimated total LYs and QALYs [redacted] – versus [redacted] for ET alone). QALY losses associated with AEs were incurred for both ABE + ET and ET-alone. These losses had little impact on the total QALY estimates. ABE + ET was also associated with the highest estimated total cost ([redacted]), while the difference in costs between ABE + ET and ET-alone was predominantly driven by the cost of drug acquisition.

Overall, ABE + ET resulted in both higher estimated costs and effects and was associated with an estimated pairwise ICUR of [redacted] per QALY gained vs. ET-alone.

Table 58. Base case results, discounted estimates

	ABE + ET	ET	Difference
Total drug-related costs pre-MR	[redacted]	[redacted]	[redacted]
Total disease management pre-MR	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]
Total costs in MR	[redacted]	[redacted]	[redacted]
Patient time and transport costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
LYs, IDFS	[redacted]	[redacted]	[redacted]
LYs, NMR	[redacted]	[redacted]	[redacted]
LYs, Remission	[redacted]	[redacted]	[redacted]
LYs, MR ETR	[redacted]	[redacted]	[redacted]
LYs, MR ETS	[redacted]	[redacted]	[redacted]
Total life years	[redacted]	[redacted]	[redacted]
QALYs - IDFS	[redacted]	[redacted]	[redacted]
QALYs - NMR	[redacted]	[redacted]	[redacted]
QALYs - REM	[redacted]	[redacted]	[redacted]
QALYs - MR-ETR	[redacted]	[redacted]	[redacted]
QALY - MR – ETS	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	
[redacted]		[redacted]	

Abbreviations: ABE= Abemaciclib; ET= endocrine treatment; MR= ; ETR= ; ETS= ; NA= not applicable; QALY= quality-adjusted life-years; IDFS= ; NMR=; REM= remission; ICER= incremental cost-effectiveness ratio

12.2 Sensitivity analyses

Both deterministic analysis (DSA) and Probabilistic analyses (PSA) are conducted. For the sensitivity analyses, each model parameter is specified a certain distribution, where the mean of the distribution is typically equal to the point estimate. The standard error of the distribution is set according to any distributional information provided in the original source. If no distributional information is available, the standard error is typically assumed to be 20% of the mean estimate unless stated otherwise.

For event rates and utilities, a beta distribution is used to restrict draws to the 0-1 space. For costs and resource use estimates, a gamma distribution is fitted to prevent values less than zero. For correlated parameters, such as the parameters defining the survival extrapolation curves and the coefficients of the utility regression model, a Cholesky decomposition of the variance-covariance matrix is used to capture the joint uncertainty.

12.2.1 Deterministic sensitivity analyses

The DSA involves varying one parameter at a time and assessing the subsequent impact on the incremental costs, incremental QALYs, and ICUR. Each parameter is allocated a 'low' value and a 'high' value; unless otherwise stated, the low value is the lower bound of the 95% CI and the high value is the upper bound of the 95% CI. By adjusting each parameter one at a time, the DSA assesses the impact of uncertainty around individual input parameters around the model out-comes.

To account for uncertainty around the input parameters used in the base case analysis, a DSA was conducted. Please note the DSA does not include parameters which require assessment of joint uncertainty (e.g., survival parameters), these correlated parameters are assessed within the PSA.

The 15 parameters with the greatest impact on the ICUR are displayed in Figure 16. The tornado plot displays the results in order of the impact on the ICUR, with the key cost-effectiveness drivers at the top. The parameters that had the greatest impact on change in the ICUR were the proportion of patients moving to NMR ET, the proportion of patients moving to NMR ABE+ET, Age-related utility by age group:50-69 years and the Age-related utility by age group:70-79 years.

Figure 16. ABE + ET vs ET-alone: ICUR

Abbreviations: ABE= Abemaciclib; CDK4&6I= Cyclin-dependent kinase 4&6 inhibitors; ETR= Endocrine therapy-resistant; ETS= Endocrine therapy-sensitive; FUL= Fulvestrant; IDFS= Invasive disease-free survival; ICUR= Incremental cost-utility ratio; LY= Life years; MR= Metastatic recurrence; NMRABE= Non-metastatic recurrence – abemaciclib; NMRET= Non-metastatic recurrence - endocrine therapy; NSAI= Non-steroidal aromatase inhibitor; PFS= Progression-free survival; PFS1= Progression-free survival first-line advanced breast cancer; PFS2= Progression-free survival second-line advanced breast cancer; PPS= Post-progression survival; PAL= Palbociclib; Prop= Proportion; REM= Remission; TMX= Tamoxifen

Univariate parameter uncertainty was tested using univariate sensitivity analysis, in which all model parameters were systematically and independently varied over a plausible range determined by ±20% or by a specific standard errors or predefined upper and lower limits (hence lower value and upper value are provided in the table below). The 10 most influential model parameters with regards to impact on range of impact on the base case ICER are presented in Table 59 and as a tornado diagram above.

Table 59. One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	NA	NA	[redacted]	[redacted]	[redacted]
Lower bound					
Prop. moving to NMRET	[redacted]	Range of impact on the base case ICER	[redacted]	[redacted]	[redacted]
Prop. moving to NMRABE + ET	[redacted]	See above	[redacted]	[redacted]	[redacted]
CDK4&6i + NSAI ETS Pathway - PFS treatment duration	[redacted]	-	[redacted]	[redacted]	[redacted]
Prop. moving to MRABE + ET	[redacted]	-	[redacted]	[redacted]	[redacted]
Proportion having Second Primary NMR ABE + ET	[redacted]	-	[redacted]	[redacted]	[redacted]
Proportion having Second Primary NMR ET	[redacted]	-	[redacted]	[redacted]	[redacted]
ETS Pathway CDK4&6i + NSAI PFS1 Utility values	[redacted]	-	[redacted]	[redacted]	[redacted]
ETS Pathway CDK4&6i + NSAI LYs in PFS1	[redacted]	-	[redacted]	[redacted]	[redacted]
ETS Pathway ABE-NSAI LYs in PFS1	[redacted]	-	[redacted]	[redacted]	[redacted]
ETS Pathway CDK4&6i + NSAI PPS Utility values	[redacted]	-	[redacted]	[redacted]	[redacted]
Upper bound					
Prop. moving to NMRET	[redacted]	-	[redacted]	[redacted]	[redacted]
Prop. moving to NMRABE + ET	[redacted]	-	[redacted]	[redacted]	[redacted]
CDK4&6i + NSAI ETS Pathway - PFS treatment duration	[redacted]	-	[redacted]	[redacted]	[redacted]
Prop. moving to MRABE + ET	[redacted]	-	[redacted]	[redacted]	[redacted]
Proportion having Second Primary NMR ABE + ET	[redacted]	-	[redacted]	[redacted]	[redacted]
Proportion having Second Primary NMR ET	[redacted]	-	[redacted]	[redacted]	[redacted]
ETS Pathway CDK4&6i + NSAI PFS1 Utility values	[redacted]	-	[redacted]	[redacted]	[redacted]
ETS Pathway CDK4&6i + NSAI LYs in PFS1	[redacted]	-	[redacted]	[redacted]	[redacted]
ETS Pathway ABE-NSAI LYs in PFS1	[redacted]	-	[redacted]	[redacted]	[redacted]
ETS Pathway CDK4&6i + NSAI PPS Utility values	[redacted]	-	[redacted]	[redacted]	[redacted]

Abbreviations: TTD=; ET= endocrine treatment; ICER= incremental cost-effectiveness ratio; QALY= quality-adjusted life-years

Table 60 provides an overview of the incremental results of the scenario analyses. The overview shows that, scenarios of TTD curve extrapolations in ET arm changed to log-logistic and stopping rule for ET made to 7 years had the minimal impact on the incremental outcomes and so on ICUR.

Table 60. Scenario analysis

	Change	Reason / Rational / Source	Incremental cost (DKK)	ICER (DKK/QALY)
Base case	NA	NA	[redacted]	[redacted]
TTD curve extrapolations in ET (intervention & comparator) arm	Dependent log-logistic	To illustrate the impact on TTD extrapolations	[redacted]	[redacted]
Stopping rule ET	Stopping rule at 7 years	To reflect clinical practice scenario	[redacted]	[redacted]

Abbreviations: TTD=; ET= endocrine treatment; ICER= incremental cost-e0ffectiveness ratio; QALY= quality-adjusted life-years

12.2.2 Probabilistic sensitivity analyses

The PSA involves drawing values for each variable from its individual uncertainty distribution. The distribution itself is selected based on the bounds that a parameter is naturally constrained between e.g., a beta distribution is used for parameters bounded between 0 and 1. For event rates and utilities, a beta distribution was used to restrict draws to the 0-1 space. For costs and resource use estimates, a gamma distribution was fit to prevent values less than zero. For correlated parameters, such as the parameters

defining the survival extrapolation curves and the coefficients of the utility regression model, a Cholesky decomposition of the variance-covariance matrix was used to capture the joint uncertainty. Distributions of included parameters can be adjusted/found in the sheet “Inputs” in the Excel model (via drop-down).

The PSA is performed for all input parameters simultaneously and the resulting incremental results are recorded. This constitutes one ‘simulation’. One thousand simulations are performed, which gives a distribution of incremental results, and consequently, an idea of the overall uncertainty surrounding cost-effectiveness results (please refer to convergence plots in Appendix G.1. Using the net monetary benefit (NMB) approach, the probability of each treatment to be cost-effective at different levels of Willingness-To-Pay (WTP) per QALY is presented in the cost-effectiveness acceptability curve (CEAC) and cost-effectiveness acceptability frontier (CEAF).

Figure 17 illustrates the incremental results in a cost-effectiveness scatterplot. All simulations are in the north-eastern quadrant, indicating that compared to ET-alone, ABE + ET results in an improvement in QALYs but incurring higher costs.

Figure 17. Incremental costs and QALYs of ABE + ET vs ET-alone

Abbreviations: ABE=, Abemaciclib; ET= Endocrine therapy; QALY= Quality-adjusted life years

The CEAC is presented in Figure 18.The curves illustrate the probability of a treatment being cost-effective at any given WTP threshold ranging from 0 kr. to 1,000,000 kr. ABE + ET can be considered cost-effective starting from a threshold of [redacted]. ABE + ET has [redacted]

Figure 18. Multi-way cost-effectiveness acceptability curves

Abbreviations: ABE + ET= abemaciclib + endocrine therapy, ET= endocrine therapy; QALY= Quality-adjusted life years

Convergence plots for incremental costs and QALYs can be found in Appendix G.1. Parameter uncertainty was investigated both deterministically and probabilistically. Full details of parameter specifications, including details of how they varied in the model can be found in Appendix G.

13. Budget impact analysis

The budget impact model (BIM) was developed to estimate the expected budget impact of recommending abemaciclib (Verzenios®) in combination with ET as a possible standard treatment in Denmark. The budget impact was estimated per year for the first 5 years after the introduction of abemaciclib in Denmark.

In accordance with DMC guidelines (54), the BIM was nested within the cost-effectiveness, and therefore any changes in the settings of the cost-effectiveness model would affect the results of the BIM. If any change is made to the cost-effectiveness model, the budget impact will have to be updated, by activating the button in the BIM sheet. The budget impact result is representative of the population in the cost-effectiveness model and the survival outcome of this population.

The analysis was developed by comparing the costs for the Danish regions per year over five years in the scenario where abemaciclib is recommended in combination with ET as standard treatment and the scenario where abemaciclib in combination with ET is not recommended as standard treatment in the relevant treatment comparison. The total budget impact per year is the difference between the two scenarios.

Number of patients (including assumptions of market share)

Refer to Table 3 for expected full patient population (over 5 years). The assumed market shares are shown in Table 61.

Table 61. Market share assumptions

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Abemaciclib + ET	10%	20%	30%	40%	50%
ET	90%	80%	70%	60%	50%
			Non-recommendation		
Abemaciclib + ET	5%	5%	5%	5%	5%
ET	95%	95%	95%	95%	95%

Abbreviations: ET= endocrine treatment

Table 62. Number of new patients expected to be treated over the next five-year period if Verzenios is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Abemaciclib + ET	40	84	128	174	223
ET	362	334	300	261	223
			Non-recommendation		

	Year 1	Year 2	Year 3	Year 4	Year 5
Abemaciclib + ET	20	21	21	22	22
ET	382	397	407	413	423

Abbreviations: ET= endocrine treatment

Budget impact

Table 63. Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
Abemaciclib is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abemaciclib is NOT recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

14. List of experts

- Malgorzata Tuxen, MD, PhD, Oncology, Herlev and Gentofte Hospital
- Ann Knop, MD, ph.d., Onkologisk klinik, Rigshospitalet

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Appendix A. Main characteristics of studies included

Table 64. Main characteristic of studies included

Trial name: MonarchE	NCT number: NCT03155997
Objective	*To demonstrate that abemaciclib in combination with ET as adjuvant therapy is superior compared to ET alone in improving IDFS as defined by STEEP as 1L treatment for patient with HR+/HER2-, node-positive, high-risk eBC.*
Publications – title, author, journal, year	• *Abemaciclib Combined with Endocrine Therapy for the Adjuvant Treatment of HR+, HER2–, Node-Positive, High-Risk, Early Breast Cancer (monarchE). Johnston, S.R.D., et al., Journal of Clinical Oncology, 2020. 38(34): p. 3987-3998.* • *Adjuvant Abemaciclib Plus Endocrine Therapy for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative, High-Risk Early Breast Cancer: Results from a Preplanned monarchE Overall Survival Interim Analysis, Including 5-Year Efficacy Outcomes. Rastogi P, et al., Journal of Clinical Oncology, 2024. 42(9):987-993.*
Study type and design	Multicenter, open-label, randomized, Phase III trial to compare the efficacy and safety of abemaciclib in combination with ET versus ET alone in 1L treatment of patients with HR+/HER2-, node-positive, high-risk eBC.
Sample size (n)	*5,637 patients randomized in the trial*

Main inclusion criteria	• *Male or female ≥18 years*
	• *Confirmed HR+, HER2- status with high risk EBC*
	• *Undergone definitive surgery of primary breast tumour and randomised within 16 months of surgery*
	• *If on ET at study entry, may have up to 12 weeks of ET following the last nonendocrine therapy*
	• *Fulfil one of the following criteria:*
	• *Fulfil one of the following criteria:*
	  ○ *Pathological tumour involvement in ≥4 ipsilateral axillary lymph nodes, or*
	  ○ *Pathological tumour involvement in 1-3 ipsilateral axillary lymph node(s) and at least 1 of the following:*
	  ▪ *Grade 3 disease*
	  ▪ *Tumour size ≥5 cm*
	  ▪ *Ki-67 index of ≥20%*

Main exclusion criteria	• *Metastatic disease, node-negative breast cancer, inflammatory breast cancer*

Trial name: MonarchE	NCT number: NCT03155997
	• *Previous history of breast cancer except for ipsilateral ductal carcinoma in-situ treated by locoregional therapy alone ≥five years ago* • *Pregnant or lactating* • *Previous exposure to CDK 4 & 6 inhibitors* • *Prior ET for breast cancer prevention or raloxifene* • *Any previous history of venous thromboembolic event* *Active systemic infections or viral load*
Intervention	Abemaciclib, 150mg BID in combination with ET, 2,808 patients were randomized to receive abemaciclib in combination with ET
Comparator(s)	ET alone, 2,829 patients was randomized to receive ET alone in the trial
Follow-up time	Median follow-up of 27.1 months
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	The primary endpoint was invasive disease-free survival (IDFS) as assessed by the investigator, according to STEEP system. Secondary endpoints were: • IDFS in Ki67 high population • Disease relapse-free survival • Overall survival • Treatment-emergent adverse events, serious adverse events, hospitalizations, Laboratory measures, Vital signs, and physical examinations • Pharmacokinetics • Health-related quality of life (HRQoL) Other endpoints: • IDFS in C1-Ki67L population • IDFS in C2 population¨ • DRFS in Ki-67H population • DRFS in Ki-67L population DRFS in C2 population
Method of analysis	Efficacy, including invasive disease-free survival, distant relapse-free survival, and overall survival, was assessed in the ITT population, and in cohort 1, cohort 2, and in prespecified subpopulations of cohort 1 Ki-67 high (≥20%)

Trial name: MonarchE	NCT number: NCT03155997
	or cohort 1 Ki-67 low (<20%) populations. For each efficacy endpoint, the Kaplan-Meier method was used to estimate the efficacy outcomes in each treatment group, including the absolute difference in rates estimated by means of normal approximation at each year up to a timepoint when fewer than 200 patients were at risk. HRs were estimated by means of stratified Cox proportional hazard models. The proportional hazards assumption was tested by means of a time-varying Cox model and a regression of the weighted Schoenfeld residuals over time. A post-hoc exploratory analysis was done by assuming a Bayesian exponential hazard model within each year of the observation period to estimate piecewise yearly HR for invasive disease-free survival and distant relapse-free survival. Another post-hoc summary was done to present the number of patients who have died or developed metastatic disease by survival status at each analysis timepoint. For the assessment of effect size across prespecified subgroups defined by demographics and baseline disease characteristics, unstratified Cox proportional hazard models were fitted and presented in the forest plot, including treatment group, subgroup, and their interaction variable. A similar interaction model was also used to evaluate the consistency of the effect size across cohorts as a post-hoc analysis.
Subgroup analyses	• Age, years • Region • Menopausal status • Prior chemotherapy • Race • Baseline Eastern Cooperative Oncology Group performance status • Primary tumor size, cm • No. of positive lymph nodes • Histologic grade • Progesterone receptor Tumor stage
Other relevant information	*No*

Abbreviations: ET= endocrine treatment; IDFS= invasive disease-free survival; STEEP= Safe, Timely, Effective, Efficient, Equitable and Patient-centered care; HR+= hormone receptor positive ; HER2= human epidermal receptor 2; eBC= early breast cancer; CDK=Cyclin-dependent kinase; BID= twice daily; HRQoL= health-related quality of life; DRFS=Distant relapse-free survival; ITT= intention to treat

Appendix B. Efficacy results per study

Results per study

Cohort 1 enrolled a total of 5120 patients with high-risk EBC based on their clinicopathological features including the number of positive lymph nodes, tumor size, and tumor grade. At OS IA3, the median follow-up time in Cohort 1 was approximately 54 months (IQR: 49.5, 59.5) in both treatment arms. As C1 comprises more than 91% of the patients in the study and 94% of the IDFS events observed in the ITT population at OS IA3, the established treatment benefit in C1 was highly consistent with the ITT population. Therefore, the positive efficacy results observed in the entire study was primarily driven by the substantial treatment benefit in the C1 population.

IDFS and DRFS in Cohort 1

With longer follow-up time at OS IA3, the treatment benefit of abemaciclib in IDFS and DRFS was maintained beyond the 2-year treatment period of abemaciclib. In the abemaciclib plus ET arm, there was a robust and clinically meaningful effect in reducing the risk of developing an IDFS event by 33% (IDFS HR = 0.670, 95% CI: 0.588, 0.764; See figure below). For the secondary efficacy endpoint DRFS, the addition of abemaciclib to ET demonstrated a 33.5% reduction in the risk of developing distant metastatic disease or death (DRFS HR = 0.665, 95% CI: 0.577, 0.765; See figure below.

Table 65. Results per study

Results of MonarchE (NCT03155997)												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
IDFS (54 months)	Abemaciclib + ET	2,555	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*A log-rank test stratified by randomization factors was used. A stratified Cox proportional hazard model with treatment arm as a variable*	MonarchE July 2023 DCO
	ET alone	2,565	[redacted]								

Results of MonarchE (NCT03155997)											
										was used to estimate the HR and the corresponding 95% CI.	
DRFS (54 months)	Abemaciclib + ET	2,555	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*A log-rank test stratified by randomization factors was used. A stratified Cox proportional hazard model with treatment arm as a variable was used to estimate the HR and the corresponding 95% CI. However, there was no α control for statistical significance on this end point.*	MonarchE July 2023 DCO
	ET alone	2,565	[redacted]								
OS (54 months)	Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*The OS analyses was calculated using the Lan-Demets method based on O'Brien-Fleming type stopping boundary (Demets and Lan 1994). Therefore, the actual p-value boundary for the OS analysis is based on actual number of death events observed.*	MonarchE July 2023 DCO
	ET alone	[redacted]	[redacted]								

Abbreviations: NA= not applicable; OS= overall survival; ET= endocrine treatment; IDFS= invasive disease-free survival; DRFS=Distant relapse-free survival ; HRa= hazard ratio: CI= confidence interval

Appendix C. Comparative analysis of efficacy

Presenting the Post Hoc Efficacy Analyses of IDFS, DRFS, and OS, Cohort 1 Population – please refer to the sections below (DRFS, OS, and IDFS).

Table 66. Comparative analysis of studies comparing abemaciclib + ET to ET for patients with eBC.

Results of the MonarchE study comparing abemaciclib + ET to ET for patients with eBC									
		Absolute difference in effect			Relative difference in effect				
Outcome	**Studies included in the analysis**	**Difference**	**CI**	***P* value**	**Difference**	**CI**	***P* value**	**Method used for quantitative synthesis**	**Result used in the health economic analysis?**
IDFS	MonarchE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*A log-rank test stratified by randomization factors was used. A stratified Cox proportional hazard model with treatment arm as a variable was used to estimate the HR and the corresponding 95% CI.*	*Yes*
DRFS	MonarchE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*A log-rank test stratified by randomization factors was used. A stratified Cox proportional hazard model with treatment arm as a variable was used to estimate the HR and the corresponding 95% CI. However, there was no α control for statistical significance on this end point.*	*Yes*
OS	MonarchE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	The OS analyses was calculated using the Lan-Demets method based on O'Brien-Fleming type stopping boundary (Demets and Lan 1994). Therefore, the actual p-value boundary for the OS analysis are based on actual number of death events observed.	*Yes*
TEAE	MonarchE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	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 [27].	*Yes*
SAE	MonarchE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	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 [27].	*Yes*

Abbreviations: eBC= early breast cancer; IDFS= invasive disease-free survival; DRFS=Distant relapse-free survival ; OS= overall survival; TEAE= treatment emergent adverse events; SAE= serious adverse events; CTCAE= Cancer Institute Common Terminology Criteria for Adverse Events; ; NR= not reported; CI= confidence invertal
HR is stratified

C.1 DRFS

	LY2835219-150mg+EDT (N=2555)	EDT (N=2565)	Treatment Effect/Difference / p-value*f
Number of Events, n (%)	325 (12.7)	477 (18.6)	
Death without Distant Relapse, n (%)	44 (1.7)	36 (1.4)	
Distant Relapse, n (%)	281 (11.0)	441 (17.2)	
Number of Patients Censored, n (%)	2230 (87.3)	2088 (81.4)	
Distant Relapse prior to randomization, n (%)	2 (0.1)	3 (0.1)	
Distant relapse more than 1 year after last disease assessment or randomization, n (%)	0	1 (0.0)	
No Post-Baseline Assessment, n (%)	22 (0.9)	41 (1.6)	
No documented DR with regular assessment, n (%)	2206 (86.3)	2043 (79.6)	
Minimum *a, month	0.03+	0.03	
25th percentile (95% CI)	- (- , -)	- (62.96, -)	
Median (95% CI)	- (- , -)	- (- , -)	-
75th percentile (95% CI)	- (- , -)	- (- , -)	
Maximum	69.30+	70.82+	
Restricted Mean (95% CI) with restriction time = 67.40 month *b	61.71(61.11, 62.32)	59.16(58.46, 59.86)	2.55(1.63, 3.48) p = <.0001*e
p-value (2-sided) - Log Rank Unstratified			p = <.00001

Abbreviations: CI = Confidence Interval; N = total number of subjects in the population within the treatment group; n = number of patients; NC = not calculable.
Note: Quartiles and Distant Relapse-Free Survival Time Survival rates, along with 95% CIs, were estimated using the Kaplan-Meier method. Corresponding 95% CIs were estimated using the methods of Brookmeyer and Crowley, and Greenwood, respectively.
*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 are <=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 EDT
Program Location: /lillyce/prd/ly2835219/i3y_mc_jpcf/csr5/programs/stat/tfl/o_tte_summ_pfs_3_p5401826_t5401834.sas
Output Location: /lillyce/prd/ly2835219/i3y_mc_jpcf/csr5/output/shared/o_tte_summ_drfs_cohort1.rtf
Data Location: /lillyce/prd/ly2835219/i3y_mc_jpcf/csr5/data/analysis/shared/adam

Summary of Distant Relapse-Free Survival — Page 2 of 2
Cohort 1 Population — 12:30 16AUG2023
I3Y-MC-JPCF — PDPM
Data cutoff: 03JUL2023

Figure 19 Summary of Investigator-Assessed DRFS

	LY2835219-150mg+EDT (N=2555)	EDT (N=2565)	Treatment Effect/Difference / p-value*f
- Log Rank Stratified*c			p = <.00001
Hazard Ratio (95% CI) - UnStratified			0.668(0.580, 0.769)
- Stratified*c			0.665(0.577, 0.765)
Distant Relapse-Free Survival Time Survival Rate (%) with 95% CI *d			
12 - month	97.5 (96.7, 98.0)	96.3 (95.4, 96.9)	1.2 (0.2, 2.2) p = 0.0166
24 - month	94.0 (93.0, 94.9)	91.1 (89.9, 92.2)	2.9 (1.4, 4.4) p = 0.0001
36 - month	90.5 (89.3, 91.6)	86.1 (84.6, 87.4)	4.4 (2.6, 6.3) p = <.0001
48 - month	88.0 (86.6, 89.2)	82.3 (80.7, 83.8)	5.6 (3.6, 7.7) p = <.0001
60 - month	85.6 (84.0, 87.1)	78.5 (76.6, 80.3)	7.1 (4.8, 9.5) p = <.0001

Abbreviations: CI = Confidence Interval; N = total number of subjects in the population within the treatment group;
n = number of patients; NC = not calculable.
Note: Quartiles and Distant Relapse-Free Survival Time Survival rates, along with 95% CIs, were estimated using the Kaplan-Meier method. Corresponding 95% CIs were estimated using the methods of Brookmeyer and Crowley, and Greenwood, respectively.
*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 are <=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 EDT
Program Location: /lillyce/prd/ly2835219/i3y_mc_jpcf/csr5/programs/stat/tfl/o_tte_summ_pfs_3_p5401826_t5401834.sas
Output Location: /lillyce/prd/ly2835219/i3y_mc_jpcf/csr5/output/shared/o_tte_summ_drfs_cohort1.rtf
Data Location: /lillyce/prd/ly2835219/i3y_mc_jpcf/csr5/data/analysis/shared/adam

Figure 20 Summary of Investigator-Assessed DRFS – continued

C.2 OS

	LY2835219-150mg+EDT (N=2555)	EDT (N=2565)	Treatment Effect/Difference / p-value*f
Number of Deaths, n (%)	197 (7.7)	223 (8.7)	
Number of Patients Censored, n (%)	2358 (92.3)	2342 (91.3)	
Alive, n (%)	2132 (83.4)	2079 (81.1)	
Lost to follow-up, n (%)	48 (1.9)	48 (1.9)	
Withdrawal by subject, n (%)	178 (7.0)	215 (8.4)	
Minimum *a, month	0.03+	0.03+	
25th percentile (95% CI)	- (67.82, -)	- (- , -)	
Median (95% CI)	- (- , -)	- (- , -)	-
75th percentile (95% CI)	- (- , -)	- (- , -)	
Maximum	69.30+	70.82+	
Restricted Mean (95% CI) with restriction time = 67.79 month *b	64.65(64.21, 65.10)	64.31(63.85, 64.77)	0.35(-0.29, 0.99) p = 0.2880*e

Abbreviations: CI = Confidence Interval; N = total number of subjects in the population within the treatment group;
n = number of patients.
Note: Quartiles and OS rates were estimated using the Kaplan-Meier method. Corresponding 95% CIs were estimated using the methods of Brookmeyer and Crowley, and Greenwood, respectively.
*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 are <=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 EDT
Program Location: /lillyce/prd/ly2835219/i3y_mc_jpcf/csr5/programs/stat/tfl/o_tte_summ_os_3_p5401826_t5401846.sas
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Data Set Location: /lillyce/prd/ly2835219/i3y_mc_jpcf/csr5/data/analysis/shared/adam

Figure 21 Summary of OS Cohort 1 Population Data Cutoff: 03 July 2023 for OS Interim Analysis 3

	LY2835219-150mg+EDT (N=2555)	EDT (N=2565)	Treatment Effect/Difference / p-value*f
p-value (2-sided) - Log Rank Unstratified			p = 0.23185
- Log Rank Stratified*c			p = 0.25354
Hazard Ratio (95% CI) - UnStratified			0.890(0.735, 1.078)
- Stratified*c			0.894(0.738, 1.084)
Survival Rate (%) with 95% CI *d			
12 - month	99.1 (98.6, 99.4)	99.1 (98.7, 99.4)	-0.1 (-0.6, 0.5)
			p = 0.8362
24 - month	97.5 (96.8, 98.0)	97.2 (96.4, 97.8)	0.3 (-0.6, 1.2)
			p = 0.5132
36 - month	95.0 (94.1, 95.8)	95.0 (94.0, 95.8)	0.1 (-1.2, 1.3)
			p = 0.9203
48 - month	93.4 (92.3, 94.3)	92.5 (91.3, 93.5)	1.0 (-0.5, 2.4)

Abbreviations: CI = Confidence Interval; N = total number of subjects in the population within the treatment group;
n = number of patients.
Note: Quartiles and OS rates were estimated using the Kaplan-Meier method. Corresponding 95% CIs were estimated using the methods of Brookmeyer and Crowley, and Greenwood, respectively.
*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 are <=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 EDT
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Output Location: /lillyce/prd/ly2835219/i3y_mc_jpcf/csr5/output/shared/o_tte_summ_os_cohort1.rtf
Data Set Location: /lillyce/prd/ly2835219/i3y_mc_jpcf/csr5/data/analysis/shared/adam

Figure 22 Summary of OS Cohort 1 Population Data Cutoff: 03 July 2023 for OS Interim Analysis 3 – continued

C.3 IDFS

	LY2835219-150mg+EDT (N=2555)	EDT (N=2565)	Treatment Effect/Difference / p-value*f
Number of Events, n (%)	382 (15.0)	553 (21.6)	
Death without Invasive Disease, n (%)	35 (1.4)	25 (1.0)	
Invasive Disease, n (%)	347 (13.6)	528 (20.6)	
Number of Patients Censored, n (%)	2173 (85.0)	2012 (78.4)	
Invasive Disease prior to randomization, n (%)	2 (0.1)	3 (0.1)	
No Post-Baseline Assessment, n (%)	22 (0.9)	41 (1.6)	
No documented ID with regular assessment, n (%)	2149 (84.1)	1968 (76.7)	
Minimum *a, month	0.03+	0.03	
25th percentile (95% CI)	- (- , -)	62.63(56.02, -)	
Median (95% CI)	- (- , -)	- (- , -)	-
75th percentile (95% CI)	- (- , -)	- (- , -)	
Maximum	69.30+	70.82+	
Restricted Mean (95% CI) with restriction time = 67.27 month *b	60.54(59.88, 61.19)	57.71(56.97, 58.46)	2.83(1.84, 3.82) p = <.0001*e
p-value (2-sided) - Log Rank Unstratified			p = <.00001
- Log Rank Stratified*c			p = <.00001

Abbreviations: CI = Confidence Interval; N = total number of subjects in the population within the treatment group; n = number of patients; NC = not calculable.
Note: Quartiles and Invasive Disease-Free Survival Time 1 Survival rates, along with 95% CIs, were estimated using the Kaplan-Meier method. Corresponding 95% CIs were estimated using the methods of Brookmeyer and Crowley, and Greenwood, respectively.
*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 are <=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 EDT
Program Location: /lillyce/prd/ly2835219/i3y_mc_jpcf/csr5/programs/stat/tfl/o_tte_summ_pfs_3_p5401826_t5401828.sas
Output Location: /lillyce/prd/ly2835219/i3y_mc_jpcf/csr5/output/shared/o_tte_summ_idfs_cohort1.rtf
Data Location: /lillyce/prd/ly2835219/i3y_mc_jpcf/csr5/data/analysis/shared/adam

Figure 23 Summary of Investigator-Assessed IDFS Cohort 1 Population Data Cutoff: 03 July 2023 for OS Interim Analysis 3

	LY2835219-150mg+EDT (N=2555)	EDT (N=2565)	Treatment Effect/Difference / p-value*f
Hazard Ratio (95% CI) - UnStratified			0.674(0.592, 0.768)
- Stratified*c			0.670(0.588, 0.764)
Invasive Disease-Free Survival Time 1 Survival Rate (%) with 95% CI *d			
12 - month	96.5 (95.7, 97.2)	95.4 (94.5, 96.1)	1.1 (0.0, 2.3) p = 0.0422
24 - month	92.6 (91.5, 93.6)	89.4 (88.2, 90.6)	3.2 (1.6, 4.8) p = 0.0001
36 - month	88.9 (87.5, 90.1)	83.8 (82.2, 85.2)	5.1 (3.1, 7.0) p = <.0001
48 - month	85.6 (84.1, 86.9)	79.2 (77.6, 80.8)	6.4 (4.2, 8.5) p = <.0001
60 - month	83.2 (81.5, 84.7)	75.3 (73.4, 77.2)	7.9 (5.4, 10.4) p = <.0001

Abbreviations: CI = Confidence Interval; N = total number of subjects in the population within the treatment group; n = number of patients; NC = not calculable.
Note: Quartiles and Invasive Disease-Free Survival Time 1 Survival rates, along with 95% CIs, were estimated using the Kaplan-Meier method. Corresponding 95% CIs were estimated using the methods of Brookmeyer and Crowley, and Greenwood, respectively.
*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 are <=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 EDT
Program Location: /lillyce/prd/ly2835219/i3y_mc_jpcf/csr5/programs/stat/tfl/o_tte_summ_pfs_3_p5401826_t5401828.sas
Output Location: /lillyce/prd/ly2835219/i3y_mc_jpcf/csr5/output/shared/o_tte_summ_idfs_cohort1.rtf
Data Location: /lillyce/prd/ly2835219/i3y_mc_jpcf/csr5/data/analysis/shared/adam

Figure 24 Summary of Investigator-Assessed IDFS Cohort 1 Population Data Cutoff: 03 July 2023 for OS Interim Analysis 3 - continued

Appendix D. Extrapolation

The IPD from the MonarchE trial was used to generate the IDFS, TTD, and OS (without distant recurrence) outcomes for both ABE + ET and ET-alone. The parametrised curves for IDFS, TTD, and OS were utilised in the CEM. The parametrisation of the IDFS, TTD, and OS curves for ABE + ET and ET-alone aids in estimating long-term outcomes for patients beyond the trial period and subsequently allows for modelling over a longer time. At the OS IA3 analysis, the median duration of follow-up was approximately 54 months in both trial arms. The median treatment duration of abemaciclib was 23.7 months. The analyses were carried out using SAS Software 9.4 (SAS Institute, Cary NC; traditional parametric models) and R 3.6.2 Software (cubic spline models). Please refer to the SAP for further details (77).

Parametric models were fitted to the KM data of the MonarchE trial. The models provided a more granular overview of the survival data and the approach enabled estimation of long-term outcomes to inform the lifetime horizon of the CEM. The parametric model fitting for IDFS, TTD and OS without distant recurrence were conducted according to the following steps recommended in the NICE Decision Support Unit (DSU) 14 (78):

- Proportional hazards (PH) assumption was tested between treatment arms, which inferred the choice of fitting independent or dependent models. If the PH assumption could not be rejected, a single dependent model for each survival curve was estimated, with treatment modelled as a single covariate. Otherwise, an independent model was fit.
- Following the PH test, parametric survival models were fit to the survival data of the pivotal trial (i.e., MonarchE in this case).
- An initial selection of extrapolation models was based on visual inspection and statistical fit of the models to the trial data, based on Akaike's Information Criterion (AIC) and the Bayesian Information Criterion (BIC), as well as visual inspection of the survival and hazard curves.
- The models were further evaluated against additional evidence from external sources (trials included in the clinical SLR report for IDFS) and further discussed with TLs for their opinion. For outcomes where no additional evidence was available, model selections were based on the outcomes of step 3.

Proportional hazards assumption

The assumption that indicates whether it may be preferable to separately fit parametric models to each treatment arm, was tested. Fitting separate parametric models to each treatment arm involves fewer assumptions, although it does also require the estimation of more parameters. Depending on the PH assumption results, two different approaches could be selected to fit different extrapolation models to the observed trial data:

- If the PH assumption was not rejected, a single dependent model was fit to both arms of the trial data, incorporating an adjustment factor for treatment effect. For PH

models, this adjustment factor takes the form of a hazard ratio (HRa). That is, a covariate affecting the hazard function. For accelerated failure time (AFT) models, the adjustment factor is an accelerated failure rate, which is a covariate affecting the logarithm of the survival time. This means that the adjustment factors for treatment effect cannot be directly compared across models and should be interpreted per model.

- If the PH assumption was rejected, independent distributions were separately fit to survival data of both trial arms. In accordance with NICE technical guidance (78), the same distribution was selected for both treatment arms.

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

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. If the PH assumption was not violated, the curves of the different treatment arms would be approximately parallel. Crossing of hazards in the plot can indicate that a single parametric model may not be appropriate to model survival. In this instance independent distributions were fitted to the treatment arms. 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.

Schoenfeld residuals test

The PH assumption was also tested by assessment of the Schoenfeld residuals. Testing for time dependency of the HRa is equivalent to testing for a non-zero slope in a generalised linear regression of the scaled Schoenfeld residuals. A non-zero slope is an indication of a violation of the PH assumption. The Schoenfeld residuals should be flat and centred around log(HRa), showing no clear pattern, independent of time. In case the log(HRa) does not fall within the 95% confidence interval (CI) bands, it could be a strong indicator for violation of proportionality between the two curves.*Grambsch and Therneau test*

Grambsch and Therneau test

In addition to graphical assessments, statistical goodness of fit tests was 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 will be used for this purpose (95). 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

The parametric distributions fitted to the MonarchE trial are exponential, Weibull, Gompertz, log-normal, log-logistic, gamma and generalised gamma. An overview of the parametric distributions, the survival function and the main characteristic of these distributions are presented in Table 67. The table defines whether the model is a PH or an accelerated failure time (AFT) model. A PH model operates on the hazards scale, and the effect of determinants is proportional (multiplicative) on hazards. Treatment effect is expressed as a HRa. For example, a HRa of 1.5 increases the hazard function by a factor of 1.5. An AFT model operates on the time scale, and the effect of determinants is proportional (multiplicative) on survival time. Treatment effect is expressed as an acceleration factor, which either accelerates or delays the time to an event. If a coefficient of the treatment (on the log scale) is log (2), then applying treatment versus no treatment would give half the expected survival time.

Table 67. Parametric distributions

Parametric distribution	Survival function	Notation	Main characteristics
Exponential	$S(t) = \exp(-\lambda t)$	λ rate t time	• PH model • Constant hazard • 1 parameter
Weibull	$S(t) = \exp\left(-\left(\frac{t}{\lambda}\right)^{p}\right)$	λ scale parameter p shape parameter	• AFT model • Either increase or decrease monotonically • 2 parameters
Gompertz	$S(t) = \exp\left(\left(\frac{\lambda}{p}\right)(1 - e^{pt})\right)$	λ scale parameter p shape parameter	• PH model • Either increase or decrease monotonically • 2 parameters
Log-normal	$S(t) = 1 - \Phi\left(\frac{\ln(t) - \mu}{\sigma}\right)$	Φ standard normal function μ meanlog σ sdlog	• AFT model • Hazard increases initially to a maximum, before decreasing as t increases • 2 parameters
Log-logistic	$S(t) = \frac{1}{1 + \left(\frac{t}{\lambda}\right)^{p}}$	λ scale parameter p shape parameter	• AFT model • Can be non-monotonic with respect to time • 2 parameters
Generalised gamma	$S(t) = 1 - \frac{\gamma(k, (t/\lambda)^{\alpha})}{\Gamma(k)}$	α shape λ scale parameter	• AFT model

	$\gamma(k,\mathrm{x}) = \int_0^x \lambda^{k-1} e^{-x} dx$	k shape parameter $\gamma(k,\mathrm{x})$ lower incomplete gamma function	• Includes Weibull, gamma and log-normal as cases • 3 parameters • When α = 1, the distribution collapses to a gamma • When k = 1, the distribution collapses to a Weibull • When k = 1 & α = 1, the distribution collapses to an exponential

Abbreviations: AFT, Accelerated failure time; PH, Proportional hazards

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. For example, three intermediate knots would imply a heterogeneous population of at least four subgroups with distinct survival profiles. An overview of the spline model, the survival function and the main characteristic of the model is shown in Table 68.

Table 68. Hazard spline distribution

Spline models	Survival function	Transformed survival function and notation	Main characteristics
Proportional hazards (hazard spline model)	$S(t) = \exp(-\exp(g($	$g(S(t)) = \gamma_0 + \gamma_1 \cdot \log(t) + \gamma_2 \cdot [(\log(t) - k_1)_+^3 - \lambda_1 \cdot (\log(t) - k_{min})_+^3 - (1 - \lambda_1) \cdot (\log(t) - k_{max})_+^3]$ $\lambda_i = \frac{k_{max} - k_j}{k_{max} - k_{min}}$ k_j = knot in log-time y_j = spline coefficient (i.e., ancillary parameters)	$g(S(t)) = \log(-\log(S(t,z))) = \log(H(t,z)) = \log cumulative\ hazard$ Zero knots: Weibull distribution

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. These criteria will be discussed in the following sections.

Statistical fit criteria

Model selection based on statistical model fit will be based on the AIC and BIC for the models.

Both the AIC and BIC assess goodness of fit using a log likelihood function. While the AIC penalises models for additional and potentially inefficient additional parameter, the BIC also considers the sample size (number of observations).

$$AIC = -2 * loglikelihood + 2 * number\ of\ estimated\ parameters$$

$$BIC = -2 * loglikelihood + \ln(\text{number of observations}) * (number\ of\ estimated\ parameters)$$

In situations where there is a misalignment in AIC and BIC to select the best-fitting model, BIC will be chosen as the best model in terms of statistical fit. As the BIC is more stringent towards both type I and type II errors, it can potentially protect against overfitting (79).

When comparing AIC and BIC values between models, aside of selecting the model with the best statistical fit criteria, it is important to know which distribution is second-best, as well as some measure of its standing with respect to the best model. Table 69 gives an overview of rules of thumb that were used in assessing whether there is a considerable difference between two models and the interpretation between differences in AIC and BIC values. Differences in AIC values of ≤ 2 indicate that there is substantial support of evidence that the two compared models have the same merits. Differences in BIC values between 0-2 indicate weak evidence of difference between the two compared models.

Table 69. Interpretation of AIC and BIC differences

AIC difference - Burnham and Anderson (2004) (96)			BIC difference - Raftery (1995) (97)		
AIC difference		**Evidence**	**BIC difference**		**Evidence of difference**
	≤ 2	Substantial support		0-2	Weak
	2 < Δ < 4			2-6	Positive
	4 ≤ Δ ≤ 7	Considerably less support		6-10	Strong
	4 < Δ ≤ 10			>10	Very strong
	Δ > 10	Essentially no support			

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion

Visual inspection of extrapolation curves

Models were also assessed based on the visual fit following the recommendations in the NICE DSU Technical Support Document 14 (78). It should be noted that this method needs to be used with caution and only complementary to the other model selection methods. Due to censoring and clustered data points in the KM curve, some parts of the extrapolated curve may fit the observed data very well, while in other parts it will not. This does not necessarily mean that the model is inappropriate. If the parametric curves closely

follow the observed data, this does not necessarily mean that they are able to correctly predict the survival beyond the trial duration, especially at the tail of the curve.

Visual inspection of smoothed hazard curves

In addition to visual assessment of the extrapolation curves, a visual assessment of the smoothed hazard curves was performed. The smoothed hazard curve indicates whether observed hazards are likely to be constant, monotonic, or non-monotonic. In general, the hazards of the exponential models will provide the best fit when the observed hazard is approximately constant and non-zero. The Weibull and Gompertz models incorporate monotonic hazards, while the log-logistic and log-normal models can incorporate non-monotonic hazards. The generalised gamma and the spline models are generally more flexible in incorporating multiple turning points in hazards. Like with the visual inspection of extrapolation curves (and other validation criteria), the observed smoothed hazard curves do not always predict the hazards beyond trial period.

D.1 Extrapolation of IDFS

D.1.1 Data input

IDFS data of the cohort 1 population of the MonarchE trial.

D.1.2 Model

The parametric distributions fit to the monarchE trial are exponential, Weibull, Gompertz, log-normal, log-logistic, gamma and generalised gamma (refer to Model selection above).

Selected parametric distributions used in the analysis:

[redacted]

[redacted]

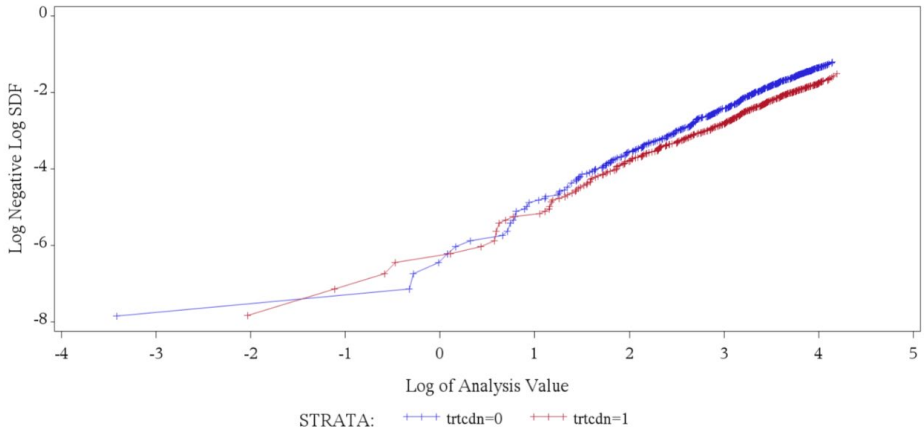
Dependent model (single model with treatment coefficient) assumed with a [redacted] following internal validity checks and assessment of external evidence for OS IA3 data cut.

D.1.3 Proportional hazards

The PH assumption between treatment arms was tested. The log-cumulative plot in Figure 25 shows the treatment arms are crossing at the beginning, after which they appear to move in parallel. Although, the crossing of the treatment arms suggests a violation of the PH assumption, indicating that the hazard ratio is not constant over time, it occurs only for a small part of the observed data. Over time the treatment arms start to move parallel, indicating a constant hazard over time. Furthermore, the Grambsch and Therneau test could not be labelled as statistically significant (p-value = 0.705) as it exceeded p = 0.05. This is consistent with the residuals visualisation in which no time trend can be observed, and the slope generally aligns the zero slope, suggesting no violation of the PH assumption.

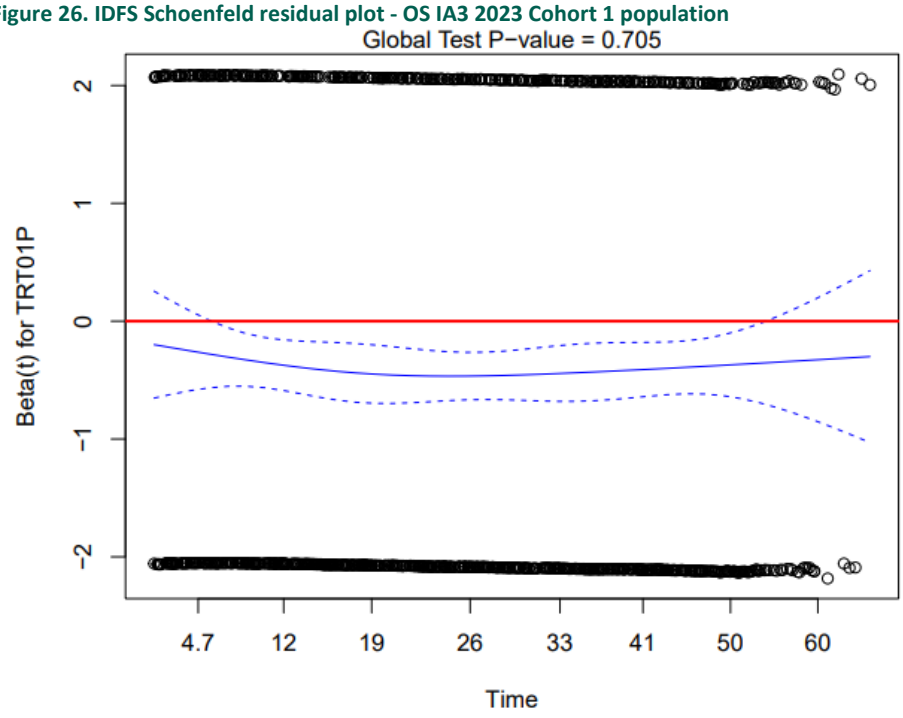
Therefore, a single model including an adjustment factor for treatment effect (HRa), instead of independent models, was fitted to the IDFS data of the cohort 1 population of the MonarchE trial.

Figure 25. IDFS log-cumulative hazard plot - OS IA3 2023 Cohort1 population



Abbreviations: ET: endocrine therapy; IDFS: invasive disease-free survival, SDF: survival distribution function; TRTCDN = 0: ABE + ET, TRTCDN=1: ET alone

Figure 26. IDFS Schoenfeld residual plot - OS IA3 2023 Cohort 1 population



Abbreviations: IDFS, Invasive disease-free survival; OS IA3, Overall survival interim analysis 3 data cut
* The red line indicates no treatment effect

D.1.4 Evaluation of statistical fit (AIC and BIC)

Seven parametric distributions and two spline models were fit to the IDFS KM data and were evaluated based on AIC and BIC values of the dependent models. It is not directly obvious which survival curve to select based on statistical fit. The best statistical fit based on BIC value is provided by the log-logistic distribution, which also provides a relatively

low AIC value, approximately four points away from the lowest AIC value (Table 22). The next best statistical fit was found within the hazard spline knot 1 distribution, which deviates five points for the log-logistic distribution in BIC value, and three points from the distribution with the lowest AIC value.

Table 70: AIC and BIC values for IDFS extrapolations - OS IA3 2023 Cohort 1 population

Dependent distributions			
Distributions	AIC	Distributions	BIC
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; IDFS, Invasive disease-free survival; OS IA3, Overall survival interim analysis 3 data cut. **Note**: the first best-fitting curve is in bold, while the second and third best-fitting curves are underlined. All curves within 2.0 points from the best-fitting AIC and BIC value are grey highlighted.

D.1.5 Evaluation of visual fit

When comparing the five-year landmark IDFS rates of the ET-alone arm of the MonarchE trial with the extrapolation curves at five years, the log-logistic shows a good fit with the OS IA3 data (Table 10). The five-year extrapolations of all curves are close to each other (75.2-75.6), except for the log-normal (76.2). The log-logistic estimate for the ABE + ET arm is slightly lower than the five-year the OS IA3 data. However, all extrapolation curves estimate the five-year IDFS rate slightly under the observed five-year data of the MonarchE trial for ABE + ET. As can be seen in Table 10, the five-year extrapolations of all curves are close to each other (82.5-82.8). On visual inspection, all extrapolated curves seem to fit the MonarchE trial data for the observed time-period relatively well (Figure 3). Although the curves follow a similar pattern for the first five years, over time the curves show more variation in the extrapolated IDFS.

Table 71. Landmark IDFS rates for ABE + ET and ET-alone arms - OS IA3 2023 Cohort 1 population

	Five-year rates	Ten-year rates

	ABE + ET	ET-alone	ABE + ET	ET-alone
MonarchE trial	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[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 knot 1	[redacted]	[redacted]	[redacted]	[redacted]
Hazard spline knot 2	[redacted]	[redacted]	[redacted]	[redacted]

* Abbreviations: ABE, Abemaciclib; AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; ET, Endocrine Therapy; IDFS, Invasive disease-free survival; ITT, Intention to treat; N/A, Not available; OS IA3, Overall survival interim analysis 3 data cut
Note: The best performing distribution is made bold. Please note that treatment waning is accounted for in these comparisons.

Figure 27. Long-term IDFS extrapolations – Cohort 1 population; left panel ABE+ET and right panel ET-alone

D.1.6 Evaluation of hazard functions

For the fit of standard parametric functions to be evaluated for IDFS, a plot of the hazard rates over time for all 9 distributions overlaid by the smoothed hazard function was created. Additionally, a plot with the smoothed and unsmoothed hazard overlaid, as well as plots of transformations for standard parametric functions were created for the same purpose.

ABE + ET arm

The hazard functions for the 9 candidate distributions for IDFS for the ABE+ET arm is displayed to enable visual inspection of the survival curves overlaid by KM estimates of observed data. The smoothed hazard function was considered as observed hazard overlying the candidate distributions (Figure 28).

However, unlike the KM curves for survival probabilities, smoothed hazard curves are not robust and may be extremely sensitive to a few datapoints. Therefore, additional figure (Figure 29), showing smoothed and unsmoothed hazard rates, are added to illustrate the fluctuation of instantaneous hazards and to invite to caution when interpreting smoothed hazard functions.

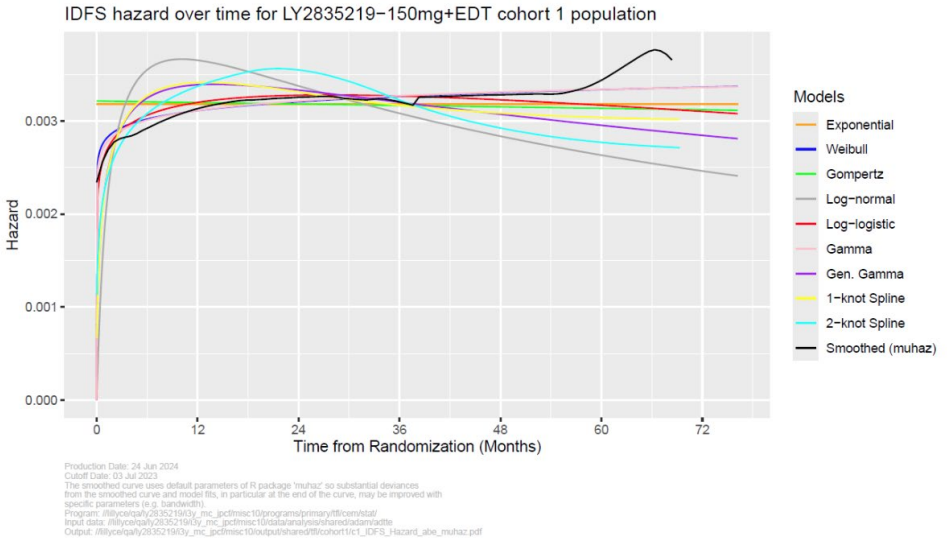


Figure 28 IDFS hazard over time for ABE + ET, Cohort 1

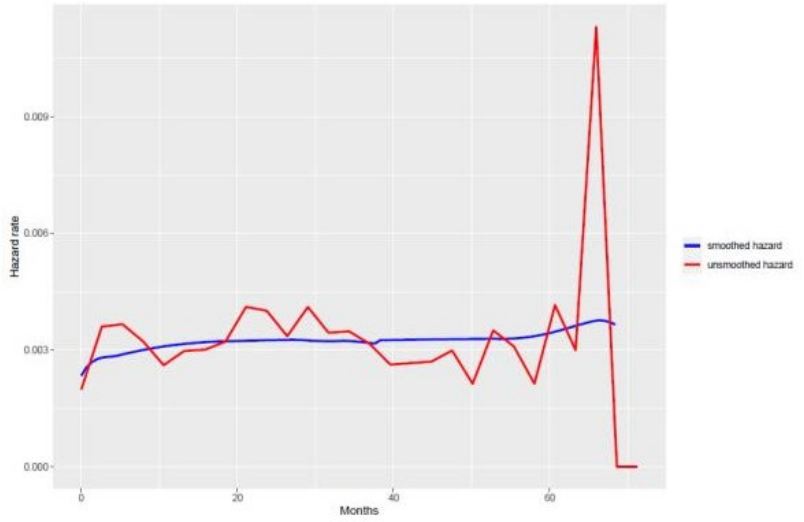


Figure 29 Smoothed and unsmoothed hazard, IDFS, ABE + ET

ET alone arm

The hazard functions for the 9 candidate distributions for IDFS for the ET Alone arm are displayed to enable visual inspection of the survival curves overlaid by KM estimates of observed data. The smoothed hazard function was considered as observed hazard overlying the candidate distributions (Figure 30).

However, unlike the KM curves for survival probabilities, smoothed hazard curves are not robust and may be extremely sensitive to a few datapoints. Therefore, additional figure (Figure 31), showing smoothed and unsmoothed hazard rates, are added to illustrate the fluctuation of instantaneous hazards and to invite to caution when interpreting smoothed hazard functions.

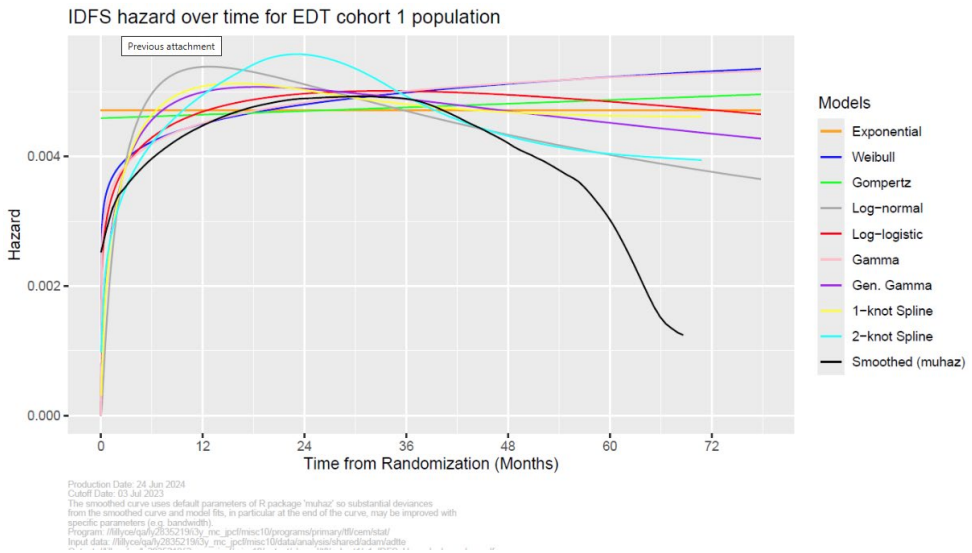


Figure 30 IDFS hazard over time for ET, Cohort 1

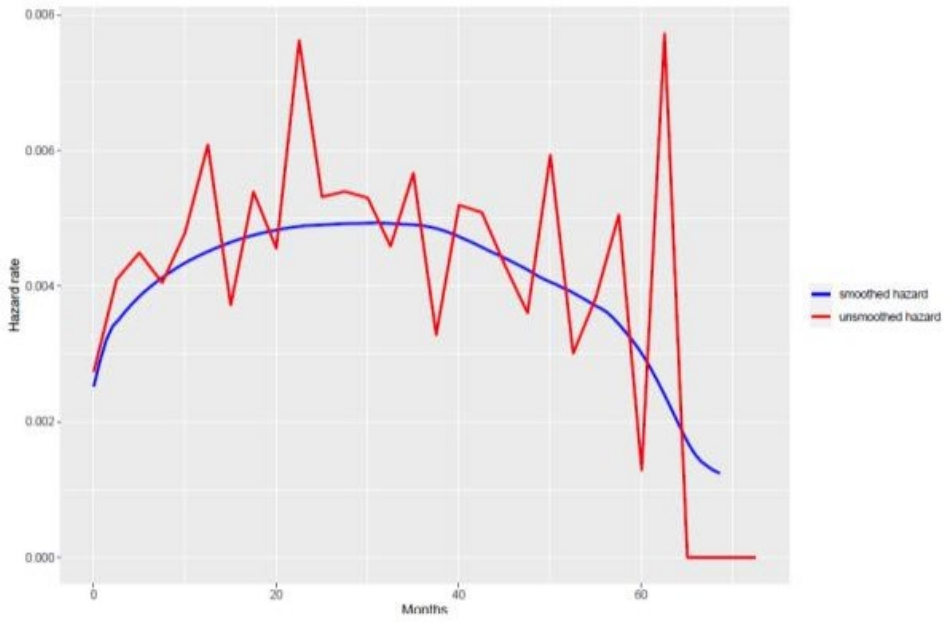


Figure 31 Smoothed and unsmoothed hazard, OS without distant recurrence, ET alone

Please also see D.1.3

D.1.7 Validation and discussion of extrapolated curves

No external validation has been performed in the cohort 1 population due to a lack of comparable studies.

Lilly conducted a SLR to identify RCTs evaluating adjuvant ET-based regimens in patients with HR+, HER2- EBC. The review identified 201 publications reporting on 38 RCTs evaluating adjuvant ET-based regimens. Nine studies reported data where >80% of the trial population were HER2-. Invasive disease-free survival defined using the STEEP criteria was assessed as the primary outcome in four studies: monarchE, PALLAS , PENELOPE, and SWOG. An overview of those studies is provided in Table 11. The follow-up time of these trials were limited to approximately 3 to 4 years. The four-year IDFS rates reported in these trials could support the validation of the ET alone arm of the monarchE trial.

Of the remaining five studies of the nine trials, different definitions of disease-free survival (DFS) were used as the primary outcome. One trial did only report the pooled data of tamoxifen to AI vs. AI for the three different AI treatments, anastrozole, letrozole, and exemestane (FATA-GIM3). Another trial only reported safety data as outcome (SUCCESS). HOBOE, FACE and SOFT were comparable to monarchE with the exception of the additional event types excluded from their DFS definition. The five-year IDFS rates for tamoxifen, letrozole and anastrozole reported in HOBOE and FACE were higher than the 5-year rates for the ET alone arm observed in the OS IA3 in the monarchE trial (see table below).

Analysing the monarchE trial findings with external evidence, particularly considering long-term follow-up data, posed challenges. For the trials presented in Table 11, the follow-up was equal to or shorter than the follow-up of the OS IA3 data cut of the monarchE trial, which does not allow for external validity of the survival extrapolation conducted for this model. The SLR identified trials for which populations were not directly comparable to the monarchE population, or the endpoints were not directly translatable to the IDFS endpoint. There are no data to refute the selection of the dependent log-logistic model for both ABE + ET and ET alone.

Trial name	Treatment	Latest publication	Timepoint for rate (years)	Population	Outcome	Rate (%)	IDFS /DFS excludes
monarchE (98)	ET + CDK4&6 inhibitors vs. ET	2023	~ 4	ITT	IDFS	ABE + ET: 85.8 ET: 79.4	DCIS New primary breast cancer

Trial name	Treatment	Latest publication	Timepoint for rate (years)	Population	Outcome	Rate (%)	IDFS /DFS excludes
PALLAS (99)		2020	~ 4	mITT	IDFS	Palbociclib + ET: 84.2 ET: 84.5	DCIS New primary breast cancer
PENELOPE (100)		2021	~ 4	ITT	IDFS	Palbociclib + ET: 73.0 ET: 72.4	DCIS New primary breast cancer
SWOG (101)	Everolimus vs. ET	2022	~ 3	mITT	IDFS	Everolimus + ET: 74.8 ET: 73.9	DCIS New primary breast cancer
HOBOE (102)	Tamoxifen vs. AI	2019	~ 5	ITT	DFS	Tamoxifen: 85.4 (80.9-88.9) Letrozole: 93.2 (89.7-95.5)	Ipsilateral New primary breast cancer

Trial name	Treatment	Latest publication	Timepoint for rate (years)	Population	Outcome	Rate (%)	IDFS /DFS excludes
FATA-GIM3 (103)	Tamoxifen to AI vs. AI	2018	~ 5	ITT	DFS	Tamoxifen to anastrozole and anastrozole pooled: 90.0 (87.9 – 91.7) Tamoxifen to letrozole and letrozole pooled: 89.4 (87.3-91.1) Tamoxifen to exemestane and exemestane pooled: 88.0 (85.8-89.9)	Ipsilateral DCIS New primary breast cancer
SUCCESS (104)	Tamoxifen to AI vs. AI	2018	NR	ITT	Safety only	NR	NR

Trial name	Treatment	Latest publication	Timepoint for rate (years)	Population	Outcome	Rate (%)	IDFS /DFS excludes
FACE (105)	AI vs AI	2017	~ 5	mITT	DFS	Letrozole: 84.9 (83.2-86.2) Anastrozole: 82.9 (81.2-84.5)	Ipsilateral DCIS New primary breast cancer Second Non-breast cancer
SOFT (106)	Tamoxifen + OFS vs. AI + OFS	2023	~12	mITT	DFS	Tamoxifen: 71.9 Tamoxifen + OFS: 76.1 Exemestane + OFS: 79.0	Ipsilateral DCIS New primary breast cancer

D.1.8 Adjustment of background mortality

Conducted in line with DMC guidelines (54).

D.1.9 Adjustment for treatment switching/cross-over

NA

D.1.10 Waning effect

Waning of treatment effect was applied from year eight and no treatment effect exists beyond year 26, lasting for 18 years. At 26 years, the risk of disease recurrence from IDFS was equal to or less than background mortality.

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 (Cuzick et al. (2010)). However, the ATAC trial does not report data on HER2 status. The authors of the paper demonstrate the falling recurrence rates for HR+ patients on anastrozole versus tamoxifen over time with 'carryover benefit' lasting up to eight years following which the treatment effect begins to wane (figure below).

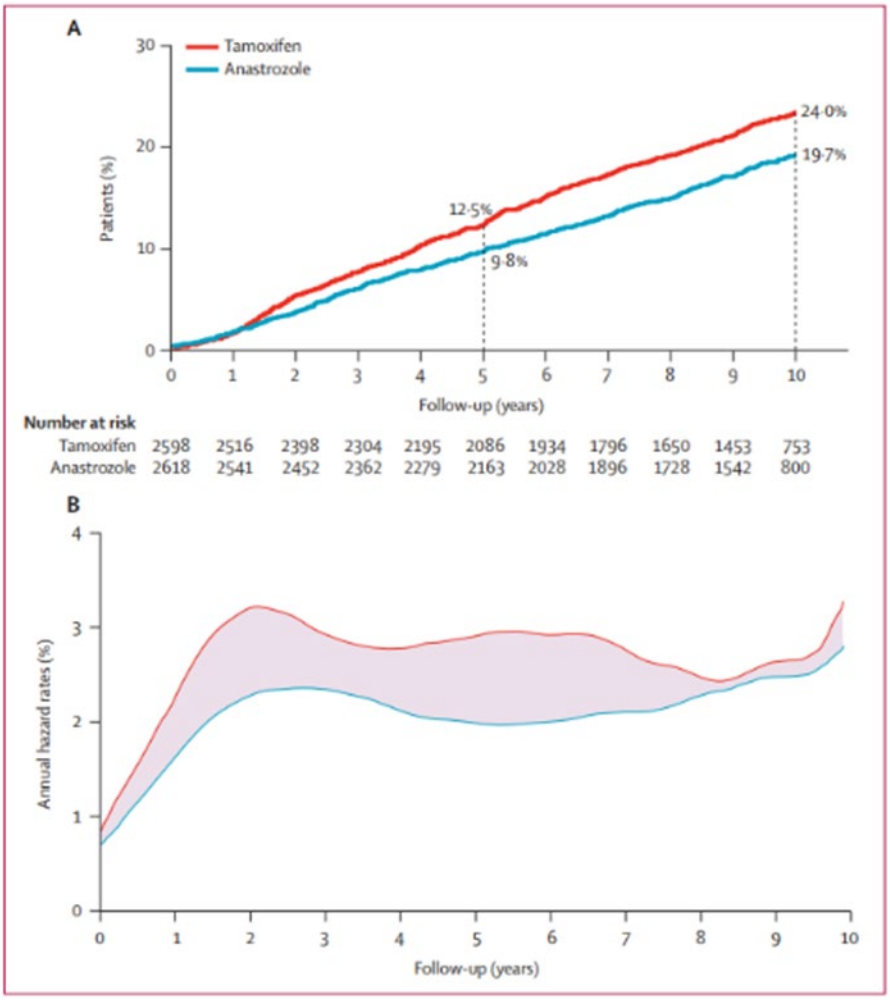


Figure 1: **Curves for time to recurrence in hormone-receptor-positive patients**
(A) Kaplan-Meier prevalence curves and (B) smoothed hazard rate curves.[8] Numbers at risk differ in some cases from those provided in the 100-month analysis[3] because of additional follow-up data.

Figure 32 Curves for time to recurrence in HR+ patients

Although the population of the Cuzick et al. (2010) paper is not directly comparable to monarchE, it was assumed that the treatment effect between ABE + ET and ET alone would follow a similar trend to what was observed beyond more effective ET treatments. We have assumed that treatment effect lasts for at least eight years but starts to wane afterward. By year 26, the model assumed no further treatment benefit remains. Year 26 was the point in the model where the IDFS hazard rate equals the hazard rate of background mortality (figure below), aligned with the approach from TA612 in the HER2+ space.

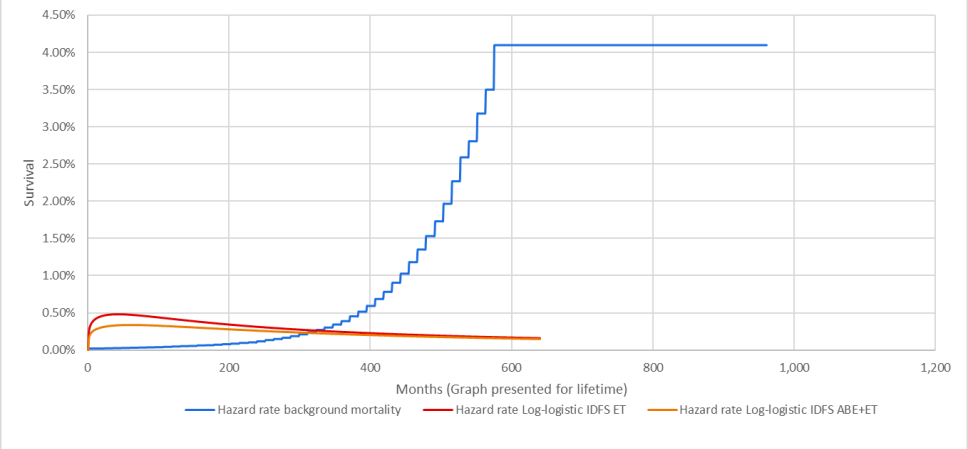


Figure 33 IDFS - Crossing of the hazard rate with general population mortality.

The observed IDFS OS IA3 data of the monarchE trial did not indicate a treatment waning effect, although ABE treatment stopped at two years. Figure below illustrates the IDFS hazard rates of the ABE + ET (in black) and ET alone (in pink) arms at six monthly intervals over 60 months. The curves show the second order polynomial trendline of the individual six-monthly hazard rates (presented in dots). The curves show that after approximately 36 months the IDFS hazard rates start to decline for both treatment arms. Based on visual inspection, the relative effect between the treatment arms are not narrowing as the two curves are not converging, suggesting a continued treatment effect from ABE. It cannot be ruled out that over time the IDFS hazard rates of ABE + ET and ET alone will converge.

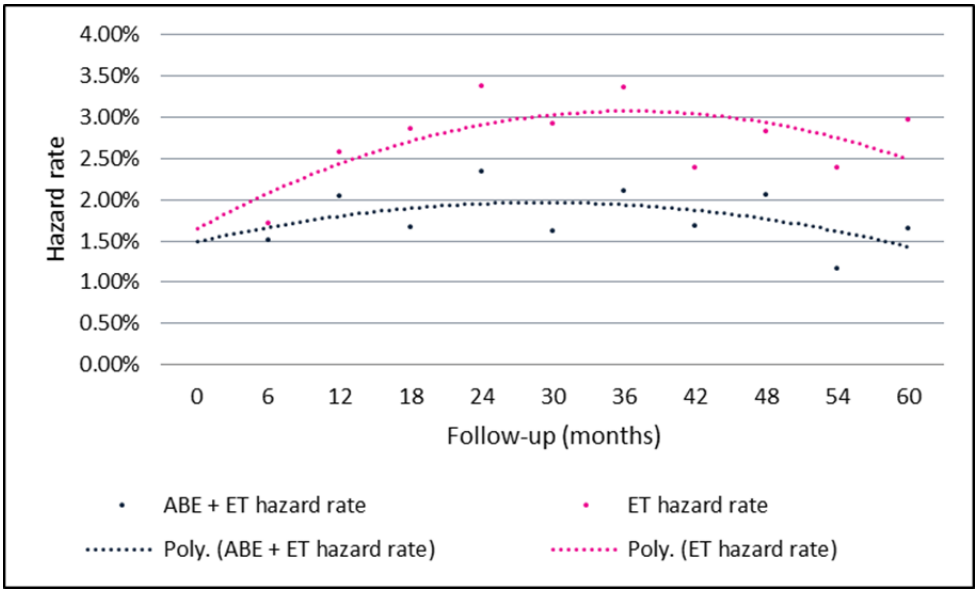


Figure 34 Curves of IDFS hazard rates of ABE + ET and ET alone arms - ITT DCO 2023

D.1.11 Cure-point

NA

D.2 Extrapolation of TTD

Evidence from the MonarchE trial was deemed the most recent and relevant for the validation of the TTD extrapolations of the ET-arms. For the ABE treatment, the KM curve was used, which falls to zero at two years, in accordance with the 2-year on-study treatment period. For the ET-arms, clinical and economic stopping rules were applied at five years, which means that there is limited risk of bias being introduced into the model by selection of the TTD extrapolation curves

D.2.1 Data input

The duration of treatment is determined by the TTD curves of the ABE + ET and ET-alone 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. Due to the maximum two-year treatment duration permitted for ABE, and the follow-up period of the OS IA3 2023 data cut, the full KM curve was used to estimate TTD for ABE in the base case.

The MonarchE trial was set up with a 2-year on-study treatment period for both treatment arms, after which patients could enter the study follow-up period and receive post-discontinuation therapies (including ET). This means that data on TTD were already considered final at the OS IA2 data cut and were not updated in the OS IA3 data cut. Therefore, OS IA2 data is used to inform TTD. However, ABE has been approved for EBC patients with node-positive HR+ / HER2- in combination with a minimum of five years of adjuvant ET. As such, TTD data of the MonarchE trial for the ET treatment arms should be extrapolated to reflect the full treatment period as approved. The ET data used for extrapolation was re-censored at month 20, to prevent that a drop in TTD towards the end of the 2-year on-study treatment period has an impact on the long-term extrapolation.

D.2.2 Model

Extrapolations based on within trial data were used to inform the ET-arms. Independent models assumed with [redacted] distribution following internal validity checks.

Selected parametric distributions used in the analysis:

[redacted]

[redacted]

The [redacted] distribution is recommended as the base case, as no crossing of curves can be seen when this curve is selected. Based on the AIC and BIC values for the ET intervention arm, the log-normal could be selected as an alternative distribution, although it is a poor fit for the ET comparator arm.

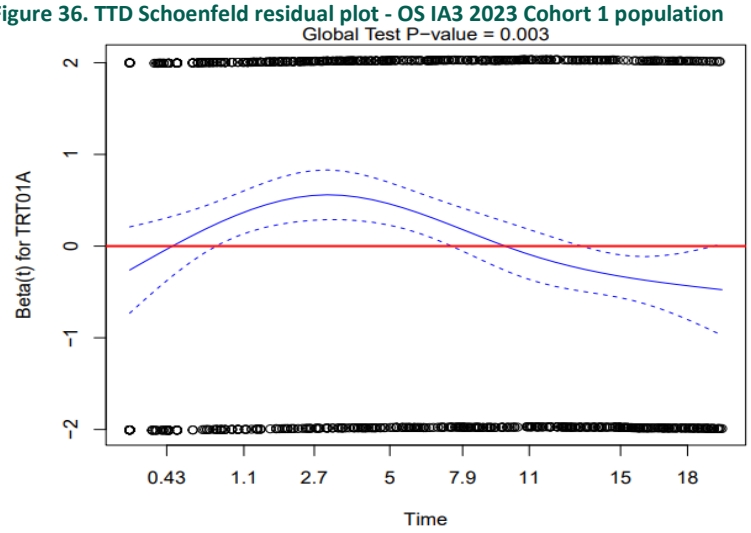
D.2.3 Proportional hazards

The log-cumulative plot in [redacted] shows that there is convergence of the trial arms at several points in the plot, indicating that the PH assumption is violated. Furthermore, the Grambsch and Therneau test could be labelled as statistically significant (p-value = 0.003) as it fell below p = 0.05. This is consistent with the Schoenfeld residuals visualisation (Figure 36), in which a trend can be observed, suggesting a violation of the PH assumption. Therefore, two independent models were fitted to the ET data of the MonarchE trial.

Figure 35. TTD log-cumulative hazard plot - OS IA3 2023 Cohort 1 population

[redacted]

Figure 36. TTD Schoenfeld residual plot - OS IA3 2023 Cohort 1 population



Abbreviations: OS IA2, Overall survival interim analysis 2 data cut; TTD, Time to treatment discontinuation
* The red line indicates no treatment effect

D.2.4 Evaluation of statistical fit (AIC and BIC)

The seven parametric distributions and two spline models were fitted independently to the TTD KM data and were evaluated based on AIC and BIC values, as presented in Table 72. (ET intervention arm) and Table 73 (ET comparator arm). The best statistical fit, when considering both trial arms, is provided by the hazard spline knot 2 distribution, followed by the hazard spline knot 1 distribution. Figure 37 gives a visual presentation of the TTD curves. The selection of the hazard spline knot 2 distribution eventually leads to a crossing of the TTD curves in the model. This can be considered as an unrealistic estimation, as it would be expected that ET in both trial arms follows the same pattern. Therefore, the hazard spline knot 1 distribution is recommended as the base case, as no crossing of curves can be seen when this curve is selected. Based on the AIC and BIC values for the ET intervention arm, the log-normal could be selected as an alternative distribution, although it is a poor fit for the ET comparator arm.

Table 72: AIC and BIC values for TTD extrapolations – ET intervention arm - OS IA3 2023 Cohort 1

ET intervention arm – Independent distributions			
Distributions	**AIC**	**Distributions**	**BIC**
[redacted]			

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; IDFS, Invasive disease-free survival; OS IA3, Overall survival interim analysis 3 data cut. **Note**: the first best-fitting curve is in bold, while the second and third best-fitting curves are underlined. All curves within 2.0 points from the best-fitting AIC and BIC value are grey highlighted.

Table 73: AIC and BIC values for TTD extrapolations – ET comparator arm - OS IA3 2023 Cohort 1

ET intervention arm – Independent distributions			
Distributions	**AIC**	**Distributions**	**BIC**
[redacted]			

Log-logistic	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; IDFS, Invasive disease-free survival; OS IA3, Overall survival interim analysis 3 data cut. **Note**: the first best-fitting curve is in bold, while the second and third best-fitting curves are underlined. All curves within 2.0 points from the best-fitting AIC and BIC value are grey highlighted.

Figure 37. Long-term extrapolations – Cohort 1 population; left panel ET intervention arm and right panel ET comparator arm

D.2.5 Evaluation of visual fit

Please see above section

D.2.6 Evaluation of hazard functions

Please see above sections

D.2.7 Validation and discussion of extrapolated curves

No extrapolation, and thus external validation, was required for ABE as the full KM curve was used. Evidence from the monarchE trial was deemed the most recent and relevant data to validate the TTD extrapolations of ET. A clinical and economic stopping rule was applied at five years, limiting the risk of bias through selection of the TTD extrapolation curves.

D.2.8 Adjustment of background mortality

NA

D.2.9 Adjustment for treatment switching/cross-over

NA

D.2.10 Waning effect

NA

D.2.11 Cure-point

NA

D.3 Extrapolation of OS without distant recurrence

D.3.1 Data input

OS (without distant recurrence) data of the MonarchE trial

D.3.2 Model

A single model, including an adjustment factor for treatment effect (HRa), was fitted to the OS (without distant recurrence) data of the MonarchE trial.

Selected parametric distributions used in the analysis:

[redacted]

[redacted]

D.3.3 Proportional hazards

The PH assumption between treatment arms was tested. The log-cumulative hazard plot in [redacted] shows the treatment arms are crossing at two time points, indicating a violation of the PH assumption. Furthermore, the Grambsch and Therneau test could not be labelled as statistically significant (p-value = 0.737) as it exceeded p = 0.05. This is consistent with the Schoenfeld residuals visualisation [redacted], in which no time trend can be observed. Therefore, the PH assumption cannot be rejected. These results can be considered volatile due to the small number of OS without distant recurrence events observed in the trial. The data are too immature to assume a PH violation.

Figure 38. OS without distant relapse log-cumulative hazard plot - OS IA3 2022 Cohort 1 population

Figure 39.OS without distant relapse Schoenfeld residual plot - OS IA3 2023 Cohort 1 population

D.3.4 Evaluation of statistical fit (AIC and BIC)

Seven parametric distributions and two spline models were fit 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 are presented in Table 13. The best statistical fit is provided by the exponential distribution as it presents the lowest BIC value and is less than 2 points away from the lowest AIC value. Therefore, the exponential distribution was used in the base case analysis. Despite the Weibull distribution presenting the lowest AIC value, the BIC value is around six points from the exponential distribution. A second alternative distribution is the log-logistic, being the second and third best-fit on AIC and BIC, respectively. The Weibull and log-logistic distributions were explored through scenario analyses. [redacted] gives a visual presentation of the OS without distant relapse curves.

Table 74. AIC and BIC values for OS without distant relapse extrapolations – OS IA3 2023 Cohort 1 population

Dependent distributions			
Distributions	AIC	Distributions	BIC
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; IDFS, Invasive disease-free survival; OS IA3, Overall survival interim analysis 3 data cut. **Note**: the first best-fitting curve is in bold, while the second and third best-fitting curves are underlined. All curves within 2.0 points from the best-fitting AIC and BIC value are grey highlighted.

Figure 40. Long-term OS without distant relapse extrapolations – Cohort 1 population; left panel ABE + ET and right panel ET-alone

D.3.5 Evaluation of visual fit

When comparing the five-year landmark IDFS rates of the ET-alone arm of the MonarchE trial with the extrapolation curves at five year, the log-logistic shows a good fit with the OS IA3 data. The five-year extrapolations of all curves are close to each other (75.2-75.6), except for the log-normal (76.2). The log-logistic estimate for the ABE + ET arm is slightly lower than the five-year the OS IA3 data. However, all extrapolation curves estimate the

five-year IDFS rate slightly under the observed five-year data of the MonarchE trial for ABE + ET. As can be seen in Table 10, the five-year extrapolations of all curves are close to each other (82.5-82.8). On visual inspection, all extrapolated curves seem to fit the MonarchE trial data for the observed time-period relatively well. Although the curves follow a similar pattern for the first five years, over time the curves show more variation in the extrapolated IDFS.

Table 75. Landmark IDFS rates for ABE + ET and ET-alone arms - OS IA3 2023 Cohort 1 population

	Five-year rates		Ten-year rates	
	ABE + ET	ET-alone	ABE + ET	ET-alone
[redacted]				

* Abbreviations: ABE, Abemaciclib; AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; ET, Endocrine Therapy; IDFS, Invasive disease-free survival; ITT, Intention to treat; N/A, Not available; OS IA3, Overall survival interim analysis 3 data cut
Note: The best performing distribution is made bold. Please note that treatment waning is accounted for in these comparisons.

Figure 41. Long-term IDFS extrapolations – Cohort 1 population; left panel ABE+ET and right panel ET-alone

[redacted]

D.3.6 Evaluation of hazard functions

For the fit of standard parametric functions to be evaluated for OS without distant disease recurrence, a plot of the hazard rates over time for all 9 distributions overlaid by the smoothed hazard function was created. Additionally, a plot with the smoothed and unsmoothed hazard overlaid, as well as plots of transformations for standard parametric functions were created for the same purpose.

ABE + ET arm

The hazard functions for the 9 candidate distributions for OS without distant recurrence for the ABE+ET arm is displayed to enable visual inspection of the survival curves overlaid by KM estimates of observed data. The smoothed hazard function was considered as observed hazard overlying the candidate distributions (Figure 42).

However, unlike the KM curves for survival probabilities, smoothed hazard curves are not robust and may be extremely sensitive to a few datapoints. Therefore, additional figure (Figure 43), showing smoothed and unsmoothed hazard rates, are added to illustrate the fluctuation of instantaneous hazards and to invite to caution when interpreting smoothed hazard functions.

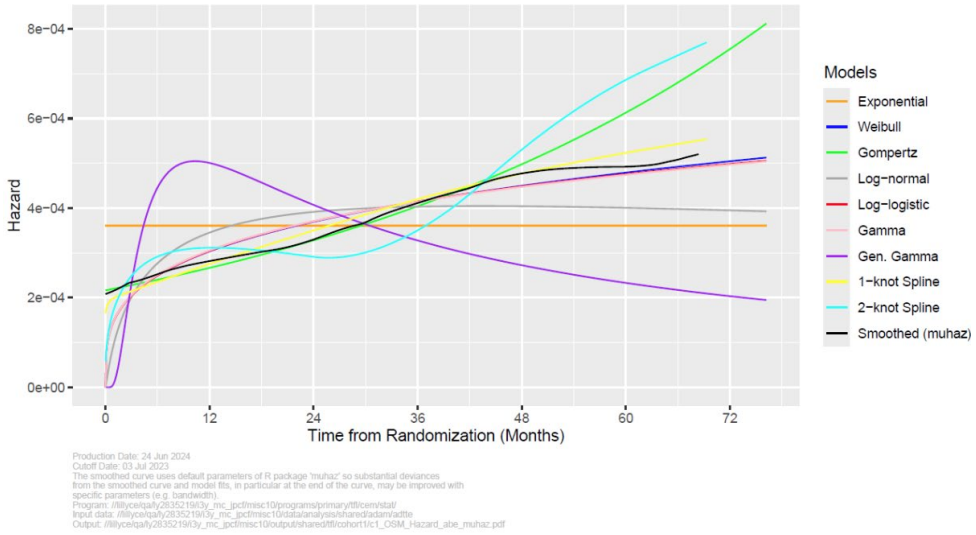


Figure 42 Smoothed zard and parametric function, OS without distant recurrence, ABE + ET

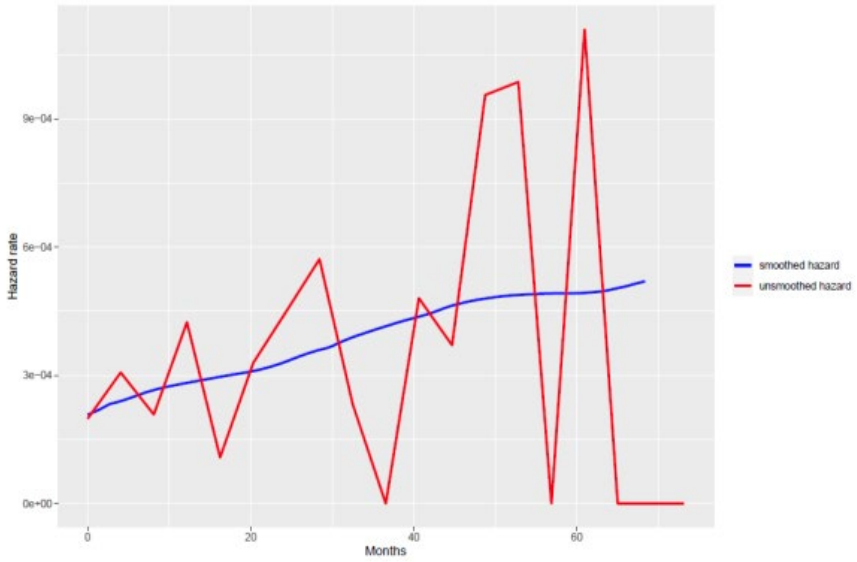


Figure 43 Smoothed and unsmoothed hazard, OS without distant recurrence, ABE + ET

ET alone arm

The hazard functions for the 9 candidate distributions for OS without distant recurrence for the ET Alone arm is displayed to enable visual inspection of the survival curves overlaid by KM estimates of observed data. The smoothed hazard function was considered as observed hazard overlying the candidate distributions (Figure 44).

However, unlike the KM curves for survival probabilities, smoothed hazard curves are not robust and may be extremely sensitive to a few datapoints. Therefore, additional figure (Figure 45), showing smoothed and unsmoothed hazard rates, are added to illustrate the fluctuation of instantaneous hazards and to invite to caution when interpreting smoothed hazard functions.

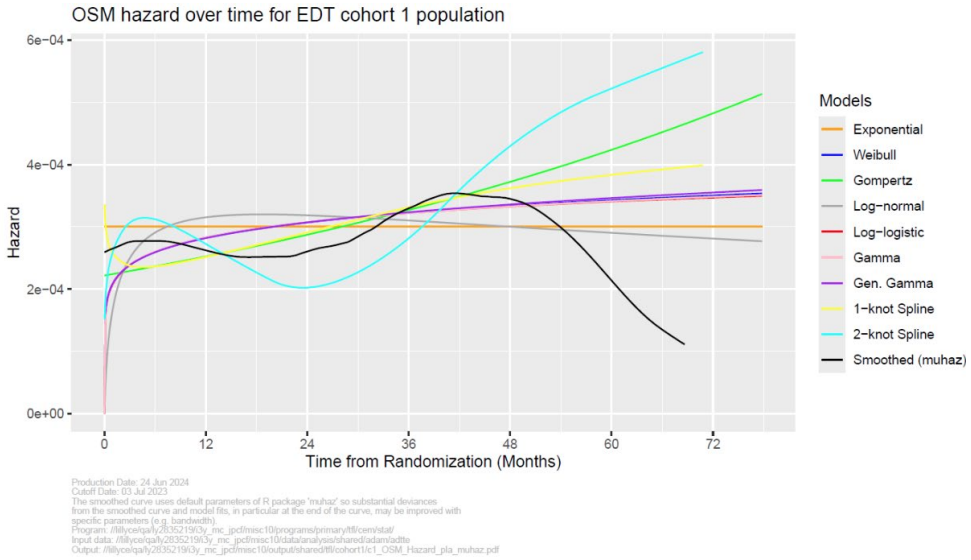


Figure 44 Smoothed hazard and parametric functions, OS without distant recurrence, ET alone

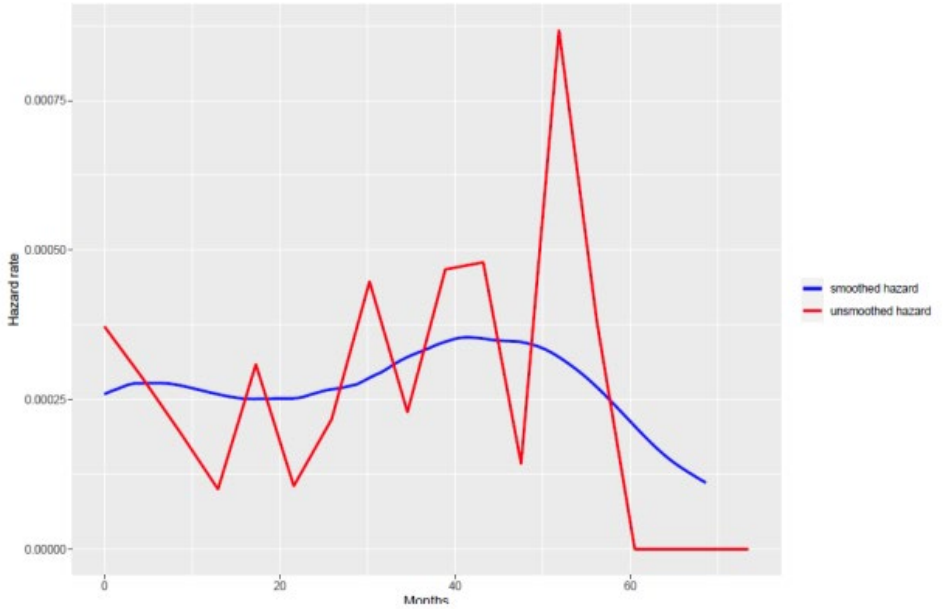


Figure 45 Smoothed and unsmoothed hazard, OS without distant recurrence, ET alone

Please see D.1.3

D.3.7 Validation and discussion of extrapolated curves

Evidence from the MonarchE trial was deemed the most recent and relevant for the validation of the OS without distant recurrence extrapolations. The final choice of the distribution was based on internal validations.

Within the framework of the model, the selected OS extrapolations for base case and scenarios provide a hazard rate which is just below the hazard rate of age and gender corrected background mortality for the first few years. After which, the OS curve is bound by background mortality in the model. Considering the risk of death is low from a NMR, the likelihood of any bias is minimal.

D.3.8 Adjustment of background mortality

Within the framework of the model, the selected OS extrapolations for base case and scenarios provide a hazard rate which is just below the hazard rate of age and gender corrected background mortality for the first few years. After which, the OS curve is bound by background mortality in the model. Considering the risk of death is low from a NMR, the likelihood of any bias is minimal.

D.3.9 Adjustment for treatment switching/cross-over

NA

D.3.10 Waning effect

NA

D.3.11 Cure-point

NA

Appendix E. Serious adverse events

Overall, there were minimal changes at OS IA3 compared to OS IA2 in the incidences of any-grade TEAEs, Grade ≥3 TEAEs, and SAEs.

	Abemaciclib + ET N = 2,791 n (%)		ET alone N = 2,800 n (%)	
	OS IA2[a]	OS IA3[b]	OS IA2[a]	OS IA3[b]
Patients with ≥1 TEAE	2746 (98.4)	2746 (98.4)	2488 (88.9)	2488 (88.9)
Patients with ≥1 CTCAE Grade ≥3 TEAE	1393 (49.9)	1395 (50.0)	472 (16.9)	474 (16.9)
Patients with ≥1 TE-SAE	433 (15.5)	435 (15.6)	256 (9.1)	258 (9.2)
Patients who discontinued all study treatment due to AE	180 (6.4)	180 (6.4)	30 (1.1)	30 (1.1)
Patients who died due to AE on study therapy or within 30 days of iscontinuation from study treatment	15 (0.5)	15 (0.5)	11 (0.4)	11 (0.4)
Patients who died due to AEs more than 30 days after the discontinuation from study treatment	24 (0.9)	39 (1.4)	23 (0.8)	36 (1.3)

Table 76. Overview of Safety in MonarchE by Analysis Data Cutoff (83)

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; ET = endocrine therapy; N = number of patients; n = number of patients in the specified category; OS IA2 = Overall Survival Interim Analysis 1; OS IA3 = Overall Survival Interim Analysis 2; TEAE = treatment-emergent adverse event, TE-SAE = treatment-emergent serious adverse event.a Data cutoff: 01 July 2022; b Data cutoff: 03 July 2023.

Table 77 summarizes TEAEs by maximum CTCAE grade and PT that occurred in ≥10% of patients in Arm A with a >2% difference to Arm B. The most frequently reported TEAEs with at least 20% incidence in Arm A included diarrhea, neutropenia, fatigue, leukopenia, abdominal pain, nausea, arthralgia, and anemia. The most common Grade ≥3 TEAEs with at least 2% incidence in Arm A included neutropenia, leukopenia, diarrhea, lymphopenia, fatigue, ALT increased, and anemia. There was one Grade 5 event of diarrhea in Arm A.

Table 77. Treatment-Emergent Adverse Events by Preferred Term in ≥10% of Patients Receiving Abemaciclib (83)

	Arm A Abemaciclib + ET N = 2,791		Arm B ET N = 2,800	
	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Diarrhea	2333 (83.6)	219 (7.8)	245 (8.8)	6 (0.2)
Neutropenia	1282 (45.9)	548 (19.6)	157 (5.6)	24 (0.9)
Fatigue	1140 (40.8)	79 (2.8)	506 (18.1)	4 (0.1)
Leukopenia	1054 (37.8)	319 (11.4)	185 (6.6)	11 (0.4)
Abdominal Pain	996 (35.7)	39 (1.4)	278 (9.9)	9 (0.3)
Nausea	826 (29.6)	14 (0.5)	254 (9.1)	2 (0.1)
Arthralgia	740 (26.5)	9 (0.3)	1063 (38.0)	29 (1.0)
Anemia	686 (24.6)	59 (2.1)	108 (3.9)	12 (0.4)
Headache	553 (19.8)	8 (0.3)	425 (15.2)	5 (0.2)
Vomiting	491 (17.6)	15 (0.5)	131 (4.7)	4 (0.1)
Hot flush	432 (15.5)	4 (0.1)	646 (23.1)	10 (0.4)
Cough	392 (14.0)	1 (0.0)	224 (8.0)	0
Lymphopenia	398 (14.3)	151 (5.4)	96 (3.4)	14 (0.5)
Thrombocytopenia	373 (13.4)	36 (1.3)	53 (1.9)	4 (0.1)
Alanine aminotransferase increased	351 (12.6)	77 (2.8)	157 (5.6)	20 (0.7)
Lymphoedema	352 (12.6)	5 (0.2)	256 (9.1)	1 (0.0)
Urinary tract infection	338 (12.1)	16 (0.6)	210 (7.5)	6 (0.2)
Aspartate aminotransferase increased	337 (12.1)	53 (1.9)	139 (5.0)	15 (0.5)

Constipation	337 (12.1)	2 (0.1)	171 (6.1)	1 (0.0)
Decreased appetite	331 (11.9)	16 (0.6)	70 (2.5)	2 (0.1)
Alopecia	318 (11.4)	0	79 (2.8)	0
Rash	316 (11.3)	11 (0.4)	129 (4.6)	0
Blood creatinine increased	311 (11.1)	3 (0.1)	28 (1.0)	0

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; ET = endocrine therapy; N = number of patients in the safety population; n = number of patients in the specified category; OS = overall survival. Data cutoff: 03 July 2023.

Appendix F. Health-related quality of life

Please consult Section 10 for information on health-related quality of life.

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 (no linkage – copied in) for the Health State Index and Table 15 (no linkage – copied in) 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 (no linkage – copied in).

F.1 HRQoL data from MonarchE

F.1.1 Study design and measuring instrument

In the MonarchE trial, utility data was collected on therapy or up to "Short Term Follow-Up" or Q12M (one year after discontinuation). The MonarchE trial was set up with a 2-year on-study treatment period for both treatment arms, after which patients could enter the study follow-up period. This means that all patients were off the study treatment for at least a year at the OS IA2 data cut and as such, utility data was considered final at the OS IA2 data cut. Therefore, utility data was not updated with the OS IA3 data cut and OS IA2 data is used to inform the utility analysis (DCO 2021).

Different PROs were used to measure HRQoL: FACT-B, FACT-ES, FACIT-F, and EQ-5D-3L. After the baseline assessment, FACT-B, FACT-ES, 2 FACIT-sourced items of cognitive symptoms, 3 FACIT-sourced items for bladder symptoms, EQ-5D-5L questionnaires were next administered to patients at visit 6, visit 9, visit 15, and visit 21 (approximate timepoints of visits, 3, 6, 12 and 18 months respectively). Questionnaires were given at visit 27 (end of on study treatment period) and follow-up visits are not included in IA2 due to <25% of patients having an assessment at those visits.

For this submission, EQ-5D-5L is used to inform HSUVs. The analyses on PROs were based on the safety population (DCO 2021) (results reported in 10.1.3). A mixed effects repeated measures (MMRM) model was applied to compare treatment arms by assessment with respect to each of the summary scores and select items. The summary scores were

calculated as per the FACIT guidance. An effect size of one-half standard deviation (0.5 SD) was used. This represents a conservative estimate of a minimally important difference (MID) (Norman 2003). For the analysis of individual items, a change of one point was deemed meaningful.

As a result of the large sample size necessary to support other efficacy endpoints, all statistical comparisons of PRO data are overpowered and it is likely that any numerical differences between arms will be deemed statistically significant regardless of clinical significance. Because patients are disease-free at enrolment and the majority of patients in either arm do not experience disease recurrence, the majority of changes in patient-felt symptoms or impacts are assumed to be treatment-related. Therefore, differences across treatment arms were evaluated based on numerical estimates and the interpretation should be viewed as exploratory.

F.1.2 Results

The mean scores for the FACT-B and FACT-ES subscales are shown in Table 78 and Table 79respectively. The mean scores and changes from baseline scores were similar in both arms for all measures. Changes in the Well-being scores, Breast Cancer Subscale, Trial Outcome Index, and FACT-B Total Score were less than the minimally important difference MID of 0.5 of the baseline standard deviation (SD). Changes in FACT-ES and FACIT-F Total Score were less than the MID of 0.5 of the baseline SD.

In terms of Item HI7, “I feel fatigue”, mean scores within both arms remained around 1 for subsequent visits, indicating patients in both arms felt fatigue “a little bit”. 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 1 for all post-baseline visits, indicating most patients reported “not at all” 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 similar between arms, being around 1, indicating patients experience these cognitive symptoms “a little bit”.

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.

Refer to Appendix F.2 for charts showing the mean change in HRQoL results from baseline.

Table 78. FACT-B - Cohort 1 safety population (DCO 8 July 2020)

FACT-B Total Score	Abemaciclib + ET (N=2,555)			ET alone (N=2,565)			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]						
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; 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 (84). Data cut-off: 08 July 2020.

Table 79. FACT-ES - Cohort 1 safety population (DCO 8 July 2020)

FACT-ES Total Score	Abemaciclib + ET (N=2,555)			ET alone (N=2,565)			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]						
Visit 6 (3 months)	[redacted]						
Visit 9 (6 months)	[redacted]						
Visit 15 (12 months)	[redacted]						
Visit 21 (18 months)	[redacted]						
All post-baseline	[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 (84). Data cut-off: 08 July 2020

The visual analogue scale (VAS) demonstrated similar results as the index value; scores were similar between the two treatment arms for all baseline and post-baseline visits (refer to Section 10).

Table 80 Summary of EQ-5D-5L VAS score, in MonarhE, safety population (DCO 8 July 2020)

	ABE			ET alone			ABE + ET vs ET LSM Change Difference (SE)
	n	Mean (SD)	CfB, LSM (SE)	n	Mean (SD)	CfB, LSM (SE)	
Visual analogue scale							
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: EQ-5D 5L= EuroQol 5-Dimension 5-Level; LSM= least squares mean; SE= standard error; SD= standard deviation; CfB= change from baseline; ET= endocrine therapy.
Source: Lilly Data on File. Clinical Study Report: MonarchE. Data cut-off: 08 July 2020.

F.2 Charts showing the mean change from baseline

F.2.1 FACT-B - Cohort 1 safety population (DCO 8 July 2020)

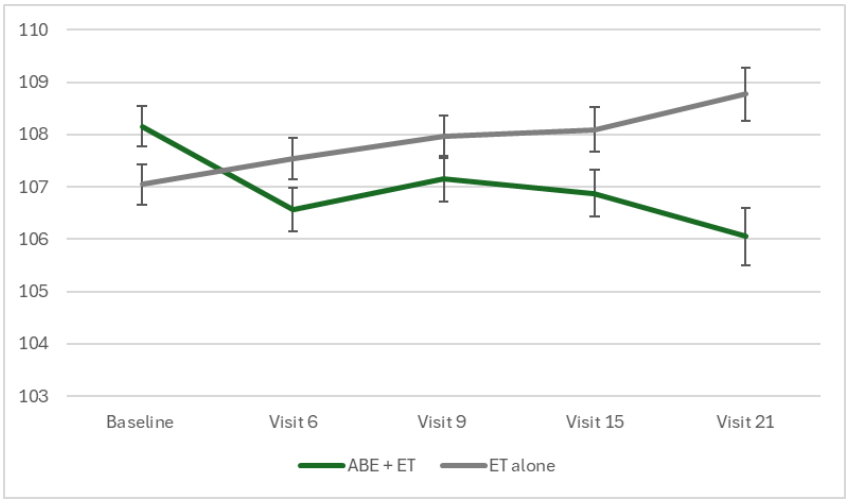


Figure 46 Mean change from baseline - FACT-B

F.2.2 FACT-ES - Cohort 1 safety population (DCO 8 July 2020)

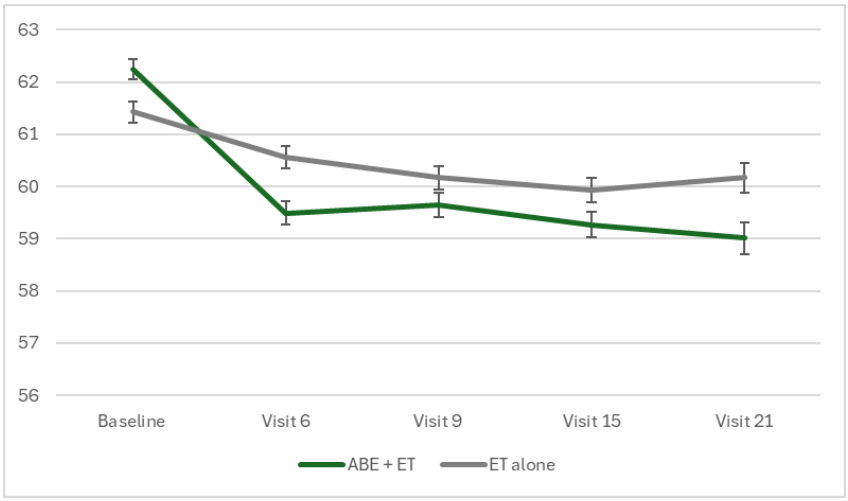


Figure 47 Mean change from baseline - FACT-ES - ESS-19

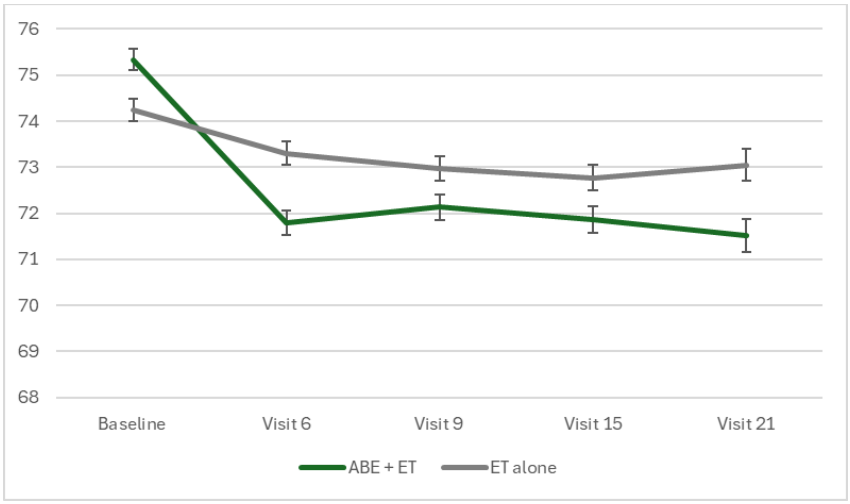


Figure 48 Mean change from baseline - FACT-ES - ESS-23

F.3 Compliance rate for EQ-5D-4L by visit, Cohort 1 Population – safety population (DCO 2021)

Figures below show the compliance rate and reasons for noncompliance for EQ-5D-5L by visit.

Planned visit		LY2835219-150mg +EDT (N=2539) n (%)	EDT (N=2539) n (%)
BASELINE	n	2539	2539
	Compliant with Questionaire	2468 (97.20)	2433 (95.83)
	Main reason if not compliant		
	SUBJECT REFUSAL	12 (0.47)	19 (0.75)
	STUDY SITE FAILED TO ADMINISTER	18 (0.71)	21 (0.83)
	TRANSLATION NOT AVAILABLE	1 (0.04)	1 (0.04)
	OTHER	32 (1.26)	54 (2.13)
	MISSING	8 (0.32)	11 (0.43)
VISIT6	n	2401	2433
	Compliant with Questionaire	2274 (94.71)	2282 (93.79)
	Main reason if not compliant		
	SUBJECT REFUSAL	28 (1.17)	18 (0.74)
	STUDY SITE FAILED TO ADMINISTER	42 (1.75)	47 (1.93)
	TRANSLATION NOT AVAILABLE	0 (0.00)	1 (0.04)
	OTHER	45 (1.87)	78 (3.21)
	MISSING	12 (0.50)	7 (0.29)
VISIT9	n	2325	2379
	Compliant with Questionaire	2201 (94.67)	2246 (94.41)
	Main reason if not compliant		
	SUBJECT REFUSAL	16 (0.69)	19 (0.80)
	STUDY SITE FAILED TO ADMINISTER	39 (1.68)	31 (1.30)
	TRANSLATION NOT AVAILABLE	1 (0.04)	2 (0.08)
	OTHER	56 (2.41)	71 (2.98)
	MISSING	12 (0.52)	10 (0.42)

Abbreviations: N = number of subjects in each treatment arm;
n = number of subjects who are expected to contribute data values at a given visit, which is used as denominator for pecentage calculation.

Planned visit		LY2835219-150mg +EDT (N=2539) n (%)	EDT (N=2539) n (%)
VISIT15	n	2233	2299
	Compliant with Questionaire	2097 (93.91)	2112 (91.87)
	Main reason if not compliant		
	SUBJECT REFUSAL	21 (0.94)	21 (0.91)
	STUDY SITE FAILED TO ADMINISTER	32 (1.43)	46 (2.00)
	TRANSLATION NOT AVAILABLE	2 (0.09)	1 (0.04)
	OTHER	69 (3.09)	108 (4.70)
	MISSING	12 (0.54)	11 (0.48)
VISIT21	n	2159	2197
	Compliant with Questionaire	2001 (92.68)	1990 (90.58)
	Main reason if not compliant		
	SUBJECT REFUSAL	21 (0.97)	27 (1.23)
	STUDY SITE FAILED TO ADMINISTER	31 (1.44)	43 (1.96)
	TRANSLATION NOT AVAILABLE	2 (0.09)	1 (0.05)
	OTHER	92 (4.26)	120 (5.46)
	MISSING	12 (0.56)	16 (0.73)
VISIT27	n	1879	1901
	Compliant with Questionaire	1752 (93.24)	1716 (90.27)
	Main reason if not compliant		
	SUBJECT REFUSAL	26 (1.38)	21 (1.10)
	STUDY SITE FAILED TO ADMINISTER	11 (0.59)	28 (1.47)
	TRANSLATION NOT AVAILABLE	1 (0.05)	1 (0.05)
	OTHER	78 (4.15)	119 (6.26)
	MISSING	11 (0.59)	16 (0.84)

Abbreviations: N = number of subjects in each treatment arm;
n = number of subjects who are expected to contribute data values at a given visit, which is used as denominator for pecentage calculation.

Planned visit		LY2835219-150mg +EDT (N=2539) n (%)	EDT (N=2539) n (%)
FOLLOW UP	n	2026	2049
	Compliant with Questionaire	1718 (84.80)	1673 (81.65)
	Main reason if not compliant		
	SUBJECT REFUSAL	61 (3.01)	71 (3.47)
	STUDY SITE FAILED TO ADMINISTER	50 (2.47)	49 (2.39)
	TRANSLATION NOT AVAILABLE	3 (0.15)	2 (0.10)
	OTHER	159 (7.85)	218 (10.64)
	MISSING	35 (1.73)	36 (1.76)
ADDITIONAL FOLLOW UP 1	n	1144	1165
	Compliant with Questionaire	897 (78.41)	891 (76.48)
	Main reason if not compliant		
	SUBJECT REFUSAL	65 (5.68)	58 (4.98)
	STUDY SITE FAILED TO ADMINISTER	30 (2.62)	34 (2.92)
	TRANSLATION NOT AVAILABLE	1 (0.09)	2 (0.17)
	OTHER	134 (11.71)	160 (13.73)
	MISSING	17 (1.49)	20 (1.72)
ADDITIONAL FOLLOW UP 2	n	509	519
	Compliant with Questionaire	343 (67.39)	351 (67.63)
	Main reason if not compliant		
	SUBJECT REFUSAL	40 (7.86)	39 (7.51)
	STUDY SITE FAILED TO ADMINISTER	22 (4.32)	18 (3.47)
	OTHER	87 (17.09)	93 (17.92)
	MISSING	17 (3.34)	18 (3.47)
	TRANSLATION NOT AVAILABLE	0 (0.00)	0 (0.00)

Abbreviations: N = number of subjects in each treatment arm;
n = number of subjects who are expected to contribute data values at a given visit, which is used as denominator for pecentage calculation.

Appendix G. Probabilistic sensitivity analyses

G.1 Convergence plots

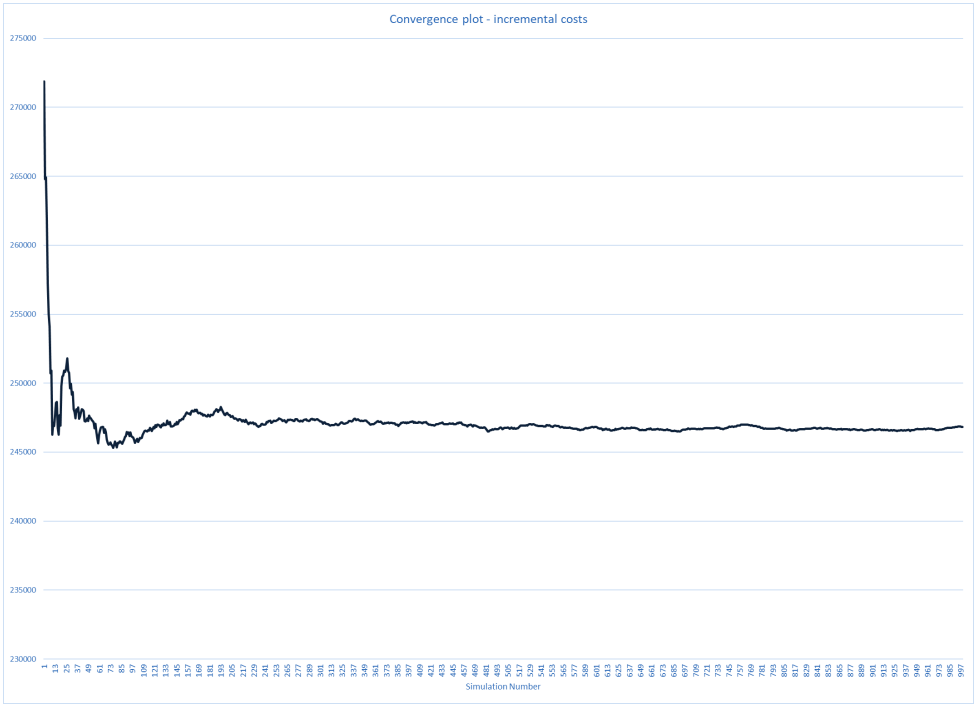


Figure 49 Convergence plot - incremental costs

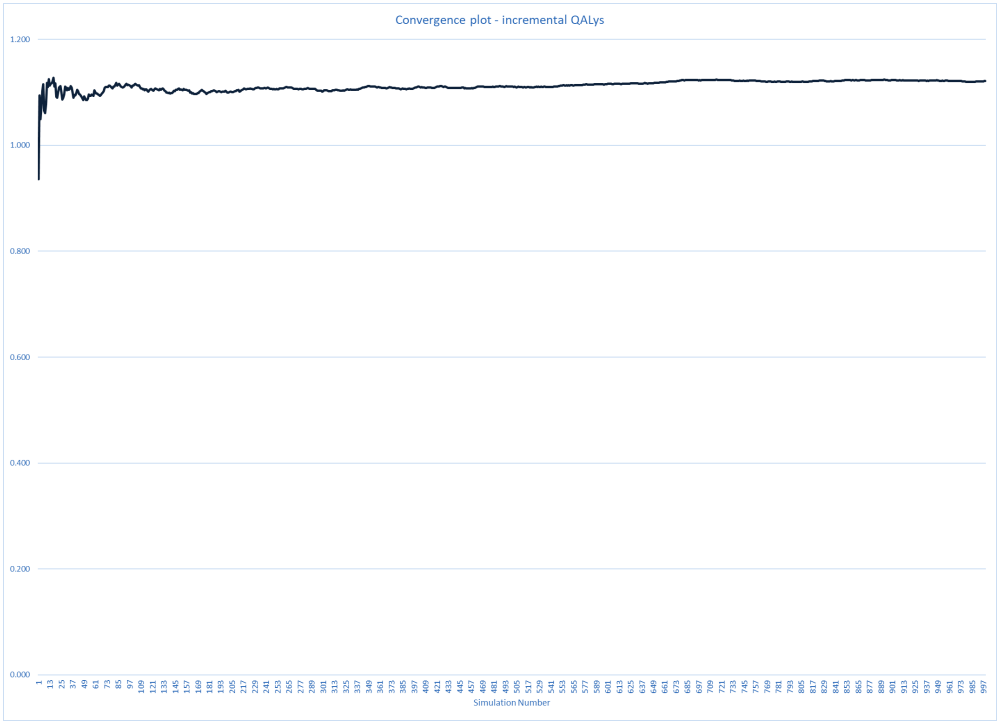


Figure 50 Convergence plot - incremental QALY

Table 81. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution	Where in the model? "Inputs" K column
Female (%)	0.99	0.99	0.99	Beta	K25
Age	52.2	51.89	52.51	Normal	K26
Bodyweight	71.48	71.03	71.93	Normal	K26
Height	161.71	161.51	161.91	Normal	K27
Proportion Letrozole	50%	0.5	0.5	Dirichlet	K42
Proportion Anastrozole	10%	0.1	0.1	Dirichlet	K43
Proportion Tamoxifen	30%	0.3	0.3	Dirichlet	K44
Proportion Exemestane	10%	0.1	0.1	Dirichlet	K45
Prop. moving to NMRABE	29%	0.10	0.48	Beta	K88
Prop. moving to NMRET	26%	0.081	0.466	Beta	K90
Prob.of moving from REM to MR	0.76%	0.005	0.011	Beta	K104
Resource use					
IDFS: Oncologist visit, first	0.306639	0.1984	0.4380	Gamma	K309
IDFS: Mammogram	0.051107	0.0331	0.0730	Gamma	K310
IDFS: Oncologist visit, first	0.15	0.099	0.219	Gamma	K329
IDFS: Mammogram	0.05	0.033	0.073	Gamma	K330

NMR: Oncologist visit, follow-up	0.15332	0.099	0.219	Gamma	K370
NMR: Mammogram	0.051107	0.033	0.073	Gamma	K371
NMR: Local: Major breast procedures (if patients originally had mastectomy)	0.75	0.485	1.071	Gamma	K372
NMR: Local/Regional: Delayed breast reconstruction	0.1	0.065	0.143	Gamma	K373
NMR: Local/Regional: Mastectomy with reconstruction (if patients orginally had breast conserving surgery)	0.3	0.194	0.429	Gamma	K374
NMR: Contralateral: Major breast procedures (if patients originally had mastectomy)	0.95	0.615	1.357	Gamma	K375
NMR: Contralateral: Delayed breast reconstruction	0.1	0.065	0.143	Gamma	K376
NMR: Contralateral: Mastectomy with reconstruction (if patients originally had breast conserving surgery)	0.3	0.194	0.429	Gamma	K377
NMR: Radiotherapy	1	0.647	1.428	Gamma	K378
NMR: Chemotherapy (cycle 1)	0.05	0.032	0.071	Gamma	K379
NMR: Chemotherapy (cycle 2-6)	0.05	0.032	0.071	Gamma	K380
NMR: Chemotherapy (subsequent cycles)	0.05	0.032	0.071	Gamma	K381
NMR: Complete blood count	0.05	0.032	0.071	Gamma	K382
NMR: Multidisciplinairy team meeting	1	0.647	1.428	Gamma	K383
REM: GP visit	0.31	0.198	0.438	Gamma	K390
REM: Oncologist visit, follow-up	0.05	0.033	0.073	Gamma	K391
MR-ETR: CT scan PFS	0.5	0.324	0.714	Gamma	K410
MR-ETR: MRI scan PFS	0.5	0.324	0.714	Gamma	K411
MR-ETR: PET scan PFS	0.5	0.324	0.714	Gamma	K412
MR-ETR: X-Ray PFS	0.5	0.324	0.714	Gamma	K413
MR-ETR: Electrocardiogram PFS	0.5	0.324	0.714	Gamma	K414
MR-ETR: Complete blood count PFS	1	0.647	1.428	Gamma	K415
MR-ETR: Serum Chemistry PFS	1	0.647	1.428	Gamma	K416
MR-ETR: Biochemistry PFS	0.23	0.149	0.329	Gamma	K417

MR-ETR: Clinical nurse (specialist) PFS	0.23	0.149	0.329	Gamma	K418
MR-ETR: Oncologist visit, follow-up PFS	1	0.647	1.428	Gamma	K419
MR-ETR: Hospitalisation PFS	0.01	0.007	0.016	Gamma	K420
MR-ETR: CT scan PPS	0.50	0.324	0.714	Gamma	K430
MR-ETR: MRI scan PPS	0.50	0.324	0.714	Gamma	K431
MR-ETR: PET scan PPS	0.50	0.324	0.714	Gamma	K432
MR-ETR: Electrocardiogram PPS	0.50	0.324	0.714	Gamma	K433
MR-ETR: Complete blood count PPS	1.00	0.647	1.428	Gamma	K434
MR-ETR: Serum Chemistry PPS	1.00	0.647	1.428	Gamma	K435
MR-ETR: Oncologist visit, follow-up PPS	1.00	0.647	1.428	Gamma	K436
MR-ETR: Clinical nurse (specialist) PPS	1.00	0.647	1.428	Gamma	K437
MR-ETR: Hospitalisation PPS	0.01	0.004	0.010	Gamma	K438
MR-ETS: CT scan PFS1	0.42	0.272	0.600	Gamma	K450
MR-ETS: Electrocardio gram PFS1	0.33	0.214	0.471	Gamma	K451
MR-ETS: Complete blood count PFS1	1	0.647	1.428	Gamma	K452
MR-ETS: Serum chemistry PFS1	1	0.647	1.428	Gamma	K453
MR-ETS: Oncologist visit, follow-up PFS1	1	0.647	1.428	Gamma	K454
MR-ETS: X-Ray PFS1	0.42	0.272	0.600	Gamma	K455
MR-ETS: Hospitalisation PFS1	0.01	0.006	0.012	Gamma	K457
MR-ETS: CT scan PFS2	0.42	0.272	0.600	Gamma	K470
MR-ETS: Electrocardio gram PFS2	0.33	0.214	0.471	Gamma	K471
MR-ETS: Complete blood count PFS2	1	0.647	1.428	Gamma	K472
MR-ETS: Serum chemistry PFS2	1	0.647	1.428	Gamma	K473
MR-ETS: Oncologist visit, follow-up PFS2	1	0.647	1.428	Gamma	K474
MR-ETS: X-Ray PFS2	0.42	0.272	0.600	Gamma	K476
MR-ETS: Hospitalisation PFS2	0.01	0.005	0.013	Gamma	K478
MR-ETS: CT scan PPS	0.42	0.272	0.600	Gamma	K490
MR-ETS: Electrocardio gram PPS	0.33	0.214	0.471	Gamma	K491
MR-ETS: Complete blood count PPS	1	0.647	1.428	Gamma	K492

MR-ETS: Serum chemistry PPS	1	0.647	1.428	Gamma	K493
MR-ETS: Oncologist visit, follow-up PPS	1	0.647	1.428	Gamma	K494
MR-ETS: District nurse (home visit) PPS	0.23	0.149	0.329	Gamma	K495
MR-ETS: Hospitalisation PPS	0.03	0.019	0.041	Gamma	K496
Utilities					
Utility: IDFS	0.852	0.847	0.857	Beta	K560
Utility: Abemaciclib + ET IDFS	0.776	0.770	0.782	Beta	K561
Utility: Endocrine therapy IDFS	0.777	0.771	0.783	Beta	K562
Utility: NMR	0.812915	0.405	0.996	Beta	K563
Adverse events					
ABE + ET Grade I/II AE incidence. : Diarrhoea	0.758	0.408	0.973	Beta	K624
ABE + ET Grade I/II AE incidence. : Neutropenia	0.263	0.167	0.372	Beta	K625
ABE + ET Grade I/II AE incidence. : Fatigue	0.379	0.237	0.532	Beta	K626
ABE + ET Grade I/II AE incidence. : Leukopenia	0.263	0.167	0.372	Beta	K627
ABE + ET Grade I/II AE incidence. : ALT increase	0.362	0.227	0.509	Beta	K628
ABE + ET Grade I/II AE incidence. : Abdominal pain	0.343	0.216	0.483	Beta	K629
ABE + ET Grade I/II AE incidence. : AST increase	0.314	0.198	0.443	Beta	K630
ABE + ET Grade I/II AE incidence. : Nausea	0.291	0.184	0.411	Beta	K631
ABE + ET Grade I/II AE incidence. : Anaemia	0.224	0.143	0.318	Beta	K632
ABE + ET Grade I/II AE incidence. : Arthralgia	0.262	0.166	0.371	Beta	K633
ABE + ET Grade I/II AE incidence. : Hot flush	0.153	0.098	0.218	Beta	K634
ABE + ET Grade I/II AE incidence. : ILD/Pneumonitis (composite term)	0.029	0.019	0.041	Beta	K635
ABE + ET Grade I/II AE incidence. : VTE (composite term)	0.011	0.007	0.016	Beta	K636
ET Grade I/II AE incidence. : Diarrhoea	0.085	0.055	0.121	Beta	K644
ET Grade I/II AE incidence. : Neutropenia	0.047	0.030	0.067	Beta	K645
ET Grade I/II AE incidence. : Fatigue	0.179	0.114	0.254	Beta	K646

ET Grade I/II AE incidence. : Leukopenia	0.062	0.040	0.088	Beta	K647
ET Grade I/II AE incidence. : ALT increase	0.232	0.148	0.329	Beta	K648
ET Grade I/II AE incidence. : Abdominal pain	0.096	0.062	0.137	Beta	K649
ET Grade I/II AE incidence. : AST increase	0.174	0.111	0.247	Beta	K650
ET Grade I/II AE incidence. : Nausea	0.089	0.057	0.127	Beta	K651
ET Grade I/II AE incidence. : Anaemia	0.035	0.023	0.050	Beta	K652
ET Grade I/II AE incidence. : Arthralgia	0.369	0.231	0.519	Beta	K653
ET Grade I/II AE incidence. : Hot flush	0.226	0.144	0.320	Beta	K654
ET Grade I/II AE incidence. : ILD/Pneumonitis (composite term)	0.013	0.008	0.019	Beta	K655
Proportion of patients with grade III/IV adverse events					
ABE + ET Grade III/IV AE incidence: Neutropenia	0.196	0.125	0.278	Beta	K667
ABE + ET Grade III/IV AE incidence: Leukopenia	0.114	0.073	0.162	Beta	K668
ABE + ET Grade III/IV AE incidence: Diarrhoea	0.078	0.050	0.111	Beta	K669
ABE + ET Grade III/IV AE incidence: Lymphopenia	0.054	0.035	0.077	Beta	K670
ABE + ET Grade III/IV AE incidence: Fatigue	0.028	0.018	0.040	Beta	K671
ABE + ET Grade III/IV AE incidence: Aspartate aminotransferase increase	0.019	0.012	0.027	Beta	K672
ABE + ET Grade III/IV AE incidence: Alanine aminotransferase increase	0.028	0.018	0.040	Beta	K673
ABE + ET Grade III/IV AE incidence: Thrombocytopenia	0.013	0.008	0.019	Beta	K674
ABE + ET Grade III/IV AE incidence: Anaemia	0.021	0.014	0.030	Beta	K675
ABE + ET Grade III/IV AE incidence: Abdominal pain	0.014	0.009	0.020	Beta	K676
ABE + ET Grade III/IV AE incidence: Venous thromboembolic event	0.014	0.009	0.020	Beta	K677
ET Grade III/IV AE incidence: Neutropenia	0.009	0.006	0.013	Beta	K687

ET Grade III/IV AE incidence: Leukopenia	0.004	0.003	0.006	Beta	K688
ET Grade III/IV AE incidence: Diarrhoea	0.002	0.001	0.003	Beta	K689
ET Grade III/IV AE incidence: Lymphopenia	0.005	0.003	0.007	Beta	K690
ET Grade III/IV AE incidence: Fatigue	0.001	0.001	0.001	Beta	K691
ET Grade III/IV AE incidence: Aspartate aminotransferase increase	0.005	0.003	0.007	Beta	K692
ET Grade III/IV AE incidence: Alanine aminotransferase increase	0.007	0.005	0.010	Beta	K693
ET Grade III/IV AE incidence: Thrombocytopenia	0.001	0.001	0.001	Beta	K694
ET Grade III/IV AE incidence: Anaemia	0.004	0.003	0.006	Beta	K695
ET Grade III/IV AE incidence: Abdominal pain	0.003	0.002	0.004	Beta	K696
ET Grade III/IV AE incidence: Venous thromboembolic event	0.003	0.002	0.004	Beta	K697
Dose intensity					
Intensity: Abemaciclib + ET: Abemaciclib	100%	1	1	Beta	K853
Intensity: Abemaciclib + ET: Letrozole	100%	1	1	Beta	K854
Intensity: Abemaciclib + ET: Anastrozole	100%	1	1	Beta	K855
Intensity: Abemaciclib + ET: Tamoxifen	100%	1	1	Beta	K856
Intensity: Abemaciclib + ET: Exemestane	100%	1	1	Beta	K857
Intensity: Endocrine therapy: Letrozole	100%	1	1	Beta	K858
Intensity: Endocrine therapy: Anastrozole	100%	1	1	Beta	K859
Intensity: Endocrine therapy: Tamoxifen	100%	1	1	Beta	K860
Intensity: Endocrine therapy: Exemestane	100%	1	1	Beta	K861
Concomitant therapy, IDFS					
Concomitant tx: Abemaciclib + ET to Loperamide	0.666	0.384	0.894	Beta	K936

Concomitant tx: Abemaciclib + ET to Ibuprofen	0.091	0.059	0.130	Beta	K937
Concomitant tx: Abemaciclib + ET to Amoxicillin; Glavulanic acid	0.078	0.050	0.111	Beta	K938
Concomitant tx: Abemaciclib + ET to Amoxicillin	0.056	0.036	0.080	Beta	K939
Concomitant tx: Abemaciclib + ET to Colecalciferol	0.073	0.047	0.104	Beta	K940
Concomitant tx: Abemaciclib + ET to Calcium carbonate; colecalciferol	0.062	0.040	0.088	Beta	K941
Concomitant tx: Abemaciclib + ET to Vitamin D Nos	0.056	0.036	0.080	Beta	K942
Concomitant tx: Abemaciclib + ET to Zolederonic acid	0.099	0.064	0.141	Beta	K943
Concomitant tx: Abemaciclib + ET to Paracetamol	0.246	0.156	0.348	Beta	K944
Concomitant tx: Abemaciclib + ET to Levothyroxine	0.093	0.060	0.132	Beta	K945
Concomitant tx: Abemaciclib + ET to Metformin	0.058	0.037	0.083	Beta	K946
Concomitant tx: Endocrine therapy to Loperamide	0.019	0.012	0.027	Beta	K948
Concomitant tx: Endocrine therapy to Ibuprofen	0.097	0.062	0.138	Beta	K949
Concomitant tx: Endocrine therapy to Amoxicillin; Glavulanic acid	0.054	0.035	0.077	Beta	K950
Concomitant tx: Endocrine therapy to Amoxicillin	0.048	0.031	0.068	Beta	K951
Concomitant tx: Endocrine therapy to Colecalciferol	0.084	0.054	0.120	Beta	K952
Concomitant tx: Endocrine therapy to Calcium carbonate; colecalciferol	0.073	0.047	0.104	Beta	K953
Concomitant tx: Endocrine therapy to Vitamin D Nos	0.054	0.035	0.077	Beta	K954
Concomitant tx: Endocrine therapy to Zolederonic acid	0.109	0.070	0.155	Beta	K955
Concomitant tx: Endocrine therapy to Paracetamol	0.21	0.134	0.298	Beta	K956
Concomitant tx: Endocrine therapy to Levothyroxine	0.086	0.055	0.123	Beta	K957

Concomitant tx: Endocrine therapy to Metformin	0.055	0.035	0.078	Beta	K958
Patient costs					
Patient costs hours: IDFS	0.25	0.16	0.36	Gamma	K1031
Patient costs hours: NMR	0.25	0.16	0.36	Gamma	K1032
Patient costs hours: REM	0.25	0.16	0.36	Gamma	K1033
Travel: No. of visits IDFS	0.15	0.10	0.21	Gamma	K1037
Travel: No. of visits NMR	0.15	0.10	0.21	Gamma	K1038
Travel: No. of visits REM	0.15	0.10	0.21	Gamma	K1039
Proportion long-term absence	0.1	0.065	0.143	Gamma	K1048
Duration of AEs					
Duration monarchE: Neutropenia	15.09	9.8	21.6	Gamma	K1071
Duration monarchE: Leukopenia	13.96	9.0	19.9	Gamma	K1072
Duration monarchE: Diarrhea	8	5.2	11.4	Gamma	K1073
Duration monarchE: Lymphopenia	34	22.0	48.6	Gamma	K1074
Duration monarchE: Fatigue	12.7	8.2	18.1	Gamma	K1075
Duration monarchE: Alanine aminotransferase increase	28	18.1	40.0	Gamma	K1077
Duration monarchE: Thrombocytopenia	23.21	15.0	33.2	Gamma	K1078
Duration monarchE: Anaemia	16.07	10.4	23.0	Gamma	K1079
Duration monarchE: Abdominal pain	8.82	5.7	12.6	Gamma	K1080
AE costs – costs applied to the proportion of patients with grade III/IV AEs					
grade III/IV AE cost ETR ABE+ET arm: Anaemia	62.16	40.2	88.8	Gamma	K1137
grade III/IV AE cost ETR ABE+ET arm: Diarrhea	103.15	66.8	147.3	Gamma	K1138
grade III/IV AE cost ETR ABE+ET arm: Dyspnoea	25.90	16.8	37.0	Gamma	K1139
grade III/IV AE cost ETR ABE+ET arm: Gamma-glutamyltransferase (GGT) increase	62.93	40.7	89.9	Gamma	K1140
grade III/IV AE cost ETR ABE+ET arm: Hyperglycemia	89.71	58.1	128.1	Gamma	K1141
grade III/IV AE cost ETR ABE+ET arm: Leukopenia	0.00	0.0	0.0	Gamma	K1142
grade III/IV AE cost ETR ABE+ET arm: Neutropenia	20.41	13.2	29.2	Gamma	K1143
grade III/IV AE cost ETR ABE+ET arm: Stomatitis	62.86	40.7	89.8	Gamma	K1144

grade III/IV AE cost ETS ABE+ET arm: Alanine aminotransferase increase	14.82	9.59	21.16	Gamma	K1147
grade III/IV AE cost ETS ABE+ET arm: Anaemia	16.00	10.35	22.85	Gamma	K1148
grade III/IV AE cost ETS ABE+ET arm: Aspartate aminotransferase increase	21.74	14.07	31.06	Gamma	K1149
grade III/IV AE cost ETS ABE+ET arm: Diarrhea	59.25	38.34	84.64	Gamma	K1150
grade III/IV AE cost ETS ABE+ET arm: Hypertension	19.22	12.44	27.46	Gamma	K1151
grade III/IV AE cost ETS ABE+ET arm: Leukopenia	0.00	0.00	0.00	Gamma	K1152
grade III/IV AE cost ETS ABE+ET arm: Lymphopenia	0.00	0.00	0.00	Gamma	K1153
grade III/IV AE cost ETS ABE+ET arm: Nausea	133.32	86.28	190.43	Gamma	K1154
grade III/IV AE cost ETS ABE+ET arm: Neutropenia	0.00	0.00	0.00	Gamma	K1155
grade III/IV AE cost ETR ET arm: Anaemia	73.45	47.5	104.9	Gamma	K1159
grade III/IV AE cost ETR ET arm: Diarrhea	222.51	144.0	317.8	Gamma	K1160
grade III/IV AE cost ETR ET arm: Dyspnoea	26.31	17.0	37.6	Gamma	K1161
grade III/IV AE cost ETR ET arm: Gamma-glutamyltransferase (GGT) increase	57.46	37.2	82.1	Gamma	K1162
grade III/IV AE cost ETR ET arm: Hyperglycemia	79.67	51.6	113.8	Gamma	K1163
grade III/IV AE cost ETR ET arm: Leukopenia	32.25	20.9	46.1	Gamma	K1164
grade III/IV AE cost ETR ET arm: Neutropenia	115.82	75.0	165.4	Gamma	K1165
grade III/IV AE cost ETR ET arm: Stomatitis	54.31	35.1	77.6	Gamma	K1166
grade III/IV AE cost ETS ET arm: Alanine aminotransferase increase	73.96	47.9	105.6	Gamma	K1169
grade III/IV AE cost ETS ET arm: Anaemia	73.54	47.6	105.0	Gamma	K1170
grade III/IV AE cost ETS ET arm: Aspartate aminotransferase increase	47.49	30.7	67.8	Gamma	K1171

grade III/IV AE cost ETS ET arm: Diarrhea	412.12	266.7	588.7	Gamma	K1172
grade III/IV AE cost ETS ET arm: Hypertension	147.77	95.6	211.1	Gamma	K1173
grade III/IV AE cost ETS ET arm: Leukopenia	134.35	86.9	191.9	Gamma	K1174
grade III/IV AE cost ETS ET arm: Lymphopenia	40.61	26.3	58.0	Gamma	K1175
grade III/IV AE cost ETS ET arm: Nausea	100.28	64.9	143.2	Gamma	K1176
grade III/IV AE cost ETS ET arm: Neutropenia	364.60	235.9	520.8	Gamma	K1177
grade III/IV AE cost ETS ET arm: Alanine aminotransferase increase	73.96	47.9	105.6	Gamma	K1169
grade III/IV AE cost ETS ET arm: Anaemia	73.54	47.6	105.0	Gamma	K1170
HSUV					
ETR Pathway CDK4&6i + FUL PFS Utility values	0.75	0.41	0.97	Beta	K1240
ETR Pathway EXE-EVE PFS Utility values	0.75	0.41	0.97	Beta	K1241
ETR Pathway FUL PFS Utility values	0.75	0.41	0.97	Beta	K1242
ETR Pathway CAP PFS Utility values	0.75	0.41	0.97	Beta	K1243
ETR Pathway EXE PFS Utility values	0.75	0.41	0.97	Beta	K1244
ETS Pathway CDK4&6i + NSAI PFS1 Utility values	0.72	0.40	0.95	Beta	K1248
ETS Pathway NSAI PFS1 Utility values	0.72	0.40	0.95	Beta	K1249
ETS Pathway RIBO-FUL PFS1 Utility values	0.72	0.40	0.95	Beta	K1250
ETS Pathway TMX PFS1 Utility values	0.72	0.40	0.95	Beta	K1251
ETS Pathway FUL PFS1 Utility values	0.72	0.40	0.95	Beta	K1252
ETS Pathway CDK4&6i + NSAI PFS2 Utility values	0.69	0.39	0.92	Beta	K1256
ETS Pathway NSAI PFS2 Utility values	0.69	0.39	0.92	Beta	K1257
ETS Pathway RIBO-FUL PFS2 Utility values	0.69	0.39	0.92	Beta	K1258
ETS Pathway TMX PFS2 Utility values	0.69	0.39	0.92	Beta	K1259

ETS Pathway FUL PFS2 Utility values	0.69	0.39	0.92	Beta	K1260
ETR Pathway CDK4&6i + FUL PPS Utility values	0.70	0.40	0.93	Beta	K1266
ETR Pathway EXE-EVE PPS Utility values	0.70	0.40	0.93	Beta	K1267
ETR Pathway FUL PPS Utility values	0.70	0.40	0.93	Beta	K1268
ETR Pathway CAP PPS Utility values	0.70	0.40	0.93	Beta	K1269
ETR Pathway EXE PPS Utility values	0.70	0.40	0.93	Beta	K1270
ETS Pathway CDK4&6i + NSAI PPS Utility values	0.51	0.31	0.70	Beta	K1274
ETS Pathway NSAI PPS Utility values	0.51	0.31	0.70	Beta	K1275
ETS Pathway RIBO-FUL PPS Utility values	0.51	0.31	0.70	Beta	K1276
ETS Pathway TMX PPS Utility values	0.51	0.31	0.70	Beta	K1277
ETS Pathway FUL PPS Utility values	0.51	0.31	0.70	Beta	K1278
Survival in MR					
ETR Pathway CDK4&6i + FUL LYs in PFS	2.39	0.8527	0.1980	Lognormal	K1284
ETR Pathway EXE-EVE LYs in PFS	1.81	0.5750	0.1980	Lognormal	K1285
ETR Pathway FUL LYs in PFS	0.94	-0.0816	0.1980	Lognormal	K1286
ETR Pathway CAP LYs in PFS	1.97	0.6579	0.1980	Lognormal	K1287
ETR Pathway EXE LYs in PFS	0.73	-0.3377	0.1980	Lognormal	K1288
ETS Pathway CDK4&6i + NSAI LYs in PFS1	2.97	1.0704	0.1980	Lognormal	K1292
ETS Pathway NSAI LYs in PFS1	1.68	0.5015	0.1980	Lognormal	K1293
ETS Pathway RIBO-FUL LYs in PFS1	4.07	1.3843	0.1980	Lognormal	K1294
ETS Pathway TMX LYs in PFS1	1.46	0.3603	0.1980	Lognormal	K1295
ETS Pathway FUL LYs in PFS1	2.25	0.7930	0.1980	Lognormal	K1296
ETS Pathway CDK4&6i + NSAI LYs in PFS2	0.69	-0.3935	0.1980	Lognormal	K1300
ETS Pathway NSAI LYs in PFS2	1.37	0.2931	0.1980	Lognormal	K1301

ETS Pathway RIBO-FUL LYs in PFS2	0.27	-1.3464	0.1980	Lognormal	K1302
ETS Pathway TMX LYs in PFS2	1.34	0.2747	0.1980	Lognormal	K1303
ETS Pathway FUL LYs in PFS2	1.13	0.1063	0.1980	Lognormal	K1304
ETR Pathway CDK4&6i + FUL LYs in PPS	1.98	0.6665	0.1980	Lognormal	K1310
ETR Pathway EXE-EVE LYs in PPS	1.66	0.4857	0.1980	Lognormal	K1311
ETR Pathway FUL LYs in PPS	2.55	0.9181	0.1980	Lognormal	K1312
ETR Pathway CAP LYs in PPS	2.47	0.8865	0.1980	Lognormal	K1313
ETR Pathway EXE LYs in PPS	2.48	0.8870	0.1980	Lognormal	K1314
ETS Pathway CDK4&6i + NSAI LYs in PPS	1.7	0.5090	0.1980	Lognormal	K1318
ETS Pathway NSAI LYs in PPS	1.95	0.6491	0.1980	Lognormal	K1319
ETS Pathway RIBO-FUL LYs in PPS	1.32	0.2605	0.1980	Lognormal	K1320
ETS Pathway TMX LYs in PPS	1.92	0.6307	0.1980	Lognormal	K1321
ETS Pathway FUL LYs in PPS	1.93	0.6369	0.1980	Lognormal	K1322
ETR pathway - CDK4&6i + FUL					
% receiving ETR pathway - CDK4&6i + FUL - ABE-FUL	85%	0.85	0.85	Dirichlet	K1328
% receiving ETR pathway - CDK4&6i + FUL - RIBO-FUL	10%	0.1	0.1	Dirichlet	K1329
% receiving ETR pathway - CDK4&6i + FUL - PAL-FUL	5%	0.05	0.05	Dirichlet	K1330
ETS pathway - CDK4&6i + FUL					
% receiving ETS pathway - CDK4&6i + NSAI - ABE-NSAI	85%	0.85	0.85	Dirichlet	K1333
% receiving ETS pathway - CDK4&6i + NSAI - PAL-NSAI	5%	0.05	0.05	Dirichlet	K1334
% receiving ETS pathway - CDK4&6i + NSAI - RIBO-NSAI	10%	0.1	0.1	Dirichlet	K1335
Survival in MR ET and ES					
ETR Pathway ABE-FUL LYs in PFS	2.47	1.60	3.53	Gamma	K1338
ETR Pathway RIBO-FUL LYs in PFS	2.12	1.37	3.03	Gamma	K1339
ETR Pathway PAL-FUL LYs in PFS	1.58	1.02	2.25	Gamma	K1340
ETR Pathway ABE-FUL LYs in PPS	1.92	1.24	2.74	Gamma	K1343
ETR Pathway RIBO-FUL LYs in PPS	2.23	1.44	3.19	Gamma	K1344

ETR Pathway PAL-FUL LYs in PPS	2.62	1.69	3.74	Gamma	K1345
ETS Pathway ABE-NSAI LYs in PFS1	2.98	1.93	4.26	Gamma	K1348
ETS Pathway PAL-NSAI LYs in PFS1	2.97	1.92	4.25	Gamma	K1349
ETS Pathway RIBO-NSAI LYs in PFS1	2.91	1.88	4.16	Gamma	K1350
ETS Pathway ABE-NSAI LYs in PFS2	0.69	0.45	0.98	Gamma	K1353
ETS Pathway PAL-NSAI LYs in PFS2	0.68	0.44	0.97	Gamma	K1354
ETS Pathway RIBO-NSAI LYs in PFS2	0.69	0.45	0.99	Gamma	K1355
ETS Pathway ABE-NSAI LYs in PPS	1.69	1.09	2.42	Gamma	K1358
ETS Pathway PAL-NSAI LYs in PPS	1.71	1.10	2.44	Gamma	K1359
ETS Pathway RIBO-NSAI LYs in PPS	1.74	1.12	2.48	Gamma	K1360
ABE + ET, % receiving					
% receiving ETR Pathway CDK4&6i + FUL	0%	0	0	Dirichlet	K1363
% receiving ETR Pathway EXE-EVE	31%	0.3112	0.3112	Dirichlet	K1364
% receiving ETR Pathway FUL	32%	0.3167	0.3167	Dirichlet	K1365
% receiving ETR Pathway CAP	7%	0.0678	0.0678	Dirichlet	K1366
% receiving ETR Pathway EXE	30%	0.3043	0.3043	Dirichlet	K1367
% receiving ETS Pathway CDK4&6i + NSAI	0%	0.0000	0.0000	Dirichlet	K1371
% receiving ETS Pathway NSAI	76%	0.7579	0.7579	Dirichlet	K1372
% receiving ETS Pathway RIBO-FUL	0%	0.0000	0.0000	Dirichlet	K1373
% receiving ETS Pathway TMX	19%	0.1895	0.1895	Dirichlet	K1374
% receiving ETS Pathway FUL	5%	0.0526	0.0526	Dirichlet	K1375
ET alone, % receiving					
% receiving ETR Pathway CDK4&6i + FUL	15%	0.15	0.15	Dirichlet	K1381
% receiving ETR Pathway EXE-EVE	26%	0.26	0.26	Dirichlet	K1382
% receiving ETR Pathway FUL	27%	0.27	0.27	Dirichlet	K1383
% receiving ETR Pathway CAP	6%	0.06	0.06	Dirichlet	K1384
% receiving ETR Pathway EXE	26%	0.26	0.26	Dirichlet	K1385

% receiving ETS Pathway CDK4&6i + NSAI	61%	0.612	0.612	Dirichlet	K1389
% receiving ETS Pathway NSAI	29%	0.294	0.294	Dirichlet	K1390
% receiving ETS Pathway RIBO-FUL	0%	0.000	0.000	Dirichlet	K1391
% receiving ETS Pathway TMX	7%	0.073	0.073	Dirichlet	K1392
% receiving ETS Pathway FUL	2%	0.020	0.020	Dirichlet	K1393
Duration on treatment in months, ETR – PFS PFS treatment					
CDK4&6i + FUL ETR Pathway - PFS treatment duration	17.58	11.38	25.11	Gamma	K1399
EXE-EVE ETR Pathway - PFS treatment duration	13.65	8.83	19.50	Gamma	K1400
FUL ETR Pathway - PFS treatment duration	8.96	5.80	12.79	Gamma	K1401
CAP ETR Pathway - PFS treatment duration	12.72	8.23	18.16	Gamma	K1402
EXE ETR Pathway - PFS treatment duration	8.73	5.65	12.47	Gamma	K1403
Duration on treatment in months, ETS – PFS PFS1 treatment					
CDK4&6i + NSAI ETS Pathway - PFS1 treatment duration	32.03	20.73	45.75	Gamma	K1409
NSAI ETS Pathway - PFS1 treatment duration	20.7	13.39	29.57	Gamma	K1410
RIBO-FUL ETS Pathway - PFS1 treatment duration	32.11	20.78	45.87	Gamma	K1411
TMX ETS Pathway - PFS1 treatment duration	12.87	8.33	18.38	Gamma	K1412
FUL ETS Pathway - PFS1 treatment duration	23.54	15.23	33.62	Gamma	K1413
Duration on treatment in months, ETR – PPS PFS2 treatment					
CDK4&6i + NSAI ETS Pathway - PFS2 treatment duration (PPS)	8.81	5.70	12.58	Gamma	K1439
NSAI ETS Pathway - PFS2 treatment duration (PPS)	7.36	4.76	10.51	Gamma	K1440
RIBO-FUL ETS Pathway - PFS2 treatment duration (PPS)	11.34	7.34	16.20	Gamma	K1441
TMX ETS Pathway - PFS2 treatment duration (PPS)	10.99	7.11	15.69	Gamma	K1442
FUL ETS Pathway - PFS2 treatment duration (PPS)	10.99	7.11	15.70	Gamma	K1443
Duration on treatment in months, ETS – PFS2 treatment					
CDK4&6i + NSAI ETS Pathway - PFS2 treatment duration	7.56	4.89	10.80	Gamma	K1449

NSAI ETS Pathway - PFS2 treatment duration	7.56	4.89	10.80	Gamma	K1450
RIBO-FUL ETS Pathway - PFS2 treatment duration	6.53	4.23	9.33	Gamma	K1451
TMX ETS Pathway - PFS2 treatment duration	7.56	4.89	10.80	Gamma	K1452
FUL ETS Pathway - PFS2 treatment duration	6.53	4.23	9.33	Gamma	K1453
Duration on treatment in months, ETS – PPS treatment					
CDK4&6i + NSAI ETS Pathway - PPS treatment duration	8.68	5.62	12.40	Gamma	K1459
NSAI ETS Pathway - PPS treatment duration	8.68	5.62	12.40	Gamma	K1460
RIBO-FUL ETS Pathway - PPS treatment duration	8.72	5.64	12.45	Gamma	K1461
TMX ETS Pathway - PPS treatment duration	8.68	5.62	12.40	Gamma	K1462
FUL ETS Pathway - PPS treatment duration	8.72	5.64	12.45	Gamma	K1463
Transition probabilities					
Prop. moving to NMRABE + ET	27%	0.099	0.484	Beta	K88
Prop. moving to MRABE + ET	73%	0.516	0.901	Beta	K89
Prop. moving to NMRET	25%	0.081	0.466	Beta	K90
Prop. moving to MRET	75%	0.534	0.919	Beta	K91
Time from iDFS to ET sensitive pathway in months	72.00	71.804	72.196	Normal	K92
Number of months patients stay in NMR	13	13.045	13.045	Normal	K93
Proportion having (Loco)regional NMR ABE + ET	55%	0.350	0.739	Beta	K88
Proportion having Contralateral NMR ABE + ET	12%	0.005	0.375	Beta	K89
Proportion having Second Primary NMR ABE + ET	33%	0.155	0.542	Beta	K90
Proportion having (Loco)regional NMR ET	56%	0.357	0.745	Beta	K91
Proportion having Contralateral NMR ET	11%	0.003	0.371	Beta	K92
Proportion having Second Primary NMR ET	33%	0.155	0.542	Beta	K93

Reweighted Proportion having (Loco)regional NMR ABE + ET	82%	0.402	0.998	Beta	K94
Reweighted Proportion having Contralateral NMR ABE + ET	18%	0.113	0.252	Beta	K95
Reweighted Proportion having (Loco)regional NMR ET	83%	0.397	0.999	Beta	K96
Reweighted Proportion having Contralateral NMR ET	17%	0.107	0.237	Beta	K97
Prob.of moving from REM to MR	0.76%	0.005	0.011	Beta	K98
Number of months for transiting from NMR to MR	13	13.045	13.045	Normal	K108

Appendix H. Appendix I. Literature searches for the clinical assessment

Clinical SLR is not used in the submission. Therefore, considered not applicable.

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

A targeted literature review (TLR) 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.

Table 82 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
NA	NA	NA	NA

Abbreviations: NA= not available

Table 83 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NICE	www.nice.org.uk	Breast cancer' was the search term used. The search was conducted on 31st August 2020, limited to 'Guidance' and the date was limited to 2015 onwards.	22 June 2021

Abbreviations: NICE= National Insititute for Health and Care Excellence

Table 84 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	NA	NA	NA	NA

Abbreviations: NA= not available

I.1.1 Search strategies

The eligibility criteria for the economic TLR are summarised in Table 85.

Table 85: Eligibility criteria for the economic TLR

PICOS	Inclusion criteria	Exclusion criteria
Population (P)	• Early-stage breast cancer (Stage I-IIIC)	• Advanced or metastatic

		breast cancer (Stage IV)
Interventions (I)	• NA	• NA
Comparators (C)	• NA	• NA
Outcomes (O)	• (Incremental) costs • (Incremental) (quality adjusted) life years • Incremental costeffectiveness ratio	• Outcomes other than specified under inclusion criteria
Study design (S)	• Cost-effectiveness analysis • Cost-utility analysis	• Study designs other than those specified under inclusion criteria
Language	• All languages	• No restrictions regarding language
Time limit	• 2015 onwards	• NA

Abbreviations: NA= not available

An iterative search process was adopted for the TLR. The first step was to identify data from only UK health technology assessment (HTA) websites. The NICE website was searched to retrieve critical appraisals and key learnings from previous assessments. 'Breast cancer' was the search term used. The search was conducted on 31st August 2020, limited to 'Guidance' and the date was limited to 2015 onwards.

Study selection

Study selection

Searches of HTA databases and HTA websites were performed by a single reviewer. The HTA reports which did not meet the economic SLR inclusion criteria (Table 86) were assessed for inclusion for the targeted review.

Data extraction

After the list of included HTAs was finalised, the relevant data were extracted. One reviewer extracted the data, and a second reviewer independently reviewed all data extracted from the HTAs. The second reviewer checked the file for accuracy and completeness, by checking if all data presented in the Excel file corresponded directly with what was presented in the selected articles.

Search results

Following hand searching of the NICE website, 22 reports were identified, of which four HTAs met the inclusion criteria specified in Table 29. A list of HTAs identified by the TLR for extraction is provided in Table 86.

Three of the NICE HTAs identified by the TLR specifically modelled a HER2+ patient population. The most recent submission was for trastuzumab emtansine (TA632, 2020)(80), which superseded the neratinib (TA612, 2019)(82) and adjuvant pertuzumab in combination with trastuzumab and chemotherapy (TA569, 2019)(107) submissions. One submission was identified which targeted patients who were eligible for early operable breast cancer with INTRABEAM radiotherapy (TA501, 2018)(108).

Table 86: NICE HTA submissions identified by the economic TLR

TA , year	Country	Study design	Technology manufacturer	Patient population	Intervention	Comparator
TA632, 2020(80)	UK	HTA submission (STA)	Roche Products	HER2-positive EBC	Trastuzumab emtansine	Standard adjuvant therapy including trastuzumab
TA612, 2019(82)	UK	HTA submission (STA)	Puma Biotechnology, Inc.	Early HR+, HER2+ BC	Neratinib	Standard treatment with no further HER2-directed therapy
TA569, 2019(107)	UK	HTA submission (STA)	Roche Products	HER2+ EBC	Adjuvant pertuzumab in combination with trastuzumab & chemotherapy	Standard adjuvant therapy without pertuzumab
TA501, 2018(108)	UK	HTA submission (MTA)	Carl Zeiss UK	Early operable BC	INTRABEAM radiotherapy	External beam

Abbreviations: BC= Breast cancer; eBC= early breast cancer; HTA= Health technology assessment; MTA= Multiple technology appraisal; STA= Single technology appraisal

Included studies: HRQoL Data

An overview of the health state utility values used across the four identified HTA submission is provided in Table 87

Table 87: Summary of health state utility values and AE disutility valyes used in the identified HTA submissions

Author, year	Health state specific utility	Adverse event specific disutility
TA632, 2020(80)	Non-metastatic recurrence: 0.775 Remission: 0.788 1L MBC: 0.765 2L MBC: 0.508	NA
TA612, 2019(82)	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(107)	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(108)	Recurrence free in 1st year: 0.7728 Recurrence free after first year: 0.8112 Local recurrence: 0.8112	NA

	Disease-free after local recurrence: 0.8112 Any other recurrence: 0.685	

Abbreviations: AE= adverse event; EQ-5D= euroQol-5 dimensions; IDFS= invasive disease-free survival; MBC= metastatic breast cancer; NA= not applicable; 1L= first-line; 2L= second-line.

Table 88 Search strategy for [Not applicable]

No.	Query	Results
#1	NA	NA

Abbreviations: NA= not applicable

I.1.2 Quality assessment and generalizability of estimates

All hits identified has been assessed as high quality given that they are NICE assessment reports.

I.1.3 Unpublished data

Not applicable

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

The methodology of an economic TLR to identify relevant cost and resource use data is described in Appendix I.

J.1.1 Ex. Systematic search for […]

Please see Appendix I.

J.1.2 Ex. Targeted literature search for [estimates]

Please see Appendix I.

Appendix K. Safety data detailed

Tables below provides a detailed description of the included and modelled (Grade 3 or above) AEs.

Table 89 Full list of Grade 3 AEs, safety population

Table JPCF.5.13. Treatment-Emergent Adverse Events by Preferred Term in ≥10% of Patients Receiving Abemaciclib Plus Endocrine Therapy with a ≥2% Difference to Endocrine Therapy Alone Arm
Safety Population
OS Interim Analysis 3

	Arm A Abemaciclib + ET N = 2791		Arm B ET N = 2800	
Preferred Term	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Diarrhea	2333 (83.6)	219 (7.8)	245 (8.8)	6 (0.2)
Neutropenia	1282 (45.9)	548 (19.6)	157 (5.6)	24 (0.9)
Fatigue	1140 (40.8)	79 (2.8)	506 (18.1)	4 (0.1)
Leukopenia	1054 (37.8)	319 (11.4)	185 (6.6)	11 (0.4)
Abdominal Pain	996 (35.7)	39 (1.4)	278 (9.9)	9 (0.3)
Nausea	826 (29.6)	14 (0.5)	254 (9.1)	2 (0.1)
Arthralgia	740 (26.5)	9 (0.3)	1063 (38.0)	29 (1.0)
Anemia	686 (24.6)	59 (2.1)	108 (3.9)	12 (0.4)
Headache	553 (19.8)	8 (0.3)	425 (15.2)	5 (0.2)
Vomiting	491 (17.6)	15 (0.5)	131 (4.7)	4 (0.1)
Hot flush	432 (15.5)	4 (0.1)	646 (23.1)	10 (0.4)
Cough	392 (14.0)	1 (0.0)	224 (8.0)	0
Lymphopenia	398 (14.3)	151 (5.4)	96 (3.4)	14 (0.5)
Thrombocytopenia	373 (13.4)	36 (1.3)	53 (1.9)	4 (0.1)
Alanine aminotransferase increased	351 (12.6)	77 (2.8)	157 (5.6)	20 (0.7)
Lymphoedema	352 (12.6)	5 (0.2)	256 (9.1)	1 (0.0)
Urinary tract infection	338 (12.1)	16 (0.6)	210 (7.5)	6 (0.2)
Aspartate aminotransferase increased	337 (12.1)	53 (1.9)	139 (5.0)	15 (0.5)
Constipation	337 (12.1)	2 (0.1)	171 (6.1)	1 (0.0)
Decreased appetite	331 (11.9)	16 (0.6)	70 (2.5)	2 (0.1)
Alopecia	318 (11.4)	0	79 (2.8)	0
Rash	316 (11.3)	11 (0.4)	129 (4.6)	0
Blood creatinine increased	311 (11.1)	3 (0.1)	28 (1.0)	0

Table 90 Full list of Grade 3 AEs, safety population - continued

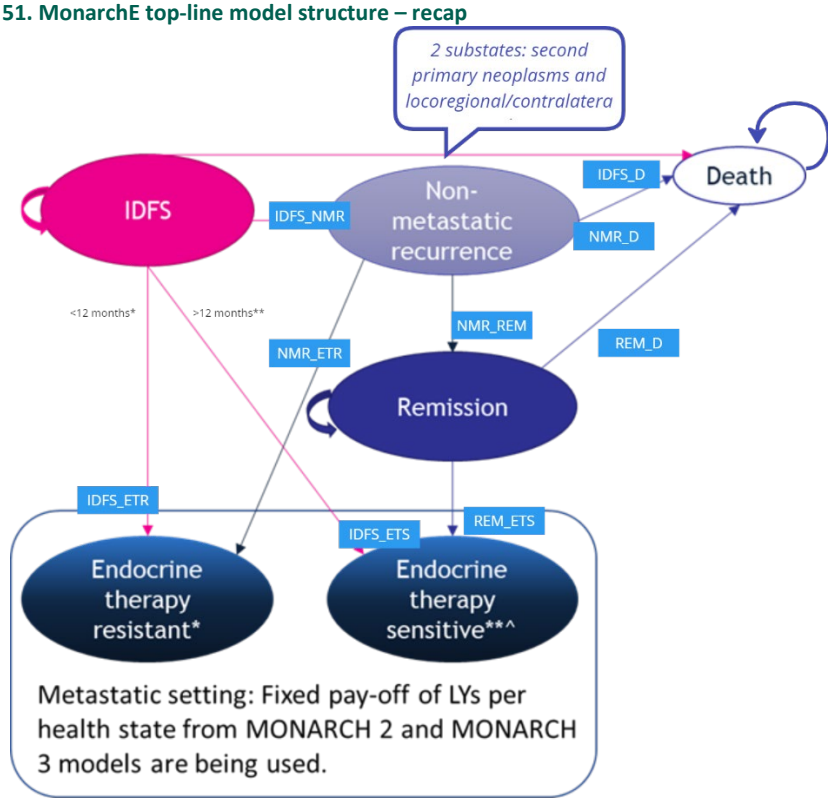
	Arm A Abemaciclib + ET N = 2791		Arm B ET N = 2800	
Preferred Term	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Dizziness	305 (10.9)	4 (0.1)	192 (6.9)	1 (0.0)
Upper respiratory tract infection	302 (10.8)	6 (0.2)	238 (8.5)	0
Back pain	286 (10.2)	9 (0.3)	351 (12.5)	9 (0.3)
Pyrexia	281 (10.1)	2 (0.1)	131 (4.7)	0

Abbreviations: 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 specified category; OS = overall survival.
MedDRA Version 25.0; CTCAE Version 4.
Data cutoff: 03 July 2023.

Appendix L. Detailed model structure description

Based on technical correspondence, it is acknowledged that the model structure and the transitions in the model need further description.

Figure 51. MonarchE top-line model structure – recap



Abbreviations: ET= Endocrine therapy; IDFS= Invasive disease-free survival; ETS= endocrine therapy sensitive; ETR = endocrine therapy resistant; NMR= non metastatic recurrence; MR= metastatic recurrence; D= death; LYs= Life years
*ET-resistant= Disease recurrence while receiving or within 12 months of completing prior adjuvant ET or within 12 months of entering the NMR health state.
**ET-sensitive= Disease recurrence at least 12 months after completion of prior adjuvant ET.
^Includes treatment with tamoxifen (51, 52).
Note: Metastatic recurrence is defined as either endocrine-resistant or endocrine-sensitive, based on the time of recurrence during treatment with endocrine therapy (before or after 12 months following completion of endocrine therapy).

L.1 IDFS

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. 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 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.

Note: 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.

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. 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 Pnmr denotes the constant proportion of NMR, then the transition probability to the NMR health state from the IDFS state is Pnmr x (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. Table 91 summarizes the transitions from the IDFS health state to the NMR and MR health states.

Table 91. Transition from IDFS

Starting state (from)	*To*	*Transition probabilities*
IDFS	*IDFS: S(t)*	*Remaining in IDFS: S(t)*
	NMR: Pnmr	*IDFS_NMR: p × (1 – IDFS(t) – Prb_{death} (t))*
	MR: Pmr	*IDFS_MR: (1 – p) × (1 – IDFS(t) – Prb_{death} (t))*

Abbreviations: IDFS= invasive disease free survival NMR= non metastatic recurrence; MR= metastatic recurrence; Prb= probaility

Survival after progression to MR from IDFS was attributed to a fixed life-year gain based on two previous breast cancer models from Monarch 2 and Monarch 3.

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. 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.

L.2 NMR

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.

NMR to MR ET resistant (NMR_ETR

Patients experiencing non-metastatic disease recurrence were assumed to have a low risk of experiencing disease metastases during the 12-month treatment period. At the time of the last data cut (OS IA3) the monarchE trial had follow-up data of 54 months, allowing data to be used to estimate a transition to MR from NMR. Due to the limited data, and uncertainty, an exponential distribution was fit based on a single constant hazard over time. The assumption of a constant hazard was deemed the most suitable. An independent exponential model was the only model which converted when fit to the OS IA3 data of the ITT population of monarchE. Consequently, the independent exponential model for the ITT population was used for all populations in the model.

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.

L.3 Remission

Remission to MR 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. 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.

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.

Appendix M. Metastatic health state

The metastatic disease setting could in theory be modelled in three different ways using the MONARCH 2 and MONARCH 3 models. The table below**Error! Reference source not found.** provides an overview of the three methods and their pros and cons. An assessment of the three methods of implementation concluded that the first 'fixed pay-off' method was the most appropriate. The approach incorporates a suitable level of complexity by allowing the model cohort to move to the metastatic disease setting via both faster and slower pathways (i.e., ET-resistant [MONARCH 2] and ET-sensitive pathways [MONARCH 3]). The method allows crucial survival, utility, and cost data from both CMs to be incorporated into the monarchE model while maintaining the computational power of the Excel model.

Table 92. Pros and cons of three approaches to model the metastatic health state

Approach	Pros	Cons (* = major issues)
1. Pay-off approach (using MONARCH 2 & MONARCH 3 CM reports only): • Outputs used from MONARCH 2 & MONARCH 3 CMs: LYs (QALYs will be used to cross-check results). • Inputs used from MONARCH 2 & MONARCH 3 CMs: All utilities, costs & resource use inputs. SE will be assumed to include in PA.	1. Simple. 2. Flexible in terms of country adaptations. Limited critique of inputs and assumptions.	1. Uncertainty from the MONARCH 2 & MONARCH 3 will not be applied for LYs. • Crude assumption of SE. 2. Population heterogeneity • Age: 8-11 year difference between monarchE (~52 yrs.) & MONARCH 2 (60 yrs.) & MONARCH 3 (63 yrs.) patient populations. 3. Incorporating the costing (1L + 2nd line) part from both MONARCH 2 & MONARCH 3 is going to be time consuming and will also slow the model down. 4. Other models did not use a pay-off approach as external data with long-term follow-up were available for the HER2+ EBC CMs. Patient distribution within the health state external to monarchE CM.
2. Pay-off approach (using MONARCH 2 & MONARCH 3 CMs): Outputs used from MONARCH 2 + MONARCH 3:	1. Very simple & Efficient. 2. QALY & LY & Costs from MONARCH 2 & MONARCH 3.	1. Costing part more complex for country adaptations. 2. External to monarchE CM.

Approach	Pros	Cons (* = major issues)
QALY + LYs + costs, SE from PA.	3. Inclusion of uncertainty from MONARCH 2 & MONARCH 3 CMs. The cons of the complex CMs are less apparent.	3. Questions surrounding assumptions will be challenging to address. 4. Population heterogeneity. Other models did not use this pay-off approach.
Including MONARCH 2 & MONARCH 3 CMs in the monarchE CM.	1. Models all pathways. 2. Comprehensive view of QALY & LY & Costs from MONARCH 2 & MONARCH 3 CMs. If the HTA body critiques the input and assumption these can be addressed in the monarchE CM since it will not be external to the Excel structure.	1. Population heterogeneity remain. 2. Time consuming for countries that do not have MONARCH 2 & MONARCH 3 up to date CMs available to them. 3. Complex structure and slow to run PA. Opening up to further critique for the various inputs & assumptions needed for this model framework.

All approaches had two key limitations, population heterogeneity and critique of input assumptions being transferred over to the monarchE model from the MONARCH 2 and MONARCH 3 models. There was an eight- and 11-year difference in age between the patients enrolled in the monarchE trial compared to MONARCH 2 and MONARCH 3, respectively. All assumptions surrounding the costs and utilities would be directly transferred from the MONARCH 2 and MONARCH 3 CMs into the monarchE model.

The first option was considered for implementation in the model whereby survival outcomes following disease recurrence to the metastatic health state from either the IDFS or the remission health states at the point of disease recurrence were attributed a 'fixed pay-off' of LYs from these advanced breast cancer models. The costs and utilities associated with each health state within the respective metastatic disease pathways were combined with the LYs to determine the estimated total costs and QALY outcomes for the metastatic disease setting in the monarchE model. Section M.1 below provides further details on the approach. The additional limitations of this approach related to the including crude assumptions of uncertainty for the LYs in the model.

The second approach was even simpler compared to the first, where total LYs and total costs could be implemented in the model. The costing aspect of this approach would make the model incompatible for country adaptations or specific patient access schemes (PAS). Consequently, this approach was no longer considered appropriate.

The final approach was the most transparent whereby one would incorporate three models into one framework. Given the computational running time for the probabilistic analysis in the MONARCH 2 model alone takes several hours, the monarchE model would take even longer to run. Despite the additional transparency of this method, this final approach would be unable to overcome the two key limitations discussed above, across the first two approaches. The additional complexity and loss of computational power were key reasons for excluding this approach as an option.

M.1 Metastatic health state “pay-off” approach

The relevant treatment received in themetastatic disease setting was dictated by advanced breast cancer guidelines, data from the monarchE trial, TL opinion, and market share information. It is acknowledged that patients may be rechallenged with a CDK4&6 inhibitor in clinical practice following distant disease recurrence. There is currently no clinical evidence to support the use of a CDK4&6 inhibitor following disease recurrence on a prior CDK4&6 inhibitor-based regimen. In the CM, patients who received ABE + ET in the adjuvant setting would not receive a CDK4&6 inhibitor treatment following distant disease recurrence. Figure 52 provides the proposed treatment options currently programmed in the model based on the respective metastatic disease pathway. The treatment regimens modelled for disease progression in the MR health state are the same as the original MONARCH 2 and MONARCH 3 CMs. The model user can specify treatment regimens and associated efficacy data from alternative sources where available and if deemed more appropriate.

ET-resistant

- CDK 4&6 inhibitors (i.e., ABE, PAL, RIBO) in combination with FUL
- EXE
- EXE-EVE
- FUL
- CAP

ET-sensitive

- CDK 4&6 inhibitors (i.e., ABE, PAL, RIBO) in combination with NSAI
- FUL
- NSAI
- RIBO-FUL
- TMX

Figure 52 Treatment regimens received per metastatic disease pathway

Abbreviations: Abbreviations: ABE, Abemaciclib; CAP, Capecitabine; CDK 4&6, Cyclin-dependent kinase 4 and 6; EVE, Everolimus; EXE, Exemestane; FUL, Fulvestrant; NSAI, Non-steroidal aromatase inhibitor; PAL, Palbociclib; RIBO, Ribociclib; TMX, Tamoxifen

Source: 2019-8101 Abemaciclib MONARCH 2 Global CEM - Technical Report - March 2022; 2019-8863 Abemaciclib MONARCH 3 Global CEM - Technical Report - FINAL - March 2022

M.2 ET-resistant metastatic recurrence pathway

The MONARCH 2 CM used 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, while efficacy of other treatment regimens not included in these trials were assessed by means of a network meta-analysis

(NMA). The PPS health state was estimated by taking the difference between 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, patients moving directly from the IDFS health state to the metastatic disease setting after experiencing a disease recurrent event while receiving adjuvant ET or within the 12 months after completing adjuvant ET (minimum 5 years plus 12 months), were assumed to follow the ET-resistant pathway. 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.

Table 93 provides an overview of the treatment options modelled per monarchE treatment arm based on current market share data provided by Lilly (data on file). Table 94 provides the clinical outcomes taken from MONARCH 2 CM.

To calculate the combined LYs for the CDK4&6 inhibitors + FUL treatments, a weighted average of the ABE-FUL, PAL-FUL, and RIBO-FUL LYs were used. The monarchE CM used the undiscounted LYs from MONARCH 2 CM, while the respective health state specific utility values were applied to calculate the total QALYs. A financial 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:

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

The present value '(PV) function' has been used to translate the formula into an Excel format.

As the monarchE CM used mean LYs from the MONARCH 2 model we assumed that all patients were alive until the mean LY point was reached. This may lead to under or overestimating the survival outcomes of the population. As we do not use individual survival curves from the MONARCH 2 model this is acknowledged as a limitation in the CM.

The same approach to discounting QALYs has been applied to costing of resource use. The same limitations apply. Please note LYs have not been discounted in addition to QALY and cost discounts to avoid double discounting.

Table 93. Proportion of patients receiving each treatment regimen who had a distant disease recurrent event and followed the ET-resistant pathway

	ABE + ET	*ET alone*
CDK4&6 inhibitors-FUL	0%	15%
EXE-EVE	31%	26%

	ABE + ET	*ET alone*
FUL	32%	27%
CAP	7%	6%
EXE	30%	26%

Abbreviations: ABE, Abemaciclib; CAP, Capecitabine; CDK 4&6, Cyclin-dependent kinase 4 and CDK 6; ET, Endocrine therapy; EXE, Exemestane; EXE-EVE, Exemestane – Everolimus; FUL, Fulvestrant
Source: Lilly data on file

Table 94. Discounted LYs and mean time on treatment from the MONARCH 2 CM (Version of November 30, 2021)

Treatment options	PFS LYs	PPS LYs	Mean ToT (months)
ABE-FUL	2.47	1.92	17.58
RIBO-FUL	2.12	2.23	18.80
PAL-FUL	1.58	2.62	15.12
EXE-EVE	1.81	1.66	13.65
FUL	0.94	2.55	8.96
CAP	1.97	2.47	12.72
EXE	0.73	2.48	8.73

Abbreviations: ABE, Abemaciclib; CAP, Capecitabine; CM, Cost-utility model; EVE, Everolimus; EXE, Exemestane; FUL, Fulvestrant; LYs, Life years; PAL, Palbociclib; PFS, Progression-free survival; PPS, Post-progression survival; RIBO, Ribociclib; ToT, Time on Treatment

Source: 2019-8101 Abemaciclib MONARCH 2 Global CEM - Technical Report - March 2022

M.3 ET-sensitive metastatic recurrence pathway

The MONARCH 3 CM used a cohort state transition model with three health states: PFS for first-line, PPS, and death. The PFS health state was modelled as a Markov state. Following disease progression on their first advanced breast cancer ET regimen, patients were allocated a fixed pay-off for PPS, using costs and outcomes from the MONARCH 2 model.

In the monarchE CM framework, when a distant disease recurrence occurs more than 12 months after completing adjuvant ET or while in remission following an NMR event, patients were assumed to follow the MONARCH 3 pathway. 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 first-line advanced PFS, second-line advanced PFS or PPS.

The same approach to discounting of QALYs and costs in the ET-resistant pathway was applied. The same limitations apply. Please note LYs have not been discounted in addition to QALY and cost discounts to avoid double discounting.

Table 95 provides an overview of the treatment options modelled per monarchE treatment arm based on current market share data provided by Lilly (data on file). Table 96 provides the clinical outcomes taken from the MONARCH 3 CM. To calculate the

combined LYs for the CDK4&6 inhibitors + NSAI treatment regimens, a weighted average of the ABE-NSAI, PAL-NSAI, and RIBO-NSAI LY were used.

Table 95. Average proportion of patients receiving each treatment regimen who had a distant disease recurrent event and followed the ET-sensitive pathway

	ABE + ET	*ET alone*
CDK4&6 inhibitors-NSAI	0%	61%
NSAI	76%	29%
RIBO- FUL	0%	0%
TMX	19%	7%
FUL	5%	2%

Abbreviations: ABE, Abemaciclib; CAP, Capecitabine; CDK 4&6, Cyclin-dependent kinase 4 and CDK 6; ET, Endocrine therapy; EXE, Exemestane; EXE-EVE, Exemestane – Everolimus; FUL, Fulvestrant
Source: Lilly data on file

Table 96. Discounted LYs from the MONARCH 3 CM (Version of November 30, 2021)

Treatment	First-line advanced PFS	Mean ToT (months)	Second-line advanced PFS	PPS
ABE-NSAI	2.98	32.11	1.31	1.87
PAL-NSAI	2.97	31.88	1.33	1.89
RIBO-NSAI	2.91	31.40	1.35	1.92
NSAI	1.68	20.70	1.37	1.95
RIBO-FUL	4.07	32.11	1.31	1.94
TMX	1.46	12.87	1.34	1.92
FUL	2.25	23.54	1.32	1.97

Abbreviations: ABE, Abemaciclib; EXE, Exemestane; FUL, Fulvestrant; LYs, Life years; NSAI, Non-steroidal aromatase inhibitor (Letrozole + Anastrozole); PAL, Palbociclib; RIBO, Ribociclib; TMX, Tamoxifen; ToT, Time on treatment

Source: 2019-8863 Abemaciclib MONARCH 3 Global CEM - Technical Report - FINAL - March 2022

M.4 Metastatic health state costing approach

M.4.1 ET-resistant

To inform the ET-resistant metastatic pathway the costing approach from the MONARCH 2 model was used.

The following resource use categories were captured in the analysis:

- Drug acquisition
- Drug administration (same administration costs for intravenous (IV) and subcutaneous (SC) administration as in early breast cancer setting, so not explicitly mentioned here)
- BSC
- Follow-up care
- AE

- Hospitalisations
- Post-progression therapy

Costs were sourced for the year 2017 in MONARCH 2 report.

M.4.1.1 Drug costs

Drug acquisition costs are calculated by combining dosing regimens, relative dose intensity (RDI) adjustments and mean patient body surface area (BSA) data. Treatment regimens are based on the abemaciclib-fulvestrant (ABE-FUL) and placebo-fulvestrant (PBO-FUL) regimens received in the MONARCH 2 trial (ABE-FUL: 150mg twice daily/28 days; FUL: 500mg every 28 days) and the primary publications used in the NMA. RDI was set to be 100% for all therapies in the base case setting.

Treatment regimens and drug acquisition costs for each comparator are presented in Table 97 and Table 98, respectively. For fulvestrant that is administered intramuscular, drug acquisition costs per patient were calculated by determining the number of vials needed to provide the required dose multiplied by the unit price of the vial.

Table 97 Treatment regimens

Treatment	Study	Dose (mg)	Admins per cycle	Cycle length	RDI	Comments
ABE-FUL	MONARCH 2	ABE: 150mg FUL: 500mg	ABE: 56 FUL: 1 (2 in cycle 1 and 1 thereafter)	28	ABE: 100% FUL: 100%	RDI assumed to be 100% for oral and IM treatment
RIBO-FUL	MONALEESA-3	RIBO: 600 FUL: 500	RIBO: 21 FUL: (2 in cycle 1 and 1 thereafter)	28	RIBO: 100% FUL: 100%	RDI assumed to be 100% for oral and IM treatment
FUL	MONARCH 2	500mg	1 (2 in cycle 1 and 1 thereafter)	28	100%	RDI assumed to be 100% for IM treatment
EXE	BOLERO 2	25mg	28	28	100%	RDI assumed to be 100% for oral treatment
EXE-EVE	BOLERO 2	EXE: 25mg EVE: 10mg	EXE: 28 EVE: 28	28	EXE: 100% EVE: 100%	RDI assumed to be 100% for oral treatment
PAL-FUL	PALOMA 3	PAL: 125mg	PAL: 21 FUL: 1 (2 in cycle 1 and	28	PAL: 100%	RDI assumed to be 100% for oral

Treatment	Study	Dose (mg)	Admins per cycle	Cycle length	RDI	Comments
		FUL: 500mg	1 thereafter)		FUL: 100%	and IM treatment

Abbreviations: ABE, Abemaciclib; EVE, Everolimus; EXE, Exemestane; FUL, Fulvestrant; IM, Intramuscular; mg, Milligram; PAL, Palbociclib; RDI, Relative dose intensity; RIBO, Ribociclib

Table 98 Medicine costs of subsequent treatments, ETR setting

Medicine	Strength	Package size	Pharmacy purchase price [DKK]
Abemaciclib	150 mg	56 pcs	18,077
	150 mg	28 pcs	9,199
Exemestane	25 mg	100 pcs	3,650
Fulvestrant	250 mg	2 vials	462
Ribociclib	200 mg	63 pcs	22,797
Palbociclib	125 mg	21 pcs	22,854
Everolimus	10 mg	30 pcs	19,500

M.4.1.2 Best supportive care

A summary of the BSC components and resource utilisation are provided in the tables below.

Table 99 BSC components and resource use

BSC component	Medication	Proportion	Units per admin	Duration (days)	Frequency per unit	Source	Comments
Pain management*	Oxycodone	9.49%	200.00	On-going	Daily	MONARCH 2 CSR; dose-BNF	Assumed half of daily max dose(mg) for immediate- release oxycodone
Anti-emesis or antinauseants	Ondansetron	9.79%	16.00	5	Daily	MONARCH 2 CSR; dose-BNF	8mg every 12 hours for up to 5 days
Depression or anxiety	Alprazolam	8.28%	500.00	5	Daily	MONARCH 2 CSR; dose-BNF	250 micrograms 2-3 times per day (short term use assumed)
Cancer-associated venous thromboembolic disease	Rivaroxaban	3.46%	30.00	21	Daily	MONARCH 2 CSR; dose-BNF	15 mg twice daily. Recommended dosage is for initial treatment of deep vein thrombosis
Growth factors	Filgrastim	4.22%	357.4	14	Weekly	MONARCH 2 CSR; dose-BNF	5mcg/kg daily for up to 14 days for the reduction of neutropenia and incidence of febrile neutropenia

Table 100 BSC components

BSC treatment	Active ingredients	Dose per tablet or vial	Unit	Units per package	Price per package	Reference
Oxycodone	Oxycodone hydrochloride	5mg	Capsule	100 pcs	64	Medicinpriser.dk

Ondansetron	Ondansetron (as Ondansetron hydrochloride)	4 mg	tablets	100 pcs	106
Alprazom	Alprazolam	0.25 mg	tablets	100 pcs	43
Rivaroxaban	Rivaroxaban	2.5 mg	tablets	100 pcs	656
Filgrastim	Filgrastim	12 mio IE/0.2 ml	solution	5 x 0.2 ml	970

Abbreviations: pcs = pieces

M.4.1.3 Follow-up care

The follow-up care components, proportions and frequencies are listed in Table 101.

Table 101 Follow-up care resource use

Health state	Component	Proportion	Frequency	Source
PFS	CT scan	89.6%	1 per alternate cycle	MONARCH 2 IPD
	MRI scan	6.6%	1 per alternate cycle	MONARCH 2 IPD
	PET scan	3.9%	1 per alternate cycle	MONARCH 2 IPD
	X-ray	2.50%	1 per alternate cycle	MONARCH 2 IPD
	Electrocardiogram	100%	1 per alternate cycle	MONARCH 2 CSR
	Complete blood count	100%	1 per cycle	MONARCH 2 CSR
	Serum chemistry	100%	1 per cycle	MONARCH 2 CSR
	Oncologist consultation	100%	1 per cycle	MONARCH 2 CSR
	GP visit	100%	1 per month	NICE clinical guideline 81 (package 1)
	Community nurse	100%	1 per fortnight	NICE clinical guideline 81 (package 1)
	Clinical nurse specialist	100%	1 per month	NICE clinical guideline 81 (package 1)
PPS	CT scan	85.8%	1 per alternate cycle	MONARCH 1 IPD
	MRI scan	8.9%	1 per alternate cycle	MONARCH 1 IPD
	PET scan	5.3%	1 per alternate cycle	MONARCH 1 IPD
	Electrocardiogram	100%	1 per cycle	MONARCH 1 IPD
	Complete blood count	100%	1 per cycle	MONARCH 1 IPD
	Serum chemistry	100%	1 per cycle	MONARCH 1 IPD
	Oncologist consultation	100%	1 per cycle	MONARCH 1 IPD
	GP visit	100%	1 every fortnight	NICE clinical guideline 81 (package 2)
	Community nurse	100%	1 per week	NICE clinical guideline 81 (package 2)

Clinical nurse specialist	100%	1 per week	NICE clinical guideline 81 (package 2)
Therapist	100%	1 every fortnight	NICE clinical guideline 81 (package 2)

Abbreviations: CSR, Clinical study report; CT, Computed tomography; GP, General practice; IPD, Individual patient level data; MRI, Magnetic resonance imaging; NICE, National Institute for Health and Care Excellence; PET, Positron emission tomography; PFS, Progression-free survival; PPS, Post-progression survival

The proportions for scan modalities were sourced from the MONARCH 2 trial for the pre-progression state and the MONARCH 1 trial for the post-progression state are listed in Table 102 and Table 103.

Table 102 Scan modalities received by patients in MONARCH 2

Scan modality	Number of patients	Proportion	Rescaled proportion	Comments
CT scan	202	24.1%	89.6%	Included in rescaled total, includes Spiral CT
MRI	51	6.1%	6.6%	Included in rescaled total
Other	11	1.3%	-	Not included in rescaled total
PET and MRI scan	1	0.1%	-	Not included in rescaled total
PET/CT scan	30	3.6%	3.9%	Included in rescaled total
Scintigraphy	51	6.1%	-	Not included in rescaled total
Spiral CT	493	58.8%	-	Included in total and CT scan %
Total	839	100%	100%	

Abbreviations: CT, Computed tomography; MRI, Magnetic resonance imaging; PET, Positron emission tomography

Table 103 Scan modalities received by patients in MONARCH 1

Scan modality	Number of patients	Proportion	Rescaled proportion	Comments
CT scan	50	27.6%	85.8%	Included in rescaled total, includes Spiral CT
MRI	15	8.3%	8.9%	Included in rescaled total
Other	10	5.5%	-	Not included in rescaled total
PET and MRI scan	1	0.6%	-	Not included in rescaled total
PET/CT scan	9	5.0%	5.3%	Included in rescaled total
Scintigraphy	1	0.6%	-	Not included in rescaled total
Spiral CT	95	52.5%	-	Included in total and CT scan %
Total	181	100%	100%	

Abbreviations: CT, Computed tomography; MRI, Magnetic resonance imaging; PET, Positron emission tomography

Table 104 Follow-up care costs

Component	Cost	Source
CT scan	DKK 2,585	DRG 2024 - Kvinde , 51 År (DC509)Brystkræft UNS, 30PR06 - CT-skanning, kompliceret
MRI scan	DKK 3,620	DRG 2024 - Kvinde, 51 År (DC509)Brystkræft UNS, 36PR07 - Klinisk fysiologi/nuklearmedicin grp. G
PET scan	DKK 3,620	DRG 2024 - Kvinde, 51 År (DC509)Brystkræft UNS, 36PR07 - Klinisk fysiologi/nuklearmedicin grp. G
Electrocardiogram	DKK 2,681	DRG 2024 - Kvinde, 51 År (DC509)Brystkræft 37PR01 - Klinisk neurofysiologi grp. 1
Complete blood count	DKK 46	Sum of different Tests at Rigshospitalet include: leukocytes,haemoglobine, thrombocytes. No price exist for each test, since the tests performed varies - price of haemoglobine has been used in this estimation, since this test is always include
Serum chemistry	DKK 139	Sum of different Tests at Rigshospitalet Total test price of sodium, potassium, magnesium, creatinine and calcium lab tests
Oncologist consultation	DKK 1,625	DRG 2024 - 09MA98 - MDC09 1-dagsgruppe, pat. mindst 7 år
GP visit	DKK 153.63	DMC Værdisætning af enhedsomkostninger
Community nurse	DKK 1,625	DRG 2024 - 09MA98 - MDC09 1-dagsgruppe, pat. mindst 7 år
Clinical nurse specialist	DKK 592	DMC Værdisætning af enhedsomkostninger
Therapist	DKK 592	DMC Værdisætning af enhedsomkostninger

Abbreviations: CT, Computed tomography; GP, General practitioner; MRI, Magnetic resonance imaging

M.4.1.4 Adverse events

The AE rates included in the model are provided in Table 129. Unit costs were based on Danish DRG tariff data base (can be found in Section 11.5).

M.4.1.5 Hospitalisations

The cost of hospitalisation was estimated by combining a probability of hospitalisation, an estimate of length of stay and a unit cost per day. Only hospitalisations due to non-treatment related AEs were modelled to avoid double counting costs that would be captured through modelling Grade III/IV AEs. The length of stay was estimated based on

the MONARCH 2 data for PFS and post-progression periods, assuming this was the same between ABE-FUL and PBO-FUL. Refer to Table 105.

Table 105 Length of stay for patients in MONARCH 2

Cohort	Treatment	Number of hospitalisations	Mean (days)	Standard deviation
Base case:				
Pre-progression	ABE-FUL & PBO-FUL	73	7.74	8.57
Post-progression	ABE-FUL & PBO-FUL	23	7.65	4.90
Scenarios:				
Overall	ABE-FUL & PBO-FUL	96	7.72	7.82
Pre-progression	ABE-FUL	63	7.05	7.19
Post-progression	ABE-FUL	16	6.50	4.56
Overall	ABE-FUL	79	6.94	6.72
Pre-progression	PBO-FUL	10	12.10	14.36
Post-progression	PBO-FUL	7	10.29	4.96
Overall	PBO-FUL	17	11.35	11.22

Abbreviations: ABE, Abemaciclib; FUL, Fulvestrant; PBO, Placebo

The rate of hospitalisation was estimated based on an analysis of the MONARCH 2 data. This involved estimating rates of hospitalisation by pre- and post-progression states based on the observed number of hospitalisations and total follow-up time. Refer for Table 106.

Table 106 Hospitalisation rate and probability data from MONARCH2

Disease state	Treatment	Total hospitalisation	Total follow-up (days)	Rate of hospitalisation / week	Probability of hospitalisation / week
Base case:					
Pre-progression	ABE-FUL & PBO-FUL	86	214841	0.003	0.003

Post-progression	ABE-FUL & PBO-FUL	11	11393	0.007	0.007
Scenarios:					
Overall	ABE-FUL & PBO-FUL	97	226234	0.003	0.003
Pre-progression	ABE-FUL	68	151079	0.003	0.003
Post-progression	ABE-FUL	6	6120	0.007	0.007
Overall	ABE-FUL	74	157199	0.003	0.003
Pre-progression	PBO-FUL	18	63762	0.002	0.002
Post-progression	PBO-FUL	5	5273	0.007	0.007
Overall	PBO-FUL	23	69035	0.002	0.002

Abbreviations: ABE, Abemaciclib; FUL, Fulvestrant; PBO, Placebo

Hospitalisation costs were assumed the same as in the early breast cancer (EBC) setting.

M.4.1.6 Post-progression therapy

Post-progression therapy was included in the analysis as a weighted average cost. This was thought to be reasonable as differences in long-term outcomes associated with these therapies are unlikely to differ between regimens sufficient to impact on cost-effectiveness estimates.

Based on clinical input received, an assumption was made that patients would not be re-treated with the same treatment regimen or drug component in post-progression (i.e., the probability of receiving the same treatment regimen/drug component in post-progression as was received in pre-progression was set to zero). The distributions were subsequently rescaled to sum to 100%

For ET-resistant patients, the distribution of treatments administered during the endocrine therapy (ET)-resistant progression-free survival (PFS) phase is informed by insights from medical experts consulted by Eli Lilly, as detailed in Appendix M.2 Table 93 and Table 94 (informed by MONARCH 2 CM). No re-treatment using the same medication after disease progression) was assumed. The distribution of subsequent treatments

administered after progression (PPS) is presented in 51. The pricing for each drug per package/unit utilized during endocrine-resistant PFS is provided in Table 53.

Table 107. Distribution of post-progression therapy regimens

Regimen	*Therapy*						
	ABE-FUL	RIBO-FUL	PAL-FUL	EXE-EVE	FUL	CAP	EXE
CAP	17.59%	17.59%	17.59%	32.23%	16.03%	0.00%	34.5%
PAC	17.59%	17.59%	17.59%	0.00%	16.03%	19.50%	0.0%
VNB	4.61%	4.61%	4.61%	9.40%	5.83%	7.09%	16.0%
ERI	5.48%	5.48%	5.48%	0.00%	4.37%	5.32%	0.0%
FUL	0.00%	0.00%	0.00%	30.89%	0.00%	0.00%	22.2%
LTZ	6.34%	6.34%	6.34%	0.00%	8.01%	9.75%	0.0%
EXE	14.71%	14.71%	14.71%	0.00%	17.85%	21.72%	0.0%
EVE	11.54%	11.54%	11.54%	0.00%	13.11%	15.96%	0.0%
CYC	4.04%	4.04%	4.04%	12.09%	2.55%	3.10%	11.1%
GEM	2.31%	2.31%	2.31%	5.37%	2.55%	3.10%	6.2%
BEV	5.77%	5.77%	5.77%	0.00%	3.64%	4.43%	0.0%

Abbreviations: ABE= Abemaciclib; BEV= Bevacizumab; CAP= Capecitabine; CYC= Cyclophosphamide; ERI= Eribulin; EVE= Everolimus; EXE= Exemestane; EXE-EVE= Exemestane + everolimus; FUL= Fulvestrant; GEM= Gemcitabine; LTZ= Letrozole; PAC= Paclitaxel; PAL-FUL= Palbociclib + fulvestrant; PFS= Progression-free survival; RIBO-FUL= Ribociclib + fulvestrant; VNB= Vinorelbine
Source: ABE-FUL, MONARCH 2; CAP, BOLERO 6; FUL, MONARCH 2; EXE and EXE-EVE, BOLERO-2; PAL-FUL & RIBO-FUL, assumed same as ABE-FUL

Post-progression therapy costs comprised drug acquisition and drug administration. These were assigned to the proportion of patients experiencing disease progression in each cycle. This was based on the PFS curve for each comparator adjusted by the proportion of PFS events which were progressive disease rather than death (Table 108). The proportion of PFS events which were progressive disease for ABE was estimated based on the MONARCH 2 trial. Data were unavailable from the primary publications for the comparators. This proportion was assumed to be equivalent across all comparators.

Table 108 Progression-free survival events

Comparator	Number of PFS events	Number of deaths	Proportion of PFS events which are death
ABE-FUL	379	15	3.96%

Post-progression therapy acquisition costs were calculated as per the treatment drug acquisition costs. Treatment regimens and RDI were assumed equivalent to pre-progression where available. Regimens for CYC, GEM and BEV were based on publications cited by the National Comprehensive Cancer Network guidelines. Refer to Table 109. Acquisition costs are presented in Table 110.

Table 109. Post-progression therapy regimens

Drug	Study	Dose(mg)	Admins per cyclle	Cycle lenght	Number of cycles	Comments
CAP	Kaufman (2015)	1250mg/ m2	28	21 days	TD	RDI assumed to be 100% for oral treatment
PAC	Perez (2001)	80mg / m2	4	28 days	TD	From Beuselinck (2010), RDI was
VNB	Meier (2008)	30mg / m2	3	56 days	TD - only 4	78% in initial 8
ERI	Kaufman (2015)	1.4mg /m2	1.33	consecut ive cycles allowed		weeks then 71% from 8 weeks to TD
FUL	MONARCH 2	500mg	1 (2 in cycle 1	21 days	TD	RDI assumed to be 100%, NR in Meier (2008)
LTZ	and 1 thereafter)			28 days	TD	-
EXE	Rose (2003)	2.5mg	28	28 days	TD	Assumed equal to PFS
EVE	BOLERO 2	25mg	28	28 days	TD	Assumed equal to PFS
CYC	BOLERO 2	10mg	28	28 days	TD	Assumed equal to PFS
EPI	Ackland (2001)	400mg / m2	2	28 days	TD – max of 6-9 cycles depending on response	Assumed equal to PFS
FLU	Ackland (2001)	50mg / m2	2	28 days	TD – max of 6-9 cycles depending on response	Median estimate of RDI in Ackland (2001)
GEM	Ackland (2001)	500mg / m2	2	28 days	TD – max of 6-9 cycles depending on response	Median estimate of RDI in Ackland (2001)
BEV	Brodowicz (2000)	1250mg/ m2	3	28 days	TD	Median estimate of RDI in Ackland (2001)

Abbreviations: BEV= Bevacizumab; CAP= Capecitabine; CYC= Cyclophosphamide; EPI= Epirubicin; ERI= Eribulin; EVE= Everolimus; EXE= Exemestane; FLU= Fluorouracil; FUL= Fulvestrant; GEM= Gemcitabine; LTZ= Letrozole; NR= Not reported; PAC= Paclitaxel; PFS= Progression-free survival; RDI= Relative dose intensity; TD= Treatment discontinuation; VNB= Vinorelbine
Note: RDI = 100% for all comparators

Table 110. Post-progression therapy costs

Drug	*Units (mg/ml)*	*Vial size*	*Unit cost*	*Reference*
CAP	150 mg	60 pcs	658,00	Medicinpriser.dk
PAC	6 mg/ml	50ml	202,00	Medicinpriser.dk
VNB	10 mg/ml	5ml	1,240	Medicinpriser.dk
ERI	0.44 mg/ml	2ml	2,283	Medicinpriser.dk
FUL	250 mg	2 vials	462,00	Medicinpriser.dk
LTZ	-	-	-	Discontinued
EXE	25 mg	100 pcs	3,650	Medicinpriser.dk
EVE	10 mg	30 pcs	18,200	Medicinpriser.dk
CYC	50 mg	100 pcs	923,00	Medicinpriser.dk
EPI	2 mg/ml	100ml	443,00	Medicinpriser.dk
FLU	50 mg/ml	100ml	300,00	Medicinpriser.dk
GEM	10 mg/ml	220ml	420,00	Medicinpriser.dk
BEV	25 mg/ml	1 x 16ml	7,144	Medicinpriser.dk

Abbreviations: BEV= Bevacizumab; CAP= Capecitabine; CYC= Cyclophosphamide; EPI= Epirubicin; ERI= Eribulin; EVE= Everolimus; EXE= Exemestane; FLU= Fluorouracil; FUL= Fulvestrant; GEM= Gemcitabine; LTZ= Letrozole; NR= Not reported; PAC= Paclitaxel; PFS= Progression-free survival; RDI= Relative dose intensity; TD= Treatment discontinuation; VNB= Vinorelbine

Drug administration

Post-progression therapy administration costs were calculated as per the treatment drug acquisition costs. Infusion times were based on publications used to inform the treatment regimens. These data are presented in Table 111.

The drug administration costs for each treatment regimens are presented in Table 112.

Table 111. Post-progression therapy infusion times

Drug	Study	Infusion time
CAP	Kaufman (2015)	N/A
PAC	Beuselinck (2010)	1 hour
VNB	Meier (2008)	NR
ERI	Kaufman (2015)	2-5 minutes
FUL	MONARCH 2	N/A
LTZ	Rose (2003)	N/A
EXE	BOLERO 2	N/A
EVE	BOLERO 2	N/A
CYC	Ackland (2001)	NR
EPI	Ackland (2001)	NR
FLU	Ackland (2001)	NR
GEM	Brodowicz (2000)	NR
BEV	Miller (2007)	N/A

Abbreviations: BEV= Bevacizumab; CAP= Capecitabine; CYC= Cyclophosphamide; EPI= Epirubicin; ERI= Eribulin; EVE= Everolimus; EXE= Exemestane; FLU= Fluorouracil; FUL= Fulvestrant; GEM= Gemcitabine; LTZ= Letrozole; NR= Not reported; PAC= Paclitaxel; PFS= Progression-free survival; RDI= Relative dose intensity; TD= Treatment discontinuation; VNB= Vinorelbine

Table 112 Drug administration costs, ETR setting, post-progression therapy

Drug	Administration frequency per cycle	Admin costs per cycle	Source / comments
CAP	28	0.00 DKK	Oral
PAC	4	6,500 DKK	DRG tariff /IV
VNB	3	4,875 DKK	DRG tariff /IV
ERI	1.33	2,166.67 DKK	DRG tariff /IV
FUL	1	1,625 DKK	SC
LTZ	28	0.00 DKK	Oral
EXE	28	0.00 DKK	Oral
EVE	4	6,500 DKK	DRG tariff /IV
CYC	A: 2	3,250 DKK	DRG tariff /IV
	B: 2	3,250 DKK	DRG tariff /IV
	C: 2	3,250 DKK	DRG tariff /IV
EPI	NA	NA	DRG tariff /IV
FLU	NA	NA	DRG tariff /IV
GEM	3	4,875 DKK	DRG tariff /IV
BEV	2	3,250 DKK	DRG tariff /IV

Note: CYC= cyclophosphamide, epirubicin, fluorouracil can be combined

M.4.2 ET-sensitive

To inform the ET-sensitive metastatic pathway the costing approach from the MONARCH 3 model was used.

The following resource use categories were included:

- Drug acquisition
- Drug administration (same administration costs for IV and SC administration as in EBC setting, so not explicitly mentioned here)
- Pre-medications
- BSC
- Follow-up care
- AEs
- Hospitalisations
- Post-progression therapy

Costs were sourced for the year 2017 in MONARCH 3 report

M.4.2.1 Drug costs

The doses required for each treatment were calculated by combining dosing regimens, and mean patient weight or BSA data (where applicable). Treatment regimens were based on the ABE-NSAI and NSAI regimens received in the MONARCH 3 trial (ABE: 150mg twice daily/28 days; NSAI: LTZ 2.5mg or ANAS 1mg once daily/28 days) and the primary publications used in the NMA.

Unit costs for all PFS, PPS and supportive care medications were primarily sourced from the eMIT national database and the BNF. Treatment regimens and drug acquisition costs for each comparator are presented in Table 113 and Table 114, respectively. Drug acquisition costs per patient were calculated by determining the number of vials/packs needed to provide the required dose and multiplying by the unit price per vial/pack. This is applied to the monthly dose delivered to calculate the acquisition cost per month.

Table 113 Treatment regimens for 1L advanced ET-sensitive patients

Treatment	Dose (mg)	Admins per cycle	Cycle length	Study
ABE-NSAI	ABE: 150mg LTZ: 2.5mg ANAS: 1mg	ABE: 56 LTZ/ANAS: 28	28	MONARCH 3
NSAI	ANAS: 1mg LTZ: 2.5mg	28	28	MONARCH 3
FUL	500mg	2* doses in cycle 1 and 1 thereafter	28	FIRST/FALCON
RIBO-FUL	RIBO: 600mg FUL: 500mg	RIBO: 21 FUL: 2* doses in cycle 1 and 1 thereafter	28	MONALEESA-3
TMX	40mg	28	28	Milla-Santos 2001, Nordic, Gill 1993, Milla-Santos 2003
RIBO-NSAI	RIBO: 600mg LTZ: 2.5mg	RIBO: 21 LTZ: 28	28	MONALEESA-2
PAL-NSAI	PAL: 125mg LTZ: 500mg	PAL: 21 LTZ: 28	28	PALOMA 3

Abbreviations: ABE, Abemaciclib; ANAS, Anastrozole; ET, Endocrine therapy; FUL, Fulvestrant; LTZ, Letrozole; mg, Milligram; NSAI, Non-steroidal aromatase inhibitors; PAL, Palbociclib; RIBO, Ribociclib; TMX, Tamoxifen
*1 loading dose and first per cycle dose

Table 114 Medicine costs of subsequent treatments, ETS setting

Medicine	Strength	Package size	Pharmacy purchase price [DKK]
Abemaciclib	150 mg	56 pcs	18,077
	150 mg	28 pcs	9,199
Exemestane	25 mg	100 pcs	3,650
Fulvestrant	250 mg	2 vials	462
Ribociclib	200 mg	63 pcs	22,797
Palbociclib	125 mg	21 pcs	22,854
Tamoxifen	100mg	20	154
Anastrozole	1mg	1	38
Letrozole	2.5mg	2.5	135

M.4.2.2 Best supportive care

Components of BSC were identified from clinical guidelines, the MONARCH 3 trial (PFS health state) and the MONARCH 2 trial (PPS health state). BSC was defined as treatment that patients would receive because of their disease: pain management, anti-emetics or antinauseants, growth factors, bone modifying agents, treatments for anxiety/depression, erythropoietic agents, and treatments for venous thromboembolic disease.

It is possible that some of these BSC components were included in the treatment of AE, which could result in the double counting of costs. Given that the BSC components are assigned equally across treatment arms with the same associated frequencies and to the same proportion of patients, the potential double counting of costs is unlikely to have a material impact on the incremental cost-effectiveness. BSC components were selected based on the treatment with the highest utilisation in the trial to capture BSC costs that are most likely to occur in this patient population. These are presented in Table 115 and the unit cost of each component is presented in Table 116.

Table 115 BSC components and resource use

BSC component	Medication	Proportion	Standard error	Units	Frequency	Source
PFS						
Pain management	Oxycodone	8.6%	0.09%	200.00	Daily	MONARCH 2 CSR
Anti-diarrheal	Loperamide	49.6%	0.50%	16.00	Daily	MONARCH 2 CSR
Anti-emesis or anti-nauseants	Ondansetron	8.6%	0.09%	16.00	Daily	MONARCH 2 CSR
Bone modifying agents	Denosumab	23.8%	0.24%	60.00	Bi-annually	MONARCH 2 CSR
Erythropoietic agents	Erythropoietin	0.6%	0.01%	450.00	Weekly	MONARCH 2 CSR
Growth factors	Filgrastim	3.3%	0.03%	5.00	Weekly	MONARCH 2 CSR
PPS						MONARCH 2 CSR
Pain management*	Oxycodone	9.5%	0.09%	200.00	Daily	MONARCH 2 CSR
Anti-emesis or anti-nauseants	Ondansetron	9.8%	0.10%	16.00	Daily	MONARCH 2 CSR

BSC component	Medication	Proportion	Standard error	Units	Frequency	Source
Depression or anxiety	Alprazolam	8.3%	0.08%	16.00	Daily	MONARCH 2 CSR
Cancer-associated venous thromboembolic disease	Placeholder	3.5%	0.03%	-		MONARCH 2 CSR
Growth factors	Filgrastim	4.2%	0.04%	5.00	Weekly	MONARCH 2 CSR

Abbreviations: BSC, Best supportive care; CSR, Clinical study report; PFS, progression-free survival; PPS, post-progression survival

Table 116 BSC components

BSC treatment	Active ingredients	Dose per tablet or vial	Unit	Units per package	Price per package	Reference
Oxycodone	Oxycodone hydrochloride	5mg	Capsule	100 pcs	64	Medicinpriser.dk
Ondansetron	Ondansetron (as Ondansetron hydrochloride)	4 mg	tablets	100 pcs	106	Medicinpriser.dk
Alprazom	Alprazolam	0.25 mg	tablets	100 pcs	43	Medicinpriser.dk
Loperamide	Loperamide hydrochloride	2mg	Tablets	100 pcs	182.15	Medicinpriser.dk
Denosumab	Denosumab	60mg	solution	1 pcs	1,814.56	Medicinpriser.dk
Erythropoietin	Rivaroxaban	4000	solution	6 pcs	2,280.02	Medicinpriser.dk
Filgrastim	Filgrastim	12 mio IE/0.2 ml	solution	5 x 0.2 ml	970	Medicinpriser.dk

Abbreviations: pcs = pieces

M.4.2.3 Follow-up care

Components of follow-up care were identified from the MONARCH 3 trial for the PFS health state, the MONARCH 2 trial for the PPS 'pay-off' and NICE clinical guidelines. Follow-up care was defined as the routine monitoring of patients. The components of follow-up care alongside their corresponding proportions and frequencies are listed in Table 117.

Table 117 Follow-up care

Component	Proportion	SE	Frequency			Frequency per	Source
			PFS	PFS2	PPS		
CT scan	100.00%	1.00%	0.42	0.50	0.50	Cycle	MONARCH 3 CSR
Electrocardiogram	100.00%	1.00%	0.33	0.50	1.00	Cycle	MONARCH 3 CSR
Complete blood count	100.00%	1.00%	1.00	1.00	1.00	Cycle	MONARCH 3 CSR
Serum chemistry	100.00%	1.00%	1.00	1.00	1.00	Cycle	MONARCH 3 CSR
Oncologist consultation	100.00%	1.00%	1.00	1.00	1.00	Cycle	MONARCH 3 CSR
GP visit	100.00%	1.00%	0.23	0.23	0.50	Cycle	NICE clinical guideline 81 (package 1 PFS, package 2 PPS)
Community nurse	100.00%	1.00%	0.50	0.50	1.00	Week	NICE clinical guideline 81 (package

(home visit)							1 PFS, package 2 PPS)
Clinical nurse specialist (home visit)	100.00 %	1.00%	0.23	0.23	1.00	Week	NICE clinical guideline 81 (package 1 PFS, package 2 PPS)
X-ray	0.40% (PFS) / 2.5% (PFS2)	0.00%	0.50	0.50	0.00	Week	MONARCH 3 CSR/MONARCH 2 CSR
Therapist	100.00 %				0.50	week	NICE CG81 clinical guidelines Package 2

Abbreviations: CT, Computed tomography; CSR, Clinical study report; GP, general practitioner; NICE, National Institute for Health and Care Excellence; PFS, Progression-free survival; PPS, Post-progression survival
Notes: Assumed to be 1% around the mean

M.4.2.4 Adverse events

The cost impact of AEs was captured in the model as one-off fixed cost in the first cycle of the model. The rates of AEs for patients on ABE-NSAI and NSAI were based on the treatment related adverse events (TRAE) which occurred in the ITT population of the MONARCH 3 trial. AE rates for the comparators were based on the primary publications used in the NMA. AEs were selected for inclusion if they were Grade III/IV events occurring in more than 5% of patients for at least one comparator. The AE rates included in the model are provided in Table 130. Unit costs were based on Danish DRG tariff data base (can be found in Section 11.5).

M.4.2.5 Hospitalisations

Hospitalisation data were included in the PFS state for first-line patients based on the MONARCH 3 trial data. Hospitalisation data were included in the PPS state for second-line advanced patients based on the PFS and PPS data in the FUL arm of the MONARCH 2 trial.

The cost of hospitalisation was estimated by combining a probability of hospitalisation, an estimate of length of stay and a unit cost per day. Only hospitalisations due to non-TRAEs were modelled to avoid double counting costs that would be captured through modelling Grade III/IV AEs.

MONARCH 3 hospitalisations

The length of stay was estimated based on the MONARCH 3 data for PFS and PPS periods, assuming this was the same between ABE-NSAI and NSAI. See table below.

Table 118 Lenght of stay for patients in MONARCH 3

Cohort	Treatment	Number of hospitalisations	Mean (days)	Standard deviation
Pre-progression (PFS1)	ABE-NSAI & PBO-NSAI	72	8.58	10.99

Abbreviations: ABE, Abemaciclib; NSAI, Non-steroidal aromatase inhibitors; PBO, Placebo; PFS1, Progression-free survival first-line advanced breast cancer

The unit cost per day were assumed equal to those in the EBC setting.

MONARCH 2 hospitalisations

The same approach used to estimate the cost per hospitalisation for MONARCH 3 was applied to the MONARCH 2 data for PFS2 and PPS. Only hospitalisations due to non-TRAEs were modelled to avoid double counting costs that would be captured through modelling Grade III/IV AEs. Unlike the analysis of clinical outcome data where the MONARCH 2 trial population assessed was restricted based on prior ET in the advanced setting, no restriction was placed on the population modelled for hospitalisations. This was due to the lack of event data observed from the MONARCH 2 trial. An assumption was made that the probability of hospitalisation and length of stay for all second-line advanced treatments was the same as FUL.

The length of stay data for FUL based are presented in the table below.

Table 119 Lenght of stay for patients in MONARCH 2

Cohort	Treatment	Number of hospitalisations	Mean (days)	Standard deviation
Pre-progression survival (PFS2)	PBO-FUL	10	12.10	14.36
Post-progression survival (PPS)	PBO-FUL	7	10.29	4.96

Abbreviations: ABE, Abemaciclib; NSAI, Non-steroidal aromatase inhibitors; PBO, Placebo; PFS1, Progression-free survival first-line advanced breast cancer

As more events were observed in the pre-progression period of the MONARCH 2 trial for patients receiving FUL compared to the post-progression period of the MONARCH 3 trial, the respective MONARCH 2 length of stay data were used in the base case for PFS2.

The rates of hospitalisations by pre- and post-progression periods were estimated based on the observed number of hospitalisations and total follow-up time. The rate was then converted to a monthly probability to include in the CE model. The resulting hospitalisation rates and probabilities are provided in Table 120.

Table 120 Hospitalisation rate and probability data from MONARCH 2 - PBO-FUL

Cohort	Treatment	Total hospitalisation	Total follow-up (days)	Rate of hospitalisation / month	Probability of hospitalisation / month
Pre-progression survival (PFS2)	PBO-FUL	18	63762	0.000009	0.00001
Post-progression survival (PPS)	PBO-FUL	5	5273	0.000031	0.00003
Overall	PBO-FUL	23	69035	0.000011	0.00001

Summary of hospitalisations probabilities

Based on the analysis of rates of hospitalisation, a summary of the monthly probability of hospitalisation is provided in table below.

Treatment	PFS1	PFS2	PPS
ABE-NSAI	0.0085	0.0086	0.0288
RIBO-FUL	0.0085	0.0086	0.0288
NSAI	0.0085	0.0086	0.0288
TMX	0.0085	0.0086	0.0288
FUL	0.0085	0.0086	0.0288
PAL-NSAI	0.0085	0.0086	0.0288

RIBO-NSAI	0.0085	0.0086	0.0288

Note: Find these values in the CEM – "Calculations" for MTR ETS PFS1, PFS2, and PPS AD to AQ row 35 to 57.

M.4.2.6 Post-progression therapy

M.4.2.6.1 Second-line advanced treatment costs

Therapies received for second-line advanced disease were modelled in the same way as treatments received for first-line advanced disease. Drug acquisition costs were calculated by combining dosing regimens, and mean patient weight or BSA data (where applicable).

Drug acquisition costs per patient were calculated by determining the number of vials/tablets needed to provide the required dose and multiplying by the unit price per vial/tablet. This is applied alongside the monthly dose delivered to calculate the acquisition cost per month.

The proportions of patients in each arm of the model receiving each therapy were based on the proportions suggested by the ERG in TA503 (109). An assumption was made that patients would not be re-treated with the same treatment following progression (i.e., those receiving first-line advanced NSAI-based combination would not receive NSAI after progression). Consequently, distributions (where applicable) were subsequently rescaled to sum to 100%; these data are presented in Table 121.

Table 121. Distribution of PFS2 (ETS) therapy regimens

Regimen	*Therapy*						
	ABE+NSAI	**PAL-NSAI**	**RIBO-NSAI**	**NSAI**	**RIBO-FUL**	**TMX**	**FUL**
FUL	10.9%	10.9%	10.9%	10.9%	12.7%	9.0%	0.0%
ANAS	0.0%	0.0%	0.0%	0.0%	20.2%	14.3%	13.5%
LTZ	0.0%	0.0%	0.0%	0.0%	17.7%	12.5%	12.0%
EXE	37.0%	37.0%	37.0%	37.0%	0.0%	30.5%	26.6%
TMX	18.5%	18.5%	18.5%	18.5%	21.5%	0.0%	14.2%
EXE-EVE	8.0%	8.0%	8.0%	8.0%	0.0%	8.0%	8.0%
CAP	12.3%	12.3%	12.3%	12.3%	13.4%	12.3%	12.3%
PAC	6.2%	6.2%	6.2%	6.2%	6.7%	6.2%	6.2%
DOC	7.2%	7.2%	7.2%	7.2%	7.8%	7.2%	7.2%
FUL	10.9%	10.9%	10.9%	10.9%	12.7%	9.0%	0.0%

Abbreviations: ABE= Abemaciclib; BEV= Bevacizumab; CAP= Capecitabine; CYC= Cyclophosphamide; ERI= Eribulin; EVE= Everolimus; EXE= Exemestane; EXE-EVE= Exemestane + everolimus; FUL= Fulvestrant; GEM= Gemcitabine; LTZ= Letrozole; PAC= Paclitaxel; PAL-FUL= Palbociclib + fulvestrant

Post-progression therapy costs comprise drug acquisition and drug administration.

Drug costs

Treatment regimens for second-line advanced disease are based on studies identified in the SLR, previous TAs and dosing guidance published by BNF (Table 122). Acquisition costs are presented in Table 123.

Table 122 Second-line advanced treatments

Treatment	Drug	Dose (mg)	Per unit	Admins per cycle cycle	Cycle length	Source
CAP	CAP	1250	m^2	28	21	TA495 - company submission table 44
PAC	PAC	175	m^2	1	21	Perez 2001; EMC Accessed 16th March 2018
DOC	DOC	75	m^2	1	21	EMC Accessed 16th March 2018
FUL	FUL	500	fixed	2	28	BNF Online, Accessed 13th March 2018
	FUL	500	fixed	1	28	BNF Online, Accessed 13th March 2018
ANAS	ANAS	1	fixed	28	28	BNF Online, Accessed 13th March 2018; EMC Accessed 16th March 2018
LTZ	LTZ	2.5	fixed	28	28	TA495 - table 45; EMC Accessed 16th March 2018
EXE	EXE	25	fixed	28	28	TA495 - table 46; EMC Accessed 16th March 2018
TMX	TMX	20	fixed	30	30	BNF Online, Accessed 13th March 2018; EMC Accessed 16th March 2018
EVE-EXE	EVE	10	fixed	28	28	TA495 - table 46; EMC Accessed 16th March 2017
	EXE	25	fixed	28	28	TA495 - table 46; EMC Accessed 16th March 2018

Abbreviations: ANAS, Anastrozole; BNF, British National Formulary; CAP, Capecitabine; DOC, Docetaxel; EVE, Everolimus; EXE, Exemestane; FUL, Fulvestrant; LTZ, Letrozole; NSAI, Non-steroidal aromatase inhibitors; PAC, Paclitaxel; TA, Technical appraisal; TMX, Tamoxifen

Table 123. Second-line advanced therapy drug acquisition costs

Drug	
CAP	
PAC	
DOC	

TMX
ANAS
FUL

LTZ

EXE

EVE

Abbreviations: BEV= Bevacizumab; CAP= Capecitabine; CYC= Cyclophosphamide; EPI= Epirubicin; ERI= Eribulin; EVE= Everolimus; EXE= Exemestane; FLU= Fluorouracil; FUL= Fulvestrant; GEM= Gemcitabine; LTZ= Letrozole; NR= Not reported; PAC= Paclitaxel; PFS= Progression-free survival; RDI= Relative dose intensity; TD= Treatment discontinuation; VNB= Vinorelbine

Drug administration

Second-line advanced therapy administration costs were calculated as per the first-line advanced drug acquisition costs (see table below).

Table 124 Drug administration costs, ETS setting, post-progression therapy

Drug	Administration frequency per cycle	Admin costs per cycle	Source / comments
CAP	28	0.00 DKK	Oral
PAC	4	6,500 DKK	DRG tariff /IV
DOC	1.33	2,166.67 DKK	DRG tariff /IV
FUL (loading)	1	1,625 DKK	SC
FUL	1	1,625 DKK	SC
LTZ	28	0.00 DKK	Oral
EXE	28	0.00 DKK	Oral
TMX	28	0.00 DKK	Oral
EVE	4	6,500 DKK	DRG tariff /IV

Note: CYC= cyclophosphamide, epirubicin, fluorouracil can be combined

M.4.2.6.2 Third-line advanced treatment costs

Treatments received following disease progression on second-line advanced therapy were included in the analysis as a weighted cost. This was thought to be reasonable as differences in long-term outcomes associated with these therapies were unlikely to differ between comparators sufficiently to impact on cost-effectiveness estimates.

A fixed cost of post-progression therapy was assigned to the proportion of patients who progressed in each cycle (per month) for each first-line advanced treatment. The fixed cost of post-progression therapy was calculated by combining:

- Monthly costs of acquisition and administration for each post-progression therapy,
- Time on post-progression therapy in months,
- Proportion of patients who receive each post-progression therapy.

The proportion of patients who receive each post-progression therapy was informed by the proportions used in the manufacturer's submission in TA503 (109). Fifty-four percent of patients were assumed to receive systemic therapy following progression from second-line advanced disease. An assumption was made that patients would not be re-treated with the same treatment in post-progression (i.e., those receiving TMX in the first-line advanced setting would not receive TMX following progression). Consequently, the distributions (where applicable) were subsequently rescaled to sum to 100%. These data are presented in Table 125.

Table 125. Distribution of PPS (ETS) therapy regimens

Regimen	*Therapy*						
	ABE-NSAI	PAL-NSAI	RIBO-NSAI	NSAI	RIBO-FUL	TMX	FUL
CAP	24.8%	24.8%	24.8%	24.8%	24.8%	24.8%	24.8%
ERI	5.6%	5.6%	5.6%	5.6%	5.6%	5.6%	5.6%
FUL	11.2%	12.0%	0.0%	10.1%	11.2%	12.0%	0.0%
ANAS	4.3%	4.6%	6.2%	0.0%	4.3%	4.6%	6.2%
EXE	0.0%	7.4%	8.2%	6.2%	0.0%	7.4%	8.2%
TMX	8.6%	0.0%	9.6%	7.7%	8.6%	0.0%	9.6%

Abbreviations: ABE= Abemaciclib; BEV= Bevacizumab; CAP= Capecitabine; CYC= Cyclophosphamide; ERI= Eribulin; EVE= Everolimus; EXE= Exemestane; EXE-EVE= Exemestane + everolimus; FUL= Fulvestrant; GEM= Gemcitabine; LTZ= Letrozole; PAC= Paclitaxel; PAL-FUL= Palbociclib + fulvestrant

Treatment regimens were informed by previous TAs and dosing guidance published in the BNF; and are presented in Table 126.

Table 126 Third-line advanced treatment regimens

Treatment	Drug	Dose	Per unit	Admins per cycle	Cycle length	Source
CAP	CAP	1250	M2	28	21	TA495 – company submission table 44
ERI	ERI	1.23	M2	2	21	BNF Online, Accessed 13th March 2018; EMC Accessed 16th March 2018
FUL	FUL	500	fixed	2	28	BNF Online, Accessed 13th March 2018
	FUL	500	fixed	1	28	
ANAS	ANAS	1	fixed	28	28	BNF Online, Accessed 13th March 2018; EMC Accessed 16th March 2018
EXE	EXE	25	fixed	28	28	TA495 - table 46; EMC Accessed 16th March 2018
TMX	TMX	25	fixed	28	28	BNF Online, Accessed 13th March 2018; EMC Accessed 16th March 2018

Abbreviations: ANAS, Anastrozole; BNF, British National Formulary; CAP, Capecitabine; ERI, Eribulin; EXE, Exemestane; FUL, Fulvestrant; TA, Technical appraisal; TMX, Tamoxifen

Third-line advanced therapy costs comprised drug acquisition (Table 127) and drug administration (Table 128). This was based on the PFS adjusted by the proportion of PFS events that were disease progression rather than death.

Table 127. Third-line advanced therapy drug acquisition costs

Drug	*Units (mg/ml)*	*Vial size*	*Unit cost*	*Reference*
CAP	150 mg	60 pcs	658,00	Medicinpriser.dk
ERI	0.44 mg/ml	2ml	2,283	Medicinpriser.dk
TMX	100mg	20	154	Medicinpriser.dk
ANAS	1mg	1	38	Medicinpriser.dk
FUL	250 mg	2 vials	462,00	Medicinpriser.dk
EXE	25 mg	100 pcs	3,650	Medicinpriser.dk

Abbreviations: ANAS, Anastrozole; CAP, Capecitabine; ERI, Eribulin; EXE, Exemestane; FUL, Fulvestrant; TMX, Tamoxifen

Table 128 Drug administration costs, ETS setting, post-progression therapy

Drug	Administration frequency per cycle	Admin costs per cycle	Source / comments
CAP	28	0.00 DKK	Oral
ERI	1.33	2,166.67	DRG tariff / IV
FUL (loading)	1	1,625 DKK	SC
FUL	1	1,625 DKK	SC
EXE	28	0.00 DKK	Oral
TMX	28	0.00 DKK	Oral
ANAS	28	0.00 DKK	Oral

Note: CYC= cyclophosphamide, epirubicin, fluorouracil can be combined

M.5 Safety figures

M.5.1 ET-resistant

Table 129. Adverse events used in the health economic model, metastatic setting / ET-resistant

Adverse events	ABE-FUL	RIBO-FUL	EXE	EXE-EVE	FUL	PAL-FUL	CAP
Anaemia	7.26%	3.11%	0.00%	7.05%	0.90%	2.61%	6.86%
Diarrhoea	13.38%	0.62%	0.00%	2.07%	0.45%	0.00%	7.84%
Dyspnoea	2.72%	0.00%	0.00%	4.98%	1.35%	0.29%	0.00%
Gamma-glutamyltransferase increase	1.81%	0.00%	2.94%	7.05%	0.45%	0.00%	0.00%
Hyperglycaemia	0.68%	0.00%	0.00%	4.98%	0.45%	0.00%	0.98%
Leukopenia	8.84%	14.08%	0.00%	0.00%	0.00%	25.22%	0.00%
Neutropenia	26.53%	53.42%	0.00%	0.00%	1.79%	62.03%	5.88%
Stomatitis	0.45%	0.00%	0.00%	8.09%	0.00%	0.58%	6.86%

Abbreviations: ABE, Abemaciclib; CAP, Capecitabine; EVE, Everolimus; EXE, Exemestane; FUL, Fulvestrant; PAL, Palbociclib; RIBO, Ribociclib

Source: ABE-FUL, MONARCH 2; CAP, BOLERO 6; EXE, BOLERO 2; EXE-EVE, BOLERO 2; FUL, MONARCH 2; PAL-FUL, Turner 2015

M.5.2 ET-sensitive

Table 130. Adverse events used in the health economic model, metastatic setting / ET-sensitive

Adverse events	ABE-NSAI	PAL-NSAI	RIBO-NSAI	NSAI	RIBO-FUL	TMX	FUL
Anaemia	6.10%	0.20%	9.00%	1.00%	0.00%	0.00%	1.00%
Diarrhoea	5.50%	5.90%	2.40%	1.00%	3.11%	0.00%	0.00%
Dyspnoea	3.40%	0.00%	6.00%	1.00%	0.00%	2.00%	1.00%
Gamma-glutamyltransferase increase	9.20%	1.40%	2.40%	1.00%	0.62%	0.00%	0.00%
Hyperglycaemia	0.30%	0.00%	10.00%	0.00%	0.00%	0.00%	2.00%
Leukopenia	8.30%	24.80%	21.00%	0.00%	14.08%	0.00%	0.00%
Neutropenia	3.10%	0.00%	7.00%	0.00%	0.00%	0.00%	0.00%
Stomatitis	0.90%	0.20%	2.40%	1.00%	0.00%	5.00%	0.00%

Appendix N. Post discontinuation therapy

Figures below show the post discontinuation therapy for the cohort 1 population.

Summary of Post Discontinuation Therapy
COHORT1 Population
I3Y-MC-JPCF
Data cutoff: 03JUL2023

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DDDM

Parameter	LY2835219-150mg +EDT (N=2555) n(%)	EDT (N=2565) n(%)	Total (N=5120) n(%)
Surgical procedure	60 (2.3)	86 (3.4)	146 (2.9)
Radiotherapy	70 (2.7)	95 (3.7)	165 (3.2)
Systemic therapy			
Overall	2340 (91.6)	2344 (91.4)	4684 (91.5)
Chemo	150 (5.9)	192 (7.5)	342 (6.7)
ALBUMIN HUMAN;PACLITAXEL	0 (0.0)	1 (0.0)	1 (0.0)
AZACITIDINE	1 (0.0)	1 (0.0)	2 (0.0)
CAPECITABINE	70 (2.7)	85 (3.3)	155 (3.0)
CARBOPLATIN	31 (1.2)	35 (1.4)	66 (1.3)
CARBOPLATIN;GEMCITABINE	1 (0.0)	0 (0.0)	1 (0.0)
CARBOPLATIN;PACLITAXEL	1 (0.0)	0 (0.0)	1 (0.0)
CISPLATIN	11 (0.4)	14 (0.5)	25 (0.5)
CISPLATIN;GEMCITABINE	1 (0.0)	0 (0.0)	1 (0.0)
CYCLOPHOSPHAMIDE	15 (0.6)	13 (0.5)	28 (0.5)
CYCLOPHOSPHAMIDE;DOXORUBICIN	1 (0.0)	0 (0.0)	1 (0.0)
CYTARABINE	0 (0.0)	1 (0.0)	1 (0.0)
DAUNORUBICIN	0 (0.0)	1 (0.0)	1 (0.0)
DECITABINE	0 (0.0)	1 (0.0)	1 (0.0)

Abbreviations: N = number of subjects in COHORT1 Population; n = number of subjects in the specified category.
Program Location: /lillyce/qa/ly2835219/i3y mc jpcf/misc10/programs/primary/tfl/cohort1/o cm pdt sum 5 p7882000 t7882005.sas
Output Location: /lillyce/qa/ly2835219/i3y mc jpcf/misc10/output/shared/tfl/cohort1/o cm pdt sum c1.rtf
Data Set Location: /lillyce/qa/ly2835219/i3y mc jpcf/csr5/data/analysis/shared/adam

Summary of Post Discontinuation Therapy
COHORT1 Population
I3Y-MC-JPCF
Data cutoff: 03JUL2023

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DDDM

Parameter	LY2835219-150mg +EDT (N=2555) n(%)	EDT (N=2565) n(%)	Total (N=5120) n(%)
DOCETAXEL	12 (0.5)	25 (1.0)	37 (0.7)
DOXORUBICIN	12 (0.5)	15 (0.6)	27 (0.5)
EPIRUBICIN	3 (0.1)	5 (0.2)	8 (0.2)
ERIBULIN	25 (1.0)	24 (0.9)	49 (1.0)
ETOPOSIDE	0 (0.0)	1 (0.0)	1 (0.0)
FLUOROURACIL	3 (0.1)	5 (0.2)	8 (0.2)
FLUOROURACIL;FOLINIC ACID;OXALIPLATIN	1 (0.0)	0 (0.0)	1 (0.0)
GEMCITABINE	34 (1.3)	32 (1.2)	66 (1.3)
GIMERACIL;OTERACIL;TEGAFUR	2 (0.1)	10 (0.4)	12 (0.2)
HYDROXYCARBAMIDE	0 (0.0)	1 (0.0)	1 (0.0)
IRINOTECAN	1 (0.0)	2 (0.1)	3 (0.1)
IXABEPILONE	0 (0.0)	1 (0.0)	1 (0.0)
METHOTREXATE	3 (0.1)	3 (0.1)	6 (0.1)
MITOMYCIN	2 (0.1)	0 (0.0)	2 (0.0)
MITOXANTRONE	3 (0.1)	0 (0.0)	3 (0.1)
NEDAPLATIN	0 (0.0)	1 (0.0)	1 (0.0)
OXALIPLATIN	1 (0.0)	2 (0.1)	3 (0.1)
PACLITAXEL	54 (2.1)	64 (2.5)	118 (2.3)
SACITUZUMAB GOVITECAN	8 (0.3)	5 (0.2)	13 (0.3)
TEMOZOLOMIDE	1 (0.0)	2 (0.1)	3 (0.1)

Abbreviations: N = number of subjects in COHORT1 Population; n = number of subjects in the specified category.
Program Location: /lillyce/qa/ly2835219/i3y mc jpcf/misc10/programs/primary/tfl/cohort1/o cm pdt sum 5 p7882000 t7882005.sas
Output Location: /lillyce/qa/ly2835219/i3y mc jpcf/misc10/output/shared/tfl/cohort1/o cm pdt sum c1.rtf
Data Set Location: /lillyce/qa/ly2835219/i3y mc jpcf/csr5/data/analysis/shared/adam

Summary of Post Discontinuation Therapy
COHORT1 Population
I3Y-MC-JPCF
Data cutoff: 03JUL2023

Parameter	LY2835219-150mg +EDT (N=2555) n(%)	EDT (N=2565) n(%)	Total (N=5120) n(%)
TESETAXEL	1 (0.0)	1 (0.0)	2 (0.0)
VINCRISTINE	2 (0.1)	0 (0.0)	2 (0.0)
VINORELBINE	10 (0.4)	17 (0.7)	27 (0.5)
Endocrine	2289 (89.6)	2284 (89.0)	4573 (89.3)
AMCENESTRANT	0 (0.0)	1 (0.0)	1 (0.0)
ANASTROZOLE	548 (21.4)	530 (20.7)	1078 (21.1)
BICALUTAMIDE	1 (0.0)	0 (0.0)	1 (0.0)
CAMIZESTRANT	1 (0.0)	0 (0.0)	1 (0.0)
EXEMESTANE	272 (10.6)	321 (12.5)	593 (11.6)
FULVESTRANT	94 (3.7)	161 (6.3)	255 (5.0)
GIREDESTRANT	0 (0.0)	1 (0.0)	1 (0.0)
GONADORELIN	1 (0.0)	0 (0.0)	1 (0.0)
GOSERELIN	242 (9.5)	254 (9.9)	496 (9.7)
LETROZOLE	971 (38.0)	920 (35.9)	1891 (36.9)
LEUPRORELIN	147 (5.8)	154 (6.0)	301 (5.9)
SELECTIVE ESTROGEN RECEPTOR MODULATORS	1 (0.0)	1 (0.0)	2 (0.0)
TAMOXIFEN	652 (25.5)	638 (24.9)	1290 (25.2)
TOREMIFENE	8 (0.3)	3 (0.1)	11 (0.2)
TRIPTORELIN	28 (1.1)	27 (1.1)	55 (1.1)

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Summary of Post Discontinuation Therapy
COHORT1 Population
I3Y-MC-JPCF
Data cutoff: 03JUL2023

Parameter	LY2835219-150mg +EDT (N=2555) n(%)	EDT (N=2565) n(%)	Total (N=5120) n(%)
Other	28 (1.1)	27 (1.1)	55 (1.1)
ATEZOLIZUMAB	4 (0.2)	3 (0.1)	7 (0.1)
DENDRITIC CELLS CYTOKINE INDUCED KILLER CELLS	1 (0.0)	0 (0.0)	1 (0.0)
DENOSUMAB	4 (0.2)	1 (0.0)	5 (0.1)
ETHANOL	1 (0.0)	0 (0.0)	1 (0.0)
IMMUNOTHERAPY	1 (0.0)	1 (0.0)	2 (0.0)
INVESTIGATIONAL DRUG	5 (0.2)	6 (0.2)	11 (0.2)
IODINE (131 I)	0 (0.0)	1 (0.0)	1 (0.0)
OTHER ANTINEOPLASTIC AGENTS	0 (0.0)	1 (0.0)	1 (0.0)
PEMBROLIZUMAB	5 (0.2)	4 (0.2)	9 (0.2)
PERTUZUMAB	7 (0.3)	5 (0.2)	12 (0.2)
PREDNISOLONE	1 (0.0)	1 (0.0)	2 (0.0)
RITUXIMAB	2 (0.1)	0 (0.0)	2 (0.0)
ZOLEDRONIC ACID	1 (0.0)	4 (0.2)	5 (0.1)
Target	111 (4.3)	234 (9.1)	345 (6.7)
ABEMACICLIB	14 (0.5)	76 (3.0)	90 (1.8)
ALPELISIB	6 (0.2)	4 (0.2)	10 (0.2)
BEVACIZUMAB	18 (0.7)	18 (0.7)	36 (0.7)

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Summary of Post Discontinuation Therapy
COHORT1 Population
I3Y-MC-JPCF
Data cutoff: 03JUL2023

Parameter	LY2835219-150mg +EDT (N=2555) n(%)	EDT (N=2565) n(%)	Total (N=5120) n(%)
CAPIVASERTIB	1 (0.0)	0 (0.0)	1 (0.0)
CHIDAMIDE	1 (0.0)	0 (0.0)	1 (0.0)
EVEROLIMUS	9 (0.4)	14 (0.5)	23 (0.4)
FLUZOPARIB	0 (0.0)	1 (0.0)	1 (0.0)
NERATINIB	1 (0.0)	0 (0.0)	1 (0.0)
OLAPARIB	4 (0.2)	5 (0.2)	9 (0.2)
PALBOCICLIB	41 (1.6)	88 (3.4)	129 (2.5)
PERTUZUMAB;TRASTUZUMAB	1 (0.0)	0 (0.0)	1 (0.0)
PROTEIN KINASE INHIBITORS	0 (0.0)	1 (0.0)	1 (0.0)
RIBOCICLIB	22 (0.9)	53 (2.1)	75 (1.5)
TALAZOPARIB	1 (0.0)	4 (0.2)	5 (0.1)
TRASTUZUMAB	10 (0.4)	6 (0.2)	16 (0.3)
TRASTUZUMAB DERUXTECAN	4 (0.2)	8 (0.3)	12 (0.2)
TRASTUZUMAB EMTANSINE	3 (0.1)	0 (0.0)	3 (0.1)
TUCATINIB	1 (0.0)	0 (0.0)	1 (0.0)
VENETOCLAX	0 (0.0)	1 (0.0)	1 (0.0)
XENTUZUMAB	0 (0.0)	2 (0.1)	2 (0.0)
Not coded	1 (0.0)	2 (0.1)	3 (0.1)
FULVESTRANT;PALBOCICLIB	0 (0.0)	2 (0.1)	2 (0.0)

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Parameter	LY2835219-150mg +EDT (N=2555) n(%)	EDT (N=2565) n(%)	Total (N=5120) n(%)
Term to be coded	1 (0.0)	0 (0.0)	1 (0.0)

Abbreviations: N = number of subjects in COHORT1 Population; n = number of subjects in the specified category.
Program Location: /lillyce/qa/ly2835219/i3y mc jpcf/misc10/programs/primary/tfl/cohort1/o cm pdt sum 5 p7882000 t7882005.sas
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Appendix O. AIC and BIC values for IDFS extrapolations, independent distributions

Table 131: AIC and BIC values for IDFS extrapolations - OS IA3 2023 Cohort 1 population

Independent distributions – ABE +ET arm			
Distributions	**AIC**	**Distributions**	**BIC**
Log-logistic	5159.67	Exponential	5165.82
Exponential	5159.97	Log-logistic	5171.36
Gamma	5160.23	Log-normal	5172.90
Generalised gamma	5159.67	Weibull	5172.92
Hazard spline knot 1	5160.23	Gompertz	5173.66
Log-normal	5161.21	Generalised gamma	5177.77
Weibull	5161.23	Gamma	5177.77
Hazard spline knot 2	5161.34	Hazard spline knot 1	5177.99
Gompertz	5161.97	Hazard spline knot 2	5184.73

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; IDFS: invasive disease-free survival.

Table 132: AIC and BIC values for IDFS extrapolations - OS IA3 2023 Cohort 1 population

Independent distributions ET alone			
Distributions	**AIC**	**Distributions**	**BIC**
Hazard spline knot 2	7023.46	Log-logistic	7036.71
Gamma	7024.43	Exponential	7038.34
Generalised gamma	7024.431	Log-normal	7039.21
Log-logistic	7025.01	Weibull	7041.59
Hazard spline knot 1	7025.13	Gamma	7041.98

Log-normal	7027.51	Generalised gamma	7041.98
Weibull	7029.89	Hazard spline knot 1	7042.68
Exponential	7032.49	Gompertz	7046.19
Gompertz	7034.49	Hazard spline knot 2	7046.86

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; IDFS: invasive disease-free survival.

Table 133: AIC and BIC values for OS without distant disease recurrence extrapolations - OS IA3 2023 Cohort 1 population

Independent distributions ABE + ET arm			
Distributions	**AIC**	**Distributions**	**BIC**
Generalised gamma	381.10	Generalised gamma	398.64
Gompertz	786.12	Exponential	793.59
Weibull	786.99	Gompertz	797.81
Log-logistic	787.04	Weibull	798.69
Exponential	787.74	Log-logistic	798.73
Log-normal	788.33	Log-normal	800.02
Hazard spline knot 1	788.67	Hazard spline knot 1	806.21
Gamma	788.95	Gamma	806.49
Hazard spline knot 2	789.22	Hazard spline knot 2	812.60

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; IDFS: invasive disease-free survival.

Table 134: AIC and BIC values for OS without distant disease recurrence extrapolations - OS IA3 2023 Cohort 1 population

Independent distributions ET alone			
Distributions	**AIC**	**Distributions**	**BIC**
Exponential	657.92	Exponential	663.77
Gompertz	658.76	Gompertz	670.46
Weibull	659.42	Weibull	671.12

Log-logistic	659.46	Log-logistic	671.15
Log-normal	660.21	Log-normal	671.91
Hazard spline knot 1	661.00	Hazard spline knot 1	678.56
Hazard spline knot 2	661.21	Gamma	678.94
Gamma	661.39	Generalized Gamma	678.94
Generalized Gamma	661.39	Hazard spline knot 2	684.61

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; IDFS: invasive disease-free survival.

Medicinrådet

Danish Medicines Council
Secretariat
Dampfærgevej 21-23, 3rd floor
DK-2100 Copenhagen Ø