Medicinrådet

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

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. abemaciclib
2. Forhandlingsnotat fra Amgros vedr. abemaciclib
3. Ansøgers endelige ansøgning vedr. abemaciclib

Lilly Danmark A/S (Lilly) har læst udkastet til rapporten vedr. abemaciclib i kombination med endokrin behandling, som adjuvant behandling for patienter med tidlig, høj-risiko, lymfeknudepositiv ER+/HER2- brystkræft og har følgende kommentarer;

Patientpopulationen:
Medicinrådet henviser til den amerikanske SEER-database og skriver i rapporten (side 30) at "Patienternes prognose er relativt god, hvor over 90 % af patienter med tidlig ER+/HER2- brystkræft er i live fem år efter deres diagnose (1). Der findes ikke tilsvarende prognoserater for den højrisikogruppe, der blev randomiseret i monarchE, men den er formentlig lavere." I beskrivelsen af patientpopulationen gør vi opmærksom på, at selvom prognosen for ER+/HER2 brystkræft generelt er god, har patienter som er inkluderet i monarchE-studiet høj risiko for recidiv. Et dataudtræk fra samme SEER-database viser at patienter med HR+, HER2- tidlig brystkræft som opfyldte monarchE klinikopatologiske højrisiko kriterier havde en statistisk signifikant øget risiko for mortalitet i 5-års perioden, sammenlignet med patienter som ikke opfyldte monarchE klinikopatologiske højrisiko kriterier, og havde næsten samme risiko for mortalitet som patienter med tidlig TNBC (2). En anden analyse baseret på data fra US Flat Iron, bekræfter disse fund og viste, at monarchE højrisikopatienter (n = 557) havde signifikant og 3 gange højere risiko for IDFS - og DFRS-hændelser end ikke-højrisikogruppen (n = 3471), efter 5 år (3). Lilly mener derfor, at det er dokumenteret at patienter med højrisiko har en signifikant højere risiko for tilbagefald. At Medicinrådet henviser til en anden patientpopulation, skaber unøjagtighed omkring konteksten af data, og dette bør korrigeres.

Relevansen af IDFS som endepunkt, IDFS og korrelation til OS og umodne OS data
I Medicinrådets vurdering af Trastuzumab i ER+/HER+ tidlig brystkræft (4), blev det hævdet at: "Det overordnede mål med den adjuverende behandling er at mindske risikoen for tilbagefald og dermed mindske risikoen for uhelbredelig brystkræft. Netop derfor er IDFS et standard primært effektmål i brystkræftstudier (da det både belyser frekvensen af tilbagefald og død). IDFS er således i høj grad anerkendt og anvendt som et surrogatendepunkt." Derudover rapporterede Medicinrådet, at "I lyset af den gode prognose for patienter med tidlig HER2+ brystkræft betragter fagudvalget OS som et vigtigt endepunkt snarere end kritisk" (4).

Brugen af surrogat-endepunkter i onkologi er også blevet fremhævet som rimelig og nødvendig af eksperter. I Hudis et al, 2007 (5) nævnes: "The use of a surrogate is reasonable because the relatively long expected survival time for patients, even those with metastatic recurrence after treatment in adjuvant trials, can make it take decades before improvements in OS can reliably be confirmed. Combined with the heterogeneous and somewhat unpredictable natural history of breast cancer, it would not be practical to wait for OS to serve as the primary end point of many adjuvant trials. Sole use of OS could slow the development of improved therapies".

OS indgår i monarchE-studiet som sekundært endepunkt, og der vil over tid genereres data, som viser effekten på overlevelse. IDFS er i forbindelse med en tidligere proces i Medicinrådet anvendt som et vigtigt effektmål, og her nævnes det, at det pågældende lægemiddel vurderes til at have en merværdi, da IDFS-kurverne adskiller sig tidligt og forbliver adskilt – hvilket også gør sig gældende for abemaciclib i monarchE-studiet.

<u>Lilly vil insistere på relevansen af IDFS til højrisiko patienter med tidlig brystkræft bla. grundet den forventede tidshorisont på OS data.</u>

IDFS og korrelation til OS
Medicinrådet henviser til Gyawali B et al 2020 (6): "Korrelationen mellem forbedret IDFS og forbedret overlevelse er dog ikke veletableret (18) ". Gyawali B et al 2020 (6) henviser i sin artikel til DFS (disease free survival) og ikke til IDFS. Det fremstår derfor som svært unøjagtigt, at Medicinrådet henviser til en artikel, som faktisk ikke dokumenterer deres egen påstand. Videre har Medicinrådet selv, i en tidligere vurdering (neratinib til behandling af ER+ og HER2+ brystkræft (7) , grundigt beskrevet forskellen på DFS og IDFS. Det er vigtigt at påpege at uanset, at det ikke er dokumenteret at IDFS *ikke korrelerer* med OS, betyder det ikke implicit, at IDFS og OS *ikke potentielt har en korrelation (8)*.

Umodne OS data
Medicinrådet specifiserer selv i rapporten, hvordan abemaciclibs fordel målt ved både IDFS og DRFS er blevet påvist ud over den 2-årige behandlingsperiode. Medicinrådet nævner, at der findes yderligere data fra en 42 måneders opfølgningsanalyse for både IDFS og DRFS, men at denne analyse kun er baseret på ITT-populationen. Lilly ønsker at understrege, at denne analyse også er udført på kohorte 1 populationen, og er publiseret så langt tilbage som december 2022 (8). Analysen bekræfter fundende i ITT populationen og viser, at armene bliver yderligere adskilt til fordel for abemaciclib. Samme publikation viser, at antallet af patienter som lever med

metastatisk sygdom er dobbelt så høj i komparatorarmen (n=249) sammenlignet med abemaciclib+ET armen (n=125) ved 42 måneder.

Tilgængelige data fra monarchE med op til 42 måneders opfølgning viser konsekvent en uddybende forskel til fordel for abemaciclib gennem IDFS og DRFS (og nummerisk ved OS). Medicinrådet påpeger, at DRFS er et specielt vigtigt endepunkt, da dette endepunkt ser specifikt på overlevelse uden fjernmetastaser. Der er en etableret konsensus om, at fjernmetastaser er uforenelig med helbredelig sygdom. De tilgængelige surrogatdata peger udelukkende til fordel for abemaciclib, og usikkerheden, som Medicinrådet tillægger umodne OS-data, virker overdrevet og ubalanceret. Det burde ikke medføre en komplet afvisning af en sundhedsøkonomisk analyse.

Vurdering af livskvalitet
Medicinrådet påpeger, at QoL data først er målt tre måneder efter randomisering. Lilly anerkender, at det med nutidens viden havde været optimalt at måle QoL hyppigere i behandlingsstarten, men vi anerkender ikke, at det bør overskygge effektdata. Desuden understøtter den relativt beskedne forskel i drop out rater mellem patienterne i ET+abemaciclib-armen (6,5%) og ET-armen (1,1%), at bivirkningerne har været forudsigelige og håndterbare.

Post-study treatment med endokrin behandling
Medicinrådet påpeger, at "Det er uklart, hvor stor en andel af patienterne i begge arme, der stadig modtager endokrin behandling på tidspunktet for data udtrækket, eller om der er forskel i endokrin compliance mellem de to arme". Lilly vil gerne påpege, at disse data er tilgængelige i bilag 5, tabel 12 i udkast til rapporten, hvor det er klart, at endokrin-compliance mellem de to arme på tidspunktet for dataudtrækket er balanceret.

Scanning i monarchE afspejler klinisk praksis i Danmark
Medicinrådet hævder, at "der var ikke krav om diagnostisk scanning ved randomisering i modsætning til dansk klinisk standard." Lilly noterer, at det er faktuelt forkert at hævde, at det er gældende dansk klinisk standard. Danske onkologer bekræfter, at der er divergerende rutiner klinikkerne imellem, men at alle patienter scannes ved diagnose og igen ved tegn til sygdomsprogression. I monarchE blev alle patienter scannet for sygdom før randomisering, omend ikke nødvendigvis ved randomisering. Dette gav en tidshorisont på op til maks. tre måneder til påbegyndt behandling, hvilket afspejler forholdene i de danske klinikker.

Afvisning af en sundhedsøkonomisk evaluering af abemaciclib
Medicinrådet vurderer, at usikkerheder i datagrundlaget er for store til at kunne udføre en sundhedsøkonomisk analyse. Usikkerhederne bliver omtalt i rapporten, men usikkerhedernes indvirkning på resultatet (ICER/ICUR) bliver ikke fremlagt for Medicinrådet i en sundhedsøkonomisk analyse. Usikkerheder i data og antagelser bør håndteres ved følsomhedsanalyser samt modellering af forskellige scenarier.

Udsagnet om, at de leverede kliniske data ikke er tilstrækkelige til en troværdig sundhedsøkonomisk vurdering, er ikke korrekt. Grundige HTA-vurderinger er blevet udført af myndigheder som NICE, SMC, TLV, HILA/FIMEA og NOMA. Lilly blev ikke informeret forud for modtagelse af udkastet til rapporten om, at den sundhedsøkonomiske evaluering ville blive udeladt. Dette kunne med fordel have været drøftet med Lilly undervejs i processen for at finde løsninger.

Lilly vil i øvrigt gerne påpege, at abemaciclib nu er tilskudberettiget til behandling af højrisiko ER+/HER2-, lymfeknude positiv tidlig brystkræft, efter positiv anbefaling i Sverige (9) , Scotland, England (10) in 2022 og Finland i 2023 (11) blandt flere.

Afsluttende bemærkning
Lilly insisterer på relevansen af IDFS til højrisiko patienter med tidlig brystkræft. Lilly anmoder Medicinrådet om at overveje det etiske aspekt i at afvente OS data grundet den ukendte tidshorisont og sandsynlige underbehandling af højrisikopatienter med yderligere dårlig prognose til følge. Eventuelle usikkerheder burde have været evalueret ved Medicinrådets vurdering af den sundhedsøkonomiske analyse.

Med venlig hilsen

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

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Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

27. april 2023

DBS/BMC

Forhandlingsnotat

Dato for behandling i Medicinrådet	24.05.2023
Leverandør	Eli Lilly Danmark A/S
Lægemiddel	Verzenios (abemaciclib)
Ansøgt indikation	Abemaciclib i kombination med endokrin behandling er indiceret til adjuverende behandling af voksne patienter med hormonreceptor (HR)-positiv, human epidermal vækstfaktor receptor 2 (HER2) -negativ, tidlig brystcancer med positiv lymfeknude spredning med høj risiko for recidiv.
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har følgende aftalepris på Verzenios (abemaciclib):

Tabel 1: Aftalepris

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP (DKK)	Rabatprocent ift. AIP
Verzenios	50 mg	28 stk.	9.406,14	[redacted]	[redacted]
Verzenios	100 mg	28 stk.	9.406,14	[redacted]	[redacted]
Verzenios	100 mg	56 stk.	18.483,35	[redacted]	[redacted]
Verzenios	150 mg	28 stk.	9.406,14	[redacted]	[redacted]
Verzenios	150 mg	56 stk.	18.483,35	[redacted]	[redacted]

Aftaleforhold

Den nuværende aftale løber indtil 31.12.2023 med mulighed for at forlænge i 12 måneder og med mulighed for prisregulering.

Et nyt udbud sættes i gang når behandlingsvejledningen er opdateret.

Det forventes, at den nuværende aftale forlænges med 2-3 måneder, så en ny aftale på baggrund af den opdaterede behandlingsvejledning kan starte i foråret 2024.

Konkurrencesituationen

[redacted]

I dag indgår Verzenios i Medicinrådets behandlingsvejledning vedrørende CDK4/6- hæmmere til ER+/HER2- lokalt fremskreden eller metastatisk brystkræft.

[redacted]

I nedenstående tabel ses lægemiddeludgiften per år for Verzenios med den nuværende pris, som er givet i forbindelse med den aftale, der løber frem til den 31.12.2023.

Til sammenligning er prisen for et års behandling med Kisqali indenfor indikationen CDK4/6- hæmmere til ER+/HER2- lokalt fremskreden eller metastatisk brystkræft

Tabel 1: Sammenligning af lægemiddeludgifter

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Lægemiddeludgift pr. år (SAIP, DKK)
Verzenios (abemaciclib)	150 mg	56 stk.	300 mg daglig	[redacted]
Kisqali (ribociclib)	200 mg	60 stk.	600 mg daglig i 21 dage efterfulgt af 1 uges pause i en 28 dages cyklus.	[redacted]

Status fra andre lande

Land	Status	Kommentar	Link
Norge	Ikke anbefalet		Abemaciclib (Verzenios) - Indikasjon III (nyemetoder.no)
England	Anbefalet		1 Recommendations | Abemaciclib with endocrine therapy for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence | Guidance | NICE

Konklusion

[redacted]

Updated Application for the assessment of abemaciclib (Verzenios) for high-risk HR+/HER2-, node-positive early breast cancer

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1. Basic information

Contact information	
Name	**Mai Juul Børgesen**
Title	Pricing & Access Manager Denmark
Phone number	+45 31141804
E-mail	borgesen_mai_juul@lilly.com
Name	**Astrid Torstensson**
Title	Senior Clinical Research Scientist, Oncology
Phone number	+468-7378800 (office) | +46 767 72 57 88 (mobile)
E-mail	torstensson_astrid@lilly.com

Overview of the pharmaceutical	
Proprietary name	Verzenios®
Generic name	Abemaciclib
Marketing authorization holder in Denmark	Eli Lilly Denmark A/S
ATC code	L01XE50
Pharmacotherapeutic group	CDK 4/6 inhibitor
Active substance(s)	Abemaciclib
Pharmaceutical form(s)	Oral therapy
Mechanism of action	Abemaciclib blocks the activity of enzymes CDK4 and CDK6, which play a key role in regulating the way cells grow and divide. In some cancers, including hormone receptor-positive (HR+) and human epidermal receptor 2 negatives (HER2-) breast cancer, the activity of CDK 4 and CDK6 is increased, which helps the cancer cells to multiply uncontrollably. By blocking CDK4 and CDK6, abemaciclib in combination with adjuvant endocrine therapy has been shown to improve invasive disease-free survival in patients with HR+/HER2-, node-positive early breast cancer at high risk of early recurrence
Dosage regimen	300 mg daily (150 mg, 1 tablet BID). A 2 years stopping rule is applied.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, 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

Overview of the pharmaceutical	
Other approved therapeutic indications	Advanced breast cancer
Will dispensing be restricted to hospitals?	Yes
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.
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
Orphan drug designation	No

2. Abbreviations

Abbreviation term	Definition
1L	First-line
AE	Adverse events
BC	Breast Cancer
BID	Twice a day
CDK	Cyclin-dependent kinase
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
DBCG	Danish Breast Cancer Group
DMC	Danish Medicine Council
DRFS	Distant relapse-free survival
eBC	Early Breast Cancer
ER	Estrogen Receptor
ESMO	Society of Medical Oncology
ET	Endocrine therapy
FACIT-F	Functional Assessment of Chronic Illness Therapy - Fatigue
FACT-B	Functional Assessment of Cancer Therapy - Breast
FACT-ES	Functional Assessment of Cancer Therapy – Endocrine Symptoms
HER2	Human epidermal growth factor receptor 2
HR	Hormone receptor
HRQoL	Health-related quality of life
IDFS	Invasive disease-free survival
ITC	indirect treatment comparisons
IWRS	interactive, web-based randomisation scheme
MID	Minimally important difference
PgR	Progesterone receptor
Rb	Retinoblastoma

OD	Once a day
SLR	Systematic literature review
TEAE	Treatment-emergent adverse events
TNM	Tumour size, nodal status, and identification of distant metastasis

3. Tables and Figures

3.1 List of Tables

4. Summary

4.1 Indication

This single technology assessment relates to abemaciclib in combination with endocrine therapy (ET) for the adjuvant treatment of HR+/HER2-, node-positive early breast cancer (eBC) at high risk of recurrence. Patients are considered high risk when they have <4 positive lymph nodes or 1-3 positive lymph nodes with either Grade 3 or < 5cm tumour size.

In Denmark, approximately 500 patients are newly diagnosed with high-risk HR+/HER2-, node-positive eBC [1] with high risk of recurrence.. Currently the standard of care (SoC) for patients with high-risk HR+/HER2-, node-positive eBC is chemotherapy , radiotherapy and extended adjuvant ET. The ET regimens used as SoC in Denmark consists of tamoxifen, letrozole, anastrozole, and exemestane that all are endocrine therapies used for patients expressing hormone receptors to inhibit the stimulations of oestrogen hormones involved in tumour growth [1] [2]. The choice of ET depends on the patient's menopausal status, pre-menopausal women and men are recommended to receive tamoxifen and postmenopausal women are recommended to receive treatment with an aromatas inhibitor (AI) either letrozole, anastrozole, or exemestane.

Despite treatment for eBC being of curative intent, unfortunately, 30 % of patients with HR+ eBC will relapse following primary treatment. There is therefore an unmet need for novel targeted agents that are effective in reducing the recurrence risk of invasive or distant disease, and the subsequent associated mortality and decreasein health-related quality of life (HRQoL). In 2020, trastuzumab was recommended by the DMC as a targeted biological treatment for patients with HER2+ early breast cancer [3]. This targeted treatment has been proven to reduce the risk of cancer returning after surgery in early-stage HER2+ cancer. In comparison, there are no similarly effective targeted therapies available for patients with high-risk HR+/HER2-, node-positive eBC other than the recommended SoC.

4.2 The pharmaceutical

Abemaciclib is a CDK4/6 inhibitor active against the activity of enzymes CDK4 and CDK6, which play a key role in regulating the way cancer cells grow and divide in breast cancer [4]. Abemaciclib is currently recommended in Denmark as a possible standard treatment for the first and second-line treatment of locally advanced or metastatic ER + / HER2- breast cancer in combination with aromatase inhibitor or fulvestrant [4-6] [7].
Moreover, abemaciclib has recently received positive opinion from the Committee for Medical Products for Human Use (CHMP) confirming the approved amendment of the Marketing authorisation, extending the label of abemaciclib to adjuvant use [8] [9]. Results from the randomized, Phase III, monarchE- study showed a significant reduction in disease recurrence for patients with HR+/HER2-, node positive, early breast cancer. This submission is based on the above study [2].

4.3 Comparator

As mentioned above, the SoC in monarchE trial matches the Danish clinical practice [1] and is in line with the DBCG guidelines [10]. For this reason, the monarchE comparator arm is representative for the Danish clinical practice definition of SoC.

4.4 Efficacy and safety endpoints

Patients in the monarchE trial were randomly assigned to receive either abemaciclib with ET or ET alone. A 1:1. randomisation was performed using an interactive, web-based randomisation scheme (IWRS) and was stratified according to:

- Prior treatment (neoadjuvant chemotherapy versus adjuvant chemotherapy versus no chemotherapy)
- Menopausal status (premenopausal versus postmenopausal, as determined by investigator and based on patient's status at the time of diagnosis)
- Region (North America and Europe versus Asia versus Other)

The primary endpoint of the monarchE trial was invasive disease-free survival (IDFS) as defined by the 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 [39].

IDFS is considered to be a particularly relevant endpoint for comparing treatment regimens for the management of early breast cancer, where maintaining a disease-free state, i.e., a functional cure, is the primary goal of treatment, this endpoint have also been used in previous assessment for pertuzumab in combination with trastuzumab as adjuvant treatment for HER2+ eBC [3]. Secondary endpoints include distant relapse-free survival (DRFS), overall survival without distant recurrence (OS), and Health-Related Quality of Life (HRQoL) as measured by the Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F), Functional Assessment of Cancer Therapy - Breast (FACT-B), Functional Assessment of Cancer Therapy - Endocrine Symptoms (FACT-ES), and European Quality of Life 5 Dimension 5 Level Version (EuroQOL EQ-5D-5L).

The efficacy for abemaciclib plus adjuvant endocrine therapy versus adjuvant endocrine therapy alone in the ITT population including both Cohort 1 and Cohort 2. Eligibility for Cohort 1 was tumour involvement in ≥4 ipsilateral axillary lymph nodes (ALNs), or pathological tumour involvement in 1–3 ALNs, alongside Grade 3 disease and/or a primary tumour size of ≥5 cm, which are aligned with the overall continuum of factors used to identify high risk of recurrence in Danish clinical practice. Cohort 2 was enrolled at a later stage with eligibility based solely on Ki-67 as per regulatory recommendation from FDA. Ki-67 is not included in the EMA approved label and is very limited used in Danish clinical practice. Moreover, Cohort 1 included 91% of the ITT population. As such, the generalizability of monarchE to Danish clinical practice in terms of the definition of high risk of recurrence is greatest for Cohort 1. Hence, results from Cohort 1 are used to inform this application.

In the monarchE study, the combination of abemaciclib and ET reduced the risk of developing invasive disease by 32.0% (stratified HR=0.680, 95% CI: 0.572, 0.808) versus ET alone for the Cohort 1 population. The same was true for DRFS where abemaciclib plus ET showed a 33.1% (stratified HR HR=0.669, 95% CI: 0.554, 0.809) reduction in the risk of developing distant relapse. The endpoint OS did not show a significant difference due to immature data. It should, however, 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 [11-13]. Considering that patients may first spend several years in the eBC setting before progressing to metastatic breast cancer, a trial long enough to capture OS would not be ethical possible. This would mean that a randomised controlled trial (RCT) trial with a timeframe of >5 years had to be done where some of the patients would not receive the optimal treatment. This would not be justifiable and would contradict the ethical principles when conducting clinical data. The endpoint of HRQoL data reflected that patient would maintain their health status and abemaciclib plus ET was a tolerable treatment.

The abemaciclib plus ET regimen demonstrated tolerability in the monarchE study. The median duration of exposure was similar between the two treatment arms, 23.7 months for abemaciclib plus ET vs. 23.8 months for ET alone. During the study period, 93.6% in the abemaciclib plus ET arm and 88.8% in the ET arm experienced at

least one treatment-emergent adverse event (TEAE). Patients did generally experience more serious adverse events in the abemaciclib plus ET arm than the ET arm alone. Patients discontinued treatment due to AEs were 515 patients in the abemaciclib plus ET arm. Of these patients, 181 discontinued all study treatment due to an AE, compared with 30 patients discontinuing in the ET alone arm. The most common TEAE in the abemaciclib plus ET arm leading to discontinuations was diarrhoea, with [redacted] of patients reporting the adverse event (Grade I or II).

4.5 Structure of the economic analysis

A five state Markov model informed the cost utility analysis (CUA). Cost and outcomes were calculated over a lifetime horizon (49 years). The five health states were IDFS, non-metastatic recurrence, remission, metastatic recurrence, and death. A maximum treatment duration of two years was assumed for ABE (150mg) and five years for physicians' choice ET (up to a maximum of 10 years). Relative efficacy of the ET alone arm was directly informed by the monarchE trial. The CUA was from a Danish restricted societal perspective.

The model uses the latest data cut from additional follow-up one (AFU1) with median follow-up of 27 months specifically for Cohort 1 [14]. Resource use included drug acquisition and administration, best supportive care, adverse events, indirect cost, hospitalisations, post-progression therapies and associated resources in the metastatic health state. Unit costs were derived from national sources and previous health technology appraisals. Health state utility values were applied from the monarchE trial and literature sources. The outcomes of the CUA included health state specific total discounted costs and QALYs, cost per QALY, cost per LYs. Uncertainty in the model outcomes was tested through one-way sensitivity, probabilistic, and scenario analyses.

4.6 Sources for the relative efficacy of the economic model

A summary of the sources of relative efficacy is presented here per health state:

- iDFS: monarchE Cohort 1 APRIL 2021 DCO [14].
- Non-metastatic recurrence: monarchE Cohort 1 APRIL 2021 DCO and Literature TA632, TA612 and TA569
- Remission: Hamilton et al. (2015) [15]
- OS without distant recurrence (OS) : monarchE Cohort 1 APRIL 2021 DCO data [14].
- Metastatic recurrence with ET-resistant pathway, TA725 [16]
- Metastatic recurrence with ET-sensitive pathway, TA763 [17]

4.7 Results of Economic analysis

For the HR+, HER2-, node-positive, high risk EBC population modelled, the total discounted costs incurred over a 49-year time horizon were 637.719 kr. for ABE + ET and 332.700 kr. for ET alone. The total discounted QALYs were 12,47 for ABE + ET and 11.25 for ET alone. For the ABE + ET arm higher LYs and QALY gains were observed due to estimated improvements in IDFS. A lower proportion of patients treated with ABE + ET experienced a distant recurrence. Compared to ET alone, the CUA result estimated that ABE + ET has higher QALYs and higher costs, resulting in an incremental cost utility ratio of 250.016 kr./QALY and 114.313 kr./LY.

5. The patient population, the intervention and choice of comparator(s)

5.1 The medical condition and patient population

5.1.1 Pathophysiology and epidemiology of breast cancer

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 [18]. 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 [18, 19]. The 5-year survival for patients with BC is approximately 90 % [18]. Today 72,193 Danish women are living with the diagnosis of BC [20].

Breast cancer occurs to genomic instability caused by defects in DNA damage repair, transcription, DNA replication, telomere maintenance, and mitotic chromosome segregation [21]. 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, 22].

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 [23]. 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) [24-26]. These features are assigned individual scores, which are then combined to identify the stage (Stage 0-IV) [27].

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 [28]. Breast cancer incidence is strongly age-dependent, with more than 80% of cases occurring in women over the age of 50 [29]. 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 [30].

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 [31].

Based on the above estimations and on the Danish Health and Medicines Authority reports of the last few years [32-36] (please see Table 1), it is expected that around 3.200 patients per year will have HR+/HER2- BC. Moreover, based on Danish clinical experts [1] and on a Real World Evidence report from Norway [37], 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 [1].

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

Year	Year, 2015 [36]	Year, 2016 [32]	Year, 2017 [33]	Year, 2018 [34]	Year, 2019 [35]
Observed Incidence in Denmark	3.242	3.305	3.329	3.399	3.471
Observed Prevalence in Denmark	43.767	45.121	46.423	47.712	49.091

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 [32-36]. 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 [22]. Estimates for 2020 and 2021 are not available at the time of submission.

As no report was published yet by the Danish Health and Medicines Authority [32-36] 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 based on the latest figures reported in the DBCG report for 2020 [10]. According to this document, 3.252 patients were diagnosed in 2020 with HER2 negative BC. 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 2015-219 presented in Table 1. The estimated number of incident patients in the next five years is presented in Table 2.

Of these patients, [redacted]% is expected to be high-risk patients [1, 37]. 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	2022	2023	2024	2025	2026
Expected incident HR+ HER2 negative BC patients in DK [10]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Year	2022	2023	2024	2025	2026
Expected incident HR+ HER2 high-risk patients in DK	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5.1.2 Patient populations relevant for this application

The population of interest for this submission is patients with a high-risk for recurrence that are HR+/HER2−, node-positive eBC in an adjuvant setting. Eli Lilly does not envision abemaciclib to replace the current standard of care, rather abemaciclib should be given in combination with endocrine therapy after adjuvant chemotherapy, if indicated.

Danish clinical experts have confirmed that the definition of high-risk eBC patients in Denmark [38] is in line with the definition in the monarchE trial and the approved EMA indication [8]. 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 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 EMA have not included ki67 in the approved indication.

5.2 Current treatment options and choice of comparator(s)

5.2.1 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] expression, HER2 expression, and gene expression prognostic panels [or multi-gene assays]) are now increasingly important in determining prognosis and response to treatment [26].

5.2.1.1 Danish treatment guidelines

The 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 performed by the DBCG.

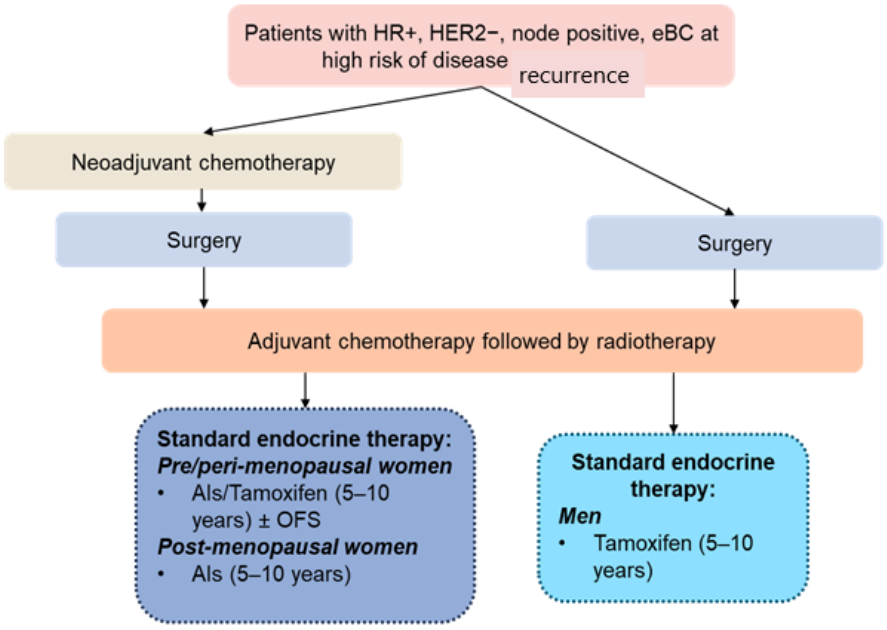
The DBCG recommends surgery and breast radiotherapy as standard treatment for patients with eBC[10]. Patients with eBC should undergo breast-conserving surgery and appropriate (neo)adjuvant therapy as a treatment for their disease unless significant comorbidity precludes surgery. Prior to surgery, neoadjuvant chemotherapy may be considered as an option to shrink tumor size to allow surgery with curative intent, if chemotherapy is indicated [39].

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 [30].

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 [30]. 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 [30]. Additionally, bisphosphonates (zoledronic acid) may be offered as add-on adjuvant therapy for postmenopausal women with node-positive invasive breast cancer [30]. 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 [40]



Abbreviations: AIs: aromatize inhibitors; HER2–: human epidermal growth factor receptor-2 negative; HR+: hormone receptor-positive; OFS: ovarian function suppression.
Source: St Gallen guidelines [40].

5.2.1.2 International guidelines

Table 4 and

Figure 2, present a summary of treatment recommended by existing international guidelines from the European Society of Medical Oncology (ESMO) [41].

Table 4. International treatment guidelines applicable in the Europe

Region/ country	Guideline	Recommendation	Considerations for specific groups
Europe	ESMO [42]	**HR+, HER2-**: ESMO recommends ET, with or without chemotherapy for the adjuvant treatment of patients	**Women** • **Pre-menopausal**: Tamoxifen is recommended for five to ten years as standard of care. Among those patients with a high-risk of disease recurrence, the

with HR+, HER2- EBC. Chemotherapy is generally recommended for patients at higher risk of recurrence (e.g., high tumour burden).

guideline recommends considering replacement of tamoxifen with an AI in combination with OFS.

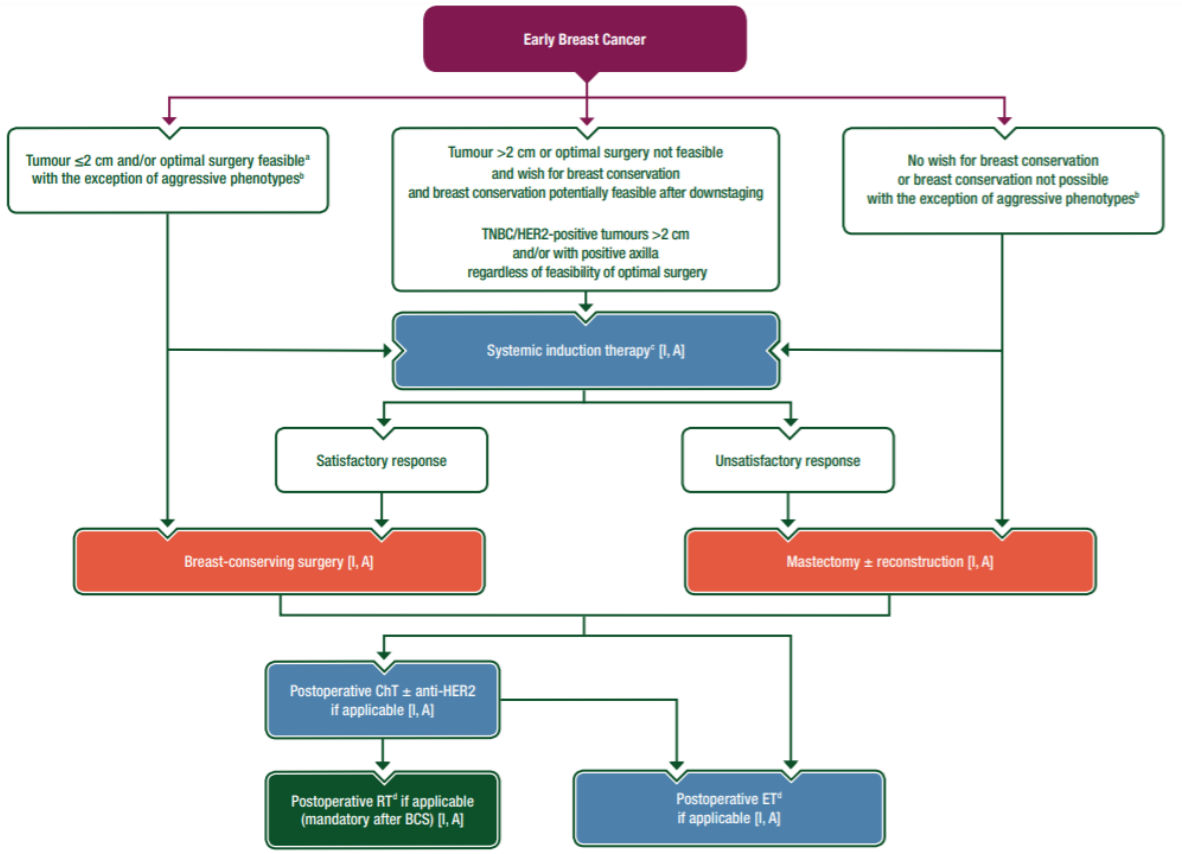
- **Post-menopausal**: AIs and tamoxifen are considered standard treatments. The AIs (NSAI or exemestane) can be used upfront or after two to three years of tamoxifen. Letrozole or anastrozole can be used as extended adjuvant therapy, after five years of tamoxifen. Extended adjuvant therapy with AIs (i.e., more than five years of AIs) is associated with only a minimal benefit.

Men

- Tamoxifen is the standard adjuvant ET in male breast cancer patients.
- If a strong contraindication exists for the use of tamoxifen, a combination of an AI plus LHRH agonist may be considered, but its higher toxicity must be discussed with the patient to avoid compliance issues.
- An AI alone should not be used as adjuvant ET in male breast cancer patients.

Abbreviations: AI: aromatase inhibitor; EBC: early breast cancer; ESMO: European Society for Medical Oncology; ET: endocrine therapy; GNRH: gonadotropin-releasing hormone; HER2-: human epidermal growth factor receptor 2-negative; HR+: hormone receptor-positive; LHRH: luteinizing hormone-releasing hormone; NSAI: non-steroidal aromatase inhibitor; OFS: ovarian function suppression

Figure 2 Early breast cancer treatment algorithm [41]



Abbreviations: [a] Biology that requires ChT (TNBC, HER2-positive, luminal B-like), to assess response and prognosis and eventually decide on postoperative therapies, should preferentially receive preoperative ChT.

[b] Aggressive phenotypes: TNBC or HER2-positive breast cancer.

[c] If ChT is planned, it should all be given as neoadjuvant.

[d] Concomitant postoperative RT, postoperative ET and anti-HER2 therapy.

BCS, breast-conserving surgery; ChT, chemotherapy; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; RT, radiotherapy, TNBC, triple-negative breast cancer

5.2.1.2.1 Unmet need

Despite treatment for eBC being of curative intent, regrettably, 30 % of patients with HR+ eBC will relapse following primary treatment. There is therefore an unmet need for novel targeted agents that are effective in reducing the recurrence of invasive or distant disease, and the subsequent associated mortality and decreased in health-related quality of life (HRQoL). Effective eBC treatment that can reduce the risk of recurrence may therefore reduce the incidence of, and protect patients from, the substantial burden of advanced and incurable metastatic disease.

This unmet need is heightened by a historical lack of new treatments for patients with HR+/HER2− eBC with high risk of recurrence, particularly in comparison to other breast cancer subtypes, such as HER2+ eBC. In 2018, trastuzumab was recommended by the DMC as a targeted biological treatment for patients with HER2+ early breast cancer. This targeted treatment has been proven to reduce the risk of cancer returning after surgery in early-stage HER2+ cancer.

In comparison, there are no similarly effective targeted therapies available for patients with HER2- eBC. Other than the recent recommendation of add-on adjuvant treatment with bisphosphonates (zoledronic acid), alongside ET, for some postmenopausal women [30], chemotherapy, radiotherapy, and/or ET have remained the standard of care for these patients for over a decade. There remains an unmet need for the introduction of novel, more effective treatments to help to prevent recurrence and progression to advanced stages of the disease.

5.2.2 Choice of comparator(s)

The comparator was selected based on the current treatment guidelines recommended by the Danish Breast Cancer Group (DBCG) [10] and validated by Danish clinical experts [1]. DBCG guidelines recommend that following surgery, adjuvant treatment such as chemo-therapy 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. Pre-menopausal women and men are offered Tamoxifen as SoC, with or withoutovarian 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 [1]:

- 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.

5.2.3 Description of the comparator(s)

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 [43-45]. These four types of ET have been confirmed to be relevant in treatment of high-risk HR+/HER2-, node-positive eBC by Danish clinicians [1].

Table 5. Description of tamoxifen

Subject	Description
Generic name (ATC-code)	Tamoxifen (L02BA01)
Mode of action	Inhibits the stimulations of estrogen hormones involving in tumor growth.
Pharmaceutical form	Tablets/Film-Coated Tablets
Posology	20 mg orally OD
Method of administration	Oral
Treatment duration / Criteria for end of treatment:	5-10 years, if no progression or unacceptable toxicity
Need for diagnostic or other test	The precent of ER must be confirmed using validated examinations by a pathologist
Packaging	Mylan® 20mg, 100 pcs. tablets – Each tablet contains 20mg tamoxifen Sandoz® 20mg, 100 pcs. coated tablets (blister) – Each tablet contains 20mg tamoxifen

Abbreviations: OD, Once a day.

Table 6. Description of Letrozole

Subject	Description
Generic name (ATC-code)	Letrozole (L02BG04)[44]
Mode of action	Aromatase inhibitor. Inhibits the stimulations of estrogen hormones involving in tumor growth.
Pharmaceutical form	Tablets/Film-Coated Tablets
Posology	2.5 mg orally OD
Method of administration	Oral
Treatment duration / Criteria for end of treatment:	5 years, if no progression or unacceptable toxicity
Need for diagnostic or other test	The precent of ER must be confirmed using validated examinations by a pathologist

Subject	Description
Packaging	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)

Table 7. Description of Anastrozole

Subject	Description
Generic name (ATC-code)	Anastrozole (L02BG03)[45]
Mode of action	Aromatase inhibitor. Inhibits the stimulations of estrogen hormones involving in tumor growth.
Pharmaceutical form	Tablets/Film-Coated Tablets
Posology	1 mg orally OD
Method of administration	Oral
Treatment duration / Criteria for end of treatment:	5 years, if no progression or unacceptable toxicity
Need for diagnostic or other test	The precent of ER must be confirmed using validated examinations by a pathologist
Packaging	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)

Table 8. Description of Exemestane

Subject	Description
Generic name (ATC-code)	Exemestane (L02BG06)[43]
Mode of action	Aromatase inhibitor. Inhibits the stimulations of estrogen hormones involving in tumor growth.
Pharmaceutical form	Tablets/Film-Coated Tablets
Posology	25 mg orally OD
Method of administration	Oral
Treatment duration / Criteria for end of treatment:	5 years, if no progression or unacceptable toxicity
Need for diagnostic or other test	The precent of ER must be confirmed using validated examinations by a pathologist
Packaging	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)

5.3 The intervention

Abemaciclib is an oral therapy administrated 150 mg film-coated tablets BID. Currently, abemaciclib is recommended for treatment of HR+/HER2- advanced/metastatic BC (aBC)[5]. 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 [8].

Abemaciclib is a potent, and selective small-molecular inhibitor of CDK4 and CDK6 [46]. CDKs are a family of enzymes that regulate the progression of the cell cycle through the G1 (growth), S (DNA synthesis), G2 (growth), and M (mitosis) phases. CDKs and cyclins interact at 'checkpoints' between each phase, to tightly control the orderly progression of the cycle [47]. The cyclin D-CDK4 and 6 complexes promote phosphorylation of the retinoblastoma (Rb) tumor-suppressor protein, initiating a sequence of events that allows the cell to proceed to the S phase and continue through the cell cycle, ultimately promoting cell division and proliferation [48].

As an inhibitor of CDK4 and 6, abemaciclib prevents the phosphorylation of the Rb protein, thereby blocking the progression from G1 phase into S phase of the cell cycle. By inhibiting DNA synthesis, cell cycle arrest is induced, and cell proliferation and tumor growth are suppressed [49].

In the clinical trial, monarchE [2], the combination of abemaciclib plus ET has been shown to reduce the risk of developing an invasive disease-free survival (IDFS) event with 32 % compared to ET alone. This result indicates a meaningful improvement for patients with HR+/HER2−, node-positive, eBC at high-risk of recurrence [2]. An efficacy summary is provided in Table 9 and further details can be found in Appendix D Efficacy and safety results per study.

Table 9. Description of abemaciclib (Verzenios®)

Subject	Description
Generic name (ATC-code)	Abemaciclib (L01XE50)
Mode of action	Abemaciclib, blocks the activity of enzymes CDK4 and CDK6, which play a key role in regulating the way cells grow and divide. In some cancers, including hormone receptor positive (HR+) and human epidermal receptor 2 negative (HER2-) breast cancer, the activity of CDK 4 and CDK6 is increased, which helps the cancer cells to multiply uncontrollably. By blocking CDK4 and CDK6, abemaciclib in combination with adjuvant endocrine therapy has shown to improved invasive disease-free survival in patients with HR+/HER2-, node-positive early breast cancer at high-risk of early recurrence
Pharmaceutical form	Film-Coated Tablets
Posology	300 mg orally (two 150mg tablets) BID
Method of administration	Oral
Should the pharmaceutical be administered with other medicines	No
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 [5].
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. Before treatment initiation, absolute neutrophil count [5].
Need for diagnostic or other test	No

Abbreviations: BID: twice a day; SmPC: Summary of product characteristic; ALT: Alanine aminotransferase; AST: Aspartate aminostransferase

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

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 [50].

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 [2]. 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 [1] [50].

6.2 List of relevant studies

For full detailed information on MonarchE study characteristics of the included studies, please consult ***Appendix B Main characteristics of the included***

Table 10. presents an overview of all studies investigating abemaciclib in breast cancer.

Table 10. New or Ongoing Clinical Trials of Abemaciclib in Breast Cancer

Trial Alias	Treatment Arms	Study Design	Disease Studied	Primary Outcome Measure	NCT Number/Status
Phase 4					
I3Y-MC-JPCU[9]	ABE FULV Standard chemotherapy	Open-label	HR+, HER2- MBC	ORR	NCT04031885 Terminated
I3Y-MC-JPCX	ABE NSAI	Open-label	MBC	PFS	NCT03988114 Withdrawn
I3Y-IN-JPEC 17782	ABE NSAI FULV	Open-label	Breast Neoplasms Neoplasm Metastasis	Safety	NCT04707196 Recruiting
Phase 3					
eMonarcHER I3Y-MC-JPCW[10] 17384	ABE + ET PBO + ET	Randomized double-blind	Breast Neoplasms	IDFS	NCT04752332 Active, not recruiting

2020-004035-24					
MONARCH 3[11] I3Y-MC-JPBM	ABE + NSAI (ANAS or LET) PBO + NSAI (ANAS or LET)	Randomized double-blind	HR+, HER2-negative, locoregionally recurrent or MBC	PFS	NCT02246621 Active, not recruiting
MONARCH 2[12,13] I3Y-MC-JPBL	ABE + FULV PBO + FULV	Randomized double-blind	HR+, HER2-negative inoperable locally advanced or MBC	PFS	NCT02107703 Active, not recruiting
monarchE[14-20] I3Y-MC-JPCF	ABE + Standard adjuvant ET Standard adjuvant ET	Open-label, randomized	High risk, early stage, node positive, HR+, HER2- BC	IDFS	NCT03155997 Active, not recruiting
MONARCH plus[21] I3Y-CR-JPBQ	ABE + NSAI PBO + NSAI ABE + FULV PBO + FULV	Double-blind, placebo-controlled, randomized	HR+, HER2-, locoregionally recurrent or MBC	PFS	NCT02763566 Active, not recruiting
Phase 2					
MONARCH 1[22,23] I3Y-MC-JPBN	ABE	Single-arm	Refractory HR+, HER2- MBC	ORR at 12 mo and after last pt enters TX	NCT02102490 Completed
neoMONARCH [24-26] I3Y-MC-JPBY	ABE + ANAS ABE ANAS Then: ABE + ANAS	Open-label	HR+, HER2-BC	Change from baseline to 2 wk in Ki67 expression	NCT02441946 Completed
monarcHER[27,28] I3Y-MC-JPBZ	ABE + TRAS + FULV ABE + TRAS Physician's choice SOC CTX + TRAS	Open-label	HR+, HER2+ MBC	PFS	NCT02675231 Active, not recruiting
nextMONARCH 1[29,30] I3Y-MC-JPCG	ABE + TAM ABE ABE + Prophylactic Loperamide	Open-label	HR+, HER2- MBC	PFS	NCT02747004 Active, not recruiting
I3Y-MC-JPCP[31]	ABE with a meal ABE without a meal ABE without regard to food	Open-label	Previously treated HR+, HER2- MBC	Impact of food on tolerability	NCT03703466 Active, not recruiting
UCI 18-79 2020-5660	ABE + FULV	Open-label	Breast neoplasm HR+ BC	pCR	NCT04305236 Recruiting
GEICAM/2019-01 2019-002123-15	DOX CYC TAX LET ABE LHRH Analogue	Open-label	EBC	RCB	NCT04293393 Recruiting
Phase 1					

I3Y-MC-JPBH[32]	ABE + LET ABE + ANAS ABE + TAM ABE + EXE ABE + EXE + EVE ABE + TRAS	Open-label	MBC	Pts with >1 drug-related AE	NCT02057133 Active, not recruiting
KEYNOTE 287 I3Y-MC-JPCE[33-36]	ABE+PEMBRO	Open-label, phase 1b	Stage IV KRAS mutant, PD-L1 positive NSCLC or HR+, HER2- BC	# of pts with ≥1 SAE; # of pts with nonserious AE	NCT02779751 Active, not recruiting
2019-00174 Neoadjuvant breast pilot	ABE DUR AI	Open-label	BC female Locally advanced BC HR+ malignant neoplasm of breast	Safety and tolerability	NCT04088032 Withdrawn
EMBER 17502 J2J-MC-JZLA 2019-003581-41	ABE LY3484356 EVE ALP TRAS AI	Open-label	BC ABC MBC Endometrial Cancer	# of pts with DLTs	NCT04188548 Recruiting

Abbreviations: ABC = advanced breast cancer; ABE = abemaciclib; AE = adverse event; AI = aromatase inhibitor; ALP = alpelisib; ANAS = anastrozole; BC = breast cancer; CTX = chemotherapy; CYC = cyclophosphamide; DLTs = dose limiting toxicities; DOX = doxorubicin; DUR = durvalumab; EBC = early breast cancer; ET = endocrine therapy; EVE = everolimus; EXE = exemestane; FULV = fulvestrant; HER2- = human epidermal growth factor receptor 2 negative; HR+ = hormone receptor-positive; IDFS = invasive disease free survival; KRAS = Kirsten rate sarcoma; LET = letrozole; LHRH = luteinizing hormone-releasing hormone; MBC = metastatic breast cancer; NSCLC = non-small cell lung cancer; NSAI = nonsteroidal aromatase inhibitor; ORR = overall response rate; PBO = placebo; pCR = pathological complete response; PD-L1 = programmed death-ligand 1; PEMBRO = pembrolizumab; PFS = progression-free survival; pt(s) = patient(s); RCB = residual cancer burden; SAE = serious adverse event; SOC = standard of care; TAM = tamoxifen; TAX = taxane; TRAS = trastuzumab; TX = treatment.

7. Efficacy and safety

Chapter 7 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 7.1.1 a description of the monarchE trial will be provided. Followed by the section 7.1.2 where efficacy and safety data of the trials is presented.

7.1 Efficacy and safety of abemaciclib combined with endocrine therapy compared to endocrine therapy for HR+/HER2-, node-positive, early breast cancer with high risk of recurrence

7.1.1 Relevant studies

7.1.1.1 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

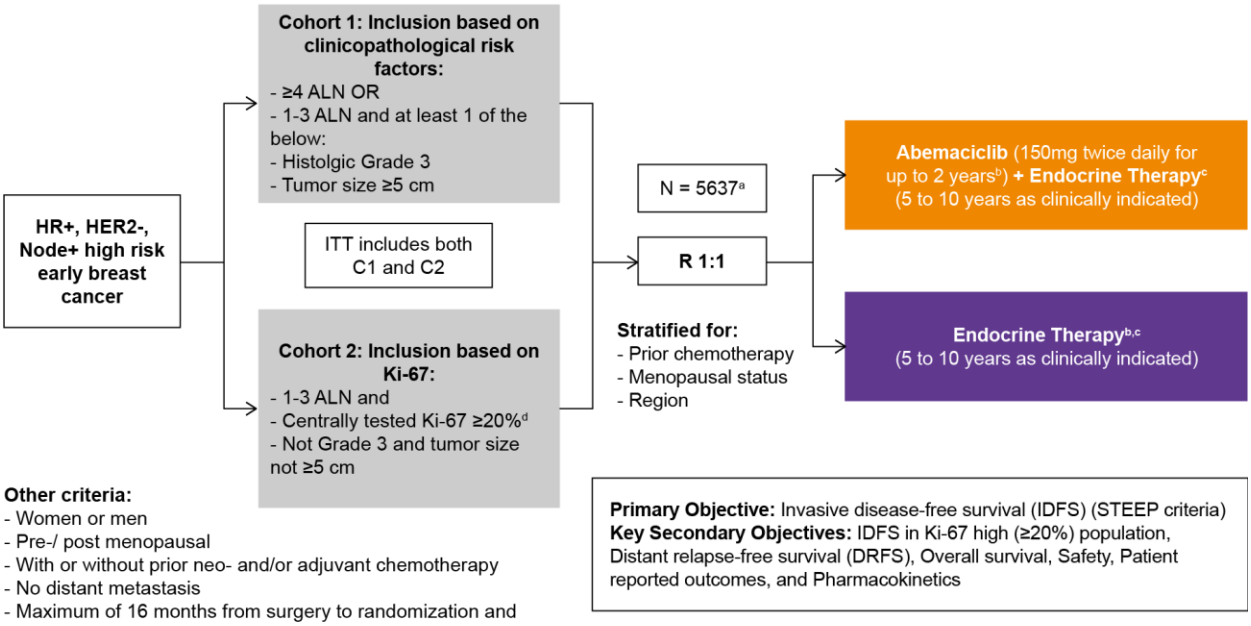
Figure 3, Table 11, and Table 12.

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. 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 [51]



[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

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 11. Summary presentation of monarchE trial

Trial name	monarchE
Trial design	MonarchE is a multicentre, open-label, randomised, Phase III trial to compare the efficacy and safety of abemaciclib in combination with ET versus ET alone as adjuvant treatment of patients with HR+/HER2-, node-positive, high-risk eBC. Trial design summarised in Figure 3.
Primary 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.
Secondary objectives	• To compare DRFS of subjects treated with abemaciclib in combination with ET versus ET alone. • To compare OS of subjects treated with abemaciclib in combination with ET versus ET alone. • To compare safety and tolerability of treatment with abemaciclib in combination with ET versus ET, including the assessment of the proportion of subjects who discontinued treatment due to toxicity. • To compare the impact of treatment on HRQoL as assessed by using the scores of Functional Assessment of Chronic Illness Therapy – Breast (FACT-B), Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F), and Functional Assessment of Chronic Illness Therapy – Endocrine subscale (FACT-ET), and the European Quality of Life 5 Dimension 5 Level Version (EuroQOL EQ-5D-5L) instruments for subjects treated with abemaciclib in combination with ET versus ET. • Pharmacokinetics
Intervention and comparator	Patients in the monarchE trial were randomised to one of the following treatment arms: Interventions:

Trial name	monarchE
	• Arm A: Abemaciclib 150mg BID for 2 years in combination with ET OD for 5 to 10 years N=2,808 Comparator: • Arm B: Endocrine therapy alone OD for 5 to 10 years N=2,829
Follow-up period	The data cut-off (DCO) used in this submission is primarily the DCO from 1st of April 2021. In April 2021 a 27-month follow-up period was captured where 91% of the patients had completed the 2-year study period. Patient reported outcomes endpoints were not analysed at the April 2021 DCO. HRQoL results presented in this submission are from the July 2020 DCO
Number of randomised patients	Planned: 7,372 patients ITT population: 5,637 patients (abemaciclib + ET: 2,808; ET: 2,829) including both Cohort 1 and Cohort 2 Cohort 1: 5,120 (abemaciclib + ET: 2,555; ET: 2,565) Cohort 2: 517 (abemaciclib + ET: 253; ET: 264) Cohort 2 eligibility was based solely on Ki-67 eligibility as per regulatory recommendation from FDA Safety population: 5,591 patients (abemaciclib + ET: 2,791; ET: 2,800)

Inclusion and exclusion criteria for patients	**Inclusion**
	• 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:
	  ○ 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% (only cohort 2)
	Exclusion
	• Metastatic disease, node-negative breast cancer, inflammatory breast cancer
	• 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

Analysis sets	• Full Analysis Set (FAS) (Intent-to-Treat Analysis Population): All randomised subjects regardless of the treatment actually received. This is the primary analysis population used for all efficacy analyses, using the intent-to-treat principle. • Per Protocol (PP) Analysis Set: Subjects who received at least 1 dose of any study drug, had no major protocol deviations, and had both baseline and at least 1 postbaseline tumour assessment. Subjects who died before the first postbaseline tumour assessment were also included. The PP Analysis Set was the secondary analysis set for efficacy endpoints. • Safety Analysis Set (SAS): Subjects who received at least 1 dose of any study drug. This was the analysis population for all safety analyses, which was based on the as-treated principle.

Trial name	monarchE
	• Pharmacokinetic Analysis Set: Subjects who received at least 1 dose of study drug and had sufficient pharmacodynamic data to derive at least 1 pharmacokinetic parameter and with documented dosing history. • HRQoL Analysis Set: All subjects who had any HRQoL data and received at least 1 dose of study treatment.
Baseline characteristics	Baseline characteristics are presented in detail in Appendix C Baseline characteristics of patients in the study used for the analyses of efficacy and safety.
Relevant subgroups	• 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

Table 12. monarchE trial summary of endpoint

Endpoint	Definition	Collection	Analysis
Primary			
IDFS, defined by STEEP system	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.	The primary objective was to test the superiority of abemaciclib + ET versus ET alone on IDFS using a log-rank test stratified by randomization factors. A stratified Cox proportional hazard model with treatment arm as a variable was used to estimate the HR and the corresponding 95% CI.
Key secondary endpoints			
DRFS	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 primary endpoint	To test the superiority of abemaciclib + ET versus ET alone on DRFS using a log-rank test stratified by randomization factors. 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.
OS	Time from the date of randomization to the date of death from any cause	See collection primary endpoint	The overall type 1 error for the OS analyses was controlled by a sequential gatekeeping testing

Endpoint	Definition	Collection	Analysis
			strategy, with the p-value boundary at each OS analysis 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 each OS analysis are based on actual number of death events observed.
TEAEs	TEAE are reported as events that first occurred or worsened in severity while on therapy and until 30 days after treatment discontinuation, or serious events beyond 30 days of treatment discontinuation but were related to study treatment.	See collection primary endpoint	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].
SAE	Any adverse event that resulted in one of the following outcomes: • Death • Initial or prolonged inpatient hospitalization • A life-threatening experience (that is, immediate risk of dying) • Persistent or significant disability/incapacity • Congenital anomaly/birth defect • Considered significant by the investigator for any other reason: important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious, based upon appropriate medical judgment.	See collection primary endpoint	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].
HRQoL	A health outcome directly reported by the patient who experienced it.	PROs were collected on day 1 of the study treatment period, at Months 6, 9, 15, 21 and 27, 30 days post treatment discontinuation and during the first and second long-term follow-up visit. FACT-B 37-item questionnaire FACT-ES 19-item subscale - 2 FACIT-sourced items of cognitive symptoms - 3 FACIT-sourced items for bladder symptoms FACIT-F 13-item subscale EQ-5D-5L	A Mixed-effect model repeated measure (MMRM) model was applied to compare, by treatment arms, the assessment of mean summary scores and means scores for the PRO instruments. The summary scores were calculated as per the FACIT guidance.

Abbreviations: IDFS: Invasive disease-free survival; DRFS: Distant relapse-free survival; OS: Overall survival; TEAE: Treatment-emergent adverse event; SAE: Serious adverse events; PRO: Patient-reported outcomes

7.1.2 Efficacy and safety – Results

As mentioned previously, only results from the monarchE trial are reported in this submission. The 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.
Additionally, of the outcomes reported in Table 12, the results of IDFS, DRFS, OS, HRQoL, and safety are presented. The relevant study outcomes presented are based on the latest DCO from April 2021, with the exception of the results of PROs regarding HRQoL which are based on the DCO from July 2020.

7.1.2.1 Results monarchE – Efficacy

7.1.2.1.1 monarchE - IDFS

A total of 536 patients experienced IDFS events, including 218 (8.5%) in the abemaciclib + ET arm and 318 (12.4%) in the ET alone arm. The median follow-up time was 27.1 months in abemaciclib plus ET arm and 27.2 months in the ET alone arm. With the additional follow-up, abemaciclib plus ET reduced the risk of developing invasive disease by 32.0% (stratified HR=0.680, 95% CI: 0.572, 0.808 [p=0.00001]) versus ET alone, together with a 3-year IDFS rate: 88.6% vs 82.9%, 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 13, result of IDFS from the latest DCO from April 2021 is presented.

Figure 4. Kaplan Meier IDFS by investigator assessment - Cohort 1 population (DCO 1 April 2021).

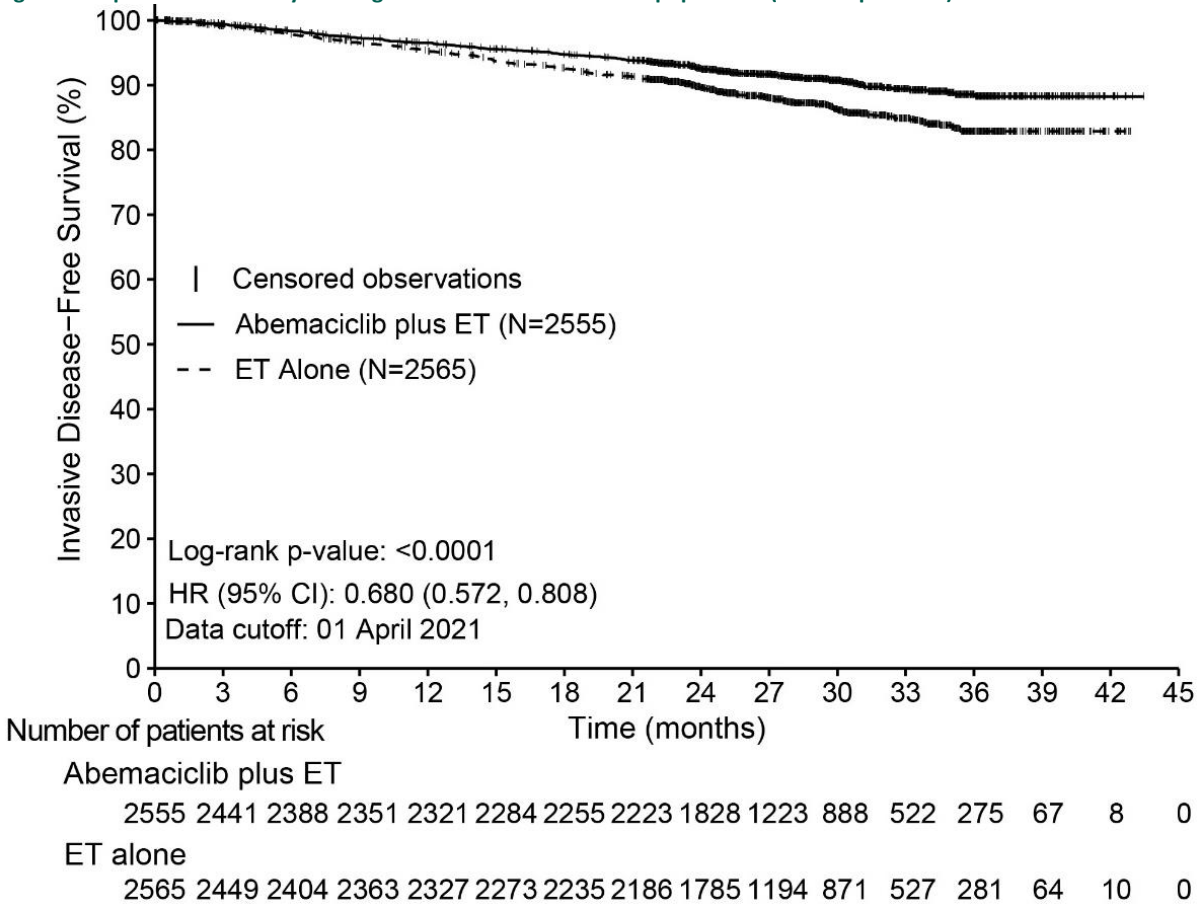


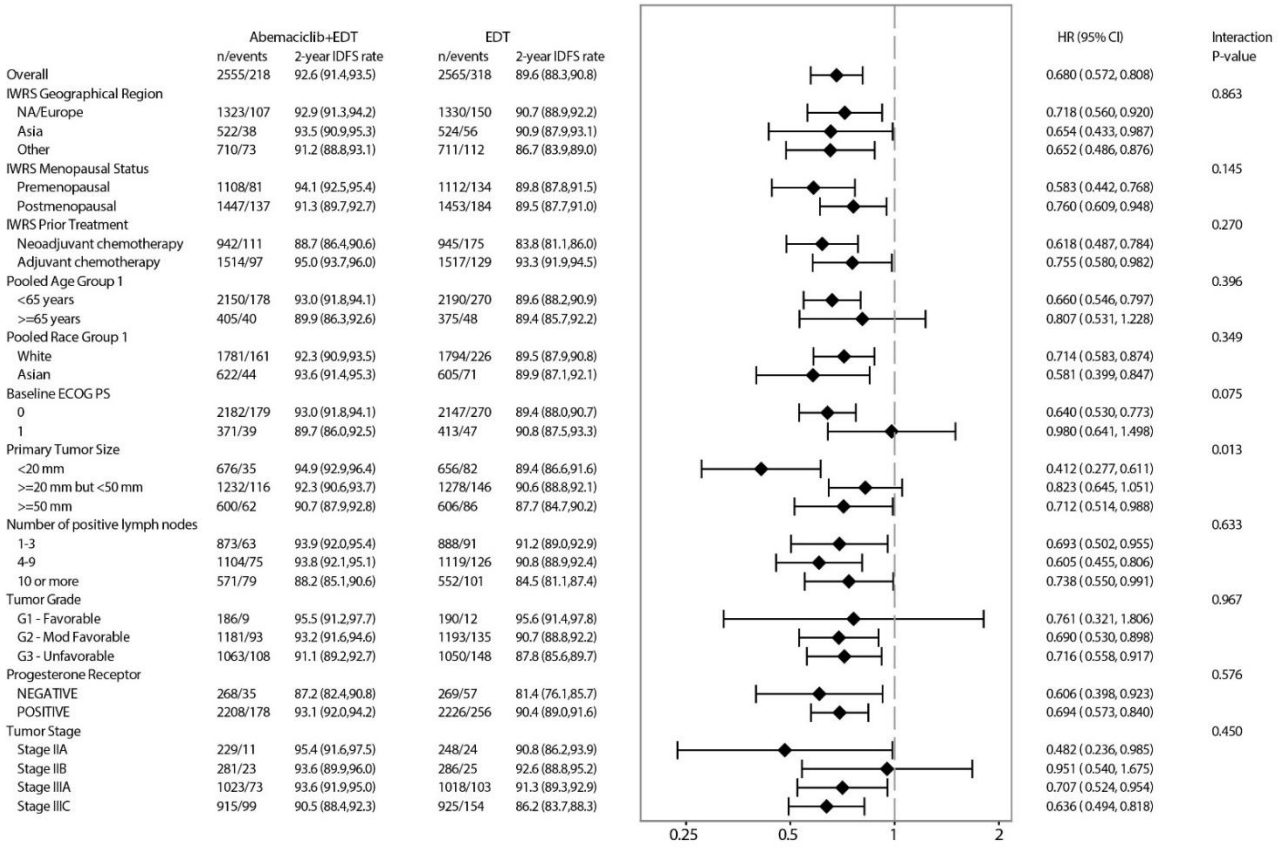
Table 13. Summary of investigator assessed IDFS in Cohort 1 (DCO 1 April 2021).

Outcome	Study arm	N	Result	Hazard Ratio
Number of events	Abemaciclib + ET	2,555	218 (8.5%)	Stratified HR[a]: 0.680 (0.572, 0.808 [p=0.00001]) Unstratified HR[a]: 0.682 (0.574, 0.811 [p=0.00001])
	ET alone	2,565	318 (12.4%)	
IDFS rate % (95% CI)[b]	**Study arm**	**N**	**Result**	**Treatment difference**
12 months	Abemaciclib + ET	2,555	96.5 (95.7, 97.2)	1.2 (0.1, 2.3) p=0.0360
	ET alone	2,565	95.3 (94.4, 96.1)	
24 months	Abemaciclib + ET	2,555	92.6 (91.4, 93.5)	3.0 (1.3, 4.6) p=0.0003
	ET alone	2,565	89.6 (88.3, 90.8)	
36 months	Abemaciclib + ET	2,555	88.6 (86.7, 90.1)	5.7 (3.0, 8.4) p<0.0001
	ET alone	2,565	82.9 (80.7, 84.8)	

Footnotes: [a]Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [b]Treatment Effect/Difference/p-values are computed based on comparator ET.
Abbreviations: CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; IDFS: invasive disease-free survival; N: number of patients in the Cohort1 population.
Source: Lilly Data on File. Clinical Study Report: monarchE [14]. Data cut-off: 01 April 2021 (IA1 analysis).

No statistically significant interactions were observed, supporting a consistent treatment benefit across all pre-specified subgroups. Figure 5 display the forest plot of IDFS, suggesting addition of abemaciclib to ET translates to a reduction in the risk of disease recurrence in the majority of the subgroups analysed, including patients from different regions and pre- and post- menopausal women. There were a few subgroups with hazard ratio point estimates greater than 1 and wide confidence intervals, primarily driven by the small number of events observed within those subgroups.

Figure 5. Subgroup forest plot of IDFS – Cohort1 population (DCO 1 April 2021)

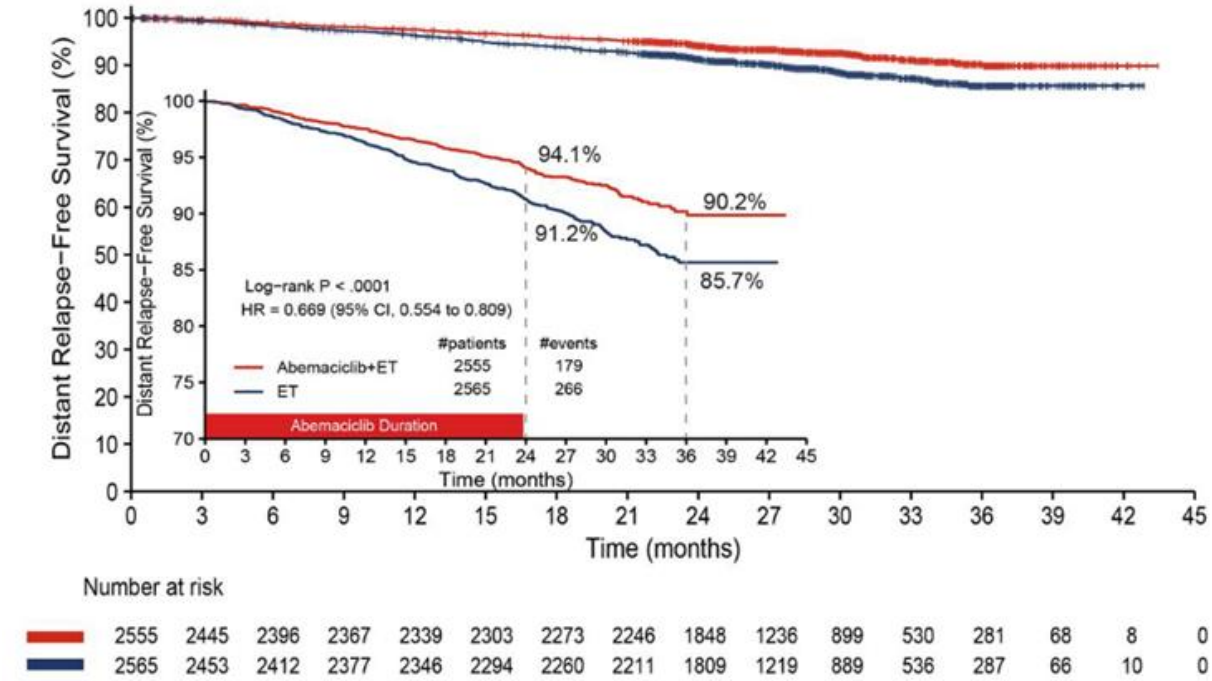


Abbreviations: CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EDT: endocrine therapy; IDFS: invasive disease-free survival; ITT: intent-to-treat; IWRS: interactive web-response system; NA: North America; n: number of patients in the specific population.
Source: Lilly Data on File. Clinical Study Report: monarchE [14]. Data cut-off: 01 April 2021

7.1.2.1.2 monarchE - DRFS

A total number of 445 DRFS events were observed, including 179 in the abemaciclib + ET arm and 266 in the ET alone arm. The DRFS (stratified HR=0.669, 95% CI: 0.554, 0.809), reflecting a 33.1% reduction in the risk of developing distant relapse, and a 4.5% difference in 3-year DRFS rates (90.2% versus 85.7%) for patients treated with abemaciclib in combination with ET, compared to patients treated with ET alone. The figure in the middle shows the curves with a truncated y-axis (70% to 100%) without any censoring ticks to better visualize the separation of curves.

Figure 6. Kaplan-Meier plot of DRFS by investigator assessment – Cohort 1 population (DCO 1 April 2021)



Footnotes: [a]Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [b]Treatment Effect/Difference/p-values are computed based on comparator ET.
Abbreviations: CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; IDFS: invasive disease-free survival; N: number of patients in the Cohort1 population.
Source: Lilly Data on File. Clinical Study Report: monarchE [14]. Data cut-off: 01 April 2021

Table 14. Summary of investigator assessed DRFS in Cohort 1 (DCO 1 April 2021)

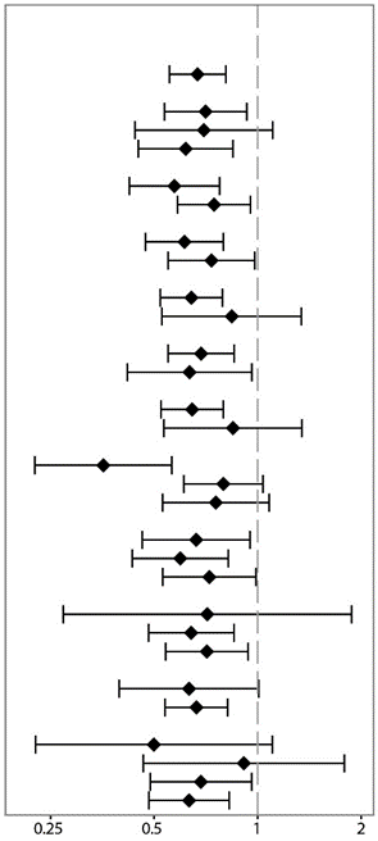
Outcome	Study arm	N	Result	Hazard Ratio
Number of events	Abemaciclib + ET	2,555	179 (7.0%)	Stratified HR[a]: 0.669 (0.554, 0.809 [p=0.00003]) Unstratified HR[a]: 0.671 (0.555, 0.810 [p=0.00003])
	ET alone	2,565	266 (10.4%)	
DRFS rate % (95% CI)[b]	**Study arm**	**N**	**Result**	**Treatment difference**
12 months	Abemaciclib + ET	2,555	97.5 (96.8, 98.1)	1.2 (0.3, 2.2) p=0.0124
	ET alone	2,565	96.3 (95.5, 97.0)	
24 months	Abemaciclib + ET	2,555	94.1 (93.0, 95.0)	2.8 (1.4, 4.3) p=0.0002
	ET alone	2,565	91.2 (90.0, 92.3)	
36 months	Abemaciclib + ET	2,555	90.2 (88.4, 91.7)	4.5 (2.0, 7.0) p=0.0004
	ET alone	2,565	85.7 (83.6, 87.5) (83.6, 87.5)	

Footnotes: [a]Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [b]Treatment Effect/Difference/p-values are computed based on comparator ET.
Abbreviations: DRFS: Distant relapse-free survival; CI**:** confidence interval; ET: endocrine therapy; HR: hazard ratio; IDFS: invasive disease-free survival; N: number of patients in the Cohort1 population.
Source: Lilly Data on File. Clinical Study Report: monarchE [14]. Data cut-off: 01 April 2021

The majority of prespecified subgroups analysed showed consistent DRFS effects favouring abemaciclib + ET. Consistent with what was observed in the subgroup analysis of IDFS, the addition of abemaciclib to ET translates to a reduction in the risk of developing DRFS events in most subgroups analysed, including patients from different regions and pre- and post- menopausal women. No statistically significant interactions were observed, supporting a consistent treatment benefit with the Cohort 1 population, see Figure 7.

Figure 7. Subgroup forest plot of DRFS – Cohort 1 population (DCO 1 April 2021)

	Abemaciclib+EDT		EDT		HR (95% CI)	Interaction P-value
	n/events	2-year DRFS rate	n/events	2-year DRFS rate		
Overall	2555/179	94.1 (93.0,95.0)	2565/266	91.2 (90.0,92.3)	0.669 (0.554, 0.809)	
IWRS Geographical Region						0.809
NA/Europe	1323/86	94.5 (93.0,95.6)	1330/123	92.3 (90.7,93.7)	0.706 (0.536, 0.930)	
Asia	522/31	94.8 (92.5,96.4)	524/43	92.9 (90.2,94.8)	0.698 (0.440, 1.107)	
Other	710/62	92.8 (90.6,94.6)	711/100	88.1 (85.4,90.3)	0.618 (0.450, 0.848)	
IWRS Menopausal Status						0.185
Premenopausal	1108/67	95.3 (93.8,96.4)	1112/113	91.4 (89.5,93.0)	0.573 (0.424, 0.776)	
Postmenopausal	1447/112	93.1 (91.6,94.4)	1453/153	91.1 (89.5,92.5)	0.747 (0.585, 0.953)	
IWRS Prior Treatment						0.363
Neoadjuvant chemotherapy	942/92	90.7 (88.5,92.5)	945/147	86.0 (83.6,88.2)	0.613 (0.472, 0.795)	
Adjuvant chemotherapy	1514/79	96.1 (95.0,97.0)	1517/108	94.4 (93.1,95.5)	0.734 (0.549, 0.981)	
Pooled Age Group 1						0.304
<65 years	2150/146	94.4 (93.3,95.3)	2190/228	91.2 (89.9,92.4)	0.642 (0.521, 0.790)	
>=65 years	405/33	92.3 (89.0,94.6)	375/38	91.5 (88.0,94.0)	0.841 (0.527, 1.340)	
Pooled Race Group 1						0.754
White	1781/132	93.9 (92.6,95.0)	1794/193	90.9 (89.4,92.2)	0.685 (0.549, 0.855)	
Asian	622/37	94.8 (92.6,96.3)	605/55	92.1 (89.6,94.1)	0.634 (0.418, 0.962)	
Baseline ECOG PS						0.296
0	2182/148	94.4 (93.3,95.3)	2147/222	91.2 (89.8,92.3)	0.645 (0.524, 0.794)	
1	371/31	92.3 (89.0,94.7)	413/43	91.8 (88.6,94.1)	0.848 (0.534, 1.345)	
Primary Tumor Size						0.009
<20 mm	676/25	96.3 (94.5,97.5)	656/68	91.2 (88.7,93.2)	0.356 (0.225, 0.563)	
>=20 mm but <50 mm	1232/97	93.8 (92.2,95.0)	1278/126	91.8 (90.0,93.2)	0.795 (0.610, 1.037)	
>=50 mm	600/53	92.3 (89.8,94.2)	606/70	90.2 (87.4,92.4)	0.756 (0.529, 1.080)	
Number of positive lymph nodes						0.699
1-3	873/49	95.4 (93.7,96.6)	888/74	92.9 (90.9,94.4)	0.663 (0.462, 0.951)	
4-9	1104/59	95.4 (93.9,96.6)	1119/101	92.7 (90.9,94.1)	0.596 (0.432, 0.821)	
10 or more	571/70	89.6 (86.7,91.9)	552/91	85.6 (82.3,88.4)	0.724 (0.530, 0.989)	
Tumor Grade						0.875
G1 - Favorable	186/7	97.2 (93.4,98.8)	190/10	96.1 (92.1,98.1)	0.714 (0.272, 1.877)	
G2 - Mod Favorable	1181/77	94.6 (93.0,95.8)	1193/120	91.7 (89.9,93.2)	0.641 (0.482, 0.854)	
G3 - Unfavorable	1063/87	93.0 (91.2,94.4)	1050/120	90.0 (88.0,91.8)	0.712 (0.540, 0.939)	
Progesterone Receptor						0.881
NEGATIVE	268/29	89.5 (84.9,92.7)	269/45	84.4 (79.4,88.3)	0.632 (0.396, 1.007)	
POSITIVE	2208/145	94.6 (93.6,95.5)	2226/218	91.8 (90.6,92.9)	0.664 (0.538, 0.819)	
Tumor Stage						0.665
Stage IIA	229/9	96.3 (92.7,98.1)	248/19	93.0 (88.8,95.7)	0.499 (0.226, 1.104)	
Stage IIB	281/16	95.5 (92.2,97.4)	286/18	94.1 (90.5,96.3)	0.912 (0.465, 1.789)	
Stage IIIA	1023/56	95.5 (94.0,96.7)	1018/82	93.2 (91.4,94.7)	0.684 (0.487, 0.961)	
Stage IIIC	915/87	91.8 (89.7,93.5)	925/136	87.5 (85.1,89.5)	0.632 (0.483, 0.827)	



Abbreviations: CI: confidence interval; DRFS: distant relapse-free survival; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EDT: endocrine therapy; ITT: intent-to-treat; IWRS: interactive web-response system; NA: North America; n: number of patients in the specific population.
Source: Lilly Data on File. Clinical Study Report: monarchE [14]. Data cut-off: 01 April 2021

7.1.2.1.3 monarchE - OS

A total number of 178 deaths (3.5%) were observed, including 90 (3.5%) in the abemaciclib + ET arm and 88 (3.4%) in the ET alone arm. The HR estimate for OS was 1.044 (95% CI: 0.778, 1.401). No significant differences in OS between the two treatment arms were observed. Despite the longer duration of follow-up at 36 months from the DCU in April 2021, the OS data remained immature with a 3.3% event rate and 47.7% of the 390 events required for the final OS analysis. 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 [11-13]. Considering that patients may first spend a number of years in the early breast cancer setting before progressing to metastatic breast cancer, it is evident that insufficient time has passed for the 3-year OS data in monarchE to capture any treatment effect of abemaciclib on OS. KM curves of OS are displayed in Figure 8.

Figure 8. Kaplan-Meier plot of OS – Cohort 1 population first OS interim analysis (DCO 1 April 2021)

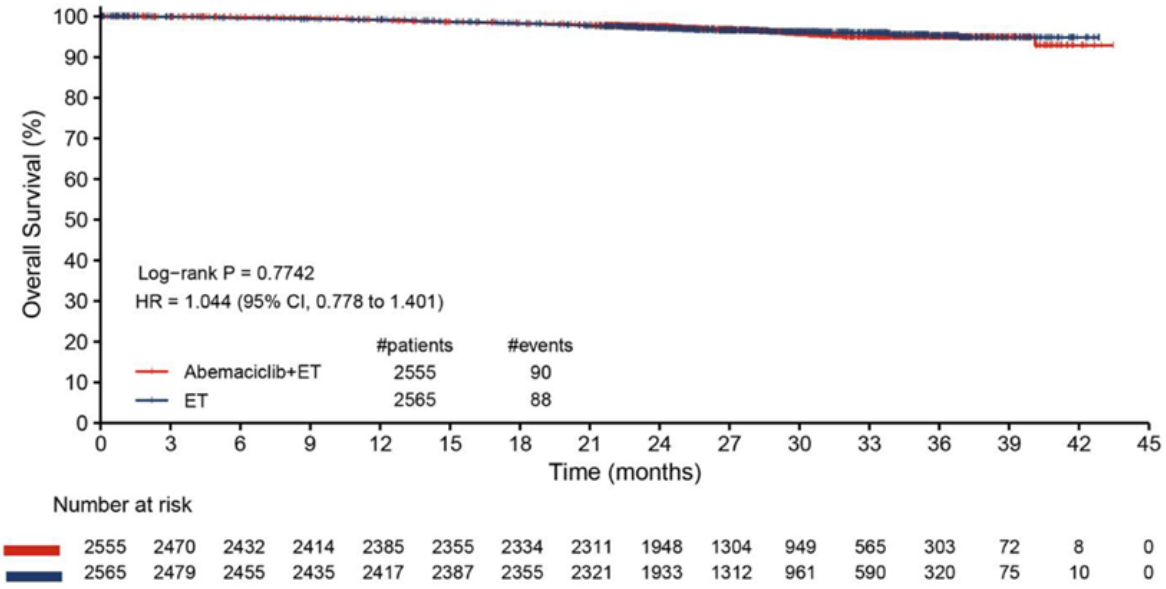


Table 15. Summary of OS in Cohort 1 (DCO 1 April 2021)

Outcome	Study arm	N	Result	Hazard Ratio
Number of events	Abemaciclib + ET	2,555	90 (3.5%)	Stratified HR[a]: 1.044 (0.778, 1.401 [p=0.77420]) Unstratified HR[a]: 1.032 (0.770, 1.385 [p=0.83157])
	ET alone	2,565	88 (3.4%)	
OS rate % (95% CI)[b]	**Study arm**	**N**	**Result**	**Treatment difference**
12 months	Abemaciclib + ET	2,555	99.1 (98.6, 99.4)	–0.1 (–0.6, 0.5) p=0.8402
	ET alone	2,565	99.1 (98.7, 99.4)	
24 months	Abemaciclib + ET	2,555	97.5 (96.8, 98.0)	0.3 (–0.6, 1.2) p=0.5024
	ET alone	2,565	97.2 (96.4, 97.8)	
36 months	Abemaciclib + ET	2,555	94.9 (93.7, 96.0)	–0.4 (–2.0, 1.2) p=0.6305
	ET alone	2,565	95.3 (94.0, 96.3)	

Footnotes: [a]Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status; [b]Treatment Effect/Difference/p-values are computed based on comparator ET.
Abbreviations: DRFS: Distant relapse-free survival; CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; IDFS: invasive disease-free survival; N: number of patients in the Cohort1 population.
Source: Lilly Data on File. Clinical Study Report: monarchE [14]. Data cut-off: 01 April 2021

7.1.2.1.4 monarchE - HRQoL

Patient reported outcomes endpoints were not analysed at the April 2021 DCO. Results in the following section are from the July 2020 DCO. Different PROs were used to measure HRQoL: FACT-B, FACT-ES, FACIT-F, and EQ-5D-5L.

For health outcomes and quality of life assessments, for each instrument, percentage compliance was calculated as the number of completed assessments divided by the number of expected assessments (i.e., patients still on study). A mixed effect, repeated measures model was applied to compare treatment arms by assessment with respect to each subscale and item score. The models included baseline score as a covariate and an unstructured covariance matrix was utilized. For each of the subscales and item scores, the analysis included all visits for which

at least 25% of patients in each arm have an assessment. In the absence of published data on the minimally important difference of changes in the summary scores in the population of patients with EBC, an effect size of one-half standard deviation (0.5 SD) was used to represent an estimate of a minimally important difference (MID).

7.1.2.1.4.1 FACT-B, FACT-ES, and FACIT-F

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.

The mean scores for the FACT-B and FACT-ES subscales are shown in Table 16 and Table 17 respectively. 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 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.

Table 16. 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	2,165	108.16 (18.03)	NA	2,184	107.05 (18.06)	NA	NA
Visit 6 (3 months)	2,100	106.56 (19.04)	−1.53 (0.27)	2,108	107.54 (18.58)	0.38 (0.27)	−1.91 (0.38)
Visit 9 (6 months)	2,045	107.16 (19.56)	−1.08 (0.29)	2,058	107.96 (18.52)	0.70 (0.29)	−1.78 (0.41)
Visit 15 (12 months)	1,947	106.88 (19.58)	-1.53 (0.32)	1939	108.09 (18.81)	0.83 (0.32)	-2.36 (0.45)

Visit 21 (18 months)	1,300	106.05 (19.75)	-2.03 (0.37)	1298	108.77 (18.46)	1.25 (0.37)	-3.28 (0.52)
All post-baseline	NE	NE	-1.54 (0.25)	NE	NE	0.79 (0.25)	-2.33 (0.35)

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 [14]. Data cut-off: 08 July 2020.

Table 17. 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	2173	62.24 (9.07)	NA	2188	61.43 (9.49)	NA	NA
Visit 6 (3 months)	2113	59.49 (10.28)	-2.68 (0.15)	2116	60.57 (9.80)	-1.02 (0.15)	-1.66 (0.21)
Visit 9 (6 months)	2054	59.65 (10.61)	-2.69 (0.16)	2072	60.17 (10.13)	-1.44 (0.16)	-1.25 (0.23)
Visit 15 (12 months)	1957	59.27 (10.86)	-3.06 (0.18)	1949	59.94 (10.35)	-1.74 (0.18)	-1.32 (0.25)
Visit 21 (18 months)	1308	59.01 (10.85)	-3.34 (0.21)	1302	60.17 (10.29)	-1.75 (0.21)	-1.59 (0.29)
All post-baseline	NE	NE	-2.94 (0.14)	NE	NE	-1.49 (0.14)	-1.45 (0.20)
ESS-23[b]							
Baseline	2128	75.33 (10.62)	NA	2145	74.25 (11.23)	NA	NA
Visit 6 (3 months)	2040	71.79 (12.06)	-3.49 (0.17)	2054	73.30 (11.69)	-1.20 (0.17)	-2.29 (0.25)
Visit 9 (6 months)	1984	72.13 (12.48)	-3.35 (0.19)	2007	72.97 (12.00)	-1.57 (0.19)	-1.78 (0.27)
Visit 15 (12 months)	1884	71.86 (12.69)	-3.66 (0.21)	1890	72.77 (12.22)	-1.85 (0.21)	-1.81 (0.29)
Visit 21 (18 months)	1265	71.51 (12.78)	-4.06 (0.24)	1260	73.05 (12.23)	-1.75 (0.24)	-2.30 (0.35)
All post-baseline	NE	NE	-3.64 (0.17)	NE	NE	-1.59 (0.16)	-2.05 (0.23)

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 [14]. Data cut-off: 08 July 2020

7.1.2.1.4.2 EQ-5D-5L

EQ-5D-5L index values were very similar between arms for all baseline and post-baseline assessments in the Cohort 1 population presented in **Error! Reference source not found.**. Overall, index values in most post-baseline assessments were stable and similar to baseline values for both treatment arms. Scores were similar between the two treatment arms for all baseline and post-baseline visits, **Error! Reference source not found.**. The details of compliance rate and reasons for noncompliance for EQ-5D-5L by Visit are reported in Appendix F in Figure 36 to Figure 38.

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

The mean scores by visits are presented in Table 18 and have also been added to section 8.4.1. The last row of the table presents the mean iDFS utility value derived from the monarchE trial.

Table 18. **Overview of utility values derived from MonarchE trial (Cohort 1 population)**

Visit	Number of respondents	Mean	Standard deviation	Standard error	95% Confidence interval (lower-upper bound)	P value~
Baseline	4325	0.86	0.14	0.0021	0.856-0.864	0.813
Visit 6	4092	0.85	0.14	0.0022	0.846-0.854	0.919
Visit 9	3989	0.85	0.15	0.0024	0.845-0.855	0.855
Visit 15	3785	0.85	0.15	0.0024	0.845-0.855	0.195
Visit 21	3593	0.85	0.15	0.0025	0.845-0.855	0.297
Visit 27	3140	0.85	0.16	0.0029	0.844-0.856	0.939
Overall (mean) iDFS	-	0.85	-	0.0029	0.844-0.856	0.571

~- p-values are from Type 3 sums of squares MMRM Model: Change from Baseline = Treatment + Visit + Treatment*Visit + Baseline.
The analysis will include all cycles for which at least 25% of patients in each arm have a non-missing postbaseline change from baseline EQ-5D-5L Index Score.

[redacted]

	Abemaciclib + ET (N=2,539)			ET alone(N=2,539)			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]						
Visit 6 (3 months)	[redacted]						
Visit 9 (6 months)	[redacted]						

Visit 15 (12 months)	[redacted]						
Visit 21 (18 months)	[redacted]						
Visit 27	[redacted]						
All post-baseline	[redacted]						

Abbreviations: EQ-5D 5L: EuroQol 5-Dimension 5-Level; LSM: least squares mean; SE: standard error; SD: standard deviation.
Source: Lilly Data on File. Clinical Study Report: monarchE. Data cut-off: 08 July 2020.

7.1.2.2 Results monarchE – Safety

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. 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. With 90% of patients having completed or discontinued early from the study treatment period by the time of the latest DCO, the safety data is considered mature.

At the latest DCO, 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 the median duration of ET was approximately 23.8 months (with a mean of approximately 21 months. In the ET alone arm the median duration of treatment was approximately and 23.8 months (with a mean of approximately 21 months). At the time of the April 2021 DCO 265 patients (9.4%) in the abemaciclib plus ET arm and 273 patients (9.7%) in the ET alone arm remained on study treatment. Overall, 91% of total patients had completed two years on study treatment.

The safety of abemaciclib in combination with ET was evaluated through the assessment of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), TEAEs leading to discontinuation, and TEAEs leading to deaths, Table 19.

Table 19. Summary of safety outcomes – Safety population (DCO 01 April 2021)

Outcome	Study arm	N	Result	p-value	Reference
TEAEs by SOC in ≥1% patients (all grades) – n (%)	Abemaciclib + ET	2,791	2,745 (98.4)	NA	[28]
	ET alone	2,800	2,486 (88.8)		[28]
SAEs – n (%)	Abemaciclib + ET	2,791	424 (15.2)	NA	[28]
	ET alone	2,800	247 (8.8)		[28]
Treatment discontinuation due to AEs – n (%)	Abemaciclib + ET	2,791	181 (6.5)	NA	[14]
	ET alone	2,800	30 (1.1)		[14]
TEAS leading to deaths – n (%)	Abemaciclib + ET	2,791	95 (3.4)	NA	[28]
	ET alone	2,800	89 (3.2)		[28]

Abbreviations: AEs: Adverse events; TEAE: Treatment-emergent adverse events; CI: Confidence interval; SOC: system organ classes
Source: Lilly Data on File. Clinical Study Report: monarchE [14]. Data cut-off: 01 April 2021 .

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

During the study period, a total of 5,231 patients (93.6%) experienced at least one TEAE, including 2,745 patients (98.4%) in the abemaciclib plus ET arm and 2,486 patients (88.8%) of patients in the ET alone arm, Table 20.

Table 20. Treatment-emergent adverse events by maximum CTCAE grade experienced by ≥10% of population of either arm of monarchE, safety population

TEAE, n (%)	Abemaciclib + ET (n=2,791)						ET alone (N=2,800)					
	CTCAE Grade											
	1	2	3	4	5	Any	1	2	3	4	5	Any
Patients with ≥1 TEAE	165 (5.9)	1,192 (42.7)	1,284 (46.0)	89 (3.2)	15 (0.5)	2,745 (98.4)	634 (22.6)	1396 (49.9)	424 (15.1)	22 (0.8)	10 (0.4)	2,486 (88.8)
Diarrhea	1,255 (45.0)	857 (30.7)	218 (7.8)	0 (0.0)	1 (0.0)	2,331 (83.5)	184 (6.6)	52 (1.9)	6 (0.2)	0 (0.0)	0 (0.0)	242 (8.6)
Neutropenia	178 (6.4)	554 (19.8)	527 (18.9)	19 (0.7)	0 (0.0)	1278 (45.8)	66 (2.4)	68 (2.4)	19 (0.7)	4(0.1)	0 (0.0)	157 (5.6)
Fatigue	632 (22.6)	421 (15.1)	80 (2.9)	0 (0.0)	0 (0.0)	1133 (40.6)	378 (13.5)	117 (4.2)	4 (0.1)	0 (0.0)	0 (0.0)	499 (17.8)
Leukopenia	170 (6.1)	562 (20.1)	313 (11.2)	4 (0.1)	0 (0.0)	1049 (37.6)	93 (3.3)	82 (2.9)	11 (0.4)	0 (0.0)	0 (0.0)	186 (6.6)
Abdominal pain	693 (24.8)	260 (9.3)	39 (1.4)	0 (0.0)	0 (0.0)	992 (35.5)	189 (6.8)	77 (2.8)	9 (0.3)	0 (0.0)	0 (0.0)	275 (9.8)
Nausea	623 (22.3)	187 (6.7)	14 (0.5)	0 (0.0)	0 (0.0)	824 (29.5)	198 (7.1)	52 (1.9)	2 (0.1)	0 (0.0)	0 (0.0)	252 (9.0)
Anaemia	383 (13.7)	241 (8.6)	56 (2.0)	1 (0.0)	0 (0.0)	681 (24.4)	75 (2.7)	19 (0.7)	9 (0.3)	1 (0.0)	0 (0.0)	104 (3.7)
Arthralgia	509 (18.2)	224 (8.0)	9 (0.3)	0 (0.0)	0 (0.0)	742 (26.6)	729 (26.0)	302 (10.8)	29 (1.0)	0 (0.0)	0 (0.0)	1060 (37.9)
Headache	415 (14.9)	123 (4.4)	8 (0.3)	0 (0.0)	0 (0.0)	546 (19.6)	321 (11.5)	95 (3.4)	5 (0.2)	0 (0.0)	0 (0.0)	421 (15.0)
Vomiting	375 (13.4)	101 (3.6)	15 (0.5)	0 (0.0)	0 (0.0)	491 (17.6)	98 (3.5)	29 (1.0)	3 (0.1)	0 (0.0)	0 (0.0)	130 (4.6)
Hot flush	326 (11.7)	97 (3.5)	4 (0.1)	0 (0.0)	0 (0.0)	427 (15.3)	496 (17.7)	137 (4.9)	10 (0.4)	0 (0.0)	0 (0.0)	643 (23.0)
Lymphopenia	75 (2.7)	169 (6.1)	148 (5.3)	3 (0.1)	0 (0.0)	395 (14.2)	38 (1.4)	45 (1.6)	13 (0.5)	0 (0.0)	0 (0.0)	96 (3.4)
Stomatitis[a]	309 (11.1)	72 (2.6)	4 (0.1)	0 (0.0)	0 (0.0)	385 (13.8)	133 (4.8)	18 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	151 (5.4)
Cough	310 (11.1)	80 (2.9)	1 (0.0)	0 (0.0)	0 (0.0)	391 (14.0)	177 (6.3)	45 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	222 (7.9)
Thrombocy-topenia	276 (9.9)	61 (2.2)	28 (1.0)	8 (0.3)	0 (0.0)	373 (13.4)	40 (1.4)	8 (0.3)	2 (0.1)	2 (0.1)	0 (0.0)	52 (1.9)
Decreased appetite	243 (8.7)	70 (2.5)	16 (0.6)	0 (0.0)	0 (0.0)	329 (11.8)	53 (1.9)	13 (0.5)	2 (0.1)	0 (0.0)	0 (0.0)	68 (2.4)
Lymphoe-dema	258 (9.2)	84 (3.0)	5 (0.2)	0 (0.0)	0 (0.0)	347 (12.4)	204 (7.3)	45 (1.6)	1 (0.0)	0 (0.0)	0 (0.0)	250 (8.9)
Urinary tract infection	2 (0.1)	318 (11.4)	16 (0.6)	0 (0.0)	0 (0.0)	336 (12.0)	0 (0.0)	205 (7.3)	6 (0.2)	0 (0.0)	0 (0.0)	211 (7.5)
Constipation	282 (10.1)	49 (1.8)	2 (0.1)	0 (0.0)	0 (0.0)	333 (11.9)	144 (5.1)	23 (0.8)	1 (0.0)	0 (0.0)	0 (0.0)	168 (6.0)
URTI	0 (0.0)	295 (10.6)	6 (0.2)	0 (0.0)	0 (0.0)	301 (10.8)	1 (0.0)	237 (8.5)	0 (0.0)	0 (0.0)	0 (0.0)	238 (8.5)
ALT in-creased	184 (6.6)	82 (2.9)	72 (2.6)	5 (0.2)	0 (0.0)	343 (12.3)	113 (4.0)	25 (0.9)	19 (0.7)	0 (0.0)	0 (0.0)	157 (5.6)

Dizziness	270 (9.7)	30 (1.1)	4 (0.1)	0 (0.0)	0 (0.0)	304 (10.9)	167 (6.0)	20 (0.7)	1 (0.0)	0 (0.0)	0 (0.0)	188 (6.7)
Rash	239 (8.6)	61 (2.2)	11 (0.4)	0 (0.0)	0 (0.0)	312 (11.2)	104 (3.7)	23 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	127 (4.5)
AST increased	220 (7.9)	58 (2.1)	49 (1.8)	3 (0.1)	0 (0.0)	330 (11.8)	103 (3.7)	19 (0.7)	15 (0.5)	0 (0.0)	0 (0.0)	137 (4.9)
Alopecia	283 (10.1)	30 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	313 (11.2)	68 (2.4)	7 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	75 (2.7)
Pain in extremity	205 (7.3)	78 (2.8)	3 (0.1)	0 (0.0)	0 (0.0)	286 (10.2)	251 (9.0)	70 (2.5)	4 (0.1)	0 (0.0)	0 (0.0)	325 (11.6)
Back pain	192 (6.9)	81 (2.9)	10 (0.4)	0 (0.0)	0 (0.0)	283 (10.1)	230 (8.2)	108 (3.9)	9 (0.3)	0 (0.0)	0 (0.0)	347 (12.4)
Pyrexia	229 (8.2)	48 (1.7)	2 (0.1)	0 (0.0)	0 (0.0)	279 (0.1)	102 (3.6)	25 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	127 (4.5)

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

The incidence of SAEs was higher in the abemaciclib plus ET arm (15.2%) as compared with the ET alone arm (8.8%). Venous thrombolytic events (VTE) and pneumonia were the most commonly reported SAEs by patients treated with abemaciclib + ET (1.2% [34/2,791] and 1.0% [28/2,791], respectively). Patients treated with ET alone reported pneumonia (0.6% [17/2,800]), cellulitis (0.4% [10/2,800]) and VTE (0.3% [8/2,800]) most commonly, Table 21.

Table 21. SAEs in ≥5 patients in either arm of the safety population, April 2021 DCO

n (%)	Abemaciclib + ET (N=2,791)	ET alone (N=2,800)
Patients with ≥1 serious adverse event	424 (15.2)	247 (8.8)
Infections and infestations	146 (15.2)	80 (2.9)
Pneumonia	28 (1.0)	17 (0.6)
Cellulitis	14 (0.5)	10 (0.4)
Urinary tract infection	14 (0.5)	4 (0.1)
Influenza	7 (0.3)	4 (0.1)
Sepsis	6 (0.2)	2 (0.1)
Upper respiratory tract infection	6 (0.2)	0 (0.0)
Breast cellulitis	5 (0.2)	5 (0.2)
Erysipelas	6 (0.2)	0 (0.0)
Gastrointestinal disorders	59 (2.1)	17 (0.6)
Diarrhoea	15 (0.5)	0 (0.0)
Abdominal pain	6 (0.2)	1 (0.0)
Pancreatitis	6 (0.2)	2 (0.1)
Colitis	5 (0.2)	3 (0.1)
Respiratory, thoracic and mediastinal disorders	38 (1.4)	12 (0.4)
Pneumonitis	8 (0.3)	0
Vascular disorders	30 (1.1)	11 (0.4)
Lymphoedema	7 (0.3)	3 (0.1)
General disorders and administration site conditions	27 (1.0)	9 (0.3)
Pyrexia	10 (0.4)	0 (0.0)
Cardiac disorders	25 (0.9)	15 (0.5)
Atrial fibrillation	8 (0.3)	1 (0.0)
Hepatobiliary disorders	22 (0.8)	9 (0.3)
Cholecystitis	10 (0.4)	4 (0.1)
Blood and lymphatic disorders	24 (0.9)	4 (0.1)
Anaemia	8 (0.3)	2 (0.1)

Febrile neutropenia	5 (0.2)	0 (0.0)
Metabolism and nutrition disorders	16 (0.6)	8 (0.3)
Dehydration	7 (0.3)	0 (0.0)
Composite terms[a]		
Venous thromboembolic event[b]	34 (1.2)	8 (0.3)
Interstitial lung disease/pneumonitis[c]	14 (0.5)	1 (<0.01)
ALT or AST increased	10 (0.4)	2 (0.1)

Footnotes: [a] Composite terms are defined as a grouping of terms from one or more PTs that are treatment-emergent events and related to a defined medical condition or area of interest; [b] VTE events included pulmonary embolism and deep vein thrombosis. [c] Interstitial lung disease/pneumonitis events were defined by SMQ of "interstitial lung disease".
Abbreviations: ET: endocrine therapy; N: number of patients in the safety population; n: number of patients within category; SAE: serious adverse event; SMQ: standardised MedDRA queries.
Source: Lilly Data on File. Clinical Study Report: monarchE [14]. Data cutoff: 01 April 2021

In the abemaciclib + ET arm, 515 patients (18.5%) discontinued abemaciclib due to AEs. Of these patients, 181 (6.5%) discontinued all study treatment due to an AE, as compared with 30 patients (1.1%) in the ET alone arm. The TEAEs that led to discontinuation of all study treatment are presented in Table 22. In the abemaciclib + ET arm, the most common TEAEs leading to all treatment discontinuations were diarrhoea (69 patients, 2.5%) and fatigue (28 patients, 1.0%). Dizziness (0.1%) led to discontinuation in the ET alone arm.

Table 22. AEs reported as reason for study treatment discontinuation (end of treatment) by ≥2 patients in either arm of the safety population, April 2020 DCO

n (%)	Abemaciclib + ET (N=2,791)	ET alone (N=2800)
Patients discontinued all study treatment due to AE[a]	181 (6.5)	30 (1.1)
Diarrhoea	69 (2.5)	0 (0.0)
Fatigue	28 (1.0)	0 (0.0)
Abdominal pain	4 (0.1)	0 (0.0)
Nausea	4 (0.1)	0 (0.0)
Depression	3 (0.1)	2 (0.1)
Vomiting	3 (0.1)	0 (0.0)
Anxiety	2 (0.1)	1 (0.0)
Cardiac arrest	2 (0.1)	0 (0.0)
Dry eye	2 (0.1)	0 (0.0)
General physical health deterioration	2 (0.1)	0 (0.0)
Neutropenia	2 (0.1)	0 (0.0)
Pain in extremity	2 (0.1)	0 (0.0)
Arthralgia	1 (0.0)	6 (0.2)
Hot flush	1 (0.0)	2 (0.1)
Dizziness	0 (0.0)	2 (0.1)
Composite terms[b]		
Infections and infestations SOC	9 (0.3)	6 (0.2)
Venous thromboembolic event[c]	6 (0.2)	2 (0.1)
Interstitial lung disease/pneumonitis[d]	2 (0.1)	0
ALT or AST increased	3 (0.1)	0

Footnotes: [a] Includes patients who died due to AE during study treatment: PT cardiac arrest and PT general physical health deterioration (n=1). [b] Composite terms are defined as a grouping of terms from one or more PT or SOC that are related to a defined medical condition or area of interest; [c] VTE events included pulmonary embolism and deep vein thrombosis. [d] Interstitial lung disease/pneumonitis events were defined by SMQ of "interstitial lung disease".
Abbreviations: AE: adverse event; ET: endocrine therapy; N: number of patients in the safety population; n: number of patients within category; SAE: serious adverse event; SMQ: standardised MedDRA queries.

Source: Lilly Data on File. Clinical Study Report: monarchE [14]. Data cutoff: 01 April 2021.

7.1.3 Comparative analyses of efficacy and safety

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

8. Health economic analysis

8.1 Model

8.1.1 Model structure

The cost-utility model (CM) structure was based on previous early breast cancer models in the HER2+ patient population, the treatment pathway of patients with HR+/HER2− early breast cancer, data availability from the monarchE trial, and feedback from clinical experts [1]. Specifically, the National Institute for Clinical Excellence assessments TA632 [52] and TA612 [53] as well as the submission of trastuzumab emtasine to the DMC, for the treatment of HER2 + eBC [54].

As in eBC there are inherently insufficient long term follow-up data to population a partitioned survival model a cohort state transition model with five health states was developed, in line with similar appraisals in HER2+ early breast cancer, a Markov structure was considered appropriate. The health states were IDFS, non-metastatic recurrence, remission, metastatic recurrence, and death. Death and metastatic recurrence were modelled as absorbing health states.

Figure 9 illustrates the top-line model structure. All patients enter the model in the IDFS health state and receive ET. Patients in the abemaciclib treatment arm additionally receive abemaciclib treatment for a maximum of two years. From the IDFS health state patients can either, i) die, ii) experience a disease recurrence and transition to the metastatic or iii) the non-metastatic recurrence health state, or iv) remain in the IDFS health state.

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

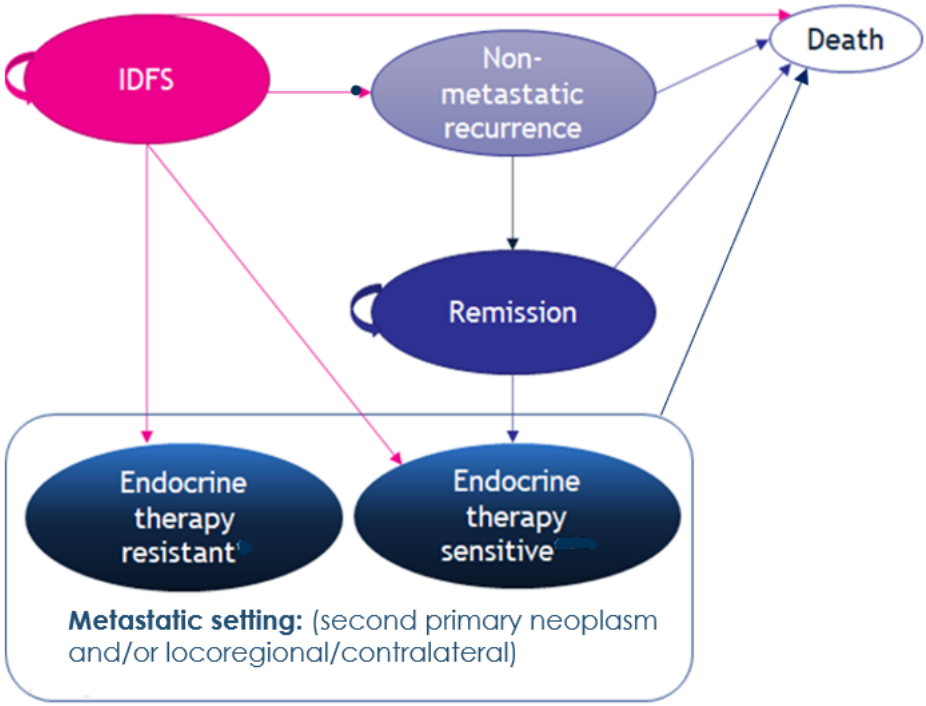
Due to limited follow up in the latest monarchE data cut ([55]; July 2020 and April 2021) it was not possible to estimate transition probabilities for patients after experiencing a metastatic recurrence. Patients who experienced either a locally advanced (with non-curative intent) or a metastatic recurrent event transitioned to the metastatic disease recurrence health state were instead modelled as entering an absorbing health state with fixed payoffs for costs, LYs and QALYs.

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

- ET-resistant: Patients who experience a disease recurrence while receiving adjuvant ET or within 12 months of completing adjuvant ET. Metastatic recurrence % 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%.
-
- ET-sensitive: Patients who experience a disease recurrence more than 12 months after completing their adjuvant ET.[56, 57] . Metastatic recurrence % from the MonarchE trial is applied to the adjusted (for mortality and treatment waning) IDFS curve. After 72 months, this decreases to 0, as all patients enter the MR (ET sensitive) health state.

The economic analysis assumes that patients who receive abemaciclib as adjuvant therapy will not be re-treated with a CDK4/6 upon relapse. This assumption is based on a wide clinical expert consultation process carried out by Eli Lilly which included clinicians from Denmark, the Nordic countries, but also the United Kingdom [1]. Clinical experts highlighted that the only case in which they could consider re-treating with a CDK4/6 would be if patients were initially misdiagnosed as early breast cancer patients where they already have a metastatic disease [1]. However, Eli Lilly is not aware of any clinical trials showing efficacy when re-challenging with a CDK4/6 nor any guidelines suggesting re-challenging at this time. Finally, in their recently published report, TLV also mentioned that there is no evidence available for re-treatment with CDK4/6s [58].

Figure 9: Structure of the model used in the economic analysis



Abbreviations: IDFS: invasive disease free survival.

Health State Specific Assumptions

Non-metastatic recurrence

From the MonarchE trial, a regional invasive breast cancer recurrence, and a contralateral invasive breast cancer are all assumed to be a non-metastatic recurrence event. This was in line with the standardised definitions for efficacy end points criteria from the STEEP system developed by Hudis et al. (2007) [59].

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

Secondary primary neoplasm

The monarchE trial includes a 'second primary non-breast invasive cancer' or a 'second primary neoplasm' as an IDFS event. The CSR (PO data) states that it is not considered as a recurrence event of 'this' breast cancer [14]. Clinical experts agreed that these events should not be considered a NMR event as their treatment pathways are different.

Based on the monarchE CSR (PO data, first occurrence), 0.6% and 0.5% of patients in the abemaciclib (ABE) + ET and ET alone arms, respectively, were diagnosed with the first occurrence of a second primary neoplasm. In the ABE + ET arm these events were thyroid, colon, and skin cancers. In the ET alone arm these events were lung, ovarian, thyroid, and cervical cancer. Following consultations with KOLs, it can be concluded that neither ABE + ET nor ET alone result in any additional risk of a second primary neoplasm. The results of the April 2021 data cut further validate this assumption. Based on these data the first occurrence of a second primary neoplasm in both the ABE + ET and ET alone arms were XXXXXXXX%.

In summary, to maintain a simple model structure, the full pathway of a second primary neoplasm is not modelled. For those patients who experience a second primary neoplasm they incur the cost of diagnosis of the event and exit the model after entering the non-metastatic recurrence health state.

8.1.2 Perspective, time horizon, cycle length and outcomes

Perspective

The analyses were undertaken from a restricted social perspective, in alignment with the DMC's guidelines [60].

Time horizon

Similarly, the cost and outcomes in the analyses were calculated over a lifetime horizon, in alignment with the DMC's guidelines [60]. 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

A 28-day cycle length has been used in the model, which was deemed sufficient to accurately capture the clinical and cost outcomes for patients from the MonarchE trial. Half cycle correction has been applied to account for events not occurring at beginning or end of every cycle.

8.1.3 Discounting

A discount rate of 3.5% until year 35 and 2.5% beyond year 35 was applied to costs, as defined by the Danish Ministry of Finance and in the DMC guidelines [60].

8.1.4 Model Outcomes

The analyses calculate benefit in terms of life years (LYs) and quality-adjusted life years (QALYs). Base case results were generated using QALYs as the measure of benefit and the primary outcome was the incremental cost per QALY. A list of model outcomes reported for the base case in the model are reported in Table 23. Graphical representation of the sensitivity results in the form of a tornado diagram for deterministic sensitivity analysis (DSA) and cost-effectiveness acceptability curve (CEAC) for probabilistic sensitivity analysis (PSA) are also included, alongside the cost-effectiveness frontier.

Table 23. Model outputs

Cost Outcomes	Health Outcomes	Incremental and Cost-effectiveness Outcomes
• Overall direct medical costs • Overall costs disaggregated by each cost category within the model: ○ Drug acquisition ○ Drug administration ○ AE management ○ Disease management ○ Patient costs ○ Subsequent treatment	• Total LYs ○ Progression-free ○ Post-progression ○ On-treatment ○ Off-treatment • Total QALYs ○ Progression-free ○ Post-progression	• Incremental costs • Incremental LYs • Incremental QALYs • Cost per life year gained (ICER) • Cost per QALY gained (ICUR)

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

8.2.1 Presentation of input data used in the model and how they were obtained

Table 24 summarises the inputs included in the model and how they were obtained/estimated.

Table 24. Summary of efficacy inputs included in the economic model

Name of estimates	Results from study	Input value used in the model	How is the input value obtained/estimated
iDFS	See section 7.1.2.1.1	See section 8.3.1.2.1	monarchE [14]
OS (without distant recurrence)	See section 7.1.2.1.3	See section 8.3.1.2.3	monarchE [14]
Time to treatment discontinuation	See section 8.3.1.2.2	See section 8.3.1.2.2	monarchE [14]
Remission	A monthly transition probability of 0.00760 from remission to the metastatic health state	A monthly transition probability of 0.00760 from remission to the metastatic health state	Derived from TA632 [52], based on clinical expert feedback
Metastatic setting (ET-resistant and ET-sensitive)	See section 8.3.3 and [redacted] Appendix M Metastatic health state – Endocrine resistant pathway	See section 8.3.3 and [redacted] Appendix M Metastatic health state – Endocrine resistant pathway	ET-resistant (based on MONARCH 2) and ET-sensitive (based on MONARCH 3) [16, 17]
Adverse events	See section 7.1.2.2	See sections 8.5.4	monarchE [14]

Abbreviations: IIR, independent reviewer; ITT, intention to treat; I/P, intermediate/poor; LEN+PEM, lenvatinib pembrolizumab; NIVO+IPI, nivolumab ipilimumab; OS, overall survival; PFS, progression-free survival; TTD, Time-to-treatment discontinuation; TEAE, treatment emergent adverse events; TRAE, treatment-related adverse events

8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

8.2.2.1 Patient population

The population for this economic assessment 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 ALNs, or pathological tumour involvement in 1–3 ALNs, alongside Grade 3 disease and/or a primary tumour size of ≥5 cm.

As mentioned in section 5.1.2, 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 [8]. 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 25 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 [10].

Table 25. Cohort 1 population characteristics of MonarchE trial, and Danish clinical practice according to DBCG report [10].

Patient population Important baseline characteristics	MonarchE (n= 5120) [1]	Used in the model	Danish clinical practice [10]
Age, median (range)	51.0 (22, 89)	51.0 (22, 89)	Same as MonarchE [1]
Female , %	5088 (99.4)	5088 (99.4)	Same as MonarchE [1]
Race, n (%)			
White	3575 (70.8)	3575 (70.8)	Slightly higher than in MonarchE [1]
Asian	1227 (24.3)	1227 (24.3)	Lower than in MonarchE [1]
Menopausal status, n (%)			
Premenopausal	2220 (43.4)	2220 (43.4)	Same as MonarchE [1]
Postmenopausal	2896 (56.6)	2896 (56.6)	Same as MonarchE [1]
Number of Positive Lymph nodes, %			[10]
0	12 (0.2)	12 (0.2)	2.113 (56,3)
1-3	1761 (34.4)	1761 (34.4)	765 (20,4)
4-9	2223 (43.4)	2223 (43.4)	205 (5,5)*
≥10	1123 (21.9)	1123 (21.9)	NA
Missing	1 (0.0)	1 (0.0)	NA
Histopathological Diagnosis Grade			[10]
G1 – Favourable	425 (7.5)	425 (7.5)	127 (23,6)
G2 – Moderately Favourable	2772 (49.2)	2772 (49.2)	382 (71,1)
G3 – Unfavourable	2150 (38.1)	2150 (38.1)	28 (5,2)
GX – Cannot be Accessed	267 (4.7)	267 (4.7)	NA
Missing	23 (0.4)	23 (0.4)	NA

Abbreviations: ET, endocrine therapy
*>= 4

8.2.2.2 Intervention

Abemaciclib is an oral therapy administrated 150mg film-coated tablets BID. Currently, abemaciclib is recommended for treatment of HR+/HER2- advanced BC (aBC) [2]. Abemaciclib has received a confirmation letter that the marketing

authorization has been extended to the use in combination with endocrine therapy in the adjuvant setting, for the treatment of adult patients with HR+/HER2−, node-positive, early breast cancer at high risk of recurrence [8] [9]. Abemaciclib is an oral therapy expected to be administered twice a day, with 150mg film-coated tablets, until recurrence, for a maximum of two years, or until unacceptable toxicity occurs.

Table 26. Description of the intervention as used in the model

Intervention	Clinical documentation	Used in the model	Expected Danish clinical practice
Posology	Abemaciclib is an oral therapy administrated 150mg film-coated tablets twice a day (a total of 300 mg daily) in combination with ET	Abemaciclib is an oral therapy administrated 150mg film-coated tablets twice a day (a total of 300 mg daily) in combination with ET	Abemaciclib is an oral therapy administrated 150mg film-coated tablets twice a day (a total of 300 mg daily) in combination with ET
Length of treatment (time on treatment) (mean/median)/ criteria for discontinuation	Until recurrence, for a maximum of two years, or until unacceptable toxicity occurs	Until recurrence, for a maximum of two years, or until unacceptable toxicity occurs	Until recurrence, for a maximum of two years, or until unacceptable toxicity occurs
The pharmaceutical's position in Danish clinical practice	NA	Adjuvant treatment of adult patients with HR+/HER2−, node-positive, early breast cancer at high risk of recurrence	Adjuvant treatment of adult patients with HR+/HER2−, node-positive, early breast cancer at high risk of recurrence

8.2.2.3 Comparators

As discussed in section 5.2.3, different ET therapies are approved in the EU and recommended in Denmark for the 1L adjuvant ET treatment of patients with high-risk HR+/HER2-, node-positive eBC. These four types of ET have been confirmed to be relevant in treatment of high-risk HR+/HER2-, node-positive eBC by a Danish clinician [1]. These therapies are used in the model in alignment with Danish clinical practice [1].

Table 27. Comparators

Comparator	Clinical documentation	Used in the model	Expected Danish clinical practice
Tamoxifen			
Posology	20 mg orally OD	20 mg orally OD	20 mg orally OD
Length of treatment	5-10 years, if no progression or unacceptable toxicity	5-10 years, if no progression or unacceptable toxicity	5-10 years, if no progression or unacceptable toxicity
The comparator's position in Danish clinical practice	Adjuvant treatment of patients with high-risk HR+/HER2-, node-positive eBC	Adjuvant treatment of patients with high-risk HR+/HER2-, node-positive eBC	Adjuvant treatment of patients with high-risk HR+/HER2-, node-positive eBC
Letrozole [44]			
Posology	2.5 mg orally OD	2.5 mg orally OD	2.5 mg orally OD
Length of treatment	5 years, if no progression or unacceptable toxicity	5 years, if no progression or unacceptable toxicity	5 years, if no progression or unacceptable toxicity

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Comparator	Clinical documentation	Used in the model	Expected Danish clinical practice
The comparator's position in Danish clinical practice	Adjuvant treatment of patients with high-risk HR+/HER2-, node-positive eBC	Adjuvant treatment of patients with high-risk HR+/HER2-, node-positive eBC	Adjuvant treatment of patients with high-risk HR+/HER2-, node-positive eBC
Anastrazole [45]			
Posology	1 mg orally OD	1 mg orally OD	1 mg orally OD
Length of treatment	5 years, if no progression or unacceptable toxicity	5 years, if no progression or unacceptable toxicity	5 years, if no progression or unacceptable toxicity
The comparator's position in Danish clinical practice	Adjuvant treatment of patients with high-risk HR+/HER2-, node-positive eBC	Adjuvant treatment of patients with high-risk HR+/HER2-, node-positive eBC	Adjuvant treatment of patients with high-risk HR+/HER2-, node-positive eBC
Exemestane [43]			
Posology	25 mg orally OD	25 mg orally OD	25 mg orally OD
Length of treatment	5 years, if no progression or unacceptable toxicity	5 years, if no progression or unacceptable toxicity	5 years, if no progression or unacceptable toxicity
The comparator's position in Danish clinical practice	Adjuvant treatment of patients with high-risk HR+/HER2-, node-positive eBC	Adjuvant treatment of patients with high-risk HR+/HER2-, node-positive eBC	Adjuvant treatment of patients with high-risk HR+/HER2-, node-positive eBC

Abbreviations: eBC, early breast cancer; HR+/HER2- , hormone receptor-positive / human epidermal growth factor receptor 2; mg, milligram; OD, once a day

8.2.2.4 Relative efficacy outcomes

In the previous DMC assessments of pertuzumab in combination with herceptin for HER2+ breast cancer [3] and of trastuzumab with emtasin [54], iDFS, DRFS and OS rates have been identified as relevant outcomes to assess the relative efficacy of treatments for eBC [3]. The manufacturer therefore believes that the included efficacy outcomes are highly relevant to assess the value of ET + abemaciclib in HR+, HER2 negative, node positive, high risk eBC patients in Denmark. This is summarised in Table 28.

Table 28. Relevance of model efficacy inputs in Danish clinical practice

Clinical efficacy outcome	Clinical documentation	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
iDFS	See Table 13	Traditionally used in evaluations of drugs in breast cancer	Traditionally used in evaluations of drugs in breast cancer
DRFS	See Table 14	Traditionally used in evaluations of drugs in breast cancer	Traditionally used in evaluations of drugs in breast cancer
OS	See Table 15	Traditionally used in evaluations of drugs in oncology	Traditionally used in evaluations of drugs in oncology

Abbreviations: iDFS, invasive disease-free survival; DRFS, distant-relapse free survival; OS, overall survival

8.2.2.5 Adverse reaction outcomes

Similarly to the efficacy outcomes, in the abovementioned DMC assessments [3] [54], Grade 3-4 AEs and Serious AEs have been identified as relevant outcomes to assess the relative safety of treatments for eBC. However, only Grade 3-4 (and Grade I for Diarrhea) are included in the economic model)

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Table 29. Adverse reaction outcomes

Adverse reaction outcome	Clinical documentation	Used in the model (numerical value)
Grade 3-4 AEs	See Table 20	See Table 47and Table 48
Serious AEs	See Table 21	NA

8.3 Extrapolation of relative efficacy

8.3.1 Time to event data – summarized:

The individual patient level data (IPD) from the MonarchE trial was used to generate the IDFS, TTD, and OS (without distant recurrence) outcomes for both abemaciclib + ET and ET. The parametrised curves for IDFS, TTD, and OS were utilised in the model. The parametrisation of the IDFS, TTD, and OS curves for abemaciclib + ET and ET aids in estimating long term outcomes for patients beyond the trial period and subsequently allows for modelling over a longer time period. At the April 2021 analysis, the median duration of follow-up was approximately 27 months in both trial arms. The median treatment duration of abemaciclib was 23.6 months and the median duration of ET was not reached in both trial arms. The analyses were carried out using SAS (traditional parametric models) and R (cubic spline models).
Parametric models were fit to the KM data of the monarchE trial. The parametric model fitting for IDFS, TTD and OS without distant recurrence was conducted according to the following steps recommended in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 [61].

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

8.3.1.1 Methodology

Proportional hazards assumption

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

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

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

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

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

Survival extrapolation approaches

In accordance with NICE DSU TSD 14,[61] the range of parametric distributions fitted to the monarchE trial were: exponential, Weibull, Gompertz, log-normal, log-logistic, gamma and generalised gamma. In addition to the standard parametric distributions, Weibull spline models (from now on, referred to as hazard splines) with one and two intermediate knots were examined. Spline models with more intermediate knots were not considered, as these are deemed clinically implausible and associated with the risk of "overfitting" the data.

Model selection

A selection of extrapolation models was based on statistical fit of the models to the trial data, based on AIC and the BIC, as well as visual inspection of the survival curves and hazard plots. Consideration was given to the following, as per the recommendations provided in NICE DSU TSD 14.[61]

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

8.3.1.2 Analysis outcomes

8.3.1.2.1 iDFS

The PH assumption between treatment arms was tested. The log-cumulative plot in Figure 10 shows the treatment arms are crossing during the first four months, after which they appear to move in parallel. The Grambsch and Therneau test could not be labelled as statistically significant (p-value = 0. 0.415). This is consistent with the Schoenfeld residuals visualisation Figure 11 in which no clear time trend can be observed, suggesting no violation of the PH assumption. As such, a single model, including an adjustment factor for treatment effect (HR), could be fitted to the IDFS curve of the monarchE data.

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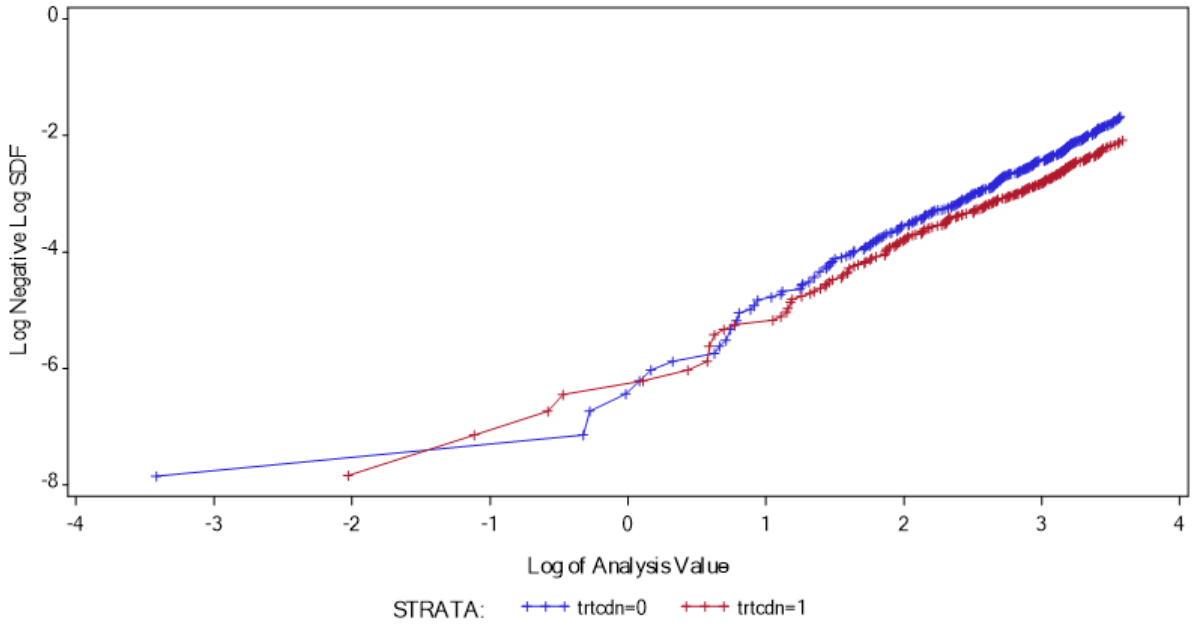
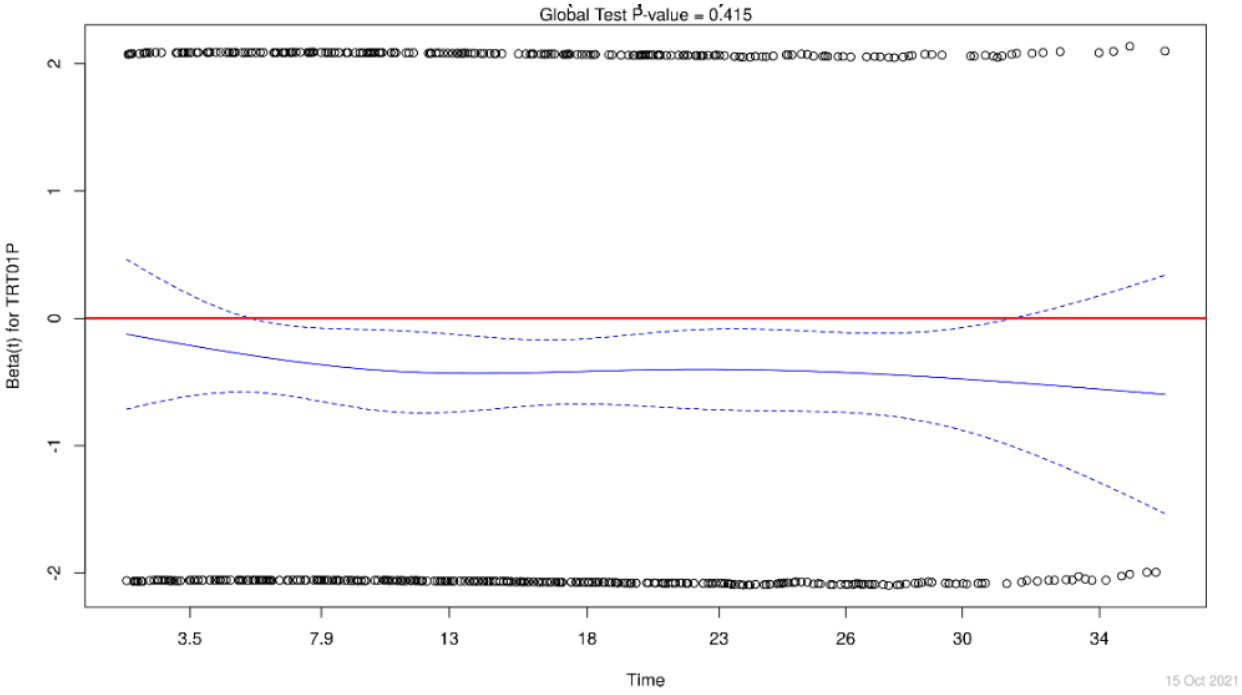
Figure 10. IDFS log-cumulative hazard plot – APRIL 2021 Cohort 1 population



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

Figure 11: IDFS Schoenfeld residual plot – APRIL 2021 Cohort 1 population



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

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 is presented in Table 30. The best statistical

fit is provided by the [redacted] as it presents both the lowest AIC and BIC values. The [redacted] is followed by the [redacted], which deviates less than 2.0 points from the Weibull distribution in both AIC and BIC. As the [redacted] provides ET IDFS values that closely resemble the external data, [redacted] should be used as the base case, in which it will be combined with a treatment waning assumption.

Table 30: AIC and BIC values - APRIL 2021 Cohort 1 population

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

Note: 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 [redacted].

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; IDFS: invasive disease-free survival.

External validation

As well as statistical fit, the choice of extrapolation to model IDFS was informed by comparing the landmark IDFS estimates for abemaciclib + ET and ET alone predicted by the model to external data sources. As described in **Appendix A – Literature search for efficacy and safety of intervention and comparator(s)**, a clinical SLR was conducted to identify relevant RCTs evaluating ET-regimens in patients with HR+, HER2− early breast cancer. The review identified 163 publications reporting on 37 RCTs. Nine studies reported data where >80% of the trial population was HER2-. An overview of the studies has been provided in Table 31. The IDFS endpoints which are directly comparable with monarchE were from trials assessing CDK4&6 inhibitors + ET. The follow-up time of these trials were limited and like the 1st April 2021 data cut for monarchE (~3-4 years). Out of the six trials assessing ET regimes only, two trials did not include patients who were offered pre-treatment with neoadjuvant and adjuvant therapies. One trial only reported safety data. FATA-GIM3 [62] and FACE [62] were the remaining trials which were comparable to MonarchE, with the exception of the additional event types included in their disease-free survival (DFS) definition. The five-year DFS rates reported in these trials were used for external validation of extrapolations for the ET arm in the model.

Table 31. Comparison of HR+ HER2– early breast cancer trials identified from the clinical SLR reporting relevant survival outcomes

Trial name	Treatment	Latest publication	Timepoint for rate (Years)	IDFS / DFS	IDFS/DFS rate (%) [95% CI]	IDFS /DFS excludes	Prior neo/adjuvant treatment (x = both included)
PALLAS [63]	ET + CDK4&6 inhibitors	2020	~ 3	IDFS	Palbociclib + ET:87.9 ET:88.4	DCIS New primary breast cancer	x
PENELOPE [64]		2020	~ 4	IDFS	Palbociclib + ET:73 ET:72.4	DCIS New primary breast cancer	x
monarchE [65]		2020	~ 3	IDFS	ABE + ET: 92.2 ET: 88.7	DCIS New primary breast cancer	x
HOBOE [66]	Tamoxifen vs. AI	2019	~ 5	DFS	Tamoxifen: 85.4 (80.9-88.9) Letrozole: 93.2 (89.7-95.5)	Ipsilateral New primary breast cancer	x
FATA-GIM3 [67]	Tamoxifen to AI vs. AI	2018	**~ 5**	DFS	Anastrozole pooled Letrozole pooled Exemestane pooled	Ipsilateral DCIS New primary breast cancer	x
SUCCESS [68]	Tamoxifen to AI vs. AI	2018	N/A	Safety only	N/A	N/A	x
FACE [62]	AI vs AI	2017	**~ 5**	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	x
SOFT [69]	Tamoxifen + OFS vs. AI + OFS	2015	~8	DFS	Tamoxifen: 78.9 Exemestane + OFS: 85.9	Ipsilateral DCIS New primary breast cancer	Prior adjuvant chemotherapy
TEXT [70]		2014	N/A	DFS	Prior adjuvant chemotherapy received: Total events % Tamoxifen + triptorelin:12.59 Exemestane + triptorelin:16.25	Ipsilateral DCIS New primary breast cancer	Prior adjuvant chemotherapy

Footnotes: [a] 3-year IDFS rates from the APRIL 2021. [b] The TEXT trial reported the total events, rather than the IDFS/DFS rate.
Abbreviations: AI: aromatase inhibitor; CDK: cyclin-dependent kinase; DFS: disease-free survival; ET: endocrine therapy; HER2–: human epidermal receptor 2 negative; HR+: hormone receptor positive; IDFS: invasive disease-free survival; N/A, Not applicable; OFS: ovarian function suppression; SLR: systematic literature review.

The landmark IDFS rates for abemaciclib + ET and ET alone for the seven parametric distributions and the two spline models are presented in Table 32.

The comparisons of the ET arm from monarchE and the external trials, should be approached cautiously as the populations and endpoints used in the external trials are not directly comparable with monarchE. External trials incorporated a mixture of patients, including those at lower risk of disease recurrence and hence had slightly better outcomes in the ET alone arms. For example, the FACT-GIM3 trial included patients with any pathological tumour size and axillary lymph nodal status. However, this was considered to be the most plausible method for validation of the extrapolations by global clinical experts. When comparing the monarchE trial data with the five-year IDFS/DFS estimates for ET from the FACE trial (letrozole: 84.9% [95% CI: 83.2%, 86.2%] and anastrozole: 82.9% [95% CI: 81.2%, 84.5%]), all the extrapolations appear to estimate pessimistic outcomes for the ET arm as the monarchE trial only included patients at high risk of disease recurrence and therefore with worse disease prognosis [65].

Table 32. Comparison of HR+ HER2- EBC trials identified from the clinical SLR

	Five-year rates		Ten-year rates	
	Abemaciclib + ET	ET	Abemaciclib + ET	ET
[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]	[redacted]	[redacted]	[redacted]	[redacted]

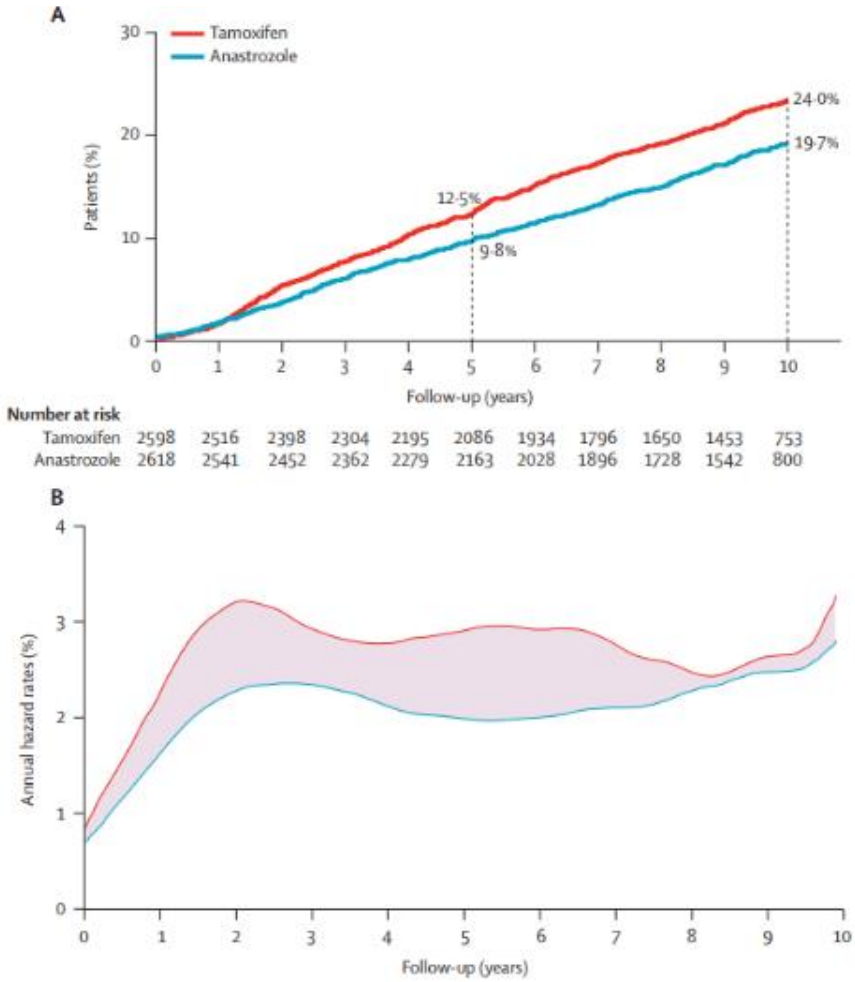
***** The [redacted] is best at resembling the external data

Abbreviations: ABE, Abemaciclib; AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; ET, Endocrine Therapy

Note: The best performing distribution is made bold.

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. The 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 (Cuzick *et al*, 2010 [71], as shown in). In an earlier publication (Cuzick *et al*. 2006 [72]) 'carryover' effect was also discussed. Based on the results of Early Breast Cancer Trialists' Collaborative Group, 2005 and ATAC Trialists' Group, 2005 [73] it was highlighted that the effect of tamoxifen and AIs on recurrence rates were maintained for at least five and six years, respectively, after stopping treatment.

Figure 12: Curves for time to recurrence in HR+ patients in the ATAC trial



Footnotes: A) KM prevalence curves and B) smoothed hazard rate curves. Numbers at risk differ in some cases from those provided in the 100-month analysis because of additional follow-up data.
Abbreviations: ATAC: Arimidex, Tamoxifen, Alone or in Combination; HR+: hormone receptor positive.
Source: Cuzick *et al.* (2010)[74]

[redacted]In the absence of longer follow up data from other trials reporting specifically on HER2- status, using the data published by the most recent ATAC trial [71] we have assumed that treatment effect between ABE + ET and ET alone arms would be similar to what is seen beyond more effective ET treatments such as anastrozole. We have assumed that treatment effect lasts for at least [redacted] years at which point treatment effect starts to wane.

An assumption was taken that treatment effect waning continue until year [redacted]. Year [redacted] was chosen as this was the point in the model where IDFS rates equal background mortality (**Error! Reference source not found.**).

Data from monarchE demonstrates the existence of a treatment effect of abemaciclib + ET beyond discontinuation. A piecewise analysis for IDFS in monarchE was performed at the most recent data cut-off in the ITT population, demonstrating that the magnitude of the treatment benefit of abemaciclib, in terms of the reduced risk of an IDFS event, continued to increase over time in the follow-up period, and the HRs continue to deepen between Year 1–2 and Year 2+, by which time most patients will have discontinued treatment with abemaciclib (2). A similar analysis for Cohort 1 of monarchE is not available, however seeing as Cohort 1 comprises 91% of the ITT population, the HRs based on the ITT population are a suitable proxy.

Eli Lilly acknowledge that the exact duration of the long-term treatment effect is uncertain due to a lack of long-term clinical evidence on the treatment benefit of abemaciclib + ET. However, in the absence of longer-term clinical data for abemaciclib + ET, assumptions informing the duration of the abemaciclib treatment effect, and the waning of this effect, were based on long-term data for ET.

The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial was one of the few trials reporting on long term follow up data for anastrozole and tamoxifen for up to 10 years and clinical experts noted that the ATAC trial was the most relevant to inform treatment waning assumptions [72]. The data for tamoxifen and aromatase inhibitors are used as the best available proxy to inform the plausible duration of treatment effect for abemaciclib, in the absence of data specific to abemaciclib; this data demonstrated a lasting treatment benefit of up to 8 years for one ET over the other. Based on this, Eli Lilly maintains the base case assumption that a full treatment effect of abemaciclib + ET versus ET alone is experienced until at least [redacted] Please note, Eli Lilly believe that applying assumptions that mimic ET based on the ATAC study is the most conservative assumption that remains plausible given that a significant and deepening treatment effect has been demonstrated over ET in the monarchE trial.

A full treatment effect for abemaciclib + ET was assumed to last for [redacted] after which treatment effect wanes until Year 28, which represents the point in the model where IDFS rates equal background mortality.
Clinical trial data from Colleoni et al. (2016) further supports the long-term waning of the treatment effect by demonstrating that the highest risk of recurrence from early breast cancer occurs in the first 5 years following initiation of adjuvant therapy [72]. The hazards of IDFS recurrence in the ET alone arm and the abemaciclib + ET arm under Eli Lilly's base case treatment waning. Assumptions are consistent with this data. This can be observed visually in **Error! Reference source not found.** which presents the hazard of recurrence of the abemaciclib + ET and ET alone arm over the model lifetime under Eli Lilly base case treatment waning assumptions.
When treatment waning is assumed to occur over a longer period, such as year 28 in Eli Lilly's base case, the trend of the hazard of recurrence of the abemaciclib + ET arm is aligned with the trend of the hazard in the ET alone arm. It gradually wanes to the hazard of IDFS in the ET alone arm, following a plausible pattern that is also consistent with Colleoni *et al.* (2016) where the risk of recurrence decreases over time [75]. Based on this evidence, the treatment benefit of abemaciclib + ET should be gradually waned until it reaches background population mortality, in line with the Eli Lilly's base case assumptions.

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

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[redacted] (Cohort 1 population) with numbers at risk

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

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Figure 13. XXXXXXXX (Cohort 1 population) 360 months

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Figure 14. [redacted]Cohort 1 population) with numbers at risk

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Figure 15. [redacted] (Cohort 1 population

. The joint loglogistic model was chosen It resulted in five and ten years iDFS rates most resembling the external rates presented in Table 32. No additional Danish specific data has been identified.

[redacted] ([redacted]

8.3.1.2.2 TTD

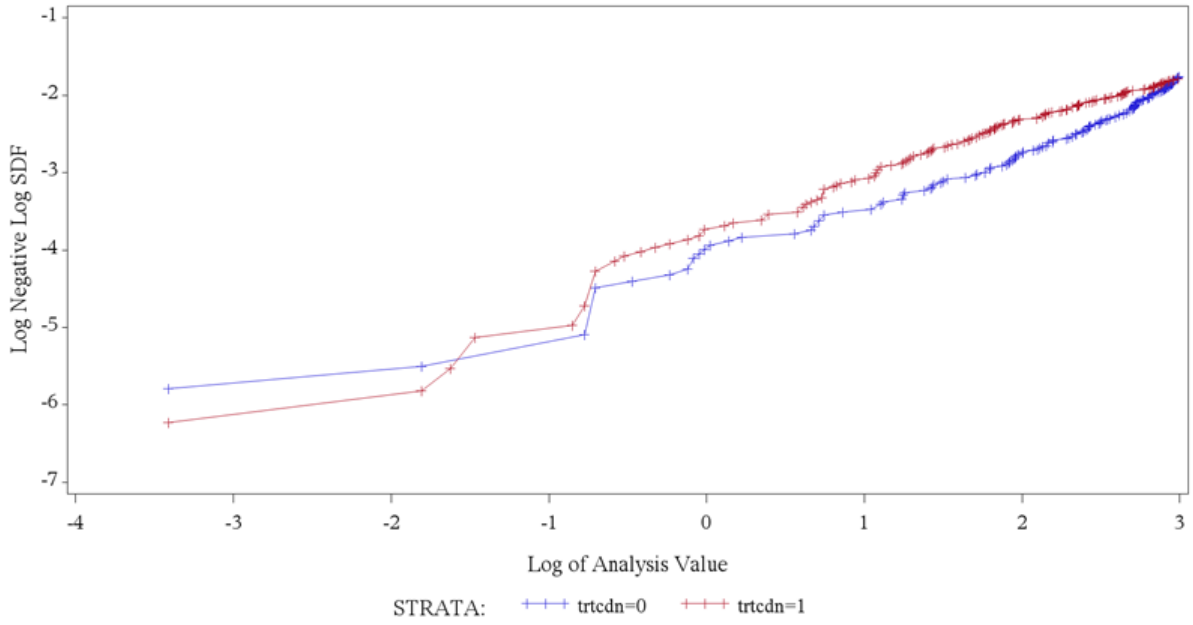
The duration of treatment is determined by the TTD curves of the abemaciclib + ET and ET only treatment arms from the monarchE trial. In the monarchE trial, patients remained on treatment until they 1) reached a limit defined by a clinical stopping rule, 2) discontinued treatment due to toxicity, or 3) withdrew from study or experienced disease re-currence. Due to the maximum two-year treatment duration permitted for ABE, and the follow up period of the APRIL 2021 DCO, the full KM curve was used to estimate TTD for ABE in the base case. The parametric assessments for ABE have been included to allow a parametric distribution to be considered for a part of or the whole TTD time horizon.

The PH assumption was tested between ET in the intervention arm and ET in the comparator arm. The log-cumulative plot in Independent models were fitted to the trial data of ET.

Figure 16 shows that there is convergence of the trial arms at several points in the plot, most noticeably during the first month and after 20 months. The Grambsch and Thernau test should be interpreted as statistically significant (p-value = [redacted]). This is consistent with the Schoenfeld residuals visualisation (Figure 17), in which clear time trends can be observed, suggesting violation of the PH assumption.

Independent models were fitted to the trial data of ET.

Figure 16. TTD log-cumulative hazard plot - APRIL 2021 DCO Cohort 1 population



TRTCDN = 0: ABE + ET, TRTCDN=1: ET alone Abbreviations: ABE, abemaciclib; ET, endocrine therapy

Figure 17. TTD Schoenfeld residual plot - APRIL 2021 DCO Cohort 1 population

[redacted]

Footnotes: The red line indicates no treatment effect.

Abbreviations: TTD: time to treatment discontinuation.

The seven parametric distributions and two spline models were fitted independently to the TTD KM data and were evaluated based on AIC and BIC, as presented in **Error! Reference source not found.** to **Error! Reference source not found.** below.

The seven parametric distributions and two spline models were fitted independently to the TTD KM data and were evaluated based on AIC and BIC, as presented in **Error! Reference source not found.** (ABE), **Error! Reference source not found.** (ET intervention arm) and**Error! Reference source not found.** (ET comparator arm). The best statistical fit for abemaciclib is provided by the [redacted] distribution. Compared to the [redacted] distribution, the other distributions appeared to provide a significantly worse statistical fit for all treatment arms. All distributions had a BIC value difference that was larger than five, when compared to the [redacted]. For ET in the intervention and ET in the comparator arm, the best fit was provided by the [redacted] distribution, which performed best on AIC for the intervention arm and AIC

and BIC for the comparator arm. As this distribution results in unrealistic long-term survival outcomes, the [redacted] was chosen for the base case; this distribution reflects the ITT TTD the closest.

[redacted]

[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Hazard spline 2 knots	[redacted]	[redacted]
Hazard spline 1 knot	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]

***** Model did not converge

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

Note: the first best-fitting curve is in bold, while the second and third-best fitting curves are underlined.

[redacted]

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

***** Models did not converge

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion Note: the first best-fitting curve is in bold, while the second and third-best fitting curves are underlined.

[redacted]

[redacted]	[redacted]	[redacted]
Hazard spline 2 knots	[redacted]	[redacted]
Hazard spline 1 knot	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]

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Exponential	[redacted]	[redacted]

Note: the first best-fitting curve is in bold, while the second and third-best fitting curves are underlined.

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion. ET: endocrine therapy; TTD: time to treatment discontinuation.

Evidence from the monarchE trial was deemed the most recent and relevant for the validation of the TTD extrapolations. Since a clinical and economic stopping rule was applied for the ET arm, there is limited risk of bias being introduced into the model.

[redacted]

Based on feedback from Danish KOLs that they expect approximately 85% of patients to still receive ET at 10 years, the loglogistic extrapolations for TTD was also explored as scenario analysis. Similarly, based on this feedback from Danish KOLs, a 7-year stopping rule for the ET arm has been explored in an additional a scenario analysis.

The long-term extrapolations for TTD for abemaciclib + ET and ET alone using the models selected for the base case economic analysis ***(before the base case stopping rules are applied)*** are presented in Figure 18.

Figure 18: Long-term TTD extrapolations for the ET alone arm in the base case economic analysis – independent fit (Cohort 1 population) with numbers at risk

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

Figure 19. Long-term TTD extrapolations for the ET alone arm in the base case economic analysis – independent fit (Cohort 1 population) 360 months

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Figure 20: Long-term TTD extrapolations for the abemaciclib + ET arm in the base case economic analysis – independent fit *(before the base case stopping rules for abemaciclib and ET are applied) (Cohort 1 population) with numbers at risk*

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

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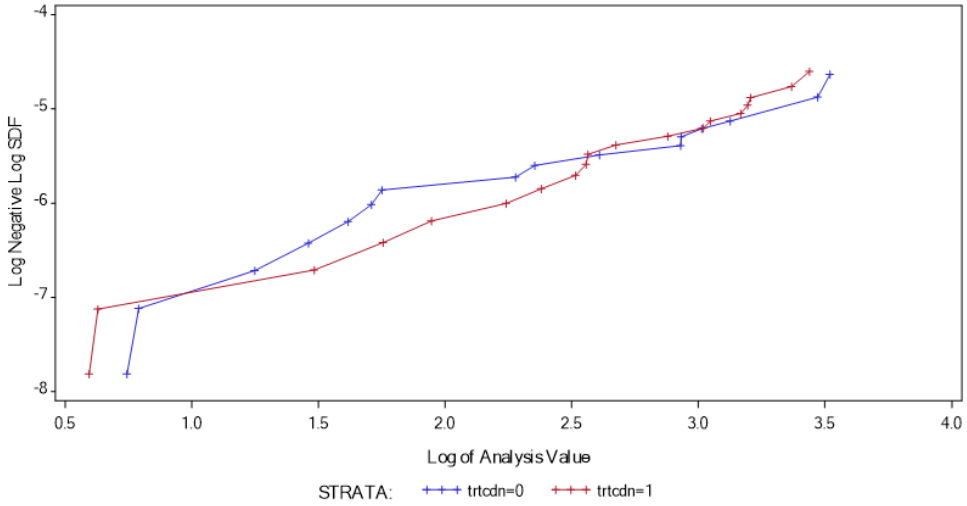
Figure 21. Long-term TTD extrapolations for the abemaciclib + ET arm in the base case economic analysis – independent fit (Cohort 1 population) 360 months

8.3.1.2.3 OS without distant recurrence

The log-cumulative hazard plot is displayed in Figure 22 the log-cumulative hazard plot moderately indicates PH violation due to the slight crossing of the ABE + ET and the ET alone curves. The Grambsch and Thernau test could not be labelled as statistically significant (p-value = 0.544), which means that the PH assumption cannot be rejected based on this test. The Schoenfeld residuals plot (Figure 23) appears to suggest a slight increasing trend. It should be noted that these results can be considered volatile, as few OS without distant recurrence events were observed in the trial. A single model, including an adjustment factor for treatment effect (HR), was fit to the monarchE trial data.

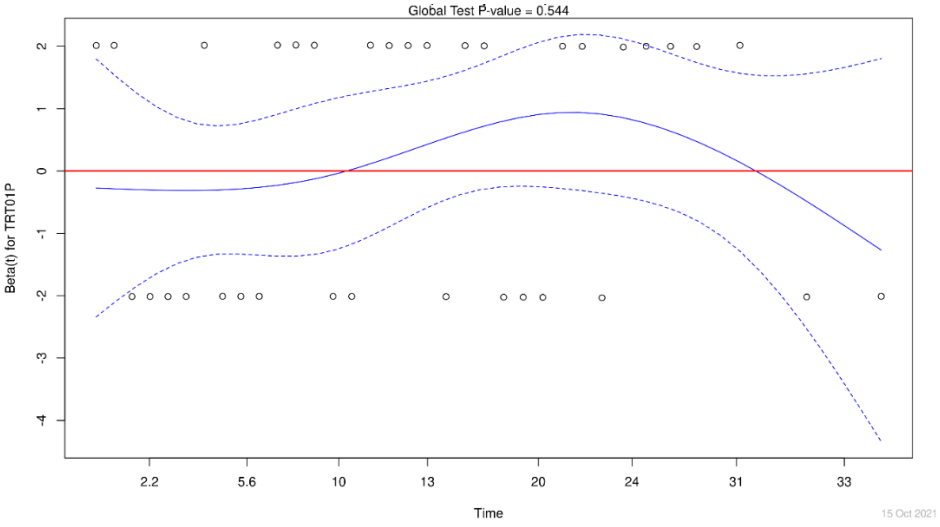
Figure 22. OS without distant relapse log-cumulative hazard plot - APRIL 2021 DCO Cohort 1 population



Abbreviations: ABE, abemaciclib; ET, endocrine therapy

TRTCDN = 0: ABE + ET, TRTCDN=1: ET alone

Figure 23. OS without distant relapse Schoenfeld residual plot - APRIL 2021 DCO Cohort 1 population



Footnotes: The red line indicates no treatment effect.

Abbreviations: OS: overall survival.

A summary of all the AIC and BIC values are presented in **Error! Reference source not found.**. The best statistical fit was provided by the exponential distribution as it presents the lowest AIC and BIC values. This distribution was used in the base case. The second-best performing curve was the log-normal curve.

[redacted]AIC and BIC values[redacted]APRIL 2021 DCO [redacted]

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

Log-logistic	[redacted]	Log-logistic	[redacted]
Weibull	[redacted]	Weibull	[redacted]
Gompertz	[redacted]	Gompertz	[redacted]
Hazard spline 1 knot	[redacted]	Hazard spline 1 knot	[redacted]
Hazard spline 2 knots	[redacted]	Hazard spline 2 knots	[redacted]
Generalised gamma	[redacted]	Generalised gamma	[redacted]
Exponential	[redacted]	Exponential	[redacted]

* The generalised gamma distribution did not converge; the statistical fit of this model was not assessed.
Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion
Note: the first best-fitting curve is in bold, while the second and third-best fitting curves are underlined.

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 the distribution was based on internal validations.

Within the framework of the model, the OS extrapolations are close to the background mortality rate. Given risk of death from a non-metastatic recurrence is limited, the risk of any bias is low, as the OS curve is bound by background mortality. The long-term OS extrapolations for abemaciclib + ET and ET alone using the exponential model are presented in Figure 24.

[redacted]

Figure 24: Long-term OS extrapolations for abemaciclib + ET arm in the base case economic analysis – single fit (Cohort 1 population) with numbers at risk

[redacted]

Footnotes: These extrapolations include the treatment waning assumptions.

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Abbreviations: ET: endocrine therapy; OS: overall survival; KM: Kaplan-Meier.

Figure 25. Long-term OS extrapolations for abemaciclib + ET - single fit (Cohort 1 population) 360 months

Figure 26: Long-term OS extrapolations for ET alone arm in the base case economic analysis – single fit (Cohort 1 population) with numbers at risk

Footnotes: These extrapolations include the treatment waning assumptions.

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Abbreviations: ET: endocrine therapy; OS: overall survival; KM: Kaplan-Meier.

Figure 27. Long-term OS extrapolations for ET alone - single fit (Cohort 1 population

A summary of the base case extrapolations for IDFS, OS and TTD for abemaciclib + ET and ET alone is provided in **Error! Reference source not found.**.

XXXXXXXXXXXXXXX

	Abemaciclib + ET		ET alone
Base case IDFS extrapolation			
Base case OS extrapolation			
	Abemaciclib	**ET (for patients receiving abemaciclib)**	**ET alone**
Base case TTD extrapolation			

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

8.3.2 Remission health state

1.132 The clinical SLRs reported in **Appendix A – Literature search for efficacy and safety of intervention and comparator(s**) and the economic SLR reported in **Appendix L: Published cost-effectiveness results** identified a lack of data surrounding the non-metastatic recurrence and onwards pathway for the monarchE patient population. Following consultation with clinical experts, assumptions previously made in early breast cancer models, specifically for the HER2+ patient population, were considered the most appropriate data source. In the previous DMC assessment of pertuzumab in

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combination with herceptin for HER2+ breast cancer [3], the study (Hamilton et al. (2015) of 12,836 patients with early breast cancer which estimated the risk of incurring a second malignancy following adjuvant therapy [15] was used to inform the transition probability of patients moving from remission to the metastatic health state. The study reported a median time until progression of 7.6 years (91.2 months). The median time to progression was converted into a monthly transition probability of 0.00760. In line with the DMC assessment of pertuzumab in combination with herceptin [3] and with clinical expert feedback [1], recurrence rate from the remission health state was assumed to remain constant over time, and an exponential distribution was used to estimate the recurrence rate and convert this into a monthly probability (0.00760).

Non metastatic recurrence was modelled as a tunnel state with patients receiving treatments dictated by the type/location of the disease recurrence experienced. Patients can die at any point from non-metastatic recurrence. Those who do not die are assumed, in the base case, to receive 12 months of treatment before transitioning to the remission health state. This setting is included in cell E91 of the Survival sheet. The same assumption on the duration of the NMR tunnel state being of 12 months was previously made in the application dossier of Trastuzumab and was accepted by the DMC on September 2020. [76]

Once in remission, patients remain there unless they die from any cause, or they experience another recurrence; a further recurrence of this kind is assumed to be non-curative. A tunnel state is only used for non-metastatic recurrence. The remission state is not a tunnel state and is defined by the probability of 0.00757 (cell E102 of the Survival sheet) derived by Hamilton et al, 2015 [15].

8.3.3 Metastatic health state

At the time of the last data cut (APRIL 2021 DCO) the monarchE trial had limited median follow up data (27 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 and 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 as a treatment from advanced breast cancer in these settings. The MONARCH 2 [46] and MONARCH 3 [12] trials are the foundation of this evidence base. The key inclusion and exclusion criteria for these trials have been provided in Appendix P Eligibility criteria of Monarch2 and Monarch3 trials - Clinical trials informing the endocrine treatment resistant and endocrine treatment sensitive metastatic pathways. The MONARCH 2 trial included HR+, HER2- locally advanced or metastatic breast cancer patients who had disease recurrence on or immediately after prior ET. The MONARCH 3 trial included post-menopausal 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 MONARCH 2 and MONARCH 3 did not exclusively include monarchE like patients. However, the CMs which used these trial data were deemed the most recent, robust, comprehensive, and relevant data sources to inform the metastatic recurrence health state. The CMs which used MONARCH2 and MONARCH3 were used both in UK [16] [17] and Danish [7] submissions. Where possible, inputs from the abemaciclib submission for aBC submitted to the DMC were preferred [7]. However, due to limited level of detail included in the abemaciclib submission for aBC submitted to the DMC, it is assumed in this submission that inputs from NICE's TA725 [16] and TA563 [17] are representative of the Danish clinical setting.

The metastatic disease setting could in theory be modelled in three different ways using the MONARCH 2 and MONARCH 3 models. **Table 33** provides an overview of the three methods and their pros and cons.

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 trials compared to the MONARCH 2 and MONARCH 3 trials, respectively. All assumptions surrounding the costs and utilities would be directly transferred from the MONARCH 2 and MONARCH 3 models 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 point of 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 setting in the monarchE model. The sections labelled 'Metastatic health state 'pay-off' approach' provide 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 an 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 third approach was the most transparent whereby one would incorporate three models into one framework. Given the computational running time for the probabilistic sensitivity 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.

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Table 33. Overview of 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 3. Limited critique of inputs and assumptions	1. Uncertainty from the MONARCH 2 + MONARCH 3 CMs will not be applied for LYs. • Crude assumption of SE. 2. Population heterogeneity* • Age: 9-10 year difference between mE (~52 yrs) + MONARCH 2 (60 yrs) + MONARCH 3 (63 yrs)*. 3. Incorporating the costing (1L + 2nd line) part from both MONARCH 2 + MONARCH 3 CMs would be time consuming and slow the model down. 4. Other models did not use pay off approach as external data with long term follow-up was available for the HER2+ EBC models 5. Patient distribution within the health state external to monarchE model.
2. Pay-off approach (MONARCH 2 + MONARCH 3 CMs) • Outputs used from MONARCH 2 + MONARCH 3 CMs: QALYs, Lys & costs, SE from PA.	1. Very simple + Efficient 2. QALY, LY & Costs from MONARCH 2 + MONARCH 3 CMs 3. Inclusion of uncertainty from MONARCH 2 + MONARCH 3 CMs 4. The cons of the complex models are less apparent	1. Costing part more complex for country adaptations. 2. External to monarchE model. 3. Questions surrounding assumptions would be challenging to address. 4. Population heterogeneity*. 5. Other models did not use this pay-off approach.
3. Including MONARCH 2 + MONARCH 3 CMs in the monarchE model.	1. Models all pathways. 2. Comprehensive view of QALY, LY & Costs from MONARCH 2 + MONARCH 3 CMs 3. If the HTA body critiques the input and assumption these can be addressed in the monarchE model as it would not be external to the excel structure	1. Population heterogeneity remains*. 2. Time consuming for countries that do not have MONARCH 2 + MONARCH 3 CMs up to date models available to them*. 3. Complex structure and slow to run PA*. 4. Opening up to further critique for the various inputs & assumptions needed for this model framework*.

Abbreviations: CM, cost-effectiveness model; ERG, Evidence review group; LY, Life years; PA, Probabilistic analysis; QALYs, Quality adjusted life years; SE, Standard erro

An assessment of the three methods of implementation concluded that the first 'fixed pay-off' method in Table 33 was the most appropriate. The approach incorporates a suitable level of complexity by allowing the model cohort to move to the metastatic setting via a faster and a slower pathway (i.e., ET-resistant [MONARCH 2] and ET-sensitive pathways [MONARCH 3]). The method allows crucial survival, utility, and cost data from both models to be incorporated into the monarchE model while maintaining the computational power of the excel model.

Metastatic health state 'pay-off' approach

The relevant treatment received in the metastatic setting was dictated by advanced breast cancer guidelines, data from the monarchE trial, Danish 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 recurrence. This was confirmed to be a realistic assumption by the interviewed Danish clinical experts [1]. Table 34 provides the proposed treatments options currently programmed in the model based on the respective metastatic recurrence pathways. The treatment regimens modelled for disease progression in the metastatic recurrence health state are derived from the MONARCH 2 and MONARCH 3 CMs from TA725 [16] and TA563 [17] for the efficacy inputs and from the Danish aBC submission to the DMC [7] for the resource use. This is further detailed in section 8.5.6.4.

Table 34: Treatments received in each metastatic pathway

Endocrine treatment resistant	Endocrine treatment sensitive

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

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

It is important to note that the outcomes of the metastatic health state are not directly modelled. Aggregate values of what would have been achieved in this health state are assumed to follow Monarch2 and Monarch3 economic models. Therefore, curves are not submitted in the submission. Rather, mean values were used representing the area under the curve which would have been obtained had the metastatic health state been modelled expressively. OS values correspond to the sum of the PPS, and PPS LYs as reported below. These tables have been modified to include mean OS (please see Table 42 and Table 44 below).
As previously mentioned, it was decided to take this modelling approach because, at the data cut off, the monarchE trial had a limited follow-up time with immature data regarding overall survival, and so Eli Lilly decided to model survival in case of metastatic recurrence disease using study data from Monarch 2 and 3. For patients receiving treatment with CDK4/6 inhibitors, fulvestrant or aromatase inhibitors, efficacy data are drawn from Monarch 2 and 3. The proportion of patients on each treatment is used to calculate a fixed

number of life years which is assigned in the metastatic condition in the respective treatment arm. The fixed life years are used to calculate the overall survival in the metastatic health state in the model. It is possible for the DMC to check the impact of these LYs values by simply changing them in the model.
It is however worth noting that the overall impact of the metastatic absorbing health state on the overall model outcomes is limited. Rather, and as showed in the model by the tornado diagrams in the DSA sheet, the difference in the proportions of patients moving from iDFS to NMR is of highest interest. This is further supported by the conclusion reached by TLV on page 18 of their recently published report: "the assumption taken are associated with some uncertainties. However, adjusting these has a very small impact on the cost per QALY."[58]

Modelling of the ET-resistant metastatic setting

The MONARCH 2 CM (TA725) [16] model 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 with the means of a NMA. The PPS health state was estimated by taking the difference with the OS and PFS curves. LYs were accrued according to the proportion of patients in the PFS and PPS health states over time. As such, the inputs and assumptions used to inform the clinical outcomes for the ET-resistant metastatic setting are based on those used in TA725 [16].

In the monarchE model in this submission, 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, were assumed to follow the ET-resistant metastatic pathway, based on TA725 and the DMC submission for aBC. For each of the possible treatment options, patients received a pay-off of LYs. To enable adjustment for utilities, these LYs were split according to PFS or PPS.
The treatment options modelled per monarchE treatment arm, based on company budget impact analyses from TA725 are provided in Table 35. The clinical outcomes used in the ET-resistant metastatic setting are provided in Table 36 are also derived from the TA725 CM. To calculate the combined LYs for the CDK4/6 inhibitors + fulvestrant treatments, a weighted average of the ABE + FUL and PAL + FUL, LYs were used. The monarchE CM used the undiscounted LYs were used for the TA725 model, the respective health state specific utility values were applied to calculate the total QALYs. Then a discounting formula was applied to calculate the appropriate discounted LYs in the monarchE model. The financial discounting formula is commonly used to calculate the present and future value of annuities and the concept has also been applied in the model:

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

As the monarchE model uses mean LY from the TA725 model we assumed that all patients are alive until the mean LY point is reached. This may lead to under or overestimating the survival outcomes of the population. As we do not use individual survival curves from the TA725 model this is a limitation of the model.

The same approach to discounting of QALYs has been applied to the MONARCH 2 costs and MONARCH 3 inputs (costs and QALYs). The same limitations apply. Please note LYs have not been discounted in addition to QALY and cost discounts to avoid double discounting.

Table 35. Proportion of patients receiving each treatment regimen who had a disease recurrent event and followed the ET-resistant pathway

	Abemaciclib + ET	ET
CDK4&6 inhibitors + FUL	[redacted]	[redacted]
EXE-EVE	[redacted]	[redacted]
FUL	[redacted]	[redacted]
CAP	[redacted]	[redacted]
EXE	[redacted]	[redacted]

Notes:

Abbreviations: ABE+FUL: abemaciclib + fulvestrant; ET: endocrine therapy; FUL: fulvestrant; PAL+FUL: palbociclib + fulvestrant;

Table 36. Undiscounted LYs and mean time on treatment from the TA725 model

Comparator	LYs		Time on treatment	LYs	Source
Treatment options	**PFS**	**PPS**	**Mean**	**OS**	
ABE-FUL	[redacted]	[redacted]	[redacted]	[redacted]	TA725
RIBO-FUL	[redacted]	[redacted]	[redacted]	[redacted]	TA725
PAL-FUL	[redacted]	[redacted]	[redacted]	[redacted]	TA725
EXE-EVE	[redacted]	[redacted]	[redacted]	[redacted]	TA725
FUL alone	[redacted]	[redacted]	[redacted]	[redacted]	TA725
CAP	[redacted]	[redacted]	[redacted]	[redacted]	TA725
EXE	[redacted]	[redacted]	[redacted]	[redacted]	TA725

Abbreviations: ABE+FUL: abemaciclib + fulvestrant; FUL: fulvestrant; LYs: life years; PAL+FUL: palbociclib + fulvestrant; PFS: progression free survival; PPS: post-progression survival;

Source: Lilly Data on File [46] [77]. Source: 2019-8101 Abemaciclib MONARCH 2 Global CEM - Technical Report - March 2022

Modelling ET-sensitive metastatic setting

The MONARCH 3 (TA563 [17]) 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 progression on their first advanced breast cancer ET regimen, patients were allocated a fixed pay-off for PPS (which is modelled as a PSA), using costs and outcomes from the TA563 model. As such, the inputs and assumptions used to inform clinical outcomes for the ET-sensitive metastatic setting are based on those used in TA563 [17].

In the monarchE CM, when a distant disease recurrence occurs more than 12 months after completing adjuvant ET or while in remission following a NMR event patients were assumed to follow the MONARCH 3 pathway, based on TA563 [17]. For each of the possible treatment options, these patients received a pay-off of LY. 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.

The treatment options modelled per monarchE treatment arm, based on company budget impact analyses from TA563, are provided in Table 37. To calculate the combined LY for the CDK4&6 inhibitors + NSAI treatments, a weighted average of the ABE-NSAI, PAL-NSAI, and RIBO-NSAI LY were used.

Table 37. The clinical outcomes used in the ET-resistant metastatic setting are provided in Table 38 are also derived from the TA563 CM. To calculate the combined LY for the CDK4&6 inhibitors + NSAI treatments, a weighted average of the ABE-NSAI, PAL-NSAI, and RIBO-NSAI LY were used.

Table 37. Weighted average proportion of patients receiving each treatment regimen who had a distant disease recurrent event and followed the ET-sensitive pathway

	Abemaciclib + ET	ET
CDK4&6 inhibitors + NSAI	[redacted]	[redacted]
NSAI	[redacted]	[redacted]
RIBO + FUL	[redacted]	[redacted]
TMX	[redacted]	[redacted]
FUL	[redacted]	[redacted]
CDK4&6 inhibitors + NSAI	[redacted]	[redacted]
NSAI	[redacted]	[redacted]

Abbreviations: CDK 4&6, Cyclin-dependent kinase (CDK) 4 and CDK 6; EXE, Exemestane; FUL, Fulvestrant; NSAI, Non-steroidal aromatase inhibitor (Letrozole + Anastrozole); TMX, Tamoxifen

Table 38. Undiscounted LYs from the TA563 model

Treatment	First-line advanced PFS	Mean ToT (months)	Second-line advanced PFS	PPS	OS	Source
ABE + NSAI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TA563
RIB + NSAI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TA563
PAL + NSAI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TA563
NSAI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TA563
EXE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TA563
TMX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TA563

FUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TA563

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

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

There is no place in the model specifically pointing out the number of patients receiving 1st line treatment in the metastatic setting. However, it is important to note endocrine resistant and endocrine sensitive patients entering the metastatic setting in the economic model following the IDFS recurrence are both 1st line metastatic. The patient trace shows that people do not move to ETS until cycle 63 (~58 months). This will be the proportion coming from NMR to remission to MR (ETS). After 6 years (5yrs ET plus 12 months) no patient should be moving from IDFS to ETR but all patients should go to ETS.
In the economic model, columns ED: EG show the transition to MR.

8.4 Documentation of health-related quality of life (HRQoL)

8.4.1 Health state utility values (HSUV) derived from clinical trials

Utility values derived from the EQ-5D-5L data collected in the monarchE trial were used to evaluate patients' health status to inform decision modelling for health economic evaluation in the iDFS health state. The iDFS utility score as derived from the MonarchE clinical trial are presented in **Table 39**.

Mean utility scores at baseline for two treatment groups were firstly summarized using descriptive statistics. For each post-baseline estimate, the mixed effect model for repeated measures (MMRM) method was used to estimate and compare the mean difference in change from baseline of EQ-5D utility scores between the two treatment arms. MMRM provided the overall treatment difference across all scheduled post-baseline measurements, regardless of specific visit. MMRM was pre-specified in the statistical analysis plan of the monarchE trial for all patient-reported outcomes (PRO). Specifically, MMRM was specified in SAS proc mixed as follows: Change from Baseline = Treatment + Visit + Treatment*Visit + Baseline. The analysis will include all cycles for which at least 25% of patients in each arm have a non-missing postbaseline change from baseline EQ-5D-5L Index Score. Only pre-recurrence visits (IDFS health state) were included for the MMRM for cost-effectiveness. The unstructured covariance structure is used first for MMRM model. The results of the MMRM showed no time and treatment difference on utility for patients in IDFS health state. Therefore, for efficient use of the available data, overall summary utility scores were applied.

Table 39. Overview of utility values derived from MonarchE trial (Cohort 1 population)

Visit	Number of respondents	Mean	Standard deviation	Standard error	95% Confidence interval (lower-upper bound)	P value~
Baseline	4325	0.86	0.14	0.0021	0.856-0.864	0.813
Visit 6	4092	0.85	0.14	0.0022	0.846-0.854	0.919
Visit 9	3989	0.85	0.15	0.0024	0.845-0.855	0.855
Visit 15	3785	0.85	0.15	0.0024	0.845-0.855	0.195
Visit 21	3593	0.85	0.15	0.0025	0.845-0.855	0.297
Visit 27	3140	0.85	0.16	0.0029	0.844-0.856	0.939
Overall (mean) iDFS	-	0.85	-	0.0029	0.844-0.856	0.571

```
~- p-values are from Type 3 sums of squares MMRM Model: Change from Baseline = Treatment +
Visit + Treatment*Visit + Baseline.
 The analysis will include all cycles for which at least 25% of patients in each arm have
a non-missing postbaseline change from baseline EQ-5D-5L Index Score.
```

As the data showed no significant difference between treatment arms, overall utilities were applied to both treatment arms instead of treatment-specific utilities. In addition, mean change from baseline in mean index scores were estimated using Mixed effect Model Repeat Measurement (MMRM) regression and included independent variables treatment, visit, treatment*visit, and baseline.

8.4.2 Health state utility values used in the health economic model

Danish preference weights

In accordance to the DMC guidelines for the assessment of pharmaceuticals, EQ-5D values derived from the MonarchE trial were weighted based on the general Danish population preferences based on the method suggested by the DMC guidelines [78] and derived from Jensen et al, 2021 [79].

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, in accordance with the methods suggested by the DMC [78]. 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.

Table 40. EQ-5D Population Norms in the Denmark

Age Group	QoL	Source
18 –29	**0,871**	**DMC guidelines for the assessment of pharmaceuticals [78]**
30 –39	**0,848**	
40 –49	**0,834**	
50 –69	**0,818**	
70 –79	**0,813**	
80+	**0,721**	

An overview of the utilities that are used in the model are presented in Table 41. 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.

It has been decided it is reasonable to assumed lower utility value in the first 3 months of the NMR stage. Clinical expert opinion indicated patients would receive intensive treatment for loco-regional/contralateral recurrence for the first few months, which is expected to be associated with a detrimental impact on HRQoL. Following this, patients would return to their previous HRQoL. The use of Lidgren *et al.,* 2007 [80] is aligned with prior NICE appraisal TA612 in the absence of trial utility data from monarchE to inform this state.

Dis-utilities are not applied in the model nor in the submission, as utilities measured within the trial are expected to already have captured the detrimental effect of adverse events within the QoL value observed.

Table 41. Overview of utility values used in the model

Health State	Utility Value	Source
IDFS	0,852 for both trial arms	monarchE (Cohort 1) MMRM

Health State	Utility Value	Source
		APRIL 2021 DCO data cut Lilly statistics team [55]
NMR	0.813. (0,696 for first 3 months and 0,852 for last 9 months for both trial arms)	First 3 months: Lidgren et al. 2007 [80] Last 3 months: assumed equal to IDFS
REM	0,852 for both trial arms	Assumed to be equal to IDFS, TA632 assumption [52]
ETR – PFS	0,747 for all ETR treatments	ERG report, Table 17, pg 55 - ERG preferred HSUVs (TA725) [16]
ETR – PPS	0,704	ERG report, Table 17, pg 55 - ERG preferred HSUVs (TA725) [16]
ETS – PFS1	0,724 for all ETS treatments	MONARCH3 Technical report, MONARCH 3 trial [17]
ETS – PFS2	0,690 for all ETS treatments	ACD committee papers , page 467 - ERG preferred (TA563) [17]
ETS – PPS	0,505 for all ETS treatments	ACD committee papers, page 467 - ERG preferred (TA563) [17]

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

8.5 Resource use and costs

8.5.1 Drug acquisition

Drug acquisition costs were calculated by combining dosing regimens with relative dose intensity adjustments derived from the monarchE trial data. All pharmacy purchase prices (PPP) have been fetched for the drug acquisition cost from Medicinpriser.dk. The drug unit cost for each comparator is described below and summarized in Table 42.

Table 43 provides the dosing schedule and dose intensities. Dose intensites 100% is assumed for all medicines in the health economic analysis due to flat pricing of Verzenios. This means that the cost of the treatment will be the same independently of whether patients receive an dose inferior to the dose recommended by the European Medicines Agency [4]. This is therefore a conservative approach which has been accepted by the Tandvårds- och läkemedelsförmånsverket. As noted in section 8.3.1.2.2, the TTD curves capture discontinuation of treatment for any cause, as such these curves are used alongside acquisition costs and clinical stopping rules to determine treatment cost.

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 ET. The study identified that adherence rates to ET decline with each refill, with adherence expected to drop to 60% after 2 years2 [81]. Given the short follow up, extrapolating the TTD curve long-term may introduce moderate uncertainty in the CM. In Table 43 the dosing of each treatment is presented to enable the calculation of drug cost per patient.

Among patients in the A+ET arm, 72% had at least 1 dose modification (dose omission or dose reduction). Dose omissions were made in 1908 (68%) of patients in the abemaciclib arm. Per protocol, a maximum of 2 dose reductions was allowed, first to 100 mg twice daily and thereafter to 50 mg twice daily. Approximately 44% of patients in the A+ET arm had at least one dose reduction, and 14% had two dose reductions. Almost all were due to AEs. Abemaciclib dose modifications due to AEs were very common, with 1212 patients (43.4%) with at least 1 dose reduction and 1721 patients (61.7%) with at least 1 dose omission.

A total of 387 patients (13.9 %) needed 2 dose reductions due to AEs. The most frequent reason for dose modifications of abemaciclib in monarchE was AEs, specifically diarrhoea, fatigue, and haematological toxicities: neutropenia and leukopenia. Most patients could continue treatment with the reduced dose. Thus, in general treatment-emergent AEs (TEAEs) related to abemaciclib could be managed with appropriate dose modifications allowing most patients to remain on treatment. Most dose reductions occurred early on during study treatment. Also, most dose omissions due to AEs occurred early on during study treatment. The median duration of the abemaciclib dose omissions represented 4.9% of the overall study treatment duration per patient. The most common AEs leading to dose reduction or dose omission were diarrhoea, neutropenia, fatigue and leukopenia.

Figure 28. Dose modification for abemaciclib in the A-ET arm (01 April 2021 data cut-off)

Parameter	LY2835219-150mg+EDT (N=2791) LY2835219 n (%)
Patients with at least one Dose Adjustment n(%)	2014(72.2)
Number of Patients with Dose Reduction	1217(43.6)
Patients with 1 dose reduction	829(29.7)
Patients with 2 dose reductions	387(13.9)
Patients with >= 3 dose reductions	1(0.0)
Reasons leading to dose reduction	
Adverse Events*	1212(43.4)
Diarrhoea	482(17.3)
Neutropenia	226(8.1)
Fatigue	125(4.5)
Leukopenia	99(3.5)
PROTOCOL	3(0.1)
Number of Patients with Dose Omission	1908(68.4)
Patients with 1 dose Omission	805(28.8)
Patients with 2 dose Omissions	536(19.2)
Patients with >= 3 dose Omissions	567(20.3)
Reasons leading to Dose Omissions	
Adverse Events*	1721(61.7)
Diarrhoea	543(19.5)
Neutropenia	440(15.8)
Leukopenia	195(7.0)
Fatigue	140(5.0)
PRE-PLANNED SURGERY	363(13.0)
SCHEDULING CONFLICT	114(4.1)
TREATMENT AVAILABILITY	26(0.9)
Number of Patients with Dose Increase	11(0.4)

Abbreviations: N = number of subjects in Safety Population; n = number of subjects in the specified category.
* AE preferred terms reported in more than 3% of patients.

Table 42 Pharmaceutical costs used in the model

Drug	Units/Pack	Strength/unit (mg)	Pack cost (DKK)	Cost per mg (DKK)	Source
abemaciclib	56	150	19.941,92 kr.	2,37 kr/mg	Medicinpriser.dk [82]
letrozole	100	25	116,00 kr.	0,46 kr/mg	Medicinpriser.dk [82]
anastrozole	100	1	38,00 kr.	0,38 kr.	Medicinpriser.dk [82]
tamoxifen	100	20	189,00 kr.	0,09 kr.	Medicinpriser.dk [82]
exemestane	100	25	160 kr.	0,06 kr.	Medicinpriser.dk [82]

Table 43. Dosing scheme and relative dose intensity

Treatment	Dosing schedule	Relative dose intensity	Cost per admin
ABE	150mg BID	100%	356.11 kr.

ET	-		
Anastrozole	1mg QD	100%	1.16 kr.
Exemestane	25mg QD	100%	0.38 kr.
Letrozole	2.5mg QD	100%	1.89 kr.
Tamoxifen	20 mg QD	100%	1.60 kr.

Abbreviations: ABE: abemaciclib; BID: twice (two times) a day; ET: endocrine therapy: QD: once daily.

Source: Dosing Schedule: SmPC [4]

Body and body surface area (BSA)

Body weight and BSA are required to calculate drug dosage (where relevant for the non-metastatic and metastatic settings). BSA data were not collected in the monarchE trial. Height and body weight data were collected and used to estimate BSA using the DuBois formula:

$$BSA\ (m^2) = 0.007184 \times Height^{0.725} \times Weight^{0.425}$$

8.5.2 Drug administration

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

Table 44. Drug administration costs

Treatments	Cost per administration per cycle	Source
IV (For first attendance & Subsequent cycles)	2.041,0 kr.	DRG 2022 - Kvinde , 51 År (DC509) Brystkræft UNS, 09MA98 - MDC09 1-dagsgruppe, pat. mindst 7 år
Oral	0,0 kr.	Assumption
SC	2.041,0 kr.	DRG 2022 - Kvinde , 51 År (DC509) Brystkræft UNS, 09MA98 - MDC09 1-dagsgruppe, pat. mindst 7 år

Abbreviations: IV, Intravenous; SC, Subcutaneous

Source: DRG Tariffs, 202247

8.5.3 Transportation and Patient costs

Productivity costs (defined as patient costs in DMC guidelines) and transportation cost are included in the model in line with the DMC method guidelines [95]. The unit cost per patient hour is assumed to be DKK 181. The transportation cost per visit was assumed to be DKK 3.51 per km and the average distance to health care provider was 40 km round trip, in line with the DMC guidelines, which was sourced from DMCs unit cost catalogue [83]. Patient hours and mean number of visits per cycle were confirmed with Danish KOLs and presented in Table 46.

Table 45. Unit costs hourly wage and travel costs

Resource	Unit cost (DKK)	Source
Average hourly wage	181,00 kr.	Medicinrådet - [83]
Travel costs per km	3,51 kr.	Medicinrådet - [83]

Table 46. Travel costs

Resource	Frequency of use per week	Source
Patient hours per cycle in IDFS	0,25	Danish KOL interview [1]
Patient hours per cycle in NMR	0,25	Danish KOL interview [1]
Patient hours per cycle in REM	0,25	Danish KOL interview [1]
Mean number of visits per cycle in IDFS	0,15	Danish KOL interview [1]
Mean number of visits per cycle in NMR	0,15	Danish KOL interview [1]
Mean number of visits per cycle in REM	0,15	Danish KOL interview [1]

8.5.4 Adverse events costs and resource use

Adverse event probabilities for abemaciclib + ET and ET are informed by the APRIL 2021 DCO of the monarchE trial [55]. The model base case includes Grade III/IV TEAEs reported in the APRIL 2021 DCO of the monarchE trial, with an incidence of ≥ 1% in the respective treatment arms in the trial, as well as Grade I/II TEAEs with an incidence of ≥ 50% (only Grade I/II diarrhoea had an incidence ≥ 50%). A summary of the TEAEs rates for each treatment and the related sources are shown in Table 47. Adverse events are assumed to occur once within the first cycle of the model, for patients receiving treatment. AEs are assumed to occur once within the first cycle of the model, for patients receiving treatment. AEs are associated with one-off costs, which are then multiplied by the AEs incidence to obtain the total costs associated with AEs.

Clinicians expect at least 2-3 additional clinic visits compared to their endocrine treatment schedule, which is otherwise that they see pts. at the beginning day 0, 3 months, 6 months. In addition to the 2-3 extra clinic visits, clinicians expect there will be a close need for blood tests in the beginning, approximately every 14 days for the first 3 months. Clinicians also emphasized that treatment control and side effect follow-up for this treatment will be as with any other new treatment; frequent check-ups at first until doctors find out what the necessity is. They are likely to adjust the need as they gain experience with the treatment.

Table 47: Summary of Grade III/IV TEAEs used in the base case

Adverse event type	Treatment Arms	
	Abemaciclib + ET	ET
Grade I/II		
Diarrhoea	[redacted]	[redacted]
Grade III/IV		
Neutropenia	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]

Diarrhoea	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Aspartate aminotransferase increase	[redacted]	[redacted]
Alanine aminotransferase increase	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Venous thromboembolic event	[redacted]	[redacted]

Abbreviations: ET: endocrine therapy.
Source: Lilly Data on File APRIL 2021 DCO CSR [14]

Table 48. Adverse events costs [84]

Adverse event	Cost (DKK)	Source
Grade III/IV TEAE incidence		
Neutropenia	3.176,00 kr.	DRG 2022, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD709: Neutropeni UNS
Leukopenia	3.176,00 kr.	DRG 2022, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD709: Neutropeni UNS
Diarrhoea	6.756,00 kr.	DRG 2022, 06MA11: Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag., Diagnosis: DK529B: Ikke-infektiøs diaré UNS
Lymphopenia	3.176,00 kr.	DRG 2022, 16MA10: Øvrige sygdomme i blod og bloddannende organer, Diagnosis: DD728D: Lymfopeni
Fatigue	4.460,00 kr.	DRG 2022, 23MA03: Symptomer og fund, u. kompl. bidiag., Diagnosis: DR539A: Udmattelse
Aspartate aminotransferase increase	1.905,00 kr.	DRG 2022, 23MA98: MDC23 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR740: Transaminase- og laktatdehydrogenaseforhøjelse
Alanine aminotransferase increase	1.905,00 kr.	DRG 2022, 23MA98: MDC23 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR740: Transaminase- og laktatdehydrogenaseforhøjelse
Thrombocytopenia	3.176,00 kr.	DRG 2022, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD696: Trombocytopeni UNS
Anaemia	3.176,00 kr.	DRG 2022, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD592: Hæmolytisk ikke-autoimmun anæmi forårsaget af lægemiddel
Diarrhoea	5.,130 kr.	DRG 2022, 06MA11: Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag., Diagnosis: DK529B: Ikke-infektiøs diaré UNS
Abdominal pain	6.756,00 kr.	
Venous thromboembolic event	22.502,00 kr.	DRG 2022, 05MA12: Perifer karsygdom, Diagnosis: DI829: Emboli eller trombose i vene UNS
Grade I/II TEAE incidence		
Diarrhea	6.756,00 kr.	DRG 2022, 06MA11: Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år u. kompl. bidiag., Diagnosis: DK529B: Ikke-infektiøs diaré UNS

8.5.5 Hospitalisations

The monarchE trial provides a summary of all hospitalisations (on therapy or within 30 days of Treatment Disposition). The hospitalisation rates collected are either 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 Cohort 1 population.

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

Table 49. Hospitalisation rates (Cohort 1) and costs [84]

	ABE + ET	ET	Source
Proportion			
Cost of hospitalisation 2022 indexed unit cost	35.099,00 kr.	35.099,00 kr.	DRG 2022 - (DC509)Brystkræft UNS DRG gruppe 09MA08 – mammacancer
Duration of resource use	2 years	5 years	Assumed only for the duration of treatment. Source: APRIL 2021 DCO Lilly statistics
Probability of hospitalization per cycle	422 hospitalisations / 2539 patients / 2 years (26 cycles) = 0,00669 per cycle	262 hospitalisations / 2539 patients / 5 years (65 cycles) = 0,00415 per cycle	Source: APRIL 2021 DCOLilly statistics team

8.5.6 Health state costs and resource use

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 [1] and on the MonarchE trial [14]. For the metastatic recurrence health state, resource use was informed by global experts feedback and the DMC submissions for aBC previously mentioned in section 8.3.3.

8.5.6.1 iDFS

Based on Danish KOL [1] opinion, Table 50 provides a summary of the resources and associated resource use costs included in the economic model for the iDFS health state [84].

Table 50: List of costs in the economic model associated with the IDFS health state

Resource use	Unit cost (DKK)	Reference	Annual resource use frequency		Source
			Year 1	Years > 1.5	

Oncologist visit, number per 28 days	2.041,00 kr.	Interaktiv DRG 2022 - 09MA98 - MDC09 1-dagsgruppe, pat. mindst 7 år [84].	0,31	0,15	Danish KOL interview [1]
Mammogram, number per 28 days	690,00 kr.	DRG 2022, 30PR14: Mammografi, ukompliceret, Diagnosis: UXRC45: Afhængighed af hjælpemiddel eller apparat UNS Procedure: UXRC45 Mammografi, screening [84].	0,05	0,05	Danish KOL interview [1]

Abbreviations: IDFS: invasive disease-free survival;

Best supportive care

Components of best supportive care (BSC) were identified based on the concomitant medications prescribed in the monarchE trial. Specifically, concomitant medications taken by ≥5% of the Cohort 1 population in either treatment arm due to prophylaxis and/or medical history, as defined in the monarchE CSR. As adverse events are costed separately (Section 8.5.4) to avoid double-counting, concomitant medications prescribed specifically for adverse events have not been included (with the exception of loperamide for the treatment of diarrhoea). In the model, BSC costs are incurred during the pre-recurrence/IDFS health state.

Table 51 provides and overview of the type of concomitant medications being modelled per treatment arm. Table 52 lists the dosing and cost assumptions for each concomitant medication.

Table 51: Type of concomitant medication by treatment arm

Agent	Abemaciclib + ET %	ET %
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: ET: endocrine therapy.
Source: MonarchE CSR Table JPCF.4.11 PO data[14]

Table 52: Drug cost and dosing options used

Concomitant treatment dosing & administration	Cost per package (DKK)	Total package dose	Dose per admin	Number of administrations per cycle (N)	Administration route	Source
Loperamide	123,18 kr.	120	2	28,00	Oral	Medicinpriser.dk [82]
Ibuprofen	4,47 kr.	10.000	500	28,00	Oral	Medicinpriser.dk [82]

Amoxicillin; Clavulanic acid	38,00 kr.	80.000	400	28,00	Oral	Medicinpriser.dk [82]
Amoxicillin	16,40 kr.	18.750	625	28,00	Oral	Medicinpriser.dk [82]
Colecalciferol	74,50 kr.	7.500	750	28,00	Oral	Medicinpriser.dk [82]
Calcium carbonate; colecalciferol	110,00 kr.	4000,0	20,00	28,00	Oral	Webapoteket.dk [85]
Vitamin D Nos	74,50 kr.	96.000	400	28,00	Oral	Webapoteket.dk [85]
Zolederonic acid	85,00 kr.	4000,0	20,00	28,00	Oral	Webapoteket.dk [85]
Paracetamol	8,52 kr.	7.500,00	75	28,00	Oral	Medicinpriser.dk [82]
Levothyroxine	33,59 kr.	63.000	500	28,00	Oral	Medicinpriser.dk [82]
Metformin	339,40 kr.	400	400	0,15	IV	Medicinpriser.dk [82]

Abbreviations: IU: international units; SC: sub-cutaneous.
Sources: Medicinpriser.dk [82], Webapoteket.dk [85]

8.5.6.2 Non-Metastatic Recurrence

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 [86]. Danish clinical experts were then consulted to assess the relevance of these inputs in the Danish system [1]. 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 final guidance for early and locally advanced breast cancer diagnosis and management were closely consulted to estimate the treatment mix offered48. 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 status48. The HER2+ or HER2- status would not impact the type of treatment a patient is offered for that area of recurrence. Consequently, the CM excludes HER2+ targeted treatment, but includes the rechallenge with ET prescribed during the IDFS health state, for the treatment of a NMR event.
The NG101 guideline [86] specified that people with locoregional, regional or contralateral disease recurrence would undergo a mastectomy if they originally had breast conserving surgery. 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.

Table 53 provides a breakdown of the type of treatment mix allocated to each type of recurrence. The proportion of patients experiencing their first local/regional and contralateral disease recurrence based on the monarchE CSR [14]. Table 54 provides the costs per treatment type and associated costs were sourced from Danish DRG tariffs 2022 [84] .
To capture ET for a NMR event, the same cost ET in each cycle in the IDFS health state was applied to each cycle in the non-metastatic health state, irrespective of recurrence type. Clinical experts agreed that ET would be offered to patients who experienced a non-metastatic recurrence.

Table 53: Breakdown of treatment algorithm applied for non-metastatic recurrence pathway

Recurrence type	(Loco)regional	Contralateral
Oncologist, follow-up, number per 28 days	0,153 (0,031)	0,153 (0,031)
Mammogram, number per 28 days	0,05 (0,01)	0,05 (0,01)
% (SE) receiving mastectomy with reconstruction (if originally had breast conserving surgery)	75 (0,150)	95 (0,19)
% (SE) receiving major breast procedure (if originally had mastectomy)	10 (0,02)	10 (0,02)
% (SE) receiving delayed breast reconstruction	30 (0,060)	30 (0,060)
% (SE) receiving radiotherapy (proportion not received prior radiotherapy)	100 (0,2)	NA
% (SE) receiving Chemotherapy (cycle 1)	5 (0,01)	5 (0,01)
% (SE) receiving Chemotherapy (cycle 2-6)	5 (0,01)	5 (0,01)
% (SE) receiving Chemotherapy (subsequent cycles)	5 (0,01)	5 (0,01)
% (SE) receiving Complete blood count	5 (0,01)	5 (0,01)
% (SE) Multidisciplinary team meeting	100 (0,2)	100 (0,2)

Abbreviations: ET: endocrine therapy; SE: standard error.

Source: Danish KOL interview [1]

Table 54: Costs of resources used in the non-metastatic recurrent health state [84].

Parameter	2022 costs	Reference
Oncologist visit	2.041,00 kr.	Interaktiv DRG 2022 - 09MA98 - MDC09 1-dagsgruppe, pat. mindst 7 år
Mammogram	690,00 kr.	DRG 2022, 30PR14: Mammografi, ukompliceret, Diagnosis: UXRC45: Afhængighed af hjælpemiddel eller apparat UNS Procedure: UXRC45 Mammografi, screening
Radiotherapy	10.874,00 kr. .	DRG 2022 - 27MP13 - Stråleplanlægning kompleks
Chemotherapy cost per cycle (Cycle 1)	18.164,00 kr.	DRG 2022, 04MA98: MDC04 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DC349: Kræft i lunge UNS Procedure: BWAA6 Medicingivning intravenøst
Chemotherapy cost per cycle (Cycle 2–6)	18.164,00 kr.	DRG 2022, 04MA98: MDC04 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DC349: Kræft i lunge UNS Procedure: BWAA6 Medicingivning intravenøst
Chemotherapy cost per cycle (subsequent cycles until disease progression)	18.164,00 kr.	DRG 2022, 04MA98: MDC04 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DC349: Kræft i lunge UNS Procedure: BWAA6 Medicingivning intravenøst
Multidisciplinary team meeting	2.041,00 kr.	DRG 2022, 04MA98: MDC04 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DC349: Kræft i lunge UNS Procedure: BWAA6 Medicingivning intravenøst

Complete blood count	46,00 kr.	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 included
Major breast procedures (if patients originally had mastectomy)		
Local: Major breast procedures (if patients originally had mastectomy)	37.890,00 kr.	DRG 2021 - 09MP03 - Stor mammakirugisk operation
Regional: Major breast procedures with lymph node clearance (for regional recurrences in patients that originally had mastectomy)	79.197,00 kr.	DRG 2021 - 09MP08 - Sekundar rekonstruktion af bryst med protese eller transplantat, dobbelt
Mastectomy with reconstruction (if patients originally had breast conserving surgery)	113.402,00 kr.	DRG 2021 - 09MP01 - Mastektomi med rekonstruktion med stilket lap og dobbeltsidigmastektomi med protese

Second primary neoplasm

As noted above, the model assumed patients who experience a second primary non-breast cancer event, receive the cost of detecting the second primary neoplasm (i.e., one oncology multidisciplinary team [MDT] meeting; 2,041.00 kr.) and exit the model.

8.5.6.3 Remission

Following consultation with clinical experts, resource use in the remission health state was assessed to be comparable to the resource use in the iDFS health state. Resource use in Remission is therefore assumed equal to resource use in the iDFS state.

Table 55: Cost and resource use for remission health state

Resource use	Unit cost (DKK)	Reference	% patients	Per cycle frequency	Source
Oncologist visit, number per 28 days	2.041,00 kr.	Interaktiv DRG 2022 - 09MA98 - MDC09 1-dagsgruppe, pat. mindst 7 år [84].	100	0,307	Danish KOL interview [1]
Mammogram, number per 28 days	690,00 kr.	DRG 2022, 30PR14: Mammografi, ukompliceret, Diagnosis: UXRC45: Afhængighed af hjælpemiddel eller apparat UNS Procedure: UXRC45 Mammografi, screening [84].	100	0,051	Danish KOL interview [1]

8.5.6.4 Metastatic recurrence

ET-resistant

For the ET-resistant metastatic patient pathway, the following cost and resource use categories from the MONARCH 2 model submitted in support of the DMC aBC submission [7] were incorporated within the monarchE model:

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

For the health state specific resource use costs, the per cycle cost of each resource use was multiplied with the applicable number of cycles. To inform the total cycles the mean PFS, PPS, and time on treatment (ToT) values specified in Table 36 was used. A detailed breakdown of the individual costs incorporated has been provided in Appendix M Metastastic health state – Endocrine resistant pathway.

ET-sensitive

For the ET-sensitive distant recurrence patient pathway, cost categories considered from the Monarch 3 CM were incorporated within the in the monarchE CM as used in the model submitted in support of the DMC aBC submission [7] have been provided in Table 56.

Table 56: MONARCH 3 cost and resource categories considered in the ET-sensitive metastatic patient pathway

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

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

Note: The second-line PFS treatment costs were calculated using the same method as first-line PFS treatment costs. Drug acquisition costs were combined with the respective dosing regimens. The appropriate mean weight or BSA was applied along with the RDI. 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 metastatic pathway, for the health state specific resource use costs, the per cycle cost of each resource use was multiplied with the number of cycles the resource use was applicable for. To inform the total cycles, the mean 1st line advanced PFS, 2nd line advanced PFS, PPS, and ToT values specified in Table 38 were used. A detailed breakdown of the individual costs incorporated has been provided in Appendix N Metastatic health state – Endocrine sensitive pathway.

8.6 Results

8.6.1 Key clinical assumptions to be considered in the economic results

Table 57. Key clinical assumptions (APRIL 2021 DCO Cohort 1)

Model input	Assumption	Scenario
IDFS curves	• Dependent model (single model with treatment coefficient) assumed with a log-logistic distribution following internal validity checks and assessment of external evidence from TA632 for APRIL 2021 DCO • Constant proportions between IDFS events have been assumed	No scenario is assessed
TTD curves	• Extrapolations based on within trial data were used to inform ET irrespective of arm • Two year stopping rule applied for abemaciclib • Five year stopping rule was applied for ET	• Log-logistic distribution was explored for ET arm as Danish KOLs expect 75-80% of patients to remain on treatment with ET at 10 years • Seven years stopping rule for ET arm was applied as Danish KOLs expect Pre-menopausal ER+ high risk patients to remain on treatment with ET for 10 years
ET regimens	• The first ET regimen administered in monarchE was used for the ET cost estimate The proportion of ET received uses the % given any time during the study.	No scenario is assessed as we anticipate low cost of ET will have minimal impact on the overall outcomes
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 same as hazard of dying in the NMR and REM health states	No scenario is assessed
Long-term treatment effect	• Waning of treatment effect was applied from year eight until year 28.	No scenario is assessed
NMR health state • Duration of tunnel state • Utility estimate	• All patients who experience a non-metastatic recurrence are assumed to receive additional adjuvant therapy for 12-months. After 12 months, patients are assumed to either transition into the remission health state or die due to all-cause mortality. • An average utility value has been applied to the NMR health state. The average takes account of three months of potential acute treatment as discussed in third TL meeting. The method could lead to not assigning discount rates proportionately.	No scenario is assessed
Probability for type of non-metastatic recurrence	• The proportion of patients having a second primary, (loco)regional or contralateral disease recurrence when a non-metastatic recurrence event takes place was assumed to be constant over time.	Assessed in OWSA and PA

Model input	Assumption	Scenario
Probability of disease recurrence from REM health state	• A constant monthly probability of transition from remission to the metastatic disease health state	Assessed in OWSA and PA
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.	Assessed in OWSA and PA
Hospitalisation costs	• Hospitalisation costs for pre-recurrence (i.e., IDFS health state) and post-recurrence (i.e., any patient leaving the IDFS health state who remain alive) related to treatment related and non-treatment related AEs was applied	No scenario is assessed

8.6.2 Base case and scenario analyses overview

Table 58. Modelling base-case overview and conducted scenario analyses

Setting	Option for base case	Scenarios
Population	HR+, HER2-, node-positive, high risk EBC (Cohort 1)	N/A
Perspective	Danish restricted societal perspective	N/A
Time horizon	49 years (lifetime)	N/A
Cycle length	28 days	N/A
Discount rate QALYs	Until year 35: 3.50%, After year 35: 2.50%	N/A
Discount rate costs	Until year 35: 3.50%, After year 35: 2.50%	N/A
Intervention	ABE+ Physicians' choice ET	N/A
Comparator	Physicians' choice ET	N/A
Curve used for cost estimates	TTD for active treatment costs of ABE + ET and ET IDFS – Disease management and background therapy DRFS (OS without distant recurrence) – Terminal care costs for IDFS, non-metastatic recurrence and remission health states	Stopping rule for ET 7 years
Endpoint for utility estimates	monarchE trial for IDFS utility Published utility values for post-IDFS health states. MONARCH 2 and MONARCH 3 models for metastatic health state utilities	N/A
Consideration of extrapolations	Yes, TTD from last data point of AFU1from monarchE trial till year five when clinical stopping rule is introduced. Yes, IDFS and DRFS, for the full time horizon chosen by the user	N/A
Curve fitting	Dependent model fitting for IDFS and OS without distance recurrence	N/A
IDFS distribution	Log-logistic Waning of treatment effect assumed to start after eight years with no treatment effect assumed after 28 years.	N/A
OS without distant recurrence distribution	Exponential	N/A
TTD distribution	Extrapolations carried out using generalized gamma for ABE and Weibull for ET arm. Clinical stopping rule at five years applied	log-logistic for ET arm
Consideration of subsequent therapies	Yes, clinical guidelines inform the treatments included in the non-metastatic recurrence setting.	N/A

	Yes, treatments prescribed for ET-resistant and ET-sensitive metastatic recurrences have been included based on the MONARCH 2 and MONARCH 3	
Maximum time on treatment	monarchE clinical trial, ET clinical guidelines	N/A
Wastage considered	No / NA all oral treatments modelled as assumed to be accounted under 100% RDI	N/A
Utilities applied	Pre- and post-progression utility estimates applied from literature	N/A
Age adjusted utilities	Yes	N/A

8.6.3 Base case results

Discounted (3.5% until year 35 and 2.5% after year 35 per annum for QALYs) disaggregated LYs and QALYs ABE + ET was associated with the highest total LYs and QALYs of 24.896 and 12.469 respectively. Results are presented in Table 59.

Table 59. Results of the base case economic analysis for MonarchE Cohort 1 population

Per patient	Abemaciclib + ET	ET	Difference
Life years gained			
Total life years	24,896	22,228	2,668
QALYs			
Total QALYs	12,469	11,249	1,220
QALYs (iDFS)	10,634	9,328	1,306
QALYs (NMR)	0,095	0,092	0,003
QALYs (REM)	0,676	0,669	0,007
QALYs (METASTATIC ETR)	0,256	0,372	-0,115
QALYs (METASTATIC ETS)	0,806	0,787	0,019
Costs (DKK)			
Total costs	637.719 kr.	332.700 kr.	305.019 kr.
Drug-related costs pre-metastatic	428.776 kr.	5.748 kr.	423.028 kr.
Disease management costs pre-metastatic	31.296 kr.	30.336 kr.	961 kr.
Costs in Metastatic setting – ETR	65.075 kr.	103.664 kr.	-38.588 kr.
Costs in Metastatic setting – ETS	92.303 kr.	180.268 kr.	-87.964 kr.
Patient and transport costs	12.636 kr.	11.269 kr.	1.366 kr.
AE costs	7.632 kr.	1.415 kr.	6.217 kr.
Incremental results ABE + ET vs. ET			
ICER (per LY)	114.313 kr.		
ICER (per QALY)	250.016 kr.		

8.6.4 Scenario analyses results

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. Overview of scenario analyses

Parameter	Base Case	Scenario	Incremental costs	Incremental QALYs	ICUR
Base case			**305.019 kr.**	**1,220**	**250.016 kr.**
TTD curve extrapolations in ET (intervention & comparator) arm	Dependent Weibull	Dependent log-logistic	305.473 kr.	1,220	250.388 kr.
Stopping rule ET	Stopping rule at 5 years	Stopping rule at 7 years	305.013 kr.	1,220	250.011 kr.

Abbreviations: ET, endocrine therapy; ICUR, incremental cost utility ratio; QALY, quality-adjusted life year; TTD, time to treatment discontinuation

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8.7 Sensitivity analyses

Both deterministic analysis (DA) and Probabilistic analyses (PA) 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.

8.7.1 Deterministic sensitivity analyses

The DA 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 DA assesses the impact of uncertainty around individual input parameters around the model outcomes. Results are presented in tables and tornado plots, which clearly present the parameters that have the greatest effect on the relevant model outcomes. The top fifteen parameters are displayed (ordered in terms of impact).

To account for uncertainty around the input parameters used in the base case analysis, a DA was conducted. Please note the DA does not include parameters which require assessment of joint uncertainty (e.g., survival parameters), these correlated parameters are assessed within the PA. The fifteen parameters with the greatest impact on the ICUR are displayed in Figure 29. 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 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.

Figure 29: XXXXXXXX

Abbreviations: CDK4&6I, cyclin-dependent kinase 4&6 inhibitors; ETR: endocrine treatment resistant, ETS: endocrine treatment sensitive; IDFS, invasive disease-free survival; ICUR, incremental cost-utility ratio; NMETR: non-metastatic recurrence - endocrine treatment resistant, NMRETS: non-metastatic recurrence - endocrine treatment sensitive; NSAI, non-steroidal aromatase inhibitor; LY, life years; PFS, progression free survival; PFS1, progression free survival 1st line advance breast cancer; PFS2, progression free survival 2nd line advance breast cancer; PPS, post-progression survival

8.7.2 Probabilistic sensitivity analyses

The PA 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. This 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. 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). A table containing a list of the inputs used in PSA is presented in Appendix J Probabilistic sensitivity analyses.

Figure 30 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 as well as incurring higher costs. The CEAC is presented in

Figure 31. 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 247.500 kr./QALY. ABE + ET has a 99% probability of being the most cost-effectiveness treatment at a WTP of 400.000 kr./QALY.

Figure 30: XXXXXXXX

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XXXXXXXX

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

Figure 31: XXXXXXXX

XXXXXXXX

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

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9. Budget impact analysis

The Budget impact model (BIM) was developed to estimate the expected budget impact of recommending 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 Verzenios in Denmark.
In accordance with DMC guidelines, 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 Verzenios is recommended in combination with ET as standard treatment and the scenario where Verzenios 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

[redacted]

	2022	2023	2024	2025	2026
For the pharmaceutical under consideration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

	2022	2023	2024	2025	2026
For the pharmaceutical under consideration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Expenditure per patient

Table 61. Costs per patient per year - if the pharmaceutical is recommended

	2022	2023	2024	2025	2026
For the pharmaceutical under consideration					
Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 62. Costs per patient per year - if the pharmaceutical is NOT recommended

	2022	2023	2024	2025	2026
For the pharmaceutical under consideration					
Abemaciclib + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Budget impact

Table 63. Expected budget impact of recommending the pharmaceutical for the current indication

	2022	2023	2024	2025	2026
The pharmaceutical under consideration is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Minus: The pharmaceutical under consideration is NOT recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

10. Discussion on the submitted documentation

The documentation submitted for this single-technology assessment stems from a comprehensive clinical development program, where abemaciclib have been evaluated in adult patients with HR+/HER2-, node-positive eBC with high risk for recurrence.

In Denmark, the current SoC for these patients is ET / AI, chemotherapy, and radiotherapy. In 2018, trastuzumab was recommended by the DMC as a targeted biological treatment for patients with HER2+ eBC. This targeted treatment has been proven to reduce the risk of cancer returning after surgery in early-stage HER2+ cancer. However, no targeted treatment has been recommended for patients with HER2- cancer, with the exception of the recent recommendation of add-on adjuvant treatment with bisphosphonates. This leaves these patients with an medical unmet need. Eli Lilly expects abemaciclib if recommended, to be placed as a 1L treatment for patients with high-risk, HR+/HER2-, node-positive eBC.

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For the scope of the assessment to reflect the clinical practice of HR+/HER2- eBC treatment in Denmark safety and efficacy analysis has been presented for one large phase 3 study for abemaciclib (monarchE). The assessment of both safety and efficacy was for this reason based on a head-to-head study where abemaciclib in combination with ET was compared to ET alone.

The advantage of having a head-to-head study is the presence of the best comparative evidence of treatment effect and safety. Furthermore, this direct comparison excludes the risk of bias from using indirect treatment comparisons (ITC). Therefore, Eli Lilly considers, that the most appropriate assessment of efficacy and safety will be based on the monarchE study to avoid information bias by involving more studies and hence the need to make an ITC that would lead to uncertain results.

The monarchE trial was assessed to reflect the Danish clinical practice. Patients and treatment regimen in the study was similar to the Danish patients and treatment management. Minor inequalities in the definition of high-risk patients were found between the study and the Danish clinical experts. The monarchE trial is using the biomarker ki67 to diagnose/as a criterion for high-risk patients, this is not used in Denmark as clinical do not recognize this to have an impact on the diagnosis. Furthermore, another deviation between the trial and the opinion from the clinical expert was the proportion of patients receiving anastrozole and exemestane, however, this difference is of minor importance as the Danish clinicians use exemestane due to its higher chemical difference to letrozole than anastrozole.

In conclusion, the weaknesses of the submitted documentation is in a minor relevance and reflects potential treatment deviations that may occur in the treatment of patients with HR+/HER2- eBC.

Health economic analysis

Strengths of the economic evaluation

The model structure was deemed appropriate for this decision problem, as it aligned with the model structures adopted in the cost-effectiveness analysis captured in the SLR and consistent with prior relevant NICE and DMC submissions. The treatment pathways included in the model were based on the treatments available for patients in Danish clinical practice.

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

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

Other strengths of the evaluation are that the analysis meets all aspects of the DMC guidelines on the development of a health economic submission [60], including performance of a cost-utility analysis from an semi-social perspective, assessment of HRQoL using the EQ-5D and progressive discounting of costs and benefits throughout the time horizon.

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Limitations of the economic evaluation

Despite the monarchE trial having met its primary endpoint, the follow-up time for the trial data remain relatively immature for the purpose of extrapolating lifetime outcomes. Literature reviews were unable to identify long term outcomes for a monarchE comparable population. Heterogenous patient populations and endpoints, trials such as ATAC39, FACE31 and FATA-GIM330 were used as the best possible proxy evidence to externally validate IDFS curve selection. The OS without distant recurrence extrapolations were reliant on internal validation of the DRFS monarchE trial data which could introduce bias in the cost-utility analysis by under or overestimating the long-term survival outcomes of the monarchE population.

Clinical assumptions surrounding the post-NMR pathway and the NMR death rates were driven by data from a HER2+ population. The main limitation was the assumptions surrounding a constant risk of recurrence or death. The CUA was not able to appropriately capture the monarchE patient pathway and has the risk of introducing bias. The model also currently does not allow a second primary neoplasm cancer event to be captured in the EBC pathway apart from when the patient enters the non-metastatic recurrent health state. Patients in the ABE + ET or ET alone arms may experience second primary neoplasms after their first breast cancer related recurrent event further down the patient pathway. Given the lack of data surrounding the post-recurrent events and following TL advice, at the time of the model development this assumption was deemed the most appropriate approach.

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

Unmet need

The current treatment for eBC is of curative intent. However, approximately 30 % of patients with HR+ eBC will relapse following primary treatment. Indicating that an unmet medical need remains. In the phase 3 monarchE study, patients treated with the combination of abemaciclib and ET had a reduced risk of 30.4% of developing invasive disease together with a tree year IDFS rate of 88.8% vs 83.4% compared to ET alone. The same was true for the risk of developing a distant relapse that was reduced with 31.3 % compared to ET alone [2]. The results simulate that patients with HR+/HER2- eBC would benefit from the treatment with abemaciclib in combination with ET and that abemaciclib would be able to accommodate the unmet medical need.

11. List of experts

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

[redacted]

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Appendix A – Literature search for efficacy and safety of intervention and comparator(s)

No SLR was collected in accordance with the DMC guidelines as the included study monarchE was a head-to-head study representative for the Danish clinical practice as argued in section 6.1. The SLR presented here is a global SLR which was conducted in support of the overall strategy to collect evidence of the efficacy and safety of abemaciclib in combination with ET for the treatment of HR+ HER2- patients in the adjuvant setting. It therefore contains two sections, one on Randomised controlled trials and one on Observational studies.

SLR of randomised controlled studies

Identification and selection of relevant studies

A clinical SLR was conducted to identify relevant clinical evidence for the efficacy and safety of adjuvant endocrine therapy (ET)-based regimens routinely used in patients with HR+, HER2-.

The SLR was conducted in DistillerSR® (a systematic review software that manages; tracks and streamlines the screening, data extraction, and reporting processes[87]), according to good practice guidelines:

- Cochrane collaboration[88]
- Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA)[89]
- Centre for Reviews and Dissemination (CRD's) best practice recommendations[90].

Eligibility criteria

The original SLR was conducted in 2019 prior to the disclosure of monarchE data. The eligibility criteria were specified in terms of population, intervention, comparators, outcomes, and study design (PICOS, Table 64). Due to the specificity of monarchE population and heterogeneity in reporting across published studies, it was anticipated that the volume of relevant literature would be low if the SLR used the same eligibility criteria as monarchE. Divergences were permitted to be able to capture studies that may present data largely comparable to monarchE participants. As a result, PICOS statement was broader. Table 65 documents the divergences and rationale. In addition, during the development of the SLR update 1 (October 2020 update), the protocol was amended to consider longer-term data and strengthen the evidence base established in the original SLR. The original SLR did not extract data beyond five years of follow up.

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Table 64 Eligibility criteria for the clinical SLR of randomized controlled trials (RCTs)

Study Characteristic	Inclusion	Exclusion
Patient population	Patients: • aged ≥18 years • HR+ (i.e. ER+/PR−, ER−/PR+, and ER+/PR+) • HER2− (if reported) or unknown HER2 status[a] • non-metastatic (early–locally advanced) and invasive breast cancer any menopausal status	Patients with: • evidence of distant metastases • DCIS only • inflammatory breast cancer and and • recurrent locally advanced breast cancer For mixed populations (HR/HER2 status): • Exclude if <50% of population HR+ • Exclude if >20% of population HER2+
Intervention	• Tamoxifen • Letrozole • Anastrozole • Exemestane • Abemaciclib + ET • Palbociclib + ET • Ribociclib + ET • Everolimus + ET Combination of above treatments with LHRH or GnRH agonists will be included	Any other treatment
Comparators	• Any of the above-listed interventions • Placebo • No treatment	Any other treatment

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Outcomes	**Efficacy** • Invasive disease-free survival (IDFS)b • Disease-free survival (DFS) • Distant relapse-free survival (DRFS) • Locoregional recurrence-free survival (LRRFS) • Overall survival (OS) **Safety** • Overall (any cause) discontinuation • Discontinuation due to adverse events (AEs) • Discontinuation due to serious AEs (SAEs) • Treatment-related death • Death • The overall incidence of Grade 3-5 (CTCAE) • Anaemia • Constipation • Diarrhoea • Fatigue/asthenia • Febrile neutropenia • Infections • Leukopenia • Nausea/vomiting • Neutropenia • Pulmonary embolism (PE, including VTE) • Thrombocytopenia • Interstitial lung disease • SAE **Health-related quality of life (HRQoL)[c]** • EQ-5Dd • FACT-B • FACT-ES • FACIT - fatigue, cognitive items, bladder symptoms	NA
Study design	• RCTs	• Non-randomised study • PK/PD studies • Case reports/series • Commentaries, letters, editorials, opinions • Guidelines/consensus statements • Observational study design
Language	• All languages • Non-English language papers will have an additional screening before the full translation	NA

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Footnotes: [a] HER2 is often not reported in older studies as this may not have been the standard procedure and such studies were not excluded. [b] Components of IDFS: Distant events/locoregional events were not extracted. The scope of SLR was expanded to include DFS outcome irrespective of the definition to check for the similarity in definitions across the studies. [c] Instruments reporting HRQoL were not limited to those listed in the table. These were noted in data extraction for future reference, full extraction of these data was not required as per agreed protocol. [d] Both EQ-5D-5L and EQ-5D-3L were included; 3L and/or 5L were specified in data extraction. **Abbreviations:** AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; DCIS: ductal carcinoma in-situ; DFS: disease-free survival; DRFS: distant relapse-free survival EQ-5D: EuroQol-5D; ER: oestrogen receptor; ET: endocrine therapy; FACIT: Functional Assessment of Chronic Illness Therapy; FACT-B: Functional Assessment of Cancer Therapy-Breast Cancer; FACT-ES: Functional Assessment of Cancer Therapy-Endocrine Subscale; GnRH: gonadotropin-releasing hormone; HER2: human epidermal growth factor receptor 2; HER2-: human epidermal growth factor receptor 2 negative; HER2+: human epidermal growth factor receptor 2 positive; HR: hormone receptor; HR+: hormone receptor positive; HRQoL: health-related quality of life; IDFS: invasive disease-free survival; LHRH: luteinising hormone-releasing hormone; LRRFS: locoregional recurrence-free survival; OS: overall survival; PD: pharmacodynamics; PE: pulmonary embolism; PK: pharmacokinetics; PR: progesterone receptor; SAE: serious adverse event; VTE: venous thromboembolism.

Table 65 Divergences between monarchE and the SLR criteria

monarchE criteria	SLR criteria	Rationale for divergence in criteria
Node-positive patients only	No restriction on nodal status.	The broader population was allowed by not restricting to nodal status to identify studies that did not state specifics in their eligibility criteria and to avoid excluding potentially relevant studies of patients who were at a similar risk of recurrence. To align with monarchE population, subgroup data for node-positive and nodenegative were extracted, wherever reported.
HR+ patients only	Exclude studies with <50% of HR+ patients or where the HR status was not reported.	Patients with HR+ >50% were included to avoid excluding potentially relevant studies of patients who were at a similar risk of recurrence.
HER2-negative patients only	Exclude studies that explicitly recruit >20% of the population with HER2+.	HER2 status is often not reported in older studies as this may not have been the standard procedure. Hence, studies that did not report HER2 status were not excluded.

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High risk patients only, defined in monarchE as ≥Node 4 or Node 1 to ≤3 Node and ≥T3 (≥5 cm tumour size), and ≥Grade 3 tumour (or) Ki-67 ≥20	No restriction on nodal status, tumour size, tumour grade or Ki-67 levels.	The broader population was allowed by not restricting the risk of recurrence. This led to the inclusion of studies with the patient population largely comparable to monarchE participants.
Efficacy outcomes assessed did not include LRRFS	LRRFS was also assessed.	LRRFS was included in the SLR as new studies were expected to include this outcome as a key outcome of the assessment.

Abbreviations: HER2: human epidermal growth factor receptor 2; HER2-: human epidermal growth factor receptor 2 negative; HER2+: human epidermal growth factor receptor 2 positive; HR: hormone receptor; HR+: hormone receptor positive; LRRFS: locoregional recurrence-free survival; SLR: systematic literature review. ; PK: pharmacokinetics; PR: progesterone receptor; SAE: serious adverse event; VTE: venous thromboembolism.

Search Strategy

Searches for the original SLR were conducted from database inception to 09 July 2019. Updated searches were conducted on 22nd October 2020 (Update #1) and 18th December 2020 (Update #2). The reason for the close proximity of these searches was the disclosure of key data shortly after Update #1. A third update was conducted on 22 June 2021 (Update #3) to align with the read out of the latest OS data cut and ensure latest available evidence have been identified. This application does not contain the additional follow-up 1 (APRIL 2021 DCO) OS data from monarchE [55] .

The search strategies combined free text and controlled vocabulary terms (Medical Subject Headings [MeSH] in MEDLINE and CENTRAL and EMTREE terms in EMBASE) for the disease, population, and comparators of interest. Study design search filters were used in MEDLINE and EMBASE, applying existing, validated randomised controlled trial (RCT) design filters (e.g. the Cochrane-recommended RCT filters for EMBASE)[91]. Search strategies are presented in the Cochrane-recommended RCT filters for EMBASE)[91]. Search strategies are presented in Table 67.

Published studies

The following medical literature databases were searched to identify relevant publications for inclusion in the SLR using the OVID® platform:

Databases:

- Medical Literature Analysis and Retrieval System Online (MEDLINE®)
- MEDLINE® In-Process
- Excerpta Medica Database (EMBASE®)
- Cochrane Central Register of Controlled Clinical Trials (CCTR)
- Latin American and Caribbean Health Sciences Literature (LILACS)

These sources were consistent with the requirements of all major health technology assessment (HTA) bodies and were recommended by the Cochrane Collaboration [88].

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Conference proceedings

To complement the search of published studies from the medical databases, a search for conference abstracts submitted and/or presented at the following professional societies and associated conferences were conducted:

- San Antonio Breast Cancer Symposium
- American Society of Clinical Oncology
- European Society for Medical Oncology
- European Society for Medical Oncology Breast
- American Association for Cancer Research
- St. Gallen Consensus International Breast Cancer Conference

The same eligibility criteria applied to published studies (described above) was applied. Posters and slide decks relating to abstracts that were potentially eligible for inclusion were also retrieved from the conference websites.

Ongoing Trials

Identification of ongoing trials that are likely to publish evidence within 12 months of an indication being appraised is an important aspect of HTA submissions. Three trial databases were searched to identify ongoing trials:

- Clinicaltrials.gov
- World Health Organization International Clinical Trials Registry Platform Search Portal
- Australian New Zealand Clinical Trials Registry (https://anzctr.org.au/TrialSearch.aspx)

Table 66 documents the search criteria applied for the identification of ongoing trials.

Table 66 Selection criteria for ongoing trials

Search Criteria	Limitations
Patients, comparators, and outcomes	As described in the section on eligibility criteria
Recruitment status	**Open studies** • Recruiting • Not yet recruiting • Expanded access: available • Enrolling by invitation **Closed studies** • Active, not recruiting • Completed Studies with unknown status will not be included.

Search terms

Original SLR

The search strategies for the databases searched in the original clinical SLR are presented in Table 67-

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Table 67 EMBASE® search strategy based on Cochrane RCT filters run on 09 July 2019

#	Search strings	Hits
1	exp Breast Neoplasms/	519744
2	((breast$ or mamma or mammary) adj3 (adenocarcinoma* or cancer* or carcinoma* or neoplasm* or tumour* or tumor*)).tw,kw.	474516
3	1 or 2	595348
4	early.ti,ab,kw.	2027400
5	invasive.ti,ab,kw.	505369
6	(stage 1 or stage 2 or stage I or stage II or stage 3 or stage III).ti,ab,kw.	159559
7	adjuvant.ti,ab.	196269
8	4 or 5 or 6 or 7	2732792
9	Letrozole.mp.	11585
10	Anastrozole.mp.	9471
11	Exemestane.mp.	6082
12	Abemaciclib.mp.	680
13	Palbociclib.mp.	2517
14	Ribociclib.mp.	879
15	Tamoxifen.mp.	64619
16	9 or 10 or 11 or 12 or 13 or 14 or 15	75656
17	clinical trial/	981086
18	randomized controlled trial/	559838
19	single blind procedure/	35702
20	double blind procedure/	164969
21	crossover procedure/	60129
22	placebo/	347861
23	prospective study/	533979
24	randomization/	83290
25	(randomised controlled adj1 trial*).mp.	53151
26	(randomized controlled adj1 trial*).mp.	761600
27	rct.mp.	34799
28	randomly allocated.mp.	33070
29	random allocation.mp.	2123
30	allocated randomly.mp.	2486
31	(allocated adj2 random).mp.	969
32	(single adj1 blind*).mp.	47476
33	(double adj1 blind*).mp.	251134
34	((treble or triple) adj1 blind*).mp.	1142
35	placebo*.mp.	446604
36	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35	2190426
37	animal/ not (animal/ and human/)	1453252
38	36 not 37	2155057
39	3 and 8 and 16 and 38	5988

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#	Search strings	Hits
40	(Comment or Letter or Editorial or Case Reports or Review or Practice Guideline).pt.	4207536
41	**39 not 40**	**3986**

Table 68 MEDLINE® search strategy based on Cochrane RCT filters run on 09 July 2019

#	Search strings	Hits
1	exp Breast Neoplasms/	277656
2	((breast$ or mamma or mammary) adj3 (adenocarcinoma* or cancer* or carcinoma* or neoplasm* or tumour* or tumor*)).tw,kw.	291533
3	1 or 2	352086
4	early.ti,ab,kw.	1277404
5	invasive.ti,ab,kw.	283315
6	(stage 1 or stage 2 or stage I or stage II or stage 3 or stage III).ti,ab,kw.	83288
7	adjuvant.ti,ab.	114962
8	4 or 5 or 6 or 7	1681377
9	Tamoxifen.mp.	25170
10	Letrozole.mp.	2655
11	Anastrozole.mp.	1965
12	Exemestane.mp.	1237
13	Abemaciclib.mp.	101
14	Palbociclib.mp.	508
15	Ribociclib.mp.	158
16	9 or 10 or 11 or 12 or 13 or 14 or 15	28433
17	randomized controlled trial.pt.	484342
18	controlled clinical trial.pt.	93115
19	randomized.ti,ab.	426868
20	placebo.ti,ab.	188142
21	drug therapy.xs.	0
22	randomly.ti,ab.	274031
23	trial.ti,ab.	484402
24	groups.ti,ab.	1722724
25	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	2535961
26	3 and 8 and 16 and 25	2589
27	(Comment or Letter or Editorial or Case Reports or Review or Practice Guideline).pt. or exp Guidelines as Topic/	5685416
28	**26 not 27**	**1914**

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Table 69 Cochrane database search strategy based on Cochrane RCT filters run on 09 July 2019

#	Search strings	Hits
1	exp Breast Neoplasms/	12498
2	((breast$ or mamma or mammary) adj3 (adenocarcinoma* or cancer* or carcinoma* or neoplasm* or tumour* or tumor*)).tw,kw.	37860
3	1 or 2	38755
4	early.ti,ab,kw.	108983
5	invasive.ti,ab,kw.	26905
6	(stage 1 or stage 2 or stage I or stage II or stage 3 or stage III).ti,ab,kw.	19445
7	adjuvant.ti,ab.	25450
8	4 or 5 or 6 or 7	165945
9	Tamoxifen.mp.	5254
10	Letrozole.mp.	2012
11	Anastrozole.mp.	1263
12	Exemestane.mp.	956
13	Abemaciclib.mp.	93
14	Palbociclib.mp.	300
15	Ribociclib.mp.	152
16	9 or 10 or 11 or 12 or 13 or 14 or 15	7693
17	randomized controlled trial.pt.	474352
18	controlled clinical trial.pt.	90982
19	randomized.ti,ab.	590050
20	placebo.ti,ab.	276527
21	drug therapy.xs.	0
22	randomly.ti,ab.	222783
23	trial.ti,ab.	533320
24	groups.ti,ab.	432804
25	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	1180173
26	3 and 8 and 16 and 25	2831
27	(Comment or Letter or Editorial or Case Reports or Review or Practice Guideline).pt. or exp Guidelines as Topic/	14157
28	**26 not 27**	**2800**

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Table 70 LILACS search strategy run on 09 July 2019

#	Search strings	Hits
1	Breast Neoplasms OR (breast$ or mamma or mammary) OR “breast cancer” OR early OR invasive OR ("stage 1" or "stage 2" OR "stage I" OR "stage II" OR "stage 3" OR "stage III") OR adjuvant	23694
2	((PT "randomized controlled trial" OR PT "controlled clinical trial" OR PT "multicenter study" OR MH "randomized controlled trials as topic" OR MH "controlled clinical trials as topic" OR MH "multicenter studies as topic" OR MH "random allocation" OR MH "double-blind method" OR MH "single-blind method") OR ((ensaio$ OR ensayo$ OR trial$) AND (azar OR acaso OR placebo OR control$ OR aleat$ OR random$ OR enmascarado$ OR simpleciego OR ((simple$ OR single OR duplo$ OR doble$ OR double$) AND (cego OR ciego OR blind OR mask))) AND clinic$)) AND NOT (MH animals OR MH rabbits OR MH rats OR MH primates OR MH dogs OR MH cats OR MH swine OR PT "in vitro")	12997
3	Tamoxifen OR Letrozole OR Anastrozole OR Exemestane OR Abemaciclib OR Palbociclib OR Ribociclib	350
4	(tw:(Breast Neoplasms OR (breast$ or mamma or mammary) OR “breast cancer” OR early OR invasive OR ("stage 1" or "stage 2" OR "stage I" OR "stage II" OR "stage 3" OR "stage III") OR adjuvant)) AND (tw:(((PT "randomized controlled trial" OR PT "controlled clinical trial" OR PT "multicenter study" OR MH "randomized controlled trials as topic" OR MH "controlled clinical trials as topic" OR MH "multicenter studies as topic" OR MH "random allocation" OR MH "double-blind method" OR MH "single-blind method") OR ((ensaio$ OR ensayo$ OR trial$) AND (azar OR acaso OR placebo OR control$ OR aleat$ OR random$ OR enmascarado$ OR simpleciego OR ((simple$ OR single OR duplo$ OR doble$ OR double$) AND (cego OR ciego OR blind OR mask))) AND clinic$)) AND NOT (MH animals OR MH rabbits OR MH rats OR MH primates OR MH dogs OR MH cats OR MH swine OR PT "in vitro"))) AND (tw:(Tamoxifen OR Letrozole OR Anastrozole OR Exemestane OR Abemaciclib OR Palbociclib OR Ribociclib))	13

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Table 71 Embase search strategy run on 22 OCT 2020

#	Search strings	Hits
1	exp Breast Neoplasms/	544317
2	((breast$ or mamma or mammary) adj3 (adenocarcinoma* or cancer* or carcinoma* or neoplasm* or tumour* or tumor*)).tw,kw.	500890
3	1 or 2	623686
4	early.ti,ab,kw.	2100885
5	invasive.ti,ab,kw.	562108
6	(stage 1 or stage 2 or stage I or stage II or stage 3 or stage III).ti,ab,kw.	173605
7	adjuvant.ti,ab.	210452
8	4 or 5 or 6 or 7	2874455
9	Letrozole.mp.	12691
10	Anastrozole.mp.	9970
11	Exemestane.mp.	6492
12	Abemaciclib.mp.	1114
13	Palbociclib.mp.	3544
14	Ribociclib.mp.	1375
15	Tamoxifen.mp.	68018
16	9 or 10 or 11 or 12 or 13 or 14 or 15	81198
17	clinical trial/	989213
18	randomized controlled trial/	628289
19	single blind procedure/	40705
20	double blind procedure/	177642
21	crossover procedure/	64938
22	placebo/	357457
23	prospective study/	637417
24	randomization/	88754
25	(randomised controlled adj1 trial*).mp.	60561
26	(randomized controlled adj1 trial*).mp.	861014

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#	Search strings	Hits
27	rct.mp.	41273
28	randomly allocated.mp.	36825
29	random allocation.mp.	2276
30	allocated randomly.mp.	2609
31	(allocated adj2 random).mp.	909
32	(single adj1 blind*).mp.	52986
33	(double adj1 blind*).mp.	262760
34	((treble or triple) adj1 blind*).mp.	1386
35	placebo*.mp.	462561
36	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35	2381105
37	animal/ not (animal/ and human/)	1085112
38	36 not 37	2344537
39	3 and 8 and 16 and 38	6253
40	(Comment or Letter or Editorial or Case Reports or Review or Practice Guideline).pt.	4463519
41	39 not 40	4230
42	limit 41 to dc=20190709-20201022	267

Table 72 MEDLINE® search strategy based on Cochrane RCT filters run on 22 OCT 2020

#	Search strings	Hits
1	exp Breast Neoplasms/	294932
2	((breast$ or mamma or mammary) adj3 (adenocarcinoma* or cancer* or carcinoma* or neoplasm* or tumour* or tumor*)).tw,kw.	310110
3	1 or 2	373209
4	early.ti,ab,kw.	1366371
5	invasive.ti,ab,kw.	309249
6	(stage 1 or stage 2 or stage I or stage II or stage 3 or stage III).ti,ab,kw.	89832
7	adjuvant.ti,ab.	122858
8	4 or 5 or 6 or 7	1804131
9	Tamoxifen.mp.	26108
10	Letrozole.mp.	2919
11	Anastrozole.mp.	2050
12	Exemestane.mp.	1333
13	Abemaciclib.mp.	211
14	Palbociclib.mp.	751
15	Ribociclib.mp.	271
16	9 or 10 or 11 or 12 or 13 or 14 or 15	29984
17	randomized controlled trial.pt.	515063
18	controlled clinical trial.pt.	93867
19	randomized.ti,ab.	470912
20	placebo.ti,ab.	199348
21	drug therapy.xs.	0
22	randomly.ti,ab.	295612
23	trial.ti,ab.	535957
24	groups.ti,ab.	1851227

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#	Search strings	Hits
25	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	2727642
26	3 and 8 and 16 and 25	2678
27	(Comment or Letter or Editorial or Case Reports or Review or Practice Guideline).pt. or exp Guidelines as Topic/	6035855
28	26 not 27	1987
29	**limit 28 to dt=20190709-20201022**	41

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Table 73 Cochrane database search strategy based on Cochrane RCT filters run on 22 OCT 2020

#	Search strings	Hits
1	exp Breast Neoplasms/	14015
2	((breast$ or mamma or mammary) adj3 (adenocarcinoma* or cancer* or carcinoma* or neoplasm* or tumour* or tumor*)).tw,kw.	42245
3	1 or 2	43225
4	early.ti,ab,kw.	124417
5	invasive.ti,ab,kw.	31971
6	(stage 1 or stage 2 or stage I or stage II or stage 3 or stage III).ti,ab,kw.	22345
7	adjuvant.ti,ab.	28710
8	4 or 5 or 6 or 7	190173
9	Tamoxifen.mp.	5533
10	Letrozole.mp.	2306
11	Anastrozole.mp.	1401
12	Exemestane.mp.	1045
13	Abemaciclib.mp.	137
14	Palbociclib.mp.	397
15	Ribociclib.mp.	210
16	9 or 10 or 11 or 12 or 13 or 14 or 15	8389
17	randomized controlled trial.pt.	503773
18	controlled clinical trial.pt.	91721
19	randomized.ti,ab.	684021
20	placebo.ti,ab.	309202
21	drug therapy.xs.	0
22	randomly.ti,ab.	255678
23	trial.ti,ab.	619237
24	groups.ti,ab.	487639
25	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	1330600
26	3 and 8 and 16 and 25	3055
27	(Comment or Letter or Editorial or Case Reports or Review or Practice Guideline).pt. or exp Guidelines as Topic/	14634
28	26 not 27	3024
29	**limit 28 to yr="2019 -Current" [Limit not valid in DARE; records were retained]**	**188**

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Table 74 LILACS search strategy run on 22 OCT 2020

#	Search strings	Hits
1	Breast Neoplasms OR (breast$ or mamma or mammary) OR “breast cancer” OR early OR invasive OR ("stage 1" or "stage 2" OR "stage I" OR "stage II" OR "stage 3" OR "stage III") OR adjuvant	23694
2	((PT "randomized controlled trial" OR PT "controlled clinical trial" OR PT "multicenter study" OR MH "randomized controlled trials as topic" OR MH "controlled clinical trials as topic" OR MH "multicenter studies as topic" OR MH "random allocation" OR MH "double-blind method" OR MH "single-blind method") OR ((ensaio$ OR ensayo$ OR trial$) AND (azar OR acaso OR placebo OR control$ OR aleat$ OR random$ OR enmascarado$ OR simpleciego OR ((simple$ OR single OR duplo$ OR doble$ OR double$) AND (cego OR ciego OR blind OR mask))) AND clinic$)) AND NOT (MH animals OR MH rabbits OR MH rats OR MH primates OR MH dogs OR MH cats OR MH swine OR PT "in vitro")	12997
3	Tamoxifen OR Letrozole OR Anastrozole OR Exemestane OR Abemaciclib OR Palbociclib OR Ribociclib	350
4	(tw:(Breast Neoplasms OR (breast$ or mamma or mammary) OR “breast cancer” OR early OR invasive OR ("stage 1" or "stage 2" OR "stage I" OR "stage II" OR "stage 3" OR "stage III") OR adjuvant)) AND (tw:(((PT "randomized controlled trial" OR PT "controlled clinical trial" OR PT "multicenter study" OR MH "randomized controlled trials as topic" OR MH "controlled clinical trials as topic" OR MH "multicenter studies as topic" OR MH "random allocation" OR MH "double-blind method" OR MH "single-blind method") OR ((ensaio$ OR ensayo$ OR trial$) AND (azar OR acaso OR placebo OR control$ OR aleat$ OR random$ OR enmascarado$ OR simpleciego OR ((simple$ OR single OR duplo$ OR doble$ OR double$) AND (cego OR ciego OR blind OR mask))) AND clinic$)) AND NOT (MH animals OR MH rabbits OR MH rats OR MH primates OR MH dogs OR MH cats OR MH swine OR PT "in vitro"))) AND (tw:(Tamoxifen OR Letrozole OR Anastrozole OR Exemestane OR Abemaciclib OR Palbociclib OR Ribociclib))	14

December 2020, update 2

Table 75 Embase search strategy run on 18 DEC 2020

#	Search strings	Hits
1	exp Breast Neoplasms/	550956
2	((breast$ or mamma or mammary) adj3 (adenocarcinoma* or cancer* or carcinoma* or neoplasm* or tumour* or tumor*)).tw,kw.	507523
3	1 or 2	631345
4	early.ti,ab,kw.	2132929
5	invasive.ti,ab,kw.	571626
6	(stage 1 or stage 2 or stage I or stage II or stage 3 or stage III).ti,ab,kw.	177080
7	adjuvant.ti,ab.	213173
8	4 or 5 or 6 or 7	2919142
9	Letrozole.mp.	12850
10	Anastrozole.mp.	10031
11	Exemestane.mp.	6556
12	Abemaciclib.mp.	1211
13	Palbociclib.mp.	3713
14	Ribociclib.mp.	1449
15	Tamoxifen.mp.	68708
16	9 or 10 or 11 or 12 or 13 or 14 or 15	82209
17	clinical trial/	997658
18	randomized controlled trial/	639251
19	single blind procedure/	41412
20	double blind procedure/	180055
21	crossover procedure/	65668
22	placebo/	361237
23	prospective study/	652619
24	randomization/	89647
25	(randomised controlled adj1 trial*).mp.	61854
26	(randomized controlled adj1 trial*).mp.	876929
27	rct.mp.	42313

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#	Search strings	Hits
28	randomly allocated.mp.	37423
29	random allocation.mp.	2323
30	allocated randomly.mp.	2638
31	(allocated adj2 random).mp.	911
32	(single adj1 blind*).mp.	53808
33	(double adj1 blind*).mp.	265737
34	((treble or triple) adj1 blind*).mp.	1422
35	placebo*.mp.	467592
36	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35	2417223
37	animal/ not (animal/ and human/)	1096885
38	36 not 37	2380400
39	3 and 8 and 16 and 38	6306
40	(Comment or Letter or Editorial or Case Reports or Review or Practice Guideline).pt.	4521138
41	39 not 40	4273
42	limit 41 to dc=20201022-20201218	44

Table 76 MEDLINE® search strategy based on Cochrane RCT filters run on 18 DEC 2020

#	Search strings	Hits
1	exp Breast Neoplasms/	297453
2	((breast$ or mamma or mammary) adj3 (adenocarcinoma* or cancer* or carcinoma* or neoplasm* or tumour* or tumor*)).tw,kw.	355730
3	1 or 2	418981
4	early.ti,ab,kw.	1559998
5	invasive.ti,ab,kw.	367387
6	(stage 1 or stage 2 or stage I or stage II or stage 3 or stage III).ti,ab,kw.	102541
7	adjuvant.ti,ab.	141516
8	4 or 5 or 6 or 7	2072655
9	Tamoxifen.mp.	28117
10	Letrozole.mp.	3409
11	Anastrozole.mp.	2259
12	Exemestane.mp.	1514
13	Abemaciclib.mp.	338
14	Palbociclib.mp.	1076
15	Ribociclib.mp.	406
16	9 or 10 or 11 or 12 or 13 or 14 or 15	32915
17	randomized controlled trial.pt.	519221
18	controlled clinical trial.pt.	93971
19	randomized.ti,ab.	545018
20	placebo.ti,ab.	219642
21	drug therapy.xs.	0
22	randomly.ti,ab.	348422
23	trial.ti,ab.	622041
24	groups.ti,ab.	2159441

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#	Search strings	Hits
25	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	3148805
26	3 and 8 and 16 and 25	2850
27	(Comment or Letter or Editorial or Case Reports or Review or Practice Guideline).pt. or exp Guidelines as Topic/	6534137
28	26 not 27	2134
29	**limit 28 to dt=20201022-20201218**	12

Table 77 Cochrane database search strategy based on Cochrane RCT filters run on 18 DEC 2020

#	Search strings	Hits
1	exp Breast Neoplasms/	14130
2	((breast$ or mamma or mammary) adj3 (adenocarcinoma* or cancer* or carcinoma* or neoplasm* or tumour* or tumor*)).tw,kw.	43033
3	1 or 2	44016
4	early.ti,ab,kw.	126807
5	invasive.ti,ab,kw.	33090
6	(stage 1 or stage 2 or stage I or stage II or stage 3 or stage III).ti,ab,kw.	22974
7	adjuvant.ti,ab.	29412
8	4 or 5 or 6 or 7	194469
9	Tamoxifen.mp.	5561
10	Letrozole.mp.	2373
11	Anastrozole.mp.	1414
12	Exemestane.mp.	1055
13	Abemaciclib.mp.	156
14	Palbociclib.mp.	425
15	Ribociclib.mp.	228
16	9 or 10 or 11 or 12 or 13 or 14 or 15	8520
17	randomized controlled trial.pt.	507674
18	controlled clinical trial.pt.	91810
19	randomized.ti,ab.	698095
20	placebo.ti,ab.	315114
21	drug therapy.xs.	0
22	randomly.ti,ab.	260657
23	trial.ti,ab.	633303
24	groups.ti,ab.	496136
25	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	1355554
26	3 and 8 and 16 and 25	3093
27	(Comment or Letter or Editorial or Case Reports or Review or Practice Guideline).pt. or exp Guidelines as Topic/	14715
28	26 not 27	3062
29	**limit 28 to yr="2020 -Current" [Limit not valid in DARE; records were retained]**	**74**

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Table 78 LILACS search strategy run on 18 DEC 2020

#	Search strings	Hits
1	Breast Neoplasms OR (breast$ or mamma or mammary) OR “breast cancer” OR early OR invasive OR ("stage 1" or "stage 2" OR "stage I" OR "stage II" OR "stage 3" OR "stage III") OR adjuvant	23694
2	((PT "randomized controlled trial" OR PT "controlled clinical trial" OR PT "multicenter study" OR MH "randomized controlled trials as topic" OR MH "controlled clinical trials as topic" OR MH "multicenter studies as topic" OR MH "random allocation" OR MH "double-blind method" OR MH "single-blind method") OR ((ensaio$ OR ensayo$ OR trial$) AND (azar OR acaso OR placebo OR control$ OR aleat$ OR random$ OR enmascarado$ OR simpleciego OR ((simple$ OR single OR duplo$ OR doble$ OR double$) AND (cego OR ciego OR blind OR mask))) AND clinic$)) AND NOT (MH animals OR MH rabbits OR MH rats OR MH primates OR MH dogs OR MH cats OR MH swine OR PT "in vitro")	12997
3	Tamoxifen OR Letrozole OR Anastrozole OR Exemestane OR Abemaciclib OR Palbociclib OR Ribociclib	350
4	(tw:(Breast Neoplasms OR (breast$ or mamma or mammary) OR “breast cancer” OR early OR invasive OR ("stage 1" or "stage 2" OR "stage I" OR "stage II" OR "stage 3" OR "stage III") OR adjuvant)) AND (tw:(((PT "randomized controlled trial" OR PT "controlled clinical trial" OR PT "multicenter study" OR MH "randomized controlled trials as topic" OR MH "controlled clinical trials as topic" OR MH "multicenter studies as topic" OR MH "random allocation" OR MH "double-blind method" OR MH "single-blind method") OR ((ensaio$ OR ensayo$ OR trial$) AND (azar OR acaso OR placebo OR control$ OR aleat$ OR random$ OR enmascarado$ OR simpleciego OR ((simple$ OR single OR duplo$ OR doble$ OR double$) AND (cego OR ciego OR blind OR mask))) AND clinic$)) AND NOT (MH animals OR MH rabbits OR MH rats OR MH primates OR MH dogs OR MH cats OR MH swine OR PT "in vitro"))) AND (tw:(Tamoxifen OR Letrozole OR Anastrozole OR Exemestane OR Abemaciclib OR Palbociclib OR Ribociclib))	14
5	Limit 4 to October to December	0

June 2021, Update 3

Table 79 Embase search strategy run on 22 JUN 2021

#	Search strings	Hits
1	exp Breast Neoplasms/	588757
2	((breast$ or mamma or mammary) adj3 (adenocarcinoma* or cancer* or carcinoma* or neoplasm* or tumour* or tumor*)).tw,kw.	540765
3	1 or 2	674532
4	early.ti,ab,kw.	2306694
5	invasive.ti,ab,kw.	597265
6	(stage 1 or stage 2 or stage I or stage II or stage 3 or stage III).ti,ab,kw.	186788
7	adjuvant.ti,ab.	225099
8	4 or 5 or 6 or 7	3131728
9	Letrozole.mp.	13370
10	Anastrozole.mp.	10279
11	Exemestane.mp.	6754
12	Abemaciclib.mp.	1459
13	Palbociclib.mp.	4213
14	Ribociclib.mp.	1654
15	Tamoxifen.mp.	70031
16	9 or 10 or 11 or 12 or 13 or 14 or 15	84502
17	clinical trial/	1027364
18	randomized controlled trial/	665429
19	single blind procedure/	43044
20	double blind procedure/	187933
21	crossover procedure/	67768
22	placebo/	378837
23	prospective study/	695775
24	randomization/	91317
25	(randomised controlled adj1 trial*).mp.	64462
26	(randomized controlled adj1 trial*).mp.	917158

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#	Search strings	Hits
27	rct.mp.	44841
28	randomly allocated.mp.	38858
29	random allocation.mp.	2419
30	allocated randomly.mp.	2700
31	(allocated adj2 random).mp.	995
32	(single adj1 blind*).mp.	55775
33	(double adj1 blind*).mp.	277106
34	((treble or triple) adj1 blind*).mp.	1559
35	placebo*.mp.	487723
36	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35	2530393
37	animal/ not (animal/ and human/)	1523960
38	36 not 37	2492866
39	3 and 8 and 16 and 38	6449
40	(Comment or Letter or Editorial or Case Reports or Review or Practice Guideline).pt.	4675006
41	39 not 40	4400
42	**limit 41 to dc=20201218-20210622**	**141**

Table 80 MEDLINE® search strategy based on Cochrane RCT filters run on 22 JUN 2021

#	Search strings	Hits
1	exp Breast Neoplasms/	306832
2	((breast$ or mamma or mammary) adj3 (adenocarcinoma* or cancer* or carcinoma* or neoplasm* or tumour* or tumor*)).tw,kw.	366912
3	1 or 2	431679
4	early.ti,ab,kw.	1612494
5	invasive.ti,ab,kw.	383074
6	(stage 1 or stage 2 or stage I or stage II or stage 3 or stage III).ti,ab,kw.	106206
7	adjuvant.ti,ab.	146465
8	4 or 5 or 6 or 7	2145310
9	Tamoxifen.mp.	28551
10	Letrozole.mp.	3551
11	Anastrozole.mp.	2301
12	Exemestane.mp.	1555
13	Abemaciclib.mp.	412
14	Palbociclib.mp.	1218
15	Ribociclib.mp.	460
16	9 or 10 or 11 or 12 or 13 or 14 or 15	33695
17	randomized controlled trial.pt.	534111
18	controlled clinical trial.pt.	94219
19	randomized.ti,ab.	567694
20	placebo.ti,ab.	224958
21	drug therapy.xs.	0
22	randomly.ti,ab.	360806
23	trial.ti,ab.	648251

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#	Search strings	Hits
24	groups.ti,ab.	2236023
25	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	3258001
26	3 and 8 and 16 and 25	2892
27	(Comment or Letter or Editorial or Case Reports or Review or Practice Guideline).pt. or exp Guidelines as Topic/	6714815
28	26 not 27	2172
29	**limit 28 to dt=20201218-20210622**	**36**

Systematic selection of studies

Included studies

A total of 9,667 records were identified across the updates (n=8,713 [Original: 09 July 2019], n=510 [Update #1: 22 October 2020], n=131 [Update #2: 18 December 2020], and n=313 [Update #3: 22 June 2021]; Figure 32). Three additional records were identified through bibliographic searching and twelve through search of conference proceedings. In addition, the CSR for monarchE at second interim analysis and CSR addendum at primary outcome analysis were included. Due to overlap of records across databases, 3053 duplicate references were removed. Screening of titles and abstracts yielded 445 relevant references for full-text review, out of which 175 records presenting 37 unique studies were included for data extraction.

One hundred and twenty-three records presenting data on 34 RCTs evaluating adjuvant ET-based regimens were included in the original SLR. The recent updates of the SLR identified five new studies. Two studies (TAM-02[92] and Stockholm study[93]) included in the original SLR were excluded in the update[1].

- **Original SLR, initiated July 2019**: The initial SLR included 79 full-text articles, 35 conference abstracts, nine clinical trial identifiers reporting on 34 RCTs.
- **Update # 1, initiated October 2020**: Fourteen full-text articles, 11 conference abstracts, and eight clinical trials identifiers were identified in the first update. Data from the clinical study report (CSR; at additional follow-up, median follow-up of 15.5 months) for monarchE were included. Four full-text articles reported additional data for previously identified studies. Ten full-text articles, 11 conference abstracts, and eight clinical trial identifiers reported data for four new studies. Three full-text articles evaluating two studies (TAM-02[92] and Stockholm study[93]) included in the original SLR were excluded in this update.
- **Update #2, initiated December 2020**: One full-text article, seven conference abstracts, and one clinical trial identifier were identified in the second update. Data from the CSR addendum (at primary outcome analysis) for monarchE were included. One full-text manuscript, five conference abstracts, and one CSR provided data for four previously identified studies. Two conference abstracts and one clinical trial identifier[94] provided data for a new study (PENELOPE-B).
- **Update #3, initiated June 2021**: Three full-text articles and, eight conference abstracts were identified. The included records provided the data for four previously identified studies. No new study was identified.

In total, 175 records presenting data on 37 RCTs evaluating adjuvant ET-based regimens were included (Figure 32).

[1] TAM-02 study: The study evaluated the effectiveness of introduction of delayed ET at least 2 years after surgery/adjuvant chemo or radiotherapy. The study was not of interest to the review as delay in the introduction of ET is not in accordance with the current standard clinical practices. Stockholm study: Comparator not of interest (adjuvant chemotherapy and radiotherapy).

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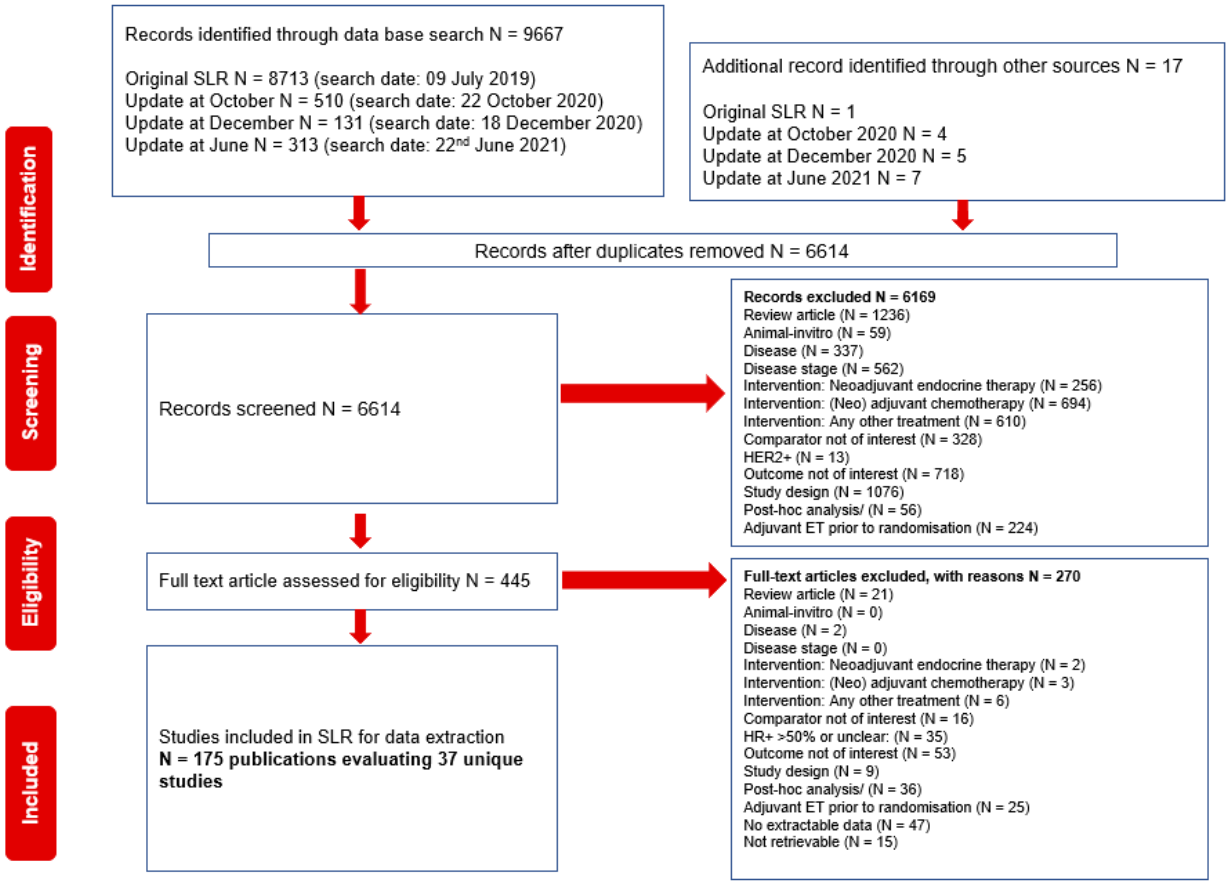
Figure 32: PRISMA diagram for the clincal SLR of RCTs: Original July 2019 clinical SLR and October 2020, December 2020 updates and June 2021 updates



ABBREVIATIONS: ET: endocrine therapy; HER2+: human epidermal growth factor receptor 2 positive; HR+: hormone receptor positive; N: number of records; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR: systematic literature review.

List of included studies

The list of included studies is presented in Table 81.

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Table 81: List of studies included in the clinical SLR of RCTs

Study Name	Primary Record	Clinical Trial Number	Treatments	Phase	Blinding	Associated Records
CDK4 and 6 inhibitor + ET vs. ET alone or placebo + ET						
monarchE	Eli Lilly and Company (CSR at primary outcome analysis)[65]	NCT03155997	• Abemaciclib + ET • ET alone	3	Open-label	Rugo et al. (2021)*[95] Toi et al. (2021)*[96] Yap et al. (2021)*[97] Martin et al. (2021)*[98] Shao et al. (2021)*[99] Jiang et al. (2020)*[100] Johnston et al. (2020a)*[101] Johnston et al. (2020b)[102] Johnston et al. (2020c)*[103] O'Shaughnessy et al. (2020)*[104] Harbeck et al. (2020)*[105] EUCTR2016-004362-26-NL[106] Eli Lilly and Company (CSR at interim analysis)[107] Rastogi et al. (2018)*[108] Rastogi et al. (2019)*[109]
PALLAS	Mayer et al. (2021)[110]	NCT02513394	• Palbociclib + ET • ET alone	3	Open-label	Mayer et al. (2020)[111] Mayer et al. (2020a)*[112] EUCTR2014-005181-30-ES[113] NCT02513394[63] Mayer et al. (2016)*[114] Mayer et al. (2017)*[115]
PENELOPE-B	Loibl et al. (2021)[64]	NCT01864746	• Palbociclib + ET • placebo + ET	3	Double-blind	Marmé et al. (2021)*[116] Denkert et al. (2021)*[117] Loibl et al. (2020)[118] JPRN-UMIN000015779[94] Von et al. (2013)*[119]
Tamoxifen vs. AI						
ATAC	Baum (2002)[120]	NCT00849030 ACTRN12606000527561 1998	• Tamoxifen, anastrozole	3	Double-blind	Cuzick et al. (2010)[71] Duffy et al. (2010)[121] Forbes et al. (2008)[122]

Study Name	Primary Record	Clinical Trial Number	Treatments	Phase	Blinding	Associated Records
			• Tamoxifen + anastrozole			Buzdar et al. (2006)[123] Anonymous et al. (2005)[73] Howell et al. (2005)[124] Anonymous et al. (2003)[125] Buzdar et al. (2003)[126] Fisher et al. (2002)[127] Cella et al. (2006)[128] Buzdar et al. (2006)[129] Fallowfield et al. (2004)[130] Howell et al. (2004)*[131] Tobias et al. (2003)*[132] Cella et al. (2002)*[133] Raab et al. (2002)*[134] Tobias et al. (2003)*[135] Baum et al. (2000)*[136] Baum et al. (2002)*[137] Fallowfield et al. (2002)*[138] ACTRN12606000527561 (1998)[139]
BIG 1-98	Thürlimann et al. (2005)[140]	NCT00004205	• Tamoxifen • Letrozole • Tamoxifen to letrozole • Letrozole to tamoxifen	3	Double-blind	Munzone et al. (2015)[141] Colleoni et al. (2011)[142] Regan et al. (2011)[143] Mouridsen et al. (2009)[144] Giobbie-Hurder et al. (2009)[145] Joerger et al. (2009)[146] Coates et al. (2007)[147] Forbes et al. (2006)[148] Monnier et al. (2006)[149] Viale et al. (2008)[150] Koeberle et al. (2007)[151] Prowell et al. (2006)[152] Mouridsen et al. (2009)*[153] Giobbie-Hurder et al. (2007)*[154] Regan et al. (2011)[155] Buechler et al. (2019)[156] Rabaglio et al. (2020)[157]

Study Name	Primary Record	Clinical Trial Number	Treatments	Phase	Blinding	Associated Records
HEART	Lin et al. (2014)[158]	NCT00537771	• Tamoxifen • Anastrozole	4	Open-label	NA
HOBOE	Perrone et al. (2019)[66]	NCT00412022	• Tamoxifen • Letrozole	3	Open-label	Rossi et al. (2009)[159] NCT00412022 (2006)[160] Perrone et al. (2018)*[161]
Tamoxifen to AI vs. AI						
FATA-GIM3	De Placido et al. (2018)[67]	NCT00541086	• Tamoxifen to anastrozole • Tamoxifen to exemestane • Tamoxifen to letrozole • Anastrozole • Exemestane • Letrozole	3	Open-label	Perrone et al. (2017)*[162] Gallo et al. (2017)*[163] EUCTR2006-004018-42-IT[164] NCT00541086 (2007)[165] De Placido et al. (2018)[166] Price et al. (2011)[155]
Success C sub-study	Schochter et al. (2018)[68]	--	• Tamoxifen to exemestane • Exemestane	3	Open-label	NA
TEAM	van de Velde (2011)[167]	NCT00036270, registered in France with ClinicalTrials.gov; NCT00279448, the Netherlands and Belgium with Netherlands Trial Register; NTR 267, the UK and Ireland with ClinicalTrials.gov; NCT00032136, the USA with ClinicalTrials.gov; NCT00036270, Germany with	• Tamoxifen to exemestane • Exemestane	3	Open-label	Derks et al. (2017)[168] van et al. (2013)[169] Van et al. (2012)[170] Jones et al. (2009)*[171] NCT00036270 (2002)[172] Takei et al. (2012)[173] JPRN-C000000057 (2005)[174] Ohsumi et al. (2010)*[175] Ohsumi et al. (2007)*[176]

Study Name	Primary Record	Clinical Trial Number	Treatments	Phase	Blinding	Associated Records
		Ethics Commission Trial; 27/2001 and Japan with University Hospital Medical Information Network-Clinical Trials Registry, C000000057				
Tamoxifen to AI vs. Tamoxifen						
ABCSG-8	Dubsky et al. (2012)[177]	NCT00291759	• Tamoxifen to anastrozole • Tamoxifen	3	Open-label	Knauer et al. (2015)*[178] Dubsky et al. (2010)*[179] Zsuzsanna et al. (2011)[180]
AI vs. AI						
ALIQUOT	Dixon et al. (2011)[181]	--	• Anastrozole • Letrozole	Not reported	Open-label	NA
FACE	Smith et al. (2017)[62]	NCT00248170	• Anastrozole • Letrozole	3b	Open-label	O'Shaughnessy et al. (2016)*[182], 2019[183] NCT00248170 (2005)[184]

Study Name	Primary Record	Clinical Trial Number	Treatments	Phase	Blinding	Associated Records
MA.27	Goss et al. (2013)[185]	NCT00066573	• Anastrozole • Exemestane	3	Open-label	Either et al. (2021)[186] Wagner et al. (2018)[187] Chapman et al. (2016)[188] EUCTR2005-001893-28-HU (2005)[189] NCT00090974 (2004) - (QoL)[190] Zhao et al. (2011)[191]
Tamoxifen + OFS vs. Tamoxifen						
ASTRRA	Kim et al. (2016)[192]	NCT00912548	• Tamoxifen + goserelin • Tamoxifen	3	Open-label	Noh et al. (2018)*[193] Kim et al. (2020)[194]
E-3193, INT-0142	Tevaarwerk et al. (2014)[195]	--	• Tamoxifen + OFS • Tamoxifen	3	Open-label	NA
Uslu et al. (2014)[196]	Uslu et al. (2014)[196]	--	• Tamoxifen + goserelin • Tamoxifen	Not reported	Not reported	NA
Yang et al. (2013)[197]	Yang et al. (2013)[197]	NCT00827307	• Tamoxifen + goserelin • Tamoxifen	Not reported	Open-label	Yang et al. (2016a)*[198] Yang et al. (2016b)*[199]
Tamoxifen + OFS vs. AI + OFS						
ABCSG-12	Gnant et al. (2009)[200]	NCT00295646	• Tamoxifen + goserelin • Anastrozole + goserelin	3	Open-label	Fox et al. (2010)[201] Gnant et al. (2009)*[202] Gnant et al. (2008)*[203] Gnant et al. (2011)[204] Grant et al. (2008)[205] Santi et al. (2012)[206]
SOFT	Francis (2015)[69]	NCT00066690	• Tamoxifen • Tamoxifen + OFS • Exemestane + OFS	3	Open-label	Pagani et al. (2014)[70] Prudence et al. (2018)[207] Regan et al. (2015)[208] Regan et al. (2016)[209] Regan et al. (2017)[210] Ribi et al. (2016)[211] Bernhard et al. (2014)*[212] Bernhard et al. (2015)[213] Pagani et al. (2018)*[214]

Study Name	Primary Record	Clinical Trial Number	Treatments	Phase	Blinding	Associated Records
						Saha et al. (2017)[215] Francis et al. (2017)*[216] Zickl et al. (2012)*[217] EUCTR2004-000166-13-IE (2007)[218] Pagani et al. (2020)[219] NCT00066690 (2003)[220]
TEXT	Pagani (2014)[70]	NCT00066703	• Tamoxifen + triptorelin • Exemestane + triptorelin	3	Open-label	Prudence et al. (2018)[207] Regan et al. (2015)[208] Regan et al. (2016)[209] Regan et al. (2017)[210] Bernhard et al. (2015)[213] Pagani et al. (2018)*[214] Saha et al. (2017)[215] Francis et al. (2017)*[216] Bernhard et al. (2014)*[212] Zickl et al. (2012)*[217] ISRCTN66949472[221] EUCTR2004-000168-28-DE (2006)[222] Pagani et al. (2020)[219] NCT00066703[223]
Tamoxifen duration comparison						
DBCG	Andersen (1998)[224]*	--	• Tamoxifen 1 year • Tamoxifen 2 years	3	Not reported	NA
Swedish Breast Cancer Cooperative Group	Rutqvist et al. (1996)[225]	--	• Tamoxifen 5 years • Tamoxifen 2 years	Not reported	Open-label	Clark et al. (1997)[226] Rosell et al. (2003)*[227] Anonymous et al. (1996)*[228] Nordenskjöld et al. (2005)[229]
Tamoxifen + OFS duration comparison						
TAP-144-SR (3M)	Shiba et al. (2016)[230]	--	• Tamoxifen + leuprorelin 2 years • Tamoxifen + leuprorelin 3 years	3	Open-label	Ohashi et al. (2018)[231]
Tamoxifen vs. placebo/no treatment						
Delozier et al. (1986)	Delozier et al. (1986)[232]	--	• Tamoxifen • No treatment	Not reported	Not reported	NA

Study Name	Primary Record	Clinical Trial Number	Treatments	Phase	Blinding	Associated Records
ECOG	Cummings et al. (1985)[233]	--	• Tamoxifen • Placebo	Not reported	Double-blind	Cummings et al. (1993)[234] Cummings et al. (1986)[235] Eudey et al. (1991)[236] Gray et al. (1984)[237]
EORTC	Morales et al. (2007)[238]	--	• Tamoxifen • No treatment	3	Not reported	NA
GABG II	Neises (1989)[239]	--	• Tamoxifen • No treatment	3	Open-label	NA
Gundersen et al. (1995)[240]	Gundersen et al. (1995)[240]	--	• Tamoxifen • No treatment	Not reported	Not reported	NA
MA.12	Bramwell et al. (2010)[241]	NCT00002542	• Tamoxifen • Placebo	3	Double-blind	Pritchard et al. (2007)*[242]
NATO	NATO (1983)[243]	--	• Tamoxifen • No treatment	Not reported	Not reported	Baum et al. (1985)[244] Anonymous et al. (1988)[245]
NSABP-14	Fisher et al. (1989)[246]	--	• Tamoxifen • Placebo	Not reported	Double-blind	Fisher et al. (1992)[247] Fisher et al. (2004)[248] Tang et al. (2015)*[249]
Potamianou (1993)[250]*	Potamianou (1993)[250]*	--	• Tamoxifen • No treatment	Not reported	Not reported	NA
Ryden et al. (2005)[251]	Ryden et al. (2005)[251]	--	• Tamoxifen • No treatment	Not reported	Not reported	Ekholm et al. (2016)[252]
SAKK	Borner et al. (1994)[253]	--	• Tamoxifen • No treatment	3	Not reported	Waeber et al. (2003)[254]
Søreide et al. (1994)[255]	Søreide et al. (1994)[255]	--	• Tamoxifen • No treatment	Not reported	Not reported	NA
Veronesi et al. (2010)[256]	Veronesi et al. (2010)[256]	--	• Tamoxifen • No treatment	Not reported	Not reported	NA

ABBREVIATIONS: AI: aromatase inhibitor; CDK: cyclin-dependent kinase; CSR: clinical study report; ET: endocrine therapy; NA: not applicable; OFS: ovarian function suppression; SLR: systematic literature review.

* Conference abstracts.

"--" Denotes not reported.

Excluded studies

List of studies excluded at the full-text review stage by the third update

Table 82List of excluded studies List of records excluded at the full-text review stage of the clinical SLR of RCTs

ID	Author	Title	Issue	Journal	Volume	Year	Reason for exclusion
134	Derks	Impact of age on breast cancer mortality and competing causes of death at 10 years followup in the adjuvant TEAM trial		European Journal of Cancer	99	2018	Post-hoc analysis/longter m follow-up
135	Ekholm	Effects of adjuvant tamoxifen over three decades on breast cancer-free and distant recurrence-free interval among premenopausal women with oestrogen receptor-positive breast cancer randomised in the Swedish SBII:2pre trial		European Journal of Cancer	110	2019	Post-hoc analysis/longter m follow-up
191	Amir	Competing risks of extended adjuvant aromatase inhibitors	1	The Lancet Oncology	20	2019	Study design
277	Jensen	Two years of tamoxifen or no adjuvant systemic therapy for patients with high-risk breast cancer: long-term follow-up of the Copenhagen breast cancer trial	1	Acta Oncologica	57	2018	HR+ve <50% or unclear
311	Fleming	Randomized comparison of adjuvant tamoxifen (T) plus ovarian function suppression (OFS) versus tamoxifen in premenopausal women with hormone receptor-positive (HR+) early breast cancer (BC): Update of the SOFT trial	4 Supplement 1	Cancer Research	78	2018	Post-hoc analysis/longter m follow-up
332	O'Shaughnessy	EarLEE-2: A phase 3 study of ribociclib + endocrine therapy (ET) for adjuvant treatment of patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-), intermediate-risk, early breast cancer (EBC)	4 Supplement 1	Cancer Research	78	2018	No extractable data

ID	Author	Title	Issue	Journal	Volume	Year	Reason for exclusion
455	Martin Jimenez	EarLEE-1: A phase 3 study of ribociclib 1 endocrine therapy (ET) for adjuvant treatment of patients (pts) with hormone receptor-positive (HR1), human epidermal growth factor receptor 2-negative (HER2-), high-risk, early breast cancer (EBC)	Supplement 5	Annals of Oncology	28	2017	No extractable data
468	De Laurentiis	The role of ribociclib in hormone receptorpositive (HR1), human epidermal growth factor receptor 2-negative (HER2-) early breast cancer: The EarLEE adjuvant clinical trials program	Supplement 6	Annals of Oncology	28	2017	No extractable data
577	Blok	10-year follow-up and biomarker discovery for adjuvant endocrine therapy; Results of the TEAM trial	4 Supplement 1	Cancer Research	77	2017	Post-hoc analysis/longter m follow-up
621	Kadakia	Patient-reported outcomes and early discontinuation in aromatase inhibitor-treated postmenopausal women with early stage breast cancer	5	Oncologist	21	2016	Adjuvant endocrine therapy prior to randomization
887	Stearns	Treatment-associated musculoskeletal and vasomotor symptoms and relapse-free survival in the NCIC CTG MA.27 adjuvant breast cancer aromatase inhibitor trial	3	Journal of Clinical Oncology	33	2015	Outcome not of interest
955	Ellis	CADER prognostic gene signature for disease free survival in hormone receptor positive breast cancer: NCIC CTG MA.12 phase III placebo-controlled tamoxifen trial	9 SUPPL. 1	Cancer Research	75	2015	Post-hoc analysis/longter m follow-up

ID	Author	Title	Issue	Journal	Volume	Year	Reason for exclusion

968	Ribi	Patient-reported endocrine symptoms, sexual functioning and quality of life (QoL) in the IBCSG SOFT trial: Adjuvant treatment with tamoxifen (T) alone versus tamoxifen plus ovarian function suppression (OFS) in premenopausal women with hormone receptorpo	9 SUPPL. 1	Cancer Research	75	2015	No extractable data
969	Goldhirsch	Randomized comparison of adjuvant tamoxifen (T) plus ovarian function suppression (OFS) versus tamoxifen in premenopausal women with hormone receptor-positive (HR+) early breast cancer (BC): Analysis of the SOFT trial	9 SUPPL. 1	Cancer Research	75	2015	Adjuvant endocrine therapy prior to randomization
978	Huober	Symptoms of endocrine treatment and outcome in the BIG 1-98 study	1	Breast Cancer Research and Treatment	143	2014	Outcome not of interest
986	Aihara	Anastrozole versus tamoxifen as adjuvant therapy for Japanese postmenopausal patients with hormone-responsive breast cancer: efficacy results of long-term follow-up data from the N-SAS BC 03 trial	2	Breast Cancer Research and Treatment	148	2014	Adjuvant endocrine therapy prior to randomization
1051	Garrone	A prospective randomised study of transvaginal ultrasound effects of tamoxifen and exemestane in postmenopausal women with early breast cancer	6	Tumori	100	2014	Outcome not of interest
1054	Knoop	Estrogen receptor, Progesterone receptor, HER2 status and Ki67 index and responsiveness to adjuvant tamoxifen in postmenopausal high-risk breast cancer patients enrolled in the DBCG 77C trial	8	European Journal of Cancer	50	2014	Comparator not of interest

ID	Author	Title	Issue	Journal	Volume	Year	Reason for exclusion

1109	Pagani	Randomized comparison of adjuvant aromatase inhibitor (AI) exemestane (E) plus ovarian function suppression (OFS) vs tamoxifen (T) plus OFS in premenopausal women with hormone receptor-positive (HR+) early breast cancer (BC): Joint analysis of IBCSG text and soft trials	18 SUPPL. 1	Journal of Clinical Oncology	32	2014	Study design
1113	Kangarloo	Pharmacokinetic analysis of tamoxifen metabolites in premenopausal women with early breast cancer: A substudy of NCIC CTG MA.12 randomized clinical trial	15 SUPPL. 1	Journal of Clinical Oncology	32	2014	Outcome not of interest
1175	Van De Water	Influence of semi-quantitative oestrogen receptor expression on adjuvant endocrine therapy efficacy in ductal and lobular breast cancer-A TEAM study analysis	2	European Journal of Cancer	49	2013	Post-hoc analysis/longter m follow-up
1209	Henry	Genetic associations with toxicity-related discontinuation of aromatase inhibitor therapy for breast cancer	3	Breast Cancer Research and Treatment	138	2013	Outcome not of interest
1223	Henry	Aromatase inhibitor-induced modulation of breast density: Clinical and genetic effects	9	British Journal of Cancer	109	2013	Outcome not of interest
1237	Sand-Dejmek	The Prognostic Significance of Wnt-5a Expression in Primary Breast Cancer Is Extended to Premenopausal Women	8	PLoS ONE	8	2013	Outcome not of interest
1243	Dezentje	CYP2D6 genotype in relation to tamoxifen efficacy in a Dutch cohort of the tamoxifen exemestane adjuvant multinational (TEAM) trial	2	Breast Cancer Research and Treatment	140	2013	Outcome not of interest
1252	Chapman	Effect of continuous statistically standardized measures of estrogen and progesterone receptors on disease-free survival in NCIC CTG MA.12 Trial and BC Cohort	4	Breast Cancer Research	15	2013	Post-hoc analysis/longter m follow-up

ID	Author	Title	Issue	Journal	Volume	Year	Reason for exclusion

1301	Chapman	Competing risks of death in NCIC CTG MA.27 adjuvant exemestane versus anastrozole	15 SUPPL. 1	Journal of Clinical Oncology	31	2013	Outcome not of interest
1315	Lin	A prospective, randomized, multicenter, comparative and open-label study on hepatotoxicity of anastrozole compared with tamoxifen in adjuvant therapy in postmenopausal women with hormone receptor+early breast cancer	SUPPL. 2	European Journal of Cancer	49	2013	Outcome not of interest
1321	Fontein	Relationship between specific adverse events and efficacy of exemestane therapy in early postmenopausal breast cancer patients	12	Annals of Oncology	23	2012	Post-hoc analysis/longter m follow-up
1325	Henry	Predictors of aromatase inhibitor discontinuation as a result of treatmentemergent symptoms in early-stage breast cancer	9	Journal of Clinical Oncology	30	2012	Adjuvant endocrine therapy prior to randomization
1357	Van De Water	Association between age at diagnosis and disease-specific mortality among postmenopausal women with hormone receptor-positive breast cancer	6	JAMA - Journal of the American Medical Association	307	2012	Post-hoc analysis/longter m follow-up
1380	Ewertz M.,Gray	Obesity and risk of recurrence or death after adjuvant endocrine therapy with letrozole or tamoxifen in the breast international group 1-98 trial	32	Journal of Clinical Oncology	30	2012	Post-hoc analysis/longter m follow-up
1387	Hadji	Effects of exemestane and tamoxifen on hormone levels within the Tamoxifen Exemestane Adjuvant Multicentre (TEAM) Trial: Results of a German substudy	5	Climacteric	15	2012	Post-hoc analysis/longter m follow-up

ID	Author	Title	Issue	Journal	Volume	Year	Reason for exclusion

1417	Ribi	Subjective cognitive complaints one year after ceasing adjuvant endocrine treatment for earlystage breast cancer	10	British Journal of Cancer	106	2012	Post-hoc analysis/longter m follow-up
1434	Iwata	Long-term follow-up data of the side effect profile of anastrozole compared with tamoxifen in Japanese women: Findings from N-SAS BC03 trial	24 SUPPL. 3	Cancer Research	72	2012	Outcome not of interest
1441	Chavez-Mac	A phase iii randomized, placebo-controlled clinical trial evaluating the use of adjuvant endocrine therapy +/-one year of everolimus in patients with high-risk, hormone receptor-HR) positive and HER2-negative breast cancer: SWOG/NSABP s1207	24 SUPPL. 3	Cancer Research	72	2012	No extractable data
1471	Van De Water	ER allred score predicts outcome of adjuvant endocrine therapy in postmenopausal breast cancer - A team study analysis	SUPPL. 1	European Journal of Cancer	48	2012	Post-hoc analysis/longter m follow-up
1479	Anonymous	Exemestane reduced invasive breast cancers in postmenopausal women	1099	Australian Journal of Pharmacy	92	2011	Review article
1498	Volovat	[Assessment of the quality of life of women with breast cancer in adjuvant treatment with tamoxifen or aromatase inhibitors--a randomized trial]	1	Revista medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi	115	2011	Outcome not of interest
1624	Chapman	Effect of treatment emergent symptoms on relapse free survival: NCIC CTG MA.12 a randomized placebo-controlled trial of tamoxifen	24 SUPPL. 3	Cancer Research	71	2011	Outcome not of interest

ID	Author	Title	Issue	Journal	Volume	Year	Reason for exclusion

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		after adjuvant chemotherapy in pre-menopausal women in early breast cancer					
1648	Perrone	Bone effects of adjuant tamoxifen (T), letrozole (L), or L plus zoledronic acid (Z) in early breast cancer (EBC): The phase III HOBOE study	15 SUPPL. 1	Journal of Clinical Oncology	29	2011	Outcome not of interest
1668	Piccart	The EORTC 10041/BIG 03-04 MINDACT (Microarray in Node Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemo-Therapy) trial: Patients' baseline characteristics and logistics aspects after a successful accrual	SUPPL. 2	European Journal of Cancer	47	2011	No extractable data
1669	Fontein	Efficacy of endocrine therapy regimens in major histological subtypes of breast cancer - A TEAM study analysis	SUPPL. 1	European Journal of Cancer	47	2011	Post-hoc analysis/longter m follow-up
1670	Gelber	BIG 1-98 update: Evaluating letrozole and tamoxifen alone and in sequence at 8 years median follow-up for postmenopausal women with steroid hormone receptor-positive breast cancer	SUPPL. 1	European Journal of Cancer	47	2011	Post-hoc analysis/longter m follow-up
1784	Rabaglio	Bone fractures among postmenopausal patients with endocrine-responsive early breast cancer treated with 5 years of letrozole or tamoxifen in the BIG 1-98 trial	9	Annals of Oncology	20	2009	Outcome not of interest
1900	Colleoni	Safety of letrozole and tamoxifen monotherapy: Updated BIG 1-98	3	European Journal of Cancer, Supplement	8	2010	Outcome not of interest

ID	Author	Title	Issue	Journal	Volume	Year	Reason for exclusion

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1952	Eidtmann	Zoledronic acid (Zometa) and aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole (Femara)	2	P and T	34	2009	Comparator not of interest
1953	Metcalfe	Goserelin improves long-term survival in premenopausal women with early breast cancer	5	Journal of the National Cancer Institute	101	2009	Review article
1977	Iwamoto	Molecular heterogeneity of estrogen receptor-positive breast cancer explains variable and contradictory results of randomized adjuvant chemotherapy trials in breast cancer	8	American Journal of Hematology/ Oncology	8	2009	Comparator not of interest
2045	Rundquist	High amplified in breast cancer 1 is a significant predictor of improved response to adjuvant tamoxifen in premenopausal women	2 Suppl. S	Cancer Research	69	2009	No extractable data
2101	Crivellari	Letrozole compared with tamoxifen for elderly patients with endocrine-responsive early breast cancer: The BIG 1-98 trial	12	Journal of Clinical Oncology	26	2008	Post-hoc analysis/longter m follow-up
2195	Mouridsen	Cardiovascular adverse events during adjuvant endocrine therapy for early breast cancer using letrozole or tamoxifen: Safety analysis of BIG 198 trial	36	Journal of Clinical Oncology	25	2007	Outcome not of interest
2297	Kraus	Breast cancer: Letrozole after completion of an adjuvant tamoxifen treatment	12	Geburtshilfe und Frauenheilkunde	68	2008	Adjuvant endocrine therapy prior to randomization
2344	Abraham	Long-term follow-up of a non-anthracycline regimen as adjuvant therapy for operable breast cancer	4	Community Oncology	4	2007	Intervention: (Neo) adjuvant chemotherapy

ID	Author	Title	Issue	Journal	Volume	Year	Reason for exclusion

2349	Jungmayr	Early breast cancer: Premenopausal treatment with LHRH agonists as supplementation	34	Deutsche Apotheker Zeitung	147	2007	Review article
2350	De Moura	Primary breast cancer: Exemestane also in extended adjuvant therapy	2	Gynakologie	12	2007	Adjuvant endocrine therapy prior to randomization
2366	Jonat	The FACE trial: Letrozole or anastrozole as initial adjuvant therapy?	1	Cancer Investigation	25	2007	Review article
2423	Saunders	Early oestrogen receptor-positive breast cancer in postmenopausal women may be treated with aromatase inhibitors	5	Pharmacy in Practice	17	2007	Review article
2521	Anonymous	Letrozole improves disease-free survival vs tamoxifen in adjuvant treatment of early breast cancer	3	Oncology (Williston Park, N.Y.)	19	2005	No extractable data
2525	Ryden	Tumor-specific expression of vascular endothelial growth factor receptor 2 but not vascular endothelial growth factor or human epidermal growth factor receptor 2 is associated with impaired response to adjuvant tamoxifen in premenopausal breast cancer	21	Journal of clinical oncology : official journal of the American Society of Clinical Oncology	23	2005	Outcome not of interest
2528	Mitsuyama	Assessment of goserelin treatment in adjuvant therapy for premenopausal patients with breast cancer in Japan-zoladex breast cancer study group trial-B	13	Gan to kagaku ryoho. Cancer & chemotherapy	32	2005	No extractable data
2659	Wenderlein	Results of extended letrozol adjuvant therapy sobering in absolute figures	2	Gynakologisch e Praxis	30	2006	Review article

ID	Author	Title	Issue	Journal	Volume	Year	Reason for exclusion

2675	Sawada	Effect of anastrozole and tamoxifen on lipid metabolism in Japanese postmenopausal women with early breast cancer	2	Acta Oncologica	44	2005	Outcome not of interest
2740	Pollow	Phase II study of goserelin adjuvant therapy combined with exemestane with or without tibolone in premenopausal women with receptor positive, node negative mammary carcinoma: ADAGIO study	6	Geburtshilfe und Frauenheilkunde	65	2005	HR+ve <50% or unclear
2830	Anonymous	Anastrozole better than tamoxifen against early breast cancer	1	Journal of Supportive Oncology	3	2005	Review article
2960	Hirrle	Aromatase inhibitors in adjuvant therapy of primary breast cancer: Exemestan after 3 years of tamoxifen therapy	3	Gynakologie fur Hausarzte	9	2004	Adjuvant endocrine therapy prior to randomization
3208	Namer	Adjuvant treatment of breast cancer in nonmenopausal women: Hormone therapy of chemotherapy?	1	Oncologie	4	2002	Review article
3209	Mustacchi	Results of adjuvant treatment in breast cancer women aged more than 70: Italian Cooperative Group experience	SUPPL. 1	Tumori	88	2002	Comparator not of interest
3210	Fisher	Tamoxifen, radiation therapy, or both for prevention of ipsilateral breast tumor recurrence after lumpectomy in women with invasive breast cancers of one centimeter or less	20	Journal of Clinical Oncology	20	2002	Comparator not of interest
3400	Ferno	Results of two or five years of adjuvant tamoxifen correlated to steroid receptor and Sphase levels	1	Breast Cancer Research and Treatment	59	2000	Post-hoc analysis/longter m follow-up

ID	Author	Title	Issue	Journal	Volume	Year	Reason for exclusion

3443	Delozier	Delayed adjuvant tamoxifen: Ten-year results of a collaborative randomized controlled trial in early breast cancer (TAM-02 trial)	5	Annals of Oncology	11	2000	Adjuvant endocrine therapy prior to randomization
3462	Nystedt	Randomized trial of adjuvant tamoxifen and/or goserelin in premenopausal breast cancer: Selfrated physiological effects and symptoms	8	Acta Oncologica	39	2000	Outcome not of interest
3489	Delozier	Late delayed adjuvant tamoxifen in early breast cancer. Results of a cooperative randomized trial	1	Bulletin du Cancer	84	1997	Adjuvant endocrine therapy prior to randomization
3597	Merimsky	Tamoxifen for disease-negative but MCApositive breast cancer patients	4	Oncology Reports	4	1997	HR+ve <50% or unclear
3622	Stewart	Randomized comparison of 5 years of adjuvant tamoxifen with continuous therapy for operable breast cancer	3	Cancer/Radiotherapie	1	1997	Review article
3641	Semiglazov	New methods in the treatment of breast cancer	1	Voprosy onkologii	43	1997	HR+ve <50% or unclear
3682	Fisher	Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors	21	Journal of the National Cancer Institute	88	1996	Adjuvant endocrine therapy prior to randomization
3705	Boccardo	Endocrine therapy of breast cancer. The experience of the Italian cooperative group for chemohormonal therapy of early breast cancer (GROCTA)		Annals of the New York Academy of Sciences	698	1993	Comparator not of interest
3758	Nakamura	A randomized clinical trial of adjuvant endocrine therapy after breast conserving surgery for early		Gan to kagaku ryoho. Cancer	21 Suppl 2	1994	HR+ve <50% or unclear

ID	Author	Title	Issue	Journal	Volume	Year	Reason for exclusion

		breast cancer. Cooperative Study Group for Breast Conserving Therapy		& chemotherapy			
3798	Borner	First isolated locoregional recurrence following mastectomy for breast cancer: Results of a phase III multicenter study comparing systemic treatment with observation after excision and radiation	10	Journal of Clinical Oncology	12	1994	Comparator not of interest
3801	Kovner	Treatment of disease-negative but mucin-like carcinoma-associated antigen-positive breast cancer patients with tamoxifen: Preliminary results of a prospective controlled randomized trial	1	Cancer Chemotherapy and Pharmacology	35	1994	HR+ve <50% or unclear
3825	Gray	The EBCTCG overview of adjuvant therapy of breast cancer	1	Pathologie Biologie	42	1994	Review article
3829	Gerard	Postmenopausal patients with node-positive resectable breast cancer. Tamoxifen vs FEC 50 (6 cycles) vs FEC 50 (6 cycles) plus tamoxifen vs control--preliminary results of a 4-arm randomised trial. The French Adjuvant Study Group		Drugs	45 Suppl 2	1993	HR+ve <50% or unclear
3848	Kurz	Adjuvant treatment with tamoxifen of lymphnode-negative breast cancer in postmenopausal women	51-52	Deutsche Medizinische Wochenschrift	117	1992	HR+ve <50% or unclear
3851	Ribeiro	The Christie hospital adjuant tamoxifen trial - Status at 10 years	6	British Journal of Cancer	57	1988	HR+ve <50% or unclear
3865	Hurny	Quality of life measures for patients receiving adjuvant therapy for breast cancer: An international trial	1	European Journal of Cancer	28	1992	Outcome not of interest

ID	Author	Title	Issue	Journal	Volume	Year	Reason for exclusion

3868	Ribeiro	The Christie Hospital adjuvant tamoxifen trial	11	Journal of the National Cancer Institute. Monographs		1992	HR+ve <50% or unclear
3871	Love	Symptoms associated with tamoxifen treatment in postmenopausal women	9	Archives of Internal Medicine	151	1991	Post-hoc analysis/longter m follow-up
3872	Rose	Adjuvant endocrine treatment of postmenopausal patients with breast cancer with high risk of recurrence. 5. Results from the DBCG (Danish Breast Cancer Cooperative Group) 77C randomized trial	33	Ugeskrift for laeger	153	1991	Intervention: Any other
3890	Mouridsen	How to improve adjuvant treatment results in postmenopausal patients		Recent results in cancer research. Fortschritte der Krebsforschun g. Progres dans les recherches sur le cancer	115	1989	Review article
3891	Ganz	Rehabilitation of patients with primary breast cancer: assessing the impact of adjuvant therapy		Recent results in cancer research. Fortschritte der Krebsforschun g. Progres dans les recherches sur le cancer	115	1989	Study design

ID	Author	Title	Issue	Journal	Volume	Year	Reason for exclusion
3898	Redmond	Treatment of stage I breast cancer: The NSABP experience	SUPPL. 1	Hormone Research	32	1989	Review article

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3901	Holt	A randomised controlled trial of adjuvant hormono-chemotherapy in Stage II breast cancer	6	European Journal of Surgical Oncology	14	1988	Intervention: (Neo) adjuvant chemotherapy
3903	Raffaele Bianco	Adjuvant therapy with tamoxifen in operable breast cancer. 10 year results of the Naples (GUN) study	8620	Lancet	2	1988	Comparator not of interest
3909	Semiglazov	A prospective randomized study of effectiveness of adjuvant hormonal therapy of breast cancer	8	Voprosy Onkologii	32	1986	HR+ve <50% or unclear
3916	Palshof	Adjuvant endocrine therapy of breast cancer. A con-trolled clinical trial of oestrogen and antioestrogen: Preliminary results of the Copenhagen breast cancer trials		Recent Results in Cancer Research	Vol 71	1980	HR+ve <50% or unclear
3917	Fornander	Response to tamoxifen and fluoxymesterone in a group of breast cancer patients with disease recur-rence after cessation of adjuvant tamoxifen	07-Aug	Cancer treatment reports	71	1987	Outcome not of interest
3939	Wilson	Six-year results of a controlled trial of tamoxifen as single adjuvant agent in management of early breast cancer	5	World Journal of Surgery	9	1985	Outcome not of interest
3942	Ribeiro	The Christie hospital tamoxifen (Nolvadex) adjuvant trial for operable breast carcinoma - 7yr results	8	European Journal of Cancer and Clinical Oncology	21	1985	HR+ve <50% or unclear

ID	Author	Title	Issue	Journal	Volume	Year	Reason for ex-clusion

3949	Fisher	A brief overview of findings from NSABP trials of adjuvant therapy		Recent results in cancer research	96	1984	Review article
3951	Rossi	Adjuvant programs for postmenopausal women with node-positive breast cancer: preliminary analysis of 5-year results		Recent results in cancer research.	96	1984	Review article
3955	Gelber	Ludwig Breast Cancer trial LBCS III: chemo- and endocrine adjuvant treatment in postmenopausal patients		Recent results in cancer research	96	1984	Intervention: Any other
3965	Wilson	A multicenter prospective randomized controlled trial of adjuvant 'Nolvadex' (tamoxifen) therapy in early breast cancer	11	British Journal of Surgery	69	1982	Not retrievable
3970	Jungi	Post-operative adjuvant trials in breast cancer-the Swiss group and the Ludwig International group		Experientia. Supplementum	41	1982	Intervention: Any other
3971	Kubli	Multi-center study of adjuvant treatment in mammary carcinoma	01-Apr	Archives of Gynecology	232	1981	Review article
3972	Hubay	Adjuvant therapy of stage II breast cancer. 48month follow-up of a prospective randomized clinical trial	1	Breast Cancer Research and Treatment	1	1981	Comparator not of interest

ID	Author	Title	Issue	Journal	Volume	Year	Reason for exclusion
3977	Palshof	Adjuvant endocrine therapy of primary operable breast cancer. Report on the Copenhagen breast cancer trials		European journal of cancer	Suppl 1	1980	HR+ve <50% or unclear

4049	Anonymous	Cyclophosphamide and tamoxifen as adjuvant therapies in the management of breast cancer. CRC Adjuvant Breast Trial Working Party.	6	British journal of cancer	57	1988	HR+ve <50% or unclear
4056	De Placido	Prolactin receptor does not correlate with oestrogen and progesterone receptors in primary breast cancer and lacks prognostic significance. Ten year results of the Naples adjuvant (GUN) study.	4	British journal of cancer	62	1990	Outcome not of interest
4125	Rutqvist	Contralateral primary tumors in breast cancer patients in a randomized trial of adjuvant tamoxifen therapy.	18	Journal of the National Cancer Institute	83	1991	HR+ve <50% or unclear
4129	Ribeiro	Adjuvant tamoxifen for operable carcinoma of the breast: report of clinical trial by the Christie Hospital and Holt Radium Institute.	6368	British medical journal (Clinical research ed.)	286	1983	Comparator not of interest
4140	Chapman	Osteoporosis therapy and outcomes for postmenopausal patients with hormone receptor-positive breast cancer: NCIC CTG MA.27.	13	Cancer	123	2017	Post-hoc analysis/longter m follow-up
4196	Kadakia	Prospective assessment of patient-reported outcomes and estradiol and drug concentrations in patients experiencing toxicity from adjuvant aromatase inhibitors.	2	Breast cancer research and treatment	164	2017	Study design
4223	Johansson	Impact of CYP19A1 and ESR1 variants on early-onset side effects during combined endocrine therapy in the TEXT trial.	1	Breast cancer research : BCR	18	2016	Outcome not of interest

ID	Author	Title	Issue	Journal	Volume	Year	Reason for exclusion
4258	Kadakia	Patient-Reported Outcomes and Early Discontinuation in Aromatase Inhibitor-Treated Postmenopausal Women With Early Stage Breast Cancer.	5	The oncologist	21	2016	Outcome not of interest

4311	Metzger Filho	Relative Effectiveness of Letrozole Compared With Tamoxifen for Patients With Lobular Carcinoma in the BIG 1-98 Trial.	25	Journal of clinical oncology: official journal of the American Society of Clinical Oncology	33	2015	Post-hoc analysis/longter m follow-up
4315	Le Rhun	A phase III randomized multicenter trial evaluating cognition in post-menopausal breast cancer patients receiving adjuvant hormonotherapy.	3	Breast cancer research and treatment	152	2015	Comparator not of interest
4351	Gnant	Zoledronic acid combined with adjuvant endocrine therapy of tamoxifen versus anastrozol plus ovarian function suppression in premenopausal early breast cancer: final analysis of the Austrian Breast and Colorectal Cancer Study Group Trial 12.	2	Annals of oncology: official journal of the European Society for Medical Oncology	26	2015	Post-hoc analysis/longter m follow-up
4362	Aihara	Anastrozole versus tamoxifen as adjuvant therapy for Japanese postmenopausal patients with hormone-responsive breast cancer: efficacy results of long-term follow-up data from the N-SAS BC 03 trial.	2	Breast cancer research and treatment	148	2014	Adjuvant endocrine therapy prior to randomization

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4431	Regan	Adjuvant treatment of premenopausal women with endocrine-responsive early breast cancer: design of the TEXT and SOFT trials.	6	Breast (Edinburgh, Scotland)	22	2013	Outcome not of interest

4473	Blamey	Radiotherapy or tamoxifen after conserving surgery for breast cancers of excellent prognosis: British Association of Surgical Oncology (BASO) II trial.	10	European journal of cancer (Oxford, England: 1990)	49	2013	HR+ve <50% or unclear
4478	Rosell	Effects of adjuvant tamoxifen therapy on cardiac disease: results from a randomized trial with long-term follow-up.	2	Breast cancer research and treatment	138	2013	Outcome not of interest
4627	Sverrisdottir	Interaction between goserelin and tamoxifen in a prospective randomised clinical trial of adjuvant endocrine therapy in premenopausal breast cancer.	3	Breast cancer research and treatment	128	2011	Post-hoc analysis/longter m follow-up
4878	Dixon	Letrozole suppresses plasma estradiol and estrone sulphate more completely than anastrozole in postmenopausal women with breast cancer.	10	Journal of clinical oncology: official journal of the American Society of Clinical Oncology	26	2008	Outcome not of interest
4906	Forbes	Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100month analysis of the ATAC trial.	1	The Lancet. Oncology	9	2008	Post-hoc analysis/longter m follow-up
4913	Khoshnoud	Long-term pattern of disease recurrence among patients with early-stage breast cancer according to estrogen receptor status and use of adjuvant tamoxifen.	1	Breast cancer research and treatment	107	2008	Post-hoc analysis/longter m follow-up

ID	Author	Title	Issue	Journal	Volume	Year	Reason for exclusion
4919	Henry	Prospective characterization of musculoskeletal symptoms in early stage breast cancer patients treated with aromatase inhibitors.	2	Breast cancer research and treatment	111	2008	Outcome not of interest

4943	O'Shaughnessy	A decade of letrozole: FACE.		Breast cancer research and treatment	105 Suppl 1	2007	Review article
5068	Baum	Adjuvant goserelin in pre-menopausal patients with early breast cancer: Results from the ZIPP study.	7	European journal of cancer (Oxford, England: 1990)	42	2006	Study design
5430	Ferno	Results of two or five years of adjuvant tamoxifen correlated to steroid receptor and Sphase levels. South Sweden Breast Cancer Group, and South-East Sweden Breast Cancer Group.	1	Breast cancer research and treatment	59	2000	Post-hoc analysis/longter m follow-up
5442	Love	Symptoms associated with oophorectomy and tamoxifen treatment for breast cancer in premenopausal Vietnamese women.	3	Breast cancer research and treatment	58	1999	Intervention: Any other
5669	Rutqvist	Randomized trial of adjuvant tamoxifen in node negative postmenopausal breast cancer. Stockholm Breast Cancer Study Group.	2	Acta oncologica (Stockholm, Sweden)	31	1992	Post-hoc analysis/longter m follow-up
5681	Kurz	[Adjuvant hormonal therapy in lymph nodenegative breast carcinoma patients in the postmenopause].	51-52	Deutsche medizinische Wochenschrift (1946)	117	1992	HR+ve <50% or unclear

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5706	Fornander	Adjuvant tamoxifen in early-stage breast cancer: effects on intercurrent morbidity and mortality.	10	Journal of clinical oncology: official journal of the American Society of Clinical Oncology	9	1991	Comparator not of interest

5714	De Placido	Steroid hormone receptor levels and adjuvant tamoxifen in early breast cancer. Ten year results of the Naples (GUN) Study.	2	Breast cancer research and treatment	16	1990	Post-hoc analysis/longter m follow-up
5744	Rutqvist	The relationship between hormone receptor content and the effect of adjuvant tamoxifen in operable breast cancer.	10	Journal of clinical oncology: official journal of the American Society of Clinical Oncology	7	1989	Adjuvant endocrine therapy prior to randomization
5751	Fornander	Adjuvant tamoxifen in early breast cancer: occurrence of new primary cancers.	8630	Lancet (London, England)	1	1989	Outcome not of interest
5782	L E Rutqvist	The Stockholm trial on adjuvant tamoxifen in early breast cancer. Correlation between estrogen receptor level and treatment effect.	3	Breast cancer research and treatment	10	1987	HR+ve <50% or unclear
5812	A Wallgren	Adjuvant tamoxifen treatment in postmenopausal patients with operable breast cancer.	6B	Journal of steroid biochemistry	23	1985	HR+ve <50% or unclear

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5928		Anastrozole had a better risk-benefit profile than tamoxifen as adjuvant treatment for breast cancer in postmenopausal women	1	ACP Journal Club	146		Review article
6038	Gray	Estrogen levels in premenopausal patients (PTS) with hormonereceptor positive (HR+) early breast cancer (BC) receiving adjuvant triptorelin (Trip) plus exemestane (E) or tamoxifen (T) in the SOFT trial: sOFT-EST substudy final analysis	4		79	2019	Outcome not of interest

6092	NCT03820830	Palbociclib for HR Positive / HER2-negative Isolated Locoregional Recurrence of Breast Cancer		A Phase III Open-label, Multicenter, Randomized Trial of Adjuvant Palbociclib in Combination With Endocrine Therapy Versus Endocrine Therapy Alone for Patients With Hormone Receptor Positive / HER2-negative Resected Isolated Locoregional Recurrence of Breast Cancer		2019	No extractable data

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6374	JPRN-C000000056	Phase III Randomized Adjuvant Study of Tamoxifen Alone Versus Sequential Tamoxifen and Anastrozole in Hormone-Responsive Postmenopausal Breast Cancer Patients				2005	No extractable data

6412	EUCTR2009-010786-22-IT	Open label, phase III, multicentric randomised trial, comparing five years of treatment with a non steroidal aromatase inhibitor, either anastrozole or letrozole, versus switching after 2-3 years to the steroidal aromatase inhibitor exemestane in early stage breast cancer patients. - DOUBLE				2009	No extractable data
6511	Seynaeve C Van Nes JGH	Variations in locoregional therapy in postmenopausal patients with early breast cancer treated in different countries	5		97	2010	Outcome not of interest
6604	Anastasi	Letrozole vs. placebo after adjuvant tamoxifen in postmenopausal breast cancer: the MA-17 study	4	Letrozolo verso placebo dopo tamoxifene adiuvante nel carcinoma mammario in postmenopaus a: studio MA17. Quale ricaduta nella pratica clinica?	3	2004	Review article
6727		Adjuvant tamoxifen in the management of operable breast cancer: the Scottish Trial. Report from the Breast Cancer Trials Committee, Scottish Cancer Trials Office (MRC), Edinburgh	8552		2	1987	No extractable data

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7118	Gordon	Eight-year follow-up of adjuvant therapy for stage II breast cancer	5		9	1985	Intervention: (Neo) adjuvant chemotherapy

7294	Colleoni M International Breast Cancer Study Group	Tamoxifen after adjuvant chemotherapy for premenopausal women with lymph nodepositive breast cancer: international Breast Cancer Study Group Trial 13-93	9		24	2006	Comparator not of interest
7596	Rea	aTTom (adjuvant Tamoxifena[Euro sign]"To offer more?): randomized trial of 10 versus 5 years of adjuvant tamoxifen among 6,934 women with estrogen receptor-positive (ER+) or ER untested breast cancera[Euro sign]"Preliminary results	15S part I		26	2008	Adjuvant endocrine therapy prior to randomization
7597	Rutqvist	Zoladex(R) and tamoxifen as adjuvant therapy in premenopausal breast cancer: a randomised trial by the Cancer Research Campaign (CRC) Breast Cancer Trials Group, the Stockholm Breast Cancer Study Group, the South-East Sweden Breast Cancer Group & the Gruppo Interdisciplinare Valutazione Interventi in Oncologia (GIVIO)			18	1999	Not retrievable
7607	Da Lafontan	A prospective randomized trial with adjuvant tamoxifen ('Nolvadex') for 452 post-menopausal operable breast cancer. A four year analysis for CCR Group (242 patients)V				1988	HR+ve <50% or unclear
7615	NCT03701334	A Trial to Evaluate Efficacy and Safety of Ribociclib With Endocrine Therapy as Adjuvant Treatment in Patients With HR+/HER2- Early Breast Cancer		A Phase III Multi-center, Randomized, Open-label Trial to Evaluate		2018	No extractable data

ID	Author	Title	Issue	Journal	Volume	Year	Reason for exclusion

				Efficacy and Safety of Ribociclib With Endocrine Therapy as an Adjuvant Treatment in Patients With Hormone Receptorpositive, HER2negartive Early Breast Cancer (New Adjuvant TriAl With Ribociclib: nATALEE)			
7617	Yau	Intratumor heterogeneity of the estrogen receptor and the long-term risk of fatal Breast cancer	7		110	2018	Outcome not of interest
7662	De Placido	Controlled trial of adjuvant tamoxifen in operable breast cancer: nine year results	Suppl		23	1989	Post-hoc analysis/longter m follow-up
7673	Low SC	Surgery versus tamoxifen in selected elderly patients with operable breast cancer: early results of a randomized trial	2		163	1994	Intervention: Neoadjuvant endocrine therapy
7686	Moeller	Adjuvant tamoxifen treatment in premenopausal patients	Suppl 2		6	1995	HR+ve <50% or unclear
7692	Moritz	Preliminary report: the CRC adjuvant breast cancer trial for patients under the age of fifty	4		6	1997	No extractable data

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7705	Baral E	Tamoxifen and combination chemotherapy as adjuvant treatment in postmenopausal women with breast cancer			96	1984	No extractable data
7710	Burgers	Adjuvant tamoxifen in breast cancer: interim results of a comprehensive cancer center Amsterdam (CCCA) trial	3		50	1998	Adjuvant endocrine therapy prior to randomization
7715	Meakin	Adjuvant tamoxifen in postmenopausal women with axillary node positive breast cancer: an update			5	1987	No extractable data
7725	Anonymous	Scottish Pilot B Trial: a randomised study of adjuvant tamoxifen therapy in post-menopausal women with breast cancer; UKCCCR-B33				2002	Not retrievable
7726	Houghton J	Arimidex, tamoxifen alone or in combination (ATAC) adjuvant trial in postmenopausal breast cancer V				1998	No extractable data
7730	Petit	Two years versus long term adjuvant tamoxifen in breast cancer: multicentric randomized trialV				1991	No extractable data
7732	Switsers	Postponed adjuvant tamoxifen in breast cancer a multicentric randomized trialV				1991	Adjuvant endocrine therapy prior to randomization
7737	Scholten	Adjuvant hormonal therapy in lymph nodenegative breast carcinoma patients in the postmenopause (see comments)]. Comment in: deutsche Medizinische Wochenschrift 1993 Jun 25;118(25): 961-2 [German	51-52	Adjuvante Hormontherapi e bei lymphknotennegativen Mammakarzino mpatientinnen in der	117	1992	HR+ve <50% or unclear

ID	Author	Title	Issue	Journal	Volume	Year	Reason for exclusion

				Postmenopause			
7740	Kaufmann	Randomized trials to assess the effectivity of tamoxifen as adjuvant treatment in nodenegative and receptor positive breast cancer. The Heidelberg II and GABG II trials V				1998	No extractable data
7741	Wilson	A randomised, double blind trial comparing arimidex alone with nolvadex (tamoxifen) alone with arimidex and nolvadex (tamoxifen) in combination, as adjuvant treatment in postmenopausal women with breast cancer; NRR N0287023214				1999	Not retrievable
7746	Borrelli	SITAM-01: an Italian clinical trial comparing 2 versus 5 years of adjuvant tamoxifen in breast cancer patients aged > 50 years. Preliminary results			19	2000	Adjuvant endocrine therapy prior to randomization
7760	Putter	Abstract PD08-03: competing Causes of Mortality vs. Breast Cancer Mortality at 5-Years among 9766 Postmenopausal Women with Hormone Receptor Positive Early Breast Cancer Treated on the TEAM Study of Adjuvant Hormonal Therapy			70	2010	No extractable data
7776	Ingle	Abstract S1-1: final Analysis of NCIC CTG MA.27: a Randomized Phase III Trial of Exemestane Versus Anastrozole in Postmenopausal Women with Hormone Receptor Positive Primary Breast Cancer			70	2010	No extractable data

ID	Author	Title	Issue	Journal	Volume	Year	Reason for exclusion

7780	Hasenburg	Five Years of Exemestane as Initial Therapy Compared to 5 Years of Tamoxifen Followed by Exemestane: the TEAM Trial, a Prospective, Randomized, Phase III Trial in Postmenopausal Women with Hormone-Sensitive Early Breast Cancer	24 Supplement		69	2010	No extractable data
7781	Chapman	Treatment-Emergent Symptoms and the Risk of Breast Cancer Recurrence in the NCIC CTG MA.27 Adjuvant Aromatase Inhibitor Trial	24 Supplement		69	2010	Study design
7789	Colleoni	Adjusting for Selective Crossover in Analyses of Letrozole (Let) Versus Tamoxifen (Tam) in the BIG 1-98 Trial	24 Supplement		69	2010	No extractable data
7809	NCT01758146	Impact of Obesity on the Efficacy of Endocrine Therapy With Aromatase Inhibitors		Impact of Obesity on the Efficacy of Endocrine Therapy With Aromatase Inhibitors in Postmenopausal Patients With Early Breast Cancer		2012	No extractable data

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7811	NCT02097459	Prognostic Evaluation of Changing Endocrine Therapy in Women With Breast Cancer		Prognostic Evaluation of Changing Endocrine Therapy in Perimenopaus al and Recently Postmenopaus al Women With Early-stage Hormone Receptor-Positive Breast Cancer		2014	Adjuvant endocrine therapy prior to randomization
7817	NCT02338310	Trial of Perioperative Endocrine Therapy - Individualising Care				2014	Intervention: Neoadjuvant endocrine therapy
7828	NCT00553410	Letrozole in Preventing Cancer in Postmenopausal Women Who Have Received 4-6 Years of Hormone Therapy for Hormone Receptor-Positive, Lymph Node-Positive, EarlyStage Breast Cancer		SOLE, Study of Letrozole Extension, A Phase III Trial Evaluating the Role of Continuous Letrozole Versus Intermittent Letrozole Following 4 to 6 Years of Prior Adjuvant		2007	Adjuvant endocrine therapy prior to randomization

ID	Author	Title	Issue	Journal	Volume	Year	Reason for exclusion

				Endocrine Therapy for Postmenopaus al Women With HormoneRecep-tor Positive, Node Positive Early Stage Breast Cancer			
7830	NCT03078751	Adjuvant Ribociclib With Endocrine Therapy in Hormone Receptor+/HER2- High Risk Early Breast Cancer		A Phase III, Mul-ticenter, Randomized, Double-blind, Placebocon-trolled Study to Evaluate Efficacy and Safety of Ribociclib With Endocrine Therapy as an Adjuvant Treatment in Patients With Hormone Recep-tor-		2017	No extractable data

ID	Author	Title	Issue	Journal	Volume	Year	Reason for ex-clusion

				positive, HER2negative, High Risk Early Breast Cancer			
7831	NCT03081234	Adjuvant Ribociclib With Endocrine Therapy in Hormone Receptor+/HER2- Intermediate Risk Early Breast Cancer		A Phase III, Multicenter, Randomized, Double-blind, Placebocontrolled Study to Evaluate Efficacy and Safety of Ribociclib With Endocrine Therapy as an Adjuvant Treatment in Patients With Hormone Receptorpositive, HER2-		2017	No extractable data

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				negative, Inter-mediate Risk Early Breast Cancer			
7840	NCT02062489	Evaluation of Tamoxifen's Efficacy for ER/PR Negative, ER-beta Positive Operable Breast Cancer Patients				2014	HR+ve <50% or unclear
7862	NCT03137368	A Study to Evaluate Exemestane Tablets Combined With Ovarian Function Suppression/Ablation in Treatment of Premenopausal Breast Cancer Patients With CYP2D6*10 Mutations (STEP,		A Randomized Controlled Study to Evaluate Exemestane Tablets Combined With Ovarian Function Sup-pression/A blation in Treatment of Premenopausa l Breast Cancer Patients With CYP2D6*10		2017	No extractable data

ID	Author	Title	Issue	Journal	Volume	Year	Reason for ex-clusion

				Mutations (STEP,			
7863	NCT00002460	Adjuvant Hormone Therapy in Treating Women With Operable Breast Cancer		Phase III Randomized Study of Adjuvant Therapy With Tamoxifen vs Endocrine Ablation vs Tamoxifen Plus Endocrine Ablation vs No Adjuvant Therapy in Patients Under Age 50 With Operable Breast Cancer		1999	HR+ve <50% or unclear

ID	Author	Title	Issue	Journal	Volume	Year	Reason for exclusion

7866	NCT00002542	Tamoxifen in Treating Women With High-Risk Breast Cancer		DOUBLEBLIND RANDOMIZED TRIAL OF TAMOXIFEN VERSUS PLACEBO IN PATIENTS WITH NODE POSITIVE BREAST CANCER WHO HAVE COMPLETED CMF, CEF OR AC ADJUVANT CHEMOTHER APY		1999	HR+ve <50% or unclear
7871	NCT00002582	Tamoxifen, Ovarian Ablation, and/or Chemotherapy in Treating Women With Stage I, Stage II, or Stage IIIA Breast Cancer		UKCCCR RANDOMISED TRIAL OF ADJUVANT ENDOCRINE THERAPY AND CHEMOTHER APY IN WOMEN WITH EARLY BREAST CANCER, THE ADJUVANT BREAST		1999	HR+ve <50% or unclear

ID	Author	Title	Issue	Journal	Volume	Year	Reason for ex-clusion

				CANCER (ABC) TRIAL			
7918	NCT00201851	Adjuvant Oophorectomy and Tamoxifen in Premenopausal Women With Hormone Receptor-Positive Breast Cancer		Phase III Randomized Study of Immediate Versus Luteal Phase Adjuvant Oopho-rectomy and Tamoxifen in Premenopausa l Women With Hormone Recep-torpositive Breast Cancer		2005	Comparator not of interest
7929	NCT02914158	Adjuvant Ovarian Suppression Plus Aromatase Inhib-itor or Tamoxifen in Young Women		Adjuvant Ovarian Suppression Plus Aromatase Inhibitor or Tamoxifen for Hormone Recep-tor-Positive Breast Cancer in Women Younger Than 35: a		2016	No extractable data

ID	Author	Title	Issue	Journal	Volume	Year	Reason for ex-clusion

				Multicenter Randomized Clinical Trial			
7958	Chebil	Adjuvant tamoxifen to premenopausal women reduces contralateral breast cancer. Results from a prospective randomized multicenter study with long-time follow-up				2003	Post-hoc analysis/longter m follow-up
7981	Gnant	Tamoxifen and anastrozole as a sequencing strategy in postmenopausal women with hormone-responsive early breast cancer: updated data from the Austrian breast and colorectal cancer study group trial 8				2008	No extractable data
7985	On behalf of the ATAC Trialists' Group	Analysis of time to recurrence in the ATAC (arimidex, tamoxifen, alone or in combination) trial according to estrogen receptor and progesterone receptor status				2003	Post-hoc analysis/longter m follow-up
8063	Switsers O	Late delayed adjuvant tamoxifen in breast cancer: results of a multicentric randomized trial	Suppl 2		6	1995	Adjuvant endocrine therapy prior to randomization
8075	Keshaviah	BIG 1-98: a randomized double-blind phase III study comparing letrozole and tamoxifen given in sequence vs. alone as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer			24	2006	No extractable data
8080	Geisler	Effect of exemestane on bone: a randomized placebo controlled study in postmenopausal women with early breast cancer at low risk				2004	Outcome not of interest

ID	Author	Title	Issue	Journal	Volume	Year	Reason for exclusion
8089	Geisler	Lipid and coagulation profile in postmenopausal women with early breast cancer at low risk treated				2004	Disease

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		with exemestane: a randomized, placebo-controlled study					
8093	Fumoleau	Preliminary results of a four arms randomized trial comparing tamoxifen vs FEC 50 vs FEC 50 + tamoxifen vs control in post menopausal, node positive breast cancer patients			12	1993	HR+ve <50% or unclear
8094	Gelber	Randomized comparison of adjuvant tamoxifen (Tam) versus no hormonal treatment for premenopausal women with node-positive (N+), early stage breast cancer: first results of International Breast Cancer Study Group Trial 13-93				2004	Comparator not of interest
8099	Coates	Tamoxifen (TAM) for the prevention of breast cancer: importance of specific aspects of health-related quality of life (HRQL) to global health status in the ANZ BCTG substudy of IBIS-1 (ANZ 92P1)			26	2008	Outcome not of interest
8109	Morabito	Endocrine effects of adjuvant letrozole versus tamoxifen in postmenopausal early breast cancer patients: data from the HOBOE randomized trial	Supplement 8		19	2009	Outcome not of interest
8110	Babiera	ACOSOG Z1031: a randomized phase II trial comparing exemestane, letrozole, and anastrozole in postmenopausal women with clinical stage II/III estrogen receptor-positive breast cancer	18 Suppl		28	2010	Outcome not of interest

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8111	De la Cruz	Use of progesterone receptor (PR) expression to predict benefit from prolonged adjuvant tamoxifen (TAM) in breast cancer: results of a biomarker study from the TAMO1 randomized Trial	15S Part I		27	2009	Outcome not of interest
8175		Extending aromatase-inhibitor adjuvant therapy to 10 years				2016	Adjuvant endocrine therapy prior to randomization
8185	Jackson	The ATAC (arimidex, tamoxifen, alone or in combination) adjuvant breast cancer trial in post-menopausal women: baseline endometrial sub-protocol data				2001	Outcome not of interest
8188	Alonso	Randomized trial of two versus four years of adjuvant tamoxifen (AT) for postmenopausal women with node positive breast cancer	Suppl 1		34	1998	HR+ve <50% or unclear
8191	Keshaviah	BIG 1-98: randomized double-blind phase III study to evaluate letrozole (L) vs. tamoxifen (T) as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer	16 Suppl		23	2005	No extractable data
8199	Geisler	A randomized placebo controlled feasibility study of exemestane in postmenopausal women with early breast cancer at low risk			22	2003	Disease
8203	Burris	The Head to Head trial: letrozole vs anastrozole as adjuvant treatment of postmenopausal patients with node positive breast cancer			24	2006	No extractable data

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8207	Xolalpa	Survival of breast cancer patients treated with inhibitors of the aromatasa vs tamoxifen.	10	Supervivencia de pacientes con cancer de mama tratadas con inhibidores de la aromatizacion vs tamoxifeno	72	2004	No extractable data
8211	Principe	Endometrial effects of tamoxifen (T) and exemestane (E) in early breast cancer patients (EBCP). A randomized phase III trial			23	2004	Outcome not of interest
8212	Jackson TL on behalf of the ATAC Trialists' Group	The ATAC ('Arimidex', tamoxifen, alone or in combination) early breast cancer (EBC) trial in postmenopausal (PM) patients: endometrial sub-protocol results			21 (Pt 1)	2002	Outcome not of interest
8223	Meakin	A prospective randomized controlled trial of adjuvant tamoxifen in postmenopausal women with axillary node positive breast cancer			2	1983	No extractable data
8232	Switsers	Efficacy of delayed adjuvant tamoxifen (TAM) in early breast cancer: a multicenter randomized trial			12	1993	Adjuvant endocrine therapy prior to randomization
8241	Morabito	ENDOCRINE EFFECTS OF ADJUVANT LETROZOLE VERSUS TAMOXIFEN IN POSTMENOPAUSAL EARLY BREAST CANCER PATIENTS: DATA FROM THE HOBOE RANDOMIZED TRIAL			19	2008	Outcome not of interest

ID	Author	Title	Issue	Journal	Volume	Year	Reason for exclusion
8245	Duffy	The ATAC (arimidex, tamoxifen, alone or in combination) adjuvant breast cancer trial in post-menopausal women: baseline endometrial sub-protocol data				2000	Outcome not of interest

8247	Larsson	Trials with adjuvant hormonal and cytotoxic treatment in operable breast cancer patients (Breast Cancer Group in Northern Sweden)				1987	HR+ve <50% or unclear
8249	White	Long-term (5yrs) adjuvant tamoxifen				1987	HR+ve <50% or unclear
8258	Baum	The ATAC (Arimidex, Tamoxifen, Alone or in Combination) adjuvant breast cancer trial in post-menopausal (PM) women	3		69	2001	Outcome not of interest
8261	Gelber	Adjuvant systemic therapy in elderly patients with node positive breast cancer			6	2000	Intervention: Any other
8266	Rea	Phase III randomized study of adjuvant exemestane versus adjuvant tamoxifen in postmenopausal women with early breast cancer				2002	Not retrievable
8275	Jackson	Fewer endometrial abnormalities with anastrozole than tamoxifen: endometrial subprotocol results form the ATAC ('Arimidex'. tamoxifen, Alone or in Conjuction) early breast cancer (EBC) trial in post-menonpausal (PM) patients (on behalf of the ATAC Trialists's Group)	Suppl 5		13	2002	Outcome not of interest
8277	Alonso	4-years randomized study of adjuvant tamoxifen in women with positive-node breast cancer	Suppl 1	Ensayo aleatorio de cuatro anos respecto a dos	1	1999	Not retrievable

ID	Author	Title	Issue	Journal	Volume	Year	Reason for exclusion

				anos de tamoxifeno adyuvante en mujeres con cancer de mama ganglios positivos			
8278	ATAC Trialists Group Sainsbury R	Anastrozole is superior to tamixifen in the treatment of post-menpopausal women with early breast cancer - first results of the ATAC ('Arimidex', Tamoxifen, alone of in combination) trial	Suppl 13			2002	Not retrievable
8282	Naja	Adjuvant tamoxifen treatment versus control in post-menopausal breast cancer patients: a randomized study	Suppl		116	1990	HR+ve <50% or unclear
8283	Grischke	German adjuvant breast cancer group (GABG) Trial IV-93-D: antiestrogen therapy with tamoxifen vs. control in post-menopausal patients with node-negative / node-positive breast cancer after adjuvant pretreatment with chemotherapy	Suppl 1		126	2000	No extractable data
8299	Perez	Phase III Randomized Study of Ovarian Function Suppression and Tamoxifen or Exemestane With Versus Without Adjuvant Chemotherapy in Premenopausal Women With Endocrine-Responsive Resected Breast Cancer				2003	Not retrievable
8300	Steindorfer	Adjuvant tamoxifen therapy for early breast cancer: a controlled clinical trial	Suppl		107	1984	No extractable data
8311	Anonymous	A clinical trial using tamoxifen as adjuvant hormone therapy in women with operable breast cancer				2002	Not retrievable

ID	Author	Title	Issue	Journal	Volume	Year	Reason for exclusion

8312	Anonymous	A collaborative trial to evaluate Nolvadex (Tamoxifen) as an adjuvant agent in the management of early breast cancer				2002	Not retrievable
8317	Anonymous	A randomized study with Tamoxifen (5 years) vs Tamoxifen (2 years) followed by an Aromataseinhibitor (3 years) in the adjuvant therapy of breast cancer in postmenopausal patients with 0-9 involved lymph nodes and positive hormone receptor status. ECCTR				1997	Not retrievable
8318	Anonymous	A randomized trial with postoperative risk adapted chemotherapy in postmenopausal women with negative hormone receptor status, followed by Tamoxifen (5 years) or control in the adjuvant treatment of breast cancer.; ECCTR				1997	Not retrievable
8319	Anonymous	A United Kingdom multicentre randomised trial of hormono chemotherapy for early poor risk breast carcinoma. UKCCCR-B26				2002	Not retrievable
8321	Delozier	Two year versus long term adjuvant Tamoxifen in breast cancer. A multicentric randomized trial.	Suppl 2		27	1991	No extractable data
8328	Alonso	Randomised trial of adjuvant tamoxifen four years vs two years in node positive breast cancer women	Suppl 2		35	1999	Adjuvant endocrine therapy prior to randomization
8345	Andersen	Re: randomized trial of two versus five years of adjuvant tamoxifen for postmenopausal early stage breast cancer (2)	9		89	1997	Review article

ID	Author	Title	Issue	Journal	Volume	Year	Reason for exclusion

8350	Mamounas	NCI High Priority Clinical Trial --- Phase III trial of adjuvant therapy with tamoxifen vs placebo, plus radiotherapy, in the management of patients with clinically occult, invasive, node- negative breast cancer treated by lumpectomy				1998	No extractable data
8352	Delozier	Long term adjuvant tamoxifen in early breast cancer. A cooperative randomised trial	Suppl XII		62	1990	Not retrievable
8354	Nordenskjold	Adjuvant treatment of premenopausal breast cancer with zoladex and tamoxifen: results from randomised trials by the Cancer Research Campaign (CRC) Breast Cancer Trials Group, The Stockholm Breast Cancer Study Group, the South East Sweden Breast Cancer Group and Gruppo Interdisciplinare Valutazione Intervention Oncologia (GIVIO)	Suppl 4		35	1999	Study design
8359	Stewart	Adjuvant tamoxifen in the management of operable breast cancer: the Scottish trial	4		14	1988	Review article
8361	Rebeiro	The Christie Hospital Adjuvant Tamoxifen (Nolvadex) Trial for Operable Breast Cancer: status at 13 years. (Abstract)	5		3	1991	HR+ve <50% or unclear
8371	Bramwell	Phase III randomised trial of tamoxifen vs placebo in patients with node-positive or highrisk node-negative breast cancer who have completed adjuvant combination chemotherapy				1998	Not retrievable
8390	Houghton	The value of relative risks when assessing treatment benefits for patients given tamoxifen in a randomised clinical trial	A			1991	HR+ve <50% or unclear

ID	Author	Title	Issue	Journal	Volume	Year	Reason for exclusion
8394	Julien	Adjuvant tamoxifen in breast cancer, ten years results of a randomised trial	Suppl 5		3	1992	Post-hoc analysis/longter m follow-up

8396	Switsers	Delayed adjuvant tamoxifen in breast cancer a multi-centric randomized trial	Suppl 5		3	1992	Adjuvant endo-crine therapy prior to randomi-zation
8410	Krarup	Two years of tamoxifen or no adjuvant systemic therapy for patients with high-risk breast cancer: long-term follow-up of the Copenhagen breast can-cer trial				2017	HR+ve <50% or unclear
8423	Seynaeve	Specific adverse events predict survival benefit in patients treated with tamoxifen or aromatase in-hibitors: an international tamoxifen exemestane adjuvant multinational trial analysis	18		31	2013	Outcome not of interest
8430	Kidwell	Prospective assessment of patient-reported out-comes and estradiol and drug concentrations in patients experiencing toxicity from adjuvant aromatase inhibitors				2017	Post-hoc analy-sis/longter m fol-low-up
8536	Shepherd	Effect of Treatment Emergent Symptoms on Relapse Free Survival: NCIC CTG MA.12 a Randomized Placebo-Controlled Trial of Tamoxifen after Adjuvant Chemotherapy in Pre-Menopausal Women in Early Breast Cancer 33	24 Supplement		71	2011	Post-hoc analy-sis/longter m fol-low-up

ID	Author	Title	Issue	Journal	Volume	Year	Reason for ex-clusion
8538	Dong	Simply Adding Together the Diameters of Tumor Foci in Patients with Multicentric or Multifocal Disease Does Not Add Any Additional Prognostic Information: An Analysis from NCIC CTG MA.12 Randomized Placebo-Controlled Trial of Tamoxifen after Adjuvant Chemotherapy in Pre-Menopausal Women with Early Breast Cancer 46	24 Supplement		71	2011	Post-hoc analy-sis/longter m fol-low-up

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8539	Osumi	Superior efficacy of anastrozole to tamoxifen as adjuvant therapy for postmenopausal patients with hormone-responsive breast cancer. Efficacy results of long-term follow-up data from N-SAS BC 03 trial 62	24 Supplement		72	2012	Post-hoc analysis/longter m follow-up
8545	Chow	De-escalating doses of letrozole in post menopausal women at high risk for breast cancer.	9 SUPPL. 1		75	2015	Outcome not of interest
8580	Lonning	Estrogens and bone metabolism in postmenopausal women with early breast cancer at low risk treated with exemestane: a randomized placebo-controlled study	14_suppl		22	2004	Outcome not of interest
8581	Geisler	Effect of exemestane on bone: A randomized placebo controlled study in postmenopausal women with early breast cancer at low risk	14_suppl		22	2004	Outcome not of interest
8590	Hille	Specific adverse events and outcome in hormone receptor positive breast cancer patients on endocrine therapy - A team study analysis.			47	2011	Post-hoc analysis/longter m follow-up

ID	Author	Title	Issue	Journal	Volume	Year	Reason for exclusion
8600	Servent	Prospective randomized and multicentric evaluation of cognition in menopausal breast cancer patients receiving adjuvant hormonotherapy: A phase III study (Preliminary results).	24 SUPPL. 3		72	2012	Outcome not of interest
8633	El-Sadda	Exemestane versus anastrozole in postmenopausal women with hormone positive early breast cancer (EBC).			50	2014	No extractable data
8681	Chapman	Effect of osteoporosis in postmenopausal breast cancer patients randomized to adjuvant exemestane or anastrozole: NCIC CTG MA.27 4672	15		30	2012	Outcome not of interest

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8716	Upadhyay	Concurrent or sequential hormonal therapy in era of hypofractionation in early breast cancer: A single-institution prospective study	9	Breast Journal	26	2020	Intervention: Any other
8724	Martin Jimenez	EarLEE-1: A phase 3 study of ribociclib + endocrine therapy (ET) for adjuvant treatment of patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-), high-risk, early breast cancer (EBC)	Supplement 5	Annals of Oncology	28	2017	Adjuvant endocrine therapy prior to randomization
8830	Mayer	A phase II feasibility study of palbociclib in combination with adjuvant endocrine therapy for hormone receptor-positive invasive breast carcinoma	9	Annals of Oncology	30	2019	Study design
8999	Francis	Adjuvant endocrine therapy for premenopausal women: risk stratification, type and duration.		Breast (Edinburgh, Scotland)	48 Suppl 1	2019	No extractable data
9013	Anonymous	Abemaciclib Reigns Over Breast Cancer in MonarchE.		Cancer discovery		2020	Study design

ID	Author	Title	Issue	Journal	Volume	Year	Reason for exclusion
9066	Sparano	Clinical and Genomic Risk to Guide the Use of Adjuvant Therapy for Breast Cancer	25		380	2019	Comparator not of interest

9110	EUCTR2018-002998-21-ES	A phase III multi-center, randomized, open-label trial to evaluate efficacy and safety of ribociclib with endocrine therapy as adjuvant treatment in patients with HR+/HER2- Early Breast Cancer		A phase III, multi-center, randomized, open-label trial toevaluate efficacy and safety of ribociclib with endocrine therapy as an adjuvant treatment in patients with hormone receptor-positive, HER2negative, early breast cancer (New Adjuvant TriAl with Ribociclib [LEE011]: NATALEE)		2019	No extractable data

ID	Author	Title	Issue	Journal	Volume	Year	Reason for exclusion

9111	EUCTR2018-003553-19-HU	A phase III clinical trial, which tests the safety and efficacy of the combination of palbociclib and endocrine therapy to learn whether the combination of these drugs works for a specific form of breast cancer (hormone receptor positive / HER2-negative isolated locoregional recurrent breast cancer)		A phase III open-label, multicenter, randomized trial of adjuvant palbociclib in combination with endocrine therapy versus endocrine therapy alone for patients with hormone receptor positive / HER2-negative resected isolated locoregional recurrence of breast cancer - POLAR		2019	No extractable data
9168	Slamon	NATALEE: phase III study of ribociclib (RIBO) + endocrine therapy (ET) as adjuvant treatment in hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) early breast cancer (EBC)			37	2019	No extractable data
9229	Leone	Clinical behavior of recurrent hormone receptor-positive breast cancer by adjuvant endocrine therapy within the Breast International Group 198 clinical trial.		Cancer		2020	No extractable data

ID	Author	Title	Issue	Journal	Volume	Year	Reason for exclusion

9276	NCT04565054	Adj. Dyn. Marker-adjusted Personalized Therapy Comparing Abemaciclib + SOC ET vs. SOC ET in Clinical or Genomic High Risk, HR+/HER2- EBC		Adjuvant Dynamic Marker - Adjusted Personalized Therapy Comparing Abemaciclib Combined With Standard Adjuvant Endocrine Therapy Versus Standard Adjuvant Endocrine Therapy in (Clinical or Genomic) High Risk, HR+/HER2- Early Breast Cancer (ADAPTlate)		2020	No extractable data
9355	Luen	Identifying oncogenic drivers associated with increased risk of late distant recurrence in postmenopausal, estrogen receptor-positive, HER2-negative early breast cancer: results from the BIG 1-98 study	10	Annals of Oncology	31	2020	Outcome not of interest

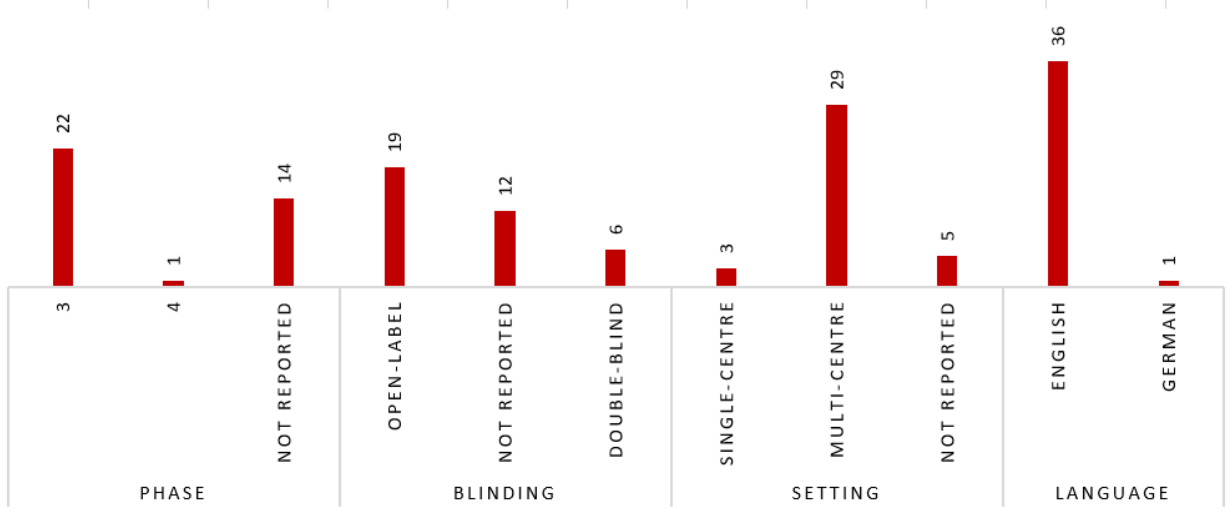
Details of included studies

Twenty-two of the included studies were Phase 3 RCTs, one was Phase 4[158], and 14 did not report the phase of the study. All studies were parallel RCTs, except one that had a crossover design (ALIQUOT)[181]. Nineteen studies were open-label, six were double-blind, and 12 did not report the blinding status. The characteristics of the included studies are presented in Figure 33.Figure 33

Most of the included studies were multicentre (n=29), three were single-centre, and setting was not reported in five studies. Thirteen studies were multinational (ATAC[120], ABCSG-12[200]Thirteen studies were multinational (ATAC[120], ABCSG-12[200], BIG 1-98[140], EORTC[238], FACE[62], MA.27[185], monarchE[65, 185], monarchE[65], NATO[243], PALLAS[110], PENELOPE-B[64], SOFT[69], TEAM[64], SOFT[69], TEAM[167], and TEXT[70]). Sixteen studies were conducted in a single country: China (HEART35 and Yang et al. [2013]152)[158, 197], Germany (GABA II189 and SUCCESS C sub-study[68, 239]), Italy (HOBOE and FATA-GIM3[66],[67]), Sweden (Swedish Breast Cancer Cooperative Group and Ryden et al. [2005][225],[251]), one each in Austria (ABCSG-8[177]), Canada (MA.12[241]), France (Delozier et al. [1986][232]), Japan (TAP-144-SR [3M][230]), Korea (ASTRRA[192]), Scotland (ALIQUOT[181]), Turkey (Uslu et al. [2014][196]), the USA (E-3193, INT-0142[195]). The NSABP-14 study[246] was conducted in Canada and the US. Seven studies did not report the country (Potamianou et al. [1993]197, SAKK[253], Veronesi et al. [2010][256], DBCG[224], ECOG[233], Gundersen et al. [1995][240], and Søreide et al. [1994][255]. All the included studies were published in English except one (published in German language [GABA II[239]).

The earliest published study was the NATO (1983)[243] evaluating tamoxifen relative to no treatment. Nineteen studies were published within the past 10 years.

Figure 33: Study characteristics of the included studies



NOTE: MA.12 and PENELOPE-B reported as double-blind in the publication, but specified as triple and quadruple-blind, respectively, in clinical trial identifiers.

For ease of reporting, the studies included were grouped by interventions assessed:

- Cyclin-dependent kinase 4 and 6 inhibitor plus ET vs. ET alone or placebo plus ET: One study evaluated abemaciclib plus ET vs. ET alone (monarchE) and two studies assessed palbociclib combined with ET vs. either ET alone (PALLAS) or placebo plus ET (PENELOPE-B).

- Tamoxifen vs. AI: Four studies compared tamoxifen with AI.
- Sequential treatment of tamoxifen to AI vs. AI or tamoxifen: Three studies assessed the comparison of sequential treatment of tamoxifen followed by AI vs. AI and one study compared the sequential treatment of tamoxifen followed by AI vs. tamoxifen.
- Aromatase inhibitor vs. AI: Three studies compared the different AIs.
- Tamoxifen plus ovarian function suppression (OFS) vs. tamoxifen: Four studies compared the impact of addition of OFS to tamoxifen with tamoxifen alone.
- Tamoxifen plus OFS vs. AI plus OFS: Three studies compared the addition of OFS to tamoxifen with that of AI.
- Duration comparison: Two studies compared the different duration of tamoxifen treatment, and one study compared the duration of tamoxifen plus OFS.
- Tamoxifen vs. placebo/no treatment: Thirteen studies compared tamoxifen to placebo or no treatment.

Abemaciclib was administered 150 mg twice daily on a continuous dosing schedule[65] for a maximum of two years. Patients also received physician choice ET for a minimum of five years (max. 10 years)[111, 118]. In the palbociclib studies, patients received ET for five years and palbociclib 125 mg/day on an intermittent dosing schedule (three week on and one week off) for two years (PALLAS[110]) and one year (PENELOPE-B[64]).[110]) and one year (PENELOPE-B[64]). For ET, the dose of tamoxifen varied across studies, 20 mg/day (27 studies), 30 mg/day (2 studies)[224, 239], 20 to 40 mg/day (2 studies)[225, 251], and 40 mg/day (1 study)[232]. The dose of anastrozole was 1 mg/day, exemestane was 25 mg/day, and letrozole was 2.5 mg/day.

Further characteristics of the studies identified in the clinical SLR are not included here as they are not considered to be relevant to the submission.

Study Selection

Two systematic reviewers independently screened all titles and abstracts according to the pre-defined eligibility criteria. Any disagreements between the reviewers were referred to a third reviewer and consensus was reached. The full-text publications meeting the abstract screening requirements were reviewed to assess eligibility for inclusion in the SLR. Discrepancies between reviewers were resolved by a third independent reviewer with consensus reached. The screening process was thoroughly documented and reported using the PRISMA flow diagram (Figure 32)[257].

Data Extraction

Data were extracted in DistillerSR® tool by two independent reviewers, and then transported into a data extraction workbook (MS Excel). For the clinical efficacy and safety endpoints, where available, number of participants, number and proportion of responders, and time point of response were extracted.

Efficacy and safety data were extracted for the overall intention-to-treat (ITT) population, as well as several subgroups of interest, where reported. Subgroups of interest were defined according to the stratification factors for randomisation in monarchE:

- Prior treatment: (neo)adjuvant chemotherapy and no chemotherapy
- Menopausal status: premenopausal and postmenopausal
- Region: North America/Europe, Asia, and other
- Ki-67 level

- Nodal status: positive and negative

Ongoing trials

The following data were extracted for ongoing trials:

- Study identifier (ID) and link for source
- Primary sponsor and collaborators
- Study design
- Population
- Interventions
- Primary outcome measures
- Secondary outcome measures
- Estimated enrolment
- Estimated primary completion date

No study results were extracted from the identified ongoing trials

Quality assessment

A quality assessment was conducted for all studies included in the SLR, as described in *Quality assessment for each trial.* The Cochrane risk of bias tool version 2.0 (2020) [258] was used to assess risk of bias across included studies. Two reviewers independently assessed the methodological quality and potential bias of the included RCTs using the quality criteria described in Chapter 8 of the Cochrane handbook for systematic reviews of interventions.

Participant flow in the relevant randomised control trials

A summary of the patient disposition in the monarchE trial is presented in Figure 34.

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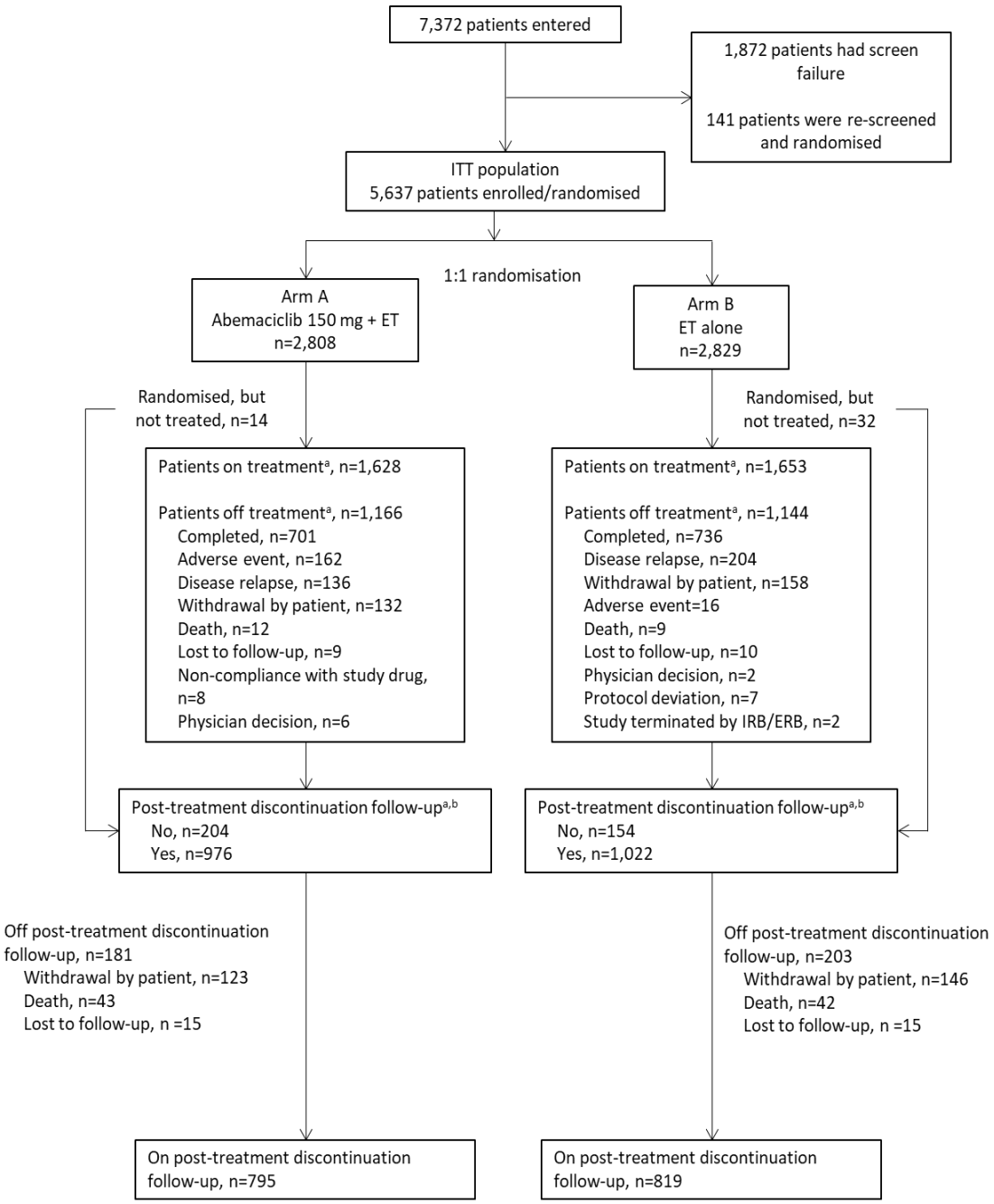
Figure 34. Flow of patients in the monarchE trial



Footnotes: [a] At the time of data cut-off on 08 July 2020. [b] Includes patients who were off treatment as well as patients who were enrolled/randomised but never treated.

Abbreviations: ERB: ethical review board; ET: endocrine therapy; IRB: institutional review board; ITT: intention-to-treat.

Source: Lilly Data on File. Clinical Study Report: monarchE[6]

Quality assessment for each trial

The original SLR used the risk of bias assessment from the NICE single technology appraisal guidance (2012). For the two SLR updates, the Cochrane risk of bias tool version 2.0, 2020 was used to assess risk of bias across included studies [258]. The risk of bias assessments were carried out for journal articles and two conference abstracts. It should be noted that important aspects of risk of bias in clinical trials are often not reported in conference abstracts owing to text restrictions. Consequently, the insufficient reporting of details may result in misleading judgements in the assessment and should be considered with caution.

Except for the GABG II study, all studies had either low risk of bias or some concern. GABG II was judged to have a high risk of bias (Table 83).

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Table 83: Risk of bias assessment using Cochrane risk of bias tool version 2.0, 2020 for RCTs

Study name	Risk of bias arising from randomisation process	Risk of bias due to deviations from intended interventions		Risk of bias due to missing outcome data	Risk of bias in measurement of the outcome	Risk of bias in selection of the reported result	Overall bias
		Effect of assignment to intervention	Effect of adhering to intervention				
ABCSG-12							
ABCSG-8							
ALIQUOT							
ASTRRA							
ATAC							
BIG 1-98							
DBCG							
Delozier et al. (1986)							
E-3193, INT-0142							
ECOG							
EORTC							
FACE							
FATA-GIM3							
GABG II							
Gundersen et al. (1995)							
HEART							
HOBOE							
MA.12							
MA.27							
monarchE							
NATO							
NSABP-14							
PALLAS							
PENELOPE-B							
Potamianou (1993)							
Ryden et al. (2005)							
SAKK							

Study name	Risk of bias arising from randomisation process	Risk of bias due to deviations from intended interventions		Risk of bias due to missing outcome data	Risk of bias in measurement of the outcome	Risk of bias in selection of the reported result	Overall bias
		Effect of assignment to intervention	Effect of adhering to intervention				
SOFT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Søreide et al. (1994)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SUCCESS C sub-study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Swedish Breast Cancer Cooperative Group	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TAP-144-SR (3M)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEAM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEXT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uslu et al. (2014)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Veronesi et al. (2010)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yang et al. (2013)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ABBREVIATION: RCT: randomised controlled trial.

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SLR observational studies

Identification and selection of relevant studies

Given the paucity of RCT data identified, a clinical SLR of observational studies was also conducted to obtain additional evidence for node-positive, HR+, HER2- patients. However, in anticipation of limited evidence specific for this population, no restriction was placed on HER2 status. If enough evidence were identified, HER2– data would be prioritised.

Methods used were in line with the guidelines for performing systematic reviews as published by the Centre for Reviews and Dissemination (CRD),[259] and the Cochrane Handbook for Systematic Reviews [260].

Eligibility criteria

The SLR was designed to obtain evidence for node-positive, HR+ and HER2−patients. The eligibility criteria are summarised in Table 84.

During the search and selection phase of the SLR, it became evident that observational data pertaining to patients with node-positive, HR+ early breast cancer were limited. To avoid excluding observational studies that could provide additional evidence, it was decided to relax the eligibility criteria relating to the patient population. This involved removing the restriction on node status and HR status meaning the population of interest was adult patients with early breast cancer irrespective of nodal, HR or HER2 status.

Table 84: Eligibility criteria for the clinical SLR of observational studies

Study Characteristic	Inclusion	Exclusion
Patient population	• Adults ≥18 years • Early breast cancer (Stage I–IIIC) • HR+ • Node-positive • Received definitive surgery of the primary breast tumour	• Advanced or metastatic breast cancer (Stage IV) • HR- • Node-negative
Intervention	• Tamoxifen • Anastrozole • Exemestane • Fulvestrant • Letrozole • Raloxifene • Toremifene Monotherapy and combination combination therapy of these interventions were considered eligible.	• Any other treatment
Comparators	• Any of the above-listed interventions	• Any other treatment
Outcomes	**Efficacy** • PFS	• NA

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	• IDFS • DFS • DRFS • OS • DOR • CR • PR • OR/ORR • ToT **AEs** • Time period for safety evaluation • Time to AE • Severe AEs • Treatment-emergent AEs • Hospitalisation due to AEs • Mortality due to AEs • Discontinuation due to AEs • HRQoL outcomes	
Study design	• Observational studies o Cohort studies o Case-control studies o Longitudinal studies o Cross-sectional studies o Hospital records and chart reviews • Database studies	• Letters • Editorials • Commentary • Systematic reviews and meta-analyses Case series • and case reports
Language	• All languages	• No restrictions regarding language

Abbreviations: AE: adverse event; CR: complete response; DFS: disease-free survival; DOR: duration of response; DRFS: distant relapse-free survival; HR: hormone receptor; HRQoL: health-realted quality of life; IDFS: invasive disease-free survival; OR: overall response; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PR: partial response; NA: not applicable; ToT: time on treatment.

Search Strategy

Data sources

Searches for the SLR were conducted from database inception to 28th August 2020.

Published studies

To identify clinical evidence in peer-reviewed journals, the Embase and Medline databases were searched by means of the ProQuest search engine.

The Embase and Medline search terms for the patient population consisted of words searched in title/abstract and as indexed terms (i.e., Emtree and MeSH). Search terms for observational studies were based on the filters provided by SIGN[261, 262].

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Conference proceedings

To complement the search of published studies from the medical databases, a search for conference abstracts submitted and/or presented at the following professional societies and associated conferences were conducted:

- ASCO
- ESMO
- European Breast Cancer Conference (EBCC)

The same eligibility criteria applied to published studies (Table 84) were applied to conference proceedings, except the search for conference abstracts was limited to 2017 onwards. Searches of conferences proceedings were limited to the last three years as it was assumed that any data before this time would be published in full in either Medline or Embase.

Search terms

The search strategies for the databases searched in the observational SLR are presented in Table 85 to Table 87.

Table 85: Embase search strategy run on 28 August 2020

Search line	Search terms	Hits
S1	EMB.EXACT.EXPLODE("breast cancer")	497950*
S2	TI,AB((breast OR mamma*) NEAR/2 (cancer* OR tumo?r* OR neoplasm* OR carcinoma*))	478199*
S3	S1 OR S2	595609*
S4	TI,AB(early OR "early-stage" OR "stage I" OR "stage one" OR "stage 1" OR "stage 1A" OR "stage IA" OR "stage IB" OR "stage 1B" OR "stage II" OR "stage two" OR "stage 2" OR "stage 2A" OR "stage IIA" OR "stage IIB" OR "stage 2B" OR "stage III" OR "stage three" OR "stage 3" OR "stage 3A" OR "stage IIIA" OR "stage IIIB" OR "stage 3B" OR "stage IIIC" OR "stage 3C")	2676299*
S5	S3 AND S4	87813*
S6	EMB.EXACT("tamoxifen")	63836*
S7	TI,AB(tamoxifen OR ICI-46,474 OR ICI-46474I OR CI-47699 OR Nolvadex OR Novaldex OR Soltamox OR "Tamoxifen Citrate" OR Tomaxithen OR Zitazonium OR "1 (para beta dimethylaminoethoxy phenyl) 1,2 diphenylbut 1 ene" OR "1 (para beta dimethylaminoethoxyphenyl) 1,2 diphenyl 1 butene" OR ebefen OR kessar OR "nsc 180973" OR tamoplac OR tamoxastatamoxifene OR "trans tamoxifen")	33973*

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S8	EMB.EXACT("anastrozole")	9751*
S9	TI,AB("2,2' [5 (1h 1,2,4 triazol 1 ylmethyl) 1,3 phenylene]bis(2 methylpropionitrile)" OR anastrazole OR arimidex OR "ici d1033"	643°

Search line	Search terms	Hits
	OR icid1033 OR trozolet OR "zd 1033" OR zd1033 OR "Zeneca ZD 1033")	
S10	EMB.EXACT("exemestane")	6296*
S11	TI,AB(exemestane OR "6 methyleneandrosta 1,4 diene 3,17 dione" OR aromasin OR aromasine OR "fce 24304" OR fce24304 OR nakides OR nikidess OR "pnu 155971" OR pnu155971)	2414°
S12	EMB.EXACT("fulvestrant")	9153*
S13	TI,AB(fulvestrant OR "7alpha [9 (4,4,5,5,5 pentafluoropentylsulfinyl)nonyl]estra 1,3,5(10) triene 3,17beta diol" OR faslodex OR "ici 182 780" OR "ici 182,780" OR "ici 182780" OR ici182780 OR "zd 182780" OR "zd 9238" OR zd182780 OR zd9238 OR "zm 182780" OR zm182780 OR "7-(9-(4,4,5,5,5-pentafluoropentylsulfinyl)nonyl)estra-1,3,5(10)-triene-3,17-diol" OR ZM-182780)	6260*
S14	EMB.EXACT("letrozole")	12271*
S15	TI,AB(letrozole OR "1 (4,4' dicyanobenzhydryl) 1,2,4 triazole" OR "4,4' (1h 1,2,4 triazol 1 ylmethylene)bis(benzonitrile)" OR "cgs 20267" OR cgs20267 OR femar OR femara OR loxifan OR "4,4'-(1H-1,2,4-triazol-1-yl-methylene)-bis(benzonitrile)" OR Fémara)	5517*
S16	EMB.EXACT("raloxifene")	11415*
S17	TI,AB("Raloxifene Hydrochloride" OR raloxifene OR "6 hydroxy 2 (4 hydroxyphenyl) 3 [4 [2 (1 piperidyl)ethoxy]benzoyl]benzo[b]thiophene" OR "6 hydroxy 2 (4 hydroxyphenyl)benzo[b]thien 3 yl 4 [2 (1 piperidinyl)ethoxy]phenyl ketone" OR "[6 hydroxy 2 (4 hydroxyphenyl)benzo[b]thien 3 yl][4 [2 (1 piperidinyl)ethoxy]phenyl]methanone" OR bonmax OR celvista OR evista OR keoxifene OR "keoxifene hydrochloride" OR loxar OR loxifen OR "ly 39481" OR "ly 156758" OR ly139481 OR ly156758 OR optruma OR raxeto OR "Raloxifene HCl")	4649°
S18	EMB.EXACT("toremifene")	2168°

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S19	TI,AB(toremifene OR "4 chloro 1 [4 (2 dimethylaminoethoxy)phenyl] 1,2 diphenyl 1 butene" OR "4 chloro 1,2 diphenyl 1 [4 [2 (n,n dimethylamino)ethoxy]phenyl] 1 butene" OR estrimex OR fareston OR "fc 1157 a" OR "fc 1157a" OR fc1157a OR "toremifene citrate" OR "FC-1157a")	809°
S20	S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19	89427*
S21	TI,AB("Case control") OR TI,AB(case control NEAR/1 (study OR studies))	171060*
S22	Cohort NEAR/1 (study OR studies)	361768*
S23	TI,AB(Cohort analys*)	445286*
S24	TI,AB(Follow up NEAR/1 (study OR studies))	81008*

Search line	Search terms	Hits
S25	TI,AB(Observational NEAR/1 (study OR studies))	205096*
S26	TI,AB("Cross sectional") OR TI,AB(cross sectional NEAR/1 (study OR studies))	471726*
S27	TI,AB(Longitudinal)	342186*
S28	TI,AB(Retrospective)	900139*
S29	EMB.EXACT("Clinical study")	313893*
S30	EMB.EXACT("Longitudinal study")	156219*
S31	EMB.EXACT("Retrospective study")	976470*
S32	EMB.EXACT("Prospective study") NOT EMB.EXACT("Randomized controlled trials")	656248*
S33	EMB.EXACT("Cohort analysis")	639632*
S34	EMB.EXACT("Case control study")	175113*
S35	EMB.EXACT("Follow up")	1728068*
S36	EMB.EXACT("Observational study")	223448*
S37	EMB.EXACT("Cross-sectional study")	374348*

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S38	EMB.EXACT("Disease registry")	15291*
S39	S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38	4758230*
S40	TI,AB(case NEAR/1 (stud* OR report))	1017787*
S41	EMB.EXACT("Case study")	129188*
S42	EMB.EXACT("Abstract report" OR "Letter")	1159697*
S43	RTYPE("Case reports")	0°
S44	RTYPE("Letter")	1132836*
S45	RTYPE("Historical article")	0°
S46	RTYPE("Conference abstract")	3837631*
S47	RTYPE("Note")	809842*
S48	S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47	6750981*
S49	S39 NOT S48	3153422*
S50	S5 AND S20 AND S49	2584°

Table 86: Medline search strategy run on 28 August 2020

Search line	Search terms	Hits
S1	MESH.EXACT.EXPLODE("Breast Neoplasms")	294141*
S2	TI,AB((breast OR mamma*) NEAR/2 (cancer* OR tumo?r* OR neoplasm* OR carcinoma*))	326636*
S3	S1 OR S2	397230*
S4	TI,AB(early OR "early-stage" OR "stage I" OR "stage one" OR "stage 1" OR "stage 1A" OR "stage IA" OR "stage IB" OR "stage 1B" OR "stage II" OR "stage two" OR "stage 2" OR "stage 2A" OR "stage IIA" OR "stage IIB" OR "stage 2B" OR "stage III" OR "stage three" OR "stage 3" OR "stage 3A" OR "stage IIIA" OR "stage IIIB" OR "stage 3B" OR "stage IIIC" OR "stage 3C")	1865908*
S5	S3 AND S4	51218*

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S6	MESH.EXACT("Tamoxifen")	19079*
S7	TI,AB(tamoxifen OR ICI-46,474 OR ICI-46474I OR CI-47699 OR Nolvadex OR Novaldex OR Soltamox OR "Tamoxifen Citrate" OR Tomaxithen OR Zitazonium OR "1 (para beta dimethylaminoethoxy phenyl) 1,2 diphenylbut 1 ene" OR "1 (para beta dimethylaminoethoxyphenyl) 1,2 diphenyl 1 butene" OR ebefen OR kessar OR "nsc 180973" OR tamoplac OR tamoxastatamoxifene OR "trans tamoxifen")	22860*
S8	MESH.EXACT("Anastrozole")	1396°
S9	TI,AB("2,2' [5 (1h 1,2,4 triazol 1 ylmethyl) 1,3 phenylene]bis(2 methylpropi-onitrile)" OR anastrazole OR arimidex OR "ici d1033" OR icid1033 OR trozolet OR "zd 1033" OR zd1033 OR "Zeneca ZD 1033")	364°
S10	TI,AB(exemestane OR "6 methyleneandrosta 1,4 diene 3,17 dione" OR aromasin OR aromasine OR "fce 24304" OR fce24304 OR nakides OR nikidess OR "pnu 155971" OR pnu155971)	1303°
S11	MESH.EXACT("Fulvestrant")	2335°
S12	TI,AB(fulvestrant OR "7alpha [9 (4,4,5,5,5 pentafluoropentylsulfinyl)nonyl]estra 1,3,5(10) triene 3,17beta diol" OR faslodex OR "ici 182 780" OR "ici 182,780" OR "ici 182780" OR ici182780 OR "zd 182780" OR "zd 9238" OR zd182780 OR zd9238 OR "zm 182780" OR zm182780 OR "7-(9-(4,4,5,5,5pentafluoropentylsulfi-nyl)nonyl)estra-1,3,5(10)-triene-3,17-diol" OR ZM-182780)	4181°
S13	MESH.EXACT("Letrozole")	2040°
S14	TI,AB(letrozole OR "1 (4,4' dicyanobenzhydryl) 1,2,4 triazole" OR "4,4' (1h 1,2,4 triazol 1 ylmethylene)bis(benzonitrile)" OR "cgs 20267" OR cgs20267 OR femar OR femara OR loxifan OR "4,4'-(1H-1,2,4-triazol-1-yl-methylene)-bis(benzonitrile)" OR Fémara)	2918°

Search line	Search terms	Hits
S15	MESH.EXACT("Raloxifene Hydrochloride")	2614°

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S16	TI,AB("Raloxifene Hydrochloride" OR raloxifene OR "6 hydroxy 2 (4 hydroxyphenyl) 3 [4 [2 (1 piperidyl)ethoxy]benzoyl]benzo[b]thiophene" OR "6 hydroxy 2 (4 hydroxyphenyl)benzo[b]thien 3 yl 4 [2 (1 piperidinyl)ethoxy]phenyl ketone" OR "[6 hydroxy 2 (4 hydroxyphenyl)benzo[b]thien 3 yl][4 [2 (1 piperidinyl)ethoxy]phenyl]methanone" OR bonmax OR celvista OR evista OR keoxifene OR "keoxifene hydrochloride" OR loxar OR loxifen OR "ly 39481" OR "ly 156758" OR ly139481 OR ly156758 OR optruma OR raxeto OR "Raloxifene HCl")	3329°
S17	MESH.EXACT("Toremifene")	557°
S18	TI,AB(toremifene OR "4 chloro 1 [4 (2 dimethylaminoethoxy)phenyl] 1,2 diphenyl 1 butene" OR "4 chloro 1,2 diphenyl 1 [4 [2 (n,n dimethylamino)ethoxy]phenyl] 1 butene" OR estrimex OR fareston OR "fc 1157 a" OR "fc 1157a" OR fc1157a OR "toremifene citrate" OR "FC-1157a")	680°
S19	S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18	36983*
S20	TI,AB("Case control") OR TI,AB(case control NEAR/1 (study OR studies))	129616*
S21	Cohort NEAR/1 (study OR studies)	427773*
S22	TI,AB(Cohort analys*)	238704*
S23	TI,AB(Follow up NEAR/1 (study OR studies))	56669*
S24	TI,AB(Observational NEAR/1 (study OR studies))	129070*
S25	TI,AB("Cross sectional") OR TI,AB(cross sectional NEAR/1 (study OR studies))	358125*
S26	TI,AB(Longitudinal)	247276*
S27	TI,AB(Retrospective)	538706*
S28	MESH.EXACT.EXPLODE("Case control studies")	287425*
S29	MESH.EXACT.EXPLODE("Cohort studies")	2024698*
S30	MESH.EXACT("Cross-sectional studies")	335510*
S31	MESH.EXACT("Longitudinal Studies")	136910*
S32	MESH.EXACT("Retrospective Studies")	835405*

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S33	MESH.EXACT("Prospective Studies")	546826*
S34	MESH.EXACT("Follow-Up Studies")	646082*
S35	MESH("Observational Studies")	5327*
Search line	**Search terms**	**Hits**
S36	S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35	3115512*
S37	TI,AB(case NEAR/1 (stud* OR report))	733622*
S38	S36 NOT S37	2953569*
S39	S5 AND S19 AND S38	987°

Table 87: Embase search strategy for conference proceedings run on 28 August 2020

Search line	Search terms	Hits
S1	EMB.EXACT.EXPLODE("breast cancer") OR MESH.EXACT.EXPLODE("Breast Neoplasms")	792091*
S1	EMB.EXACT.EXPLODE("breast cancer") OR MESH.EXACT.EXPLODE("Breast Neoplasms")	801542*
S2	TI,AB((breast OR mamma*) NEAR/2 (cancer* OR tumo?r* OR neoplasm* OR carcinoma*))	816725*
S3	S1 OR S2	1006160*
S4	TI,AB(early OR "early-stage" OR "stage I" OR "stage one" OR "stage 1" OR "stage 1A" OR "stage IA" OR "stage IB" OR "stage 1B" OR "stage II" OR "stage two" OR "stage 2" OR "stage 2A" OR "stage IIA" OR "stage IIB" OR "stage 2B" OR "stage III" OR "stage three" OR "stage 3" OR "stage 3A" OR "stage IIIA" OR "stage IIIB" OR "stage 3B" OR "stage IIIC" OR "stage 3C")	4602098*
S5	S3 AND S4	141192*
S6	EMB.EXACT("tamoxifen") OR MESH.EXACT("Tamoxifen")	83478*

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S7	TI,AB(tamoxifen OR ICI-46,474 OR ICI-46474I OR CI-47699 OR Nolvadex OR Novaldex OR Soltamox OR "Tamoxifen Citrate" OR Tomaxithen OR Zitazonium OR "1 (para beta dimethylaminoethoxy phenyl) 1,2 diphenylbut 1 ene" OR "1 (para beta dimethylaminoethoxyphenyl) 1,2 diphenyl 1 butene" OR ebefen OR kessar OR "nsc 180973" OR tamoplac OR tamoxastatamoxifene OR "trans tamoxifen")	57303*
S8	MESH.EXACT("Anastrozole") OR EMB.EXACT("anastrozole")	11250*
S9	TI,AB("2,2' [5 (1h 1,2,4 triazol 1 ylmethyl) 1,3 phenylene]bis(2 methylpropionitrile)" OR anastrazole OR arimidex OR "ici d1033" OR icid1033 OR trozolet OR "zd 1033" OR zd1033 OR "Zeneca ZD 1033")	677°
S10	EMB.EXACT("exemestane")	6366*
S11	TI,AB(exemestane OR "6 methyleneandrosta 1,4 diene 3,17 dione" OR aromasin OR aromasine OR "fce 24304" OR fce24304 OR nakides OR nikidess OR "pnu 155971" OR pnu155971)	2541°

Search line	Search terms	Hits
S12	MESH.EXACT("Fulvestrant") OR EMB.EXACT("fulvestrant")	11660*
S13	TI,AB(fulvestrant OR "7alpha [9 (4,4,5,5,5 pentafluoropentylsulfinyl)nonyl]estra 1,3,5(10) triene 3,17beta diol" OR faslodex OR "ici 182 780" OR "ici 182,780" OR "ici 182780" OR ici182780 OR "zd 182780" OR "zd 9238" OR zd182780 OR zd9238 OR "zm 182780" OR zm182780 OR "7-(9-(4,4,5,5,5pentafluoropentylsulfinyl)nonyl)estra-1,3,5(10)-triene-3,17-diol" OR ZM-182780)	10621*
S14	EMB.EXACT("letrozole") OR MESH.EXACT("Letrozole")	14548*
S15	TI,AB(letrozole OR "1 (4,4' dicyanobenzhydryl) 1,2,4 triazole" OR "4,4' (1h 1,2,4 triazol 1 ylmethylene)bis(benzonitrile)" OR "cgs 20267" OR cgs20267 OR femar OR femara OR loxifan OR "4,4'-(1H-1,2,4-triazol-1-yl-methylene)-bis(benzonitrile)" OR Fémara)	8631*
S16	MESH.EXACT("Raloxifene Hydrochloride") OR EMB.EXACT("raloxifene")	14107*

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S17	TI,AB("Raloxifene Hydrochloride" OR raloxifene OR "6 hydroxy 2 (4 hydroxyphenyl) 3 [4 [2 (1 piperidyl)ethoxy]benzoyl]benzo[b]thiophene" OR "6 hydroxy 2 (4 hydroxyphenyl)benzo[b]thien 3 yl 4 [2 (1 piperidinyl)ethoxy]phenyl ketone" OR "[6 hydroxy 2 (4 hydroxyphenyl)benzo[b]thien 3 yl][4 [2 (1 piperidinyl)ethoxy]phenyl]methanone" OR bonmax OR celvista OR evista OR keoxifene OR "keoxifene hydrochloride" OR loxar OR loxifen OR "ly 39481" OR "ly 156758" OR ly139481 OR ly156758 OR optruma OR raxeto OR "Raloxifene HCl")	8117*
S18	MESH.EXACT("Toremifene") OR EMB.EXACT("toremifene")	2250°
S19	TI,AB(toremifene OR "4 chloro 1 [4 (2 dimethylaminoethoxy)phenyl] 1,2 diphenyl 1 butene" OR "4 chloro 1,2 diphenyl 1 [4 [2 (n,n dimethylamino)ethoxy]phenyl] 1 butene" OR estrimex OR fareston OR "fc 1157 a" OR "fc 1157a" OR fc1157a OR "toremifene citrate" OR "FC-1157a")	887°
S20	S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19	127603*
S21	CF(2020 Annual Meeting of the American Society of Clinical Oncology, ASCO 2020)	3501°
S22	CF(2019 Annual Meeting of the American Society of Clinical Oncology, ASCO 2019)	4953°
S23	CF(2018 Annual Meeting of the American Society of Clinical Oncology, ASCO 2018)	5374*
S24	CF(2017 Annual Meeting of the American Society of Clinical Oncology, ASCO)	5142*
S25	CF(44th Congress of European Society for Medical Oncology, ESMO 2019)	2218°

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Search line	Search terms	Hits
S26	CF(43rd Congress of European Society for Medical Oncology, ESMO 2018)	2038°
S27	CF(42nd ESMO Congress, ESMO 2017)	1722°
S28	S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27	25006*
S29	S5 AND S20 AND S28	117°

Systematic selection of studies

Peer-reviewed Publications

Once the electronic searches were run, all retrieved references were downloaded and imported into an EndNote database and duplicates were removed. The references were then exported into DistillerSR (Version: 2.32.0), a reference screening software that was used for title/abstract and full-text screening.

Inclusion or exclusion of articles was based on the eligibility criteria specified in Table 84 and the protocol deviations detailed below. Title/abstract review of all references was performed in double and independently by two reviewers. Any discrepancies were resolved by a third reviewer. The same process was applied for articles that were selected for full-text review. During both title / abstract and full-text screening phases, excluded articles were documented with reasons for their exclusion according to the pre-defined criteria.

Conference proceedings

The clinical conference websites of ASCO, ESMO and EBCC (proceedings for the years 2017– 2020) were searched. Proceedings from ASCO (2017–2020) were searched through ProQuest, as were the proceedings for ESMO for 2018 and 2019. The proceeding for EBCC and ESMO 2020 were hand searched.

Conference searches were performed by a single reviewer and checked by a second reviewer. Conference abstracts which meet the eligibility criteria were collated in a Microsoft Excel database and were matched up to included peer-reviewed publications where relevant to determine if any additional information were provided. If duplicate data were presented in multiple conference abstracts, only the most recent abstract was included.

Deviation from the protocol

Following abstract screening and articles for full-text review were decided, papers were reviewed for inclusion and categorised based on the HER2 status of the patient populations. As HER2+ status was not routinely tested for prior to 2005 it was decided to exclude studies published prior to 2005 at the full-text screening stage [263]. To prioritise studies with a patient population similar to monarchE (HR+, HER2-, node-positive, high risk EBC) it was decided to include only those [studies] with a patient population of at least 80% HER2-, or reported results of interest for only HER2- patients. The 80% cut-off was applied to the average proportion of HER2- patients across the treatment arms. Several non-English articles were included from title and abstract screening. It was decided to prioritise English language articles at full-text review, and non-English articles were excluded at this stage for the reason of language.

Data extraction

After the list of included studies was finalised, the relevant data were extracted in DistillerSR® tool by two reviewers.

One reviewer extracted the data, and a second reviewer independently reviewed all data extracted for each endpoint. 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.

Critical appraisal

Critical appraisal of observational studies was conducted using a CRD checklist [259]. Critical appraisal was only performed for peer-reviewed publications and not for conference proceedings, as there would be insufficient methodological data to assess the study quality. One reviewer conducted the critical appraisal of included articles; a second reviewer checked the accuracy.

Study selection

The searches (undertaken on 28th of August 2020) retrieved a total of 3,571 references. Due to overlap of records across databases, 709 duplicate references were removed. After the removal of duplicates, titles, and abstracts of 2,862 publications were screened for eligibility. After excluding 2,671 publications based on title and abstract screening, 191 references were selected for full-text review.

Based on the eligibility criteria (Table 84) and the modified criteria around the patient population (see *Deviation from the protocol section just above*) a total of 178 publications were excluded after full-text screening. This resulted in 13 eligible full-text publications. A further two abstracts from conference proceedings were included.

In total, 15 observational studies (13 peer-reviewed texts, 2 conference abstracts) were included.

The record selection process is shown in the PRISMA diagram in Figure 35.

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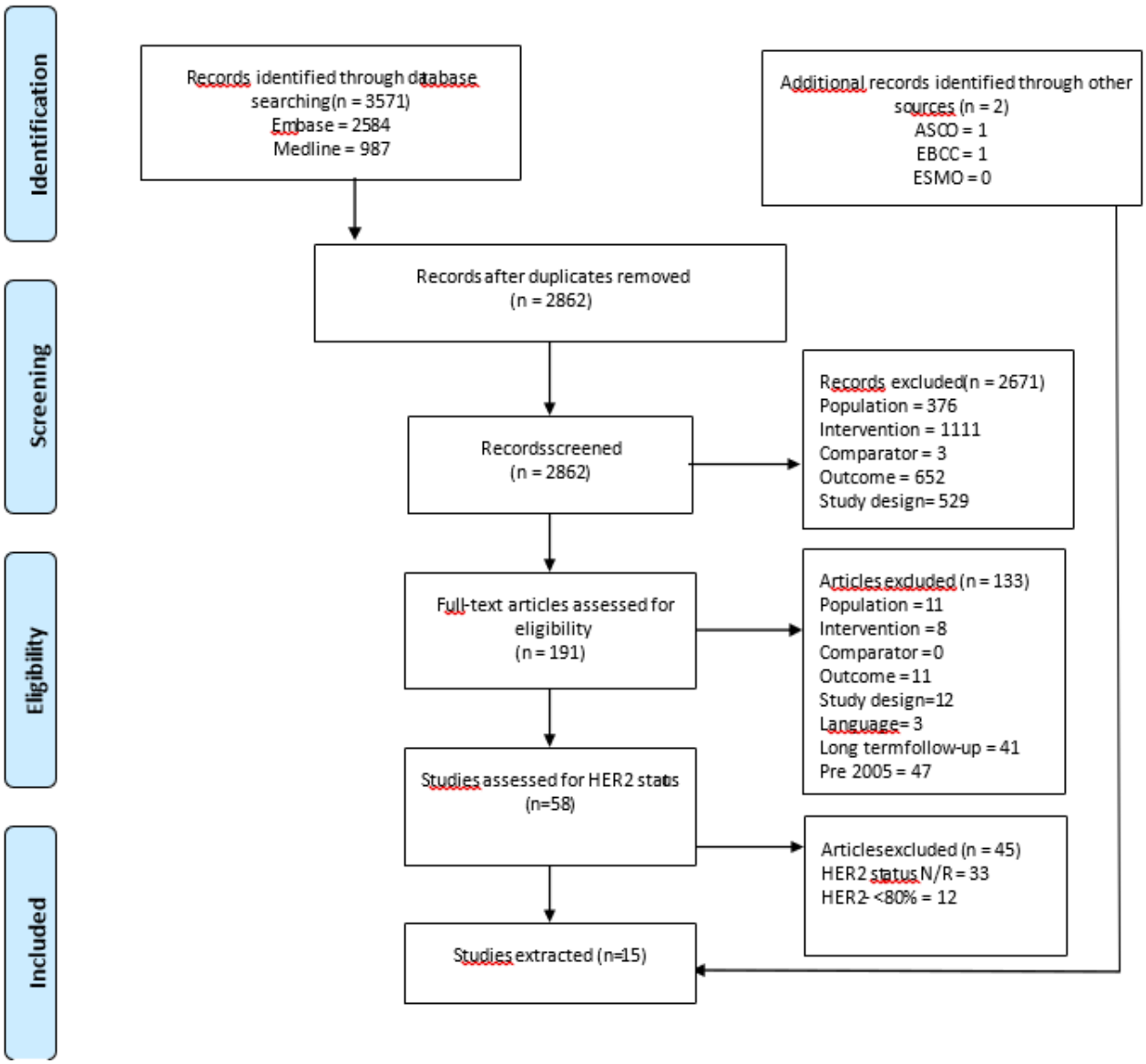
Figure 35: PRISMA diagram for the SLR of observational studies: August 2020



Abbreviations: ASCO: American Society of Clinical Oncology; EBCC: European Breast Cancer Conference; ESMO: European Society for Medical Oncology; HER2: human epidermal growth factor receptor 2; N/R: not reported; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR: systematic literature review.

Included studies

Overall, 15 publications (13 peer-reviewed texts and 2 conference abstracts) were included in the SLR.

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Table 88: List of studies included in the clinical SLR of observational studies

Study/trial ID	Intervention	Study title	Study population
Niméus, 2017	• Tamoxifen	Androgen Receptor in Stage I-II Primary Breast Cancer – Prognostic Value and Distribution in Subgroups	Patients with stage II tumours who had received 2 years tamoxifen
Yan, 2017	• Tamoxifen	The Relationship Between Tamoxifen-associated Nonalcoholic Fatty Liver Disease and the Prognosis of Patients With Early-stage Breast Cancer	ER and/or PR+ and HER2− patients
Yamada, 2018	Adjuvant hormonal therapy: • Tamoxifen only: 1033 (57.2%) • AI only: 637 (35.3%) • Tamoxifen and AI: 284 (15.7%) • No hormonal therapy: 420 (23.3%)	Improved overall survival over recent decades in patients with hormone-receptor-positive, HER2-negative breast cancer: a single-center retrospective analysis of prognostic factors	HR+, HER2- patients who underwent radical resection for early disease at the National Cancer Center Hospital East in Japan between July 1992 and December 2010.
Elzawahry, 2013	• Tamoxifen	Role of Ki67 in predicting resistance to adjuvant tamoxifen in postmenopausal breast cancer patients	HR+, postmenopausal
Ishitobi, 2014	• Concurrent RT and AI • Sequential RT and AI	Treatment Sequence of Aromatase Inhibitors and Radiotherapy and Long-term Outcomes of Breast Cancer Patients	HR+ Stage I or II breast cancer
Ferreira, 2018	• Tamoxifen monotherapy • AI sequential TAM-AI/AI-TAM • AI monotherapy • Exposure to AI	Treatment adoption and relative effectiveness of aromatase inhibitors compared to tamoxifen in early breast cancer: A multi-institutional observational study	Postmenopausal women with stage I-III HR+ EBC
Kennecke, 2008	• Tamoxifen	Risk of Early Recurrence Among Postmenopausal Women With Estrogen Receptor-positive Early Breast Cancer Treated With Adjuvant Tamoxifen	Postmenopausal ER+ EBC
Meattini, 2013	• Tamoxifen	Prognostic role of human epidermal growth factor receptor 2 status in premenopausal early breast cancer treated with adjuvant tamoxifen	Premenopausal chemotherapy naïve EBC

Sendur, 2013	• Anastrozole • Letrozole	Comparative efficacy study of 5-year letrozole or anastrozole in post-menopausal hormone receptor-positive early breast cancer	Postmenopausal HR+ EBC
Nabieva, 2018	• Letrozole	Influence of patient and tumor characteristics on early therapy persistence with letrozole in postmenopausal women with early breast cancer: results of the prospective Evaluate-TM study with 3941 patients	Postmenopausal HR+ EBC
Tang, 2019	• Tamoxifen + leuprorelin	Long-term comparisons of the efficacy, safety, and pregnancy outcomes of adjuvant tamoxifen plus ovarian function suppression in premenopausal Han and Zhuang Chinese patients with hormone receptor-positive early breast cancer	Premenopausal HR+ EBC
Wickberg, 2018	• Tamoxifen: 534 (88.9%) • AI: 67 (11.1%)	Omitting radiotherapy in women ≥65 years with low-risk early breast cancer after breast-conserving surgery and adjuvant endocrine therapy is safe	HR+ EBC
Metzger-Filho, 2019	• Endocrine therapy: 722 (89%) • Endocrine therapy ILC patients: 302 (89.6%) • Endocrine therapy IDC-L patients: 420 (88.6%)	Mixed Invasive Ductal and Lobular Carcinoma of the Breast: Prognosis and the Importance of Histologic Grade	EBC with IDC-L or ILC
Foldi ASCO, 2020	Endocrine therapy: • Tamoxifen: 44 (43%) • AI: 79 (77%)	Adherence to extended adjuvant endocrine therapy following Breast Cancer Index (BCI) testing in women with early-stage hormone receptor (HR)-positive breast cancers	HR+ stage I–III EBC
Chamalidou, EBCC 2020	Endocrine therapy: • Tamoxifen: 779 • AI: 54 • Ovarian suppression + ET: 33 • Other ET: 23	Compliance to adjuvant endocrine treatment real world data from 1019 consecutive luminal breast cancer patients with long follow-up	HR+, HER2− EBC

Abbrevations: AI: aromatase inhibitor; EBC: early breast cancer; ER: oestrogen receptor; ET: endocrine therapy; HR+: hormone receptor positive; HER2; human epidermal growth factor receptor 2; IDC-L: invasive ductal and lobular carcinoma; ILC: invasive lobular carcinoma; PR: progesterone receptor.

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List of studies excluded at the full-text review stage

Table 89: List of records excluded at the full-text review stage of the clinical SLR of observational studies

ID	Author	Title	Journal	Year	Reason for exclusion
8	Digenis	Carcinoma of the male breast: a review of 41 cases	Southern medical journal	1990	Published prior to 2005
24	Ezzat	Locally advanced breast cancer in Saudi Arabia: High frequency of stage III in a young population	Medical Oncology	1999	Published prior to 2005
26	Ribeiro	Adjuvant Tamoxifen for male breast cancer (MBC)	British Journal of Cancer	1992	Published prior to 2005
30	Pemmaraju	Retrospective review of male breast cancer patients: Analysis of tamoxifen-related sideeffects	Annals of Oncology	2012	Study design
32	Shah	Breast cancer recurrences in elderly patients after lumpectomy	The American surgeon	2002	Published prior to 2005
33	Low	Long-term follow-up for locally advanced and inflammatory breast cancer patients treated with multimodality therapy	Journal of clinical oncology : official journal of the American Society of Clinical Oncology	2004	Long term followup to clinical trial
34	Shah	Male Breast Cancer: A Clinicopathologic Study of 42 Patients in Eastern India	Indian Journal of Surgical Oncology	2012	Intervention
43	Miller	Durable remission of locally advanced breast cancer with multimodality management	Medical oncology (Northwood, London, England)	1998	Published prior to 2005
44	Hoff	Combined modality treatment of locally advanced breast carcinoma in elderly patients or patients with severe comorbid conditioNode status using tamoxifen as the primary therapy	Cancer	2000	Published prior to 2005
56	Shukla	Male breast cancer: A retrospective study from a regional cancer center in Northern India	Journal of Surgical Oncology	1996	Published prior to 2005
65	Odendaal	Limited surgery and tamoxifen in the treatment of elderly breast cancer patients	World Journal of Surgery	2003	Published prior to 2005

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ID	Author	Title	Journal	Year	Reason for exclusion
68	Ibrahim	Breast cancer in the eastern province of Saudi Arabia	Medical Oncology	1998	Published prior to 2005
69	Dünser	Tumorectomy plus tamoxifen for the treatment of breast cancer in the elderly	European journal of surgical oncology: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology	1993	Published prior to 2005
130	Marshall	Assessment of tamoxifen as adjuvant therapy in stage II breast cancer: A long-term follow-up	Journal of Laboratory and Clinical Medicine	1987	Published prior to 2005
135	Vorgias	Outcome of stage II breast cancer in Greece: A 10-year follow-up study	Medical Science Research	1998	Published prior to 2005
137	Killander	Radiotherapy and tamoxifen after mastectomy in postmenopausal women - 20 year follow-up of the South Sweden Breast Cancer group randomised trial SSBCG II:I	European Journal of Cancer	2007	Long term followup to clinical trial
157	Gnant	Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial	The Lancet. Oncology	2011	Long term followup to clinical trial
166	Sanguinetti	Locally advanced breast cancer in elderly patients: treatment standardised or tailored to individual needs?	Chirurgia italiana	2007	Language
169	Hughes	Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343	Journal of clinical oncology: official journal of the American Society of Clinical Oncology	2013	Long term followup to clinical trial
178	Mayer	CYP2D6-inhibiting medication use and inherited CYP2D6 variation in relation to adverse breast cancer outcomes after tamoxifen therapy	Cancer Causes and Control	2019	Intervention

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ID	Author	Title	Journal	Year	Reason for exclusion
184	Leborgne	Breast coNode statuservation treatment of early stage breast cancer: PatterNode status of failure	International Journal of Radiation Oncology Biology Physics	1995	Published prior to 2005
203	Fowble	The impact of tamoxifen on breast recurrence, cosmesis, complicatioNode status, and survival in estrogen receptor-positive early-stage breast cancer	International Journal of Radiation Oncology Biology Physics	1996	Published prior to 2005
204	Diratzouian	Importance of physical examination in the absence of a mammographic abnormality for the detection of early-stage breast cancer	Clinical breast cancer	2005	Intervention
206	Bender	PatterNode status of change in cognitive function with anastrozole therapy	Cancer	2015	Outcomes
251	Smith	CoNode statuservative treatment of early-stage breast cancer. The Emory experience	American journal of clinical oncology	1994	Published prior to 2005
272	Pierce	CoNode statuservative surgery and radiotherapy for stage I/II breast cancer using lung deNode statusity correction: 10-year and 15-year results	International Journal of Radiation Oncology Biology Physics	2005	Population
275	Cutuli	Breast-coNode statuserving therapy for stage I-II breast cancer in elderly women	International journal of radiation oncology, biology, physics	2004	Published prior to 2005
289	Ogawa.	CoNode statuservation treatment inteNode statusified with tamoxifen and CAF chemotherapy for subareolar breast cancers	Oncology reports	1998	Published prior to 2005
299	Fowble	The influence of young age on outcome in early stage breast cancer	International Journal of Radiation Oncology Biology Physics	1994	Published prior to 2005
300	Gasparini	CoNode statuservative surgery and irradiation (QUART) in the treatment of 243 stage I-II breast cancer patients	Anticancer research	1991	Published prior to 2005

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ID	Author	Title	Journal	Year	Reason for exclusion
301	Borazan	Clinical analysis of the our confirm of breast cancer of 307 cases of the between 1990 and 2000 years	THOD - Turk Hematoloji-Onkoloji Dergisi	2002	Published prior to 2005
318	Fodor	The impact of radiotherapy on the incidence and time of occurrence of local recurrence in earlystage breast cancer after breast coNode statuserving therapy	Neoplasma	2000	Published prior to 2005
394	Ewertz	Obesity and risk of recurrence or death after adjuvant endocrine therapy with letrozole or tamoxifen in the breast international group 1-98 trial	Journal of Clinical Oncology	2012	Long term followup to clinical trial
442	Harrell	Analysis of adjuvant endocrine therapy in practice from electronic health record data of patients with breast cancer	JCO Clinical Cancer Informatics	2017	Population
449	Bliss	Disease-related outcomes with long-term followup: An updated analysis of the intergroup exemestane study	Journal of Clinical Oncology	2012	Long term followup to clinical trial
450	Derks	Adjuvant tamoxifen and exemestane in women with postmenopausal early breast cancer (TEAM): 10-year follow-up of a multicentre, open-label, randomised, phase 3 trial	The Lancet Oncology	2017	Long term followup to clinical trial
461	Goss	Late extended adjuvant treatment with letrozole improves outcome in women with early-stage breast cancer who complete 5 years of tamoxifen	Journal of clinical oncology: official journal of the American Society of Clinical Oncology	2008	Long term followup to clinical trial
480	Buzdar	CompreheNode statusive side-effect profile of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: long-term safety analysis of the ATAC trial	The Lancet. Oncology	2006	Long term followup to clinical trial
494	Jensen	Two years of tamoxifen or no adjuvant systemic therapy for patients with high-risk breast cancer:	Acta Oncologica	2018	Long term followup to clinical trial

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ID	Author	Title	Journal	Year	Reason for exclusion
		long-term follow-up of the Copenhagen breast cancer trial			
508	DeGrendele	Benefit of letrozole in postmenopausal women after five years of tamoxifen therapy for earlystage breast cancer	Clinical Breast Cancer	2003	Published prior to 2005
535	Quintela-Fandino	Nintedanib plus letrozole in early breast cancer: A phase 0/I pharmacodynamic, pharmacokinetic, and safety clinical trial of combined FGFR1 and aromatase inhibition	Breast Cancer Research	2019	Population
541	Cuzick	Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial	The Lancet Oncology	2010	Long term followup to clinical trial
571	Rutqvist	Cardiac and thromboembolic morbidity among postmeno-pausal women with early-stage breast cancer in a randomized trial of adjuvant tamoxifen	Journal of the National Cancer INode statustitute	1993	Published prior to 2005
582	Gierach	Association of Adjuvant Tamoxifen and Aromatase Inhibitor Therapy With Contralateral Breast Cancer Risk Among US Women With Breast Cancer in a General Community Setting	JAMA oncology	2017	Outcomes
620	Yu	A prospective, multicenter, controlled, observational study to evaluate the efficacy of a patient support program in improving patients' persistence to adjuvant aromatase inhibitor medication for postmenopausal, early stage breast cancer	Breast cancer research and treatment	2012	Outcomes
621	Goss	Breaking the 5-year barrier: Results from the MA.17 extended adjuvant trial in women who have completed adjuvant tamoxifen treatment	European Journal of Cancer, Supplement	2006	Population

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ID	Author	Title	Journal	Year	Reason for exclusion
627	Rutqvist	Long-term follow-up of the randomized Stockholm trial on adjuvant tamoxifen among postmenopausal patients with early stage breast cancer	Acta oncologica (Stockholm, Sweden)	2007	Long term followup to clinical trial
669	Saarto	The prognosis of stage III breast cancer treated with postoperative radiotherapy and adriamycinbased chemotherapy with and without tamoxifen. Eight year follow-up results of a randomized trial	European Journal of Surgical Oncology	1995	Long term followup to clinical trial
680	Sugimachi	Postoperative chemo-endocrine treatment with mitomycin C, tamoxifen, and UFT is effective for patients with premenopausal estrogen receptorpositive stage II breast cancer. Nishinihon Cooperative Study Group of Adjuvant Therapy for Breast Cancer	Breast cancer research and treatment	1999	Published prior to 2005
687	Rydén	Two years of adjuvant tamoxifen in premenopausal patients with breast cancer: a randomised, controlled trial with long-term followup	European journal of cancer (Oxford, England: 1990)	2005	Long term followup to clinical trial
710	Hata	Ten-year results of a randomized trial on adjuvant chemo-endocrine therapy with tamoxifen for stage II breast cancer	Breast cancer (Tokyo, Japan)	2003	Long term followup to clinical trial
774	Rydén	Long-term effects of adjuvant tamoxifen and/or radiotherapy. The South Sweden Breast Cancer Trial	Acta oncologica (Stockholm, Sweden)	1992	Long term followup to clinical trial
848	van Zyl	Tumour excision plus continuous tamoxifen compared with modified radical mastectomy in patients over 70 years of age with operable breast cancer	Journal of surgical oncology	1995	Published prior to 2005

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ID	Author	Title	Journal	Year	Reason for exclusion
856	Chou	Major Adverse Cardiovascular Events after Treatment in Early-stage Breast Cancer Patients Receiving Hormone Therapy	Scientific reports	2020	Outcomes
865	Solin	Ten-year results of the treatment of early-stage breast carcinoma in elderly women using breastcoNode statuserving surgery and definitive breast irradiation	International journal of radiation oncology, biology, physics	1995	Published prior to 2005
870	Öksüzoğlu	Retrospective evaluation of operated stage I breast cancer patients	Turkish Journal of Cancer	2003	Published prior to 2005
873	Ngô	Clinico-pathology and prognosis of endometrial cancer in patients previously treated for breast cancer, with or without tamoxifen: A comparative study in 363 patients	European Journal of Surgical Oncology	2014	Population
883	Fiorica	Adjuvant radiotherapy on older and oldest breast cancer patients after coNode statuservative surgery: a retrospective analysis	Archives of gerontology and geriatrics	2012	Intervention
886	Belfiglio	Twelve-year mortality results of a randomized trial of 2 versus 5 years of adjuvant tamoxifen for postmenopausal early-stage breast carcinoma patients (SITAM 01)	Cancer	2005	Long term followup to clinical trial
917	Xue	The effect of breast coNode statuservation therapy on early-stage breast cancer	Chinese Journal of Clinical Oncology	2008	Language
973	Ogawa	Early experiences of breast-coNode statuservation treatment combined with tamoxifen and CAF chemotherapy for breast cancer of stages I and II	Radiation medicine	1994	Published prior to 2005
978	Hayashi	Adding hormonal therapy to chemotherapy and trastuzumab improves prognosis in patients with hormone receptor-positive and human epidermal	Breast Cancer Research and Treatment	2013	Population

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ID	Author	Title	Journal	Year	Reason for exclusion
		growth factor receptor 2-positive primary breast cancer			
1016	Nio	Comparative effects of the administration period of adjuvant chemotherapy using doxifluridine (5'DFUR) for 1 year versus 3 years after breast cancer surgery by the Shimane Breast Cancer Study Group	Anticancer Research	2006	Study design
1018	Sugimachi	Postoperative chemo-endocrine treatment with mitomycin C, tamoxifen, and UFT is effective for patients with premenopausal estrogen receptorpositive stage II breast cancer	Breast Cancer Research and Treatment	1999	Published prior to 2005
1079	Kokubo	Results of breast-coNode statuserving therapy for early stage breast cancer: Kyoto university experiences	American Journal of Clinical Oncology: Cancer Clinical Trials	2000	Published prior to 2005
1098	Fisher	Long-term follow-up of axillary node-positive breast cancer patients receiving adjuvant tamoxifen alone: PatterNode status of recurrence	International Journal of Radiation Oncology Biology Physics	1998	Published prior to 2005
1116	Stebbing	Breast cancer (non-metastatic)	BMJ clinical evidence	2011	Study design
1167	Hubay	Adjuvant therapy of stage II breast cancer: 48month follow-up of a prospective randomized clinical trial	Breast cancer research and treatment	1981	Long term followup to clinical trial
1175	Freedman	Recursive partitioning identifies patients at high and low risk for ipsilateral tumor recurrence after breast-coNode statuserving surgery and radiation	Journal of Clinical Oncology	2002	Published prior to 2005
1190	Ejlertsen	One year of adjuvant tamoxifen compared with chemotherapy and tamoxifen in postmenopausal patients with stage II breast cancer	European journal of cancer (Oxford, England: 1990)	2013	Long term followup to clinical trial

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ID	Author	Title	Journal	Year	Reason for exclusion
1256	Sánchez	Treatment results of early breast cancer. A retrospective review	Revista Medica de Chile	2007	Outcomes
1270	Martelli	Is axillary lymph node dissection necessary in elderly patients with breast carcinoma who have a clinically uninvolved axilia?	Cancer	2003	Published prior to 2005
1273	Hubay	Eight-year follow-up of adjuvant therapy for stage II breast cancer	World journal of surgery	1985	Long term followup to clinical trial
1280	Anelli	Hormone replacement therapy and the risk of breast cancer: assessment of therapy acceptance in a cohort of previously treated breast cancer patients	Revista do Hospital das Clinicas	2003	Published prior to 2005
1327	Martelli	Is axillary lymph node dissection necessary in elderly patients with breast carcinoma who have a clinically uninvolved axilla?	Cancer	2003	Published prior to 2005
1408	Banerjee	Tree-based model for breast cancer prognostication	Journal of clinical oncology: official journal of the American Society of Clinical Oncology	2004	Published prior to 2005
1459	Ruhstaller	Adjuvant letrozole and tamoxifen alone or sequentially for postmenopausal women with hormone receptor-positive breast cancer: Longterm follow-up of the BiG 1-98 trial	Journal of Clinical Oncology	2019	Long term followup to clinical trial
1466	Regan	Assessment of letrozole and tamoxifen alone and in sequence for postmenopausal women with steroid hormone receptor-positive breast cancer: The BIG 1-98 randomised clinical trial at 8·1 years median follow-up	The Lancet Oncology	2011	Long term followup to clinical trial
1492	Bradley	Contemporary systemic therapy for male breast cancer	Clinical Breast Cancer	2014	Study design

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ID	Author	Title	Journal	Year	Reason for exclusion
1535	Servitja	Bone health in a prospective cohort of postmenopausal women receiving aromatase inhibitors for early breast cancer	Breast	2012	Outcomes
1539	Morden	Long-term follow-up of The Intergroup Exemestane Study	Journal of Clinical Oncology	2017	Long term followup to clinical trial
1550	Chagpar	Determinants of early distant metastatic disease in elderly patients with breast cancer	American journal of surgery	2006	Study design
1582	Hadji	Correlation of treatment-emergent adverse events and clinical respoNode statuse to endocrine therapy in early breast cancer: A retrospective analysis of the German cohort of TEAM	Annals of Oncology	2012	Population
1598	Warm	Benefits of early and prolonged fulvestrant treatment in 848 postmenopausal advanced breast cancer patients	Breast Cancer Research and Treatment	2011	Intervention
1613	Henry	AssociatioNode status Between Patient and Anthropometric Characteristics and Aromatase Inhibitor Discontinuation	Clinical Breast Cancer	2017	Outcomes
1647	Crivellari	Letrozole compared with tamoxifen for elderly patients with endocrine-respoNode statusive early breast cancer: The BIG 1-98 trial	Journal of Clinical Oncology	2008	Study design
1658	Li	Clinical outcomes comparison of 10 years versus 5 years of adjuvant endocrine therapy in patients with early breast cancer	BMC cancer	2018	Intervention
1659	Buzdar	'Arimidex' (anastrozole) versus tamoxifen as adjuvant therapy in postmenopausal women with early breast cancer-efficacy overview	Journal of Steroid Biochemistry and Molecular Biology	2003	Published prior to 2005

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ID	Author	Title	Journal	Year	Reason for exclusion
1662	Ruddy	Extended therapy with letrozole and ovarian suppression in premenopausal patients with breast cancer after tamoxifen	Clinical breast cancer	2014	Outcomes
1710	Forbes	The Use of Early Adjuvant Aromatase Inhibitor Therapy: ContributioNode status From the BIG 1-98 Letrozole Trial	Seminars in Oncology	2006	Study design
1729	Balakrishnan	Early operable breast cancer in elderly women treated with an aromatase inhibitor letrozole as sole therapy	British Journal of Cancer	2011	Outcomes
1731	Francis	Adjuvant endocrine therapy for premenopausal women: risk stratification, type and duration	Breast (Edinburgh, Scotland)	2019	Long term followup to clinical trial
1788	Dixon	Role of ErbB2 in selection for adjuvant tamoxifen or aromatase inhibitors	Women's Health	2008	Outcomes
1793		Controlled trial of tamoxifen as single adjuvant agent in management of early breast cancer. Analysis at six years by Nolvadex Adjuvant Trial Organisation	Lancet (London, England)	1985	Long term followup to clinical trial
1795	Rugo	Incidence and time course of everolimus-related adverse events in postmenopausal women with hormone receptor-positive advanced breast cancer: INode statusights from BOLERO-2	Annals of Oncology	2014	Long term followup to clinical trial
1806	Duffy	A lower incidence of gynecologic adverse events and interventioNode status with anastrozole than with tamoxifen in the ATAC trial	American journal of obstetrics and gynecology	2009	Study design
1876	Martelli	Elderly breast cancer patients treated by coNode statuservative surgery alone plus adjuvant tamoxifen: fifteen-year results of a prospective study	Cancer	2008	Study design

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ID	Author	Title	Journal	Year	Reason for exclusion
1877	Voskuil.	Maintenance of physical activity and body weight in relation to subsequent quality of life in postmenopausal breast cancer patients	Annals of Oncology	2010	Population
1891	Peng	The adherence and tolerance of adjuvant endocrine therapy in geriatric breast cancer patients	Journal of Cancer Research and Practice	2016	Outcomes
1937	Hackshaw	Long-term benefits of 5 years of tamoxifen: 10year follow-up of a large randomized trial in women at least 50 years of age with early breast cancer	Journal of clinical oncology: official journal of the American Society of Clinical Oncology	2011	Long term followup to clinical trial
1956	Aihara	Anastrozole versus tamoxifen as adjuvant therapy for Japanese postmenopausal patients with hormone-respoNode statusive breast cancer: efficacy results of long-term follow-up data from the N-SAS BC 03 trial	Breast cancer research and treatment	2014	Long term followup to clinical trial
1966	Karlsson	Timing of Radiation Therapy and Chemotherapy After Breast-CoNode statuserving Surgery for Node-Positive Breast Cancer: Long-Term Results From International Breast Cancer Study Group Trials VI and VII		2016	Long term followup to clinical trial
1969	Baum	Results of the Cancer Research Campaign Adjuvant Trial for Perioperative Cyclophosphamide and Long-Term Tamoxifen in Early Breast Cancer reported at the tenth year of follow-up. Cancer Research Campaign Breast Cancer Trials Group	Acta oncologica (Stockholm, Sweden)	1992	Long term followup to clinical trial
1986	Thürliman	Is chemotherapy necessary for premenopausal women with lower-risk node-positive, endocrine respoNode statusive breast cancer? 10-year update of International Breast Cancer Study Group Trial 11-93	Breast cancer research and treatment	2009	Long term followup to clinical trial

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ID	Author	Title	Journal	Year	Reason for exclusion
2002	Delozier	Tamoxifen adjuvant treatment duration in early breast cancer: Initial results of a randomized study comparing short-term treatment with longterm treatment	Journal of Clinical Oncology	2000	Long term followup to clinical trial
2010	Okunade	Biological profile of oestrogen receptor positive primary breast cancers in the elderly and respoNode statuse to primary endocrine therapy	Critical Reviews in Oncology/Hematology	2009	Population
2020	Chakrabarti	A randomised trial of mastectomy only versus tamoxifen for treating elderly patients with operable primary breast cancer-final results at 20-year follow-up	Critical reviews in oncology/hematology	2011	Long term followup to clinical trial
2029	Crivellari	Adjuvant endocrine therapy compared with no systemic therapy for elderly women with early breast cancer: 21-year results of International Breast Cancer Study Group Trial IV	Journal of clinical oncology: official journal of the American Society of Clinical Oncology	2003	Long term followup to clinical trial
2061	Sauerbrei	Randomized 2 x 2 trial evaluating hormonal treatment and the duration of chemotherapy in node-positive breast cancer patients: an update based on 10 years' follow-up. German Breast Cancer Study Group	Journal of clinical oncology: official journal of the American Society of Clinical Oncology	2000	Long term followup to clinical trial
2091	Baum	Results of the cancer research campaign adjuvant trial for perioperative cyclophosphamide and long-term tamoxifen in early breast cancer reported at the tenth year of follow-up	Acta Oncologica	1992	Long term followup to clinical trial
2112	Mustacchi	Tamoxifen alone versus adjuvant tamoxifen for operable breast cancer of the elderly: Long-term results of the phase III randomized controlled multicenter GRETA trial	Annals of Oncology	2003	Long term followup to clinical trial
2131	Ganz	Quality of life in long-term, disease-free survivors of breast cancer: A follow-up study	Journal of the National Cancer INode statustitute	2002	Published prior to 2005

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ID	Author	Title	Journal	Year	Reason for exclusion
2150	De Placido	Steroid hormone receptor levels and adjuvant tamoxifen in early breast cancer. Ten year results of the Naples (GUN) Study	Breast cancer research and treatment	1990	Published prior to 2005
2164	Monda	Improvement of bone physiology and life quality due to association of risedronate and anastrozole	Frontiers in Pharmacology	2017	Outcomes
2166	Martelli	Axillary dissection versus no axillary dissection in older patients with T1N0 breast cancer: 15-year results of a randomized controlled trial	Annals of surgery	2012	Long term followup to clinical trial
2190	De Valois	Using traditional acupuncture for breast cancerrelated hot flashes and night sweats	Journal of Alternative and Complementary Medicine	2010	Intervention
2196	Gordon	Thirty-year follow-up of chemo/hormonal therapy in node-positive breast cancer	Breast Cancer Research and Treatment	2007	Long term followup to clinical trial
2212	Boccardo	Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: long term results of the Italian Tamoxifen Anastrozole trial	European journal of cancer (Oxford, England: 1990)	2013	Long term followup to clinical trial
2224	Roché	Complete hormonal blockade versus epirubicinbased chemotherapy in premenopausal, one to three node-positive, and hormone-receptor positive, early breast cancer patients: 7-year follow-up results of French Adjuvant Study Group 06 randomised trial	Annals of Oncology	2006	Long term followup to clinical trial
2266	Ursulovic	The influence of PTEN protein expression on disease outcome in premenopausal hormone receptor-positive early breast cancer patients treated with adjuvant ovarian ablation: a longterm follow-up	Journal of B.U.ON.	2018	Study design

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ID	Author	Title	Journal	Year	Reason for exclusion
2306	Vishwanathan	Role of electron beam treatment in postoperative management of carcinoma of the breast	Indian journal of cancer	1998	Published prior to 2005
2366	Mauriac	Neoadjuvant tamoxifen for hormone-seNode statusitive non-metastatic breast carcinomas in early postmenopausal women	Annals of Oncology	2002	Published prior to 2005
2371	Brennan	Patient-reported quality of life, unmet needs and care coordination outcomes: Moving toward targeted breast cancer survivorship care planning	Asia-Pacific Journal of Clinical Oncology	2016	Population
2373	Touboul	Local recurrences and distant metastases after breast-coNode statuserving surgery and radiation therapy for early breast cancer	International Journal of Radiation Oncology Biology Physics	1999	Published prior to 2005
2431	Gómez	Prognostic effect of hormone receptor status in early HER2 positive breast cancer patients	Hematology/ Oncology and Stem Cell Therapy	2010	Population
2511	Fallowfield	Quality of life in the elderly woman with breast cancer treated with tamoxifen and surgery or tamoxifen alone	Journal of Women's Health	1994	Published prior to 2005
2574	Hughes	Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer	Women's Oncology Review	2004	Published prior to 2005
2575	Bradburn	Time trends in breast cancer survival: Experience in a single centre, 1975-89	British Journal of Cancer	1998	Published prior to 2005
2586	Harris	Epidermal growth factor receptors in breast cancer: association with early relapse and death, poor respoNode statuse to hormones and interactioNode status with neu	Journal of steroid biochemistry	1989	Published prior to 2005
ID	Author	Title	Journal	Year	Reason for exclusion

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2601	Ferreira	Impact of tamoxifen (TAM) serum concentration on side effects among premenopausal patients (pts) with early breast cancer (BC) in the prospective multicenter CANTO cohort	Annals of oncology: official journal of the European Society for Medical Oncology	2019	Intervention
2719	Ferri	In situ breast cancer. A challenge for breast physiciaNode status	Salus	2005	Study design
2721	Latini	Quadrant excision and radiotherapy in the treatment of early cancer of the breast	La Radiologia medica	1986	Published prior to 2005
2813	Lu	Effects of anastrozole on lipid metabolism in Chinese postmenopausal women with breast cancer	Chinese Journal of Oncology	2011	Language

ID	Author	Title	Journal	Year	Reason for exclusion
15	Ulcickas Yood	Mortality Impact of Less-than-Standard Therapy in Older Breast Cancer Patients	Journal of the American College of SurgeoNode status	2008	HER2 status NR
53	Sopik	The relatioNode statuship between local recurrence and death in early-stage breast cancer	Breast Cancer Research and Treatment	2016	Less than 80% patients HER2−
57	Wilson	Risk of Recurrence or Contralateral Breast Cancer More than 5 Years After Diagnosis of Hormone Receptor-Positive Early-Stage Breast Cancer	Clinical breast cancer	2016	HER2 status NR
124	Oberguggenberger	Is the toxicity of adjuvant aromatase inhibitor therapy underestimated? Complementary information from patient-reported outcomes (PROs)		2011	HER2 status NR

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ID	Author	Title	Journal	Year	Reason for exclusion
146	Kim	Long-Term Safety of Letrozole and Gonadotropin Stimulation for Fertility Preservation in Women With Breast Cancer	The Journal of clinical endocrinology and metabolism	2016	Less than 80% patients HER2−
149	Harris	Impact of concurrent versus sequential tamoxifen with radiation therapy in early-stage breast cancer patients undergoing breast coNode statuservation treatment	Journal of clinical oncology : official journal of the American Society of Clinical Oncology	2005	HER2 status NR
151	Seber	Antihormonal treatment associated musculoskeletal pain in women with breast cancer in the adjuvant setting	OncoTargets and Therapy	2016	HER2 status NR
152	Kennecke	Late risk of relapse and mortality among postmenopausal women with estrogen respoNode statusive early breast cancer after 5 years of tamoxifen	Annals of Oncology	2007	HER2 status NR
187	Owusu	Effectiveness of adjuvant tamoxifen therapy among older women with early stage breast cancer	Breast Journal	2007	HER2 status NR
190	Schroth	Association between CYP2D6 polymorphisms and outcomes among women with early stage breast cancer treated with tamoxifen	JAMA - Journal of the American Medical Association	2009	HER2 status NR
199	Yeo	Menopausal symptoms in relatioNode statuship to breast cancer-specific quality of life after adjuvant cytotoxic treatment in young breast cancer survivors	Health and quality of life outcomes	2020	Less than 80% patients HER2−
235	Geiger	Recurrences and second primary breast cancers in older women with initial early-stage disease	Cancer	2007	HER2 status NR
248	Diaconu	Early recurrence in favorable stage II breast cancer--which approach is the best?	Revista medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi	2010	HER2 status NR

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ID	Author	Title	Journal	Year	Reason for exclusion
429	Cao	Health-related quality of life of postmenopausal Chinese women with hormone receptor-positive early breast cancer during treatment with adjuvant aromatase inhibitors: A prospective, multicenter, non-interventional study	Health and Quality of Life Outcomes	2016	HER2 status NR
448	Laroche	Quality of life and impact of pain in women treated with aromatase inhibitors for breast cancer. A multicenter cohort study	PLoS ONE	2017	HER2 status NR
506	Visram	Endocrine therapy for male breast cancer: Rates of toxicity and adherence	Current Oncology	2010	HER2 status NR
566	Jung	Assessment of quality of life and safety in postmenopausal breast cancer patients receiving letrozole as an early adjuvant treatment	Journal of Breast Cancer	2018	HER2 status NR
678	Ahn	Sequence of radiotherapy with tamoxifen in coNode statuservatively managed breast cancer does not affect local relapse rates	Journal of clinical oncology : official journal of the American Society of Clinical Oncology	2005	HER2 status NR
696	Monypenny	PatterNode status and predictors of early recurrence in postmenopausal women with estrogen receptor-positive early breast cancer	Breast Cancer Research and Treatment	2009	HER2 status NR
743	Liu	Progesterone receptor is a significant factor associated with clinical outcomes and effect of adjuvant tamoxifen therapy in breast cancer patients	Breast cancer research and treatment	2010	Less than 80% patients HER2-
811	Hu	Application status of tamoxifen in endocrine therapy for early breast cancer	Experimental and Therapeutic Medicine	2015	Less than 80% patients HER2−

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ID	Author	Title	Journal	Year	Reason for exclusion
959	Bowles	Patient-reported discontinuation of endocrine therapy and related adverse effects among women with early-stage breast cancer	Journal of Oncology Practice	2012	HER2 status NR
968	Chow	Male breast cancer in Hong Kong: 15-year experience from a tertiary iNode statustitution	Hong Kong Journal of Radiology	2015	Less than 80% patients HER2–
1112	Johansson	Improved survival for women with stage I breast cancer in south-east Sweden: a comparison between two time periods before and after increased use of adjuvant systemic therapy	Acta oncologica (Stockholm, Sweden)	2009	HER2 status NR
1133	Horváth	Quality of life analysis of postmenopausal, early breast cancer patients treated with anastrozole (RADAR-II)	Magyar onkologia	2012	HER2 status NR
1160	Ibrahim	Adjuvant chemotherapy in 780 patients with early breast cancer: 10-year data from Saudi Arabia	Medical oncology (Northwood, London, England)	2005	HER2 status NR
1250	Geffen	Adjuvant aromatase inhibitor therapy in patients with stage I breast cancer at a regional oncology center in Israel: implementation of a 'switching' policy in postmenopausal patients after initial tamoxifen	Oncology	2013	Less than 80% patients HER2-
1450	Goss	Extending the benefits of adjuvant therapy in early HR+ breast cancer	Breast Cancer Research and Treatment	2008	HER2 status NR
1479	Murata	Clinicopathologic features of hormone-receptorpositive breast cancer patients with late recurrence	Breast Journal	2019	HER2 status NR
1499	Moscetti	Adjuvant aromatase inhibitor therapy in early breast cancer: What factors lead patients to discontinue treatment?	Tumori	2015	HER2 status NR

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ID	Author	Title	Journal	Year	Reason for exclusion
1511	Gu	A comparison of survival outcomes and side effects of toremifene or tamoxifen therapy in premenopausal estrogen and progesterone receptor positive breast cancer patients: a retrospective cohort study	BMC Cancer	2012	Less than 80% patients HER2−
1523	Lee	Low adherence to upfront and extended adjuvant letrozole therapy among early breast cancer patients in a clinical practice setting	Oncology (Switzerland)	2014	HER2 status NR
1627	Garimella	Clinical respoNode statuse to primary letrozole therapy in elderly patients with early breast cancer: Possible role for p53 as a biomarker	International Journal of Surgery	2014	Less than 80% patients HER2-
1653	van de water	Age-specific nonpersistence of endocrine therapy in postmenopausal patients diagnosed with hormone receptor-positive breast cancer: A TEAM study analysis	Oncologist	2012	HER2 status NR
1680	Recchia	LH-RH analogues in the treatment of young women with early breast cancer: Long-term follow-up of a phase II study	International Journal of Oncology	2015	HER2 status NR
1749	Fontaine	Tolerance of adjuvant letrozole outside of clinical trials	Breast (Edinburgh, Scotland)	2008	Less than 80% patients HER2−
1766	Nabieva	Influence of side-effects on early therapy persistence with letrozole in post-menopausal patients with early breast cancer: Results of the prospective EvAluate-TM study	European Journal of Cancer	2018	HER2 status NR
2105	Pineda-Moncusí	Assessment of early therapy discontinuation and health-related quality of life in breast cancer patients treated with aromatase inhibitors: BABLE cohort study	Breast Cancer Research and Treatment	2019	HER2 status NR

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ID	Author	Title	Journal	Year	Reason for exclusion
2119	Wasserman	CoNode statuservative management of breast cancer in the elderly in a developing country	World journal of surgical oncology	2007	HER2 status NR
2345	Siegelmann-Danieli	Potent CYP2D6 Inhibiting drugs do not increase relapse rate in early breast cancer patients treated with adjuvant tamoxifen	Breast Cancer Research and Treatment	2011	HER2 status NR
2594	Martelli	Omission of radiotherapy in elderly patients with early breast cancer: 15-year results of a prospective non-randomised trial	European Journal of Cancer	2015	HER2 status NR
2639	Livi	Survival and breast relapse in 3834 patients with T1-T2 breast cancer after coNode statuserving surgery and adjuvant treatment	Radiotherapy and Oncology	2007	HER2 status NR
2671	Taketani	Early discontinuation of adjuvant hormone therapy is associated with a poor prognosis in Japanese breast cancer patients	Surgery today	2014	Less than 80% patients HER2−
2702	Syed	Long-term (37 years) clinical outcome of older women with early operable primary breast cancer managed in a dedicated clinic	Annals of Oncology	2012	Less than 80% patients HER2−
2710	Labidi	Inflammatory breast cancer in Tunisia in the era of multimodality therapy	Annals of Oncology	2008	HER2 status NR

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Details of included studies

An overview of the characteristics of the trials included in the SLR are provided in Table 90.
Patient numbers across the studies varied substantially and ranged from 70[264] to 3,844[264] patients.

Interventions

In five studies all patients received tamoxifen monotherapy [264-268]. The study by Tang *et al.* (2019; China) assessed the combination of tamoxifen with leuprorelin [269]. In three studies patients received either tamoxifen or aromatase inhibitors (AI) [270-272]. In the study by Yamada *et al.* (2018) treatments prescribed included tamoxifen monotherapy, AI monotherapy and a combination of tamoxifen and AI.[273] Similarly, in the study by Ferreira *et al.* (2018; Portugal) multiple treatments were considered, including tamoxifen monotherapy, sequential AI-tamoxifen, and AI monotherapy. Benefits of concurrent radiotherapy with AI versus sequential RT with AI were investigated in the study by Ishitobi *et al.* (2014; Japan) [274]. Two studies investigated the effects of letrozole; Nabieva *et al.* (2018; Germany) assessed 2.5 mg/day letrozole and Sendur *et al.* (2013; location not reported) investigated 2.5 mg/day letrozole compared to 1 mg/day anastrozole.

Further characteristics of the studies identified in the observational SLR are not included here as they are not considered to be relevant to the submission

Table 90: Characteristics of trials included in the SLR

Author, year	Country	Study design	Inclusion criteria	Exclusion criteria	Treatment
Niméus, 2017	Sweden	Retrospective cohort study	Stage II tumour (T2-3NO, T1-2N12); diagnosed from 1986-1994 in south Sweden Health care region; received 2 years adjuvant tamoxifen irrespective of ER status	NR	Tamoxifen (n=263)
Yan, 2017	China	Retrospective cohort study	ER and/or PR positive; HER2−; normal baseline liver function; negative anti-hepatitis C virus antibodies and hepatitis B surface antigen tests; treated with tamoxifen at least 3 months	A history of liver diseases or evidence of liver disease on physical examination; a history of alcohol abuse or other hepatotoxic drugs; a second primary cancer bilateral primary breast cancer; stage IV at diagnosis.	Tamoxifen (n=646)
Yamada, 2018	Japan	Retrospective cohort study	Newly diagnosed invasive BC; underwent radical resection for early disease at the National Cancer Center Hospital East in Japan between July 1992 and December 2010; HR positive; HER2-negative status	Male sex; Stage IV disease; having a history of other cancers.	Tamoxifen only (n=1033) AI only: (n=637) Tamoxifen and AI (n=284) No hormonal therapy (n=420)
Elzawahry, 2013	Egypt	Prospective cohort study	Postmenopausal females; histologically confirmed BC, HR positive; undergone curative surgery; receiving adjuvant tamoxifen.	Males; premenopausal female; negative for ER and PR; receiving aromatase inhibitors	Tamoxifen (n=70)
Ishitobi, 2014	Japan	Retrospective cohort study	Postmenopausal patients with clinical stage I or II breast cancer; patients treated with breast conserving surgery; tumours were oestrogen and/or progesterone receptor-positive; patients who received postoperative RT for the affected breast at a total median	Prior malignancy other than breast cancer; ductal carcinoma in situ; and patients who received neoadjuvant therapy at the initial treatment.	Concurrent RT and AI (n=158) Sequential RT and AI (n=157)

Author, year	Country	Study design	Inclusion criteria	Exclusion criteria	Treatment

			dose of 50 Gy in 2-Gy fractions or 63.2 Gy as a boost if there was a microscopically involved surgical margin; patients who received adjuvant AI (anastrozole: 1 mg, letrozole: 2.5 mg, or exemestane: 25 mg) daily for 5 years postoperatively.		
Ferreira, 2018	Portugal	Retrospective cohort study	Stage I-III disease; tumours expressing oestrogen/progesterone receptor; diagnosed and treated systemically (i.e., treatments beyond local therapy as surgery or radiotherapy) at Centro Hospitalar de Lisboa Norte, Hospitais CUF Lisboa, Hospital da Luz or Instituto Portugu^es de Oncologia Francisco Gentil de Lisboa between 2006 and 2008; Follow-up details (treatment, new tumours and vital status) were available up to December 2013.	Patients who did not have surgery and patients with other concurrent primary tumours	Tamoxifen monotherapy (n=756) AI sequential TAMAI/AI-TAM (n=322) AI monotherapy (n=205)
Kennecke, 2008	Canada	Retrospective cohort study	Class IV/V cytology, positive pathology, or, in the absence of the former, clinical diagnosis. Women were included if they had breast cancer with T1/T2 pathologic tumour classification, N0 to N3a lymph node status, and negative for metastasis (M0)	Prior or synchronous contralateral breast cancer, non-invasive disease alone, ER negative or ER-unknown status, advanced stage (including clinical or pathologic T3/T4 and clinical N2, N3, or M1 disease), or if they were referred to the BCCA only after recurrence.	Tamoxifen (n=3844)
Meattini, 2013	Italy	Retrospective cohort study	Patients who were chemo naive and affected by early BC treated with 5 years of adjuvant tamoxifen.	Previous solid tumours, age less than 18 years old, BC recurrences or contralateral tumour, tamoxifen discontinuation, adjuvant	Tamoxifen (n=425)

Author, year	Country	Study design	Inclusion criteria	Exclusion criteria	Treatment

				chemotherapy, and a follow-up shorter than 6 months	
Sendur, 2013	NR	Retrospective cohort study	Newly diagnosed breast cancer, treated and followed in clinic from 2001 to 2012 who were HR+ and postmenopausal	Triple negative, hormone receptornegative plus HER2 overexpression, patients with metastatic disease at the time of the diagnosis (N=172) and patients with missing data were excluded from analysis	Anastrozole (n=238) Letrozole (n=331)
Nabieva, 2018	Germany	Prospective cohort study	Postmenopausal HR+ EBC treated with letrozole	Metastatic patients, patients with insufficient documentation of treatment, no follow-up information available, treatment start date > 7 days before inclusion of the study	Letrozole (n=3941)
Tang, 2019	China	Retrospective cohort study	Postmenopausal HR+ EBC patients who underwent either mastectomy, modified radical surgery, or breast conserving surgery followed by radiotherapy	Menopausal patients, Postmenopausal, hormone receptornegative, or who belonged to minorities other than Zhuang, and patients unwilling to receive tamoxifen treatment	Tamoxifen + leuprorelin (n=337)
Wickberg, 2018	Sweden	Retrospective cohort study	Consecutive patients with age ≥65 years, BCS (sector resection and sentinel node biopsy) with clear margins (no tumour cells at inked border for invasive cancer, 2 mm margin for in situ cancer), T1N0M0 non lobular breast cancer tumour, Elston-Ellis histological grade 1 or 2 and oestrogen receptor (ER) positive and/or progesterone receptor (PR) positive tumour.	NR	Tamoxifen (n=534) AI (n=6)
Author, year	**Country**	**Study design**	**Inclusion criteria**	**Exclusion criteria**	**Treatment**

Metzger-Filho, 2019	Australia	Retrospective cohort study	>18, diagnosed and treated at DFCI for stage I–III breast cancer of ILC or IDC-L histology from 1997 to 2007, (IDC-L was defined as tumours in which at least 50% of the tumour is of lobular pattern and 10%–49% is of nonspecialised pattern),	Patients with metastatic disease at presentation, patients who received neoadjuvant therapy, patients who did not have surgery, and patients with other concurrent primary tumours.	Endocrine therapy (n=722) (mixed tamoxifen and/or AI)
Foldi ASCO, 2020	USA	Retrospective cohort study	Women with stage I-III HR+ breast cancer; s/p 3.5 years of adjuvant ET; BCI testing at institution (8/2013-7/2015).	Patients who had < 4 year of follow-up since BCI testing were excluded.	Tamoxifen (n=44) AI (n=79)
Chamalidou, EBCC 2020	NR	Retrospective case series	Hormone receptor positive (HR+); HER2 negative; primary BC; diagnosed from 1 January 1997 through 31 December 2003.	De novo stage IV BC; not possible to judge compliance; or lost from followup	Tamoxifen: 779 AI: 54 Ovarian suppression + ET: 33 other ET: 23

Abbreviations: AI: aromatase inhibitor; BC: breast cancer; BCI: Breast Cancer Index; BCS: breast-conserving surgery; EBC: early breast cancer; ER: oestrogen receptor; ET: endocrine therapy; HER2: human epidermal growth factor receptor 2; IDC-L: invasive ductal and lobular carcinoma; ILC: invasive lobular carcinoma; IV: intravenous; NR: not reported; PR: progesterone receptor;

Excluded Studies

List of studies excluded at the full-text review stage

List of studies excluded at the full-text review stage

Table 91. List of records excluded at the full-text review stage of the clinical SLR of observational studies

ID	Author	Title	Journal	Year	Reason for exclusion
8	Digenis	Carcinoma of the male breast: a review of 41 cases	Southern medical journal	1990	Published prior to 2005
24	Ezzat	Locally advanced breast cancer in Saudi Arabia: High frequency of stage III in a young population	Medical Oncology	1999	Published prior to 2005

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26	Ribeiro	Adjuvant Tamoxifen for male breast cancer (MBC)	British Journal of Cancer	1992	Published prior to 2005
30	Pemmaraju	Retrospective review of male breast cancer patients: Analysis of tamoxifen-related sideeffects	Annals of Oncology	2012	Study design
32	Shah	Breast cancer recurrences in elderly patients after lumpectomy	The American surgeon	2002	Published prior to 2005
33	Low	Long-term follow-up for locally advanced and inflammatory breast cancer patients treated with multimodality therapy	Journal of clinical oncology : official journal of the American Society of Clinical Oncology	2004	Long term followup to clinical trial
34	Shah	Male Breast Cancer: A Clinicopathologic Study of 42 Patients in Eastern India	Indian Journal of Surgical Oncology	2012	Intervention
43	Miller	Durable remission of locally advanced breast cancer with multimodality management	Medical oncology (Northwood, London, England)	1998	Published prior to 2005
44	Hoff	Combined modality treatment of locally advanced breast carcinoma in elderly patients or patients with severe comorbid conditioNode status using tamoxifen as the primary therapy	Cancer	2000	Published prior to 2005
56	Shukla	Male breast cancer: A retrospective study from a regional cancer center in Northern India	Journal of Surgical Oncology	1996	Published prior to 2005
65	Odendaal	Limited surgery and tamoxifen in the treatment of elderly breast cancer patients	World Journal of Surgery	2003	Published prior to 2005

ID	Author	Title	Journal	Year	Reason for exclusion
68	Ibrahim	Breast cancer in the eastern province of Saudi Arabia	Medical Oncology	1998	Published prior to 2005

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69	Dünser	Tumorectomy plus tamoxifen for the treatment of breast cancer in the elderly	European journal of surgical oncology: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology	1993	Published prior to 2005
130	Marshall	Assessment of tamoxifen as adjuvant therapy in stage II breast cancer: A long-term follow-up	Journal of Laboratory and Clinical Medicine	1987	Published prior to 2005
135	Vorgias	Outcome of stage II breast cancer in Greece: A 10-year follow-up study	Medical Science Research	1998	Published prior to 2005
137	Killander	Radiotherapy and tamoxifen after mastectomy in postmenopausal women - 20 year follow-up of the South Sweden Breast Cancer group randomised trial SSBCG II:I	European Journal of Cancer	2007	Long term followup to clinical trial
157	Gnant	Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial	The Lancet. Oncology	2011	Long term followup to clinical trial
166	Sanguinetti	Locally advanced breast cancer in elderly patients: treatment standardised or tailored to individual needs?	Chirurgia italiana	2007	Language
169	Hughes	Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343	Journal of clinical oncology: official journal of the American Society of Clinical Oncology	2013	Long term followup to clinical trial
178	Mayer	CYP2D6-inhibiting medication use and inherited CYP2D6 variation in relation to adverse breast cancer outcomes after tamoxifen therapy	Cancer Causes and Control	2019	Intervention

ID	Author	Title	Journal	Year	Reason for exclusion

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184	Leborgne	Breast coNode statuservation treatment of early stage breast cancer: PatterNode status of failure	International Journal of Radiation Oncology Biology Physics	1995	Published prior to 2005
203	Fowble	The impact of tamoxifen on breast recurrence, cosmesis, complicatioNode status, and survival in estrogen receptor-positive early-stage breast cancer	International Journal of Radiation Oncology Biology Physics	1996	Published prior to 2005
204	Diratzouian	Importance of physical examination in the absence of a mammographic abnormality for the detection of early-stage breast cancer	Clinical breast cancer	2005	Intervention
206	Bender	PatterNode status of change in cognitive function with anastrozole therapy	Cancer	2015	Outcomes
251	Smith	CoNode statuservative treatment of early-stage breast cancer. The Emory experience	American journal of clinical oncology	1994	Published prior to 2005
272	Pierce	CoNode statuservative surgery and radiotherapy for stage I/II breast cancer using lung deNode statusity correction: 10-year and 15-year results	International Journal of Radiation Oncology Biology Physics	2005	Population
275	Cutuli	Breast-coNode statuserving therapy for stage I-II breast cancer in elderly women	International journal of radiation oncology, biology, physics	2004	Published prior to 2005
289	Ogawa.	CoNode statuservation treatment inteNode statusified with tamoxifen and CAF chemotherapy for subareolar breast cancers	Oncology reports	1998	Published prior to 2005
299	Fowble	The influence of young age on outcome in early stage breast cancer	International Journal of Radiation Oncology Biology Physics	1994	Published prior to 2005
300	Gasparini	CoNode statuservative surgery and irradiation (QUART) in the treatment of 243 stage I-II breast cancer patients	Anticancer research	1991	Published prior to 2005

ID	Author	Title	Journal	Year	Reason for exclusion

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301	Borazan	Clinical analysis of the our confirm of breast cancer of 307 cases of the between 1990 and 2000 years	THOD - Turk Hematoloji-Onkoloji Dergisi	2002	Published prior to 2005
318	Fodor	The impact of radiotherapy on the incidence and time of occurrence of local recurrence in earlystage breast cancer after breast coNode statuserving therapy	Neoplasma	2000	Published prior to 2005
394	Ewertz	Obesity and risk of recurrence or death after adjuvant endocrine therapy with letrozole or tamoxifen in the breast international group 1-98 trial	Journal of Clinical Oncology	2012	Long term followup to clinical trial
442	Harrell	Analysis of adjuvant endocrine therapy in practice from electronic health record data of patients with breast cancer	JCO Clinical Cancer Informatics	2017	Population
449	Bliss	Disease-related outcomes with long-term followup: An updated analysis of the intergroup exemestane study	Journal of Clinical Oncology	2012	Long term followup to clinical trial
450	Derks	Adjuvant tamoxifen and exemestane in women with postmenopausal early breast cancer (TEAM): 10-year follow-up of a multicentre, open-label, randomised, phase 3 trial	The Lancet Oncology	2017	Long term followup to clinical trial
461	Goss	Late extended adjuvant treatment with letrozole improves outcome in women with early-stage breast cancer who complete 5 years of tamoxifen	Journal of clinical oncology: official journal of the American Society of Clinical Oncology	2008	Long term followup to clinical trial
480	Buzdar	CompreheNode statusive side-effect profile of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: long-term safety analysis of the ATAC trial	The Lancet. Oncology	2006	Long term followup to clinical trial
494	Jensen	Two years of tamoxifen or no adjuvant systemic therapy for patients with high-risk breast cancer:	Acta Oncologica	2018	Long term followup to clinical trial

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ID	Author	Title	Journal	Year	Reason for exclusion
		long-term follow-up of the Copenhagen breast cancer trial			
508	DeGrendele	Benefit of letrozole in postmenopausal women after five years of tamoxifen therapy for earlystage breast cancer	Clinical Breast Cancer	2003	Published prior to 2005
535	Quintela-Fandino	Nintedanib plus letrozole in early breast cancer: A phase 0/I pharmacodynamic, pharmacokinetic, and safety clinical trial of combined FGFR1 and aromatase inhibition	Breast Cancer Research	2019	Population
541	Cuzick	Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial	The Lancet Oncology	2010	Long term followup to clinical trial
571	Rutqvist	Cardiac and thromboembolic morbidity among postmenopausal women with early-stage breast cancer in a randomized trial of adjuvant tamoxifen	Journal of the National Cancer INode statustitute	1993	Published prior to 2005
582	Gierach	Association of Adjuvant Tamoxifen and Aromatase Inhibitor Therapy With Contralateral Breast Cancer Risk Among US Women With Breast Cancer in a General Community Setting	JAMA oncology	2017	Outcomes
620	Yu	A prospective, multicenter, controlled, observational study to evaluate the efficacy of a patient support program in improving patients' persistence to adjuvant aromatase inhibitor medication for postmenopausal, early stage breast cancer	Breast cancer research and treatment	2012	Outcomes
621	Goss	Breaking the 5-year barrier: Results from the MA.17 extended adjuvant trial in women who have completed adjuvant tamoxifen treatment	European Journal of Cancer, Supplement	2006	Population

ID	Author	Title	Journal	Year	Reason for exclusion

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627	Rutqvist	Long-term follow-up of the randomized Stockholm trial on adjuvant tamoxifen among postmenopausal patients with early stage breast cancer	Acta oncologica (Stockholm, Sweden)	2007	Long term followup to clinical trial
669	Saarto	The prognosis of stage III breast cancer treated with postoperative radiotherapy and adriamycinbased chemotherapy with and without tamoxifen. Eight year follow-up results of a randomized trial	European Journal of Surgical Oncology	1995	Long term followup to clinical trial
680	Sugimachi	Postoperative chemo-endocrine treatment with mitomycin C, tamoxifen, and UFT is effective for patients with premenopausal estrogen receptorpositive stage II breast cancer. Nishinihon Cooperative Study Group of Adjuvant Therapy for Breast Cancer	Breast cancer research and treatment	1999	Published prior to 2005
687	Rydén	Two years of adjuvant tamoxifen in premenopausal patients with breast cancer: a randomised, controlled trial with long-term followup	European journal of cancer (Oxford, England: 1990)	2005	Long term followup to clinical trial
710	Hata	Ten-year results of a randomized trial on adjuvant chemo-endocrine therapy with tamoxifen for stage II breast cancer	Breast cancer (Tokyo, Japan)	2003	Long term followup to clinical trial
774	Rydén	Long-term effects of adjuvant tamoxifen and/or radiotherapy. The South Sweden Breast Cancer Trial	Acta oncologica (Stockholm, Sweden)	1992	Long term followup to clinical trial
848	van Zyl	Tumour excision plus continuous tamoxifen compared with modified radical mastectomy in patients over 70 years of age with operable breast cancer	Journal of surgical oncology	1995	Published prior to 2005

ID	Author	Title	Journal	Year	Reason for exclusion

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856	Chou	Major Adverse Cardiovascular Events after Treatment in Early-stage Breast Cancer Patients Receiving Hormone Therapy	Scientific reports	2020	Outcomes
865	Solin	Ten-year results of the treatment of early-stage breast carcinoma in elderly women using breastcoNode statuserving surgery and definitive breast irradiation	International journal of radiation oncology, biology, physics	1995	Published prior to 2005
870	Öksüzoğlu	Retrospective evaluation of operated stage I breast cancer patients	Turkish Journal of Cancer	2003	Published prior to 2005
873	Ngô	Clinico-pathology and prognosis of endometrial cancer in patients previously treated for breast cancer, with or without tamoxifen: A comparative study in 363 patients	European Journal of Surgical Oncology	2014	Population
883	Fiorica	Adjuvant radiotherapy on older and oldest breast cancer patients after coNode statuservative surgery: a retrospective analysis	Archives of gerontology and geriatrics	2012	Intervention
886	Belfiglio	Twelve-year mortality results of a randomized trial of 2 versus 5 years of adjuvant tamoxifen for postmenopausal early-stage breast carcinoma patients (SITAM 01)	Cancer	2005	Long term followup to clinical trial
917	Xue	The effect of breast coNode statuservation therapy on early-stage breast cancer	Chinese Journal of Clinical Oncology	2008	Language
973	Ogawa	Early experiences of breast-coNode statuservation treatment combined with tamoxifen and CAF chemotherapy for breast cancer of stages I and II	Radiation medicine	1994	Published prior to 2005
978	Hayashi	Adding hormonal therapy to chemotherapy and trastuzumab improves prognosis in patients with hormone receptor-positive and human epidermal	Breast Cancer Research and Treatment	2013	Population

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ID	Author	Title	Journal	Year	Reason for exclusion
		growth factor receptor 2-positive primary breast cancer			
1016	Nio	Comparative effects of the administration period of adjuvant chemotherapy using doxifluridine (5'DFUR) for 1 year versus 3 years after breast cancer surgery by the Shimane Breast Cancer Study Group	Anticancer Research	2006	Study design
1018	Sugimachi	Postoperative chemo-endocrine treatment with mitomycin C, tamoxifen, and UFT is effective for patients with premenopausal estrogen receptorpositive stage II breast cancer	Breast Cancer Research and Treatment	1999	Published prior to 2005
1079	Kokubo	Results of breast-coNode statuserving therapy for early stage breast cancer: Kyoto university experiences	American Journal of Clinical Oncology: Cancer Clinical Trials	2000	Published prior to 2005
1098	Fisher	Long-term follow-up of axillary node-positive breast cancer patients receiving adjuvant tamoxifen alone: PatterNode status of recurrence	International Journal of Radiation Oncology Biology Physics	1998	Published prior to 2005
1116	Stebbing	Breast cancer (non-metastatic)	BMJ clinical evidence	2011	Study design
1167	Hubay	Adjuvant therapy of stage II breast cancer: 48month follow-up of a prospective randomized clinical trial	Breast cancer research and treatment	1981	Long term followup to clinical trial
1175	Freedman	Recursive partitioning identifies patients at high and low risk for ipsilateral tumor recurrence after breast-coNode statuserving surgery and radiation	Journal of Clinical Oncology	2002	Published prior to 2005
1190	Ejlertsen	One year of adjuvant tamoxifen compared with chemotherapy and tamoxifen in postmenopausal patients with stage II breast cancer	European journal of cancer (Oxford, England: 1990)	2013	Long term followup to clinical trial

ID	Author	Title	Journal	Year	Reason for exclusion

1256	Sánchez	Treatment results of early breast cancer. A retrospective review	Revista Medica de Chile	2007	Outcomes
1270	Martelli	Is axillary lymph node dissection necessary in elderly patients with breast carcinoma who have a clinically uninvolved axilia?	Cancer	2003	Published prior to 2005
1273	Hubay	Eight-year follow-up of adjuvant therapy for stage II breast cancer	World journal of surgery	1985	Long term followup to clinical trial
1280	Anelli	Hormone replacement therapy and the risk of breast cancer: assessment of therapy acceptance in a cohort of previously treated breast cancer patients	Revista do Hospital das Clinicas	2003	Published prior to 2005
1327	Martelli	Is axillary lymph node dissection necessary in elderly patients with breast carcinoma who have a clinically uninvolved axilla?	Cancer	2003	Published prior to 2005
1408	Banerjee	Tree-based model for breast cancer prognostication	Journal of clinical oncology: official journal of the American Society of Clinical Oncology	2004	Published prior to 2005
1459	Ruhstaller	Adjuvant letrozole and tamoxifen alone or sequentially for postmenopausal women with hormone receptor-positive breast cancer: Longterm follow-up of the BiG 1-98 trial	Journal of Clinical Oncology	2019	Long term followup to clinical trial
1466	Regan	Assessment of letrozole and tamoxifen alone and in sequence for postmenopausal women with steroid hormone receptor-positive breast cancer: The BIG 1-98 randomised clinical trial at 8·1 years median follow-up	The Lancet Oncology	2011	Long term followup to clinical trial
1492	Bradley	Contemporary systemic therapy for male breast cancer	Clinical Breast Cancer	2014	Study design

ID	Author	Title	Journal	Year	Reason for exclusion

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1535	Servitja	Bone health in a prospective cohort of postmenopausal women receiving aromatase inhibitors for early breast cancer	Breast	2012	Outcomes
1539	Morden	Long-term follow-up of The Intergroup Exemestane Study	Journal of Clinical Oncology	2017	Long term followup to clinical trial
1550	Chagpar	Determinants of early distant metastatic disease in elderly patients with breast cancer	American journal of surgery	2006	Study design
1582	Hadji	Correlation of treatment-emergent adverse events and clinical respoNode statuse to endocrine therapy in early breast cancer: A retrospective analysis of the German cohort of TEAM	Annals of Oncology	2012	Population
1598	Warm	Benefits of early and prolonged fulvestrant treatment in 848 postmenopausal advanced breast cancer patients	Breast Cancer Research and Treatment	2011	Intervention
1613	Henry	AssociatioNode status Between Patient and Anthropometric Characteristics and Aromatase Inhibitor Discontinuation	Clinical Breast Cancer	2017	Outcomes
1647	Crivellari	Letrozole compared with tamoxifen for elderly patients with endocrine-respoNode statusive early breast cancer: The BIG 1-98 trial	Journal of Clinical Oncology	2008	Study design
1658	Li	Clinical outcomes comparison of 10 years versus 5 years of adjuvant endocrine therapy in patients with early breast cancer	BMC cancer	2018	Intervention
1659	Buzdar	'Arimidex' (anastrozole) versus tamoxifen as adjuvant therapy in postmenopausal women with early breast cancer-efficacy overview	Journal of Steroid Biochemistry and Molecular Biology	2003	Published prior to 2005

ID	Author	Title	Journal	Year	Reason for exclusion

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1662	Ruddy	Extended therapy with letrozole and ovarian suppression in premenopausal patients with breast cancer after tamoxifen	Clinical breast cancer	2014	Outcomes
1710	Forbes	The Use of Early Adjuvant Aromatase Inhibitor Therapy: ContributioNode status From the BIG 1-98 Letrozole Trial	Seminars in Oncology	2006	Study design
1729	Balakrishnan	Early operable breast cancer in elderly women treated with an aromatase inhibitor letrozole as sole therapy	British Journal of Cancer	2011	Outcomes
1731	Francis	Adjuvant endocrine therapy for premenopausal women: risk stratification, type and duration	Breast (Edinburgh, Scotland)	2019	Long term followup to clinical trial
1788	Dixon	Role of ErbB2 in selection for adjuvant tamoxifen or aromatase inhibitors	Women's Health	2008	Outcomes
1793		Controlled trial of tamoxifen as single adjuvant agent in management of early breast cancer. Analysis at six years by Nolvadex Adjuvant Trial Organisation	Lancet (London, England)	1985	Long term followup to clinical trial
1795	Rugo	Incidence and time course of everolimus-related adverse events in postmenopausal women with hormone receptor-positive advanced breast cancer: INode statusights from BOLERO-2	Annals of Oncology	2014	Long term followup to clinical trial
1806	Duffy	A lower incidence of gynecologic adverse events and interventioNode status with anastrozole than with tamoxifen in the ATAC trial	American journal of obstetrics and gynecology	2009	Study design
1876	Martelli	Elderly breast cancer patients treated by coNode statuservative surgery alone plus adjuvant tamoxifen: fifteen-year results of a prospective study	Cancer	2008	Study design

ID	Author	Title	Journal	Year	Reason for exclusion

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1877	Voskuil.	Maintenance of physical activity and body weight in relation to subsequent quality of life in postmeno-pausal breast cancer patients	Annals of Oncology	2010	Population
1891	Peng	The adherence and tolerance of adjuvant endocrine therapy in geriatric breast cancer patients	Journal of Cancer Research and Practice	2016	Outcomes
1937	Hackshaw	Long-term benefits of 5 years of tamoxifen: 10year follow-up of a large randomized trial in women at least 50 years of age with early breast cancer	Journal of clinical oncology: official journal of the American Society of Clinical Oncology	2011	Long term followup to clinical trial
1956	Aihara	Anastrozole versus tamoxifen as adjuvant therapy for Japanese postmenopausal patients with hormone-re-spoNode statusive breast cancer: efficacy results of long-term follow-up data from the N-SAS BC 03 trial	Breast cancer research and treatment	2014	Long term followup to clinical trial
1966	Karlsson	Timing of Radiation Therapy and Chemotherapy After Breast-CoNode statuserving Surgery for Node-Positive Breast Cancer: Long-Term Results From International Breast Cancer Study Group Trials VI and VII		2016	Long term followup to clinical trial
1969	Baum	Results of the Cancer Research Campaign Adjuvant Trial for Perioperative Cyclophosphamide and Long-Term Tamoxifen in Early Breast Cancer reported at the tenth year of follow-up. Cancer Research Campaign Breast Cancer Trials Group	Acta oncologica (Stockholm, Sweden)	1992	Long term followup to clinical trial
1986	Thürliman	Is chemotherapy necessary for premenopausal women with lower-risk node-positive, endocrine re-spoNode statusive breast cancer? 10-year update of International Breast Cancer Study Group Trial 11-93	Breast cancer research and treatment	2009	Long term followup to clinical trial

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ID	Author	Title	Journal	Year	Reason for exclusion
2002	Delozier	Tamoxifen adjuvant treatment duration in early breast cancer: Initial results of a randomized study comparing short-term treatment with longterm treatment	Journal of Clinical Oncology	2000	Long term followup to clinical trial
2010	Okunade	Biological profile of oestrogen receptor positive primary breast cancers in the elderly and respoNode statuse to primary endocrine therapy	Critical Reviews in Oncology/Hematology	2009	Population
2020	Chakrabarti	A randomised trial of mastectomy only versus tamoxifen for treating elderly patients with operable primary breast cancer-final results at 20-year follow-up	Critical reviews in oncology/hematology	2011	Long term followup to clinical trial
2029	Crivellari	Adjuvant endocrine therapy compared with no systemic therapy for elderly women with early breast cancer: 21-year results of International Breast Cancer Study Group Trial IV	Journal of clinical oncology: official journal of the American Society of Clinical Oncology	2003	Long term followup to clinical trial
2061	Sauerbrei	Randomized 2 x 2 trial evaluating hormonal treatment and the duration of chemotherapy in node-positive breast cancer patients: an update based on 10 years' follow-up. German Breast Cancer Study Group	Journal of clinical oncology: official journal of the American Society of Clinical Oncology	2000	Long term followup to clinical trial
2091	Baum	Results of the cancer research campaign adjuvant trial for perioperative cyclophosphamide and long-term tamoxifen in early breast cancer reported at the tenth year of follow-up	Acta Oncologica	1992	Long term followup to clinical trial
2112	Mustacchi	Tamoxifen alone versus adjuvant tamoxifen for operable breast cancer of the elderly: Long-term results of the phase III randomized controlled multicenter GRETA trial	Annals of Oncology	2003	Long term followup to clinical trial
2131	Ganz	Quality of life in long-term, disease-free survivors of breast cancer: A follow-up study	Journal of the National Cancer INode statustitute	2002	Published prior to 2005

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ID	Author	Title	Journal	Year	Reason for exclusion
2150	De Placido	Steroid hormone receptor levels and adjuvant tamoxifen in early breast cancer. Ten year results of the Naples (GUN) Study	Breast cancer research and treatment	1990	Published prior to 2005
2164	Monda	Improvement of bone physiology and life quality due to association of risedronate and anastrozole	Frontiers in Pharmacology	2017	Outcomes
2166	Martelli	Axillary dissection versus no axillary dissection in older patients with T1N0 breast cancer: 15-year results of a randomized controlled trial	Annals of surgery	2012	Long term followup to clinical trial
2190	De Valois	Using traditional acupuncture for breast cancerrelated hot flashes and night sweats	Journal of Alternative and Complementary Medicine	2010	Intervention
2196	Gordon	Thirty-year follow-up of chemo/hormonal therapy in node-positive breast cancer	Breast Cancer Research and Treatment	2007	Long term followup to clinical trial
2212	Boccardo	Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: long term results of the Italian Tamoxifen Anastrozole trial	European journal of cancer (Oxford, England: 1990)	2013	Long term followup to clinical trial
2224	Roché	Complete hormonal blockade versus epirubicinbased chemotherapy in premenopausal, one to three node-positive, and hormone-receptor positive, early breast cancer patients: 7-year follow-up results of French Adjuvant Study Group 06 randomised trial	Annals of Oncology	2006	Long term followup to clinical trial
2266	Ursulovic	The influence of PTEN protein expression on disease outcome in premenopausal hormone receptor-positive early breast cancer patients treated with adjuvant ovarian ablation: a longterm follow-up	Journal of B.U.ON.	2018	Study design

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ID	Author	Title	Journal	Year	Reason for exclusion
2306	Vishwanathan	Role of electron beam treatment in postoperative management of carcinoma of the breast	Indian journal of cancer	1998	Published prior to 2005
2366	Mauriac	Neoadjuvant tamoxifen for hormone-seNode statusitive non-metastatic breast carcinomas in early postmenopausal women	Annals of Oncology	2002	Published prior to 2005
2371	Brennan	Patient-reported quality of life, unmet needs and care coordination outcomes: Moving toward targeted breast cancer survivorship care planning	Asia-Pacific Journal of Clinical Oncology	2016	Population
2373	Touboul	Local recurrences and distant metastases after breast-coNode statuserving surgery and radiation therapy for early breast cancer	International Journal of Radiation Oncology Biology Physics	1999	Published prior to 2005
2431	Gómez	Prognostic effect of hormone receptor status in early HER2 positive breast cancer patients	Hematology/ Oncology and Stem Cell Therapy	2010	Population
2511	Fallowfield	Quality of life in the elderly woman with breast cancer treated with tamoxifen and surgery or tamoxifen alone	Journal of Women's Health	1994	Published prior to 2005
2574	Hughes	Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer	Women's Oncology Review	2004	Published prior to 2005
2575	Bradburn	Time trends in breast cancer survival: Experience in a single centre, 1975-89	British Journal of Cancer	1998	Published prior to 2005
2586	Harris	Epidermal growth factor receptors in breast cancer: association with early relapse and death, poor respoNode statuse to hormones and interactioNode status with neu	Journal of steroid biochemistry	1989	Published prior to 2005
ID	**Author**	**Title**	**Journal**	**Year**	**Reason for exclusion**

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2601	Ferreira	Impact of tamoxifen (TAM) serum concentration on side effects among premenopausal patients (pts) with early breast cancer (BC) in the prospective multicenter CANTO cohort	Annals of oncology: official journal of the European Society for Medical Oncology	2019	Intervention
2719	Ferri	In situ breast cancer. A challenge for breast physiciaNode status	Salus	2005	Study design
2721	Latini	Quadrant excision and radiotherapy in the treatment of early cancer of the breast	La Radiologia medica	1986	Published prior to 2005
2813	Lu	Effects of anastrozole on lipid metabolism in Chinese postmenopausal women with breast cancer	Chinese Journal of Oncology	2011	Language

Table 92. List of records excluded at the full-text review stage in the SLR of observational studies due to the protocol deviation

ID	Author	Title	Journal	Year	Reason for exclusion
15	Ulcickas Yood	Mortality Impact of Less-than-Standard Therapy in Older Breast Cancer Patients	Journal of the American College of SurgeoNode status	2008	HER2 status NR
53	Sopik	The relatioNode statuship between local recurrence and death in early-stage breast cancer	Breast Cancer Research and Treatment	2016	Less than 80% patients HER2−
57	Wilson	Risk of Recurrence or Contralateral Breast Cancer More than 5 Years After Diagnosis of Hormone Receptor-Positive Early-Stage Breast Cancer	Clinical breast cancer	2016	HER2 status NR
124	Oberguggenberger	Is the toxicity of adjuvant aromatase inhibitor therapy underestimated? Complementary information from patient-reported outcomes (PROs)		2011	HER2 status NR

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ID	Author	Title	Journal	Year	Reason for exclusion
146	Kim	Long-Term Safety of Letrozole and Gonadotropin Stimulation for Fertility Preservation in Women With Breast Cancer	The Journal of clinical endocrinology and metabolism	2016	Less than 80% patients HER2−
149	Harris	Impact of concurrent versus sequential tamoxifen with radiation therapy in early-stage breast cancer patients undergoing breast coNode statuservation treatment	Journal of clinical oncology : official journal of the American Society of Clinical Oncology	2005	HER2 status NR
151	Seber	Antihormonal treatment associated musculoskeletal pain in women with breast cancer in the adjuvant setting	OncoTargets and Therapy	2016	HER2 status NR
152	Kennecke	Late risk of relapse and mortality among postmenopausal women with estrogen respoNode statusive early breast cancer after 5 years of tamoxifen	Annals of Oncology	2007	HER2 status NR
187	Owusu	Effectiveness of adjuvant tamoxifen therapy among older women with early stage breast cancer	Breast Journal	2007	HER2 status NR
190	Schroth	Association between CYP2D6 polymorphisms and outcomes among women with early stage breast cancer treated with tamoxifen	JAMA - Journal of the American Medical Association	2009	HER2 status NR
199	Yeo	Menopausal symptoms in relatioNode statuship to breast cancer-specific quality of life after adjuvant cytotoxic treatment in young breast cancer survivors	Health and quality of life outcomes	2020	Less than 80% patients HER2−
235	Geiger	Recurrences and second primary breast cancers in older women with initial early-stage disease	Cancer	2007	HER2 status NR
248	Diaconu	Early recurrence in favorable stage II breast cancer--which approach is the best?	Revista medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi	2010	HER2 status NR

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ID	Author	Title	Journal	Year	Reason for exclusion
429	Cao	Health-related quality of life of postmenopausal Chinese women with hormone receptor-positive early breast cancer during treatment with adjuvant aromatase inhibitors: A prospective, multicenter, non-interventional study	Health and Quality of Life Outcomes	2016	HER2 status NR
448	Laroche	Quality of life and impact of pain in women treated with aromatase inhibitors for breast cancer. A multicenter cohort study	PLoS ONE	2017	HER2 status NR
506	Visram	Endocrine therapy for male breast cancer: Rates of toxicity and adherence	Current Oncology	2010	HER2 status NR
566	Jung	Assessment of quality of life and safety in postmenopausal breast cancer patients receiving letrozole as an early adjuvant treatment	Journal of Breast Cancer	2018	HER2 status NR
678	Ahn	Sequence of radiotherapy with tamoxifen in coNode statuservatively managed breast cancer does not affect local relapse rates	Journal of clinical oncology : official journal of the American Society of Clinical Oncology	2005	HER2 status NR
696	Monypenny	PatterNode status and predictors of early recurrence in postmenopausal women with estrogen receptor-positive early breast cancer	Breast Cancer Research and Treatment	2009	HER2 status NR
743	Liu	Progesterone receptor is a significant factor associated with clinical outcomes and effect of adjuvant tamoxifen therapy in breast cancer patients	Breast cancer research and treatment	2010	Less than 80% patients HER2-
811	Hu	Application status of tamoxifen in endocrine therapy for early breast cancer	Experimental and Therapeutic Medicine	2015	Less than 80% patients HER2–

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ID	Author	Title	Journal	Year	Reason for exclusion
959	Bowles	Patient-reported discontinuation of endocrine therapy and related adverse effects among women with early-stage breast cancer	Journal of Oncology Practice	2012	HER2 status NR
968	Chow	Male breast cancer in Hong Kong: 15-year experience from a tertiary iNode statustitution	Hong Kong Journal of Radiology	2015	Less than 80% patients HER2–
1112	Johansson	Improved survival for women with stage I breast cancer in south-east Sweden: a comparison between two time periods before and after increased use of adjuvant systemic therapy	Acta oncologica (Stockholm, Sweden)	2009	HER2 status NR
1133	Horváth	Quality of life analysis of postmenopausal, early breast cancer patients treated with anastrozole (RADAR-II)	Magyar onkologia	2012	HER2 status NR
1160	Ibrahim	Adjuvant chemotherapy in 780 patients with early breast cancer: 10-year data from Saudi Arabia	Medical oncology (Northwood, London, England)	2005	HER2 status NR
1250	Geffen	Adjuvant aromatase inhibitor therapy in patients with stage I breast cancer at a regional oncology center in Israel: implementation of a 'switching' policy in postmenopausal patients after initial tamoxifen	Oncology	2013	Less than 80% patients HER2-
1450	Goss	Extending the benefits of adjuvant therapy in early HR+ breast cancer	Breast Cancer Research and Treatment	2008	HER2 status NR
1479	Murata	Clinicopathologic features of hormone-receptorpositive breast cancer patients with late recurrence	Breast Journal	2019	HER2 status NR
1499	Moscetti	Adjuvant aromatase inhibitor therapy in early breast cancer: What factors lead patients to discontinue treatment?	Tumori	2015	HER2 status NR

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ID	Author	Title	Journal	Year	Reason for exclusion
1511	Gu	A comparison of survival outcomes and side effects of toremifene or tamoxifen therapy in premenopausal estrogen and progesterone receptor positive breast cancer patients: a retrospective cohort study	BMC Cancer	2012	Less than 80% patients HER2−
1523	Lee	Low adherence to upfront and extended adjuvant letrozole therapy among early breast cancer patients in a clinical practice setting	Oncology (Switzerland)	2014	HER2 status NR
1627	Garimella	Clinical respoNode statuse to primary letrozole therapy in elderly patients with early breast cancer: Possible role for p53 as a biomarker	International Journal of Surgery	2014	Less than 80% patients HER2-
1653	van de water	Age-specific nonpersistence of endocrine therapy in postmenopausal patients diagnosed with hormone receptor-positive breast cancer: A TEAM study analysis	Oncologist	2012	HER2 status NR
1680	Recchia	LH-RH analogues in the treatment of young women with early breast cancer: Long-term follow-up of a phase II study	International Journal of Oncology	2015	HER2 status NR
1749	Fontaine	Tolerance of adjuvant letrozole outside of clinical trials	Breast (Edinburgh, Scotland)	2008	Less than 80% patients HER2−
1766	Nabieva	Influence of side-effects on early therapy persistence with letrozole in post-menopausal patients with early breast cancer: Results of the prospective EvAluate-TM study	European Journal of Cancer	2018	HER2 status NR
2105	Pineda-Moncusí	Assessment of early therapy discontinuation and health-related quality of life in breast cancer patients treated with aromatase inhibitors: BABLE cohort study	Breast Cancer Research and Treatment	2019	HER2 status NR

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ID	Author	Title	Journal	Year	Reason for exclusion
2119	Wasserman	CoNode statuservative management of breast cancer in the elderly in a developing country	World journal of surgical oncology	2007	HER2 status NR
2345	Siegelmann-Danieli	Potent CYP2D6 Inhibiting drugs do not increase relapse rate in early breast cancer patients treated with adjuvant tamoxifen	Breast Cancer Research and Treatment	2011	HER2 status NR
2594	Martelli	Omission of radiotherapy in elderly patients with early breast cancer: 15-year results of a prospective non-randomised trial	European Journal of Cancer	2015	HER2 status NR
2639	Livi	Survival and breast relapse in 3834 patients with T1-T2 breast cancer after coNode statuserving surgery and adjuvant treatment	Radiotherapy and Oncology	2007	HER2 status NR
2671	Taketani	Early discontinuation of adjuvant hormone therapy is associated with a poor prognosis in Japanese breast cancer patients	Surgery today	2014	Less than 80% patients HER2−
2702	Syed	Long-term (37 years) clinical outcome of older women with early operable primary breast cancer managed in a dedicated clinic	Annals of Oncology	2012	Less than 80% patients HER2−
2710	Labidi	Inflammatory breast cancer in Tunisia in the era of multimodality therapy	Annals of Oncology	2008	HER2 status NR

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Quality assessment for each trial

A quality assessment of the observational studies was conducted using the checklist CRD [259]. As noted, a quality assessment was not performed for conference proceedings, as there would be insufficient methodological data to assess the study quality. The quality assessment is presented in Table 93.

Table 93 Quality assessment of included observational studies

Author, year	What is the study design of this study?	Was the study a prospective study or a retrospectiv e study?	In case of a casecontrol study, were the groups similar at the outset of the study in terms of prognosti c factors?	Was the intervention used appropriately ?	Were the outcome measures in the study reliable?	Were the outcome measures in the study valid?	Was the statistical analysis conducted appropriatel y in the study?	Was the quality of reporting appropriate in the study?	Can the study results be generalise d to routine practice?
Niméus, 2017	Cohort study	Retrospective	NA	Not clear	Yes - standard endpoints in EBC	Yes - standard endpoints in EBC	Yes	Yes	Not clear - no info on treatment regimen
Yan, 2017	Cohort study	Retrospective	NA	Not clear	Not Clear	Not Clear	Yes	Yes	Not clear
Yamada, 2018	Cohort study	Retrospective	NA	Not clear	Yes - standard endpoints in EBC	Yes - standard endpoints in EBC	Yes	Yes	Not clear - no info on treatment regimen
Elzawahry, 2013	Cohort study	Prospective	NA	Not clear	Yes - standard endpoints in EBC	Yes - standard endpoints in EBC	Yes	Yes	Not clear - no info on treatment regimen
Ishitobi, 2014	Retrospectiv e analysis	Retrospective	NA	Not clear	Yes - standard endpoints in EBC	Yes	Yes	Yes	Yes

Ferreira, 2018	Cohort study	Retrospective	NA	Not clear	Yes - standard end-points in EBC	Yes	Yes	No - poor quality reporting with no clear distinction on patient numbers for treatment groups	Not clear - no info on treatment regimen
Kennecke, 2008	Cohort study	Retrospective	NA	Not clear	Yes - standard end-points in EBC	Yes	Yes	Yes	Not clear - no info on treatment regimen
Meattini, 2013	Cohort study	Retrospective	NA	Not clear	Yes - standard end-points in EBC	Not clear	Not clear	No - % for baseline characteristic s are very unclear in terms of what population they correspond to	Not clear - no info on treatment regimen
Sendur, 2013	Cohort study	Retrospective	NA	Yes	Yes - standard end-points in EBC	Yes	Yes	Yes	Yes
Nabieva, 2018	Cohort study	Prospective	NA	Yes	Yes - standard end-points in EBC	Not clear	Yes	Yes	Yes
Tang, 2019	Cohort study	Retrospective	NA	Yes	Yes - standard end-points in EBC	Yes	Yes	Yes	Yes

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Wickberg, 2018	Cohort study	Retrospective	NA	Not clear	Yes - standard end-points in EBC	Not clear	Yes	Yes	Not clear - no info on treatment regimen
Metzger-Filho, 2019	Cohort study	Retrospective	NA	Not clear	Yes - standard end-points in EBC	Yes	Yes	Yes	Not clear - no info on treatment regimen
Foldi ASCO, 2020	NA conference abstract								
Chamalidou , EBCC 2020	NA conference abstract								

Abbreviations: EBC: early breast cancer; NA: not applicable.

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Appendix B Main characteristics of the included study

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.*
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 and exclusion criteria	***Inclusion***
	• *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%*
	
	Exclusion
	• *Metastatic disease, node-negative breast cancer, inflammatory breast cancer*
	• *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*

Trial name: monarchE	NCT number: NCT03155997
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	*State the method of analysis, i.e. intention-to-treat or per-protocol.* *E.g.: All efficacy analyses were intention-to-treat analyses. We used the Kaplan–Meier method to estimate rates of progression-free survival and overall survival, and a stratified log-rank test for treatment comparisons.*
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*

Appendix C Baseline characteristics of patients in the study used for the analyses of efficacy and safety

Table 94 Patient demographics, Cohort 1 population

Baseline characteristics	Arm A Abemaciclib + ET N=2,555	Arm B ET Alone N=2,565	Total N=5,120
Sex, n (%)	n=2,555	n=2,565	5,120
Female, n (%)	2,535 (99.2)	2,553 (99.5)	5,088 (99.4)
Male, n (%)	20 (0.8)	12 (0.5)	32 (0.6)
Age, years	2555	2565	5120
Mean (SD)	52.2 (11.3)	52.2 (11.2)	52.2 (11.3)
Median (min, max)	51.0 (23, 89)	51.0 (22, 86)	51.0 (22, 89)
Race, n (%)	2522	2527	5049
American Indian or Alaska Native	55 (2.2)	55 (2.2)	110 (2.2)
Asian	622 (24.7)	605 (23.9)	1227 (24.3)
Black or African American	43 (1.7)	46 (1.8)	89 (1.8)
Native Hawaiian or Other			
Pacific Islander	3 (0.1)	4 (0.2)	7 (0.1)
White	1781 (70.6)	1794 (71.0)	3575 (70.8)
Multiple	18 (0.7)	23 (0.9)	41 (0.8)
Missing	33	38	71
Region, n (%)	2555	2565	5120
North America/Europe	1323 (51.8)	1330 (51.9)	2653 (51.8)
Asia	522 (20.4)	524 (20.4)	1046 (20.4)
Other	710 (27.8)	711 (27.7)	1421 (27.8)
Menopausal status, n (%)	2551	2565	5116
Premenopausal	1115 (43.7)	1105 (43.1)	2220 (43.4)
Postmenopausal	1436 (56.3)	1460 (56.9)	2896 (56.6)

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Baseline ECOG PS, n (%)	2554	2562	5116
0	2182 (85.4)	2147 (83.8)	4329 (84.6)
1	371 (14.5)	413 (16.1)	784 (15.3)
2	0	2 (0.1)	2 (<0.1)
3	1 (<0.1)	0	1 (<0.1)
Missing	1	3	4
Weight (kg)	2532	2529	5061
Mean (SD)	71.3 (16.3)	71.7 (16.2)	71.5 (16.3)
BMI (kg/m2)	2485	2507	4992
Mean (SD)	27.2 (5.9)	27.4 (5.8)	27.3 (5.9)
Median (min, max)	26.1 (15.6, 63.3)	26.4 (13.9, 65.3)	26.3 (13.9, 65.3)
Initial Pathological Diagnosis			
Invasive Ductal Breast Carcinoma	1720 (67.3)	1762 (68.7)	3482 (68.0)
Breast Cancer	421 (16.5)	420 (16.4)	841 (16.4)
Invasive Lobular Breast Carcinoma	355 (13.9)	335 (13.1)	690 (13.5)
Other	57 (2.3)	45 (1.8)	102 (2.1)
Missing	1 (0)	0	1 (0)
Primary Tumor Size by Radiology Prior to any Systemic Treatment, n	2449	2461	4910
<20 mm	695 (27.2)	673 (26.2)	1368 (26.7)
≥20 mm but <50 mm	1263 (49.4)	1325 (51.7)	2588 (50.5)
≥50 mm	491 (19.2)	463 (18.1)	954 (18.6)
Missing	106 (4.1)	104 (4.1)	210 (4.1)
Primary Tumor Size by Pathology After Definitive Surgery, n	2509	2540	5049
<20 mm	676 (26.5)	656 (25.6)	1332 (26.0)
≥20 mm but <50 mm	1322 (48.3)	1278 (49.8)	2511 (49.0)
≥50 mm	600 (23.5)	606 (23.6)	1206 (23.6)

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Missing	46 (1.8)	25 (1.0)	71 (1.4)
Axillary lymph node evaluation			
Positive	2,548 (99.7)	2,559 (99.8)	5,107 (99.7)
Negative	6 0.2)	6 (0.2)	12 (0.2)
Missing	1 (0.0)	0	1 (0.0)
Number of Positive Lymph nodes			
0	6 (0.2)	7 (0.2)	12 (0.2)
1-3	873 (34.2)	888 (34.6)	1761 (34.4)
4-9	1104 (43.2)	1119 (43.6)	2223 (43.4)
≥10	571 (22.3)	552 (21.5)	1123 (21.9)
Missing	1 (0.0)	0	1 (0.0)
Histopathological Diagnosis Grade			
G1 – Favourable	209 (7.4)	216 (7.6)	425 (7.5)
G2 – Moderately Favourable	1377 (49.0)	1395 (49.3)	2772 (49.2)
G3 – Unfavourable	1086 (38.7)	1064 (37.6)	2150 (38.1)
GX – Cannot be Accessed	126 (4.5)	141 (5.0)	267 (4.7)
Missing	10 (0.4)	13 (0.5)	23 (0.4)
Disease Stage at Initial Diagnosis			
Stage IA	2 (0.1)	1 (0)	3 (0.1)
Stage IIA	324 (11.5)	353 (12.5)	677 (12.0)
Stage IIB	392 (14.0)	387 (13.7)	779 (13.8)
Stage IIIA	1029 (36.6)	1026 (36.3)	2055 (36.5)
Stage IIIB	99 (3.5)	88 (3.1)	187 (3.3)
Stage IIIC	950 (33.8)	963 (34.0)	1913 (33.9)
Missing	12 (0.4)	11 (0.4)	23 (0.4)
Estrogen Receptor (ER) Status			
Positive	2786 (99.2)	2810 (99.3)	5596 (99.3)

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Negative	16 (0.6)	17 (0.6)	33 (0.6)
Unknown	3 (0.1)	2 (0.1)	5 (0.1)
Missing	3 (0.1)	0 (0)	3 (0.1)
Progesterone Receptor (PgR) status			
Positive	2426 (86.4)	2456 (86.8)	4882 (86.6)
Negative	298 (10.6)	295 (10.4)	593 (10.5)
Unknown	23 (0.8)	21 (0.7)	44 (0.8)
Missing	61 (2.2)	57 (2.0)	118 (2.1)
Central Laboratory Ki-67 results from Untreated Tumour (%)			
<20%	953 (33.9)	974 (34.4)	1927 (34.2)
≥20%	1262 (44.9)	1236 (43.7)	2498 (44.3)
Missing	464 (16.5)	478 (16.9)	942 (16.7)
Not Applicable a	72 (2.6)	72 (2.5)	144 (2.6)
Not Evaluable b	57 (2.0)	69 (2.4)	126 (2.2)
Aromatase inhibitors	1,929 (69.1)	2,030 (72.7)	1,892 (67.6)
Anastrozole	610 (21.9)	666 (23.9)	617 (22.0)
Exemestane	225 (8.1)	293 (10.5)	228 (8.1)
Letrozole	1,094 (39.2)	1,181 (42.3)	1,047 (37.4)
Anti-oestrogens	863 (30.9)	896 (32.1)	909 (32.5)
Tamoxifen	857 (30.7)	888 (31.8)	898 (32.1)
Toremifene	6 (0.2)	10 (0.4)	11 (0.4)
GnRH Analogues	NA	615 (22.0)	NA
Goserelin	NA	429 (15.4)	NA
Leuprorelin	NA	239 (8.6)	NA
Triptorelin	NA	28 (1.0)	NA
Prior anticancer therapy			

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Surgical procedure	2,804 (99.9)	2,829 (100.0)	5,633 (99.9)
Radiotherapy	2680 (95.4)	2700 (95.4)	5380 (95.4)
Systemic therapy	2,741 (97.6)	2,770 (97.9)	5,511 (97.8)
Surgical procedure: intent			
Curative intent	2,804 (99.9)	2,829 (100.0)	5,633 (99.9)
Radiotherapy: reason			
Neoadjuvant	71 (2.5)	82 (2.9)	153 (2.7)
Adjuvant	2,620 (93.3)	2,628 (92.9)	5,248 (93.1)
Systemic therapy: reason and type			
Neoadjuvant	1,056 (37.6)	1,070 (37.8)	2,126 (37.7)
Chemotherapy	1,026 (36.5)	1,029 (36.4)	2,055 (36.5)
ET[a]	86 (3.1)	97 (3.4)	183 (3.2)
Other[b]	8 (0.3)	6 (0.2)	14 (0.2)
Target[c]	6 (0.2)	5 (0.2)	11 (0.2)
Adjuvant	2,447 (87.1)	2,471 (87.3)	4,918 (87.2)
Chemotherapy	1,734 (61.8)	1,731 (61.2)	3,465 (61.5)
ET[a]	1,764 (62.8)	1,795 (63.4)	3,559 (63.1)
Other[b]	2 (0.1)	2 (0.1)	4 (0.1)
Target[c]	2 (0.1)	1 (0.0)	3 (0.1)
Term to be coded	1 (0.0)	0	1 (0.0)

Footnotes: [a] ET included patients treated with endocrine treatment and/or GnRH analogues; [b] "Other" is any other type of prior therapy not listed above; [c] "Target" is any prior therapy that is target therapy based on compound-wise documentation on systemic drugs.
Abbreviations: ET: endocrine therapy; GnRH: gonadotropin-releasing hormone; N: number of patients; n: number of patients within category.
Source: Lilly Data on File. Clinical Study Report: monarchE [14]. Data cut-off: 16 March 2020

Comparability of the study populations with Danish patients eligible for treatment

Patients in the studies were mainly recruited in North America and Europe, and the inclusion criteria and patient characteristics were consistent with the criteria for treatments in Denmark. Therefore, no important differences exist between the study populations and the Danish patient population.

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Appendix D Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures

Outcome measure	Definition	Validity	Clinical relevance
IDFS, as defined by the STEEP system	Measured from the date of randomization to the date of first occurrence of any of the following: • Ipsilateral invasive breast tumour recurrence • Regional invasive breast cancer recurrence • Distant recurrence • Death attributable to any cause • Contralateral invasive breast cancer and second primary non-breast invasive cancer	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 [275].	To evaluate the efficacy of abemaciclib plus adjuvant ET versus adjuvant ET alone in patients with HR+, HER2- eBC. IDFS is considered to be a particularly relevant endpoint for comparing treatment regimens for the management of early breast cancer, where maintaining a disease-free state, i.e., a functional cure, is the primary goal of treatment.

Outcome measure	Definition	Validity	Clinical relevance
DRFS	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.	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 [276].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 [276].	DRFS is also clinically relevant, as avoidance of metastatic recurrence is of particular importance, given the poor prognosis associated with advanced breast cancer, which is considered incurable.
OS	Time from the date of randomization to the date of death from any cause	The gold standard in cancer trials (FDA)(EMA) [277].The gold standard in cancer trials (FDA)(EMA) [277].	The OS is a validated measure used in clinical trials to assess the time patients remain alive on treatment. OS is included as an important longer-term outcome, confirming the benefit of treatment [275].
HRQoL	Multi-dimensional concept that includes domains related to physical, mental, emotional, and social functioning.	HRQoL is a widely used and validated outcome measure [278]	HRQoL was used to measure if the treatment with abemaciclib plus ET was associated with an improved quality of life compared to ET alone. Furthermore, HRQoL was relevant to measure in order to evaluate the health status to inform decision modeling for health economic evaluation between abemaciclib plus adjuvant ET versus adjuvant ET alone
IDFS in patients with high Ki67	Invasive disease-free survival, as defined by the STEEP system, in patients in the ITT population of monarchE with	The STEEP criteria were developed in 2007, specifically for the adjuvant breast cancer setting by breast cancer leaders to provide consistency and standardization in	IDFS is considered to be a particularly relevant endpoint for comparing treatment regimens for the management of early breast cancer, where maintaining a disease-free state, i.e., a functional cure, is the primary goal of treatment.

Outcome measure	Definition	Validity	Clinical relevance
	pre-treatment Ki-67 index ≥20% tested by a central laboratory	evaluating the risk-benefit ratio of novel treatments compared to standard of care [275].	

Results per study

Table A3a 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 (24 months)	Abemaciclib + ET	2,555	92.6% (91.4, 93.5)	3.0	1.3, 4.6	0.0003	HR: 0.680	0.572, 0.808	0.00001	*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.*	monarchE April 2021 DCO
	ET alone	2,565	89.6% (88.3, 90.8)								
DRFS (24 months)	Abemaciclib + ET	2,555	94.1 (93.0, 95.0)	2.8	1.4, 4.3	0.00002	HR: 0.669	0.554, 0.809	0.00003	*A log-rank test stratified by randomization factors was used. A stratified Cox proportional*	monarchE April 2021 DCO

Table A3a Results of monarchE (NCT03155997)											
	ET alone	2,565	91.2 (90.0, 92.3)							*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.*	
OS (24 months)	Abemaciclib + ET	2,555	97.5 (96.8, 98.0)	0.3	–0.6, 1.2	0.5024	HR: 1.044	0.778, 1.401	0.7742	*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.*	monarchE April 2021 DCO
	ET alone	2,565	97.2 (96.4, 97.8)								
TEAE	Abemaciclib + ET	2,791	2,745 (98.4%)	10.4	NR	NR	NR	NR	NR	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].	monarchE April 2021 DCO
	ET alone	2,800	2,486 (88.8%)								
SAE	Abemaciclib + ET	2,791	424 (15.2%)	6.4	NR	NR	NR	NR	NR	During the study, all AEs were recorded and graded at every visit according to the National Cancer Institute Common Terminology Criteria for Adverse	monarchE April 2021 DCO
	ET alone	2,800	247 (8.8%)								

Table A3a Results of monarchE (NCT03155997)	
	Events (CTCAE) version 4.0 [27].

Appendix E Safety data for intervention and comparator(s)

Adverse event	Abemaciclib + ET (n=2,791)	ET alone (n=2,800)
Median treatment duration, months	23.7 months	23.8 months
Any grade TEAEs, n (%)	2,745 (98.4)	2,486 (88.8)
SAEs, n (%)	424 (15.2)	247 (8.8)
Any grade TEAEs leading to discontinuation, n (%)	181 (6.5)	30 (1.1)
Total discontinuations, n (%)	515 (18.5)	30 (1.1)
Deaths occurring to TEAEs, n%	15 (0.5)	10 (0.4)
Grade ≥3 TEAEs, n (%)	95 (3.4)	89 (3.2)
All CTCAE Grade TEAEs (in Any Treatment Arm),		
Diarrhoea, n (%)	385 (13.8)	151 (5.4)
Neutropenia, n (%)	391 (14.0)	222 (7.9)
Fatigue, n (%)	373 (13.4)	52 (1.9)
Leukopenia, n (%)	329 (11.8)	68 (2.4)
Abdominal pain, n (%)	347 (12.4)	250 (8.9)

Adverse event	Abemaciclib + ET (n=2,791)	ET alone (n=2,800)
Nausea, n (%)	336 (12.0)	211 (7.5)
Anaemia, n (%)	333 (11.9)	168 (6.0)
Arthralgia, n (%)	301 (10.8)	238 (8.5)
Headache, n (%)	343 (12.3)	157 (5.6)
Vomiting, n (%)	304 (10.9)	188 (6.7)
Hot flush, n (%)	312 (11.2)	127 (4.5)
Lymphopenia, n (%)	330 (11.8)	137 (4.9)
Stomatitisa, n (%)	313 (11.2)	75 (2.7)
Cough, n (%)	286 (10.2)	325 (11.6)
Thrombocytopenia, n (%)	283 (10.1)	347 (12.4)
Decreased appetite, n (%)	279 (0.1)	127 (4.5)
Lymphoedema, n (%)	385 (13.8)	151 (5.4)
Urinary tract infection, n (%)	391 (14.0)	222 (7.9)
Constipation, n (%)	373 (13.4)	52 (1.9)
URTI, n (%)	329 (11.8)	68 (2.4)
ALT increased, n (%)	347 (12.4)	250 (8.9)
Dizziness, n (%)	336 (12.0)	211 (7.5)
Rash, n (%)	333 (11.9)	168 (6.0)
AST increased, n (%)	301 (10.8)	238 (8.5)
Alopecia, n (%)	343 (12.3)	157 (5.6)
Pain in extremity, n (%)	304 (10.9)	188 (6.7)

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Appendix F Comparative analysis of efficacy and safety

Table A4 Results of the MonarchE study comparing abemaciclib + ET to ET for patients with eBC

Outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
		Difference	CI	*P* value	Difference	CI	*P* value		
IDFS	MonarchE	3.0	1.3, 4.6	0.0003	HR: 0.680	0.572, 0.808	0.00001	*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	2.8	0.3, 2.2	0.0124	HR: 0.669	0.554, 0.809	0.00003	*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	0.3	–0.6, 1.2	0.5024	HR: 1.044	0.778, 1.401	0.7742	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*

Table A4 Results of the MonarchE study comparing abemaciclib + ET to ET for patients with eBC									
TEAE	MonarchE	10.4	NR	NR	NR	NR	NR	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	6.4	NR	NR	NR	NR	NR	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*

Figure 36. Summary of compliance rate and reasons for noncompliance for EQ-5D-5L by Visit. Cohort 1 Population - Safety population / Baseline to visit 9

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.

Table 95. EQ-5D-5L responses by visit in monarchE: mobility (July 2020 DCO) Safety population

EQ-5D dimension	Response level	Abemaciclib +ET (N=2791)	ET alone (N=2800)
Baseline	I have no problems walking	1981 (73.32)	1933 (72.23)
	I have slight problems walking	494 (18.28)	524 (19.58)
	I have moderate problems walking	188 (6.96)	178(6.65)
	I have severe problems walking	30 (1.11)	37(1.38)
	I am unable to walk	9(0.33)	4(0.15)
	Missing value	0 (0.00)	0 (0.00)
Visit 6	I have no problems walking	1774(71.45)	1811 (72.30)
	I have slight problems walking	506 (20.38)	486 (19.40)
	I have moderate problems walking	167 (6.73)	171 (6.83)
	I have severe problems walking	33 (1.33)	33 (1.32)
	I am unable to walk	3 (0.12)	4 (0.16)
	Missing value	0 (0.00)	0 (0.00)
Visit 9	I have no problems walking	1711(71.23)	1810 (73.40)
	I have slight problems walking	471 (19.61)	432 (17.52)
	I have moderate problems walking	181 (7.54)	179 (7.26)
	I have severe problems walking	32 (1.33)	37 (1.50)
	I am unable to walk	7 (0.29)	8 (0.32)
	Missing value	0 (0.00)	0 (0.00)
Visit 15	I have no problems walking	1624 (71.35)	1660 (71.77)
	I have slight problems walking	453 (19.90)	438 (18.94)
	I have moderate problems walking	154 (6.77)	177 (7.65)
	I have severe problems walking	41 (1.80)	34 (1.47)
	I am unable to walk	4 (0.18)	4 (0.17)
	Missing value	0 (0.00)	0 (0.00)
Visti 21	I have no problems walking	1013 (68.96)	1068 (72.85)
	I have slight problems walking	306 (20.83)	244 (16.64)
	I have moderate problems walking	115 (7.83)	119 (8.12)
	I have severe problems walking	31 (2.11)	34 (2.32)
	I am unable to walk	4 (0.27)	1 (0.07)
	Missing value	0 (0.00)	0 (0.00)
Visit 27	I have no problems walking	423 (65.48)	474 (71.28)

	I have slight problems walking	144 (22.29)	117 (17.59)
	I have moderate problems walking	67 (10.37)	54 (8.12)
	I have severe problems walking	10 (1.55)	19 (2.86)
	I am unable to walk	2 (0.31)	1 (0.15)
	Missing value	0 (0.00)	0 (0.00)
Follow-up	I have no problems walking	469 (66.71)	455 (69.15)
	I have slight problems walking	131 (18.63)	134 (20.36)
	I have moderate problems walking	92 (13.09)	51 (7.75)
	I have severe problems walking	9 (1.28)	16 (2.43)
	I am unable to walk	2 (0.28)	2 (0.30)
	Missing value	0 (0.00)	0 (0.00)
Additional follow-up 1	I have no problems walking	128 (66.67)	121 (69.94)
	I have slight problems walking	44 (22.92)	35 (20.23)
	I have moderate problems walking	12 (6.25)	9 (5.20)
	I have severe problems walking	8 (4.17)	8 (4.62)
	I am unable to walk	0 (0.00)	0 (0.00)
	Missing value	0 (0.00)	0 (0.00)
Additional follow-up 2	I have no problems walking	32 (66.67)	15 (60.00)
	I have slight problems walking	7 (14.58)	5 (20.00)
	I have moderate problems walking	6 (12.50)	3 (12.00)
	I have severe problems walking	3 (6.25)	2 (8.00)
	I am unable to walk	0 (0.00)	0 (0.00)
	Missing value	0 (0.00)	0 (0.00)

Table 96. EQ-5D-5L responses by visit in monarchE: self-care (July 2020 DCO) Safety population

EQ-5D dimension	Response level	Abemaciclib +ET (N=2791)	ET alone (N=2800)
Baseline	I have no problems washing or dressing myself	2465 (91.36)	2393 (89.36)
	I have slight problems washing or dressing myself	177 (6.56)	219 (8.18)
	I have moderate problems washing or dressing myself	42 (1.56)	52 (1.94)
	I have severe problems washing or dressing myself	6 (0.22)	8 (0.30)
	I have no problems washing or dressing myself	2465 (91.36)	2393 (89.36)

	I have slight problems washing or dressing myself	177 (6.56)	219 (8.18)
Visit 6	I have no problems washing or dressing myself	2232 (89.93)	2214 (88.42)
	I have slight problems washing or dressing myself	203 (8.18)	224 (8.95)
	I have moderate problems washing or dressing myself	39 (1.57)	56 (2.24)
	I have severe problems washing or dressing myself	3 (0.12)	5 (0.20)
	I am unable to wash or dress myself	5 (0.20)	5 (0.20)
	Missing value	0 (0.00)	0 (0.00)
Visit 9	I have no problems washing or dressing myself	2150 (89.55)	2183 (88.60)
	I have slight problems washing or dressing myself	182 (7.58)	212 (8.60)
	I have moderate problems washing or dressing myself	45 (1.87)	57 (2.31)
	I have severe problems washing or dressing myself	10 (0.42)	7 (0.28)
	I am unable to wash or dress myself	14 (0.58)	5 (0.20)
	Missing value	0 (0.00)	0 (0.00)
Visit 15	I have no problems washing or dressing myself	2029 (89.15)	2059 (89.06)
	I have slight problems washing or dressing myself	182 (8.00)	195 (8.43)
	I have moderate problems washing or dressing myself	50 (2.20)	40 (1.73)
	I have severe problems washing or dressing myself	7 (0.31)	12 (0.52)
	I am unable to wash or dress myself	8 (0.35)	6 (0.26)
	Missing value	0 (0.00)	0 (0.00)
Visti 21	I have no problems washing or dressing myself	1295 (88.16)	1331 (90.85)
	I have slight problems washing or dressing myself	138 (9.39)	100 (6.83)
	I have moderate problems washing or dressing myself	23 (1.57)	28 (1.91)
	I have severe problems washing or dressing myself	7 (0.48)	6 (0.41)
	I am unable to wash or dress myself	6 (0.41)	0 (0.00)
	Missing value	0 (0.00)	0 (0.00)

Visit 27	I have no problems washing or dressing myself	560 (86.69)	590 (88.59)
	I have slight problems washing or dressing myself	63 (9.75)	53 (7.96)
	I have moderate problems washing or dressing myself	20 (3.10)	14 (2.10)
	I have severe problems washing or dressing myself	2 (0.31)	6 (0.90)
	I am unable to wash or dress myself	1 (0.15)	3 (0.45)
	Missing value	0 (0.00)	0 (0.00)
Follow-up	I have no problems washing or dressing myself	604 (85.80)	565 (86.00)
	I have slight problems washing or dressing myself	67 (9.52)	68 (10.35)
	I have moderate problems washing or dressing myself	28 (3.98)	21 (3.20)
	I have severe problems washing or dressing myself	1 (0.14)	2 (0.30)
	I am unable to wash or dress myself	4 (0.57)	1 (0.15)
	Missing value	0 (0.00)	0 (0.00)
Additional follow-up 1	I have no problems washing or dressing myself	163 (84.46)	153 (88.44)
	I have slight problems washing or dressing myself	17 (8.81)	12 (6.94)
	I have moderate problems washing or dressing myself	9 (4.66)	7 (4.05)
	I have severe problems washing or dressing myself	3 (1.55)	1 (0.58)
	I am unable to wash or dress myself	1 (0.52)	0 (0.00)
	Missing value	0 (0.00)	0 (0.00)
Additional follow-up 2	I have no problems washing or dressing myself	41 (85.42)	22 (88.00)
	I have slight problems washing or dressing myself	3 (6.25)	1 (4.00)
	I have moderate problems washing or dressing myself	2 (4.17)	1 (4.00)
	I have severe problems washing or dressing myself	2 (4.17)	1 (4.00)
	I am unable to wash or dress myself	0 (0.00)	0 (0.00)
	Missing value	0 (0.00)	0 (0.00)

Table 97. EQ-5D-5L responses by visit in monarchE: usual activities (July 2020 DCO) Safety population

EQ-5D dimension	Response level	Abemaciclib +ET (N=2791)	ET alone (N=2800)
Baseline	I have no problems doing my usual activities	1690 (62.64)	1608 (60.04)
	I have slight problems doing my usual activities	699 (25.91)	740 (27.63)
	I have moderate problems doing my usual activities	254 (9.41)	277 (10.34)
	I have severe problems doing my usual activities	36 (1.33)	37 (1.38)
	I am unable to do my usual activities	19 (0.70)	16 (0.60)
	Missing value	0 (0.00)	0 (0.00)
Visit 6	I have no problems doing my usual activities	1454 (58.65)	1568 (62.59)
	I have slight problems doing my usual activities	715 (28.84)	687 (27.43)
	I have moderate problems doing my usual activities	253 (10.21)	207 (8.26)
	I have severe problems doing my usual activities	41 (1.65)	33 (1.32)
	I am unable to do my usual activities	16 (0.65)	10 (0.40)
	Missing value	0 (0.00)	0 (0.00)
Visit 9	I have no problems doing my usual activities	1443 (60.13)	1597 (64.81)
	I have slight problems doing my usual activities	687 (28.63)	617 (25.04)
	I have moderate problems doing my usual activities	221 (9.21)	209 (8.48)
	I have severe problems doing my usual activities	32 (1.33)	28 (1.14)
	I am unable to do my usual activities	17 (0.71)	13 (0.53)
	Missing value	0 (0.00)	0 (0.00)
Visit 15	I have no problems doing my usual activities	1439 (63.34)	1534 (66.38)
	I have slight problems doing my usual activities	580 (25.53)	554 (23.97)
	I have moderate problems doing my usual activities	207 (9.11)	181 (7.83)
	I have severe problems doing my usual activities	34 (1.50)	30 (1.30)

	I am unable to do my usual activities	12 (0.53)	12 (0.52)
	Missing value	0 (0.00)	0 (0.00)
Visti 21	I have no problems doing my usual activities	931 (63.46)	996 (68.08)
	I have slight problems doing my usual activities	387 (26.38)	337 (23.03)
	I have moderate problems doing my usual activities	123 (8.38)	99 (6.77)
	I have severe problems doing my usual activities	15 (1.02)	24 (1.64)
	I am unable to do my usual activities	11 (0.75)	7 (0.48)
	Missing value	0 (0.00)	0 (0.00)
Visit 27	I have no problems doing my usual activities	396 (61.40)	454 (68.27)
	I have slight problems doing my usual activities	176 (27.29)	145 (21.80)
	I have moderate problems doing my usual activities	59 (9.15)	53 (7.97)
	I have severe problems doing my usual activities	11 (1.71)	10 (1.50)
	I am unable to do my usual activities	3 (0.47)	3 (0.45)
	Missing value	0 (0.00)	0 (0.00)
Follow-up	I have no problems doing my usual activities	439 (62.45)	425 (64.59)
	I have slight problems doing my usual activities	181 (25.75)	146 (22.19)
	I have moderate problems doing my usual activities	69 (9.82)	63 (9.57)
	I have severe problems doing my usual activities	10 (1.42)	18 (2.74)
	I am unable to do my usual activities	4 (0.57)	6 (0.91)
	Missing value	0 (0.00)	0 (0.00)
Additional follow-up 1	I have no problems doing my usual activities	113 (59.16)	108 (62.43)
	I have slight problems doing my usual activities	46 (24.08)	38 (21.97)
	I have moderate problems doing my usual activities	25 (13.09)	20 (11.56)
	I have severe problems doing my usual activities	6 (3.14)	6 (3.47)
	I am unable to do my usual activities	1 (0.52)	1 (0.58)

	Missing value	0 (0.00)	0 (0.00)
Additional follow-up 2	I have no problems doing my usual activities	28(58.33)	15(60.00)
	I have no problems doing my usual activities	28(58.33)	15(60.00)
	I have no problems doing my usual activities	28(58.33)	15(60.00)
	I have no problems doing my usual activities	28(58.33)	15(60.00)
	I have no problems doing my usual activities	28(58.33)	15(60.00)
	I have no problems doing my usual activities	28(58.33)	15(60.00)

Table 98. EQ-5D-5L responses by visit in monarchE: pain or discomfort (July DCO) Safety population

EQ-5D dimension	Response level	Abemaciclib +ET (N=2791)	ET alone (N=2800)
Baseline	I have no pain or discomfort	926 (34.30)	886 (33.08)
	I have slight pain or discomfort	1297 (48.04)	1283 (47.91)
	I have moderate pain or discomfort	398 (14.74)	418 (15.61)
	I have severe pain or discomfort	63 (2.33)	68 (2.54)
	I have extreme pain or discomfort	16 (0.59)	23 (0.86)
	Missing value	0 (0.00)	0 (0.00)
Visit 6	I have no pain or discomfort	787 (31.73)	738 (29.46)
	I have slight pain or discomfort	1196 (48.23)	1193 (47.62)
	I have moderate pain or discomfort	410 (16.53)	465 (18.56)
	I have severe pain or discomfort	70 (2.82)	95 (3.79)
	I have extreme pain or discomfort	17 (0.69)	14 (0.56)
	Missing value	0 (0.00)	0 (0.00)
Visit 9	I have no pain or discomfort	763 (31.73)	731 (29.67)
	I have slight pain or discomfort	1161 (48.27)	1191 (48.34)
	I have moderate pain or discomfort	387 (16.09)	446 (18.10)
	I have severe pain or discomfort	73 (3.04)	70 (2.84)
	I have extreme pain or discomfort	21 (0.87)	26 (1.06)
	Missing value	0 (0.00)	0 (0.00)
Visit 15	I have no pain or discomfort	746 (32.75)	682 (29.46)
	I have slight pain or discomfort	1077 (47.28)	1095 (47.30)

	I have moderate pain or discomfort	362 (15.89)	426 (18.40)
	I have severe pain or discomfort	76 (3.34)	86 (3.71)
	I have extreme pain or discomfort	17 (0.75)	26 (1.12)
	Missing value	0 (0.00)	0 (0.00)
Visti 21	I have no pain or discomfort	459 (31.22)	447 (30.53)
	I have slight pain or discomfort	706 (48.03)	696 (47.54)
	I have moderate pain or discomfort	247 (16.80)	256 (17.49)
	I have severe pain or discomfort	49 (3.33)	46 (3.14)
	I have no pain or discomfort	459 (31.22)	447 (30.53)
	I have slight pain or discomfort	706 (48.03)	696 (47.54)
Visit 27	I have no pain or discomfort	195 (30.19)	207 (31.13)
	I have slight pain or discomfort	303 (46.90)	302 (45.41)
	I have moderate pain or discomfort	118 (18.27)	124 (18.65)
	I have severe pain or discomfort	24 (3.72)	24 (3.61)
	I have extreme pain or discomfort	6 (0.93)	8 (1.20)
	Missing value	0 (0.00)	0 (0.00)
Follow-up	I have no pain or discomfort	209 (29.73)	196 (29.83)
	I have slight pain or discomfort	2278	23152278
	I have moderate pain or discomfort	746 (32.75)	682 (746
	I have severe pain or discomfort	1077 (47.28)	1095 (1077
	I have extreme pain or discomfort	362 (15.89)	426 (362
	Missing value	76 (3.34)	86 (76
Additional follow-up 1	I have no pain or discomfort	47 (24.48)	53 (30.64)
	I have slight pain or discomfort	93 (48.44)	78 (45.09)
	I have moderate pain or discomfort	38 (19.79)	34 (19.65)
	I have severe pain or discomfort	13 (6.77)	6 (3.47)
	I have extreme pain or discomfort	1 (0.52)	2 (1.16)
	Missing value	0 (0.00)	0 (0.00)
Additional follow-up 2	I have no pain or discomfort	15 (31.25)	8 (32.00)
	I have slight pain or discomfort	19 (39.58)	9 (36.00)
	I have moderate pain or discomfort	12 (25.00)	4 (16.00)
	I have severe pain or discomfort	1 (2.08)	2 (8.00)

	I have extreme pain or discomfort	1 (2.08)	2 (8.00)
	Missing value	0 (0.00)	0 (0.00)

Table 99. EQ-5D-5L responses by visit in monarchE: anxiety or depression (July 2020 DCO) Safety population

EQ-5D dimension	Response level	Abemaciclib +ET (N=2791)	ET alone (N=2800)
Baseline	I am not anxious or depressed	1358 (50.30)	1406 (52.50)
	I am slightly anxious or depressed	975 (36.11)	931 (34.76)
	I am moderately anxious or depressed	290 (10.74)	271 (10.12)
	I am severely anxious or depressed	46 (1.70)	50 (1.87)
	I am extremely anxious or depressed	31 (1.15)	20 (0.75)
	Missing value	0 (0.00)	0 (0.00)
Visit 6	I am not anxious or depressed	1194 (48.22)	1314 (52.41)
	I am slightly anxious or depressed	936 (37.80)	859 (34.26)
	I am moderately anxious or depressed	274 (11.07)	258 (10.29)
	I am not anxious or depressed	1194 (48.22)	1314 (52.41)
	I am slightly anxious or depressed	936 (37.80)	859 (34.26)
	I am moderately anxious or depressed	274 (11.07)	258 (10.29)
Visit 9	I am not anxious or depressed	1198 (50.04)	1277 (51.85)
	I am slightly anxious or depressed	849 (35.46)	857 (34.79)
	I am moderately anxious or depressed	292 (12.20)	255 (10.35)
	I am severely anxious or depressed	34 (1.42)	51 (2.07)
	I am extremely anxious or depressed	21 (0.88)	23 (0.93)
	Missing value	0 (0.00)	0 (0.00)
Visit 15	I am not anxious or depressed	1116 (49.21)	1192 (51.78)
	I am slightly anxious or depressed	833 (36.73)	806 (35.01)
	I am moderately anxious or depressed	257 (11.33)	240 (10.43)
	I am severely anxious or depressed	43 (1.90)	50 (2.17)

	I am extremely anxious or depressed	19 (0.84)	14 (0.61)
	Missing value	0 (0.00)	0 (0.00)
Visti 21	I am not anxious or depressed	722 (49.22)	767 (52.50)
	I am slightly anxious or depressed	528 (35.99)	504 (34.50)
	I am moderately anxious or depressed	174 (11.86)	145 (9.92)
	I am severely anxious or depressed	26 (1.77)	29 (1.98)
	I am extremely anxious or depressed	17 (1.16)	16 (1.10)
	Missing value	0 (0.00)	0 (0.00)
Visit 27	I am not anxious or depressed	308 (47.68)	326 (48.88)
	I am slightly anxious or depressed	249 (38.54)	230 (34.48)
	I am moderately anxious or depressed	72 (11.15)	82 (12.29)
	I am severely anxious or depressed	13 (2.01)	20 (3.00)
	I am extremely anxious or depressed	4 (0.62)	9 (1.35)
	Missing value	0 (0.00)	0 (0.00)
Follow-up	I am not anxious or depressed	328 (46.79)	295 (44.90)
	I am slightly anxious or depressed	264 (37.66)	238 (36.23)
	I am moderately anxious or depressed	77 (10.98)	92 (14.00)
	I am severely anxious or depressed	23 (3.28)	23 (3.50)
	I am extremely anxious or depressed	9 (1.28)	9 (1.37)
	Missing value	0 (0.00)	0 (0.00)
Additional follow-up 1	I am not anxious or depressed	94 (48.70)	78 (45.35)
	I am slightly anxious or depressed	63 (32.64)	65 (37.79)
	I am moderately anxious or depressed	25 (12.95)	16 (9.30)
	I am severely anxious or depressed	10 (5.18)	9 (5.23)
	I am extremely anxious or depressed	1 (0.52)	4 (2.33)
	Missing value	0 (0.00)	0 (0.00)
	I am not anxious or depressed	22 (46.81)	8 (32.00)

Additional follow-up 2	I am slightly anxious or depressed	16 (34.04)	10 (40.00)
	I am moderately anxious or depressed	9 (19.15)	3 (12.00)
	I am severely anxious or depressed	0 (0.00)	4 (16.00)
	I am extremely anxious or depressed	0 (0.00)	0 (0.00)
	Missing value	0 (0.00)	0 (0.00)

Appendix G – Extrapolation

Please consult section 8.3 for information on extrapolations of time-to-event data.

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Appendix H – Literature search for HRQoL data (derived from the targeted literature review to inform cost-utility model inputs)

Identification of studies

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.

PICOs eligibility criteria

The eligibility criteria for the economic TLR are summarised in Table 100.

Table 100: 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

Search strategy

Data sources

HTA database, HTA websites

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 105) were assessed for inclusion for the targeted review (Table 100).

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.

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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 101.

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)[279], which superseded the neratinib (TA612, 2019)[280] and adjuvant pertuzumab in combination with trastuzumab and chemotherapy (TA569, 2019)[281] submissions. One submission was identified which targeted patients who were eligible for early operable breast cancer with INTRABEAM radiotherapy (TA501, 2018)[282].

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Table 101: NICE HTA submissions identified by the economic TLR

TA , year	Country	Study design	Technology manufacturer	Patient population	Intervention	Comparator
TA632, 2020[279]	UK	HTA submission (STA)	Roche Products	HER2-positive EBC	Trastuzumab emtansine	Standard adjuvant therapy including trastuzumab
TA612, 2019[280]	UK	HTA submission (STA)	Puma Biotechnology, Inc.	Early HR+, HER2+ BC	Neratinib	Standard treatment with no further HER2-directed therapy
TA569, 2019[281]	UK	HTA submission (STA)	Roche Products	HER2+ EBC	Adjuvant pertuzumab in combination with trastuzumab & chemotherapy	Standard adjuvant therapy without pertuzumab
TA501, 2018[282]	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 102

Table 102: Summary of health state utility values and AE disutility values used in the identified HTA submissions

Author, year	Health state specific utility	Adverse event specific disutility
TA632, 2020[279]	Non-metastatic recurrence: 0.775 Remission: 0.788 1L MBC: 0.765 2L MBC: 0.508	NA
TA612, 2019[280]	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[281]	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[282]	Recurrence free in 1st year: 0.7728 Recurrence free after first year: 0.8112 Local recurrence: 0.8112 Disease-free after local recurrence: 0.8112 Any other recurrence: 0.685	NA

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.

Appendix I Mapping of HRQoL data

This appendix is not relevant in this submission.

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Appendix J Probabilistic sensitivity analyses

The model the assumptions for the probabilistic analysis are found in the sheet "Inputs" of the economic model.

Table 103. PSA parameters

Name	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)
Female (%)	0.99	0.2	Beta	-0.8457946	-0.0051054
Age	52.2	0.157170731	Normal	52.2	0.157170731
Bodyweight	71.48	0.228037892	Normal	71.48	0.228037892
Height	161.71	0.10	Normal	161.71	0.103704617
Proportion Letrozole	50%	0.10	Dirichlet	0.5	0.5
Proportion Anastrozole	10%	0.02	Dirichlet	0.1	0.9
Proportion Tamoxifen	30%	0.06	Dirichlet	0.3	0.7
Proportion Exemestane	10%	0.02	Dirichlet	0.1	0.9
Prop. moving to NMRABE	29%	10%	Beta	5.721218566	13.92163184
Prop. moving to NMRET	26%	10%	Beta	4.752154595	13.50307342
Prob.of moving from REM to MR	0.76%	0.15%	Beta	24.80318	3251.706728
IDFS: Oncologist visit, first	0.306639288	0.061327858	Gamma	25	0.012265572
IDFS: Mammogram	0.051106548	0.01022131	Gamma	25	0.002044262
IDFS: Oncologist visit, first	0.15	0.03	Gamma	25	0.006132786
IDFS: Mammogram	0.05	0.01	Gamma	25	0.002044262
NMR: Oncologist visit, follow-up	0.153319644	0.030663929	Gamma	25	0.006132786
NMR: Mammogram	0.051106548	0.01022131	Gamma	25	0.002044262
NMR: Local: Major breast procedures (if patients originally had mastectomy)	0.75	0.15	Gamma	25	0.03
NMR: Local/Regional: Delayed breast reconstruction	0.1	0.02	Gamma	25	0.004
NMR: Local/Regional: Mastectomy with reconstruction (if patients	0.3	0.06	Gamma	25	0.012

Name	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)
orginally had breast conserving surgery)					
NMR: Contralateral: Major breast procedures (if patients originally had mastectomy)	0.95	0.19	Gamma	25	0.038
NMR: Contralateral: Delayed breast reconstruction	0.1	0.02	Gamma	25	0.004
NMR: Contralateral: Mastectomy with reconstruction (if patients originally had breast conserving surgery)	0.3	0.06	Gamma	25	0.012
NMR: Radiotherapy	1	0.2	Gamma	25	0.04
NMR: Chemotherapy (cycle 1)	0.05	0.01	Gamma	25	0.002
NMR: Chemotherapy (cycle 2-6)	0.05	0.01	Gamma	25	0.002
NMR: Chemotherapy (subsequent cycles)	0.05	0.01	Gamma	25	0.002
NMR: Complete blood count	0.05	0.01	Gamma	25	0.002
NMR: Multidisciplinairy team meeting	1	0.2	Gamma	25	0.04
REM: Oncologist visit, follow-up	0.31	0.06	Gamma	25	0.012265572
REM: Mammogram	0.05	0.01	Gamma	25	0.002044262
MR-ETR: CT scan PFS	0.50	0.10	Gamma	25	0.02
MR-ETR: MRI scan PFS	0.50	0.10	Gamma	25	0.02
MR-ETR: PET scan PFS	0.50	0.10	Gamma	25	0.02
MR-ETR: X-Ray PFS	0.50	0.10	Gamma	25	0.02
MR-ETR: Electrocardiogram PFS	0.50	0.10	Gamma	25	0.02
MR-ETR: Complete blood count PFS	1.00	0.20	Gamma	25	0.04
MR-ETR: Serum Chemistry PFS	1.00	0.20	Gamma	25	0.04
MR-ETR: Biochemistry PFS	0.23	0.05	Gamma	25	0.009199179
MR-ETR: Clinical nurse (specialist) PFS	0.23	0.05	Gamma	25	0.009199179

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Name	Expected value	Standard error	Probability distribution		Parameter distribution (Name: Value)	Parameter distribution (Name: Value)
MR-ETR: Oncologist visit, follow-up PFS	1.00	0.20	Gamma	25	0.04	
MR-ETR: Hospitalisation PFS	0.01	0.00	Gamma	25	0.000447704	
MR-ETR: CT scan PPS	0.50	0.10	Gamma	25	0.02	
MR-ETR: MRI scan PPS	0.50	0.10	Gamma	25	0.02	
MR-ETR: PET scan PPS	0.50	0.10	Gamma	25	0.02	
MR-ETR: Electrocardiogram PPS	0.50	0.10	Gamma	25	0.02	
MR-ETR: Complete blood count PPS	1.00	0.20	Gamma	25	0.04	
MR-ETR: Serum Chemistry PPS	1.00	0.20	Gamma	25	0.04	
MR-ETR: Oncologist visit, follow-up PPS	1.00	0.20	Gamma	25	0.04	
MR-ETR: Clinical nurse (specialist) PPS	1.00	0.20	Gamma	25	0.04	
MR-ETR: Hospitalisation PPS	0.01	0.00	Gamma	25	0.000269424	
MR-ETS: CT scan PFS1	0.42	0.08	Gamma	25	0.0168	
MR-ETS: Electrocardio gram PFS1	0.33	0.07	Gamma	25	0.0132	
MR-ETS: Complete blood count PFS1	1.00	0.20	Gamma	25	0.04	
MR-ETS: Serum chemistry PFS1	1.00	0.20	Gamma	25	0.04	
MR-ETS: Oncologist visit, follow-up PFS1	1.00	0.20	Gamma	25	0.04	
MR-ETS: X-Ray PFS1	0.42	0.08	Gamma	25	0.0168	
MR-ETS: Hospitalisation PFS1	0.01	0.00	Gamma	25	0.000340185	
MR-ETS: CT scan PFS2	0.42	0.08	Gamma	25	0.0168	
MR-ETS: Electrocardio gram PFS2	0.33	0.07	Gamma	25	0.0132	
MR-ETS: Complete blood count PFS2	1.00	0.20	Gamma	25	0.04	
MR-ETS: Serum chemistry PFS2	1.00	0.20	Gamma	25	0.04	
MR-ETS: Oncologist visit, follow-up PFS2	1.00	0.20	Gamma	25	0.04	

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Name	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)
MR-ETS: X-Ray PFS2	0.42	0.08	Gamma	25	0.0168
MR-ETS: Hospitalisation PFS2	0.01	0.00	Gamma	25	0.000343464
MR-ETS: CT scan PPS	0.42	0.08	Gamma	25	0.0168
MR-ETS: Electrocardio gram PPS	0.33	0.07	Gamma	25	0.0132
MR-ETS: Complete blood count PPS	1.00	0.20	Gamma	25	0.04
MR-ETS: Serum chemistry PPS	1.00	0.20	Gamma	25	0.04
MR-ETS: Oncologist visit, follow-up PPS	1.00	0.20	Gamma	25	0.04
MR-ETS: District nurse (home visit) PPS	0.23	0.05	Gamma	25	0.0092
MR-ETS: Hospitalisation PPS	0.03	0.01	Gamma	25	0.001153654
Utility: IDFS	0.852	0.002902327	Beta	12759.57203	2218.443819
Utility: Abemaciclib + ET IDFS	0.776	0.003165904	Beta	13457.08686	3884.51992
Utility: Endocrine therapy IDFS	0.777	0.003156029	Beta	13515.74185	3879.035305
Utility: NMR	0.812915002	0.162583	Beta	3.864209955	0.889312795
Age-related utility by age group: 18 - 29 year	0.871	0.1742	Beta	2.354	0.348640643
Age-related utility by age group: 30 - 39 year	0.848	0.1696	Beta	2.952	0.529132075
Age-related utility by age group: 40 - 49 year	0.834	0.1668	Beta	3.316	0.660019185
Age-related utility by age group: 50 - 69 year	0.818	0.1636	Beta	3.732	0.830347188
Age-related utility by age group: 70 - 79 year	0.813	0.1626	Beta	3.862	0.888307503
Age-related utility by age group: 80 + year	0.721	0.1442	Beta	6.254	2.4200638
ABE Grade I/II AE incidence: Diarrhea	0.757	0.151	Beta	5.318	1.707099075
ET Grade I/II AE incidence: Diarrhea	0.085	0.017	Beta	22.79	245.3276471

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Name	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)
ABE Grade III/IV AE incidence: Neutropenia	0.196	0.0392	Beta	19.904	81.64702041
ABE Grade III/IV AE incidence: Leukopenia	0.114	0.0228	Beta	22.036	171.2622456
ABE Grade III/IV AE incidence: Diarrhea	0.078	0.0156	Beta	22.972	271.5408205
ABE Grade III/IV AE incidence: Lymphopenia	0.054	0.0108	Beta	23.596	413.366963
ABE Grade III/IV AE incidence: Fatigue	0.029	0.0058	Beta	24.246	811.8229655
ABE Grade III/IV AE incidence: Aspartate aminotransferase increase	0.019	0.0038	Beta	24.506	1265.283474
ABE Grade III/IV AE incidence: Alanine aminotransferase increase	0.028	0.0056	Beta	24.272	842.5851429
ABE Grade III/IV AE incidence: Thrombocytopenia	0.013	0.0026	Beta	24.662	1872.414923
ABE Grade III/IV AE incidence: Anaemia	0.02	0.004	Beta	24.48	1199.52
ABE Grade III/IV AE incidence: Abdominal pain	0.014	0.0028	Beta	24.636	1735.078286
ABE Grade III/IV AE incidence: Venous thromboembolic event	0.012	0.0024	Beta	24.688	2032.645333
ET Grade III/IV AE incidence: Neutropenia	0.008	0.0016	Beta	24.792	3074.208
ET Grade III/IV AE incidence: Leukopenia	0.004	0.0008	Beta	24.896	6199.104
ET Grade III/IV AE incidence: Diarrhea	0.002	0.0004	Beta	24.948	12449.052
ET Grade III/IV AE incidence: Lymphopenia	0.005	0.001	Beta	24.87	4949.13
ET Grade III/IV AE incidence: Fatigue	0.001	0.0002	Beta	24.974	24949.026
ET Grade III/IV AE incidence: Aspartate aminotransferase increase	0.005	0.001	Beta	24.87	4949.13
ET Grade III/IV AE incidence: Alanine aminotransferase increase	0.007	0.0014	Beta	24.818	3520.610571

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Name	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)
ET Grade III/IV AE incidence: Thrombocytopenia	0.001	0.0002	Beta	24.974	24949.026
ET Grade III/IV AE incidence: Anaemia	0.004	0.0008	Beta	24.896	6199.104
ET Grade III/IV AE incidence: Abdominal pain	0.003	0.0006	Beta	24.922	8282.411333
ET Grade III/IV AE incidence: Venous thromboembolic event	0.001	0.0002	Beta	24.974	24949.026
Intensity: Abemaciclib + ET: Abemaciclib	100%	0.2	Beta	-1	0
Intensity: Abemaciclib + ET: Letrozole	100%	0.2	Beta	-1	0
Intensity: Abemaciclib + ET: Anastrozole	100%	0.2	Beta	-1	0
Intensity: Abemaciclib + ET: Tamoxifen	100%	0.2	Beta	-1	0
Intensity: Abemaciclib + ET: Exemestane	100%	0.2	Beta	-1	0
Intensity: Endocrine therapy: Letrozole	100%	0.2	Beta	-1	0
Intensity: Endocrine therapy: Anastrozole	100%	0.2	Beta	-1	0
Intensity: Endocrine therapy: Tamoxifen	100%	0.2	Beta	-1	0
Intensity: Endocrine therapy: Exemestane	100%	0.2	Beta	-1	0
Admin cost: IV	2,041.00	408.20	Gamma	25	81.64
Admin cost: SC	2,041.00	408.20	Gamma	25	81.64
Cost: GP visit	1,176.00	235.20	Gamma	25	47.04
Cost: Oncologist visit, first	2,041.00	408.20	Gamma	25	81.64
Cost: Clinical nurse (specialist)	554.00	110.80	Gamma	25	22.16
Cost: District nurse (home visit)	550.00	110.00	Gamma	25	22
Cost: Mammogram	690.00	138.00	Gamma	25	27.6

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Name	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)
Cost: ECHO scan	1,910.00	382.00	Gamma	25	76.4
Cost: CT scan	3,389.00	677.80	Gamma	25	135.56
Cost: MUGA scan	1,910.00	382.00	Gamma	25	76.4
Cost: Inpatient stay	35,099.00	7,019.80	Gamma	25	1403.96
Cost: Local: Major breast procedures (if patients originally had mastectomy)	37,890.00	7,578.00	Gamma	25	1515.6
Cost: Local/Regional: Delayed breast reconstruction	79,197.00	15,839.40	Gamma	25	3167.88
Cost: Local/Regional: Mastectomy with reconstruction (if patients orginally had breast conserving surgery)	113,402.00	22,680.40	Gamma	25	4536.08
Cost: Radiotherapy	10,874.00	2,174.80	Gamma	25	434.96
Cost: Contralateral: Major breast procedures (if patients originally had mastectomy)	37,890.00	7,578.00	Gamma	25	1515.6
Cost: Contralateral: Delayed breast reconstruction	79,197.00	15,839.40	Gamma	25	3167.88
Cost: Contralateral: Mastectomy with reconstruction (if patients originally had breast conserving surgery)	113,402.00	22,680.40	Gamma	25	4536.08
Cost: Serum Chemistry	139.00	27.80	Gamma	25	5.56
Cost: Complete blood count	46.00	9.20	Gamma	25	1.84
Cost: Electrocardiogram	2,616.00	523.20	Gamma	25	104.64
Cost: MRI scan	3,389.00	677.80	Gamma	25	135.56
Cost: PET scan	3,389.00	677.80	Gamma	25	135.56
Cost: Hospitalisation	35,099.00	7,019.80	Gamma	25	1403.96
Cost: Chemotherapy (cycle 1)	18,164.00	3,632.80	Gamma	25	726.56
Cost: Chemotherapy (cycle 2-6)	18,164.00	3,632.80	Gamma	25	726.56
Cost: Chemotherapy (subsequent cycles)	18,164.00	3,632.80	Gamma	25	726.56

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Name	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)
Cost: Multidisciplinairy team meeting	2,041.00	408.20	Gamma	25	81.64
Cost: Oncologist visit, follow-up	2,041.00	408.20	Gamma	25	81.64
Cost: X-Ray	2,041.00	408.20	Gamma	25	81.64
Cost: Biochemistry	139.00	27.80	Gamma	25	5.56
Concomitant tx: Abemaciclib + ET to Loperamide	0.666	0.1332	Beta	7.684	3.853537538
Concomitant tx: Abemaciclib + ET to Ibuprofen	0.091	0.0182	Beta	22.634	226.0912747
Concomitant tx: Abemaciclib + ET to Amoxicillin; Glavulanic acid	0.078	0.0156	Beta	22.972	271.5408205
Concomitant tx: Abemaciclib + ET to Amoxicillin	0.056	0.0112	Beta	23.544	396.8845714
Concomitant tx: Abemaciclib + ET to Colecalciferol	0.073	0.0146	Beta	23.102	293.3637534
Concomitant tx: Abemaciclib + ET to Calcium carbonate; colecalciferol	0.062	0.0124	Beta	23.388	353.8378065
Concomitant tx: Abemaciclib + ET to Vitamin D Nos	0.056	0.0112	Beta	23.544	396.8845714
Concomitant tx: Abemaciclib + ET to Zolederonic acid	0.099	0.0198	Beta	22.426	204.0992525
Concomitant tx: Abemaciclib + ET to Paracetamol	0.246	0.0492	Beta	18.604	57.02201626
Concomitant tx: Abemaciclib + ET to Levothyroxine	0.093	0.0186	Beta	22.582	220.2352043
Concomitant tx: Abemaciclib + ET to Metformin	0.058	0.0116	Beta	23.492	381.5424828
Concomitant tx: Endocrine therapy to Loperamide	0.019	0.0038	Beta	24.506	1265.283474
Concomitant tx: Endocrine therapy to Ibuprofen	0.097	0.0194	Beta	22.478	209.2539588
Concomitant tx: Endocrine therapy to Amoxicillin; Glavulanic acid	0.054	0.0108	Beta	23.596	413.366963
Concomitant tx: Endocrine therapy to Amoxicillin	0.048	0.0096	Beta	23.752	471.0813333

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Name	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)
Concomitant tx: Endocrine therapy to Colecalciferol	0.084	0.0168	Beta	22.816	248.8030476
Concomitant tx: Endocrine therapy to Calcium carbonate; colecalciferol	0.073	0.0146	Beta	23.102	293.3637534
Concomitant tx: Endocrine therapy to Vitamin D Nos	0.054	0.0108	Beta	23.596	413.366963
Concomitant tx: Endocrine therapy to Zolederonic acid	0.109	0.0218	Beta	22.166	181.1917982
Concomitant tx: Endocrine therapy to Paracetamol	0.21	0.042	Beta	19.54	73.50761905
Concomitant tx: Endocrine therapy to Levothyroxine	0.086	0.0172	Beta	22.764	241.9336744
Concomitant tx: Endocrine therapy to Metformin	0.055	0.011	Beta	23.57	404.9754545
Hourly wage patient cost	181	36.2	Gamma	25	7.24
Patient costs hours: IDFS	0.25	0.05	Gamma	25	0.01
Patient costs hours: NMR	0.25	0.05	Gamma	25	0.01
Patient costs hours: REM	0.25	0.05	Gamma	25	0.01
Distance to health care provider	40	8	Gamma	25	1.6
Travel costs per km	3.51	0.702	Gamma	25	0.1404
Travel: No. of visits IDFS	0.15	0.03	Gamma	25	0.006
Travel: No. of visits NMR	0.15	0.03	Gamma	25	0.006
Travel: No. of visits REM	0.15	0.03	Gamma	25	0.006
Proportion long-term absence	0.1	0.02	Gamma	25	0.004
Duration monarchE: Neutropenia	15.09	3.018	Gamma	25	0.6036
Duration monarchE: Leukopenia	13.96	2.792	Gamma	25	0.5584
Duration monarchE: Diarrhea	8	1.6	Gamma	25	0.32
Duration monarchE: Lymphopenia	34	6.8	Gamma	25	1.36
Duration monarchE: Fatigue	12.7	2.54	Gamma	25	0.508

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Name	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)
Duration monarchE: Alanine aminotransferase increase	28	5.6	Gamma	25	1.12
Duration monarchE: Thrombocytopenia	23.21	4.642	Gamma	25	0.9284
Duration monarchE: Anaemia	16.07	3.214	Gamma	25	0.6428
Duration monarchE: Abdominal pain	8.82	1.764	Gamma	25	0.3528
grade I/II AE cost monarchE: Diarrhea	6,756.00	1,351.20	Gamma	25	270.24
grade III/IV AE cost: Neutropenia	3,176.00	635.20	Gamma	25	127.04
grade III/IV AE cost: Leukopenia	3,176.00	635.20	Gamma	25	127.04
grade III/IV AE cost: Diarrhea	6,756.00	1,351.20	Gamma	25	270.24
grade III/IV AE cost: Lymphopenia	3,176.00	635.20	Gamma	25	127.04
grade III/IV AE cost: Fatigue	4,460.00	892.00	Gamma	25	178.4
grade III/IV AE cost: Aspartate aminotransferase increase	1,905.00	381.00	Gamma	25	76.2
grade III/IV AE cost: Alanine aminotransferase increase	1,905.00	381.00	Gamma	25	76.2
grade III/IV AE cost: Thrombocytopenia	3,176.00	635.20	Gamma	25	127.04
grade III/IV AE cost: Anaemia	3,176.00	635.20	Gamma	25	127.04
grade III/IV AE cost: Abdominal pain	6,756.00	1,351.20	Gamma	25	270.24
grade III/IV AE cost: Venous thromboembolic event	22,502.00	4,500.40	Gamma	25	900.08
grade III/IV AE cost ETR ABE+ET arm: Anaemia	93.52	18.70	Gamma	25	3.740714034
grade III/IV AE cost ETR ABE+ET arm: Diarrhea	89.14	17.83	Gamma	25	3.565616273
grade III/IV AE cost ETR ABE+ET arm: Dyspnoea	61.52	12.30	Gamma	25	2.460804097
grade III/IV AE cost ETR ABE+ET arm: Gamma-glutamyltransferase (GGT) increase	84.36	16.87	Gamma	25	3.374421664

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Name	Expected value	Standard error	Probability distribution		Parameter distribution (Name: Value)	Parameter distribution (Name: Value)
grade III/IV AE cost ETR ABE+ET arm: Hyperglycemia	70.09	14.02	Gamma	25		2.803709583
grade III/IV AE cost ETR ABE+ET arm: Neutropenia	30.71	6.14	Gamma	25		1.228343762
grade III/IV AE cost ETR ABE+ET arm: Stomatitis	55.55	11.11	Gamma	25		2.22196364
grade III/IV AE cost ETS ABE+ET arm: Alanine aminotransferase increase	15.44	3.09	Gamma	25		0.617621053
grade III/IV AE cost ETS ABE+ET arm: Anaemia	24.07	4.81	Gamma	25		0.962829474
grade III/IV AE cost ETS ABE+ET arm: Aspartate aminotransferase increase	22.66	4.53	Gamma	25		0.906378947
grade III/IV AE cost ETS ABE+ET arm: Diarrhea	51.20	10.24	Gamma	25		2.048134737
grade III/IV AE cost ETS ABE+ET arm: Hypertension	1.21	0.24	Gamma	25		0.048547368
grade III/IV AE cost ETS ABE+ET arm: Nausea	87.48	17.50	Gamma	25		3.4992
grade III/IV AE cost ETR ET arm: Anaemia	110.50	22.10	Gamma	25		4.420053435
grade III/IV AE cost ETR ET arm: Diarrhea	192.29	38.46	Gamma	25		7.691523963
grade III/IV AE cost ETR ET arm: Dyspnoea	62.50	12.50	Gamma	25		2.499853429
grade III/IV AE cost ETR ET arm: Gamma-glutamyltransferase (GGT) increase	77.02	15.40	Gamma	25		3.080947908
grade III/IV AE cost ETR ET arm: Hyperglycemia	62.25	12.45	Gamma	25		2.489865976
grade III/IV AE cost ETR ET arm: Leukopenia	48.52	9.70	Gamma	25		1.94099535
grade III/IV AE cost ETR ET arm: Neutropenia	174.25	34.85	Gamma	25		6.969870217
grade III/IV AE cost ETR ET arm: Stomatitis	48.00	9.60	Gamma	25		1.919848691
grade III/IV AE cost ETS ET arm: Alanine aminotransferase increase	77.07	15.41	Gamma	25		3.082989796

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Name	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)
grade III/IV AE cost ETS ET arm: Anaemia	110.64	22.13	Gamma	25	4.425658776
grade III/IV AE cost ETS ET arm: Aspartate aminotransferase increase	49.49	9.90	Gamma	25	1.979644898
grade III/IV AE cost ETS ET arm: Diarrhea	356.14	71.23	Gamma	25	14.24550857
grade III/IV AE cost ETS ET arm: Hypertension	9.33	1.87	Gamma	25	0.37319551
grade III/IV AE cost ETS ET arm: Leukopenia	202.13	40.43	Gamma	25	8.085188571
grade III/IV AE cost ETS ET arm: Lymphopenia	64.85	12.97	Gamma	25	2.593949388
grade III/IV AE cost ETS ET arm: Nausea	65.80	13.16	Gamma	25	2.632004082
grade III/IV AE cost ETS ET arm: Neutropenia	548.54	109.71	Gamma	25	21.94162286
ETR Pathway CDK4&6i + FUL PPS Utility values	0.70	0.14	Beta	6.696	2.815363636
ETR Pathway EXE-EVE PPS Utility values	0.70	0.14	Beta	6.696	2.815363636
ETR Pathway FUL PPS Utility values	0.70	0.14	Beta	6.696	2.815363636
ETR Pathway CAP PPS Utility values	0.70	0.14	Beta	6.696	2.815363636
ETR Pathway EXE PPS Utility values	0.70	0.14	Beta	6.696	2.815363636
ETS Pathway CDK4&6i + NSAI PPS Utility values	0.51	0.10	Beta	11.87	11.6349505
ETS Pathway NSAI PPS Utility values	0.51	0.10	Beta	11.87	11.6349505
ETS Pathway RIBO-FUL PPS Utility values	0.51	0.10	Beta	11.87	11.6349505
ETS Pathway TMX PPS Utility values	0.51	0.10	Beta	11.87	11.6349505
ETS Pathway FUL PPS Utility values	0.51	0.10	Beta	11.87	11.6349505
ETR Pathway CDK4&6i + FUL LYs in PFS	2.39	0.48	Lognormal	0.851892193	0.1980422
ETR Pathway EXE-EVE LYs in PFS	1.81	0.36	Lognormal	0.575029758	0.1980422

Name	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)
ETR Pathway FUL LYs in PFS	0.94	0.19	Lognormal	-0.081621081	0.1980422
ETR Pathway CAP LYs in PFS	1.97	0.39	Lognormal	0.657859184	0.1980422
ETR Pathway EXE LYs in PFS	0.73	0.15	Lognormal	-0.337698529	0.1980422
ETS Pathway CDK4&6i + NSAI LYs in PFS1	2.97	0.59	Lognormal	1.070393497	0.1980422
ETS Pathway NSAI LYs in PFS1	1.68	0.34	Lognormal	0.501526981	0.1980422
ETS Pathway RIBO-FUL LYs in PFS1	4.07	0.81	Lognormal	1.384307092	0.1980422
ETS Pathway TMX LYs in PFS1	1.46	0.29	Lognormal	0.360274892	0.1980422
ETS Pathway FUL LYs in PFS1	2.25	0.45	Lognormal	0.792971294	0.1980422
ETS Pathway CDK4&6i + NSAI LYs in PFS2	0.69	0.14	Lognormal	-0.393476439	0.1980422
ETS Pathway NSAI LYs in PFS2	1.37	0.27	Lognormal	0.293081059	0.1980422
ETS Pathway RIBO-FUL LYs in PFS2	0.27	0.05	Lognormal	-1.346363675	0.1980422
ETS Pathway TMX LYs in PFS2	1.34	0.27	Lognormal	0.274670921	0.1980422
ETS Pathway FUL LYs in PFS2	1.13	0.23	Lognormal	0.106260489	0.1980422
ETR Pathway CDK4&6i + FUL LYs in PPS	1.99	0.40	Lognormal	0.666512209	0.1980422
ETR Pathway EXE-EVE LYs in PPS	1.66	0.33	Lognormal	0.485682062	0.1980422
ETR Pathway FUL LYs in PPS	2.55	0.51	Lognormal	0.918108683	0.1980422
ETR Pathway CAP LYs in PPS	2.47	0.49	Lognormal	0.886501918	0.1980422
ETR Pathway EXE LYs in PPS	2.48	0.50	Lognormal	0.886960612	0.1980422
ETS Pathway CDK4&6i + NSAI LYs in PPS	1.70	0.59	Lognormal	0.470620637	0.340514564
ETS Pathway NSAI LYs in PPS	1.95	0.34	Lognormal	0.653999284	0.171302184
ETS Pathway RIBO-FUL LYs in PPS	1.32	0.81	Lognormal	0.119537839	0.56664616
ETS Pathway TMX LYs in PPS	1.92	0.29	Lognormal	0.638748727	0.151740813
ETS Pathway FUL LYs in PPS	1.93	0.45	Lognormal	0.629930711	0.230673144

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Name	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)
% receiving ETR pathway - CDK4&6i + FUL - ABE-FUL	85%	17%	Dirichlet	0.85	0.15
% receiving ETR pathway - CDK4&6i + FUL - RIBO-FUL	10%	2%	Dirichlet	0.1	0.9
% receiving ETR pathway - CDK4&6i + FUL - PAL-FUL	5%	1%	Dirichlet	0.05	0.95
% receiving ETS pathway - CDK4&6i + NSAI - ABE-NSAI	85%	17%	Dirichlet	0.85	0.15
% receiving ETS pathway - CDK4&6i + NSAI - PAL-NSAI	5%	1%	Dirichlet	0.05	0.95
% receiving ETS pathway - CDK4&6i + NSAI - RIBO-NSAI	10%	2%	Dirichlet	0.1	0.9
ETR Pathway ABE-FUL LYs in PFS	2.47	0.49	Gamma	25	0.0988
ETR Pathway RIBO-FUL LYs in PFS	2.12	0.42	Gamma	25	0.0848
ETR Pathway PAL-FUL LYs in PFS	1.58	0.32	Gamma	25	0.0632
ETR Pathway ABE-FUL LYs in PPS	1.92	0.38	Gamma	25	0.0768
ETR Pathway RIBO-FUL LYs in PPS	2.23	0.45	Gamma	25	0.0892
ETR Pathway PAL-FUL LYs in PPS	2.62	0.52	Gamma	25	0.1048
ETS Pathway ABE-NSAI LYs in PFS1	2.98	0.60	Gamma	25	0.119268776
ETS Pathway PAL-NSAI LYs in PFS1	2.97	0.59	Gamma	25	0.118898331
ETS Pathway RIBO-NSAI LYs in PFS1	2.91	0.58	Gamma	25	0.116480452
ETS Pathway ABE-NSAI LYs in PFS2	0.69	0.14	Gamma	25	0.027518061
ETS Pathway PAL-NSAI LYs in PFS2	0.68	0.14	Gamma	25	0.027151383
ETS Pathway RIBO-NSAI LYs in PFS2	0.69	0.14	Gamma	25	0.027748411
ETS Pathway ABE-NSAI LYs in PPS	1.69	0.34	Gamma	25	0.067656691
ETS Pathway PAL-NSAI LYs in PPS	1.71	0.34	Gamma	25	0.06827101
ETS Pathway RIBO-NSAI LYs in PPS	1.74	0.35	Gamma	25	0.069401906
% receiving ETR Pathway CDK4&6i + FUL	0%	0%	Dirichlet	0	1

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Name	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)
% receiving ETR Pathway EXE-EVE	31%	6%	Dirichlet	0.3112	0.6888
% receiving ETR Pathway FUL	32%	6%	Dirichlet	0.3167	0.6833
% receiving ETR Pathway CAP	7%	1%	Dirichlet	0.0678	0.9322
% receiving ETR Pathway EXE	30%	6%	Dirichlet	0.3043	0.6957
% receiving ETS Pathway CDK4&6i + NSAI	0%	0%	Dirichlet	0	1
% receiving ETS Pathway NSAI	76%	15%	Dirichlet	0.757894737	0.242105263
% receiving ETS Pathway RIBO-FUL	0%	0%	Dirichlet	0	1
% receiving ETS Pathway TMX	19%	4%	Dirichlet	0.189473684	0.810526316
% receiving ETS Pathway FUL	5%	1%	Dirichlet	0.052631579	0.947368421
% receiving ETR Pathway CDK4&6i + FUL	15%	3%	Dirichlet	0.15	0.85
% receiving ETR Pathway EXE-EVE	26%	5%	Dirichlet	0.26	0.74
% receiving ETR Pathway FUL	27%	5%	Dirichlet	0.27	0.73
% receiving ETR Pathway CAP	6%	1%	Dirichlet	0.06	0.94
% receiving ETR Pathway EXE	26%	5%	Dirichlet	0.26	0.74
% receiving ETS Pathway CDK4&6i + NSAI	61%	12%	Dirichlet	0.612244898	0.387755102
% receiving ETS Pathway NSAI	29%	6%	Dirichlet	0.293877551	0.706122449
% receiving ETS Pathway RIBO-FUL	0%	0%	Dirichlet	0	1
% receiving ETS Pathway TMX	7%	1%	Dirichlet	0.073469388	0.926530612
% receiving ETS Pathway FUL	2%	0%	Dirichlet	0.020408163	0.979591837
CDK4&6i + FUL ETR Pathway - PFS treatment duration	17.58	3.52	Gamma	25	0.703150383
EXE-EVE ETR Pathway - PFS treatment duration	13.65	2.73	Gamma	25	0.546057054
FUL ETR Pathway - PFS treatment duration	8.96	1.79	Gamma	25	0.35821292

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Name	Expected value	Standard error	Probability distribution		Parameter distribution (Name: Value)	Parameter distribution (Name: Value)
CAP ETR Pathway - PFS treatment duration	12.72	2.54	Gamma	25	0.508672603	
EXE ETR Pathway - PFS treatment duration	8.73	1.75	Gamma	25	0.349218546	
CDK4&6i + NSAI ETS Pathway - PFS1 treatment duration	32.03	6.41	Gamma	25	1.281128975	
NSAI ETS Pathway - PFS1 treatment duration	20.70	4.14	Gamma	25	0.827932853	
RIBO-FUL ETS Pathway - PFS1 treatment duration	32.11	6.42	Gamma	25	1.28442081	
TMX ETS Pathway - PFS1 treatment duration	12.87	2.57	Gamma	25	0.514620205	
FUL ETS Pathway - PFS1 treatment duration	23.54	4.71	Gamma	25	0.941401196	
CDK4&6i + FUL ETR Pathway - PPS treatment duration	8.81	1.76	Gamma	25	0.352306936	
EXE-EVE ETR Pathway - PPS treatment duration	7.36	1.47	Gamma	25	0.294366694	
FUL ETR Pathway - PPS treatment duration	11.34	2.27	Gamma	25	0.453616837	
CAP ETR Pathway - PPS treatment duration	10.99	2.20	Gamma	25	0.439503687	
EXE ETR Pathway - PPS treatment duration	10.99	2.20	Gamma	25	0.439705331	
CDK4&6i + NSAI ETS Pathway - PFS2 treatment duration	7.56	1.51	Gamma	25	0.302526193	
NSAI ETS Pathway - PFS2 treatment duration	7.56	1.51	Gamma	25	0.302526193	
RIBO-FUL ETS Pathway - PFS2 treatment duration	6.53	1.31	Gamma	25	0.261216894	
TMX ETS Pathway - PFS2 treatment duration	7.56	1.51	Gamma	25	0.302526193	
FUL ETS Pathway - PFS2 treatment duration	6.53	1.31	Gamma	25	0.261216894	
CDK4&6i + NSAI ETS Pathway - PPS treatment duration	8.68	1.74	Gamma	25	0.347338114	

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Name	Expected value	Standard error	Probability distribution		Parameter distribution (Name: Value)	Parameter distribution (Name: Value)
NSAI ETS Pathway - PPS treatment duration	8.68	1.74	Gamma	25	0.347338114	
RIBO-FUL ETS Pathway - PPS treatment duration	8.72	1.74	Gamma	25	0.34861479	
TMX ETS Pathway - PPS treatment duration	8.68	1.74	Gamma	25	0.347338114	
FUL ETS Pathway - PPS treatment duration	8.72	1.74	Gamma	25	0.34861479	

[If there is a need for longer justifications/descriptions, provide them in text.]

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Appendix K: Literature search for Cost and healthcare resource identification, measurement and valuation (derived from the targeted literature review to inform cost-utility model inputs)

Search strategy

The search strategy for an economic TLR is reported in Appendix H section (*Search strategy*).

Search results

The studies included in an economic TLR are presented in Appendix H section (*Search results*).

Included studies: Cost and resources use data

Table 104 provides an overview of the cost and resource use data used across the four identified HTA submissions.

None of the economic models identified in the economic SLR assessed the cost-effectiveness of trastuzumab emtansine, as per TA632, 2020[279]. Economic models were identified for neratinib using the ExteNET trial, adjuvant pertuzumab in combination with trastuzumab and chemotherapy using the APHINITY trial, and INTREBEAM radiotherapy [280] [281] [282].

Table 104: Summary of previous HTA submission model cost inputs

Author, year	Cost inputs	Resource use inputs
TA632, 2020[279]	Technology acquisition costs, drug administration costs, health state specific costs (cycle cost), AE management costs	Health state specific resource use costs including: Oncologist visit, mammogram, ECHO scan, MUGA scan, CT scan, GP visit, clinical nurse specialist, District nurse (home visit)
TA612, 2019[280]	Drug acquisition cost, drug administration costs, health state specific costs, AE costs	Health state specific resource use costs including: Oncologist visit, mammogram, ECHO scan, MUGA scan, CT scan, GP visit, clinical nurse specialist, District nurse (home visit), social worker
TA569, 2019[281]	Technology acquisition costs, drug administration costs, health state specific costs (cycle cost), AE management costs, subsequent therapy management costs	Health state specific resource use costs including: Oncologist visit, mammogram, ECHO scan, MUGA scan, CT scan, GP visit, clinical nurse specialist, District nurse (home visit), social worker
TA501, 2018[282]	INTRABEAM capita cost, technology maintenance and	Cost of medical procedures, staff unit costs and additional staff resources
Author, year	**Cost inputs**	**Resource use inputs**
	operating costs, consumable costs	

Abbreviations: AE: Adverse event; CT: computerised tomography; ECHO: echocardiogram; GP: General practice; MUGA; multigated acquisition.

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Appendix L: Published cost-effectiveness results

The results of the literature review for published cost-effectiveness models are only presented in an indicative way, as it was stated in the submission in paragraph 8.3.2 that a review of the literature was made to identify the most appropriate model type for early stage ER + HER2- node-positive early breast cancer.

Identification of studies

The methodology of an economic TLR to identify relevant cost and resource use data is described in Appendix H – Literature search for HRQoL data (derived from the targeted literature review to inform cost-utility model inputs)

Identification of studies

An economic SLR was carried out to identify cost-effectiveness studies which can be used to inform the development of the cost-effectiveness model (CEM) for HR+, HER2-, node-positive, high risk early breast cancer.

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Methods used were in line with the guidelines for performing systematic reviews as published by the Centre for Reviews and Dissemination (CRD),[259] and the Cochrane Handbook for Systematic Reviews [260].

PICOS eligibility criteria

The eligibility criteria for the SLR of cost-effectiveness studies are summarised in Table 105

Table 105 Eligibility criteria for the SLR of cost-effectiveness studies

Study Characteristic	Inclusion	Exclusion
Patient population[a]	• Early-stage breast cancer (Stage I-IIIC) • Hormone-receptor positive Node-positive • Adults ≥18 years • Received definitive surgery of the primary breast tumour	• Advanced or metastatic breast cancer (Stage IV) • Hormone-receptor negative Node-negative •
Intervention[b]	• NA	• NA
Comparators[b]	• NA	• NA
Outcomes	• (Incremental) costs • (Incremental) (quality adjusted) life years • Incremental cost-effectiveness ratio	• Outcomes other than specified under inclusion criteria
Study design	• Cost-effectiveness analysis • Cost utility analysis	• Study designs other than those specified under inclusion criteria • Systematic reviews and meta-analyses[c]
Language	• All languages	• No language restrictions
Time limit	• 2015 onwards	• NA

Footnotes: [a] No restriction was placed on HER2 status due to the lack of published economic models in HER2- patients. [b] The primary focus of the economic SLR was to capture data on treatment pathway, model design, economic inputs/outputs (not specific to the treatment effect). Therefore, no inclusion/exclusion criteria were applied for intervention and comparator. [c] Data from systematic reviews were not extracted into the data extraction form. The references from these publications were checked to ensure no relevant article was missed by the search strategy.
Abbrevations: NA: not applicable; SLR: systematic literature review.

Protocol deviation

During the search and selection phase of the SLR it became evident that economic data pertaining to patients with node-positive, HR+ early breast cancer were limited. To avoid excluding economic analyses that could provide informative data related to model design and model inputs, the eligibility criteria were relaxed and the restriction on node and HR status was removed.

Search strategy

Data sources

Peer-reviewed publications

To identify economic evidence in peer-reviewed journals, the Embase, Medline and EconLit databases were searched by means of the ProQuest search engine. The NHS EED was also searched via the CRD website[259] to identify relevant economic evidence.

The database searches in Medline, Embase, EconLit and NHS EED were limited to the last five years. The 5-year limit ensured that most recent economic data were identified, and relevant, and applicable costs were captured. The Embase, Medline and Econlit search terms for the patient population consisted of words searched in title/abstract and as indexed terms (i.e. Emtree and MeSH). Search terms for cost-effectiveness studies were based on the filters provided by the SIGN and Canadian Agency for Drugs and Technologies in Health (CADTH) [262, 283].

Grey literature

The HTA database and HTA websites were searched to retrieve critical appraisals and key learnings from previous assessments, which provide data on CEM included in the assessments. The HTA database was searched via the CRD website [259]. The full list of databases and websites searched are shown in Table 106.

In the conference databases, searches were limited to the last three years as it was assumed that any data before this time would be published in full. The ISPOR conference proceedings (for the years 2017-2020) were searched. ISPOR is the leading professional society for health economics and outcomes research (HEOR) globally and hosts the leading global scientific and educational conferences in HEOR. It was assumed that any relevant economic studies would be presented at these events.

All conference proceedings were indexed in Embase and were searched by means of ProQuest.

Table 106: Selected databases for the SLR of cost-effectiveness studies

Search engine	Database	Time limitations
ProQuest	• Embase • Medline Econlit	2015 onwards
CRD	• HTA Database NHS EED •	2015 onwards
HTA websites	• NICE • SMC HAS CADTH PBAC	2015 onwards
Conferences	• ISPOR	2017 onwards

Abbreviations: CADTH: Canadian Agency for Drugs and Technologies in Health; CRD: Centre for Reviews and Dissemination; EBCC: European Breast Cancer Conference; HAS: Haute Autorité de santé; HTA: Health Technology Assessment; ISPOR: International Society for Pharmacoeconomics and Outcomes Research; NHS EED: National Health Service Economic Evaluation Database; NICE: National Institute for Health and Care Excellence; PBAC: The Pharmaceutical Benefits Advisory Committee; SMC: Scottish Medicines Consortium

Search terms

The search strategies for the databases searched in the SLR for cost-effectiveness studies are presented in Table 107 to Table 110. Searches were carried out on 28th August 2020.

Peer-reviewed databases

Table 107: EconLit, Embase and Medline search strategy (ProQuest) – 28th August 2020

Search line	Search terms	Hits

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S1	EMB.EXACT.EXPLODE("breast cancer") OR MESH.EXACT.EXPLODE("Breast Neoplasms")	792091*
S2	TI,AB((breast OR mamma*) NEAR/2 (cancer* OR tumo?r* OR neoplasm* OR carcinoma*))	805153*
S3	S1 OR S2	993157*
S4	TI,AB(early OR "early-stage" OR "stage I" OR "stage one" OR "stage 1" OR "stage 1A" OR "stage IA" OR "stage IB" OR "stage 1B" OR "stage II" OR "stage two" OR "stage 2" OR "stage 2A" OR "stage IIA" OR "stage IIB" OR "stage 2B" OR "stage III" OR "stage three" OR "stage 3" OR "stage 3A" OR "stage IIIA" OR "stage IIIB" OR "stage 3B" OR "stage IIIC" OR "stage 3C")	4588794*
S5	S3 AND S4	139083*
S6	EMB.EXACT("Cost effectiveness analysis")	158283*
S7	MESH.EXACT("Cost-benefit analysis")	81558*
S8	MESH.EXACT("Economics")	449455*
S9	AB(cost NEAR/1 effectiveness) AND AB(costs or cost)	137792*

Search line	Search terms	Hits
S10	TI(cost NEAR/1 effectiveness)	55664*
S11	EMB.EXACT("Cost benefit analysis")	88065*
S12	EMB.EXACT("Economic aspect")	124864*
S13	EMB.EXACT("Socioeconomics")	149995*
S14	MESH.EXACT("Economics, pharmaceutical")	2938°
S15	EMB.EXACT("Health economics")	40371*
S16	MESH.EXACT("Costs and cost analysis")	48798*
S17	MESH.EXACT("Value of life")	5711*
S18	TI,AB(Economic* OR pharmacoeconomic* OR price* OR pricing)	1177974*
S19	TI,AB,IF(monte carlo)	125341*
S20	EMB.EXACT("Probability")	120805*
S21	MESH.EXACT("Decision Theory" OR "Decision Trees")	12090*

S22	EMB.EXACT("Decision Tree")	14240*
S23	MESH.EXACT("Markov chains")	14396*
S24	EMB.EXACT("Statistical Model")	192726*
S25	MESH.EXACT("Monte carlo method")	28447*
S26	EMB.EXACT("Decision Theory")	2804°
S27	EMB.EXACT("Monte carlo method")	42324*
S28	TI,AB,IF(markov)	66804*
S29	AB,IF(cost* NEAR/2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes))	592406*
S30	TI,AB,IF(value NEAR/2 (money or monetary))	8511*
S31	TI,AB,IF(Decision* NEAr/2 (tree* or analy* or model*))	100953*
S32	TI,IF(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed)	2416886*
S33	MESH.EXACT.EXPLODE("Costs and cost analysis")	237925*
S34	EMB.EXACT("Economics")	246128*
S35	EMB.EXACT("Cost")	62957*
S36	AB,IF(economic model*)	208010*
S37	MESH.EXACT("Models, economic")	10189*

Search line	Search terms	Hits
S38	EMB.EXACT("Cost utility analysis")	10424*
S39	TI,AB(cost NEAR/2 effectiveness)	153410*
S40	TI,AB(cost NEAR/2 utility)	17206*
S41	TI,AB(cost NEAR/2 benefit)	67298*
S42	S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41	3948484*

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S43	TI,AB(case NEAR/1 (stud* OR report))	1783998*
S44	EMB.EXACT("Case study")	129188*
S45	EMB.EXACT("Abstract report" OR "Letter")	1159697*
S46	RTYPE("Case reports")	2117649*
S47	RTYPE("Letter")	2228327*
S48	RTYPE("Historical article")	359867*
S49	RTYPE("Conference abstract")	3837631*
S50	RTYPE("Note")	809842*
S51	S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50	10449002*
S52	S42 NOT S51	3512319*
S53	S5 AND S52	6123*
S54	S53 AND PD(>20141231)	1456°

Table 108: NHS EED search strategy (CRD) - 31st August 2020

Search line	Search terms	Limit	Hits
1	(breast cancer) R (breast tumor) OR (breast tumour) OR (breast carcinoma)	2015-2020	
2	(early stage) OR (HER2) OR (node positive)	2015-2020	
3	#1 AND #2	2015-2020	0

Grey literature

Table 109: HTA database search strategy (CRD) - 31st August 2020

Search line	Search terms	Limit	Hits
1	(breast cancer) OR (breast tumor) OR (breast tumour) OR (breast carcinoma)	2015-2020	
2	(early stage) OR (HER2) OR (node positive)	2015-2020	
Search line	**Search terms**	**Limit**	**Hits**
3	#1 AND #2	2015-2020	16

Table 110: Embase conference search strategy

Search line	Search terms	Hits

S1	EMB.EXACT.EXPLODE("breast cancer")	509518*
S2	TI,AB((breast OR mamma*) NEAR/2 (cancer* OR tumo?r* OR neoplasm* OR carcinoma*))	490571*
S3	S1 OR S2	610062*
S4	TI,AB(early OR "early-stage" OR "stage I" OR "stage one" OR "stage 1" OR "stage 1A" OR "stage IA" OR "stage IB" OR "stage 1B" OR "stage II" OR "stage two" OR "stage 2" OR "stage 2A" OR "stage IIA" OR "stage IIB" OR "stage 2B" OR "stage III" OR "stage three" OR "stage 3" OR "stage 3A" OR "stage IIIA" OR "stage IIIB" OR "stage 3B" OR "stage IIIC" OR "stage 3C")	2736093*
S5	S3 AND S4	90296*
S6	CF(ISPOR Europe 2019)	2411°
S7	CF(ISPOR 2019: Rapid. Disruptive. Innovative: A New Era in HEOR)	1643°
S8	CF(ISPOR Europe 2018: New Perspectives for Improving 21st Century Health Systems)	2480°
S9	CF(23rd Annual Meeting of the International Society for Pharmacoeconomics and Outcomes Research, ISPOR 2018)	1453°
S10	CF(ISPOR 22nd Annual International Meeting)	2030°
S11	CF(ISPOR 20th Annual European Congress)	2613°
S12	CF(ISPOR 2020)	4239°
S13	S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12	16901*
S14	S5 AND S13	144°

Systematic selection of studies

Peer reviewed publications

Once the electronic searches were run, all retrieved references were downloaded and imported into an EndNote database and duplicates were removed. The references were then exported into DistillerSR (Version:2.32.0), a reference screening software that was used for title/abstract and full-text screening.

Inclusion or exclusion of articles was based on the eligibility criteria specified in Table 105. Abstract/title review of all references was performed in double and independently by two reviewers. Any discrepancies were resolved by a third reviewer. The same process was applied for articles that were selected for full-text review. During both title/abstract and full-text screening phases, excluded articles were documented with reasons for their exclusion according to the predefined criteria.

Grey literature

Searches of conference proceedings, HTA databases and HTA websites were performed by a single reviewer and

checked by a second reviewer. Conference abstracts which meet the eligibility criteria were collated in a Microsoft Excel database and were matched up to included peer-reviewed publications where relevant to determine if any additional information was provided. If duplicate data were presented in multiple conference abstracts, only the most recent abstract was included. HTA reports were also collated in a Microsoft Excel database where duplicates were removed and the reports that meet our eligibility criteria (Table 105) were included for data extraction.

Data extraction

After the list of included studies was finalised, the relevant data were extracted. One reviewer extracted the data and a second reviewer independently reviewed all data extracted for each endpoint. 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.

Quality assessment

he Drummond checklist [284] was used to critically appraise the included cost-effectiveness studies (*Quality assessment for each trial*).Critical appraisal was only performed for peer-reviewed publications. This was not performed for conference proceedings, as there would be insufficient methodological data to assess the study quality. One reviewer conducted the critical appraisal of included articles; a second reviewer checked the accuracy.

Search results

The electronic database searches (28th August 2020) identified a total of 2,106 hits, across all searchers. After the removal of duplicates, the titles and abstracts of 1,437 publications were screened for eligibility. After excluding 1,390 publications based on title and abstract screening, 47 full-texts were assessed for eligibility based on the pre-specified criteria (Table 105). A total of
24 publications were excluded after full-text screening. Reasons for exclusion were population (n=16), outcomes (n=4), study design (n=3), and language (n=1). This resulted in a total of 23 eligible full-text publications for data extraction and reporting. The record selection process is shown in the PRISMA diagram in Figure 39.

A further nine abstracts from conference proceedings were included from other sources, one of which reported on the same economic analysis published in an included peer-reviewed text. No relevant publications from the CRD (HTA & NHS EED) databases, or the HTA websites were identified. All included conference abstracts were checked for the availability of additional information (e.g. associated posters or slide presentations).

In total, 31 economic analyses reported in 32 articles (23 peer-reviewed texts, 9 conference abstracts) were included in the SLR for cost-effectiveness studies.

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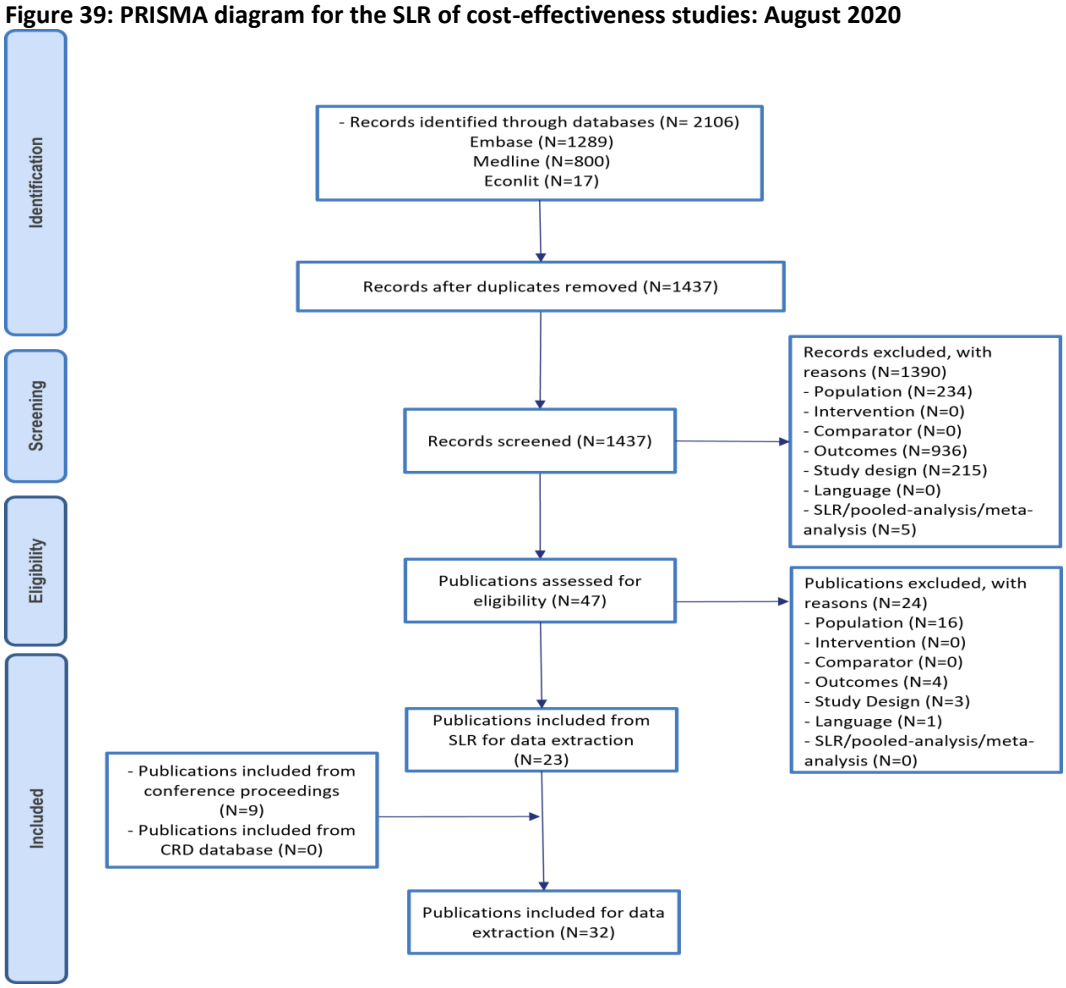
Figure 39: PRISMA diagram for the SLR of cost-effectiveness studies: August 2020



Abbreviations: CRD: Centre for Reviews and Dissemination; SLR: systematic literature review.

Included studies

In total, 31 economic analyses reported in 32 articles (23 peer-reviewed texts, 9 conference abstracts) were included.

Table 111: List of studies included in the SLR for cost-effectiveness studies

Author, year	Country	Study design	Patient population	Intervention	Comparator
Vaidya 2017	Brazil	Cost-utility analysis	Early Breast Cancer Patients	Intraoperative radiotherapy	External beam radiotherapy
Djalalov 2015	Canada	Cost-utility analysis	65-year-old postmenopausal women with ER+ early breast cancer	Tamoxifen	Aromatase inhibitor
Lamond 2015	Canada	Cost-utility analysis	Two hypothetical cohorts of women undergoing adjuvant therapy after initial surgical re-section of early-stage endo-crinesensitive breast cancer	Adjuvant endocrine therapy + zoledronic acid	Adjuvant endocrine therapy
Guan 2019	China	Cost-utility analysis	Chinese patients with HER2+ early breast cancer at high risk of recurrence (HR- or nodeposi-tive)	Pertuzumab + trastuzumab + chemotherapy	Trastuzumab + chemotherapy
Wan 2015	China	Cost-utility analysis	Patients with breast cancer with positive nodes.	No postmastectomy radiotherapy	Postmastectomy radiotherapy
Ye 2018	China	Cost-utility analysis	Postmenopausal women with early ER+ breast cancer after lumpectomy	Aromatase inhibitor - Letrozole	Standard of tamoxifen

Elshafeiz 2017	Egypt	Cost-utility analysis	Post-menopausal women with early breast cancer	Exemestane (25mg)	Tamoxifen (20mg)
Aboutorabi 2015	Iran	Cost-utility analysis	Women with HER2+ early breast cancer	Adjuvant chemotherapy + trastuzumab	Adjuvant chemotherapy alone

Author, year	Country	Study design	Patient population	Intervention	Comparator
Ansaripour 2018	Iran	Cost-utility analysis	Patients with early HER2+ BC	Trastuzumab + chemotherapy	Chemotherapy alone
Ferrandina 2017	Italy	Cost-utility analysis	Patients aged 40–49 years with hormonesensitive BC	Gonadotropin-releasing hormone	Laparoscopic bilateral salpingo-oophorectomy
Pradelli 2018	Italy	Cost-utility analysis	Patients with HER2+ early breast cancer at high risk of re-currence	Pertuzumab + standard trastuzumab-based regimen	Standard therapy
Leung 2016	New Zealand	Cost-utility analysis	Patients with nodepositive HER2+ early breast cancer	Trastuzumab	Standard chemotherapy
Genuino 2019	Philippines	Cost-utility analysis eco-nomic evaluation	Filipino women with HER2+ EBC	Trastuzumab + standard chemo-therapy (doxorubicin, cyclophos-phamide, docetaxel)	Standard chemotherapy (doxorubicin, cyclophosphamide, docetaxel)

Alshreef 2019	South Africa	Cost-utility analysis	Early breast cancer patients	Docetaxel and paclitaxelcontain-ing chemo-therapy regimens (taxanes)	Non-taxane standard regimens
Ciruelos 2018	Spain	Cost-effectiveness analy-sis	Patients with HER2+ early breast cancer	Trastuzumab + chemotherapy	Chemotherapy
Ciruelos 2019	Spain	Cost-utility analysis	Women with BC between 2006 and 2017, we selected those with early disease and amena-ble to having received trastuzumab	Trastuzumab + chemotherapy	Chemotherapy

Author, year	**Country**	**Study design**	**Patient population**	**Intervention**	**Comparator**
Colomer 2019	Spain	Cost-utility analysis	HER2+ early breast cancer(EBC) patients	Pertuzumab + trastuzumab + chemotherapy	Trastuzumab + chemotherapy
Gershon 2019	Sub-Saharan Africa (11 African countries)	Cost-utility analysis	Early stage HER2+ breast cancer patients	Trastuzumab + chemotherapy	Chemotherapy (anthracycline based)
Lang 2016	Taiwan	Cost-utility analysis	Women with HER2+ early breast cancer	Trastuzumab	No trastuzumab
Kongsakon 2019	Thailand	Cost-utility analysis	Early-stage breast cancer pa-tients	Trastuzumab + Paclitaxel	Paclitaxel

Seferina 2017	The Netherlands	Cost-utility analysis	HER2+ early breast cancer patients	Trastuzumab	No trastuzumab (Chemotherapy)
Ali 2017	United States	Cost-utility analysis	Early-stage breast cancer (elderly patients)	Breast-conserving surgery + hormonal therapy + radiotherapy	Breast-conserving surgery + hormonal therapy (without radiotherapy)
Deshmukh 2017	United States	Cost-utility analysis	Women with an age range of 45 to 75 years treated with BCS for stage I/II breast cancer	• Hypofractionated whole breast irradiation • - Intraoperative radio- therapy	Conventionally fractionated whole breast irradiation
Ezendu 2018	United States	Cost-utility analysis	Elderly women with Estrogen receptor positive (ER+) EarlyStage Breast Cancer (EBC)	External Beam Whole Breast Irradiation + tamoxifen therapy (10year)	Tamoxifen therapy (10year)
Garrison 2019	United States	Cost-utility analysis	Women with HER2+ breast cancer in the United States with a starting age of 51 years	Pertuzumab + trastuzumab + chemotherapy	Trastuzumab + chemotherapy

Author, year	**Country**	**Study design**	**Patient population**	**Intervention**	**Comparator**

Kwon 2016	United States	Cost-effectiveness analysis	Premenopausal women with ER+ early breast cancer	Tamoxifen	• Medical ovarian ablation (GnRH agonist) + an aromatase inhibitor • Surgical ovarian ablation (bilateral salpingooophorectomy) + an aromatase inhibitor
Kwon 2017	United States	Cost-effectiveness analysis	Premenopausal women with ER+ breast cancer who have completed 5 years of tamoxifen therapy and are eligible for additional endocrine therapy.	No further treatment	• 5 additional years of tamoxifen (extended tamoxifen) • Ovarian ablation accomplished by outpatient laparoscopic bilateral salpingo-oophorectomy, followed by 5 years of an aromatase inhibitor
Lester 2016	United States	Cost-utility analysis	Elderly women with oestrogen receptor positive (ER+) early-stage breast cancer (EBC)	Radiotherapy with lumpectomy cavity boost	Radiotherapy without lumpectomy cavity boost
Patel 2017	United States	Cost-utility analysis	Early stage (stage I–IIA/IIB) breast cancer	Intraoperative radiation therapy	External beam radiation therapy
Schwartz 2018	United States	Cost utility and Costeffectiveness analysis	Women with HER2+ breast cancer (Stage I-III breast cancer)	Neratinib (following treatment with trastuzumab)	Standard care strategies

Schwartz 2019	United States	Cost utility and costeffectiveness analysis	Early-Stage HER2+ Breast Cancer	Neratinib (after trastuzumab)	Observation (after trastuzumab)

Author, year	Country	Study design	Patient population	Intervention	Comparator
Ward 2019	United States	Cost-effectiveness analysis	Individuals age 70 with stage I, HR+ invasive breast cancer 2 cm in size managed with partial mastectomy with a clinically or pathologically negative axilla	Radiation therapy without aromatase inhibitor ("experimental")	Aromatase inhibitor without radiation therapy ("standard")

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Excluded studies

Table 112: List of records excluded from the SLR for cost-effectiveness studies

ID	Author	Year	Title	Journal	Volume	Issue	Pages	Reason for exclusion
12	Chandler	2018	Cost Effectiveness of Gene Expression Profile Testing in Community Practice	Journal of clinical oncology: official journal of the American Society of Clinical Oncology	36	6	554-562	Population
37	Lairson	2015	Cost-Effectiveness of Chemotherapy for Breast Cancer and Age Effect in Older Women	Value in Health	18	8	1070-1078	Population
44	Fust	2017	Cost-Effectiveness Analysis of Prophylaxis Treatment Strategies to Reduce the Incidence of Febrile Neutropenia in Patients with Early-Stage Breast Cancer or Non-Hodgkin Lymphoma	PharmacoEconomics	35	4	425-438	Population
54	Davies,	2016	Outcomes of contralateral prophylactic mastectomy in relation to familial history: A decision analysis (BRCR-D-16-00033)	Breast Cancer Research	18	1		Outcomes
90	Garrison	2015	The Lifetime Economic Burden of Inaccurate HER2 Testing: Estimating the Costs of False-Positive and FalseNegative HER2 Test Results in US Patients with Early-Stage Breast Cancer	Value in Health	18	4	541-546	Population
103	Kip	2015	Long-term cost-effectiveness of Oncotype DX® versus current clinical practice from a Dutch cost perspective	Journal of Comparative Effectiveness Research	4	5	433-445	Population

134	Alarid-Escudero	2017	Trade-offs Between Efficacy and Cardiac Toxicity of Adjuvant Chemotherapy in Early-Stage Breast Cancer Patients: Do Competing Risks Matter?	Breast Journal	23	4	401-409	Population
146	Jahn	2017	Personalized treatment of women with early breast cancer: a risk-group specific cost-effectiveness analysis of adjuvant chemotherapy accounting for companion prognostic tests OncotypeDX and Adjuvant!Online	BMC cancer	17	1	685	Population
213	Knuttel	2017	Early health technology assessment of magnetic resonance-guided high intensity focused ultrasound ablation for the treatment of early-stage breast cancer	Journal of Therapeutic Ultrasound	5	1		Population
216	Ward	2020	Cost-effectiveness analysis of endocrine therapy alone versus partial-breast irradiation alone versus combined treatment for low-risk hormone-positive early-stage breast cancer in women aged 70 years or older	Breast Cancer Research and Treatment	182	2	355-365	Population
242	Vekov	2017	Cost-effectiveness assessment and budgetary implication of the Mamma print genetic test (70 genes) to determine the risk of relapse and the therapeutic strategy for the treatment of patients with early-stage breast cancer in Bulgaria, 2017	General Medicine	19	3	34-40	Outcomes

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247	Hassett	2020	Neoadjuvant treatment strategies for HER2-positive breast cancer: costeffectiveness and quality of life outcomes	Breast Cancer Research and Treatment	181	1	43-51	Population
565	Chen	2017	A Cost-Effectiveness Analysis of Adjuvant Trastuzumab Regimens in HER2-Positive Early Breast Cancer	Chinese Pharmaceutical Journal	52	8	696-701	Language

589	Hall	2017	Value of Information Analysis of Multiparameter Tests for Chemotherapy in Early Breast Cancer: The OPTIMA Prelim Trial	Value in Health	20	10	1311-1318	Outcomes
613	Vaidya	2017	Health economics of targeted intraoperative radiotherapy (TARGITIORT) for early breast cancer: a costeffectiveness analysis in the United Kingdom	BMJ open	7	8	e014944	Population
631	Harat	2016	Whole breast irradiation vs. APBI using multicatheter brachytherapy in early breast cancer - simulation of treatment costs based on phase 3 trial data	Journal of contemporary brachytherapy	8	6	505-511	Population
658	Clarke	2017	Multi-arm Cost-Effectiveness Analysis (CEA) comparing different durations of adjuvant trastuzumab in early breast cancer, from the English NHS payer perspective	PloS one	12	3	e0172731	Study Design

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75	LesterColl	2015	Benefits and risks of contralateral prophylactic mastectomy in women undergoing treatment for sporadic unilateral breast cancer: a decision analysis	Breast Cancer Research and Treatment	152	1	217-226	Population
161	McGuffin	2017	Who Should Bear the Cost of Convenience? A Cost-effectiveness Analysis Comparing External Beam and Brachytherapy Radiotherapy Techniques for Early Stage Breast Cancer	Clinical Oncology	29	3	e57-e63	Population
438	Quintyne	2016	Cost-effectiveness analysis (CEA) of adjuvant trastuzumab therapy use in HER2-positive early-stage breast cancer (EBC)	Annals of Oncology	27		vi353	Study Design
562	Wei	2020	Cost-effectiveness Analysis of CYP2D6*10 Pharmacogenetic Testing to Guide the Adjuvant Endocrine Therapy for Postmenopausal Women with Estrogen Receptor Positive Early Breast Cancer in China	Clinical drug investigation	40	1	25-32	Outcomes
616	Ioannou	2020	Real-World Setting Cost-Effectiveness Analysis Comparing Three Therapeutic Schemes of One-Year Adjuvant Trastuzumab in HER2-Positive Early Breast Cancer from the Cyprus NHS Payer Perspective	International journal of environmental research and public health	17	12		Population
837	Elsisi	2020	Cost-effectiveness of six months versus 1-year adjuvant trastuzumab in HER2 positive early breast cancer in Egypt	Journal of Medical Economics	23	6	575-580	Population

1255	Hulme	2018	PERSEPHONE: 6 versus 12 months (m) of adjuvant trastuzumab in patients (pts) with HER2 positive (+) early breast cancer (EBC): Cost effectiveness analysis results	Annals of oncology: official journal of the European Society for Medical Oncology	29		viii703	Study Design

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Details of included studies

The majority of the identified economic evaluations were cost-utility analyses (n=25). Five publications were cost-effectiveness analyses, and two studies performed both cost-utility and cost-effectiveness analyses. As can be seen in Table 111, none of the identified economic evaluations modelled a patient population consistent with the monarchE trial population (HR+, HER2-, node-positive, high risk EBC).

Quality assessment for each trial

The included economic analyses were critically appraised using the Drummond checklist [284]. The critical appraisal was limited to analyses presented in peer-reviewed journals. Critical appraisal was not performed for conference proceedings (or associated posters and slide presentations), as there would be insufficient methodological data to assess the study quality. The quality assessment for the trials identified by the economic SLR are presented in Table 113 to Table 115.

Table 113: Drummond checklist for cost-effectiveness models (Europe and Southeast Asia)

Item		Ciruelos 2019	Ferrandina 2017	Seferina 2017	Genuino 2019	Kongsakon 2019	Lang 2016	Wan 2015	Ye 2018
	Study design								
1	The research question is stated.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	The economic importance of the research question is stated.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3	The viewpoint(s) of the analysis are clearly stated and justified.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4	The rationale for choosing alternative programmes or interventions compared is stated.	Not clear	Yes	Not clear	No	No	Not clear	Not clear	Yes
5	The alternatives being compared are clearly described.	Yes	Not clear	Not clear	Yes	No	Yes	Yes	Yes
6	The form of economic evaluation used is stated.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7	The choice of form of economic evaluation is justified in relation to the questions addressed.	Yes	Yes	Yes	No	Not clear	Not clear	Yes	Yes
	Data collection								
8	The source(s) of effectiveness estimates used are stated.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9	Details of the design and results of effectiveness study are given (if based on a single study).	Not clear	Not clear	Not clear	NA	Not clear	No	Yes	Yes

Item		Ciruelos 2019	Ferrandina 2017	Seferina 2017	Genuino 2019	Kongsakon 2019	Lang 2016	Wan 2015	Ye 2018
10	Details of the methods of synthesis or metaanalysis of estimates are given (if based on a synthesis of a number of effectiveness studies).	Yes	No	No	Yes	Not clear	No	Yes	Yes
11	The primary outcome measure(s) for the economic evaluation are clearly stated.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12	Methods to value benefits are stated.	Not clear	Not clear	Not clear	Not clear	No	Not clear	Not clear	Not clear
13	Details of the subjects from whom valuations were obtained were given.	Yes	Not clear	Not clear	Yes	Not clear	Not clear	Yes	Yes
14	Productivity changes (if included) are reported separately.	NA	NA	NA	NA	NA	NA	No	NA
15	The relevance of productivity changes to the study question is discussed.	NA	NA	NA	NA	NA	NA	No	NA
16	Quantities of resource use are reported separately from their unit costs.	No	No	No	No	No	No	Yes	No
17	Methods for the estimation of quantities and unit costs are described.	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
18	Currency and price data are recorded.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
19	Details of currency of price adjustments for inflation or currency conversion are given.	Yes	No	No	Yes	Yes	Yes	Yes	Yes

20	Details of any model used are given.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Item		Ciruelos 2019	Ferrandina 2017	Seferina 2017	Genuino 2019	Kongsakon 2019	Lang 2016	Wan 2015	Ye 2018
21	The choice of model used and the key parameters on which it is based are justified.	Not clear	Yes	Yes	Not clear	Yes	Yes	Yes	Yes
	Analysis and interpretation of results								
22	Time horizon of costs and benefits is stated.	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
23	The discount rate(s) is stated.	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
24	The choice of discount rate(s) is justified.	Yes	Not applicable	No	No	No	No	No	Yes
25	An explanation is given if costs and benefits are not discounted.	Not applicable	Yes	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
26	Details of statistical tests and confidence intervals are given for stochastic data.	Yes	No	No	No	No	No	Yes	Yes
27	The approach to sensitivity analysis is given.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
28	The choice of variables for sensitivity analysis is justified.	Not clear	Not clear	Not clear	No	Not clear	Not clear	Not clear	Not clear
29	The ranges over which the variables are varied are justified.	Not clear	Yes	Not clear	NA	Not clear	Yes	Not clear	Not clear
30	Relevant alternatives are compared.	No	Yes	Yes	Not clear	Yes	Yes	Yes	Yes
31	Incremental analysis is reported.	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes

32	Major outcomes are presented in a disaggregated as well as aggregated form.	Not clear	Yes	Yes	Not clear	Yes	Yes	Not clear	Not clear
Item		**Ciruelos 2019**	**Ferrandina 2017**	**Seferina 2017**	**Genuino 2019**	**Kongsakon 2019**	**Lang 2016**	**Wan 2015**	**Ye 2018**
33	The answer to the study question is given.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
34	Conclusions follow from the data reported.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
35	Conclusions are accompanied by the appropriate caveats.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

	Item	**Deshmukh 2017**	**Djalalov 2015**	**Garrison 2019**	**Kwon 2016**	**Kwon 2017**	**Lamond 2015**	**Lester 2016**	**Patel 2017**	**Schwartz 2019**	**Ward 2019**
	Study design										
1	The research question is stated.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	The economic importance of the research question is stated.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Table 114: Drummond checklist for cost-effectiveness models (North America)

Item		Deshmukh 2017	Djalalov 2015	Garrison 2019	Kwon 2016	Kwon 2017	Lamond 2015	Lester 2016	Patel 2017	Schwartz 2019	Ward 2019
3	The viewpoint(s) of the analysis are clearly stated and justified.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4	The rationale for choosing alternative programmes or interventions compared is stated.	Yes	Not clear	Yes	Yes	Not clear	Not clear	Not clear	No	Yes	Yes
5	The alternatives being compared are clearly described.	Yes	Yes	Yes	Not clear	Not clear	Yes	Yes	Not clear	Yes	Yes
6	The form of economic evaluation used is stated.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7	The choice of form of economic evaluation is justified in relation to the questions addressed.	Yes	No	No	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear	Yes
	Data collection										
8	The source(s) of effectiveness estimates used are stated.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9	Details of the design and results of effectiveness study are given (if based on a single study).	Yes	NA	Yes	Not clear	No	Not clear	Not clear	Not clear	Not clear	Yes

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	Item	Deshmukh 2017	Djalalov 2015	Garrison 2019	Kwon 2016	Kwon 2017	Lamond 2015	Lester 2016	Patel 2017	Schwartz 2019	Ward 2019
10	Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies).	NA	Yes	NA	No	No	Not clear	No	Not clear	Not clear	Not clear
11	The primary outcome measure(s) for the economic evaluation are clearly stated.	Not clear	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	Yes
12	Methods to value benefits are stated.	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear	No	No	Not clear
13	Details of the subjects from whom valuations were obtained were given.	Yes	Yes	Yes	Not clear	Not clear	Yes	Not clear	Not clear	Not clear	Yes
14	Productivity changes (if included) are reported separately.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
15	The relevance of productivity changes to the study question is discussed.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
16	Quantities of resource use are reported separately from their unit costs.	No	No	No	No	No	No	No	No	No	No
17	Methods for the estimation of quantities and unit costs are described.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
18	Currency and price data are recorded.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

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	Item	Deshmukh 2017	Djalalov 2015	Garrison 2019	Kwon 2016	Kwon 2017	Lamond 2015	Lester 2016	Patel 2017	Schwartz 2019	Ward 2019
19	Details of currency of price adjustments for inflation or currency conversion are given.	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes
20	Details of any model used are given.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
21	The choice of model used and the key parameters on which it is based are justified.	NA	Yes	Yes	Yes	Yes	Not clear	Yes	Yes	Yes	Yes
	Analysis and interpretation of results										
22	Time horizon of costs and benefits is stated.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
23	The discount rate(s) is stated.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
24	The choice of discount rate(s) is justified.	No	No	No	No	No	No	No	No	No	Yes
25	An explanation is given if costs and benefits are not discounted.	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
26	Details of statistical tests and confidence intervals are given for stochastic data.	NA	Yes	Not clear	No	Yes	No	No	No	No	Not clear

27	The approach to sensitivity analysis is given.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Item		Deshmukh 2017	Djalalov 2015	Garrison 2019	Kwon 2016	Kwon 2017	Lamond 2015	Lester 2016	Patel 2017	Schwartz 2019	Ward 2019
28	The choice of variables for sensitivity analysis is justified.	Not clear	Not clear	Yes	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear	Yes
29	The ranges over which the variables are varied are justified.	Yes	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear	Yes
30	Relevant alternatives are compared.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
31	Incremental analysis is reported.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
32	Major outcomes are presented in a disaggregated as well as aggregated form.	Not clear	Not clear	Not clear	Yes	Yes	Not clear	Yes	Yes	Yes	Not clear
33	The answer to the study question is given.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
34	Conclusions follow from the data reported.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
35	Conclusions are accompanied by the appropriate caveats.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

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Table 115: Drummond checklist for cost-effectiveness models (Africa and other)

Item		Aboutorabi 2015	Alshreef 2019	Ansaripour 2018	Gershon 2019	Leung 2016
	Study design					
1	The research question is stated.	Yes	Yes	Yes	Yes	Yes
2	The economic importance of the research question is stated.	Yes	Yes	Yes	Yes	Yes
3	The viewpoint(s) of the analysis are clearly stated and justified.	Yes	Yes	Yes	Not clear	Yes
4	The rationale for choosing alternative programmes or interventions compared is stated.	Yes	Not clear	Yes	Not clear	Not clear
5	The alternatives being compared are clearly described.	Yes	Yes	Yes	Not clear	Yes
6	The form of economic evaluation used is stated.	Yes	Yes	Yes	Yes	Yes
7	The choice of form of economic evaluation is justified in relation to the questions addressed.	Yes	Yes	Yes	Not clear	No
	Data collection					
8	The source(s) of effectiveness estimates used are stated.	Yes	Yes	Yes	Yes	Yes
9	Details of the design and results of effectiveness study are given (if based on a single study).	Yes	Yes	Yes	Not clear	NA
10	Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies).	Not clear	Yes	Not clear	No	Yes

11	The primary outcome measure(s) for the economic evaluation are clearly stated.	Yes	Yes	Yes	Yes	Yes

Item		Aboutorabi 2015	Alshreef 2019	Ansaripour 2018	Gershon 2019	Leung 2016
12	Methods to value benefits are stated.	Not clear	Not clear	Not clear	Not clear	Not clear
13	Details of the subjects from whom valuations were obtained were given.	Yes	Yes	Yes	Not clear	Yes
14	Productivity changes (if included) are reported separately.	No	No	NA	NA	NA
15	The relevance of productivity changes to the study question is discussed.	No	No	NA	NA	NA
16	Quantities of resource use are reported separately from their unit costs.	No	Yes	No	No	No
17	Methods for the estimation of quantities and unit costs are described.	No	Yes	No	Yes	Yes
18	Currency and price data are recorded.	Yes	Yes	Yes	Yes	Yes
19	Details of currency of price adjustments for inflation or currency conversion are given.	Yes	Yes	Yes	No	Yes
20	Details of any model used are given.	Yes	Yes	Yes	Yes	Yes
21	The choice of model used and the key parameters on which it is based are justified.	Yes	Yes	Yes	Yes	Yes
	Analysis and interpretation of results					

22	Time horizon of costs and benefits is stated.	Yes	Yes	Yes	Yes	Yes
23	The discount rate(s) is stated.	Yes	Yes	Yes	Yes	Yes
24	The choice of discount rate(s) is justified.	No	Yes	Yes	No	No
25	An explanation is given if costs and benefits are not discounted.	NA	NA	NA	NA	NA

Item		Aboutorabi 2015	Alshreef 2019	Ansaripour 2018	Gershon 2019	Leung 2016
26	Details of statistical tests and confidence intervals are given for stochastic data.	Yes	Yes	Not clear	No	Yes
27	The approach to sensitivity analysis is given.	Yes	Yes	Yes	Yes	Yes
28	The choice of variables for sensitivity analysis is justified.	Not clear	Not clear	Yes	Not clear	Not clear
29	The ranges over which the variables are varied are justified.	Not clear	Not clear	Yes	Not clear	Not clear
30	Relevant alternatives are compared.	Yes	Yes	Yes	Yes	Yes
31	Incremental analysis is reported.	Yes	Yes	Yes	Yes	Yes
32	Major outcomes are presented in a disaggregated as well as aggregated form.	Not clear	Not clear	Not clear	Yes	Not clear
33	The answer to the study question is given.	Yes	Yes	Yes	Yes	Yes
34	Conclusions follow from the data reported.	Yes	Yes	Yes	Yes	Yes
35	Conclusions are accompanied by the appropriate caveats.	Yes	Yes	Yes	Yes	Yes

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Appendix M Metastastic health state – Endocrine resistant pathway

To inform the ET-resistant metastatic pathway the costing approach from the MONARCH 2 model used in the the Danish aBC submission [7] was used.

The following resource use categories were captured in the analysis:

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

Drug acquisition

Drug acquisition costs are calculated by combining dosing regimens, relative dose intensity (RDI) adjustments and mean patient BSA data. Treatment regimens are based on the ABE-FUL and 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.
Unit costs are based on the Medicinpriser.dk database. Treatment regimens and drug acquisition costs for each comparator are presented in Table 116 and Table 117, respectively. For IV therapies, including fulvestrant that is administered IM, drug acquisition costs per patient are calculated by determining the number of vials needed to provide the required dose and multiplying by the unit price of the vial.

Table 116 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
ANAS	Rose (2003)	1mg	28	28	100%	RDI assumed to be 100% for oral 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

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Treat-ment	Study	Dose (mg)	Admins per cycle	Cycle length	RDI	Comments
EXE-EVE	BOLERO 2	EXE: 25mg EVE: 10mg	EXE: 28 EVE: 28	28	EXE: 100% EVE: 100%	RDI assumed to be 100% for oral treat-ment
LTZ	Rose (2003)	2.5mg	28	28	100%	RDI assumed to be 100% for oral treat-ment
PAL-FUL	PALOMA 3	PAL: 125mg FUL: 500mg	PAL: 21 FUL: 1 (2 in cycle 1 and 1 thereaf-ter)	28	PAL: 100% FUL: 100%	RDI assumed to be 100% for oral and IM treatment
TMX	Sten-bygaard (1993)	20mg	28	28	100%	RDI assumed to be 100% for oral treat-ment

Abbreviations: mg, milligram; RDI, relative dose intensity

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Table 117 Drug acquisition

Treat-ment	Drug	Units (mg/ml)	Vial/pack size (ml/mg)	Cost per package	Source
ABE-FUL	ABE	150	56	19,941.92 kr.	Lilly UK list price
ABE-FUL	FUL	250	2	4,450.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=416143
ANAS	ANAS	1	100	38.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=425938
FUL	FUL	250	2	4,450.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=416143
EXE	EXE	25	100	160.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=509250
EXE-EVE	EXE	25	100	160.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=509250
EXE-EVE	EVE	10	30	296.22 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=014884
LTZ	LTZ	2.5	100	116.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=073724
PAL-FUL	PAL	125	21	25,269.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=473657
PAL-FUL	FUL	250	2	4,450.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=416143
TMX	TMX	20	100	189.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=412924

Abbreviations: Mg, milligram; ml, millilitre

Source: Medicinepriser.dk

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Best supportive care

A summary of the BSC components and resource utilisation are provided in Table 118; BSC costs are provided in Table 119 updated 2022 unit costs from medicinpriser.dk were included.

Table 118 BSC components and resource use

BSC component	Medication	Proportion	Units per day	Duration in days	Frequency per unit	Resource use per week	Source
Pain management*	Oxycodone	9.49%	200.00	On-going	Daily	1400.00	MONARCH 2 CSR; dose-BNF
Anti-emesis or anti-nauseants	Ondansetron	9.79%	16.00	5	Daily	112.00	MONARCH 2 CSR; dose-BNF
Depression or anxiety	Alprazolam	8.28%	15	5	Daily	3500.00	MONARCH 2 CSR; dose-BNF
Cancer-associated venous thromboembolic disease	Rivaroxaban	3.46%	5	21	Daily	210.00	MONARCH 2 CSR; dose-BNF
Growth factors	Filgrastim	4.22%	357.50	14	Weekly	333.50	MONARCH 2 CSR; dose-BNF

*non-opioids have not been included as they were deemed inconsequential for the cost-effectiveness model

Table 119 BSC components

BSC treatment	Active Ingredients	Dose per tablet or vial	Unit	Units per package	Price per package	Unit cost	Reference
Oxycodone	Oxycodone hydrochloride	5mg	Capsule	30	25.89 kr.	0.86	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=564131

Ondansetron	**Ondansetron (as Ondansetron hydrochloride)**	**4mg**	**tablets**	**10**	**102.00 kr.**	**10.20**	**https://www.medicinpriser.dk/Default.aspx?id=15&vnr=147243**
Alprazom	**Alprazolam**	**0.25mg**	**tablets**	**20**	**22.00 kr.**	**0.22**	**https://www.medicinpriser.dk/Default.aspx?id=15&vnr=171193**
Rivaroxaban	**Rivaroxaban**	**10mg**	**tablets**	**10**	**161.61 kr.**	**16.16**	**https://www.medicinpriser.dk/Default.aspx?id=15&vnr=449868**
Filgrastim	**Filgrastim**	**30mega unit/ml**	**solution**	**5**	**970.00 kr.**	**194.00**	**https://www.medicinpriser.dk/Default.aspx?id=15&vnr=555232**

Source: Medicinpriser.dk

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Follow-up care

The follow-up care components, proportions and frequencies are listed in Table 45.

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 (Table 121 and Table 122).
Unit costs were sourced from DRG tariffs 2022.

Table 120. 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
	Electrocardio-gram	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 con-sultation	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
	Electrocardio-gram	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 con-sultation	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)

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

Table 121 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%	

Table 122 Scan modalities received by patients in MONARCH1

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%	

Table 123 Follow-up care costs

Component	Cost	Source
CT scan	3,389.00 kr.	DRG 2022, Kvinde , 51 År (DC509)Brystkræft UNS, 36PR07 - Klinisk fysiologi/nuklearmedicin grp.

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MRI scan	3,389.00 kr.	DRG 2022, Kvinde , 51 År (DC509)Brystkræft UNS, 36PR07 - Klinisk fysiologi/nuklearmedicin grp. G
PET scan	3,389.00 kr.	DRG 2022, Kvinde , 51 År (DC509)Brystkræft UNS, 36PR07 - Klinisk fysiologi/nuklearmedicin grp. G
Electrocardiogram	2,616.00 kr.	DRG- 2022 - Kvinde , 51 År (DC509)Brystkræft 37PR01 - Klinisk neurofysiologi grp. 1
Complete blood count	46.00 kr.	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 included
Serum chemistry	139.00 kr.	Sum of different Tests at Rigshospitalet Total test price of sodium, potassium, magnesium, creatinine and calcium lab tests
Oncologist consultation	2,041.00 kr.	DRG 2022 - 09MA98 - MDC09 1-dagsgruppe, pat. mindst 7 år
GP visit	1,176.00 kr.	DMC Værdisætning af enhedsomkostninger
District nurse (home visit)	550.00 kr.	DMC Værdisætning af enhedsomkostninger
Clinical nurse (specialist)	554.00 kr.	DMC Værdisætning af enhedsomkostninger

Source: DRG 2022 Database

Adverse events

The AE rates included in the model are provided in **Table 124**. Unit costs were based on DRG 2022 database (**Table 125**)

Table 124 Adverse event probabilities, by comparator

Adverse event	ABE-FUL	RIBO-FUL	PAL-FUL	EXE-EVE	FUL	CAP	EXE
Anaemia	7.26%	3.11%	2.61%	7.05%	0.90%	6.86%	0.00%
Diarrhea	13.38%	0.62%	0.00%	2.07%	0.45%	7.84%	0.00%
Dyspnoea	2.72%	0.00%	0.29%	4.98%	1.35%	0.00%	0.00%
Gamma-glutamyl-transferase (GGT) increase	1.81%	0.00%	0.00%	7.05%	0.45%	0.00%	2.94%
Hyperglycemia	0.68%	0.00%	0.00%	4.98%	0.45%	0.98%	0.00%
Leukopenia	8.84%	14.08%	25.22%	0.00%	0.00%	0.00%	0.00%
Neutropenia	26.53%	53.42%	62.03%	0.00%	1.79%	5.88%	0.00%
Stomatitis	0.45%	0.00%	0.58%	8.09%	0.00%	6.86%	0.00%

Source: ABE-FUL, MONARCH 2; ANAS, Campos 2009; EXE, BOLERO 2; EXE-EVE, BOLERO 2; FUL, MONARCH 2; LTZ, assumed equal to ANAS; PAL-FUL, Turner 2015; TMX, assumed equal to FUL

Table 125 Adverse event costs

Adverse event	Unit Cost (2022)	Source
Anaemia	3,176.00 kr.	DRG 2022, Mand , 51 År (DD649)Anæmi UNS, 16MA98 - MDC16 1-dagsgruppe, pat. mindst 7 år
Diarrhoea	6,756.00 kr.	DRG 2022, Mand , 51 År (DK529B)Ikke-infektiøs diaré UNS, 06MA11 - Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag.
Dyspnoea	3,114.00 kr.	DRG 2022, 06MA11: Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag., Diagnosis: DK529B: Ikke-infektiøs diaré UNS
Gamma- glutamyltransferase (GGT) increase	2,610.00 kr.	DRG 2022, 07MA98: MDC07 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR748: Anden abnorm serumenzymkoncentration
Hyperglycemia	3,987.00 kr.	DRG 2022, 23MA03: Symptomer og fund, u. kompl. bidiag., Diagnosis: DR739: Hyper-glykæmi UNS
Leukopenia	3,176.00 kr.	DRG 2022, Mand , 51 År (DD728H) Leukopeni 16MA98 - MDC16 1-dagsgruppe, pat. mindst 7 år
Neutropenia	3,176.00 kr.	DRG 2022, Mand , 51 År (DD709)Neutropeni UNS, 16MA98 - MDC16 1-dagsgruppe, pat. mindst 7 år
Stomatitis	1,862.00 kr.	DRG 2022, 03MA98: MDC03 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DK121B: Stomatitis UNS

Source: DRG Tariffs 2022

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 pre- and post-progression periods, assuming this was the same between ABE-FUL and PBO-FUL (**Table 126**).

Table 126 Length of stay for patients in MONARCH 2

Cohort	Treatment	Number of hospitalisations	Mean (days)	Standard Deviation
Base case:				

Pre-progres-sion	ABE-FUL & PBO-FUL	73		7.74	8.57
Post-progres-sion	ABE-FUL & PBO-FUL	23		7.65	4.90
Scenarios:					
Overall	ABE-FUL & PBO-FUL	96		7.72	7.82
Pre-progres-sion	ABE-FUL	63		7.05	7.19
Post-progres-sion	ABE-FUL	16		6.50	4.56
Overall	ABE-FUL	79		6.94	6.72
Pre-progres-sion	PBO-FUL	10		12.10	14.36
Post-progres-sion	PBO-FUL	7		10.29	4.96
Overall	PBO-FUL	17		11.35	11.22

The rate of hospitalisation was estimated based on an analysis of the MONARCH 2 data (**Table 127**). This involved estimating rates of hospitalisation by pre- and post-progression states based on the observed number of hospitalisations and total follow-up time.

Table 127 Hospitalisation rate and probability data from MONARCH2

Cohort	Treatment	Total hospi-talisation	Total follow-up (days)	Rate of hospi-talisation / week	Probability of hospitalisation/ week
Base case:					
Pre-pro-gression	ABE-FUL & PBO-FUL	86	214841	0.003	0.003
Post-pro-gression	ABE-FUL & PBO-FUL	11	11393	0.007	0.007
Scenarios:					
Overall	ABE-FUL & PBO-FUL	97	226234	0.003	0.003
Pre-pro-gression	ABE-FUL	68	151079	0.003	0.003
Post-pro-gression	ABE-FUL	6	6120	0.007	0.007
Overall	ABE-FUL	74	157199	0.003	0.003
Pre-pro-gression	PBO-FUL	18	63762	0.002	0.002

Post-pro-gression	**PBO-FUL**	**5**	**5273**	**0.007**	**0.007**
Overall	**PBO-FUL**	**23**	**69035**	**0.002**	**0.002**

The unit cost was assumed equal to those the early breast cancer setting.

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Post-progression therapy

Post-progression therapy were 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 comparators sufficiently to impact on cost-effectiveness (CE) estimates.

Based on clinical input received, an assumption was made that patients would not be re-treated with the same treatment or drug component in post-progression (i.e., the probability of receiving the same treatment/drug component in post-progression as was received in pre-progression was set to zero). The distributions were subsequently rescaled to sum to 100% (Table 128).

Table 128 Post-progression therapy distributions

Post-progression therapy	Pre-progression therapy						
	ABE-FUL	RIBO-FUL	PAL-FUL	EXE-EVE	FUL	CAP	EXE
CAP	17.6%	17.6%	17.6%	32.2%	16.0%	0.0%	34.5 %
PAC	17.6%	17.6%	17.6%	0.0%	16.0%	19.5%	0.0%
VNB	4.6%	4.6%	4.6%	9.4%	5.8%	7.1%	16.0 %
ERI	5.5%	5.5%	5.5%	0.0%	4.4%	5.3%	0.0%
FUL	0.0%	0.0%	0.0%	30.9%	0.0%	0.0%	22.2 %
LTZ	6.3%	6.3%	6.3%	0.0%	8.0%	9.8%	0.0%
EXE	14.7%	14.7%	14.7%	0.0%	17.8%	21.7%	0.0%
EVE	11.5%	11.5%	11.5%	0.0%	13.1%	16.0%	0.0%
CYC	4.0%	4.0%	4.0%	12.1%	2.5%	3.1%	11.1 %
GEM	2.3%	2.3%	2.3%	5.4%	2.5%	3.1%	6.2%
BEV	5.8%	5.8%	5.8%	0.0%	3.6%	4.4%	0.0%

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

The rescaled subsequent therapy distribution was then multiplied by the proportion of patients expected to receive active therapy on disease progression (89.97%). The proportion of patients receiving active therapy after progression was assumed to be equal between treatment arms based on the MONARCH 2 trial (90.09% [ABE-FUL] vs. 89.81% [PBO-FUL]). The corresponding post-progression therapy distributions are presented in Table 129.

Table 129 Post-progression therapy distribution, by progression therapy

Post- progression therapy	PFS therapy							
	ABE-FUL	ANAS	FUL	EXE	EXE-EVE	LTZ	PAL-FUL	TMX

CAP	17.59%	16.03%	16.03%	34.51%	32.23%	17.59%	17.59%	16.03%
PAC	17.59%	16.03%	16.03%	0.00%	0.00%	17.59%	17.59%	16.03%
VNB	4.61%	5.83%	5.83%	16.02%	9.40%	6.40%	4.61%	5.83%
ERI	5.48%	4.37%	4.37%	0.00%	0.00%	4.80%	5.48%	4.37%
FUL	0.00%	0.00%	0.00%	22.19%	30.89%	0.00%	0.00%	0.00%
LTZ	6.34%	8.01%	8.01%	0.00%	0.00%	0.00%	6.34%	8.01%
EXE	14.71%	17.85%	17.85%	0.00%	0.00%	19.59%	14.71%	17.85%
EVE	11.54%	13.11%	13.11%	0.00%	0.00%	14.40%	11.54%	13.11%
CYC	4.04%	2.55%	2.55%	11.09%	12.09%	2.80%	4.04%	2.55%
GEM	2.31%	2.55%	2.55%	6.16%	5.37%	2.80%	2.31%	2.55%
BEV	5.77%	3.64%	3.64%	0.00%	0.00%	4.00%	5.77%	3.64%

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 pre-progression curve for each comparator adjusted by the proportion of pre-progression events which were progressive disease rather than death (Table 129). For ABE-FUL these events were estimated based on the MONARCH 2 trial. Data were not available from the primary publications for the alternative regimens, thus proportions were assumed to be equivalent across all treatments.

Table 130 Pre-Progression Free Survival events

Comparator	Number of progression events	Number of deaths	Proportion of pre-progression events which were death
ABE-FUL	379	15	3.96%

Drug acquisition

Post-progression therapy acquisition costs were calculated as per the comparator 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 (Table 131). Acquisition costs are presented in Table 132.

Table 131 Post-progression treatment regimens

Treatment	Drug	Study	Dose (mg)	Admins per cycle	Cycle length	Number of cycles	RDI	Comments
CAP	CAP	Kaufman (2015)	1250mg /m^2	28	21 days	TD	100 %	RDI assumed to be 100% for oral treatment

PAC	PAC	Perez (2001)	80mg / m^2	4	28 days	TD	100 %	From Beuse-linck (2010), RDI was 78% in initial 8 weeks then 71% from 8 weeks to TD
VNB	VNB	Meier (2008)	30mg / m^2	6	56 days	TD - only 4 consecutive cy-cles allowed	100 %	RDI assumed to be 100%, NR in Meier (2008)
ERI	ERI	Kauf-man (2015)	1.4mg /m^2	2	21 days	TD	100 %	-
FUL	FUL	MON-ARCH 2	500mg	1 (2 in cycle 1 and 1 there-after)	28 days	TD	100 %	Assumed equal to PFS
LTZ	LTZ	Rose (2003)	2.5mg	28	28 days	TD	100 %	Assumed equal to PFS
EXE	EXE	BOLERO 2	25mg	28	28 days	TD	100 %	Assumed equal to PFS
EVE	EVE	BOLERO 2	10mg	28	28 days	TD	100 %	Assumed equal to PFS
CYC	CYC	Ackland (2001)	400mg / m^2	2	28 days	TD – max of 6-9 cycles depend-ing on response	100 %	Median esti-mate of RDI in Ackland (2001)
CYC	EPI	Ackland (2001)	50mg / m^2	2	28 days	TD – max of 6-9 cycles depend-ing on response	100 %	Median esti-mate of RDI in Ackland (2001)
CYC	FLU	Ackland (2001)	500mg / m^2	2	28 days	TD – max of 6-9 cycles depend-ing on response	100 %	Median esti-mate of RDI in Ackland (2001)
GEM	GEM	Brodowi cz (2000)	1250mg / $_{m^2}$	3	28 days	TD	100 %	Assumed to be 100% RDI, no data reported in Brodowicz (2000)
BEV	BEV	Miller (2007)	10mg /kg	2	28 days	TD	100 %	Assumed to be 100% RDI, no data reported in Miller (2007)

Abbreviations: TD, treatment discontinuation

Table 132 Post-progression drug acquisition costs

Treat-ment	Drug	Units (mg/ml)	Vial size (ml)	Price per package	Source
CAP	CAP	150	60	170.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=155487
PAC	PAC	300	1	201.50 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=076395
VNB	VNB	10	1	2,500.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=168997
ERI	ERI	0.88	1	2,462.67 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=176930
FUL	FUL	250	2	4,450.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=416143
LTZ	LTZ	2.5	100	116.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=073724
EXE	EXE	25	100	107.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=509250
EVE	EVE	10	30	296.22 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=014884
CYC	CYC	50	100	906.61 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=575916
CYC	EPI	200	1	666.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=456784
CYC	FLU	50	1	1,310.15 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=187406
GEM	GEM	1400	1	330.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=186162
BEV	BEV	100	1	2,038.55 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=019445

Source: Medicinpriser.dk

Drug administration

Post-progression therapy administration costs were calculated as per the comparator drug acquisition costs. Infusion times were based on publications used to inform the treatment regimens. These data are presented in Table 133.The drug administration costs for each comparator are presented in Table 134.

Table 133 Post-progression therapy infusion times

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

Abbreviations: N/A, Not applicable; NR, not reported

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Table 134 Summary of drug administration costs for post-progression therapy

Line	Treatment	Drug	Cost per admin-istration	Cost per cycle	Source
PPS	CAP	CAP	0.00 kr.	0.00 kr.	Assumed zero for oral drugs
PPS	PAC	PAC	2,041.00 kr.	8,164.00 kr.	DRG 2022 - Kvinde , 51 År (DC509) Brystkræft UNS, 09MA98 - MDC09 1-dagsgruppe, pat. mindst 7 år
PPS	VNB	VNB	2,041.00 kr.	6,123.00 kr.	DRG 2022 - Kvinde , 51 År (DC509) Brystkræft UNS, 09MA98 - MDC09 1-dagsgruppe, pat. mindst 7 år
PPS	ERI	ERI	2,041.00 kr.	2,721.33 kr.	DRG 2022 - Kvinde , 51 År (DC509) Brystkræft UNS, 09MA98 - MDC09 1-dagsgruppe, pat. mindst 7 år
PPS	FUL	FUL	2,041.00 kr.	2,041.00 kr.	DRG 2022 - Kvinde , 51 År (DC509) Brystkræft UNS, 09MA98 - MDC09 1-dagsgruppe, pat. mindst 7 år
PPS	LTZ	LTZ	0.00 kr.	0.00 kr.	Assumed zero for oral drugs
PPS	EXE	EXE	0.00 kr.	0.00 kr.	Assumed zero for oral drugs
PPS	EVE	EVE	0.00 kr.	0.00 kr.	Assumed zero for oral drugs
PPS	CYC	CYC	0.00 kr.	0.00 kr.	Assumed zero for oral drugs
PPS	CYC	EPI	2,041.00 kr.	4,082.00 kr.	DRG 2022 - Kvinde , 51 År (DC509) Brystkræft UNS, 09MA98 - MDC09 1-dagsgruppe, pat. mindst 7 år
PPS	CYC	FLU	2,041.00 kr.	4,082.00 kr.	DRG 2022 - Kvinde , 51 År (DC509) Brystkræft UNS, 09MA98 - MDC09 1-dagsgruppe, pat. mindst 7 år
PPS	GEM	GEM	2,041.00 kr.	6,123.00 kr.	DRG 2022 - Kvinde , 51 År (DC509) Brystkræft UNS, 09MA98 - MDC09 1-dagsgruppe, pat. mindst 7 år
PPS	BEV	BEV	2,041.00 kr.	4,082.00 kr.	DRG 2022 - Kvinde , 51 År (DC509) Brystkræft UNS, 09MA98 - MDC09 1-dagsgruppe, pat. mindst 7 år

Abbreviations: PPS, Post-progression survival Source: DRG Tariffs 2022[4]

Appendix N Metastatic health state – Endocrine sensitive pathway

To inform the ET sensitive metastatic pathway the costing approach from the MONARCH 3 model used in the Danish aBC submission [7] was used.

The following resource use categories were included:

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

Drug acquisition

The dose required for each treatment was calculated by combining dosing regimen, 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 pre- and post-progression, and supportive care medications were primarily sourced from the medicinpriser.dk cost database. Treatment regimens and drug acquisition costs for each comparator are presented in Table 135 and Table 136, 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 135 Treatment regimens

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
EXE	25mg	28	28	IWATA (2003)
TMX	20mg	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: mg, Milligram

Notes: *1 loading dose and first per cycle dose

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Table 136 Drug acquisition costs

Treatment	Drug	Units	Vial/Pack size	Cost	Source
ABE-NSAI	ABE	150	56	19,941.92 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=544298
ABE-NSAI	LTZ	2.5	100	38.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=544299
ABE-NSAI	ANAS	1	100	116.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=073724
NSAI	LTZ	2.5	100	38.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=073724
NSAI	ANAS	1	100	38.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=544299
EXE	EXE	25	100	107.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=509250
TMX	TMX	20	100	189.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=412924
FUL	FUL	250	2	4,450.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=416143
PAL-NSAI	PAL	125	21	25,269.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=473657
PAL-NSAI	LTZ	2.5	100	116.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=073724
PAL-NSAI	ANAS	1	100	38.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=544299
RIBO-NSAI	RIBO	200	63	24,596.29 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=539793
RIBO-NSAI	LTZ	2.5	100	116.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=073724
RIBO-NSAI	ANAS	1	100	38.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=544299

Source: Medicinpriser.dk

Best supportive care

Components of BSC were identified from clinical guidelines, the MONARCH 3 trial (pre-progression health state) and the MONARCH 2 trial (post-progression 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, erythropoetic 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 CE. 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 137 and the unit cost of each component are presented in Table 138.

Table 137 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 3 CSR; dose-BNF
Anti-diarrheal	Loperamide	49.6%	0.50%	16.00	Daily	MONARCH 3 CSR; dose-BNF
Anti-emesis or anti- nau-seants	Ondansetron	8.6%	0.09%	16.00	Daily	MONARCH 3 CSR; dose-BNF
Bone modifying agents	Denosumab	23.8%	0.24%	60.00	Bi-annually	MONARCH 3 CSR; dose-BNF
Erythropoietic agents	Erythropoietin	0.6%	0.01%	450.00	Weekly	MONARCH 3 CSR; dose-BNF
Growth factors	Filgrastim	3.3%	0.03%	5.00	Weekly	MONARCH 3 CSR; dose-BNF
PPS						
Pain management*	Oxycodone	9.5%	0.09%	200.00	Daily	MONARCH 2 CSR; dose-BNF
Anti-emesis or anti- nau-seants	Ondansetron	9.8%	0.10%	16.00	Daily	MONARCH 2 CSR; dose-BNF
Depression or anxiety	Alprazolam	8.3%	0.08%	16.00	Daily	MONARCH 2 CSR; dose-BNF

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BSC component	Medication	Proportion	Standard error	Units	Frequency	Source
Cancer-associated venous thromboembolic disease	Placeholder	3.5%	0.03%	-		MONARCH 2 CSR; dose-BNF
Growth factors	Filgrastim	4.2%	0.04%	5.00	Weekly	MONARCH 2 CSR; dose-BNF

Table 138. BSC unit costs

BSC treatment	Active Ingredients	Dose per tablet or vial	Unit	Units per package	Price per package	Unit cost	Reference
Oxycodone	Oxycodone hydrochloride	5mg	Capsule	30	25.89 kr.	0.86 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=564131
Loperamide	Loperamide hydrochloride	2mg	tablets	60	142.25 kr.	2.37 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=036459
Ondansetron	Ondansetron (as Ondansetron hydrochloride)	4mg	tablets	10	102.00 kr.	10.20 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=145872
Denosumab	Denosumab	60mg	solution	1	1,814.46 kr.	1,814.46 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=085792
Erythropoietin	Erythropoietin	60000 IU	solution	1	2,198.68 kr.	2,198.68 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=054036
Filgrastim	Filgrastim	30mega unit/ml	solution	5	970.00 kr.	194.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=100682
Alprazolam	Alprazolam	0.25mg	tablets	20	22.00 kr.	0.37 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=171193

Rivaroxaban	**Rivaroxaban**	**10**	**tablets**	**5**	**161.61 kr.**	**16.16 kr.**	**https://www.medicinpriser.dk/Default.aspx?id=15&vnr=449868**

Source: Medicinpriser.dk

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Follow-up care

Components of follow-up care were identified from the MONARCH 3 trial for the pre-progression health state, the MONARCH 2 trial for the post-progression '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 139. Unit costs were sourced from DRG 2022 database.

Table 139 Follow-up care

Component	Proportion	Standard error*	Frequency			Frequency per	Source
			PFS	PFS2	PPS		
CT scan	100.00%	1.00%	0.42	0.50	0.50	Cycle	MONARCH 3 CSR
Electrocardio gram	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
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

Notes: Assumed to be 1% around the mean

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.13 AEs were selected for inclusion if they were Grade III/IV events occurring in more than 5% of patients for at least one comparator. AE rates included in the model are provided in Table 140.

Table 140 Adverse event probabilities

Event*	ABE-NSAI	PAL-NSAI	RIBO-NSAI	NSAI	RIBO-FUL	TMX	FUL
Alanine aminotransferase increased	6.10%	0.20%	9.00%	1.00%	0.00%	0.00%	1.00%
Anaemia	5.50%	5.90%	2.40%	1.00%	3.11%	0.00%	0.00%
Aspartate aminotransferase increased	3.40%	0.00%	6.00%	1.00%	0.00%	2.00%	1.00%
Diarrhoea	9.20%	1.40%	2.40%	1.00%	0.62%	0.00%	0.00%
Hypertension	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%
Lymphopenia	3.10%	0.00%	7.00%	0.00%	0.00%	0.00%	0.00%
Nausea	0.90%	0.20%	2.40%	1.00%	0.00%	5.00%	0.00%
Neutropenia	22.30%	67.10%	59.00%	0.00%	53.42%	0.00%	0.00%

Unit costs associated with the AE are based on DRG 2022 Costs (Table 63).

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Table 69 Adverse event costs

Event	Cost	Source
Alanine aminotransferase increased	1,905.00 kr.	DRG 2022 Mand , 51 År (DR740)Transaminase- og laktatdehydrogenaseforhøjelse, 23MA98 - MDC23 1-dagsgruppe, pat. mindst 7 år
Anaemia	3,176.00 kr.	DRG 2022, Mand , 51 År (DD649)Anæmi UNS, 16MA98 - MDC16 1-dagsgruppe, pat. mindst 7 år
Aspartate aminotransferase increased	1,905.00 kr.	DRG 2022 Mand , 51 År (DR740)Transaminase- og laktatdehydrogenaseforhøjelse, 23MA98 - MDC23 1-dagsgruppe, pat. mindst 7 år
Diarrhoea	6,756.00 kr.	DRG 2022, Mand , 51 År (DK529B)Ikke-infektiøs diaré UNS, 06MA11 - Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag.
Hypertension	1,153.00 kr.	DRG 2022, 05MA98: MDC05 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DI109: Essentiel hypertension
Leukopenia	3,176.00 kr.	DRG 2022, Mand , 51 År (DD728H) Leukopeni 16MA98 - MDC16 1-dagsgruppe, pat. mindst 7 år
Lymphopenia	3,176.00 kr.	DRG 2022, Mand , 51 År (DD728D) Lymfopeni, 16MA98 - MDC16 1-dagsgruppe, pat. mindst 7 år
Nausea	5,130.00 kr.	DRG 2022, 06MA11: Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag., Diagnosis: DR119C: Opkastning
Neutropenia	3,176.00 kr.	DRG 2022, Mand , 51 År (DD709)Neutropeni UNS, 16MA98 - MDC16 1-dagsgruppe, pat. mindst 7 år

Source: DRG Tariffs 2022

Hospitalisation

Hospitalisation data were included in the pre-progression state for first-line advanced patients based on the MONARCH 3 trial data. Hospitalisation data were included in the post-progression state for second-line advanced patients based on the pre- and post-progression 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-TR AEs 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 pre- and post-progression periods, and assumed equal between ABE-NSAI and PBO-NSAI (Table 141).

Table 141 Length of stay for patients in MONARCH 3

Cohort	Treatment	Number of hospitalisations	Mean (days)	SD
Base case:				
Pre-progression	**ABE-NSAI & PBO-NSAI**	**72**	**8.58**	**10.99**

The unit cost per day was assumed equal to those in the early breast cancer setting

MONARCH 2 hospitalisation

The same approach used to estimate the cost per hospitalisation for MONARCH 3 was applied to the MONARCH 2 data. 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 treatments was the same as FUL. The length of stay data for FUL based are presented in **Table 142**.

Table 142 Length of stay for patients in MONARCH 2 – PBO-FUL

Cohort	Treatment	Number of hospitalisations	Mean (days)	Standard Deviation
Base case				
Pre-progression	**PBO-FUL**	**10**	**12.10**	**14.36**
Post-progression	**PBO-FUL**	**7**	**10.29**	**4.96**

As more events were observed in the pre-progression period of the MONARCH 2 trial for patients receiving PBO-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 143**.

Table 143 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	**PBO-FUL**	**18**	**63762**	**0.000009**	**0.00001**
Post-progression	**PBO-FUL**	**5**	**5273**	**0.000031**	**0.00003**
Overall	**PBO-FUL**	**23**	**69035**	**0.000011**	**0.00001**

Summary of hospitalisation probabilities

Based on the analysis of rates of hospitalisation, a summary of the monthly probability of hospitalisation is provided in **Table 144**.

Table 144 Summary of base case hospitalisation probabilities by health state

Treatment	Pre-progression	Pre-progression2	Post-progression
ABE+NSAI	0.0085	0.0086	0.0288
NSAI	0.0085	0.0086	0.0288
EXE	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

Source: PFS1 MONARCH 3 IPD, PFS2 and PPS MONARCH 2 IPD

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). RDI was included in the calculation of drug costs as a scenario in the model.

As noted above, unit costs were based medicinpriser.dk databases. 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 TA503.11 An assumption was made that patients would not be re-treated with the same treatment following progression (i.e., those receiving a first-line advanced NSAI-based combination regimen would not receive NSAI following disease progression). Consequently, distributions (where applicable) were subsequently rescaled to sum to 100% (Table 145).

Table 145 Second-line advanced treatment proportions

	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%
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%

Post-progression therapy costs comprise drug acquisition and drug administration.

Drug acquisition

Treatment regimens for second-line advanced therapy were based on studies identified in the SLR, previous TAs and dosing guidance published by BNF (Table 146). Acquisition costs are presented in Table 147.

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Table 146 Second-line treatment regimens

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	
FUL	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
EVE+EXE	EXE	25	fixed	28	28	TA495 - Table 46; EMC Accessed 16th March 2018

Table 147. Second-line therapy drug acquisition costs

Treatment	Drug	Units (mg/ml)	Vial size (ml)	Price	Source
CAP	CAP	150	60	170.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=155487
PAC	PAC	300	1	201.50 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=076395
DOC	DOC	80	1	150.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=170823

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Treatment	Drug	Units (mg/ml)	Vial size (ml)	Price	Source
FUL	FUL	250	2	4,450.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=416143
ANAS	ANAS	1	100	38.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=544299
LTZ	LTZ	2.5	100	116.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=073724
EXE	EXE	25	100	107.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=509250
TMX	TMX	20	100	189.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=412924
EVE+EXE	EVE	10	30	296.22 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=014884
EVE+EXE	EXE	25	100	107.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=509250

Drug administration

Second-line therapy administration costs were calculated as per the first-line comparator drug acquisition costs. Costs associated with second-line treatment are presented in Table 148.

Table 148 Second-line drug administration costs

Treat-ment	Drug	Administra-tion	Admins per cycle	Cost per ad-min	Source
CAP	CAP	Oral	28*	0.00 kr.	Assumed zero for oral drugs
PAC	PAC	IV	1	2,041.00 kr.	DRG 2022 - Kvinde , 51 År (DC509) Brystkræft UNS, 09MA98 - MDC09 1-dagsgruppe, pat. mindst 7 år
DOC	DOC	IV	1	2,041.00 kr.	DRG 2022 - Kvinde , 51 År (DC509) Brystkræft UNS, 09MA98 - MDC09 1-dagsgruppe, pat. mindst 7 år

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FUL	**FUL (loading dose)**	**IM**	**1**	**2,041.00 kr.**	**DRG 2022 - Kvinde , 51 År (DC509) Brystkræft UNS, 09MA98 - MDC09 1-dagsgruppe, pat. mindst 7 år**
FUL	**FUL**	**IM**	**1**	**2,041.00 kr.**	**DRG 2022 - Kvinde , 51 År (DC509) Brystkræft UNS, 09MA98 - MDC09 1-dagsgruppe, pat. mindst 7 år**
ANAS	**ANAS**	**Oral**	**28**	**0.00 kr.**	**Assumed zero for oral drugs**
LTZ	**LTZ**	**Oral**	**28**	**0.00 kr.**	**Assumed zero for oral drugs**
EXE	**EXE**	**Oral**	**28**	**0.00 kr.**	**Assumed zero for oral drugs**
TMX	**TMX**	**Oral**	**30**	**0.00 kr.**	**Assumed zero for oral drugs**
EVE+EXE	**EVE**	**Oral**	**28**	**0.00 kr.**	**Assumed zero for oral drugs**
EVE+EXE	**EXE**	**Oral**	**28**	**0.00 kr.**	**Assumed zero for oral drugs**

Third-line advanced treatment

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 regimens receive sufficient enough to impact on CE estimates.

A fixed cost of post-progression therapy was assigned to the proportion of patients with disease progression 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 disease progression on their second-line advanced treatment. An assumption was made that patients would not be re-treated with the same treatment in post-progression (i.e., those receiving TMX as their first-line advanced treatment would not receive TMX following disease progression). Consequently, the distributions (where applicable) were subsequently rescaled to sum to 100% (Table 149).

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Table 149 Proportion of patients receiving third-line advanced treatment

	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%

Treatment regimens were informed by previous TAs[9] and dosing guidance published in the BNF[54]; and are presented in Table 150.

Table 150 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	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

Third-line advanced therapy acquisition costs are shown **Table 151** and drug administration **Table 152**.

Table 151 Third-line advanced treatment drug acquisition costs

Treat-ment	Drug	Mg/tablet/vial	Tab-lets/vials per pack	Price per pack	Updated Source
CAP	CAP	150	60	170.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=155487
ERI	ERI	0.88	1	2,462.67 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=176930
FUL	FUL	250	2	4,450.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=416143
ANAS	ANAS	1	100	38.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=544299
EXE	EXE	25	100	107.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=509250
TMX	TMX	20	100	189.00 kr.	https://www.medicinpriser.dk/Default.aspx?id=15&vnr=412924

Table 152 Third-line therapy administration costs

Treatment	Drug	Admins per cycle	Cost per admin	Source
CAP	CAP	1	0.00 kr.	Assumed zero for oral drugs
ERI	ERI	2	2,041.00 kr.	DRG 2022 - Kvinde , 51 År (DC509) Brystkræft UNS, 09MA98 - MDC09 1-dagsgruppe, pat. mindst 7 år
FUL (loading dose)	FUL	1	2,041.00 kr.	DRG 2022 - Kvinde , 51 År (DC509) Brystkræft UNS, 09MA98 - MDC09 1-dagsgruppe, pat. mindst 7 år

FUL	FUL	1	2,041.00 kr.	DRG 2022 - Kvinde , 51 År (DC509) Brystkræft UNS, 09MA98 - MDC09 1-dagsgruppe, pat. mindst 7 år
ANAS	ANAS	28	0.00 kr.	Assumed zero for oral drugs
EXE	EXE	28	0.00 kr.	Assumed zero for oral drugs
TMX	TMX	28	0.00 kr.	Assumed zero for oral drugs

Time on third-line advanced therapy was calculated based on an assumption that patients spent approximately 37% of their time on treatment in post-progression following disease progression on second-line advanced therapy. This assumption was based on external TL opinion. Estimated TTD based on this assumption is presented in **Table 153**.

Table 153 Time on third-line treatment

Treatment	Time on treatment (months)
ABE-NSAI	8.683
PAL-NSAI	8.683
RIBO-NSAI	8.683
NSAI	8.683
RIBO-FUL	8.715
TMX	8.683
FUL	8.715

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Appendix O Efficacy and safety results for ITT population in monarchE

12.1.1.1 Results monarchE – Efficacy

12.1.1.1.1 monarchE - IDFS

A total of 565 patients experienced IDFS events, including 232 (8.3%) in the abemaciclib + ET arm and 333 (11.8%) in the ET alone arm. The median follow-up time was 27.1 months in abemaciclib plus ET arm and 27.2 months in the ET alone arm. With the additional follow-up, abemaciclib plus ET reduced the risk of developing invasive disease by 30.4% (stratified HR=0.696, 95% CI: 0.588, 0.823) versus ET alone, together with a 3-year IDFS rate: 88.8% vs 83.4%, for abemaciclib plus ET versus ET alone respectively. Kaplan Meier (KM) curves of IDFS for patients in the ITT population of monarchE who received either abemaciclib plus ET or ET alone are displayed in Figure 4. The figure in the middle shows the curves with a truncated y-axis (70% to 100%) without any censoring ticks to better visualize the separation of curves. In Table 13, result of IDFS from the latest DCO from April 2021 is presented.

Figure 40. monarchE trial, Kaplan Meier IDFS analysis for patients receiving abemaciclib in combination with ET and patients receiving ET alone.

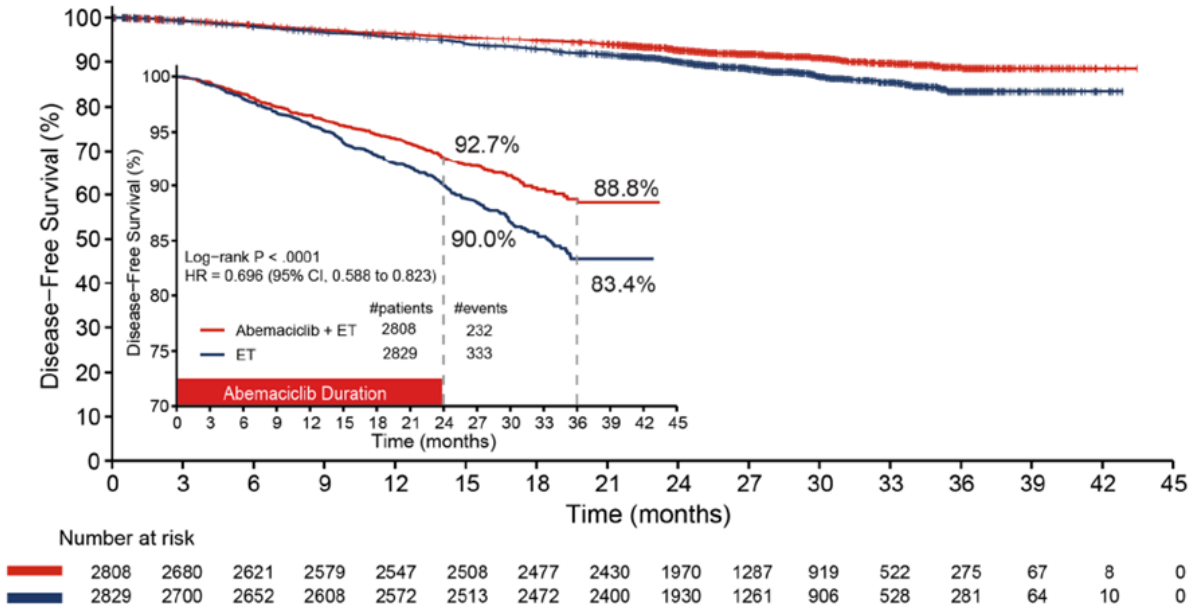

Table 154. monarchE IDFS results

Outcome	Study arm	N	Result	p-value	Reference
IDFS rate % (95% CI)	Abemaciclib + ET	2,808	88.8 (87.0-90.3)	<0.0001	[14]
	ET alone	2,829	83.4 (81.3-85.3)		[14]

Abbreviations: IDFS: Invasive disease-free survival; CI: Confidence interval.
Source: Lilly Data on File. Clinical Study Report: monarchE [14]. Data cut-off: 01 April 2021.

No statistically significant interactions were observed, supporting a consistent treatment benefit across all pre-specified subgroups. Figure 5 display the forest plot of IDFS, suggesting addition of abemaciclib to ET translates to a reduction in the risk of disease recurrence in the majority of the subgroups analysed, including patients from different regions and pre- and post- menopausal women. There were a few subgroups with hazard ratio point estimates greater than 1 and wide confidence intervals, primarily driven by the small number of events observed within those subgroups.

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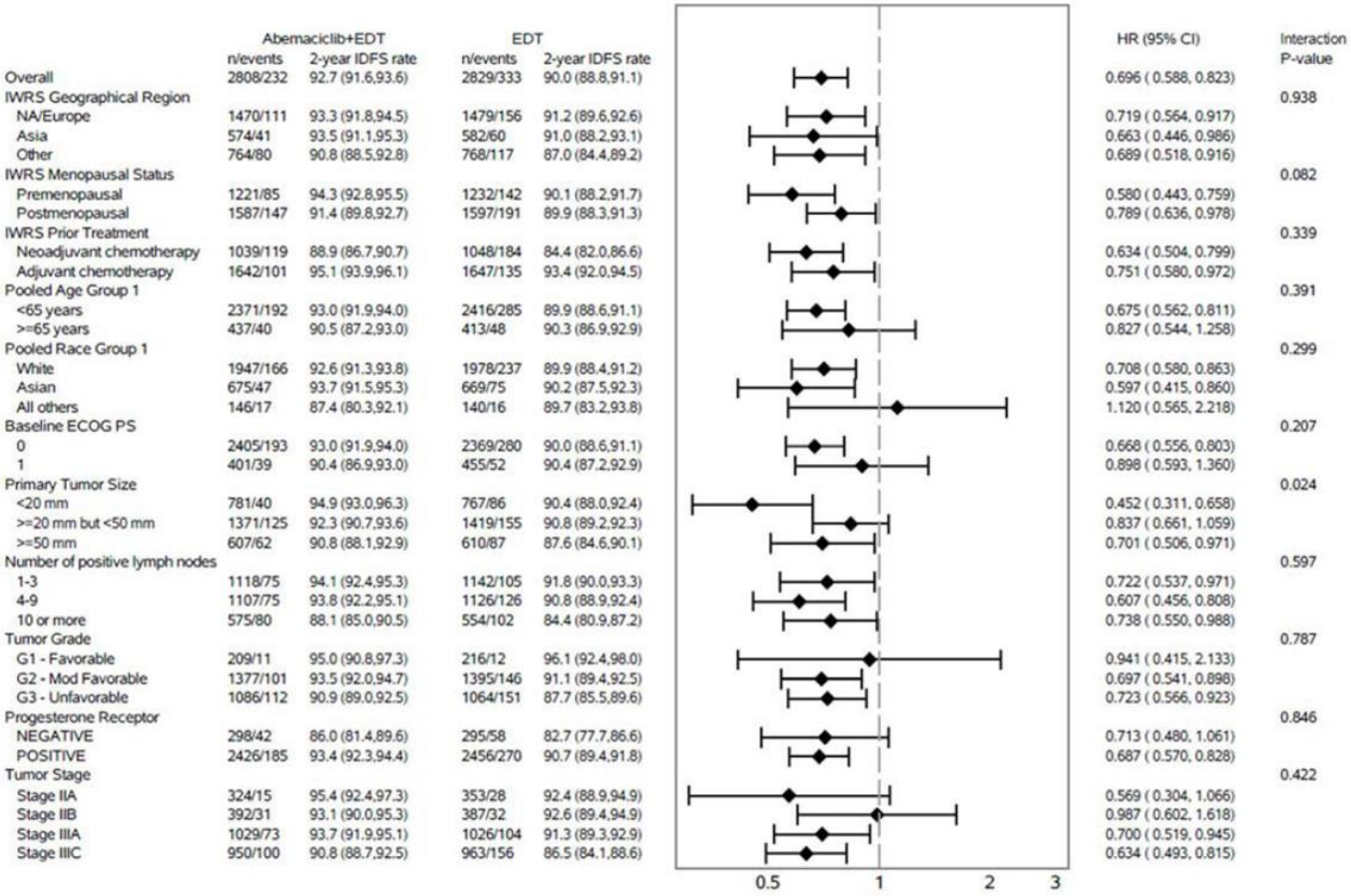
Figure 41. monarchE trial: Subgroup Analysis of IDFS



Abbreviations: CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ET: endocrine therapy; IDFS: invasive disease-free survival; ITT: intent-to-treat; IWRS: interactive web-response system; NA: North America; n: number of patients in the specific population.

Source: Lilly Data on File. Clinical Study Report: monarchE [14]. Data cut-off: 01 April 2021 monarchE - DRFS

A total number of 496 DRFS events were observed, including 191 in the abemaciclib + ET arm and 278 in the ET alone arm. The DRFS (stratified HR=0.687, 95% CI: 0.571, 0.826), reflecting a 31.3% reduction in the risk of developing distant relapse, and a 4.2% difference in 3-year DRFS rates (90.3% versus 86.1%) for patients treated with abemaciclib in combination with ET, compared to patients treated with ET alone.

Figure 42. monarchE trial, Kaplan Meier DRFS analysis for patients receiving abemaciclib in combination with ET and patients receiving ET alone.

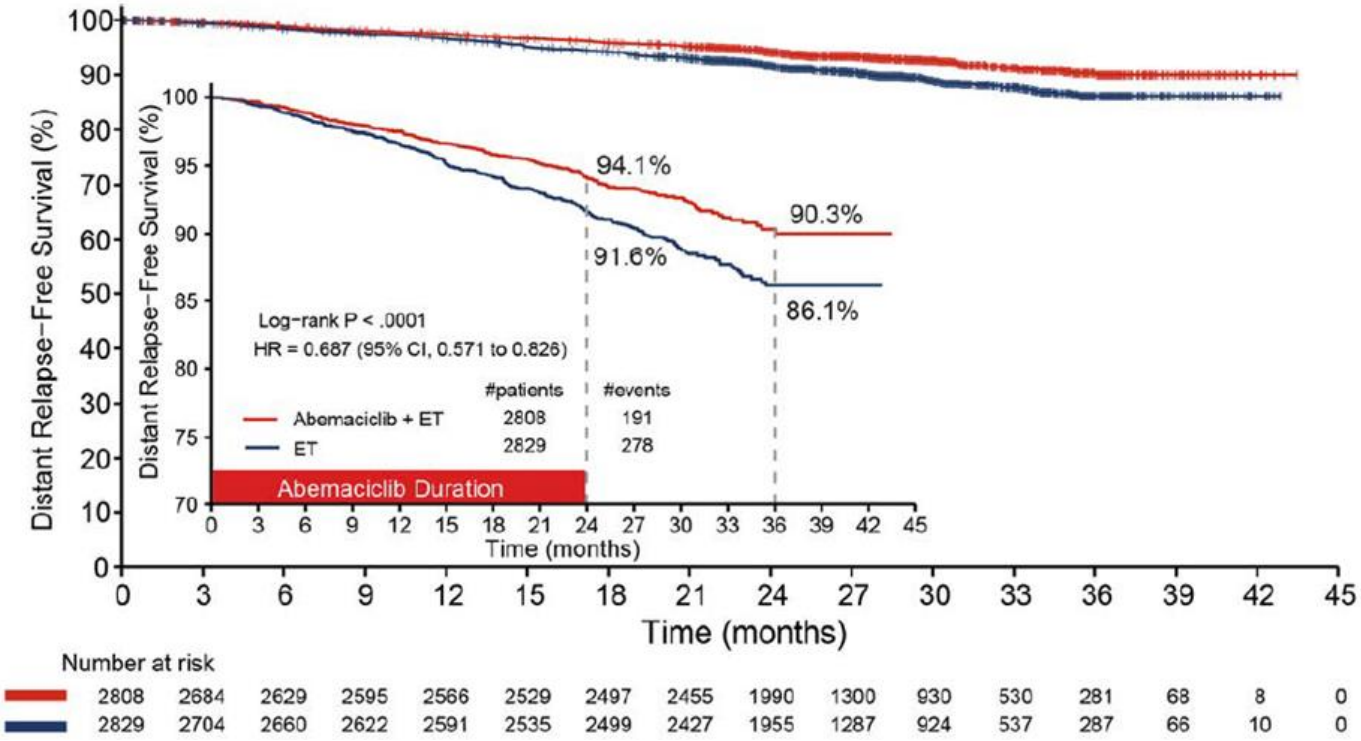


Table 155. monarchE DRFS results

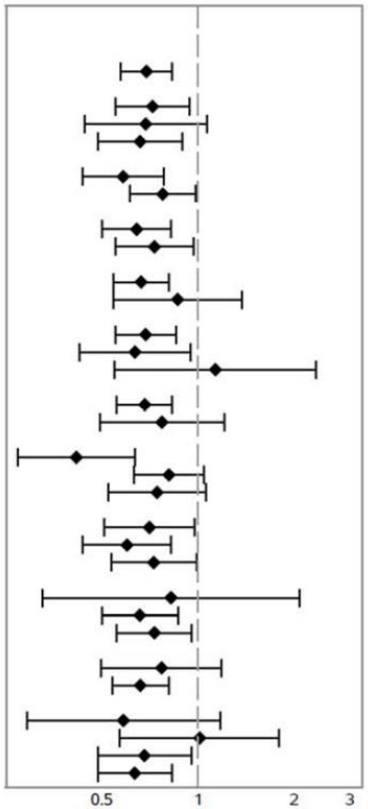
Outcome	Study arm	N	Result	p-value	Reference
DRFS rate % (95% CI)	Abemaciclib + ET	2,808	90.3 (88.6-91.8)	0.0007	[14]
	ET alone	2,829	86.1 (84.2-87.9)		[14]

Abbreviations: DRFS: Distant relapse-free survival; CI: Confidence interval.
Source: Lilly Data on File. Clinical Study Report: monarchE [14]. Data cut-off: 01 April 2021

The majority of prespecified subgroups analysed showed consistent DRFS effects favouring abemaciclib + ET, with two exceptions. Consistent with what was observed in the subgroup analysis of IDFS, the addition of abemaciclib to ET translates to a reduction in the risk of developing DRFS events in most subgroups analysed, including patients from different regions and pre- and post- menopausal women. The two subgroups with HR point estimate greater than one, had wide confidence intervals and a limited number of observed events. No statistically significant interactions were observed, supporting a consistent treatment benefit with the ITT population, see Figure 7.

Figure 43. monarchE trial: Subgroup Analysis of DRFS

	Abemaciclib+EDT		EDT		HR (95% CI)	Interaction P-value
	n/events	2-year DRFS rate	n/events	2-year DRFS rate		
Overall	2808/191	94.1 (93.2,95.0)	2829/278	91.6 (90.5,92.6)	0.687 (0.571, 0.826)	
IWRS Geographical Region						0.908
NA/Europe	1470/90	94.7 (93.4,95.8)	1479/127	92.9 (91.3,94.1)	0.718 (0.548, 0.941)	
Asia	574/33	94.9 (92.7,96.5)	582/47	92.8 (90.3,94.7)	0.683 (0.438, 1.066)	
Other	764/68	92.5 (90.3,94.2)	768/104	88.4 (85.9,90.5)	0.656 (0.483, 0.891)	
IWRS Menopausal Status						0.137
Premenopausal	1221/71	95.4 (94.0,96.4)	1232/119	91.8 (90.0,93.2)	0.580 (0.432, 0.778)	
Postmenopausal	1587/120	93.2 (91.7,94.4)	1597/159	91.5 (90.0,92.8)	0.773 (0.610, 0.980)	
IWRS Prior Treatment						0.504
Neoadjuvant chemotherapy	1039/100	90.7 (88.7,92.4)	1048/154	86.7 (84.4,88.7)	0.640 (0.497, 0.823)	
Adjuvant chemotherapy	1642/82	96.2 (95.1,97.1)	1647/113	94.5 (93.3,95.5)	0.728 (0.548, 0.968)	
Pooled Age Group 1						0.311
<65 years	2371/158	94.4 (93.3,95.3)	2416/240	91.5 (90.3,92.6)	0.661 (0.540, 0.807)	
>=65 years	437/33	92.8 (89.7,95.0)	413/38	92.2 (89.0,94.5)	0.861 (0.540, 1.373)	
Pooled Race Group 1						0.403
White	1947/136	94.2 (93.0,95.2)	1978/201	91.3 (89.9,92.5)	0.683 (0.550, 0.850)	
Asian	675/39	94.9 (92.9,96.3)	669/59	92.2 (89.8,94.1)	0.632 (0.422, 0.947)	
All others	146/15	89.0 (82.1,93.4)	140/14	91.1 (84.9,94.9)	1.133 (0.546, 2.349)	
Baseline ECOG PS						0.629
0	2405/160	94.3 (93.3,95.2)	2369/229	91.7 (90.5,92.8)	0.679 (0.554, 0.830)	
1	401/31	92.9 (89.7,95.1)	455/48	91.3 (88.2,93.7)	0.769 (0.490, 1.209)	
Primary Tumor Size						0.026
<20 mm	781/30	96.1 (94.4,97.3)	767/71	92.1 (89.9,93.9)	0.413 (0.270, 0.633)	
>=20 mm but <50 mm	1371/104	93.8 (92.4,95.0)	1419/133	92.0 (90.4,93.3)	0.809 (0.626, 1.045)	
>=50 mm	607/53	92.4 (89.9,94.3)	610/71	90.0 (87.2,92.2)	0.742 (0.520, 1.059)	
Number of positive lymph nodes						0.675
1-3	1118/59	95.4 (93.9,96.5)	1142/85	93.4 (91.8,94.8)	0.702 (0.504, 0.978)	
4-9	1107/59	95.4 (94.0,96.6)	1126/101	92.7 (91.0,94.1)	0.597 (0.433, 0.823)	
10 or more	575/71	89.5 (86.6,91.8)	554/92	85.5 (82.1,88.2)	0.724 (0.531, 0.987)	
Tumor Grade						0.815
G1 - Favorable	209/8	97.0 (93.4,98.6)	216/10	96.6 (93.0,98.4)	0.821 (0.324, 2.081)	
G2 - Mod Favorable	1377/84	94.8 (93.4,95.9)	1395/129	92.2 (90.6,93.5)	0.655 (0.497, 0.862)	
G3 - Unfavorable	1086/91	92.7 (91.0,94.2)	1064/122	90.0 (87.9,91.7)	0.728 (0.555, 0.955)	
Progesterone Receptor						0.498
NEGATIVE	298/36	88.0 (83.6,91.3)	295/46	85.4 (80.7,89.1)	0.767 (0.496, 1.186)	
POSITIVE	2426/150	94.9 (93.9,95.7)	2456/229	92.1 (90.9,93.2)	0.657 (0.535, 0.807)	
Tumor Stage						0.506
Stage IIA	324/12	96.4 (93.6,98.0)	353/22	94.3 (91.1,96.4)	0.581 (0.288, 1.175)	
Stage IIB	392/23	94.7 (91.9,96.6)	387/23	94.2 (91.3,96.2)	1.011 (0.567, 1.802)	
Stage IIIA	1029/56	95.5 (94.0,96.7)	1026/83	93.2 (91.4,94.6)	0.677 (0.482, 0.950)	
Stage IIIC	950/88	92.0 (90.0,93.6)	963/138	87.7 (85.4,89.7)	0.631 (0.483, 0.824)	



Abbreviations: CI: confidence interval; DRFS: distant relapse-free survival; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ET: endocrine therapy; ITT: intent-to-treat; IWRS: interactive web-response system; NA: North America; n: number of patients in the specific population.
Source: Lilly Data on File. Clinical Study Report: monarchE [14]. Data cut-off: 01 April 2021

12.1.1.1.2 monarchE - OS

At the time of the DCO from July 2020, there were no significant differences in OS between the two treatment arms. Despite the longer duration of follow-up at 36 months from the DCU in April 2021, the OS data remained immature with a 3.3% event rate and 47.7% of the 390 events required for the final OS analysis. 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 [11-13]. Considering that patients may first spend a number of years in the early breast cancer setting before progressing to metastatic breast cancer, it is evident that insufficient time has passed for the 3-year OS data in monarchE to capture any treatment effect of abemaciclib on OS.

A summary of OS from the latest DCO is shown in Table 15, together with the OS rate of month 12, 24, and 30. There were 186 deaths (3.3%) in the ITT population: 96 deaths (3.4%) in the abemaciclib plus ET arm, and 90 deaths (3.2%) in the ET alone arm, representing an absolute difference of six deaths between the two arms. Among patients who received at least 1 dose of study treatment, there were fewer deaths due to study disease in the abemaciclib plus ET arm (71 deaths) compared to the ET alone arm (75 deaths). However, the OS data is still immature. KM curves of OS are displayed in Figure 8.

Figure 44. monarchE trial, Kaplan Meier OS analysis for patients receiving abemaciclib in combination with ET and patients receiving ET alone.

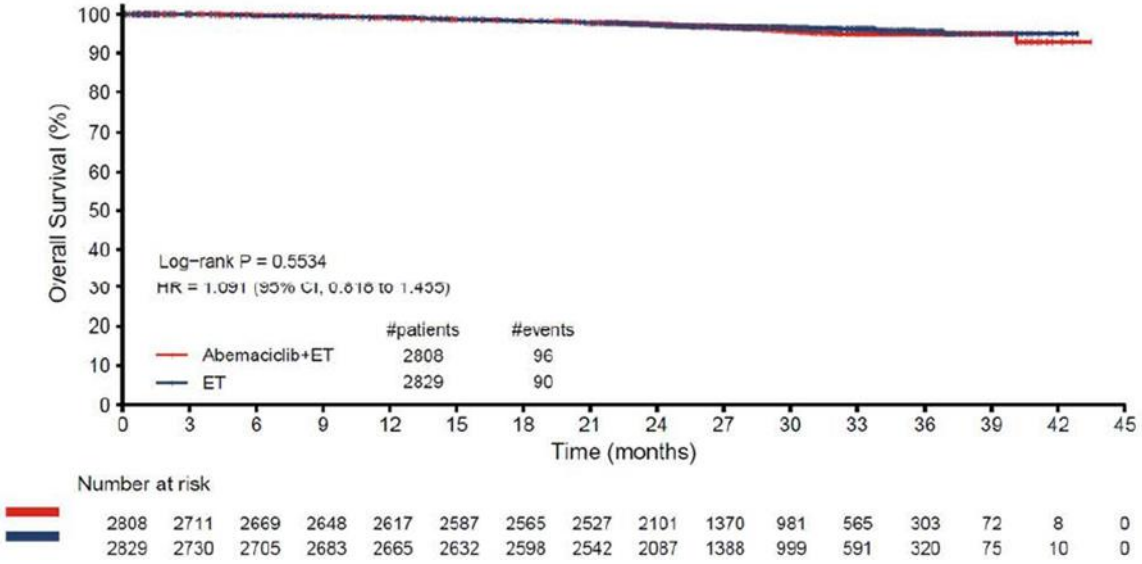


Table 156. monarchE OS results

Outcome	Study arm	N	Result	p-value	Reference
OS - n (%)	Abemaciclib + ET	2,808	96 (3.4)	0.55338	[14]
	ET alone	2,829	90 (3.2)		[14]
OS rate, % (95% CI)	Abemaciclib + ET	2,808	99.1 (98.7 – 99.4)	0.6498	[28]
12 months	ET alone	2,829	99.2 (98.8 – 99.5)		[28]
24 months	Abemaciclib + ET	2,808	97.5 (96.9 – 98.1)	0,6498	[28]
	ET alone	2,829	97.3 (96.6 – 97.9)		[28]
30 months	Abemaciclib + ET	2,808	94.9 (93.7 – 96.0)	0.4456	[28]
	ET alone	2,829	95.6 (94.3 – 96.5)		[28]

Abbreviations: OS: Overall survival; CI: Confidence interval.
Source: Lilly Data on File. Clinical Study Report: monarchE [14]. Data cut-off: 01 April 2021.

12.1.1.1.3 monarchE - HRQoL

PRO endpoints were not analysed at the April 2021 DCO. Results in the following section are from the July 2020 DCO. Different PROs were used to measure HRQoL: FACT-B, FACT-ES, FACIT-F, and EQ-5D-5L.

12.1.1.1.3.1 FACT-B, FACT-ES, and FACIT-F

[redacted]Table 157[redacted]Table 158[redacted]Table 159[redacted]

Table 157. FACT-B Summary scores

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

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 [14]. Data cut-off: 08 July 2020.

Table 158. FACT-ES Summary scores

FACT-ES Total Score	Abemaciclib + ET (N=2,791)			ET alone (N=2,800)			Abemaciclib + ET versus ET alone
	n	Mean (SD)	CfB, LSM (SE)	n	Mean (SD)	CfB, LSM (SE)	LSM Change Difference (SE)
ESS-19[a]							
Baseline	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX
Visit 6 (3 months)	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX

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

Footnotes: a 19-item Endocrine Symptom Subscale; b23-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 [14]. Data cut-off: 08 July 2020

Table 159. FACIT-F Summary scores

FACIT-F Total Score	Abemaciclib + ET (N=2,791)			ET alone (N=2,800)			Abemaciclib + ET versus ET alone
	n	Mean (SD)	CfB, LSM (SE)	n	Mean (SD)	CfB, LSM (SE)	LSM Change Difference (SE)

Baseline	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX
Visit 6 (3 months)	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX
Visit 9 (6 months)	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX
Visit 15 (12 months)	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX
Visit 21 (18 months)	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX
All post-baseline	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX

Abbreviations: CfB: change from baseline ET: endocrine therapy; FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue; LSM: least-squares mean; N: number of patients in the safety population; NA: not applicable; NE: not evaluated; SD: standard deviation; SE: standard error.
Source: Lilly Data on File. Clinical Study Report: monarchE [14]. Data cut-off: 08 July 2020.

12.1.1.1.3.2 EQ-5D-5L

The full EQ-5D-5L subscale scores for monarchE are presented in Appendix F. 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. The VAS demonstrated similar results as the index value; scores were similar between the two treatment arms for all baseline and post-baseline visits, **Error! Reference source not found.**.

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

Table 160. Summary of EQ-5D-5L Index and Visual Analogue Scale in monarchE, safety population

	Baseline Score Mean (SD)		Within-treatment Group Change from Baseline[a] LSM (SE)		Between- treatment Group Change Difference (Abemaciclib + ET vs ET alone) [a,b]		
	Abemaciclib + ET	ET Alone	Abemaciclib + ET	ET Alone	LS M (SE)	95% CI	p-Value[c]

EQ-5D-5L Health State Index	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visual analogue scale	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

12.1.1.2 Results monarchE – Safety

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. 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. With 90% of patients having completed or discontinued early from the study treatment period by the time of the latest DCO, the safety data is considered mature.

At the latest DCO, 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 the median duration of ET was approximately 23.8 months (with a mean of approximately 21 months. In the ET alone arm the median duration of treatment was approximately and 23.8 months (with a mean of approximately 21 months). At the time of the April 2021 DCO 265 patients (9.4%) in the abemaciclib plus ET arm and 273 patients (9.7%) in the ET alone arm remained on study treatment. Overall, 91% of total patients had completed two years on study treatment.

The safety of abemaciclib in combination with ET was evaluated through the assessment of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), TEAEs leading to discontinuation, and TEAEs leading to deaths, Table 19.

Table 161. MonarchE trial, Summary of safety outcomes, April 2021

Outcome	Study arm	N	Result	p-value	Reference

TEAEs by SOC in ≥1% patients (all grades) – n (%)	Abemaciclib + ET	2,791	2,745 (98.4)	NA	[28]
	ET alone	2,800	2,486 (88.8)		[28]
SAEs – n (%)	Abemaciclib + ET	2,791	424 (15.2)	NA	[28]
	ET alone	2,800	247 (8.8)		[28]
Treatment discontinuation due to AEs – n (%)	Abemaciclib + ET	2,791	181 (6.5)	NA	[14]
	ET alone	2,800	30 (1.1)		[14]
TEAS leading to deaths – n (%)	Abemaciclib + ET	2,791	95 (3.4)	NA	[28]
	ET alone	2,800	89 (3.2)		[28]

Abbreviations: AEs: Adverse events; TEAE: Treatment-emergent adverse events; CI: Confidence interval; SOC: system organ classes
Source: Lilly Data on File. Clinical Study Report: monarchE [14]. Data cut-off: 01 April 2021.

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

During the study period, a total of 5,231 patients (93.6%) experienced at least one TEAE, including 2,745 patients (98.4%) in the abemaciclib plus ET arm and 2,486 patients (88.8%) of patients in the ET alone arm, Table 20.

Table 162. Treatment-emergent adverse events by maximum CTCAE grade experienced by ≥10% of population of either arm of monarchE, safety population

TEAE, n (%)	Abemaciclib + ET (n=2,791)						ET alone (N=2,800)					
	CTCAE Grade											
	1	2	3	4	5	Any	1	2	3	4	5	Any
Patients with ≥1 TEAE	165 (5.9)	1,192 (42.7)	1,284 (46.0)	89 (3.2)	15 (0.5)	2,745 (98.4)	634 (22.6)	1396 (49.9)	424 (15.1)	22 (0.8)	10 (0.4)	2,486 (88.8)
Diarrhea	1,255 (45.0)	857 (30.7)	218 (7.8)	0 (0.0)	1 (0.0)	2,331 (83.5)	184 (6.6)	52 (1.9)	6 (0.2)	0 (0.0)	0 (0.0)	242 (8.6)
Neutropenia	178 (6.4)	554 (19.8)	527 (18.9)	19 (0.7)	0 (0.0)	1278 (45.8)	66 (2.4)	68 (2.4)	19 (0.7)	4(0.1)	0 (0.0)	157 (5.6)
Fatigue	632 (22.6)	421 (15.1)	80 (2.9)	0 (0.0)	0 (0.0)	1133 (40.6)	378 (13.5)	117 (4.2)	4 (0.1)	0 (0.0)	0 (0.0)	499 (17.8)

Leukopenia	170 (6.1)	562 (20.1)	313 (11.2)	4 (0.1)	0 (0.0)	1049 (37.6)	93 (3.3)	82 (2.9)	11 (0.4)	0 (0.0)	0 (0.0)	186 (6.6)
Abdominal pain	693 (24.8)	260 (9.3)	39 (1.4)	0 (0.0)	0 (0.0)	992 (35.5)	189 (6.8)	77 (2.8)	9 (0.3)	0 (0.0)	0 (0.0)	275 (9.8)
Nausea	623 (22.3)	187 (6.7)	14 (0.5)	0 (0.0)	0 (0.0)	824 (29.5)	198 (7.1)	52 (1.9)	2 (0.1)	0 (0.0)	0 (0.0)	252 (9.0)
Anaemia	383 (13.7)	241 (8.6)	56 (2.0)	1 (0.0)	0 (0.0)	681 (24.4)	75 (2.7)	19 (0.7)	9 (0.3)	1 (0.0)	0 (0.0)	104 (3.7)
Arthralgia	509 (18.2)	224 (8.0)	9 (0.3)	0 (0.0)	0 (0.0)	742 (26.6)	729 (26.0)	302 (10.8)	29 (1.0)	0 (0.0)	0 (0.0)	1060 (37.9)
Headache	415 (14.9)	123 (4.4)	8 (0.3)	0 (0.0)	0 (0.0)	546 (19.6)	321 (11.5)	95 (3.4)	5 (0.2)	0 (0.0)	0 (0.0)	421 (15.0)
Vomiting	375 (13.4)	101 (3.6)	15 (0.5)	0 (0.0)	0 (0.0)	491 (17.6)	98 (3.5)	29 (1.0)	3 (0.1)	0 (0.0)	0 (0.0)	130 (4.6)
Hot flush	326 (11.7)	97 (3.5)	4 (0.1)	0 (0.0)	0 (0.0)	427 (15.3)	496 (17.7)	137 (4.9)	10 (0.4)	0 (0.0)	0 (0.0)	643 (23.0)
Lymphopenia	75 (2.7)	169 (6.1)	148 (5.3)	3 (0.1)	0 (0.0)	395 (14.2)	38 (1.4)	45 (1.6)	13 (0.5)	0 (0.0)	0 (0.0)	96 (3.4)
Stomatitis[a]	309 (11.1)	72 (2.6)	4 (0.1)	0 (0.0)	0 (0.0)	385 (13.8)	133 (4.8)	18 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	151 (5.4)
Cough	310 (11.1)	80 (2.9)	1 (0.0)	0 (0.0)	0 (0.0)	391 (14.0)	177 (6.3)	45 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	222 (7.9)
Thrombocytopenia	276 (9.9)	61 (2.2)	28 (1.0)	8 (0.3)	0 (0.0)	373 (13.4)	40 (1.4)	8 (0.3)	2 (0.1)	2 (0.1)	0 (0.0)	52 (1.9)
Decreased appetite	243 (8.7)	70 (2.5)	16 (0.6)	0 (0.0)	0 (0.0)	329 (11.8)	53 (1.9)	13 (0.5)	2 (0.1)	0 (0.0)	0 (0.0)	68 (2.4)
Lymphoedema	258 (9.2)	84 (3.0)	5 (0.2)	0 (0.0)	0 (0.0)	347 (12.4)	204 (7.3)	45 (1.6)	1 (0.0)	0 (0.0)	0 (0.0)	250 (8.9)
Urinary tract infection	2 (0.1)	318 (11.4)	16 (0.6)	0 (0.0)	0 (0.0)	336 (12.0)	0 (0.0)	205 (7.3)	6 (0.2)	0 (0.0)	0 (0.0)	211 (7.5)
Constipation	282 (10.1)	49 (1.8)	2 (0.1)	0 (0.0)	0 (0.0)	333 (11.9)	144 (5.1)	23 (0.8)	1 (0.0)	0 (0.0)	0 (0.0)	168 (6.0)
URTI	0 (0.0)	295 (10.6)	6 (0.2)	0 (0.0)	0 (0.0)	301 (10.8)	1 (0.0)	237 (8.5)	0 (0.0)	0 (0.0)	0 (0.0)	238 (8.5)
ALT increased	184 (6.6)	82 (2.9)	72 (2.6)	5 (0.2)	0 (0.0)	343 (12.3)	113 (4.0)	25 (0.9)	19 (0.7)	0 (0.0)	0 (0.0)	157 (5.6)
Dizziness	270 (9.7)	30 (1.1)	4 (0.1)	0 (0.0)	0 (0.0)	304 (10.9)	167 (6.0)	20 (0.7)	1 (0.0)	0 (0.0)	0 (0.0)	188 (6.7)
Rash	239 (8.6)	61 (2.2)	11 (0.4)	0 (0.0)	0 (0.0)	312 (11.2)	104 (3.7)	23 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	127 (4.5)
AST increased	220 (7.9)	58 (2.1)	49 (1.8)	3 (0.1)	0 (0.0)	330 (11.8)	103 (3.7)	19 (0.7)	15 (0.5)	0 (0.0)	0 (0.0)	137 (4.9)
Alopecia	283 (10.1)	30 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	313 (11.2)	68 (2.4)	7 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	75 (2.7)
Pain in extremity	205 (7.3)	78 (2.8)	3 (0.1)	0 (0.0)	0 (0.0)	286 (10.2)	251 (9.0)	70 (2.5)	4 (0.1)	0 (0.0)	0 (0.0)	325 (11.6)
Back pain	192 (6.9)	81 (2.9)	10 (0.4)	0 (0.0)	0 (0.0)	283 (10.1)	230 (8.2)	108 (3.9)	9 (0.3)	0 (0.0)	0 (0.0)	347 (12.4)
Pyrexia	229 (8.2)	48 (1.7)	2 (0.1)	0 (0.0)	0 (0.0)	279 (0.1)	102 (3.6)	25 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	127 (4.5)

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

The incidence of SAEs was higher in the abemaciclib plus ET arm (15.2%) as compared with the ET alone arm (8.8%). Venous thrombolytic events (VTE) and pneumonia were the most commonly reported SAEs by patients treated with abemaciclib + ET (1.2% [34/2,791] and 1.0% [28/2,791], respectively). Patients treated with ET alone reported pneumonia (0.6% [17/2,800]), cellulitis (0.4% [10/2,800]) and VTE (0.3% [8/2,800]) most commonly, Table 21.

Table 163. SAEs in ≥5 patients in either arm of the safety population, April 2021 DCO

n (%)	Abemaciclib + ET (N=2,791)	ET alone (N=2,800)
Patients with ≥1 serious adverse event	424 (15.2)	247 (8.8)
Infections and infestations	146 (15.2)	80 (2.9)
Pneumonia	28 (1.0)	17 (0.6)
Cellulitis	14 (0.5)	10 (0.4)
Urinary tract infection	14 (0.5)	4 (0.1)
Influenza	7 (0.3)	4 (0.1)
Sepsis	6 (0.2)	2 (0.1)
Upper respiratory tract infection	6 (0.2)	0 (0.0)
Breast cellulitis	5 (0.2)	5 (0.2)
Erysipelas	6 (0.2)	0 (0.0)
Gastrointestinal disorders	59 (2.1)	17 (0.6)
Diarrhoea	15 (0.5)	0 (0.0)
Abdominal pain	6 (0.2)	1 (0.0)
Pancreatitis	6 (0.2)	2 (0.1)
Colitis	5 (0.2)	3 (0.1)
Respiratory, thoracic and mediastinal disorders	38 (1.4)	12 (0.4)
Pneumonitis	8 (0.3)	0
Vascular disorders	30 (1.1)	11 (0.4)
Lymphoedema	7 (0.3)	3 (0.1)
General disorders and administration site conditions	27 (1.0)	9 (0.3)
Pyrexia	10 (0.4)	0 (0.0)
Cardiac disorders	25 (0.9)	15 (0.5)
Atrial fibrillation	8 (0.3)	1 (0.0)
Hepatobiliary disorders	22 (0.8)	9 (0.3)
Cholecystitis	10 (0.4)	4 (0.1)
Blood and lymphatic disorders	24 (0.9)	4 (0.1)
Anaemia	8 (0.3)	2 (0.1)
Febrile neutropenia	5 (0.2)	0 (0.0)

Metabolism and nutrition disorders	16 (0.6)	8 (0.3)
Dehydration	7 (0.3)	0 (0.0)
Composite terms[a]		
Venous thromboembolic eventb	34 (1.2)	8 (0.3)
Interstitial lung disease/pneumonitisc	14 (0.5)	1 (<0.01)
ALT or AST increased	10 (0.4)	2 (0.1)

Footnotes: [a] Composite terms are defined as a grouping of terms from one or more PTs that are treatment-emergent events and related to a defined medical condition or area of interest; [b] VTE events included pulmonary embolism and deep vein thrombosis. [c] Interstitial lung disease/pneumonitis events were defined by SMQ of "interstitial lung disease".
Abbreviations: ET: endocrine therapy; N: number of patients in the safety population; n: number of patients within category; SAE: serious adverse event; SMQ: standardised MedDRA queries.
Source: Lilly Data on File. Clinical Study Report: monarchE [14]. Data cutoff: 01 April 2021

In the abemaciclib + ET arm, 515 patients (18.5%) discontinued abemaciclib due to AEs. Of these patients, 181 (6.5%) discontinued all study treatment due to an AE, as compared with 30 patients (1.1%) in the ET alone arm. The TEAEs that led to discontinuation of all study treatment are presented in Table 22. In the abemaciclib + ET arm, the most common TEAEs leading to all treatment discontinuations were diarrhoea (69 patients, 2.5%) and fatigue (28 patients, 1.0%). Dizziness (0.1%) led to discontinuation in the ET alone arm.

Table 164. AEs reported as reason for study treatment discontinuation (end of treatment) by ≥2 patients in either arm of the safety population, April 2020 DCO

n (%)	Abemaciclib + ET (N=2,791)	ET alone (N=2800)
Patients discontinued all study treatment due to AE[a]	181 (6.5)	30 (1.1)
Diarrhoea	69 (2.5)	0 (0.0)
Fatigue	28 (1.0)	0 (0.0)
Abdominal pain	4 (0.1)	0 (0.0)
Nausea	4 (0.1)	0 (0.0)
Depression	3 (0.1)	2 (0.1)
Vomiting	3 (0.1)	0 (0.0)
Anxiety	2 (0.1)	1 (0.0)
Cardiac arrest	2 (0.1)	0 (0.0)
Dry eye	2 (0.1)	0 (0.0)
General physical health deterioration	2 (0.1)	0 (0.0)
Neutropenia	2 (0.1)	0 (0.0)
Pain in extremity	2 (0.1)	0 (0.0)
Arthralgia	1 (0.0)	6 (0.2)

Hot flush	1 (0.0)	2 (0.1)
Dizziness	0 (0.0)	2 (0.1)
Composite terms[b]		
Infections and infestations SOC	9 (0.3)	6 (0.2)
Venous thromboembolic eventc	6 (0.2)	2 (0.1)
Interstitial lung disease/pneumonit-isd	2 (0.1)	0
ALT or AST increased	3 (0.1)	0

Footnotes: [a] Includes patients who died due to AE during study treatment: PT cardiac arrest and PT general physical health deterioration (n=1). [b] Composite terms are defined as a grouping of terms from one or more PT or SOC that are related to a defined medical condition or area of interest; [c] VTE events included pulmonary embolism and deep vein thrombosis. [d] Interstitial lung disease/pneumonitis events were defined by SMQ of "interstitial lung disease".
Abbreviations: AE: adverse event; ET: endocrine therapy; N: number of patients in the safety population; n: number of patients within category; SAE: serious adverse event; SMQ: standardised MedDRA queries.

Source: Lilly Data on File. Clinical Study Report: monarchE [14]. Data cutoff: 01 April 2021.

Appendix P Eligibility criteria of Monarch2 and Monarch3 trials - Clinical trials informing the endocrine treatment resistant and endocrine treatment sensitive metastatic pathways

Data from two clinical trials, SLRs, indirect comparisons, and the respective cost-effectiveness models have been used to inform the ET resistant and endocrine treatment sensitive metastatic pathways in the monarchE cost-utility model.

The key inclusion and exclusion criteria for both trials have been provided in Table 165.

Table 165. Overview of MONARCH 2 and MONARCH 3 clinical trial criteria

Inclusion criteria	Exclusion criteria
Endocrine treatment resistant pathway - MONARCH 2 trial: Randomised, Double-Blind, Placebo-Controlled, Phase 3 Study of Fulvestrant With or Without Abemaciclib, a CDK4/6 Inhibitor, for Women With Hormone Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer	
• Have a diagnosis of HR+, HER2- breast cancer • Have locally advanced disease not amenable to curative treatment by surgery or metastatic disease. In addition, participants must fulfill 1 of the following criteria: ○ relapsed with radiologic evidence of progression while receiving (neo)adjuvant ET, with no subsequent ET received following progression ○ relapsed with radiologic evidence of progression within 1 year from completion of adjuvant ET, with no subsequent ET received following progression ○ relapsed with radiologic evidence of progression more than 1 year from completion of adjuvant ET and then subsequently relapsed with radiologic evidence of progression after receiving treatment with either an anti-oestrogen or an aromatase inhibitor as first-line ET for metastatic disease. Participants may not have received more than 1 line of ET or any	• Are currently receiving an investigational drug in a clinical trial or participating in any other type of medical research judged not to be scientifically or medically compatible with this study • Have visceral crisis, lymphangitic spread, or leptomeningeal carcinomatosis visceral crisis is not the mere presence of visceral metastases but implies severe organ dysfunction as assessed by symptoms and signs, laboratory studies, and rapid progression of the disease • Have clinical evidence or history of central nervous system metastasis • Have received prior treatment with chemotherapy (except for (neo)adjuvant chemotherapy), fulvestrant, everolimus, or any CDK4&6 inhibitor. For the endocrine naïve cohort: In addition, have received treatment with any prior ET • Have received treatment with a drug that has not received regulatory approval for any indication within 14 or 21 days prior to randomisation of study drug for a non-myelosuppressive or myelosuppressive agent, respectively

prior chemotherapy for metastatic disease ○ presented de novo with metastatic disease and then relapsed with radiologic evidence of progression after receiving treatment with either an anti-oestrogen or an aromatase inhibitor as first line ET for metastatic disease. Participants may not have received more than 1 line of ET or any prior chemotherapy for metastatic disease ○ for the endocrine naïve cohort: Must not have received prior ET in current or prior disease setting • Have postmenopausal status due to either surgical/natural menopause or ovarian suppression (initiated at least 28 days prior to Day 1 of Cycle 1) with a gonadotropin-releasing hormone (GnRH) agonist such as goserelin • Have a negative serum pregnancy test at baseline (within 14 days prior to randomisation) and agree to use medically approved precautions to prevent pregnancy during the study and for 12 weeks following the last dose of abemaciclib if postmenopausal status is due to ovarian suppression with a GnRH agonist • Have either measurable disease or non-measurable bone only disease • Have a performance status ≤1 on the ECOG scale • Have discontinued previous therapies for cancer (including specifically, aromatase inhibitors, anti-oestrogens, chemotherapy, radiotherapy, and immunotherapy) for at least 21 days for myelosuppressive agents or 14 days for non-myelosuppressive agents prior to receiving study drug, and recovered from the acute effects of therapy (until the toxicity resolves to either baseline or at least Grade 1) except for residual alopecia or peripheral neuropathy	• Have received recent (within 28 days prior to randomisation) yellow fever vaccination • Have had major surgery within 14 days prior to randomisation of study drug to allow for post-operative healing of the surgical wound and site(s) • Have a personal history within the last 12 months of any of the following conditions: syncope of cardiovascular aetiology, ventricular tachycardia, ventricular fibrillation, or sudden cardiac arrest • Have inflammatory breast cancer or a history of any other cancer (except nonmelanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission with no therapy for a minimum of 3 years • Have received an autologous or allogeneic stem-cell transplant • Have active bacterial or fungal infection, or detectable viral infection • Have initiated bisphosphonates or approved Receptor activator of nuclear factor kappa-B (RANK) ligand targeted agents <7 days prior to randomisation

Endocrine treatment sensitive pathway - MONARCH 3 trial: Randomised, Double-Blind, Placebo-Controlled, Phase 3 Study of Nonsteroidal Aromatase Inhibitors (Anastrozole or Letrozole) Plus LY2835219, a CDK4/6 Inhibitor, or Placebo in Postmenopausal Women With Hormone Receptor-Positive, HER2-Negative Locoregionally Recurrent or Metastatic Breast Cancer With No Prior Systemic Therapy in This Disease Setting	
• Have a diagnosis of hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) breast cancer • Have locoregionally recurrent disease not amenable to resection or radiation therapy with curative intent or metastatic disease • Have postmenopausal status • Have either measurable disease or non-measurable bone-only disease • Have a performance status ≤1 on the Eastern Cooperative Oncology Group (ECOG) scale • Have adequate organ function • Have discontinued previous localized radiotherapy for palliative purposes or for lytic lesions at risk of fracture prior to randomisation and recovered from the acute effects of therapy • Are able to swallow capsules	• Have visceral crisis, lymphangitic spread, or leptomeningeal carcinomatosis • Have inflammatory breast cancer • Have clinical evidence or a history of central nervous system (CNS) metastasis • Are currently receiving or have previously received ET for locoregionally recurrent or metastatic breast cancer • Have received prior (neo)adjuvant ET with a disease-free interval ≤12 months from completion of treatment • Are currently receiving or have previously received chemotherapy for locoregionally recurrent or metastatic breast cancer • Have received prior treatment with everolimus • Have received prior treatment with any cyclin-dependent kinase (CDK) 4&6 inhibitor (or participated in any CDK4%6 inhibitor clinical trial for which treatment assignment is still blinded) • Have initiated bisphosphonates or approved receptor activator of nuclear factor kappa-B ligand (RANK-L) targeted agents <7 days prior to randomisation • Are currently receiving an investigational drug in a clinical trial or participating in any other type of medical research judged not to be scientifically or medically compatible with this study • Have received treatment with a drug that has not received regulatory approval for any indication within 14 or 21 days of randomisation for a non-myelosuppressive or myelosuppressive agent, respectively

	• Have had major surgery within 14 days prior to randomisation