NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Abemaciclib with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer after endocrine therapy [ID1339]

Committee Papers

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Abemaciclib with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer after endocrine therapy [ID1339]

Contents:

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

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Abemaciclib with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer after endocrine therapy

Pre-meeting briefing

PART 1

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the committee meeting

NICE 2

Key issues for consideration - clinical

- As the treatment pathway has recently changed with the availability of ribociclib and palbociclib, is the decision problem relevant?
  - ERG's clinical experts noted that people treated with palbociclib and ribociclib first line would be unlikely to be given another combination treatment
- What is the most relevant comparator?
- Is the network meta-analysis robust for overall survival, given the immaturity of the overall survival data in the MONARCH 2 trial?
- Is abemaciclib plus fulvestrant clinically effective?
- Which network meta-analysis should be used to compare treatments?
  - Hazard ratio NMA
  - Company's fractional polynomial NMA
  - ERG's fractional polynomial NMA

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Advanced breast cancer background

- Breast cancer is the most common cancer amongst women in the UK
- The cancer is said to be 'advanced' if it has spread to other parts of the body such as the bones, liver, and lungs (metastatic cancer), or if it has grown directly into nearby tissues and cannot be completely removed by surgery.
- Approximately 13% of women with breast cancer have advanced disease when they are diagnosed, and around 35% of people with early or locally advanced disease will progress to metastatic breast cancer in the 10 years following diagnosis.
- Approximately 64% of women with metastatic breast cancer in the UK have HR+/HER2− disease.
- In 2016 in England, around 45,960 people were diagnosed with breast cancer and there were 9,685 deaths from breast cancer.

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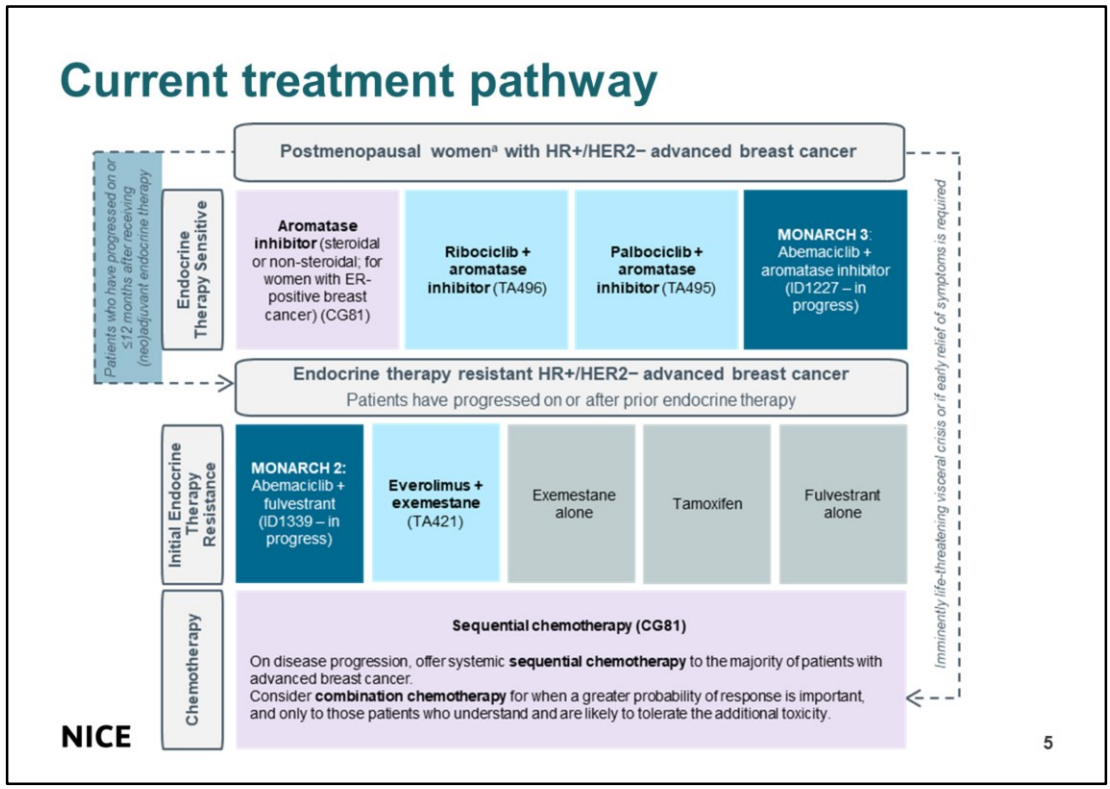
Source: company submission section B.1.3.1; NICE final scope



Source: company submission figure 2

Patient Issues (Breast Cancer Now. Breast Cancer Care)

- Diagnosis of incurable, advanced breast cancer is difficult to accept.
- The disease and its treatment impact on mental & physical health, & QoL.
- Abemaciclib combined with fulvestrant is a potential additional treatment option for disease that has progressed on previous endocrine therapy.
- Benefits include:
  - postponing or avoiding need for chemotherapy
  - limited side effects compared with chemotherapy – improved quality of life
  - extended progression-free survival – allowing people to spend more quality time with family and friends.
- Disadvantages (which may be outweighed by increased PFS) include:
  - Fulvestrant is administered by injection requiring hospital/ GP visits
  - Potential increased side effects.

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Source: Submissions from Breast Cancer Now and Breast Cancer Care

Comments from clinical experts

- Abemaciclib+fulvestrant shows a clinically important improvement in progression-free survival, likely to improve overall survival
- Could help to delay initiation of chemotherapy
- Improved quality of life with manageable side effects
- However, could be a further strain on metastatic breast cancer services

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Source: Submissions from clinical experts

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Abemaciclib (Verzenios, Eli Lilly)

Marketing authorisation (October 2018)	Indicated for the treatment of women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or **fulvestrant** as initial endocrine-based therapy, or **in women who have received prior endocrine therapy.**
Mechanism of action	Inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6), blocking cell cycle progression and leading to suppression of tumour growth
Administration and dosage	Abemaciclib administered orally, 150 mg twice daily when used in combination with endocrine therapy on a continuous 28 day cycle. Fulvestrant administered intramuscularly*, 500mg on day 1 and 15 of first cycle, day 1 of subsequent cycles.
List price	List price of abemaciclib: £[redacted] per 28-day cycle Mean time on treatment: [redacted] months (modelled) Cost per mean time on treatment (based on list price): £[redacted] A confidential patient access scheme has been proposed.

**Corrected after committee meeting*

NICE 8

Source: company submission B.1.2; summary of product characteristics.

Decision problem

	Final scope issued by NICE	Decision problem in the company's submission	Rationale if different
Population	People with advanced HR+/HER2− breast cancer that has progressed on or after endocrine therapy	Women with locally advanced or metastatic HR+/HER2− breast cancer who had progressed while receiving (neo)adjuvant ET, ≤ 12 months from the end of adjuvant therapy, or while receiving first-line ET for locally advanced or metastatic disease	Company consider patients untreated or who have progressed after ET in the advanced setting to be part of one population for this submission.
Intervention	Abemaciclib with fulvestrant	Abemaciclib with fulvestrant	N/A
Outcomes	OS PFS Response rate Adverse effects of treatment HRQoL	OS and OS rated PFS Response rates Adverse effects of treatment Patient reported outcomes	N/A

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Source: company submission B.1.1

Notes:

- There are 2 appraisals for abemaciclib
  - People with untreated advanced HR+/HER2− breast cancer (ID1227)
  - People with advanced HR+/HER2− breast cancer that has progressed on or after endocrine therapy (ID1339 – this appraisal)

Decision problem

	Final scope issued by NICE	Decision problem in the company's submission	Rationale if different
Comparators	For people with advanced hormone-receptor positive HER2-negative breast cancer that has progressed after one line of prior endocrine therapy: • Exemestane • Everolimus and exemestane • Tamoxifen • Fulvestrant • Chemotherapy	• Exemestane (EXE) • Everolimus and exemestane (EXE-EVE) • Tamoxifen (TMX) • Fulvestrant (FUL) • Capecitabine (CAP) (considered in response to clarification questions)	Company note that: • Chemotherapy is the last resort • Fulvestrant monotherapy not NICE recommended but may be used

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Source: company submission B.1.1, B1.3.3 page 23, response to clarification A3b

ERG comments on decision problem and treatment pathway

- Company's decision problem focused on the endocrine therapy-resistant population - narrower than population in final scope but the ERG considers this appropriate based on feedback from clinical experts
- ERG's clinical experts consider chemotherapy to be a relevant comparator for some patients
- ERG's clinical experts suggest that clinicians will not use abemaciclib+fulvestrant after another CDK 4/6 inhibitor (e.g. palbociclib or ribociclib with an aromatase inhibitor (AI)), because of:
  - intensity of a second combined treatment regimen
  - lack of evidence of response or reversal of endocrine therapy resistance
- Currently, most common first line treatment is a CDK 4/6 inhibitor + AI, but if abemaciclib+fulvestrant were to be recommended, a small number of patients may be given AI alone as first line treatment

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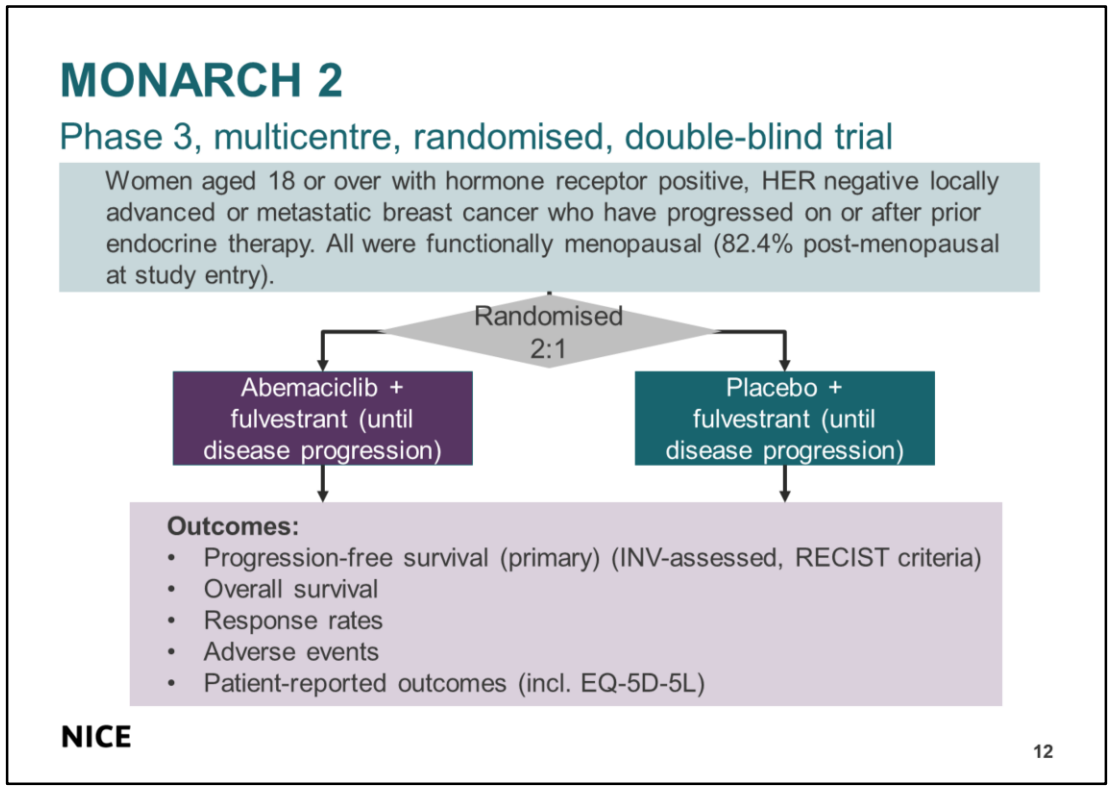
Source: ERG report section 2.2.2, 3.1



Source: company submission B.2.3

Notes

- 142 centres across 19 countries, including Australia, Belgium, Canada, Denmark, Finland, France, Germany, Italy, Japan, Republic of Korea, Mexico, Poland, Puerto Rica, Romania, Russia, Spain, Switzerland, Taiwan and United States of America
- Patients were not permitted to switch treatment groups
- If either abemaciclib or placebo was discontinued, patients were permitted to continue receiving fulvestrant. If fulvestrant required discontinuation, patients were permitted to continue receiving abemaciclib or placebo

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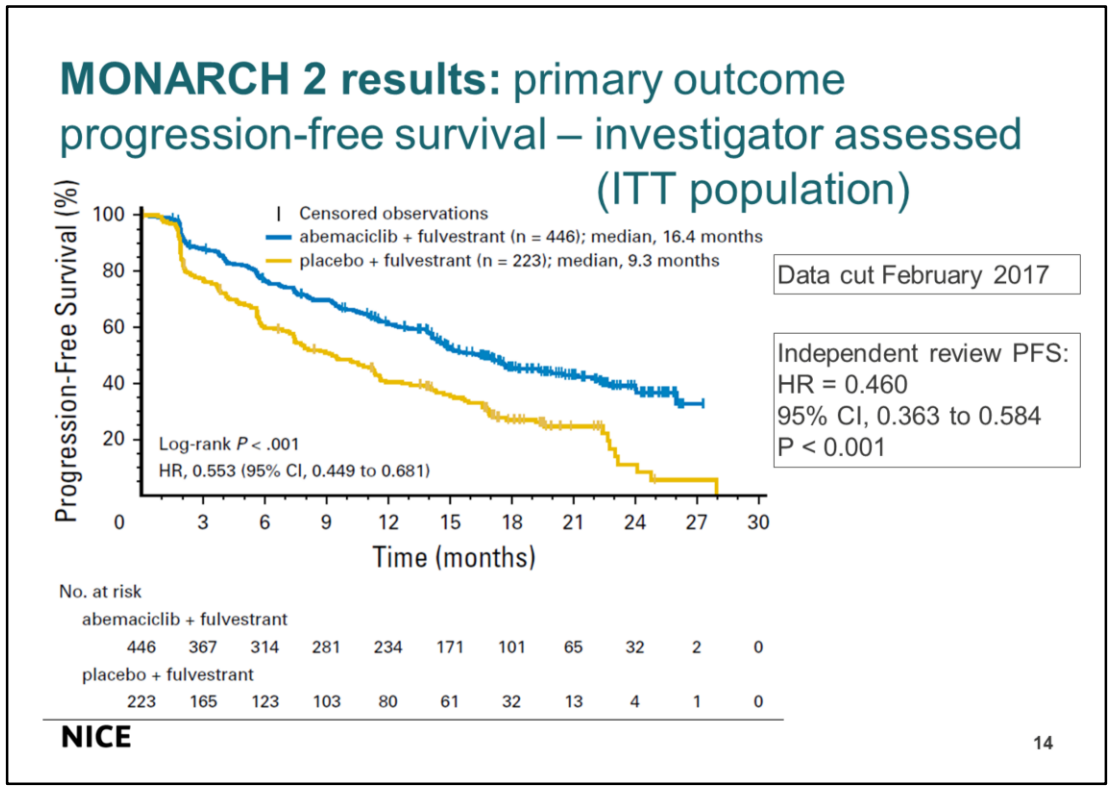
MONARCH 2 selected baseline characteristics

Baseline characteristic		AB+FUL (N=446)	Placebo+FUL (N=223)
Age, median (range)		59 (32 to 91)	62 (32 to 87)
Menopausal status, n (%)	Pre- or peri-menopause	72 (16.1)	42 (18.8)
	Post-menopause	371 (83.2)	180 (80.7)
	Natural	[redacted]	[redacted]
	Surgical	[redacted]	[redacted]
Race, n (%)	Asian	149 (33.4)	65 (29.1)
	Caucasian	237 (53.1)	136 (61.0)
	Other	29 (6.5)	13 (5.8)
ECOG performance status	0	264 (59.2)	136 (61.0)
	1	176 (39.5)	87 (39.0)
Region, n (%)	Europe	[redacted]	[redacted]
	Asia	[redacted]	[redacted]
	North America	[redacted]	[redacted]
Metastatic site, n (%)	Visceral	245 (54.9)	128 (57.4)
	Bone only	123 (27.6)	57 (25.6)
	Other	75 (16.8)	38 (17.0)
ET resistance, n (%)	Primary	111 (24.9)	58 (26.0)
	Secondary	326 (73.1)	163 (73.1)
Prior AI, n (%)	Yes	316 (70.9)	149 (66.8)
	No	130 (29.1)	74 (33.2)
Prior chemotherapy for (neo)adjuvant treatment, n (%)	Yes	267 (59.9)	134 (60.1)
	No	179 (40.1)	89 (39.9)

Source: company submission table 6



Source: company submission figure 4

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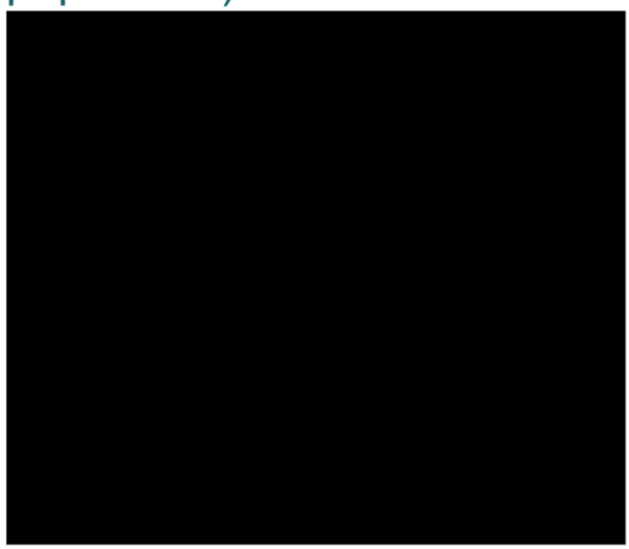
MONARCH 2 results: Overall survival (ITT population)



Data cut 14th Feb 2017
- OS data still immature
- Median OS not reached
- OS data cut-off expected April 2019
- Estimated study completion date February 2020

HR = [redacted]
95% CI [redacted]
Log-rank test p-value = [redacted]

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Source: company submission B.2.6.2, figure 7

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MONARCH 2 results: Response rates

ITT population n=669	Abemaciclib + fulvestrant (n, %)	Placebo + fulvestrant (n, %)	Odds ratio
Complete response (CR)	14 (3.1)	1 (0.4)	NA
Partial response (PR)	143 (32.1)	35 (15.7)	NA
Stable disease (SD)	213 (47.8)	133 (59.6)	NA
≥6 months	165 (37.0)	89 (39.9)	NA
Progressive disease	40 (9.0)	45 (20.2)	NA
Not evaluable	36 (8.1)	9 (4.0)	NA
Overall response rate (CR + PR)	157 (35.2)	36 (16.1)	2.82 (p<0.001)
Disease control rate (CR + PR + SD)	370 (83.0)	169 (75.8)	1.56 (p=0.025)
Clinical benefit rate (CR + PR + SD ≥6 months)	322 (72.2)	125 (56.1)	2.04 (p<0.001)

ERG notes that median time to response was [redacted] in abemaciclib+fulvestrant group and [redacted] in the placebo+fulvestrant group (based on CSR)

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Source: company submission B.2.6.3, table 12; ERG report 4.3.3

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MONARCH 2 results: Duration of response

Median duration of response:
ABE-FUL Not reached
PBO-FUL [redacted]
Patients whose disease responded who were progression-free at 12 months:
ABE-FUL 67.8%
PBO-FUL 66.9%

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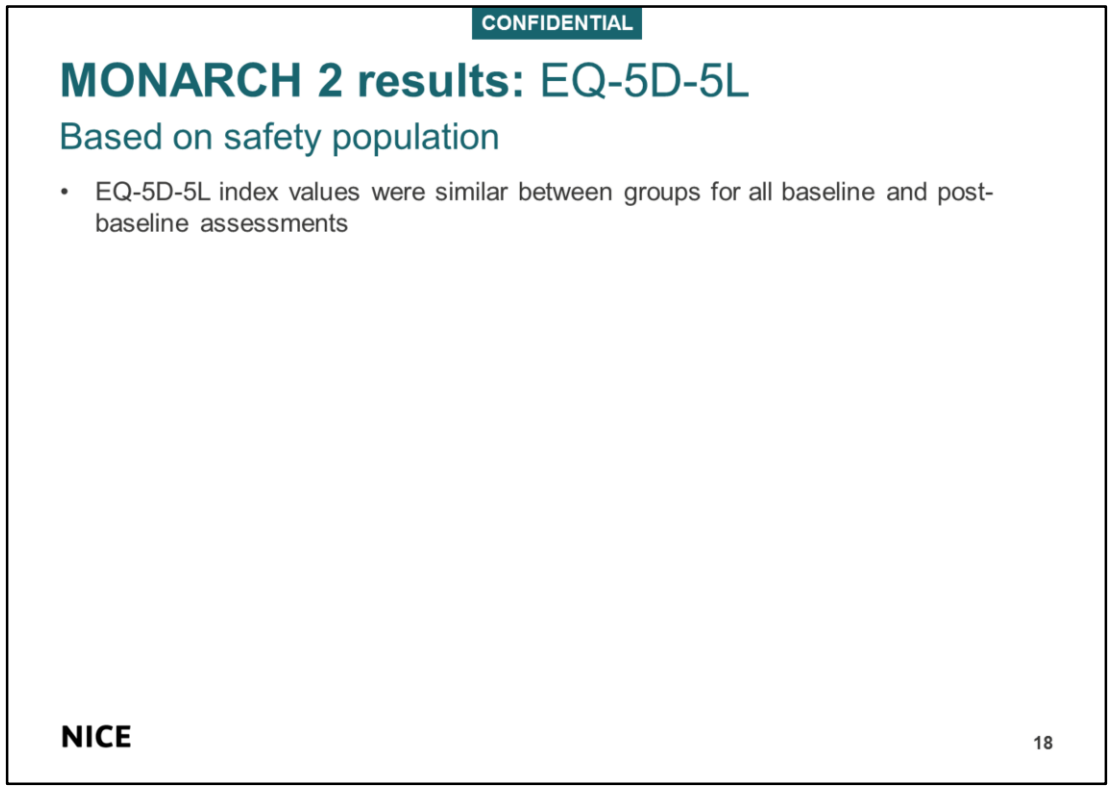
Source: company submission figure 8



Source: company submission B.2.6.7

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Treatment-emergent adverse events

	Pre-amendment population	Post-amendment population	Intent-to-treat population	
	ABE 200 mg (N=121)	ABE 150 mg (N=320)	ABE-FUL (N=441)	PBO-FUL (N=223)
Incidence of diarrhoea				
Grade 2, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Incidence of neutropenia				
Grade 3, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Grade 4, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Dose reductions due to TEAEs (%)	[redacted]	[redacted]	[redacted]	[redacted]
Dose reduced due to diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Dose reduced due to neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued any study drug due to AE (%)	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued due to diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued due to neutropenia	[redacted]	[redacted]	[redacted]	[redacted]

- Treatment discontinuations due to adverse events were more common with abemeciclib+fulvestrant compared with placebo+fulvestrant
- Diarrhoea was the most common adverse event in the abemaciclib+fulvestrant group and led to reductions in dose – after a review of preliminary safety data, the trial protocol was changed from an abemaciclib starting dose of 200 mg to 150 mg

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Source: company submission table 19

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ERG comments on MONARCH 2

- Well-designed and well-conducted trial
- Protocol amendment reduced starting dose from 200 mg to 150 mg twice daily after trial had started, based on review of preliminary safety data – potential impact on efficacy and safety results
  - Subgroup analysis showed interaction between 200 mg and 150 mg subgroup was [redacted]. However, mean relative treatment effect of abemaciclib+fulvestrant was [redacted] in 200 mg subgroup even though patients enrolled before amendment only received a median 34 days of treatment before all doses were reduced to 150 mg
- Baseline characteristics well balanced across treatment groups
  - No patients from UK but clinical experts reported the population appears representative of people in England who are likely to be eligible for treatment with abemaciclib
- Independent review of progression-free survival was done retrospectively
- Company used PFS Kaplan-Meier data adjusted for interval censoring in its base case economic model – not what is presented in the clinical effectiveness results
- Overall survival data immature – 19.1% patients had died in the abemaciclib+fulvestrant group and 21.5% in the placebo+fulvestrant group

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Source: ERG report sections 4.2, 4.3.2, 4.3.5

Company's hazard ratio network meta-analysis

Included trials	Intervention A (ITT n)	Connected to network of evidence?			
		ORR	CBR	OS	PFS
Baselga 2012 (BOLERO-2)	EXE-EVE (485), EXE (239)	✓	✓	✓	✓
*Buzdar 1997	ANAS 1 mg (128), ANAS 10 mg (130), MGA 160 mg (128)	✓	✓	✓	✓
*Buzdar 2001	LTZ 0.5 mg (202), LTZ 2.5 mg (199), MGA 160 mg (201)	✓	×	✓	✓
‡Campos 2009	EXE (65), ANAS 1 mg (65)	×	✓	✓	✓
Chia 2008 (EFECT)	FUL 250 mg (351), EXE (342)	✓	✓	×	×
Di Leo 2010 (CONFIRM)	FUL 500 mg (362), FUL 250 mg (374)	✓	✓	✓	✓
**Dombernowsky 1998	LTZ 0.5 mg (188), LTZ 2.5 mg (174), MGA 160 mg (189)	✓	✓	✓	×
Nishimura 2017 (Hi-FAIR fx)	FUL 500 mg (52), TOR (53)	✓	✓	✓	✓
‡Howell 2002	FUL 250 mg (222), ANAS 1 mg (229)	✓	✓	✓	✓
Johnston 2013 (SoFEA)	FUL 250 mg (231), EXE (249)	✓	✓	✓	✓
*Jonat 1996	ANAS 1 mg (135), ANAS 10 mg (118), MGA 160 mg 125)	✓	✓	✓	✓
**Kaufmann 2000	EXE (366), MGA 160 mg (403)	✓	✓	✓	×
**Muss 1990	MGA 160 mg (86), MGA 800 mg (84)	✓	×	✓	×
‡Osborne 2002 (Trial 0021)	FUL 250 mg (206), ANAS 1 mg (194)	✓	✓	✓	✓
**Rose 2003	LTZ 2.5 mg (356), ANAS 1 mg (357)	✓	✓	✓	×
Sledge 2017 (MONARCH 2)	ABE-FUL (446), FUL 500 mg (223)	✓	✓	✓	✓
*Turner 2015 (PALOMA 3)	PAL-FUL (347), FUL 500 mg (174)	✓	✓	✓	✓
Yamamoto 2013	TOR (46), EXE (45)	✓	✓	✓	✓
Zhang 2016	FUL 500 mg (111), FUL 250 mg (110)	✓	✓	×	✓

Subsequent FP NMA: Removed from FP NMA **Removed from OS FP NMA ‡Used in scenario analysis only

Source: company submission appendix D table 19

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HR NMA results vs fulvestrant 500mg

Heterogeneity – other trials multiple ET / prior chemotherapy vs. MONARCH 2)

PFS (random effects) | OS (fixed effects)

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Source: company submission figures 9 and 10

Notes:

- ABE+FUL, abemaciclib + fulvestrant
- EXE+EVE, exemestane + everolimus
- FUL 500, fulvestrant 500mg
- FUL 250, fulvestrant 250mg
- EXE, exemestane

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Adjusted indirect comparison

- Tamoxifen not included in NMA due to lack of evidence – adjusted indirect comparison subsequently done using Milla-Santos (2001)

	OS, HR (CrI)	PFS/TTP, HR (CrI)	Source
Toremifene vs tamoxifen	[redacted]	[redacted]	Milla-Santos 2001
Toremifene vs fulvestrant 500 mg	[redacted]	[redacted]	NMA, company submission
Adjusted indirect comparison tamoxifen vs fulvestrant 500 mg	[redacted]	[redacted]	Company submission

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Source: company submission table 16

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ERG comments on company's NMA

- Not clear why company analysed the tamoxifen trial and the NMA results in a separate analysis rather than including the trial in the original network
- Heterogeneity due to lack of published data in a similar patient population to MONARCH 2
  - all studies except MONARCH 2 (who reported it) allowed for prior chemotherapy in the advanced setting and some studies allowed for more than one prior ET in the advanced setting
- BOLERO-6 – open-label study with some imbalances in baseline characteristics. PFS benefit of capecitabine over exemestane+everolimus may be overestimated
- Subsequent therapies only reported in 4 trials. In Hi-FAIR fx and Yamamoto 2013, patients could switch to the other treatment group on progression – likely to confound OS estimates
- Proportional hazards not met for all trials for PFS and OS
  - Therefore ERG considers results of HR NMA to be misleading and challenging to interpret

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Source: ERG report section 4.4

Fractional polynomial method

- Method uses parametric survival functions, including survival distributions such as Weibull or Gompertz, together with **more flexible** fractional polynomials (FP)
- Allows for **change of hazards over time** and offers more freedom in distribution selection
- With 1st or 2nd order fractional polynomials:
  - Model hazard functions of the interventions compared in a trial
  - Consider difference in the parameters of these fractional polynomials within a trial
  - Synthesise multidimensional treatment effect (and indirectly compare) across studies
- Therefore, treatment effects are represented with multiple parameters rather than a single parameter or outcome

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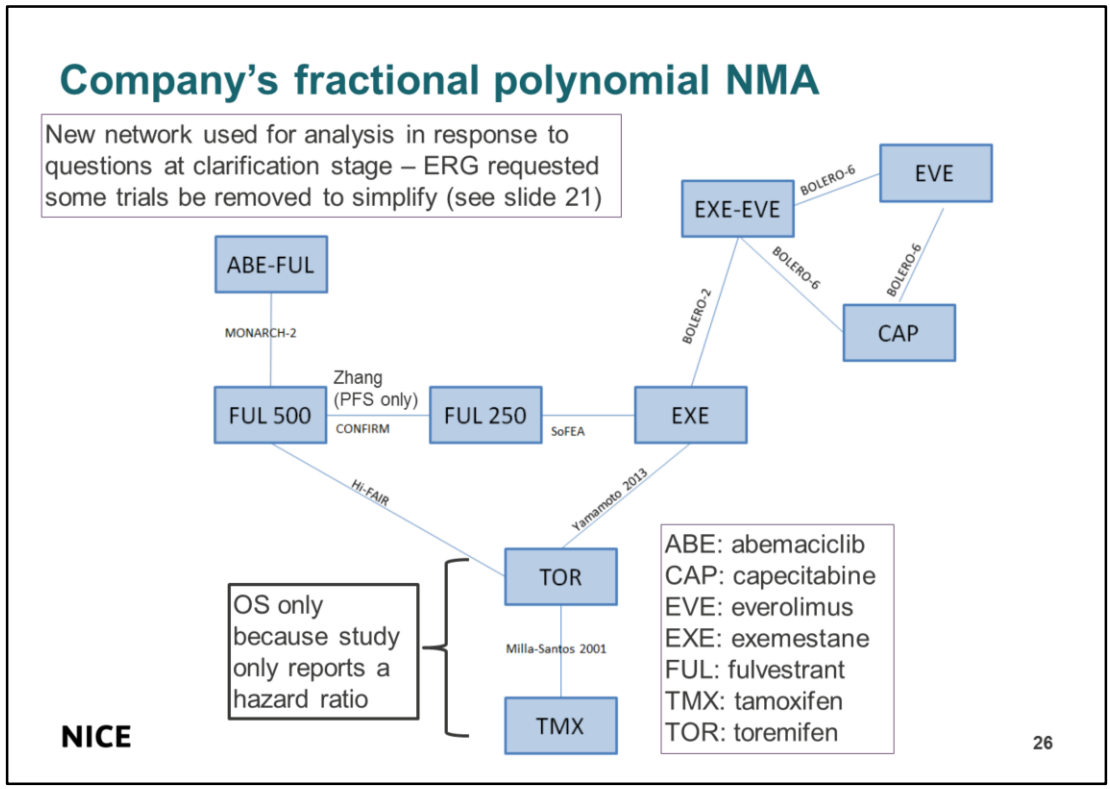

Source: company response to clarification question A3b

FP NMA (including tamoxifen for OS)

Methods

- Proportional hazards assumption did not hold for all of the trials in the revised NMA (for PFS and OS) and therefore company used a fractional polynomial approach
- Patient populations broadly similar in trial BUT MONARCH 2 more specific - people who have progressed on or after endocrine therapy and had less previous treatment. These factors could not be adjusted for.

Trial	Design	N	Intervention
BOLERO-2	Double blind	485+239	EXE-EVE, EXE
BOLERO-6	Open label	104+103+102	EXE-EVE, EVE, CAP
CONFIRM	Double blind	362+374	FUL500, FUL250
Hi-FAIR fx	Open label	53+52	TOR, FUL
Milla-Santos 2001	Double blind	106+111	TOR, TMX
MONARCH 2	Double blind	446+223	ABE-FUL, FUL
SoFEA	Partially blinded	231+249	FUL250, EXE
Yamamoto 2013	Open label	46+45	TOR, EXE
Zhang 2016	Double blind	111+110	FUL500, FUL250

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Source: company response to clarification question A3, A4

ERG comments on NMA

Hazard ratio NMA

- ERG considers it challenging to meaningfully interpret the results of the NMA based on hazard ratios when the proportional hazards assumption did not hold for all studies
- 95% credible intervals relatively wide for each comparison, particularly in overall survival

Company's PFS FP NMA

Fractional polynomial NMA

Curves presented by company do not match the curves used in the economic model – ERG unable to validate

- All models lack clinical plausibility because the plateau is not in line with the clinical trial data
- PFS curve crosses OS curve for several of the treatments, which is not biologically possible

ERG ran own NMA using fractional polynomial method

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Source: ERG report section 4.4, 4.4.3

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ERG revised FP NMA

- Excluded Hi-FAIR fx and Yamamoto 2013 and everolimus monotherapy arm from BOLERO-6 (not required to connect interventions of interest) to simplify network
- Tamoxifen not included
- Relative treatment effectiveness for capecitabine likely to have been overestimated in the BOLERO-6 trial and therefore in the FP NMA

Progression-free survival

- Consider first order FP with p=0 to have most plausible tails
- Fit to KM data may look poor but fit statistics are best average fit across the network

Overall survival

- p = -1.5 used in scenario analysis
- p = -0.5 chosen as base case based on DIC statistics, clinical plausibility and consistency in relative order of treatments compared with underlying trial data
- May be a poor fit to MONARCH 2 due to immaturity of OS data

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Source: ERG report 4.6.1, figure 19, figure 22

Cost effectiveness

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Key issues for consideration - cost

- How should treatment effectiveness be extrapolated in the model?
  - PFS and OS
  - Which NMA should be used?
- Which data should be used for time to treatment discontinuation?
- Which utility values should be used for progression-free survival and post-progression survival?
- Should adverse event-related disutilities be used in the model?
- Should age-related utility decrements be included in the model?
- What distribution of subsequent treatments should be modelled?
- How long should patients receive subsequent treatments in the model?
- How should the costs of fulvestrant and capecatibine be modelled?
- How should follow-up care costs be modelled?
- Is abemaciclib plus fulvestrant cost effective?

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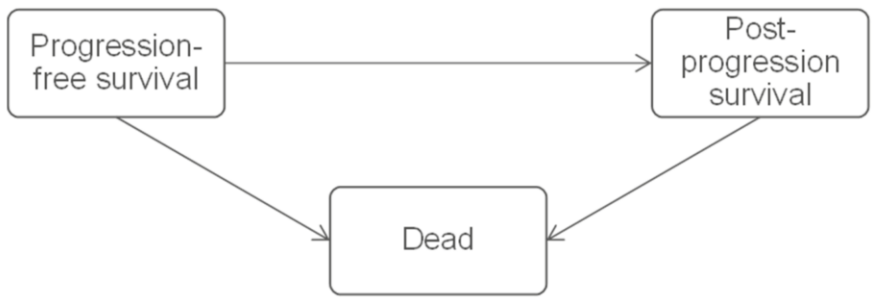
Company's economic model

- Partitioned survival model
- 3 health states
- Weekly cycle, 25 year time horizon (equivalent to lifetime)
  - ERG comment – 20 year time horizon actually used in model



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Source: company submission figure 13

Treatment effectiveness in the model

Progression-free survival - MONARCH 2

Abemaciclib+fulvestrant

[redacted]

Fulvestrant

[redacted]

Investigator assessed progression-free survival. Joint Weibull distribution fitted in the base case, chosen based on AIC/BIC statistics, fit to Kaplan-Meier data and plausibility of long-term extrapolations compared with trial data (e.g. 45 month FUL 500mg data from CONFIRM)

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Source: company submission figures 16 and 17

Treatment effectiveness in the model

Overall survival – MONARCH 2

Abemaciclib+fulvestrant

Fulvestrant

Weibull distribution chosen for both in the base case, based on AIC/BIC statistics, fit to Kaplan-Meier data and plausibility of long-term extrapolations compared to trial (CONFIRM) data. Long-term OS for abemaciclib+fulvestrant and fulvestrant was assumed to be the same after [redacted] months, after which, extrapolation was informed by CONFIRM data.

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Source: company submission figures 21 and 22

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Treatment effectiveness in the model

PFS and OS for other comparators

- Network meta-analysis used in model for progression-free survival and overall survival (original NMA used in company base case)
- Hazard ratios estimated by the NMA and applied to the fulvestrant curve based on MONARCH-2:

Comparator	PFS HR (CrI)	OS HR (CrI)
EXE (25 mg)	[redacted]	[redacted]
EXE (25 mg)-EVE (10 mg)	[redacted]	[redacted]
FUL (500 mg)	Reference	Reference

- Hazard ratios for tamoxifen compared to fulvestrant 500mg, estimated by the adjusted indirect comparison

Comparator	TTP/PFS HR (CrI)	OS HR (CrI)
TMX	[redacted]	[redacted]
FUL (500 mg)	Reference	Reference

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Source: company submission B.3.3.4, tables 26 and 27; B.3.3.5, tables 28 and 29; ERG report 5.4.5

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PFS extrapolations in company's base case

Investigator-assessed

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Source: company submission figure 19

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OS extrapolations in company's base case

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Source: company submission figure 24

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Treatment effectiveness in the model

Time to treatment discontinuation

Abemaciclib+fulvestrant

Placebo+fulvestrant

- Based on data from MONARCH 2 and used to estimate drug acquisition costs
- Joint Weibull distribution jointly fitted to MONARCH 2 KM data in base case
- Duration of therapy for comparators estimated from median duration of therapy and median PFS reported in the trial publications – HR applied to PFS distribution in model

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Source: company submission figures 26 and 27

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Utility values in the model

Health state	Utilities used in the model	Source
Pre-progression	[redacted] (company and ERG base case)	EQ-5D-5L collected in MONARCH-2 and mapped to EQ-5D-3L (van Hout approach)
Post-progression	0.505 (company's base case)	Lloyd (2006) (Company used due to immaturity of MONARCH-2 data. Used in TA421, everolimus with exemestane, in a similar population)
	[redacted] (ERG base case)	Estimated using Mitra et al. 2016
	[redacted] (ERG scenario analysis)	MONARCH 2

Company included utility decrements for adverse events. ERG removed – minimal impact on ICER

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Source: company submission B.3.2.2, B.3.4

Notes:

- The utility value from Lloyd (2006) was used for post-progression survival in the appraisals for palbociclib (TA495), ribociclib (TA496) and abemaciclib+aromatase inhibitor (ID1227)

Costs and resource use in the model

	Source for components/frequency	Source for costs
Follow-up care	NICE guidelines/ Pre-progression: MONARCH-2 Post-progression: MONARCH-1	NHS Reference costs 2016-17 / PSSRU
Subsequent therapies	Weighted average cost based on treatments in MONARCH-2 and BOLERO-2	eMIT / BNF

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Source: company submission B.3.5.3

ERG comments

Comparators

- Tamoxifen modelled as 40 mg daily while 20 mg usually used in UK

Modelling approach and structure

- Company's base case estimates that 5% patients in abemaciclib+fulvestrant group are still alive at 10 years – may suggest overestimation of long-term survival in model

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Source: ERG report 5.4.3, 5.4.4

ERG comments

Treatment effectiveness

- Company did not use hazard ratio obtained in NMA to estimate the PFS and OS abemaciclib+fulvestrant curves – used fitted curves to KM data instead
- ERG considers that models should not have been fitted jointly for treatment groups for time to treatment discontinuation, progression-free survival or overall survival because proportional hazards assumption does not hold
  - This relies even further on validity of proportional hazards assumption – ERG considers this inappropriate.
- PSA flawed because company did not account for correlation between different HRs when sampling clinical effectiveness data from HRs (and 95% credible intervals) in base case analysis
- Base case economic model uses PFS Kaplan-Meier data adjusted for interval censoring – not what is presented in the clinical effectiveness results
  - ERG does not think adjusting for interval censoring is necessary
- **Immaturity of overall survival data provides uncertainty in all results** – not accounted for through probabilistic sensitivity analyses

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Source: ERG report 5.4.3, 5.4.5

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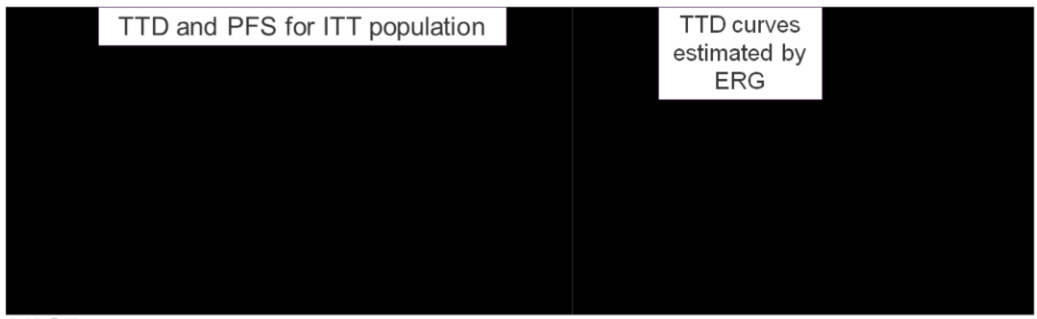
ERG comments

Time to treatment discontinuation (TTD)

- Company's base case treatment discontinuation (for EXE, EXE-EVE, TMX and chemotherapy) estimated by a ratio between median PFS and median TTD within each trial (not HRs)
- Median PFS and TTD were similar for exemestane (BOLERO 2), tamoxifen (Milla-Santos) and chemotherapy (BOLERO 6) so ERG used PFS curves as proxies to estimate TTD
- ERG estimated hazard ratio (for abemaciclib+fulvestrant, fulvestrant, and exemestane+everolimus) between cumulative survival at median duration of therapy and PFS at median TTD from trial publications (company's scenario analysis), but with PFS curves from MONARCH 2 and BOLERO 2 not the hazard ratio NMA



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Source: ERG report 5.4.5.5; figure F, G

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ERG comments

Time to treatment discontinuation

- A lot of withdrawals among patients who started on the 200mg dose. The difference between PFS and TTD KM curves is greater in the ITT population than those started on 150mg abemaciclib
- **Using the ITT TTD data underestimates the costs of ABE-FUL** compared to using the 150 mg TTD data and ERG considers is not representative of NHS clinical practice or in line with marketing authorisation of abemaciclib
- Because 150mg data not provided by company, ERG did scenario analyses varying the HR between PFS and TTD

TTD curves by abemaciclib starting dose (MONARCH 2)

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Source: ERG report 5.4.5.5; figure I

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ERG comments

Health-related quality of life

- Company stated p-values and 95% confidence intervals associated with coefficients obtained in regression models were not available, therefore ERG not able to validate
- Lloyd et al. elicited utility values from general public, rather than patients with HR positive HER2 negative advanced breast cancer, as in MONARCH 2
  - PFS utility in Lloyd [redacted] than PFS utility in MONARCH 2 so ERG considers the substantial difference between PFS and PPS in Lloyd not easily explained – used utility values from MONARCH 2 in **scenario analysis** (PFS = [redacted], PPS = [redacted])
- Alternative **ERG scenario analysis** used data from cross-sectional study, Mitra et al 2016, to apply -11% decrement to PFS utility value in MONARCH 2 to estimate PPS utility of [redacted]
- ERG also conducted **scenario analysis** to include age-related utility decrements

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Source: ERG report 5.4.8

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ERG comments: Resource and costs

Post-progression treatments

- Data on subsequent therapies in MONARCH 2 are incomplete (70% in abemaciblib+fulvestrant group had progressed or left study at end of follow-up)
- Clinical opinion that distribution of subsequent treatment would be different to company's assumptions e.g. paclitaxel use would be higher; bevacizumab not available in NHS, tamoxifen available but not included **> ERG scenario analysis**

Treatment	Time on treatment (months)		Total time in PPS (months)
	Base case	ERG scenario	
ABE-FUL	[redacted]	[redacted]	[redacted]
FUL	[redacted]	[redacted]	[redacted]
EXE	[redacted]	[redacted]	[redacted]
EXE-EVE	[redacted]	[redacted]	[redacted]
TMX	[redacted]	[redacted]	[redacted]

- Company model assumes patients on subsequent treatment for 37% of time in post-progression survival **> ERG scenario analysis** where patients remain on subsequent treatment for all but the last 3 months of life
- **Decreasing costs of subsequent treatment increases the ICER**

Treatment costs

- Fulvestrant assumed to be administered as part of consultation with oncologist and only loading dose has an associated administration cost - **ERG scenario analysis** where 32.3% subsequent fulvestrant administrations delivered in primary care and 67.7% as outpatient and administration costs applied to every treatment cycle

Follow-up care costs

- Clinical opinion that costs in model overestimate UK costs as patients would not have ECGs and would have less frequent CT scans, community nurse and oncologist visits **> ERG scenario analysis** using follow-up care costs accepted in TA496

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Source: ERG report section 5.4.9

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Company's base case results (deterministic)

Includes PAS discount for abemaciclib

Uses company's hazard ratio network meta-analysis (preferred company base case)

Technology	Total costs (£)	Total QALYs	Incremental ICER (£/QALY)	Pairwise ICER vs ABE-FUL (£/QALY)
TMX	[redacted]	[redacted]	Referent	£62,548
FUL	[redacted]	[redacted]	Dominated	£41,702
EXE	[redacted]	[redacted]	Dominated	£18,754
ABE-FUL	[redacted]	[redacted]	£62,548	-
EXE-EVE	[redacted]	[redacted]	Dominated	Dominated

Based on the latest PAS price of abemaciclib and list prices of comparators. (PAS price of abemaciclib increased after clarification.)

- **Results with the PAS discount for everolimus are presented in the part 2 confidential appendix to the PMB**
- Probablistic results are consistent with the deterministic results
- Scenario analyses show the ICER to be largely stable when varying model assumptions

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Source: company's response to clarification table 0

ERG's scenario analyses

All include PAS for abemaciclib

1. Using ERG's FP NMA-derived curves (PFS power of 0, OS power of -1.5), including ERG's estimated TTD curves
2. Using both PFS and PPS-related utility values from MONARCH 2
3. Using utility value derived using Mitra et al. 2016
4. Removing adverse event-related disutilities (ERG considers already included in PFS value from MONARCH 2)
5. Including age-related utility decrements
6. Alternative distribution of subsequent treatments
7. Patients receive subsequent treatments for all except last 3 months of PPS
8. Limited time on fulvestrant and exemestane-everolimus as subsequent treatments
9. Resource use for follow-up care from TA496 (ribociclib)
10. Fulvestrant administration costs from TA496 applied for every treatment cycle
11. Excluding cost of non-AE-related hospitalisations from analysis
12. Removing half-cycle correction
13. As scenario 1 but including first-order FP OS* curve with power -0.5

NICE **Corrected after committee meeting* 48

Source: ERG report section 6.2

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ERG alternative base case analysis [1]

	Results per patient	Incremental value ABE-FUL vs comparator ‡			
		FUL	EXE	EXE-EVE	CAP*
0	Company's base case corrected by ERG				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	£50,687	£57,247	Dominant	£82,621**
1	Using the ERG's FP NMA results for OS and PFS and adjusting TTD curves				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	£41,719	£44,089	Dominant	Dominated
3	PPS utility using a -11% relative decrement (Mitra et al. 2016) on PFS utility				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	[redacted]	[redacted]	[redacted]	[redacted]
	ICER with all above changes	£52,288	£51,578	Dominant	Dominated
4	Removed AE-related disutilities				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	[redacted]	[redacted]	[redacted]	[redacted]
	ICER with all above changes	£52,210	£51,525	Dominant	Dominated

*This refers to TMX instead of CAP for the scenario using the company's corrected base case (0)
**ABE-FUL is compared to TMX instead of CAP when the ICER is compared with the base case
‡ *Corrected after committee meeting*

Source: ERG report table 55

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ERG alternative base case analysis [2]

	Results per patient	Incremental value ABE-FUL vs comparator ‡			
		FUL	EXE	EXE-EVE	CAP*
5	Age-related utility decrements included				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	£51,757	£58,360	Dominant	£84,299**
	ICER with all above changes	£53,668	£52,778	Dominant	Dominated
6+7+8	Post-progression treatment in PPS from 37% to up to 3 months before death				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	£29,786	£53,150	Dominant	£8,384**
	ICER with all changes	£45,168	£46,116	Dominant	Dominated
9	TA496 health state costs				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	£62,737	£65,459	Dominant	£111,549**
	ICER with all above changes	£47,885	£45,994	Dominant	Dominated
10	TA496 FUL administration costs				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	£52,348	£59,546	Dominant	£88,566**
	ICER with all above changes	£49,254	£47,637	Dominant	Dominated

Source: ERG report table 55

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ERG alternative base case analysis [3]

	Results per patient	Incremental value ABE-FUL vs comparator ‡			
		FUL	EXE	EXE-EVE	CAP
11	Removing non-AE-related hospitalisation costs				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	£54,054	£59,797	Dominant	£89,595**
	ICER with all above changes	£50,725	£48,406	Dominant	Dominated
12	Remove half-cycle correction				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	£51,432	£57,790	Dominant	£84,139**
	ICER with all above changes	£52,351	£52,002	Dominant	Dominated
13	Using first-order FP OS curve with a power of -0.5 (compared to p = -1.5)				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	£42,065	£44,258	Dominant	Dominated
	ICER with all above changes	£70,634	£63,436	Dominant	Dominated
ERG base case with PFS and PPS utility values from MONARCH (OS FP p= -0.5)					
	ICER	£80,604	£68,116	Dominant	Dominated
ERG base case with PFS and PPS utility values from MONARCH (OS FP p= -1.5)					
	ICER	£55,448	£54,038	Dominant	Dominated

**ABE-FUL is compared to TMX instead of CAP when the ICER is compared with the base case

Source: ERG report table 55

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ERG scenario analysis

Using alternative HRs to estimate TTD curve for ABE-FUL

	Results per patient	Incremental value ABE-FUL vs comparator ‡			
		FUL	EXE	EXE-EVE	CAP
0	ERG base case				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	£70,634	£63,436	Dominant	Dominated
a	HR=1 for PFS vs TTD curve				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	£120,775	£87,152	Dominant	Dominated
b	Reduce HR by 5% ([redacted])				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	£78,996	£67,391	Dominant	Dominated
c	Reduce HR by 10% ([redacted])				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	£88,353	£71,817	Dominant	Dominated

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Source: ERG report table 56

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ERG scenario analysis

Varying the time patients spend on FUL and EXE-EVE as subsequent treatments

	Results per patient	Incremental value ABE-FUL vs comparator ‡			
		FUL	EXE	EVE-EXE	CAP
0	ERG base case				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	£70,634	£63,436	Dominant	Dominated
d	Decreasing time spent in FUL and EXE-EVE as subsequent treatments by 5%				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	£70,634	£63,477	Dominant	Dominated
e	Decreasing time spent in FUL and EXE-EVE as subsequent treatments by 10%				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	£72,634	£63,518	Dominant	Dominated
f	Decreasing time spent in FUL and EXE-EVE as subsequent treatments by 25%				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	£74,448	£60,649	Dominant	Dominated

Source: ERG report table 57

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Abemaciclib with fulvestrant for treating advanced HR-positive, HER2-negative breast cancer patients who have progressed on or after prior endocrine therapy [ID1339]

Document B

Company evidence submission

September 2018

File name	Version	Contains confidential information	Date
NICE Abemaciclib plus Fulvestrant Document B	Final	Yes	25/09/18

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

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Contents

Tables and figures

Abbreviations

Abbreviation	Definition
ABC	Advanced breast cancer
ABE	Abemaciclib
AE	Adverse event
AFT	Accelerated failure time
AI	Aromatase Inhibitor
AIC	Akaike information criterion
ALT	Alanine aminotransferase
ANAS	Anastrozole
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
BEV	Bevacizumab
BIC	Bayesian information criterion
BIM	Budget Impact Model
BNF	British National Formulary
BOR	Best overall response
BPI	Brief pain inventory
BSA	Body surface area
BSC	Best supportive care
CAP	Capecitabine
CBR	Clinical benefit rate
CDK	Cyclin-dependent kinase
CE	Cost-effectiveness
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CSF	Colony stimulating factor
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYC	Cyclophosphamide
CYP3A4	Cytochrome P4503A
DCR	Disease control rate
DFI	Disease-free interval
DNA	Deoxyribonucleic acid
DOC	Docetaxel
DoR	Duration of response
DOX	Doxorubicin
DSA	Deterministic sensitivity analysis

DSU	Decision Support Unit
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	Electronic market share information tool
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European Public Assessment Reports
EPI	Epirubicin
EQ-5D-5L	EuroQol 5-Dimension 5-Level
ER	Oestrogen receptor
ERG	Evidence Review Group
ERI	Eribulin
ESMO	European Society of Medical Oncology
ESO	European School of Oncology
ET	Endocrine therapy
EVE	Everolimus
FACT-B	Functional Assessment of Cancer Therapy - Breast Cancer
FE	Fixed effect
FLU	fluorouracil
FSH	Follicle stimulating hormone
FUL	Fulvestrant
G-CSF	Granulocyte-colony stimulating factor
GEM	Gemcitabine
GP	General Practitioner
HER2	Human epidermal growth factor receptor-2
HRQoL	Health-related quality of life
HR	Hormone receptor or hazard ratio
IA	Investigator-assessed
ICER	Incremental cost-effectiveness ratio
IHC	Immunohistochemistry
IM	Intramuscular
INV	Investigator
IPD	Individual patient data
IQR	Interquartile range
IRC	Independent review committee
ISH	In-situ hybridisation
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intent-to-treat
IWRS	Interactive web-based randomisation scheme
IXA	Ixabepilone

KM	Kaplan-Meier
LHRH	Luteinising hormone-releasing hormone
LS	Least squares
LTZ	Letrozole
LY	Life year
LYG	Life years gain
MAA	Marketing Authorisation Applications
mBC	Metastatic breast cancer
mBPI-sf	Modified Brief Pain Inventory- short form
mg	Milligram
MGA	Megestrol acetate
MRI	Magnetic resonance imaging
NA	Not available/applicable
Nab	Nanoparticle albumin-bound
NCCN	National Comprehensive Cancer Network
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NMA	Network meta-analysis
NMB	Net monetary benefit
NR	Not reported
NSAI	Non-steroidal aromatase inhibitor
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PAC	Paclitaxel
PAS	Patient Access Scheme
PBO	Placebo
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PgR	Progesterone receptor
PH	Proportional hazards
PPS	Post-progression survival
PR	Partial response
PROs	Patient-reported outcomes
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q12H	Every 12 hours
QALY	Quality adjusted life year

QAPFW	Quality-adjusted progression free weeks
QAPFY	Quality-adjusted progression free years
RB	Retinoblastoma
RCT	Randomised controlled trial
RDI	Relative dose intensity
RE	Random effects
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
sb	Solvent-based
SD	Stable disease or standard deviation (in context of statistical analyses)
SE	Standard error
SERD	Selective oestrogen receptor degrader
SERM	Selective oestrogen receptor modulator
SLR	Systematic literature review
SOC	System organ class
STA	Single Technology Appraisal
TD	Treatment discontinuation
TEAE	Treatment-emergent adverse event
TLSR	Trial level safety review
TMX	Tamoxifen
TOR	Toremifene
ToT	Time on treatment
TPC	Treatment of physician's choice
TRAE	Treatment-related adverse event
TSD	Technical support document
TTP	Time-to-progression
UK	United Kingdom
VAS	Visual analogue scale
VNB	Vinorelbine
WHO	World Health Organisation

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

B.1.1 *Decision problem*

The submission focusses on part of the technology's marketing authorisation. Abemaciclib is under review by the European Medicines Agency for the treatment of women with hormone receptor positive (HR+)/human epidermal growth factor receptor 2 negative (HER2−) locally advanced or metastatic breast cancer, within two distinct patient populations, which are listed below as per the Summary of Product Characteristics:

- *In combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy (ID1227, Appraisal Submitted June 2018;[1] ID1339, this submission)[2]*

The proposed patient population for this submission (ID1339)[2] is narrower than the anticipated marketing authorisation, as NICE has chosen to appraise each patient population separately. The decision problem for this submission (Table 1) involves abemaciclib in combination with fulvestrant, for women with locally advanced or metastatic breast cancer who have progressed on or after (neo)adjuvant endocrine-based therapy, or progressed during first-line endocrine-based therapy for advanced disease.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	• People with untreated advanced HR+/HER2− breast cancer • People with advanced HR+/HER2− breast cancer that has progressed on or after endocrine therapy	Women of any menopausal status[a] with locally advanced[b] or metastatic HR+/HER2− breast cancer who had progressed while receiving (neo)adjuvant ET, ≤ 12 months from the end of adjuvant therapy, or while receiving first-line ET for locally advanced[b] or metastatic disease	Patients who are untreated in the advanced setting and those who have progressed after ET in the advanced setting are considered to be part of one homogenous population for this submission. They share the ET-resistant characteristics,[c] having received prior ET as (neo)adjuvant therapy or therapy for advanced breast cancer. Patients have progressed whilst receiving or ≤ 12 months after ET, and therefore both populations represent a rapidly-progressing, hard-to-treat, ET-resistant patient population.
Intervention	Abemaciclib in combination with fulvestrant	Abemaciclib in combination with fulvestrant	N/A
Comparator(s)	For people with untreated advanced hormone-receptor positive HER2-negative breast cancer: • Palbociclib in combination with an aromatase inhibitor • Ribociclib in combination with an aromatase inhibitor • Tamoxifen (in accordance with NICE guidance CG81) For people with advanced hormone-	• Exemestane • Everolimus and exemestane • Tamoxifen • Fulvestrant	Palbociclib or ribociclib in combination with an aromatase inhibitor are not used in clinical practice for the patients in this Decision Problem, who are ET-resistant,[c] and have progressed whilst receiving or ≤ 12 months after ET, as described above. Palbociclib and ribociclib in combination with an aromatase inhibitor are utilised in endocrine-sensitive patients (see Section B.2.9.1), defined as patients who have received treatment with ET in

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	receptor positive HER2-negative breast cancer that has progressed after one line of prior endocrine therapy: • Exemestane • Everolimus and exemestane • Tamoxifen • Fulvestrant • Chemotherapy (in accordance with NICE guidance)		the (neo)adjuvant setting with a disease-free interval >12 months from completion of ET in PALOMA-1 and MONALEESA-2, respectively.[3, 4] Chemotherapy is reserved for patients in whom initial or second-line ET has failed, and is therefore positioned after ABE-FUL in the treatment pathway (see Section B.2.9.1)
Outcomes	• OS • PFS • Response rate • Adverse effects of treatment • HRQoL	• OS and OS rate[d] • PFS • Response rates o ORR o DCR o CBR o DoR • Safety and tolerability (adverse effects of treatment) • PROs: o Pain intensity (BPI) o Change in symptom burden from baseline using the EORTC QLQ-C30 and EQ-5D-5L	N/A
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY). If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in	As per NICE reference case, cost-effectiveness is expressed in terms of incremental cost QALY, and costs considered from the perspective of the NHS and PSS.	The patient access scheme for abemaciclib has been incorporated into the cost-effectiveness analysis. A patient access scheme is available everolimus. However, this is confidential and therefore cannot be considered in this submission.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective. The availability of any patient access schemes for the comparator technologies will be taken into account.		

[a] In pre- or peri-menopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone agonist to induce menopause. [b] Locally advanced disease was not amenable to curative treatment by surgery. [c] ET-resistant patients are those whose disease does not respond to ET. Relapse during the first two years of treatment with adjuvant therapy, or progressive disease within the first six months of initial ET for ABC is known as primary resistance. Secondary acquired resistance refers to patients who initially respond to ET, yet later become unresponsive (patients relapse whilst being treated with adjuvant ET but after the first 2 years of treatment, relapse within 12 months of completing adjuvant ET, or progress ≥6 months after initiating ET for ABC, while on ET).[5, 6] [d] At the time of cut-off for the MONARCH 2 trial, OS data were still immature and data are not expected within the appraisal timelines.

Abbreviations: BPI: brief pain inventory; CBR: clinical benefit rate; DCR: disease control rate; DoR: duration of response; EORTC QLQ-C: European organisation for research and treatment of cancer quality of life questionnaires-core; ET: endocrine therapy; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; HRQoL: health-related quality of life; N/A: not applicable; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PROs: patient-reported outcomes; PSS: Personal Social Services; QALY: quality-adjusted life year.

B.1.2 *Description of the technology being appraised*

A description of the technology appraised is summarised in Table 2. The summary of product characteristics (SmPC) for abemaciclib in this indication are presented in Appendix C.

Table 2: Technology being appraised

UK approved name and brand name	Abemaciclib (Verzenios)
Mechanism of action	Abemaciclib is a selective dual inhibitor of cyclin-dependent kinase 4 and 6 (CDK4 and 6) As an inhibitor of CDK4 and 6, abemaciclib prevents the phosphorylation of retinoblastoma protein, thereby blocking the progression from G1 phase into S phase of the cell cycle. By inhibiting DNA synthesis, cell cycle arrest is induced, and cell proliferation and tumour growth is subsequently suppressed.[7]
Marketing authorisation/CE mark status	EMA marketing authorisation is expected in October 2018 and UK availability is anticipated soon after.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Abemaciclib is expected to be indicated for the treatment of HR+/HER2− locally advanced or metastatic breast cancer: • In combination with an aromatase inhibitor or **fulvestrant** as initial endocrine-based therapy, or in women who have received prior endocrine therapy (ID1227, Appraisal Submitted June 2018;[1] ID1339, this submission)[2] Abemaciclib has the following contraindications: • Hypersensitivity to the active substance or to any of the excipients
Method of administration and dosage	• The dose for abemaciclib in this indication is one 150 mg oral tablet twice daily (a total of 300 mg daily) on a continuous 28-day cycle, in combination with fulvestrant (500 mg on Days 1 and 15 of the first cycle, and on Day 1 of subsequent 28-day cycles). • Dose adjustment and/or dose interruption are recommended for the management of some adverse reactions (such as haematological toxicities, diarrhoea, increased ALT), and when given in combination with CYP3A inhibitors. See Appendix C for more detailed information. • Abemaciclib should be taken continuously as long as the patient is deriving clinical benefit or until unacceptable toxicity occurs.
Additional tests or investigations	No additional test or investigations are required to determine eligibility for abemaciclib beyond those routinely conducted in NHS clinical practice.
List price and average cost of a course of treatment	List price of abemaciclib: £[redacted] per 28-day cycle Mean time on treatment: [redacted] months (modelled) Cost per mean time on treatment (based on list price): £[redacted]
Patient access scheme	A patient access scheme has been proposed for abemaciclib. The proposed abemaciclib with-PAS price is £[redacted] per 28-day cycle.

Abbreviations: ALT: alanine aminotransferase**;** CDK**:** cyclin-dependent kinase; EMA: European Medicines Agency; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; mg: milligram; N/A: not applicable; NHS: National Health Service.
Source: Sledge et al. 2017,[8] EPAR Verzenios[9]

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

B.1.3.1 Breast cancer

Disease overview and pathogenesis

Breast cancer is the most common cancer amongst women in the UK, with an age-standardised incidence rate of 95.0 per 100,000.[10] The disease is responsible for 7% of all cancer deaths in the UK, with a mortality rate of 17.1 per 100,000.[10, 11]

With an annual breast cancer incidence of 0.08%, approximately 46,700 women in England and Wales are diagnosed with breast cancer each year.[12, 13] Breast cancer incidence is strongly age-dependent with more than 80% of cases occurring in women over the age of 50,[14] and approximately 25% of cases occurring in women aged 75 and over.[15]

Approximately 90% of patients will have invasive breast cancer. The majority of these women are estimated to have early breast cancer or locally advanced disease that is amenable to curative surgical treatment, with a smaller proportion presenting with advanced disease at diagnosis (5−13%).[13, 16] Early breast cancer resides only in the breast and lymph nodes nearby, whereas locally advanced disease involves cancer in a large part of the breast and lymph nodes.[17] Approximately 35% of women with early breast cancer or operable locally advanced disease progress to advanced breast cancer.[13] Advanced breast cancer refers to locally advanced disease that is not amenable to curative treatment by surgery, or the spread of disease to other parts of the body such as the bones, liver, and lungs (metastatic cancer). The majority of advanced breast cancer patients have therefore received prior therapy for early breast cancer, yet have subsequently relapsed with disease that cannot be completely removed by surgery.[1]

Breast cancers are classified according to the cell type from which the tumour arises and are described in terms of oestrogen receptor (ER) status, progesterone receptor status (PgR) and 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 represents the most common subgroup (64% of women with metastatic breast cancer in the UK), and the patient population addressed in this submission.[18] Multiple HR+ breast cancer therapies operate by regulating oestrogen signalling, collectively referred to as endocrine therapy (ET).[19] There are two broad types of ET: therapies that target oestrogen receptors, such as selective oestrogen receptor modulators (SERMs; e.g. tamoxifen) or selective down-regulators (SERD; e.g. fulvestrant), and those that reduce the production of oestrogen through the inhibition of enzymatic activity required for the production of oestrogens, termed aromatase inhibitors (e.g. anastrozole, letrozole, and exemestane).[5]

HR+/HER2− advanced breast cancer can be further subdivided into patients with sensitivity or resistance to ET. ET-sensitive patients include those with no prior treatment with ET (*de novo* advanced), and those who have relapsed more than one year after completion of adjuvant ET with curative intent. ET-resistant patients are those whose disease does not respond to ET. Relapse during the first two years of treatment with adjuvant therapy, or progressive disease within the first six months of initial ET for ABC is known as primary resistance. Secondary acquired resistance refers to patients who initially respond to ET, yet later become unresponsive

(patients relapse whilst being treated with adjuvant ET but after the first 2 years of treatment, relapse within 12 months of completing adjuvant ET, or progress ≥6 months after initiating ET for ABC, while on ET).[5, 6] The increased use of extended adjuvant ET (>5 years) in clinical practice in patients with early breast cancer presents ET resistance issues.[17, 20] Relapsing patients would be on ET at the time of progression to advanced breast cancer, and resistance to the administered adjuvant ET may decrease likelihood of success of subsequent ET. A meta-analysis published in 2017 demonstrated that, even after five years of adjuvant ET, women with HR+ early breast cancer still had a persistent risk of recurrence and death 20 years after diagnosis. This long-term risk of recurrence for breast cancer patients demonstrates the inevitability of developing ET resistance during treatment for early or advanced breast cancer, highlighting the substantial hurdle of ET resistance in the treatment of this disease.[21]

HR loss or HR mutations have been suggested as possible mechanisms driving endocrine resistance in HR+ breast cancer.[6] HRs are key to cell proliferation and survival signalling pathways.[22, 23] Upregulation of the HR signalling pathway is a major driver of tumour development and progression in HR+ breast cancers.[22, 23] The downstream effects of HR signalling converge on the cyclin D1-CDK4 and 6-retinoblastoma cellular pathway, which controls the progression of the cell cycle.[19, 24] CDK4 and CDK6 associate with D-type cyclins to promote progression through the cell cycle, promoting cell proliferation.[19] Oestrogen signalling is known to amplify cyclin D1 activity leading to enhanced CDK4 and 6 activity, thereby driving cancer cell proliferation.[19] Overexpression of cyclin D1 has been demonstrated to occur in more than 50% of breast cancers, the majority of which are HR+.[25]

Of the HR+/HER2− breast cancer patients eligible for ET, approximately 53% progress or relapse whilst receiving, or following, such therapy.[26] This submission focusses on advanced ET-resistant breast cancer, in patients who have relapsed within one year of adjuvant treatment, or during first-line (not second or subsequent line) ET for advanced breast cancer. Patients who have relapsed after adjuvant ET (and therefore have untreated advanced breast cancer upon progression), and patients who have relapsed during ET for advanced breast cancer. Both populations represent rapidly progressing, hard-to-treat patients, and are therefore considered as one homogenous population for this submission.

Effects of breast cancer on patients and carers

Advanced breast cancer is incurable and has a poor prognosis, with a median overall survival (OS) of 2−3 years.[6] Consequently, the objective of treatment is to offer long-term disease control by improving progression-free survival (PFS) and delaying the initiation of cytotoxic chemotherapy to allow patients to maintain a good quality of life. A patient's perspective of what comprises a good quality of life could include both control of disease symptoms, and emotional and social factors such as continued attendance to work and reduced burden on friends and family members.[27]

A growing body of evidence demonstrates the negative effect of disease progression on a patient's health-related quality of life (HRQoL); impacting their ability to work and carry out daily activities. In a cross-sectional study, 235 women with metastatic breast cancer completed the FACT-B. Scores for physical, social/family, emotional and functional well-being were markedly lower than normative scores collected from a validation sample of patients of whom only 20% had metastatic breast cancer.[28] In a HRQoL Primary Care Monitor study of 102 patients with HER2− (HR+ or HR−), stage IV breast cancer, disease progression was associated with a

worsening of physical symptoms such as physical pain, fatigue, trouble sleeping, as well as treatment side effects and acute distress.[29] Pain can also increase in intensity and frequency as the disease progresses. A study of patients with HER2− (HR±) stage IV breast cancer, found that pain significantly increased with disease progression.[29] In advanced breast cancer, metastases are often associated with and are a direct cause of pain. Distant metastases are associated with significantly more pain than local or regional metastases.[29] Prevention or slowing of disease progression may therefore assist patients in avoiding the more severe pain associated with metastases.

Strategies to limit the side effects of systemic therapy whilst preventing the progression of disease and delaying subsequent cytotoxic chemotherapy are crucial aspects of breast cancer care.[29] Chemotherapy is associated with a worse side effect profile and impaired HRQoL compared with ET. In a univariate analysis of 360 patients with HR+/HER2− metastatic breast cancer, ET (without chemotherapy) was associated with more favourable HRQoL, treatment satisfaction and activity outcomes compared with chemotherapy (with/without ET). These statistically significant findings were maintained after adjustment for confounding variables.[30] Caregivers of breast cancer patients also experience a significant burden, including anxiety, stress and depression, as well as impairments to work productivity.[31] Providing improved treatment options for longer-term disease control are therefore likely to have positive effects on the caregiver as well as the patient. For example, delaying disease progression and the subsequent need for chemotherapy could reduce the need for caregivers to accompany patients to medical appointments, and reduce the level of care needed for the patient as a result of the potential toxicity burden associated with chemotherapy.[30]

Unmet need

Although ET is the preferred option for the treatment of HR+ advanced breast cancer, emergence of ET resistance is inevitable over time, meaning it is therefore a major obstacle in the successful treatment of HR+/HER2− breast cancer.[6, 32] This creates a need for alternative treatments for advanced breast cancer patients who have progressed on or after ET, with convenient administration regimens that are suitable for long-term, chronic use, to delay the introduction of cytotoxic chemotherapy, and thereby maintain quality of life whilst patients are progression free.[5, 33]

In addition to the direct effects on patients and their caregivers, breast cancer also places a significant burden on the economy, directly through the cost of treatment and drug development, but also indirectly through reduced productivity and absence from work, as well as caregiver time and costs associated.[34] Although this is beyond the perspective of the NICE reference case in terms of economic analysis, it remains a relevant consideration for the broader impact of managing breast cancer in the UK.

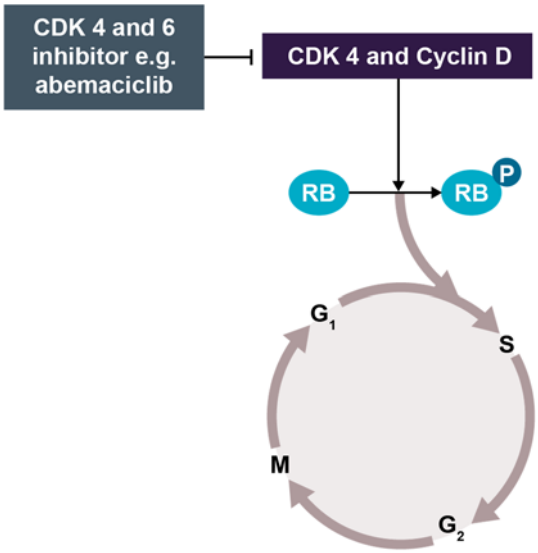
B.1.3.2 Abemaciclib

Description of abemaciclib

Abemaciclib ([LY2835219]; Verzenios, Eli Lilly & Company Limited [Lilly]) is an orally administered, potent, and selective small-molecular inhibitor of CDK4 and CDK6.[35]

CDKs are a family of enzymes that regulate the progression of the cell cycle through the G1 (growth), S (DNA synthesis), G2 (growth) and M (mitosis) phases. CDKs and cyclins interact at 'checkpoints' between each phase, to tightly control orderly progression of the cycle.[19] The cyclin D-CDK4 and 6 complexes promote phosphorylation of the retinoblastoma (Rb) tumour-suppressor protein, initiating a sequence of events that allows the cell to proceed to S phase and continue through the cell cycle, ultimately promoting cell division and proliferation (Figure 1).[36]

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



Footnotes: Adapted from Dickson 2014[37]
Abbreviations: CDK: cyclin dependent kinase; P: phosphorylation; RB: retinoblastoma

As an inhibitor of CDK4 and 6, abemaciclib prevents the phosphorylation of the Rb protein, thereby blocking the progression from G1 phase into S phase of the cell cycle. By inhibiting DNA synthesis, cell cycle arrest is induced, and cell proliferation and tumour growth is suppressed.[7] Preclinical studies have shown that abemaciclib as a single agent or in combination with endocrine therapies can suppress tumour growth in ER+ xenograft models.[7]

Abemaciclib demonstrates unique pharmacological selectivity. In enzymatic assays, abemaciclib is 14-times more selective and potent for cyclin D1/CDK4 than for cyclin D3/CDK6.[7] Cyclin D1/CDK4 has been frequently implicated in the pathogenesis of HR+ breast cancer, whereas cyclin D3/CDK6 play a large role in the maturation of haematopoietic stem cells within the bone marrow.[38, 39]

MONARCH trials

Three clinical studies have investigated the use of abemaciclib in treating HR+/HER2− advanced breast cancer, two of which represent patient populations which are subject to NICE appraisal (ID1227 for MONARCH 3 submitted in June 2018;[1] ID1339 for MONARCH 2, this submission[2]). The patient population included in the MONARCH 1 trial is not included in the licence for abemaciclib and is therefore not subject to NICE appraisal.

MONARCH 3, a randomised phase III trial, compared the efficacy and safety of abemaciclib or placebo (PBO) in combination with a non-steroidal aromatase inhibitor (NSAI; anastrozole or letrozole). This presents abemaciclib at the same position in the treatment pathway as the

recently approved CDK 4 and 6 inhibitors palbociclib (TA495)[40] and ribociclib (TA496),[41] each in combination with an aromatase inhibitor. Patients were postmenopausal diagnosed with HR+/HER2− locoregionally recurrent or metastatic breast cancer who were naïve to ET in this setting.[42] ET was permitted in the (neo)adjuvant setting if the patient had a disease-free interval (DFI) >12 months from completion of ET. PFS was significantly longer in patients treated with abemaciclib plus NSAI, compared with patients treated with PBO plus NSAI (hazard ratio [HR] = 0.54, p=0.000021). Patients treated with abemaciclib plus NSAI demonstrated a 46% reduced risk of disease progression or death compared to those treated with PBO plus NSAI.

MONARCH 1, a single-arm phase II study, evaluated abemaciclib as a monotherapy. Abemaciclib is the only CDK4 and 6 inhibitor to demonstrate single agent activity in a phase II trial. This was at a higher dose of 200 mg, and in women with refractory HR+/HER2− metastatic breast cancer.[43] These patients represent a poor-prognostic, heavily pre-treated population. At 12 months, the objective response rate (ORR) was 19.7% and median overall survival was 17.7 months. Overall, continuous dosing of single-agent abemaciclib demonstrated positive clinical activity.[43] MONARCH 3 and MONARCH 1 both demonstrated manageable safety profiles.

This submission focusses on the randomised phase III study MONARCH 2, which evaluated abemaciclib or PBO with fulvestrant for HR+/HER2− locally advanced or metastatic breast cancer, which is not amenable to curative treatment by surgery. Patients were of any menopausal status, with pre- or peri-menopausal women having received a luteinising hormone-releasing hormone (LHRH) agonist for ovarian suppression. LHRH induced menopause, and was initiated at least 28 days prior to the first cycle of abemaciclib plus fulvestrant.[8] Patients had progressed while receiving or shortly after (≤ 12 months) previous ET, therefore representing the ET-resistant patient population, and not the population considered in ID1227 (MONARCH 3),[1] TA495[40] and TA496.[41] PFS was significantly extended for abemaciclib plus fulvestrant patients versus PBO plus fulvestrant (median difference 7.1 months, hazard ratio = 0.553 [95% CI 0.449 to 0.681]). Patients treated with abemaciclib had a 45% reduced risk of disease progression or death. Treatment with abemaciclib plus fulvestrant exhibited a tolerable and manageable safety profile.[8]

Overall, clinical trial data demonstrate the efficacy of abemaciclib in combination with fulvestrant, as a treatment option for patients who have developed endocrine resistance during or after their prior ET for early or advanced HR+/HER2− breast cancer.[8, 42]

Marketing authorisation and health technology assessment

- MAA was submitted in July 2017.
- A positive CHMP opinion was received on 26 July 2018.
- Marketing authorisation is expected to be granted in October 2018.

B.1.3.3 Current treatment pathway and the position of abemaciclib

To place this submission within the broader disease context, a brief summary of treatment in early stage HR+/HER2− breast cancer is provided followed by a more detailed description of treatment for advanced disease, which is the focus of the submission.

Summary of early breast cancer therapy prior to the advanced stage

NICE Guideline 101 (NG101) recommend patients with early breast cancer undergo surgery and appropriate adjuvant therapy, unless significant comorbidity precludes surgery.[17]

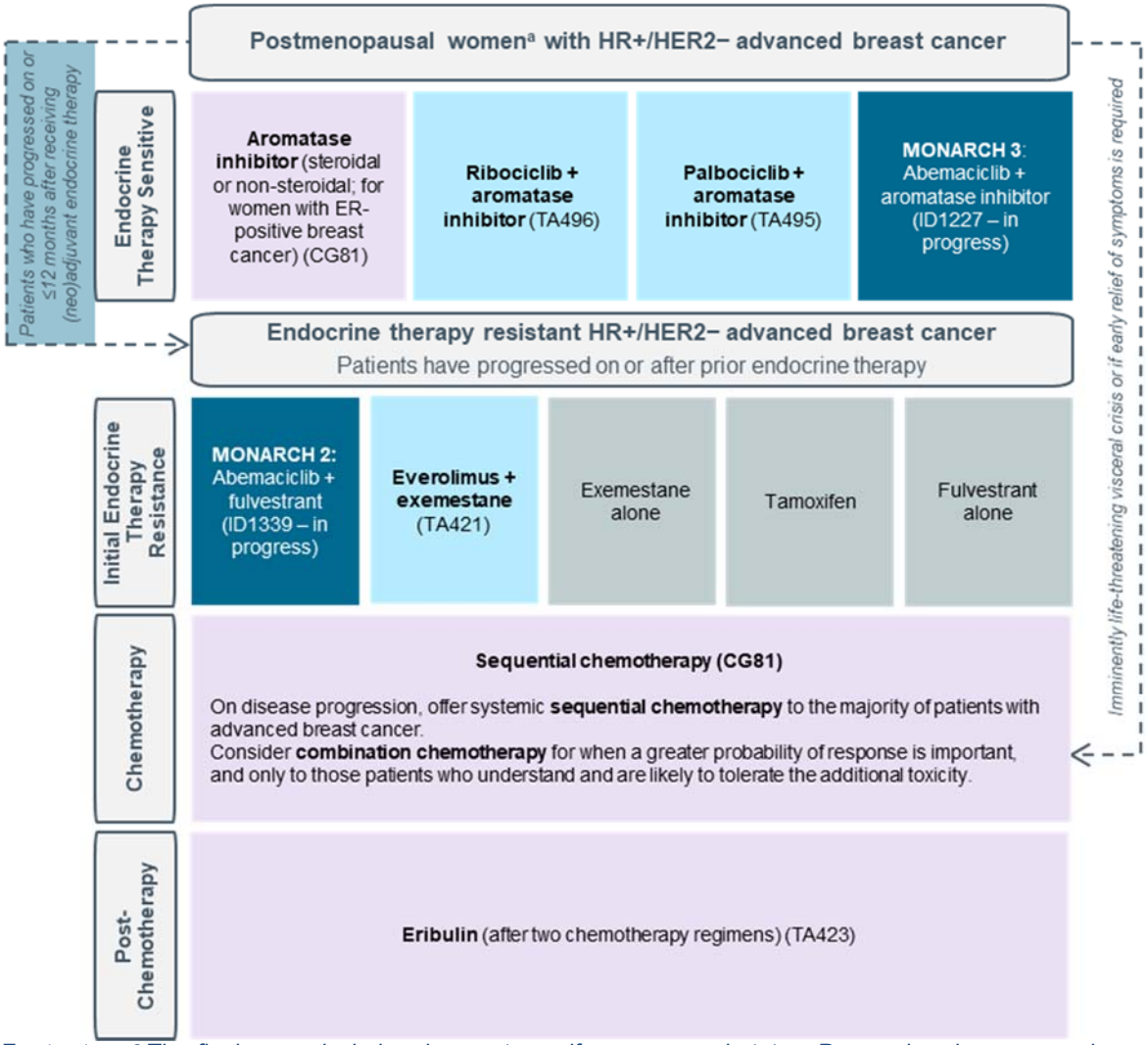
Prior to surgery, neoadjuvant chemotherapy may be considered as an option to shrink tumour size if chemotherapy is indicated. Neoadjuvant ET may be considered as an option to shrink tumour size if there is no definite indication for neoadjuvant chemotherapy, and would include tamoxifen or an aromatase inhibitor (anastrozole or letrozole).[17]

Following surgery, adjuvant therapy is prescribed based on prognostic and predictive factors. For patients with breast cancer of sufficient risk that chemotherapy is indicated, adjuvant therapy should involve taxane and anthracycline. Most HR+ breast cancer patients will receive adjuvant ET,[44] for which tamoxifen should be offered to men and premenopausal women. Adjuvant ovarian ablation or suppression in combination with ET could also be considered for premenopausal women.[17] Postmenopausal women should be offered an aromatase inhibitor if they are at medium or high risk of disease recurrence, or tamoxifen if they are at low risk. Extended ET with an aromatase inhibitor is recommended for a minimum of five years for postmenopausal women who have been taking tamoxifen for 2−5 years.[17]

Advanced breast cancer: current treatment pathway

Recommendations for the management and treatment of advanced breast cancer are provided by the NICE clinical guideline for advanced breast cancer (CG81) and by NICE single technology appraisals.[1, 2, 26, 40, 41, 45-52] The clinical pathway based on current NICE guidance for patients with advanced breast cancer, including patients who have progressed on or after ET, is presented in Figure 2. The 3rd European School of Oncology (ESO) – European Society of Medical Oncology (ESMO) International Consensus Guidelines for Advanced Breast Cancer also provide clinical guidelines relevant to this submission.[6]

Figure 2. Clinical pathway for patients with HR+/HER− advanced breast cancer, based on current NICE guidance



Footnotes: [a] The final scope includes does not specify menopausal status. Pre- and peri-menopausal women receive LHRH agonist to induce menopause. Fulvestrant alone is not recommended by NICE within its licensed indication for treatment of HR+/HER2− advanced breast cancer in postmenopausal women whose disease has progressed on or after endocrine therapy, however may have limited use in UK hospitals.
Sources: ID1227,[1] ID1339,[2] NICE CG81,[50] TA421,[26] TA423,[52] TA495,[40] TA496.[41]

Advanced breast cancer: endocrine therapy

Endocrine therapy with aromatase inhibitors has been recommended as initial treatment for patients with HR+ advanced breast cancer, unless disease is imminently life-threatening or if early relief of symptoms is required, in which case chemotherapy may be offered (NICE CG81).[50] Similarly, ESMO guidelines advise the use of systemic chemotherapy only where there is life-threatening visceral crisis or impending visceral crisis, or a need for rapid symptom and/or disease control.[6] For patients who have received chemotherapy as first-line treatment, ET is recommended following the completion of chemotherapy.[50]

Endocrine agents currently recommended by NICE include aromatase inhibitors and tamoxifen. An aromatase inhibitor (either non-steroidal or steroidal) is recommended for postmenopausal women with HR+ advanced breast cancer who have not previously received ET, or who have

been previously treated with tamoxifen. Tamoxifen is recommended with ovarian suppression for pre- or peri-menopausal women.[50]

As of December 2017, NICE recommends initial treatment with CDK4 and 6 inhibitors palbociclib (TA495)[40] or ribociclib (TA496)[41] in combination with a NSAI for postmenopausal women with HR+/HER2− advanced breast cancer.[40, 41] The ESMO guidelines support the use of palbociclib in combination with a NSAI as a preferred treatment option for advanced HR+/HER2− breast cancer in postmenopausal women.[6]

Advanced breast cancer: treatment options for endocrine therapy resistant patients

The treatment options for patients experiencing disease progression on or after ET (given as treatment for either early or advanced HR+/HER2− breast cancer) are shown in Figure 2. This patient population is expanding in size, due to the increasing number of patients progressing on ET in the adjuvant setting. The priority for these ET-resistant patients is to prolong progression-free survival (PFS) and maintain HRQoL for as long as possible. Clinical expert opinion sourced by Lilly advised that physicians aim to delay initiation of chemotherapy for as long as possible, and would prefer to exhaust all other treatment options for ET resistance first, since chemotherapy is associated with a significant toxicity burden and impact on patients' HRQoL.

Everolimus in combination with exemestane (TA421) is recommended by NICE for postmenopausal women with HR+/HER2− advanced breast cancer following ET (TA421),[26] which would provide an alternative treatment option to allow the delay of chemotherapy.[26] Further treatment options exist which some patients with ET resistance may be offered locally (shown in grey in Figure 2): exemestane alone, tamoxifen, or fulvestrant as monotherapy. Although these regimens have limited use in UK practice, clinical expert opinion sourced by Lilly advised that these options are used substantially more frequently than proceeding to chemotherapy upon disease progression on or after ET. Fulvestrant alone is not recommended by NICE as an alternative to aromatase inhibitors for the treatment of advanced breast cancer which has relapsed or progressed on or after adjuvant ET (TA503).[53] However, clinical expert opinion indicated fulvestrant is used in a small number of patients in the UK, either funded by NHS Trusts without reimbursement, or in private hospitals. Additionally, this use is supported by clinical trial data which demonstrate superior efficacy of fulvestrant alone for HR+ advanced breast cancer compared to anastrozole, with extended PFS.[54] CDK4 and 6 inhibitors palbociclib and ribociclib, in combination with fulvestrant are licensed in this patient population. The NICE appraisal for ribociclib plus fulvestrant is in process (ID1318).[47] The appraisal for palbociclib plus fulvestrant is currently suspended (ID916).[49]

Following failure of available treatment options for initial ET resistance, CG81 currently recommends systemic sequential chemotherapy.[50] Combination chemotherapy should only be considered for patients for whom treatment response is particularly important, providing the patient understands and accepts the additional toxicity.[50]

Post-chemotherapy

For patients with locally advanced or metastatic breast cancer whose disease progresses on or after sequential chemotherapy (at least 2 regimens), eribulin is recommended as a treatment option (TA423).[52]

Proposed position of abemaciclib plus fulvestrant in treatment pathway

This submission presents abemaciclib in combination with fulvestrant for women who have relapsed or progressed on or after prior ET. These hard-to-treat primary or secondary ET-resistant patients have a high unmet need for alternative treatment to re-establish disease control and delay initiation of chemotherapy. Abemaciclib plus fulvestrant (ABE-FUL) therefore provides an additional treatment option and would allow the postponement of chemotherapy and avoid its additional toxicity. This places ABE-FUL in the same position in the treatment pathway as everolimus in combination with exemestane.[26]

B.1.4 *Equality considerations*

It is considered that introduction of abemaciclib is not likely to lead to recommendations which differentially impact any patients protected by the equality legislation or disabled persons.

B.2 Clinical effectiveness

Summary of clinical effectiveness systematic literature review (SLR)

- An SLR was conducted to identify relevant clinical evidence describing the efficacy and safety of abemaciclib plus fulvestrant (ABE-FUL) for locally advanced or metastatic HR+/HER2− breast cancer in patients who have progressed on or after prior endocrine therapy (ET), *i.e.* who are considered endocrine-resistant
- The SLR identified one randomised controlled trial (RCT), MONARCH 2, for ABE-FUL in the relevant patient population, for which published data were available
- As there were few published data available in trial populations directly comparable to MONARCH 2, the eligibility criteria for the SLR were broadened, allowing mixed populations to be included with regards to baseline characteristics, including HR+ status and the number of endocrine therapies and chemotherapies received in the advanced setting, thus increasing heterogeneity across the identified studies

Summary of clinical effectiveness of ABE-FUL

- The primary outcome of MONARCH 2 was investigator-assessed (INV) progression-free survival (PFS), as defined by RECIST version 1.1
- Secondary outcomes included overall survival (OS), objective response rate (ORR), disease control rate (DCR), clinical benefit rate (CBR), duration of response (DoR), health-related quality of life (HRQoL) and safety (treatment-emergent adverse events [TEAEs])
- The results of the MONARCH 2 study demonstrate that treatment with ABE-FUL is associated with a significantly extended PFS and an improved ORR, in comparison with PBO-FUL
- The MONARCH 2 study met its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in median PFS of 7.2 months. This improvement translates to a 45% reduction in the risk of disease progression or death in comparison to placebo plus fulvestrant (PBO-FUL), both in patients with primary and secondary endocrine resistance. A significant improvement in PFS will delay the decline in HRQoL associated with further disease progression, and also delays the need to begin treatment with chemotherapy regimens associated with high toxicity
- The percentage of patients who received post-discontinuation chemotherapy was lower in the ABE-FUL arm than in the PBO-FUL arm ([redacted] vs [redacted], respectively). ABE-FUL has been shown to significantly delay the time to post-discontinuation chemotherapy compared with PBO-FUL in a *post hoc* exploratory analysis of MONARCH 2 (ABE-FUL: median not reached; PBO-FUL: median 26.33 months), with a HR of 0.65 ($p<0.01$).[55]
- At the time of data cut-off, the OS data were still very immature with 85 (19.1%) events (deaths) in the ABE-FUL arm and 48 (21.5%) in the PBO-FUL arm.
- Treatment with ABE-FUL achieved significantly greater ORR, DCR, and CBR in both the ITT population (all randomised patients regardless of starting dose) and patients with measurable disease
- At the time of analysis (after more than two years), median duration of response (DoR) for patients treated with ABE-FUL had not been reached
- Pain intensity scores were similar between the ABE-FUL and PBO-FUL arms, but tended to numerically favour ABE-FUL
- There was a significant difference of [redacted] points in EORTC QLQ-C30 diarrhoea symptom score in the ABE-FUL arm relative to the PBO-FUL arm. The highest symptom burden for diarrhoea was reported during early visits, and returned close to baseline upon treatment discontinuation. All other EORTC QLQ-C30 scores were similar between treatment arms at baseline, during

therapy and short-term follow-up study periods. Furthermore, there was no significant difference in global health status between treatment arms

- EQ-5D-5L index values and VAS scores were similar between treatment arms for all baseline and post-baseline visits, supporting that the overall health status of patients was maintained throughout the study in both treatment arms
- It is further important to note that the HRQoL data observed in MONARCH 2 do not capture the delay in the detriment to quality of life associated with initiating post-discontinuation chemotherapy treatment

Summary of indirect treatment comparison

- A NMA was conducted to compare the efficacy of interventions evaluated in patients comparable to the MONARCH 2 population using available data from RCTs identified in the SLR
- The reference treatment chosen for the analysis was fulvestrant 500 mg (FUL 500) and treatment effect results are presented for ABE-FUL, exemestane (EXE) and everolimus plus exemestane (EVE-EXE), relative to FUL 500
- With regards to tamoxifen (TMX), an additional relevant comparator, it was not possible to include this treatment in the NMA due to a lack of evidence identified in the SLR. Evidence identified in the SLR for the MONARCH 3 indication for abemaciclib (in combination with an aromatase inhibitor), was therefore explored, which resulted in the identification of Milla-Santos (2001), which compared TMX to toremifene (TOR). An adjusted indirect comparison was subsequently conducted using Milla-Santos (2001) and the principal NMA to estimate relative treatment effects for TMX vs FUL 500
- The endpoints chosen for the NMA were PFS, OS, ORR and CBR. The hazard ratios representing the treatment effects were synthesised using methodology obtained from Woods (2010)[56] for the NMA of survival endpoints (PFS and OS) and using a logit link function for the binary endpoints (ORR and CBR)
- For PFS, ABE-FUL (HR [redacted]; 95% credible interval (CrI) [redacted]) and EVE-EXE (HR [redacted]; 95% CrI [redacted]) had lower hazard rates of progression or death compared to FUL 500. This treatment effect was significant for ABE-FUL compared to FUL 500 only. EXE (HR [redacted]; 95% CrI [redacted]) had a significantly higher hazard rate of progression or death compared to FUL 500, supporting that ABE-FUL is superior at prolonging PFS
- ABE-FUL (HR [redacted]; 95% CrI [redacted]) had a lower hazard rate of death compared to FUL 500 but this treatment effect was not significant. No comparators showed a significant treatment benefit compared to FUL 500. Due to the inclusion of immature OS data from the MONARCH 2 trial, uncertainty is introduced around the associated treatment effects
- For ORR, both ABE-FUL (OR [redacted]; 95% CrI [redacted]) and EVE-EXE (OR [redacted]; 95% CrI [redacted]) showed significantly higher odds of achieving an objective response compared to the reference treatment (FUL 500). There were no other significant differences between the treatments compared with FUL 500
- For CBR, ABE-FUL showed significantly higher odds (OR [redacted]; 95% CrI [redacted]) of achieving a clinical benefit compared to FUL 500. The OR for EVE-EXE was similar to ABE-FUL but did not reach significance (OR [redacted]; 95% CrI [redacted]). The OR for CBR was significantly lower for EXE (OR [redacted]; [redacted]) in comparison with FUL 500
- It was possible to generate treatment effects for TMX vs FUL 500 for OS and PFS/time to progression (TTP) (with equivalence assumed between these two endpoints) through the adjusted indirect comparison. For PFS/TTP, the HR for TMX vs FUL was [redacted] (95% CrI [redacted] to [redacted]). For OS, the HR for TMX vs FUL was [redacted] (95% CrI [redacted] to [redacted]).
- The results of the NMA and adjusted indirect comparison support that the efficacy of ABE-FUL is at a minimum comparable to that of EVE-EXE, which is recommended by NICE as a post-ET

treatment option. The results additionally support that ABE-FUL is more efficacious than EXE and TMX, which may be used for a small number of endocrine-resistant patients in the UK
- These results should be considered in light of heterogeneity across the included trials. The patient populations included in the NMA were broadly similar for a number of characteristics such as age, post-menopausal status and performance status. The MONARCH 2 trial addressed a very specific population, which differed from the majority of clinical trials evaluating treatments for advanced breast cancer patients that have progressed on or after ET. In all other comparator trials, prior chemotherapy and multiple rounds of prior ET were permitted. These patient populations may therefore have been more heavily pre-treated than in MONARCH 2, and this could not be adjusted for in the analysis due to unavailability of subgroup data. Furthermore, due to the use of the MONARCH 3 SLR in an attempt to identify further RCTs evaluating tamoxifen, there is also likely to be heterogeneity between Milla-Santos (2001) and the other studies included in the NMA

Summary of safety of abemaciclib

- Safety was assessed in the safety population, which included all 664 randomised and treated patients who received at least one dose of study drug
- Overall, ABE-FUL was tolerable, with TEAEs being generally predictable, manageable, and reversible
- The most frequent TEAEs reported by the investigator in the ABE-FUL arm were diarrhoea, neutropenia, nausea and fatigue, although the majority were of low severity
- The majority of patients in the ABE-FUL arm experienced diarrhoea (86.4%), which was predominately of Grade 1 or 2 (73.0%), with 13.4% and 0% patients reporting Grade 3 or 4 events, respectively. Diarrhoea was manageable with standard doses of anti-diarrhoeal medications, with higher-grade diarrhoea additionally managed with dose omissions and/or dose reductions. The majority of patients (70.1%) with diarrhoea did not require any treatment modification. A small proportion of patients (2.9%) in the ABE-FUL arm discontinued study treatment because of diarrhoea ([redacted] discontinued ABE but continued to receive FUL, and [redacted] of patients discontinued treatment with ABE-FUL), suggesting that this TEAE was manageable and acceptable[8]
- The incidence of diarrhoea and the proportion of patients who discontinued treatment due to diarrhoea were higher in patients who received the starting dose ABE 200 mg compared to those who started treatment on 150 mg ABE
- Neutropenia as a TEAE was experienced by 46.0% of patients treated with ABE-FUL and 4.0% of patients treated with PBO-FUL, with 23.6% of the patients in the ABE-FUL arm experiencing Grade 3 neutropenia. Grade 4 neutropenia was reported for 2.9% of patients in the ABE-FUL arm. Only [redacted] ([redacted]) ABE-FUL-treated patients discontinued a study drug due to neutropenia, indicating that this TEAE was manageable. Febrile neutropenia was uncommon in ABE-FUL treated patients (six patients; 1.4%), and there did not appear to be a relationship between severe neutropenia and the occurrence of infection in the MONARCH 2 study
- Serious adverse events (SAEs) were more frequent in the ABE-FUL group than in the PBO-FUL arm (22.4 vs 10.8%, respectively), but only 8.8% of SAEs were considered to be related to treatment with ABE-FUL (1.3% in the PBO-FUL arm)
- The discontinuation rate for all study treatment due to AEs was [redacted] (ABE-FUL) and [redacted] (PBO-FUL arm).
- Of the patients who received a starting dose of 200 mg (N=121), a higher proportion discontinued any study treatment due to an AE ([redacted]), compared with patients who received a starting dose of 150 mg abemaciclib ([redacted], N=320), demonstrating that ABE-FUL is more tolerable at the 150 mg dose of abemaciclib

Summary of innovation

- Abemaciclib (selective CDK4/6 inhibitor) and fulvestrant (SERD) in combination provide two novel mechanisms of action for the treatment of endocrine-resistant disease; other treatment options for these patients include at least one drug with a mechanism deployed earlier in the breast cancer treatment pathway, such as the use of consecutive aromatase inhibitors
- ABE-FUL significantly improves PFS and ORR in women with locally advanced or metastatic HR+/HER2− breast cancer who have progressed on or after prior endocrine therapy, affording disease control
- Improved PFS with ABE-FUL represents an important benefit to patients as it delays the requirement for chemotherapy, which is associated with a significant negative impact on patients' quality of life
- Clinical opinion supports that ABE-FUL is associated with substantially improved tolerability in comparison to EVE-EXE, the key comparator for ABE-FUL at its specific position in the treatment pathway for HR+/HER2− advanced breast cancer. The use of this comparator in clinical practice is limited by toxicity and the risk of unpleasant side effects that may be dose-limiting and require additional monitoring, such as stomatitis, mucositis, pneumonitis and rash.[26, 57, 58]
- It is not typical for ET-based treatments to induce substantial tumour shrinkage, including EVE-EXE. Therefore the significant improvement in ORR associated with ABE-FUL versus PBO-FUL is notable. Clinical opinion sought by Lilly reported that a reduction in tumour size allows for the relief of symptoms and may reduce the need for health interventions such as analgesia. Furthermore, by prolonging the response of the tumour to treatment and inducing shrinkage, the burden of disease in later lines of therapy is likely to be lower
- Overall, ABE-FUL provides an efficacious treatment option in hard-to-treat, ET-resistant patients, whilst maintaining quality of life

Conclusion

- ABE-FUL provided clinically meaningful improvements in PFS, ORR, DCR and CBR in patients with HR+/HER− advanced breast cancer that has progressed on or after prior endocrine therapy
- ABE-FUL demonstrated a tolerable safety profile and maintained HRQoL
- The MONARCH 2 trial was methodologically robust, well reported, and considered to be at low risk of bias, whilst the results of the indirect comparison address the wider decision problem for this appraisal
- The results of MONARCH 2 are generalisable to UK clinical practice as ABE-FUL was proven to be efficacious in a patient population with comparable baseline characteristics to the UK population
- ABE-FUL represents a treatment option with a novel mechanism of action (CDK 4/6 inhibitor in combination with a SERD) that effectively delays disease progression in patients whose disease has progressed on or after ET, thereby providing a therapy that can address the obstacle of endocrine resistance

B.2.1 *Identification and selection of relevant studies*

An SLR was conducted to identify relevant clinical evidence describing the efficacy and safety of abemaciclib plus fulvestrant (ABE-FUL) and other relevant treatment options for advanced HR+/HER2− breast cancer as initial endocrine-based therapy, or in women who have received

prior endocrine therapy. Full details of the SLR search strategy, study selection process, and results can be found in Appendix D.

B.2.2 *List of relevant clinical effectiveness evidence*

The SLR identified one randomised controlled trial for abemaciclib for which published literature was available, MONARCH 2. A summary of clinical effectiveness evidence from MONARCH 2 is presented in Table 3.

Table 3. Clinical effectiveness evidence

Study	MONARCH 2 (NCT02107703)		
Study design	Phase III, multicentre, randomised, placebo-controlled, double-blind trial		
Population	Women with HR+ / HER− locally advanced or metastatic breast cancer. Patients must have relapsed with radiologic evidence of progression while receiving neo(adjuvant) ET, ≤ 12 months from completion of adjuvant ET, or relapsed while receiving first-line ET for metastatic disease. Full eligibility criteria are listed in Table 4.		
Intervention(s)	Oral abemaciclib 150 mg twice daily (every 12 hours) on a continuous 28-day treatment cycle, in combination with IM fulvestrant 500 mg on Days 1 and 15 of Cycle 1, then on Day 1 of subsequent cycles (every 28 days)		
Comparator(s)	Oral placebo twice daily (every 12 hours) on a continuous 28-day treatment cycle, in combination with IM fulvestrant 500 mg on Days 1 and 15 of Cycle 1, then on Day 1 of subsequent cycles (every 28 days)		
Indicate if trial supports application for marketing authorisation	Yes	**Indicate if trial used in the economic model**	Yes
Rationale for use/non-use in the model	MONARCH 2 is the pivotal phase III study for ABE-FUL in women with HR+/HER2− locally advanced or metastatic breast cancer that had progressed on or after prior endocrine therapy. This trial informed the marketing authorisation application and considers a population directly relevant to the decision problem addressed in the submission		

Reported outcomes specified in the decision problem	• PFS
	• OS
	• Response rate
	  o ORR (CR + PR)
	  o DCR (CR + PR + SD)
	  o CBR (CR + PR + SD ≥6 months)
	  o DoR (CR + PR)
	• Safety and tolerability
	• HRQoL:
	  o Pain intensity (BPI)
	  o EORTC QLQ-C30
	  o EQ-5D-5L		

All other reported outcomes	Resource utilisation (concomitant medications)		

Abbreviations: AE: adverse event; BPI: Brief Pain Inventory; CBR: clinical benefit rate; CR: complete response; DCR: disease-control rate; DoR: duration of response; EORTC QLQ: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; ET: endocrine therapy; HER: human epidermal growth factor receptor; HR: hormone receptor; HRQoL: health-related quality of life; IM: intramuscular; mBC: metastatic breast cancer; ORR: objective response rate; OS: overall survival PR: partial response.
Source: Lilly Data on File (Clinical Study Report). 2017[35]; Sledge et al. 2017[8]

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

B.2.3.1 Trial design

An overview of the MONARCH 2 study design is presented in Figure 3.

Figure 3. Overview of study design for MONARCH 2

* Full eligibility criteria are presented in Table 4.

Abbreviations: HR+: hormone receptor positive; HER2–: human epidermal growth factor receptor 2 negative; PD: progressive disease.
Source: Lilly Data on File (Clinical Study Report). 2017[35]

B.2.3.2 Eligibility criteria

Eligibility criteria for MONARCH 2 are presented in Table 4.

Table 4. Eligibility criteria for MONARCH 2

Inclusion criteria	Exclusion criteria
Key inclusion criteria included the following: • Women ≥18 years of age who had a diagnosis of HR+/HER2− locally advanced (not amenable to curative treatment by surgery) or mBC • Measurable disease or non-measurable bone-only disease, defined according to RECIST version 1.1.[59] • Adequate organ function and PS ≤1 on the Eastern Cooperative Oncology Group (ECOG) scale • In addition, patients must have fulfilled one of the following criteria: o Relapsed with radiologic evidence of progression while receiving neoadjuvant or adjuvant ET (with no subsequent ET received following progression) o Relapsed with radiologic evidence of progression within 1 year from completion of adjuvant ET (with no subsequent ET received following progression) o 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 AI as first-line ET for metastatic disease (patients may not have received more than 1 line of ET or any prior chemotherapy for metastatic disease) o Presented *de novo* with metastatic disease and then relapsed with radiologic evidence of progression after treatment with an anti-oestrogen or an aromatase inhibitor as first-line ET for metastatic disease (patients may not have received >1 line of ET or any prior chemotherapy for metastatic disease)	Patients were excluded from the study if they met any of the exclusion criteria. Key exclusion criteria included the following: • Had visceral crisis with severe organ dysfunction, lymphangitic spread, or leptomeningeal carcinomatosis • Had clinical evidence or history of central nervous system metastasis • Had received prior treatment with chemotherapy in the locally advanced or metastatic setting (except for neoadjuvant/adjuvant), fulvestrant, everolimus, or any CDK4 and CDK6 inhibitor • Had inflammatory breast cancer • Had initiated bisphosphonates or approved receptor activator of nuclear factor kappa-B ligand (RANK-L) targeted agents <7 days prior to randomisation

• Any menopausal status but pre/peri menopausal women received a luteinising hormone-releasing hormone agonist • Postmenopausal status due to surgical/natural menopause required at least one of the following: prior bilateral oophorectomy; age ≥60 years; age <60 years and amenorrhoeic for at least 12 months (in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression); and FSH and estradiol levels in the postmenopausal range	

Abbreviations: ASCO: American Society of Clinical Oncology; CDK: cyclin dependent kinase; ECOG: Eastern Cooperative Oncology Group; ET: endocrine therapy; FSH: follicle stimulating hormone; HER: human epidermal growth factor receptor; HR: hormone receptor; IHC: immunohistochemistry; ISH: in-situ hybridisation; mBC: metastatic breast cancer; PgR: progesterone receptor; PS: performance status; RECIST: Response Evaluation Criteria in Solid Tumours[59]
Source: Lilly Data on File (Clinical Study Report P39–49). 2017[35]

B.2.3.3 Summary of MONARCH 2 methodology

A summary of the methodology of MONARCH 2 is available in Table 5.

Table 5. Summary of MONARCH 2 methodology

Location	Multicentre
Trial Design	Phase III, randomised, double-blinded, placebo-controlled study of ABE-FUL for advanced HR+/HER2− breast cancer that has progressed on or after prior endocrine therapy Patients were randomly assigned to receive ABE-FUL or PBO-FUL in a 2:1 ratio, using an interactive, web-based randomisation scheme (IWRS). Randomisation was stratified according to: • metastatic site (visceral, bone only, or other) • and ET resistance (primary or secondary): o Primary ET resistance, as defined by ESMO guidelines, includes patients whose disease relapsed while receiving the first 2 years of neoadjuvant or adjuvant ET or progressed while receiving the first 6 months of ET for advanced breast cancer.[33] o Patients who were not considered to have primary ET resistance were defined as having secondary resistance This was a double-blind study; patients, investigational sites, and the sponsor study team did not have immediate access to treatment assignments for any patients, except in emergency (see below). A minimum number of study personnel had access to treatment assignments prior to the primary PFS analysis. Access to unblinded data/documents was restricted. Efficacy information was not shared with sites until the study was completed. Upon overall study completion, investigators may have unblinded patients to study treatment assignment. In case of an emergency, the investigator had the sole responsibility for determining whether unblinding of a patient's treatment assignment was warranted. Patient safety must have always been the first consideration in making such a determination. Emergency unblinding for AEs was performed through the IWRS.
Eligibility criteria for participants	Women with HR+/HER2− locally advanced or metastatic BC who had progressed while receiving neoadjuvant or adjuvant endocrine therapy (ET), ≤12 months from the end of adjuvant ET, or while receiving first-line ET for metastatic disease. The full inclusion and exclusion criteria are presented in Table 4.
Settings and locations where the data were collected	MONARCH 2 was an international, multicentre trial conducted in 142 centres across 19 countries, including Australia, Belgium, Canada, Denmark, Finland, France, Germany, Italy, Japan, Republic of Korea, Mexico, Poland, Puerto Rica, Romania, Russia, Spain, Switzerland, Taiwan and United States of America

<table>
<tr><td>Trial drugs</td><td colspan="2">

Patients received 500 mg fulvestrant by IM injection on Days 1 and 15 of the first cycle, and on Day 1 of subsequent cycles (every 28 days)
Patients received abemaciclib or placebo twice daily during each 28-day cycle

At study initiation, patients in the abemaciclib arm received 200 mg twice daily
After a review of preliminary safety data and dose reduction rates from a Phase I study (I3Y-MC-JPBH [Phase 1b]), and subsequent blinded, early trial level safety review (TLSR) of MONARCH 2, the protocol was amended to reduce the starting dose to 150 mg for new patients. All patients randomised to receive the 200 mg underwent a mandatory dose reduction to 150 mg; if they had not already been dose reduced. In study JPBH, there were patients that discontinued treatment early due to diarrhoea, and most patients did not complete one cycle of treatment at the 200 mg Q12H dose level; or either had a dose reduction or omission. This finding prompted an early blinded TLSR in the MONARCH 2 population, in which it was found that one third of patients required a dose modification in the first 28-day cycle (based on the 2:1 randomisation ratio, this may have corresponded up to half of the patients treated with abemaciclib).
Treatment continued until progressive disease (PD), death, or patient withdrawal

Dose interruptions and reductions of abemaciclib or placebo were permitted according to pre-specified dose-adjustment procedures for patients who exhibited treatment-related toxicities. Fulvestrant dose reductions were permitted per US label as determined by the investigator
Patients were not permitted to switch treatment groups
If either abemaciclib or placebo was discontinued, patients were permitted to continue receiving fulvestrant. If fulvestrant required discontinuation, patients were permitted to continue receiving abemaciclib or placebo

</td></tr>
<tr><td rowspan="2">Permitted and disallowed concomitant medication[60]</td><td colspan="2">All forms of pre-medication, supportive care, and concomitant medications were recorded throughout each patient’s participation in the study</td></tr>
<tr><td>

Permitted therapies
Surgery and/or radiotherapy was permitted, but such patients did not receive study treatment in the period of 7 days prior and at least 14 days after surgery and/or radiotherapy
Full supportive care as judged by the treating physician
Growth factors (in accordance with ASCO guidelines)[61, 62]
Anti-diarrhoeal agents
Bisphosphonates or approved RANK-L targeted agents

</td><td>Prohibited therapies

Radiotherapy without concomitant surgery
Therapies for cancer not listed as permitted, including:
Aromatase inhibitors
Anti-oestrogens other than fulvestrant
Chemotherapy
Immunotherapy
Grapefruit juice, and inducers or strong inhibitors of CYP3A4

</td></tr>
</table>

	• Ovarian suppression with luteinising hormone-releasing hormone agonists for postmenopausal ovarian suppression	• Bupropion • Efavirenz
Primary outcomes	• The primary efficacy measure was INV-assessed PFS as defined by the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1.[59] Tumour measurement images were collected and stored for all enrolled patients throughout the study. A blinded review of imaging scans was performed by an independent panel of radiologists. • PFS time was measured from the date of randomisation to the date of objective PD or death due to any cause, whichever was earlier. Baseline tumour measurements were performed on each patient within 28 days of randomisation by CT scans or MRI. • Tumour assessments were undertaken at baseline and approximately every 8 weeks for the first 12 months following randomisation and approximately every 12 weeks thereafter until the patient had objective disease progression, or until the primary analysis of PFS. Following objective PD, radiologic tests were no longer required, and the patient was followed up approximately every 12 weeks (±14 days) until death or overall study completion. • Bone-focussed imaging was performed in patients with bone lesions detected on baseline bone scintigraphy. Bone scintigraphy should have been repeated for all patients between Day 1 and Day 7 of every sixth cycle beginning with Cycle 7. • For those patients with non-measurable, bone-only disease, objective progression was established if at least one of the following criteria were met: • appearance of one or more new bone lesions (in bone or outside of bone), or • unequivocal progression of existing bone lesions • Pathological fracture, new compression fracture, or complications of bone metastases were not considered as evidence of disease progression, unless at least one of the above criteria were met. • For those patients with locally advanced disease for whom surgery was performed with no evidence of residual disease postoperatively, objective progression was established if at least one of the following criteria were met: • local recurrence • new development of metastatic disease • For patients with locally advanced disease for whom surgery was performed with evidence of residual disease postoperatively, new baseline measurements should have been taken and RECIST version 1.1 applied.[59] • If it was not known whether a patient had progressed or died at the time of analysis, PFS was censored at the last known progression-free assessment	

Other outcomes used in the economic model/specified in the scope	**All efficacy and safety, and PROs, were pre-specified** **Efficacy** • OS: the time from the date of randomisation to the date of death from any cause • ORR: the proportion of patients with CR or PR according to RECIST version 1.1[59] • DCR: the proportion of patients with CR, PR, or SD according to RECIST version 1.17 • DoR: the time from the date of first evidence of a confirmed CR or PR to the date of objective progression or death from any cause, whichever was earlier • CBR: the proportion of patients with CR, PR, or SD ≥6 months according to RECIST version 1.17 **Safety** • During the study, all AEs were recorded and graded at every visit according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Any AEs resulting in dose reduction or discontinuation of treatment was reported and noted • SAEs were defined as any adverse event that resulted in one of the following outcomes: o Death o A life-threatening experience (that is, immediate risk of dying) o Persistent or significant disability/incapacity o Initial or prolonged inpatient hospitalisation o Congenital anomaly/birth defect o Considered significant by the investigator for any other reason **Patient-reported outcomes** • Pain intensity o Responses for the modified Brief Pain Inventory-Short Form (mBPI-sf) items were captured through the use of 11-point numeric rating scales anchored at 0 (no pain or does not interfere) and 10 (pain as bad as you can imagine or completely interferes). o Focussed analysis was on “worst pain”. Use of pain medication was assessed, and data on each individual prescription and over-the-counter analgesic medication was recorded as per protocol. • EORTC QLQ-C30 o The EORTC QLQ-C30 questionnaire was administered as per protocol

	○ Response options for EORTC QLQ-C30 items 1 through 28 were "Not at all", "A little", "Quite a bit", and "Very much". Responses to EORTC QLQ-C30 Items 29 and 30 "Overall health" and "Quality of life" were defined on a 7-point scale ranged from 1 "Very poor" to 7 "Excellent" ○ These responses were transformed resulting in a 0 through 100 continuums with higher score representing a higher ("better") level of functioning (physical, role, emotional, cognitive, social) or QoL; or a higher ("worse") level of symptoms or financial difficulty • EQ-5D-5L ○ The EQ-5D-5L is designed to be used in conjunction with other patient-reported measures and primarily of use in cost-effectiveness analyses ○ Patients completed the 5-dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), 5-level (no problem, slight, moderate, severe, or extreme problem) assessment to provide data used for the development of patient-level utility measures. ○ The EQ-5D-5L data were scored as described by van Hout et al (2012)[63] (EQ-5D-5L to EQ-5D-3L crosswalk) ○ Patients also completed EQ-5D-5L visual analogue scale (VAS) "thermometer" measuring "Your health today" on a 100-point scale ranged from 0 "Worst health you can imagine" to 100 "Best health you can imagine". • Resource Utilisation ○ Investigators were asked to report the use of concomitant medications (in particular, analgesics, bisphosphonates, and RANK-L targeted agents), blood product transfusions, radiation therapy, surgery and hospitalisation days
Pre-planned subgroups	• Subgroup analyses of PFS were performed for each of following potential prognostic subgroup variables: ○ All baseline stratification factors ○ Starting dose (200 mg vs 150 mg) ○ Measurable disease at baseline (yes vs no) ○ Number of organs involved (1 vs 2 vs 3+) ○ Age (<65 years vs ≥65 years) ○ Region (North America, Europe, and Asia) ○ Race (Caucasian, Asian, and Other) ○ Progesterone receptor (PgR) status (positive vs negative) • Where available, subgroup analyses of OS were to be performed as described for PFS

Abbreviations: AE: adverse event**;** AI: aromatase inhibitor; ASCO: American Society of Clinical Oncology; BOR: best overall response; CBR: clinical benefit rate; CR: complete response; CTCAE: Common Terminology Criteria for Adverse Events; DCR: disease control rate; CYP3A4: Cytochrome P450 3A4; DoR: duration of response; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; ET: endocrine therapy; EQ-5D-5L: EuroQol 5-Dimension; INV: investigator; NSAI: non-steroidal aromatase inhibitor; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PgR: progesterone receptor; PR: partial response; PS: performance status; RANK-L: receptor activator of nuclear factor kappa-B ligand; RECIST: Response Evaluation Criteria in Solid Tumours; SAE; serious adverse event; SD: stable disease; TEAE: treatment emergent adverse event; TLSR: trial level safety review.
Source: Sledge et al. 2017;[8] Lilly Data on File (JPBM Clinical Study Report. P53, 77, 242-247). 2017 Lilly Monarch 2 protocol, p36–38[60]

B.2.3.4 Baseline characteristics

Patients had well-balanced baseline characteristics, with no substantial differences between the abemaciclib and placebo groups.

All patients in the MONARCH 2 study were functionally post-menopausal ([redacted]; menopausal status was not available for [redacted] patients); the majority (82.4%) of patients were post-menopausal at study entry ([redacted] natural, [redacted] surgical). The remaining [redacted] of patients were pre- or peri-menopausal, and were induced into a postmenopausal state through ovarian suppression with a LHRH agonist. At baseline, 373 patients (55.8%) presented with visceral disease and 180 (26.9%) with bone-only disease. A total of 169 patients (25.3%) had primary ET resistance, and 18 (2.7%) had locally advanced disease; 140 (20.9%) patients were progesterone receptor-negative. Most patients entered the study after progressing while receiving prior ET (8.8% of patients progressed within 12 months after completing adjuvant therapy.[8] Further detail regarding baseline characteristics of the participants included in the MONARCH 2 study are presented by treatment arm in Table 6.

Table 6. Baseline characteristics of participants in MONARCH 2

Baseline Characteristic	ABE-FUL (N=446)	PBO-FUL (N=223)
Age		
Median (range)	59 (32 to 91)	62 (32 to 87)
Menopausal status, n (%)[a]		
Pre- or peri-menopause (ovarian suppression)	72 (16.1)	42 (18.8)
Post-menopause	371 (83.2)	180 (80.7)
Natural	[redacted]	[redacted]
Surgical	[redacted]	[redacted]
Race, n (%)[b]		
Asian	149 (33.4)	65 (29.1)
Caucasian	237 (53.1)	136 (61.0)
Other	29 (6.5)	13 (5.8)
ECOG performance status[c]		
0	264 (59.2)	136 (61.0)
1	176 (39.5)	87 (39.0)
Region, n (%)		
Europe	[redacted]	[redacted]
Asia	[redacted]	[redacted]
North America	[redacted]	[redacted]
Hormone receptor status, n (%)[d]		
HR+	[redacted]	[redacted]

Baseline Characteristic	ABE-FUL (N=446)	PBO-FUL (N=223)
ER+/PgR+	[redacted]	[redacted]
ER+/PgR−	[redacted]	[redacted]
ER+/PgR unknown	[redacted]	[redacted]
ER-/PgR+	[redacted]	[redacted]
Missing	[redacted]	[redacted]
HER2 status, n (%)[e]		
Negative	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Duration of disease (months)		
Median (IQR)	[redacted]	[redacted]
Metastatic site, n (%)[f]		
Visceral	245 (54.9)	128 (57.4)
Bone only	123 (27.6)	57 (25.6)
Other	75 (16.8)	38 (17.0)
Measurable disease, n (%)		
Yes	318 (71.3)	164 (73.5)
No	128 (28.7)	59 (26.5)
ET resistance, n (%)[g]		
Primary	111 (24.9)	58 (26.0)
Secondary	326 (73.1)	163 (73.1)
Most recent ET, n (%)[h]		
(Neo)adjuvant	263 (59.0)	133 (59.6)
Metastatic	171 (38.3)	85 (38.1)
Prior AI, n (%)		
Yes	316 (70.9)	149 (66.8)
No	130 (29.1)	74 (33.2)
Prior chemotherapy for (neo)adjuvant treatment, n (%)		
Yes	267 (59.9)	134 (60.1)
No	179 (40.1)	89 (39.9)

[a] Menopausal status was not available for three patients in the abemaciclib arm and one in the placebo arm. [b] A total of 31 patients in the abemaciclib arm and nine in the placebo arm had missing race information. [c] One patient had ECOG performance status of 2 in the abemaciclib arm. [d] For three patients in the ABE-FUL arm, hormone receptor status was unknown. [e] For three patients in the ABE-FUL arm and two patients in the PBO-FUL arm, HER2 status was unknown. [f] Metastatic site was not available for three patients in the abemaciclib arm [g] ET history was not available for 12 patients in the ABE-FUL arm and five patients in the PBO-FUL; [h] Six patients in the ABE-FUL arm and two patients in PBO-FUL had not received prior ETs

Abbreviations: AI: aromatase inhibitor; ECOG: Eastern Cooperative Oncology Group; ER: oestrogen receptor; ET: endocrine therapy; HER2: human epidermal growth factor receptor-2; HR: hormone receptor; PgR: progesterone receptor.

Source: Sledge et al. 2017[8]

B.2.3.5 Concomitant Medications

Reported concomitant medications and therapies for patients in the MONARCH 2 study are summarised in Table 7. A total of [redacted] patients ([redacted]) in the ABE-FUL arm and [redacted] patients ([redacted]) in the PBO-FUL arm received concomitant medications. Concomitant medications that were reported for >25% of patients in either arm included loperamide (ABE-FUL [redacted], PBO-FUL [redacted]), paracetamol (ABE-FUL [redacted], PBO-FUL [redacted]) and denosumab (ABE-FUL [redacted], PBO-FUL [redacted]). The use of bone-modifying agents was balanced between the treatment arms; the most common bone-modifying agents were denosumab and zoledronic acid ([redacted] of patients in the ABE-FU arm and [redacted] in the PBO-FUL arm).

Table 7. Summary of categories of selected concomitant medications received during the MONARCH 2 study, safety population

Category, n (%)	ABE-FUL (N=441)	PBO-FUL (N=223)
Patients with ≥1 anti-diarrhoeal	[redacted]	[redacted]
Patients with ≥1 analgesics	[redacted]	[redacted]
Non-opioid	[redacted]	[redacted]
Opioid	[redacted]	[redacted]
Patients with ≥1 bone-modifying agents	[redacted]	[redacted]
Patients with ≥1 anti-emetics and anti-nauseants	[redacted]	[redacted]
Patients with ≥1 G-CSF/GM-CSF	[redacted]	[redacted]
Patients with ≥1 erythropoietic agents	[redacted]	[redacted]

Abbreviations: ABE-FUL: abemaciclib plus fulvestrant; G-CSF: granulocyte-colony stimulating factor; GM-CSF: granulocyte-macrophage
colony-stimulating factor; PBO-FUL: placebo plus fulvestrant.
Source: Lilly Data on File (JPBL Clinical Study Report 101–102). 2017[35]

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

The study was designed to compare the PFS for ABE-FUL to that for PBO-FUL. The study initially planned to enrol 450 patients into the intent-to-treat (ITT) population. However, after a change in the starting dose of the blinded-study drug from 200 mg to 150 mg (further details are provided in Table 5), the sample size was increased to 630 patients to ensure at least 450 patients were enrolled at the 150 mg dose. All efficacy analyses, including the primary outcome of PFS, were performed on the ITT population which included all randomised patients regardless of starting dose, and were performed by treatment arm. Safety was assessed in the safety population, which included all 664 randomised and treated patients who received at least one dose of study drug.

If it was not known whether a patient had progressed or died at the time of analysis, PFS was censored at the last known progression-free assessment. Sensitivity analyses were planned that (1) included only patients enrolled after the change in starting dose and that (2) determined progression on the basis of a blinded, independent central review.

The primary endpoint, INV-assessed PFS, was evaluated using a log-rank test stratified by metastatic site and ET resistance. The final analysis was planned at 378 PFS events, which

would provide approximately 90% power assuming a HR of 0.703 at a one-sided type I error of 0.025, which corresponds to a 2.75-month improvement over the true median PFS for the control arm of 6.5 months.[64] One efficacy interim analysis was planned to be at 70% of the final PFS events. The stratification factors for the primary and secondary analyses were:

- Nature of disease (visceral metastases vs bone-only metastases vs other)
- Sensitivity to ET (primary resistance vs secondary resistance)

At the time of data cut-off and primary analysis of PFS on 14 February 2017, 170 patients (38.1%) in the ABE-FUL arm versus 45 (20.2%) in the PBO-FUL arm were continuing to receive the study drug; the remaining 271 patients (60.8%) in the ABE-FUL arm and 178 patients (79.8%) in the PBO-FUL arm, had discontinued treatment. The majority of patients had discontinued due to PD. A full CONSORT diagram of the study population flow, and reasons for study drug discontinuation and discontinuation from the study, are provided in Appendix D. A summary of the statistical analyses for MONARCH 2 is provided in Table 8.

Table 8. Summary of statistical analyses for MONARCH 2

Hypothesis objective	The primary objective of MONARCH 2 was to compare ABE-FUL with PBO-FUL, with respect to PFS for women with HR+/HER2− locally advanced or metastatic breast cancer. The null and alternative hypotheses were defined as follows (letting SA(t) and SP(t) denote the PFS functions of ABE-FUL and PBO-FUL respectively): • Null hypothesis (H0): SA(t) = SP(t) i.e. no difference in PFS between treatment groups • Alternative hypothesis (H1): SA(t) > SP(t) i.e. superior PFS in ABE-FUL group compared with PBO-FUL group
Statistical analysis	**Primary outcome**: • All efficacy analyses, including the primary outcome of PFS, were performed on the ITT population which included all randomised patients regardless of starting dose, and were performed by treatment arm • PFS was defined as the time from the date of randomisation to the date of objective PD or death due to any cause, whichever was earlier • If it was not known whether a patient had progressed or died at the time of analysis, PFS was censored at the last known progression-free assessment • There was 1 planned interim analysis and 1 primary analysis to test the above hypotheses • The interim analysis was to be performed after approximately [redacted] (approximately [redacted] of the [redacted] planned) INV-assessed PFS events had occurred • The primary (final) PFS analysis was planned to be performed after [redacted] PFS events were observed, based on investigator assessment (corresponding to a [redacted] censoring rate, relative to the anticipated [redacted] patients enrolled in the EP stratum) • PFS was determined using a 1-sided log-rank test • PFS curves for each treatment arm were estimated using the Kaplan-Meier method[65]; PFS rates for each arm were compared at 3-month intervals up to 15 months for the difference between rates • A stratified Cox proportional hazard model[66] with treatment as a factor was used to estimate the HR between treatment arms and the corresponding CI and Wald p-value • To estimate an improvement in PFS with abemaciclib, the method of Irwin (1949)[67] detailed in Karrison (1997)[68] and Meier (2004)[69] for estimating the “difference in average PFS” was followed (and is hereafter referred to as the restricted mean difference in PFS) **Safety:** • All 664 randomised and treated patients who received at least one dose of study drug were included in the safety analyses as the safety population

	• Overall exposure to study drug, the numbers of patients completing each cycle, and the dose intensity were summarised using descriptive statistics. The number of patients with any dose adjustment was presented for the entire treatment period as well as for each cycle **Subgroup Analyses:** • Subgroup analyses of PFS and OS were performed for each of following potential prognostic subgroup variables: o All baseline stratification factors o Starting dose (200 mg vs 150 mg) o Measurable disease at baseline (yes vs no) o Number of organs involved (1 vs 2 vs 3+) o Age (<65 years vs ≥65 years) o Region (North America, Europe, and Asia) o Race (Caucasian, Asian, and Other) o PgR status (positive vs negative) • Analyses were performed within subgroup and, separately, across subgroups with a test of interactions of subgroups with treatment. Estimated HRs and 95% CIs for the within subgroup analyses were presented as a forest plot along with p-values for tests of interactions between subgroup variables and treatment
Sample size, power calculation	• Assuming a hazard ratio of 0.703, 378 events PFS yielded approximately 90% statistical power to detect superiority of the ABE-FUL arm over the PBO-FUL arm with the use of a 1-sided log-rank test and a type I error of 0.025 • If the true median PFS for the PBO-FUL arm was 6.5 months, then the hazard ratio of 0.703 amounted to an approximate 2.75 month (42%) improvement in median PFS for the ABE-FUL arm; under an additional assumption of exponential survival distribution
Data management, patient withdrawals	• All patients were followed up for progression and survival information until death or study completion, whichever occurred first. This included those patients who were randomised and never received study treatment or discontinued study treatment without objectively measured PD • For randomised patients who did not receive or discontinued study treatment without objectively measured PD, tumour response was evaluated every 8 weeks for the first 18 months and thereafter approximately 12 weeks, until the patient had objective PD or until the final PFS analysis • All randomised patients were included in the efficacy analysis

Abbreviations: ABE-FUL: abemaciclib plus fulvestrant; BOR: best overall response; CBR: clinical benefit rate; CI: confidence interval; CR: complete response; DCR: disease control rate; DoR: duration of response; HER2: human epidermal growth factor receptor 2**;** HR: hormone receptor; INV: investigator; ITT: intent-to-treat; KM: Kaplan-Meier; mBC: metastatic breast cancer; ORR: objective response rate; OS: overall survival**;** PBO-FUL: placebo plus fulvestrant; PD: progressive disease; PFS: progression-free survival; PgR: progesterone receptor; PR: partial response; RECIST: Response Evaluation Criteria In Solid Tumors;[59] SD: stable disease.
Source: Lilly Data on File (Clinical Study Report). 2017[35]

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

A summary of the quality assessment performed for MONARCH 2 is provided in Table 9. Overall, the results of the MONARCH 2 study can be considered to be at low risk of bias. Randomisation, concealment of treatment allocation and blinding of the participants and care providers were adequate. Baseline characteristics were well-balanced between the treatment groups at baseline. All randomised patients were included in the ITT analysis for primary and secondary efficacy outcomes. There was no difference in the rates of treatment discontinuation between treatment arms. However, it was unclear whether more outcomes were measured than reported; data on OS and the pharmacokinetics for abemaciclib have not yet been presented in follow-up publications.

Table 9: Overview of quality assessments for MONARCH 2

NCT02107703 (MONARCH 2)	Risk of bias
Was randomisation carried out appropriately?	Low; randomisation was performed using a computer-generated random sequence
Was the concealment of treatment allocation adequate?	Low; treatment allocation was concealed using an interactive web-based scheme
Were the groups similar at the outset of the study in terms of prognostic factors?	Low; patient baseline characteristics were well-balanced
Were the care providers, participants and outcome assessors blind to treatment allocation?	Low; double blind, placebo-controlled study
Were there any unexpected imbalances in drop-outs between groups?	Low; loss to follow-up was similar between the two treatment arms
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Unclear; the data on OS and pharmacokinetics have not been presented in follow-up publications
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Low; ITT analysis was used and missing data were not imputed

Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination
Abbreviations: ITT: intent-to-treat; OS: overall survival.

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

Summary of clinical effectiveness

- The results of the MONARCH 2 study demonstrate that treatment with ABE-FUL is associated with a significantly extended PFS and an improved ORR in comparison with PBO-FUL
- The MONARCH 2 study met its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in PFS (HR: 0.553 [95% CI: 0.449 to 0.681], p<0.001)[8] with a 45% reduction in the risk of disease progression or death in comparison to PBO-FUL
- A significant improvement in PFS delays the decline in HRQoL associated with further disease progression, and the need to begin treatment with chemotherapy regimens associated with high toxicity
- The percentage of patients who received post-discontinuation chemotherapy was lower in the ABE-FUL arm than in the PBO-FUL arm ([redacted] vs [redacted], respectively). ABE-FUL has been shown to significantly delay the time to post-discontinuation chemotherapy compared with PBO-FUL in a *post hoc* exploratory analysis of MONARCH 2 (ABE-FUL: median not reached; PBO-FUL: median 26.33 months), with a HR of 0.65 (p<0.01).[55]
- At the time of data cut-off, the OS data were still immature with 85 (19.1%) events (deaths) in the ABE-FUL arm and 48 (21.5%) in the PBO-FUL arm. These data are therefore difficult to interpret, and too early in the natural history of breast cancer to draw any firm conclusions
- Treatment with ABE-FUL leads to significantly greater ORR, DCR, and CBR in both the ITT population and patients with measurable disease
- At the time of analysis (after more than two years), median duration of response for patients treated with abemaciclib had not been reached
- Pain intensity scores were similar between ABE-FUL and PBO-FUL, but numerically favoured ABE-FUL
- HRQoL was assessed using the EORTC QLQ-C30 scores and EQ-5D-5L instruments
- There was a significant difference of [redacted] points in EORTC QLQ-C30 diarrhoea symptom score in the ABE-FUL arm relative to the PBO-FUL arm. The highest symptom burden for diarrhoea was reported during early visits, and returned close to baseline upon treatment discontinuation. All other EORTC QLQ-C30 scores were similar between treatment arms at baseline, during therapy and short-term follow up study periods. Furthermore, there was no significant difference in global health status between treatment arms
- EQ-5D-5L index values and VAS scores were EQ-5D-5L index values and VAS scores were similar between treatment arms for all baseline and post-baseline visits, supporting that the overall health status of patients was maintained throughout the study in both treatment arms
- It is further important to note that the HRQoL data observed in MONARCH 2 do not capture the delay in the detriment to quality of life associated with initiating chemotherapy treatment

The clinical effectiveness results presented in this section include the primary outcome (PFS), as well as the secondary efficacy outcomes OS, ORR, DCR, DoR, CBR and patient-reported measures (pain intensity [BPI] and HRQoL [EORTC QLQ-C30, EQ-5D-5L]). A summary of the results for each outcome is presented in Table 10. The addition of abemaciclib provides a clinically and statistically significant improvement in PFS and ORR, while maintaining patient-reported HRQoL.

Table 10. Summary of outcomes presented in MONARCH 2

INV-assessed PFS	ABE-FUL N=446		PBO-FUL N=223		Treatment Effect/Difference/p-value[a]		
Number of events, n (%)	222 (49.8)		157 (70.4)		NA		
Overall survival[a]	**ABE-FUL N=446**		**PBO-FUL N=223**		**Treatment Effect/Difference/p-value[a]**		
Number of deaths, n (%)	85 (19.1)		48 (21.5)		[redacted]		
Survival rate, % (95% CI)[c] 12 months	[redacted]		[redacted]		[redacted]		
Response rate	**ABE-FUL (N=446)**		**PBO-FUL (N=223)**		**Difference**	**OR**	**p-value**
	n (%)	**95% CI**	**n (%)**	**95%CI**			
Overall response rate (CR + PR)	157 (35.2)	30.8, 39.6	36 (16.1)	11.3, 21.0	19.1	2.82	<0.001
Disease control rate (CR + PR + SD)	370 (83.0)	79.5, 86.4	169 (75.8)	70.2, 81.4	7.2	1.56	0.025
Clinical benefit rate (CR + PR + SD ≥6 months)	322 (72.2)	68.0, 76.4	125 (56.1)	49.5, 62.6	16.1	2.04	<0.001
Duration of response	**ABE-FUL (N=446)**				**PBO-FUL (N=223)**		
Median (95% CI), months	[redacted]				[redacted]		
Pain intensity	**ABE-FUL (N=441)**				**PBO-FUL (N=223)**		
Patients experiencing at least 1 pain worsening event, n (%)	[redacted]				[redacted]		

[a] OS data were still immature at the time of analysis

Abbreviations: ABE-FUL: abemaciclib plus fulvestrant; CI: confidence interval; CR: complete response; INV: investigator; NA: not applicable; OR: odds ratio; PBO-FUL: placebo plus fulvestrant; PFS: progression-free survival; PR: partial response; SD: stable disease.

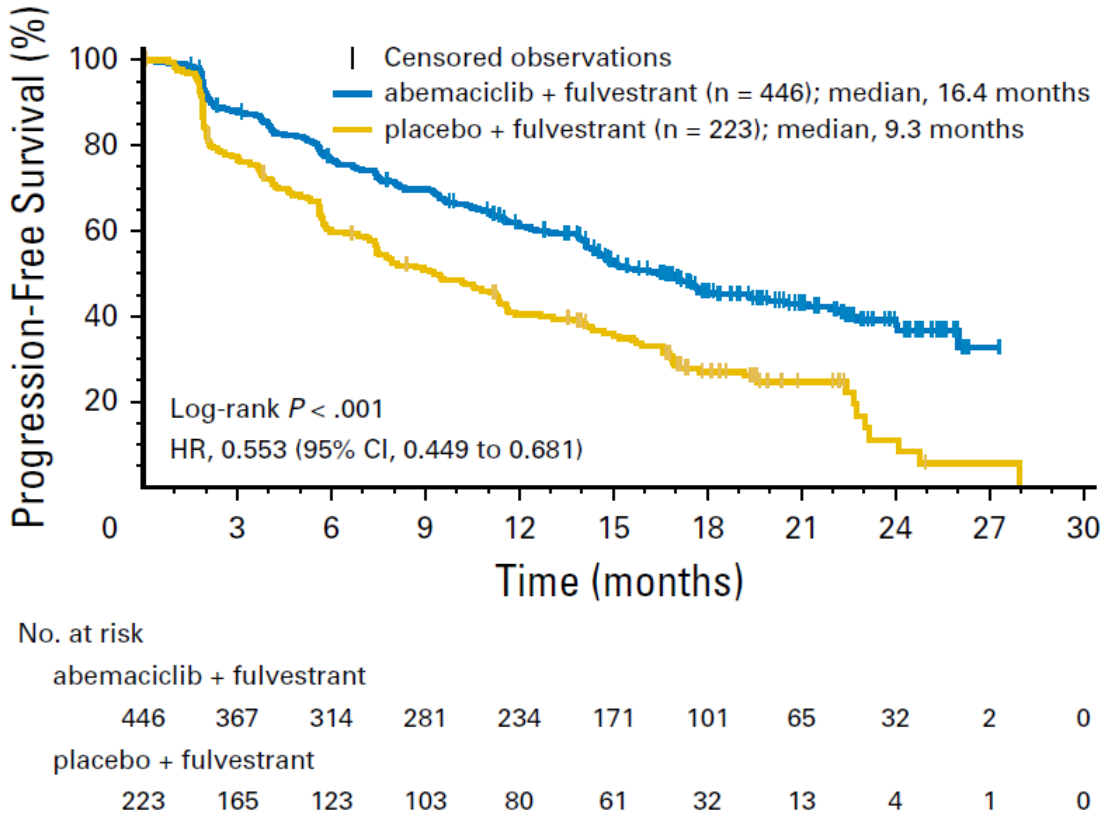
B.2.6.1 Progression-free survival

The primary PFS analysis was performed on the ITT population, including a total of 669 patients (N=446 [ABE-FUL] and N=223 [PBO-FUL]). A total of 379 patients experienced PFS events, including 222 patients (49.8%) in the ABE-FUL arm and 157 patients (70.4%) in the PBO-FUL arm. The median length of follow-up was 19.5 months. In the ABE-FUL arm, PFS data for [redacted] patients ([redacted]) were censored, while in the PBO-FUL arm, PFS data for [redacted] patients ([redacted]) were censored.[8]

Median PFS was 16.4 months in the ABE-FUL arm and 9.3 months in the PBO-FUL arm, which was a statistically significant and clinically meaningful improvement (HR=0.553 [95% CI: 0.449 to 0.681], p<0.001).[8] These results corresponded to a 45% reduction in the risk of disease progression or death and a 7.2-month improvement in median PFS for patients treated with ABE-FUL. PFS rates at 12 and 18 months were [redacted] and [redacted] in the ABE-FUL arm, respectively, and [redacted] and [redacted] in the PBO-FUL arm (p<[redacted]). The full summary of PFS by investigator assessment is presented in Appendix L.

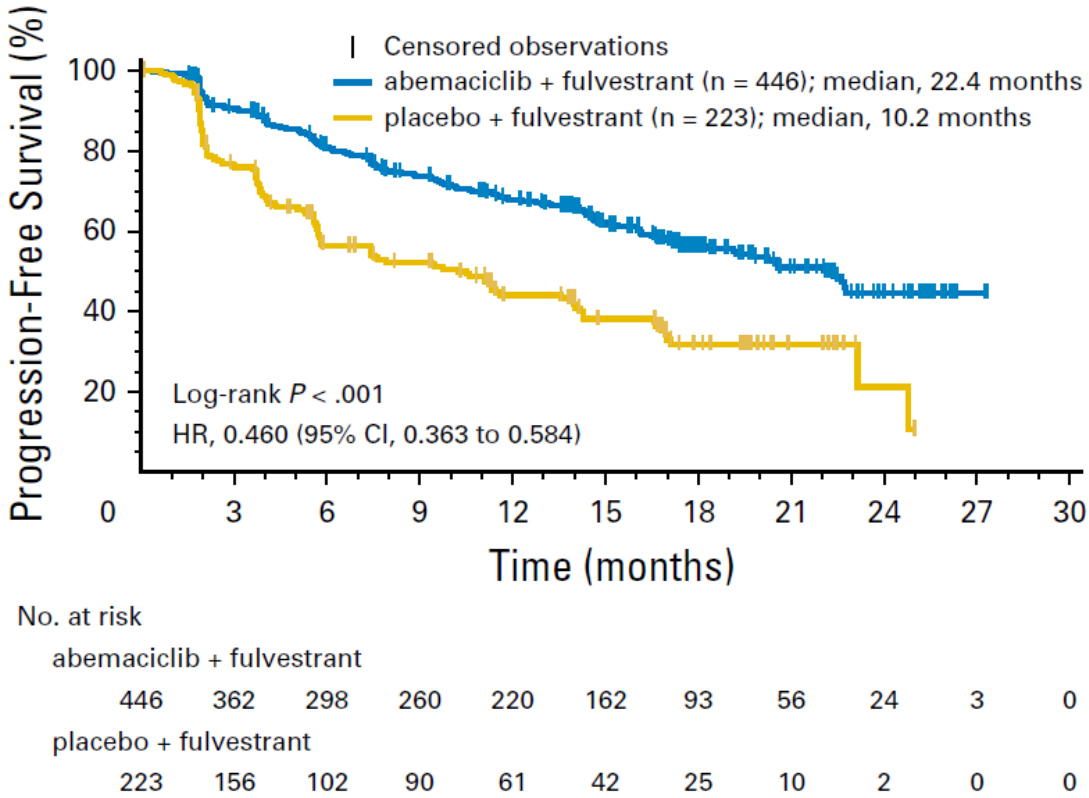
A Kaplan-Meier plot of INV-assessed PFS plot is displayed in Figure 4. Early and sustained separation by treatment arm was apparent beginning at eight weeks. A blinded central analysis also demonstrated consistent PFS results (HR: 0.460 [95% CI: 0.363 to 0.584], p<0.001). A Kaplan-Meier plot of independently-assessed PFS is displayed in Figure 5.

Figure 4. Kaplan-Meier plot of INV-assessed PFS at the final analysis in MONARCH 2 for ABE-FUL vs PBO-FUL, ITT population



Abbreviations: ABE-FUL: abemaciclib plus fulvestrant; CI: confidence interval; HR: hazard ratio; INV: investigator; ITT: intent-to-treat; PBO-FUL: placebo plus fulvestrant; PFS: progression-free survival.
Source: Sledge et al. 2017[8]

Figure 5. Kaplan-Meier plot of progression-free survival by independent review in MONARCH 2 at the final PFS analysis, ITT population

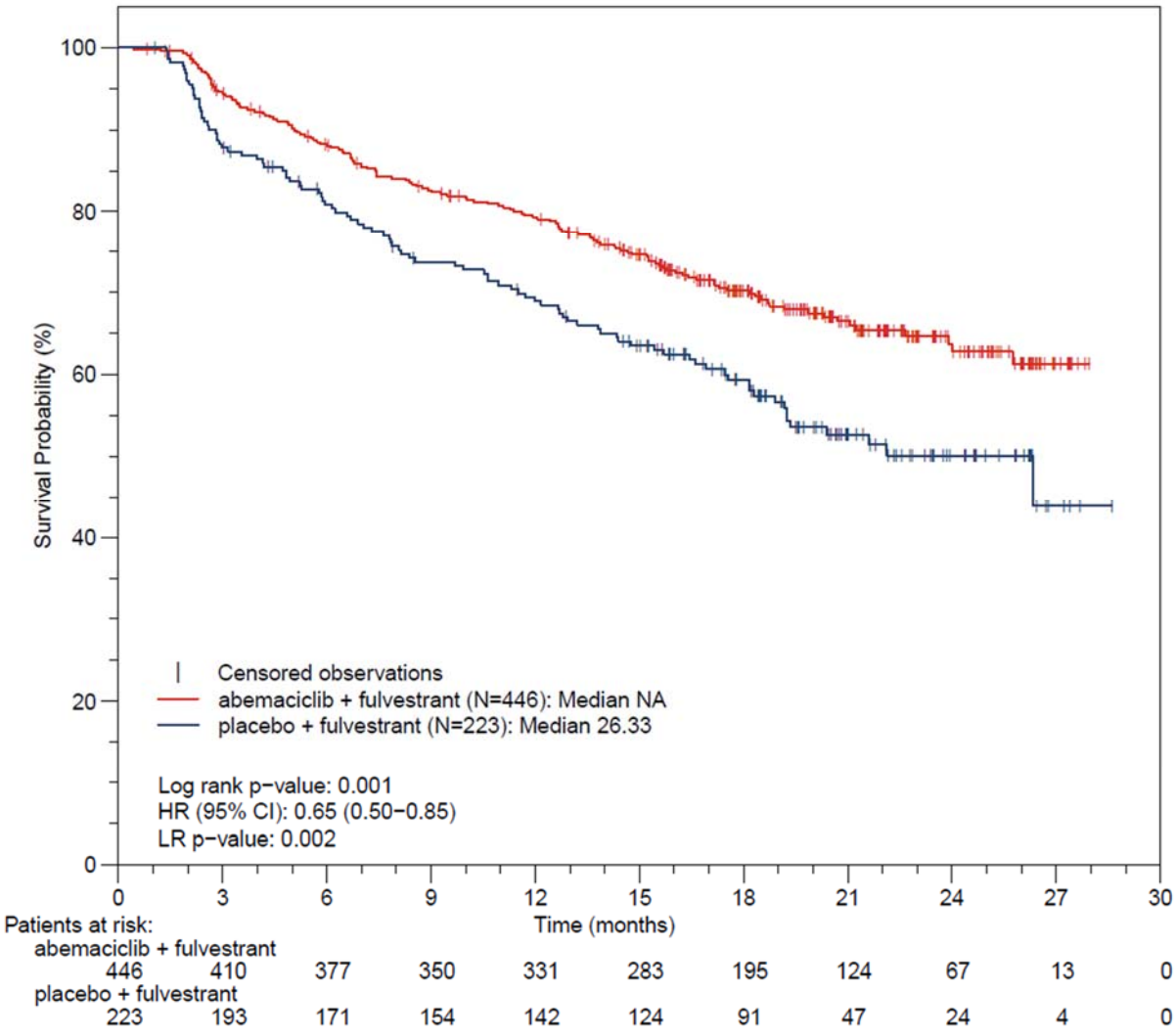


Abbreviations: HR: hazard ratio; NR: not reached; ITT: intent-to-treat; PFS: progression-free survival.
Source: Sledge et al. 2017[8]

The results of the MONARCH 2 trial demonstrate the benefits that treatment with ABE-FUL may offer patients. An extended PFS delays the decline in HRQoL associated with further disease progression, and the need to begin treatment with chemotherapy regimens associated with high toxicity. ABE-FUL has been shown to significantly delay the time to post-discontinuation chemotherapy compared with PBO-FUL in a *post hoc* exploratory analysis of MONARCH 2 (ABE-FUL: median not reached; PBO-FUL: median 26.33 months), with a HR of 0.65 (p<0.01).[55] A Kaplan-Meier plot for the *post hoc* exploratory analysis (data cut-off 14th February 2018; final PFS analysis) is presented in Figure 6.

An improvement in PFS is also likely to translate to improved OS,[70] a notion also supported by clinicians consulted by Lilly. The extent of this translation is currently uncertain.[40, 41]

Figure 6. Exploratory analysis of time to subsequent chemotherapy in MONARCH 2, based on the final PFS analysis (data cut-off 14th February 2017)



Footnotes: Survival probability represents survival to initiation of subsequent chemotherapy
Abbreviations: CI: confidence interval; HR: hazard ratio; NA: not achieved; PFS: progression-free survival.
Source: Tolaney et al. 2018[71]

B.2.6.2 Overall survival

At the time of data cut-off (14th February 2017), the OS data were still immature; mature data are not expected within the timeframe of this appraisal. Due to the immaturity of the data, the median follow-up times were similar across treatment arms ([redacted] months [ABE-FUL] and [redacted] months [PBO-FUL]). At the time of data cut-off, 85 (19.1%) events (deaths) in the ABE-FUL arm and 48 (21.5%) in the PBO-FUL arm had occurred (HR: [redacted] [95% CI: [redacted]]). The stratified log-rank test p-value was [redacted] and the 1-sided boundary p-value at this OS interim analysis was [redacted] (based on the O'Brien Fleming-like spending function[72]). A Kaplan-Meier plot for OS at the final analysis is presented in Figure 7, and a full summary of OS by investigator assessment is presented in Table 11.

Figure 7. Kaplan-Meier plot of OS for ABE-FUL vs PBO-FUL at the final analysis, ITT population

Abbreviations: ABE-FUL: abemaciclib plus fulvestrant; HR: hazard ratio; ITT: intent-to-treat; NR: not reached; OS: overall survival; PBO-FUL: placebo plus fulvestrant.
Source: Lilly Data on File (Clinical Study Report P118). 2017[35]

Table 11. OS for ABE-FUL vs PBO-FUL at the final analysis, ITT population

	ABE-FUL N=446	PBO-FUL N=223	Treatment Effect/Difference/p-value[a]
Number of deaths, n (%)	85 (19.1)	48 (21.5)	[redacted]
Number of patients censored, n (%)	[redacted]	[redacted]	[redacted]
Alive	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]
Withdrawal by patient	[redacted]	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]	[redacted]
p-value (2-sided) – log-rank test stratified[b]	[redacted]	[redacted]	[redacted]

Hazard ratio (95% CI) – stratified[b]	[redacted]	[redacted]	[redacted]
Survival rate, % (95% CI)[c]			
12 months	[redacted]	[redacted]	[redacted]

OS rates were estimated using the Kaplan-Meier method. Corresponding 95% CIs were estimated using the methods of Brookmeyer and Crowley, and Greenwood, respectively.
[a] Treatment effect/difference/p-values are computed based on comparator placebo. [b] Stratified by sensitivity to endocrine therapy and nature of disease per the Interactive Web Response System. [c] 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation.
Abbreviations: ABE-FUL: abemaciclib plus fulvestrant; CI: confidence interval; ITT: intent-to-treat; NA: not applicable; OS: overall survival; PBO-FUL: placebo plus fulvestrant.
Source: Lilly Data on File (Clinical Study Report P117). 2017[35]

B.2.6.3 Response rate

Objective response rate

Objective response rate, defined as the proportion of patients with best response or complete or partial response, was evaluated for patients in the ITT population (n=669) and for patients with measurable disease at baseline (n=482). In the ITT population, ORR was significantly higher for patients treated with ABE-FUL (35.2% [95% CI: 30.8 to 39.6) compared with patients treated with PBO-FUL (16.1% [95% CI: 11.3 to 21.0]; Table 12).[8] This resulted in an OR of 2.82 (p<0.001), indicating that patients treated with ABE-FUL had significantly higher odds of exhibiting a CR or PR than patients treated with PBO-FUL. For those treated with ABE-FUL, 14 patients achieved a CR (3.1%, including 11 patients with measurable disease) compared with one PBO-FUL-treated patient (0.4%; this patient did not have measurable disease). Tumour size reduction was more pronounced in the ABE-FUL arm, and tumour response was durable.[8]

For patients with measurable disease, the ORR was also significantly higher in the ABE-FUL arm (48.1% [95% CI: 42.6 to 53.6]) relative to the PBO-FUL arm (21.3% [95% CI: 15.1 to 27.6]; OR = 3.42, p<0.001).[8]

Clinical opinion sourced by Lilly reported that improved tumour response rate and reductions in tumour size help to relieve symptoms such as poor energy levels and pain. Reductions in tumour size may additionally reduce the need for health interventions such as analgesia, helping to maintain QOL.

Disease control rate

The DCR for patients in the ABE-FUL arm and PBO-FUL arm were 83.0% (95% CI: 79.5 to 86.4) and 75.8% (95% CI: 70.2 to 81.4), respectively. This equates to a statistically significant improvement in DCR for patients in the ABE-FUL arm (OR = 1.56; p=0.025; Table 12).[8] For the 370 patients with CR, PR, or SD in the ABE-FUL arm, the median duration of disease control was [redacted] months (95% CI: [redacted], [redacted]), and for the 169 patients with CR, PR, or SD in the PBO-FUL arm, the median duration of disease control was [redacted] months (95% CI: [redacted] to [redacted]). These results show statistically significant improvement in duration of disease control for patients in the ABE-FUL arm (p[redacted]).

For those with measurable disease, the DCR in the ABE-FUL arm showed a statistically significant improvement for these patients relative to the PBO-FUL arm: 82.4% (95% CI: 78.2 to 86.6) and 72.6% (95% CI: 65.7 to 79.4), respectively (OR = 1.77; p=0.012; Table 12).[8]

Clinical benefit rate

Across the ITT population, the CBR for patients in the ABE-FUL arm and the PBO-FUL arm were 72.2% (95% CI: 68.0 to 76.4) and 56.1% (95% CI: 49.5 to 62.6), respectively. This equates to a statistically significant improvement in CBR with treatment with ABE-FUL (OR = 2.04; p<0.001; Table 12).[8] For those with measurable disease, the CBR was significantly higher in patients treated with ABE-FUL (73.3% [95% CI: 68.4 to 78.1]) relative PBO-FUL (51.8% [95% CI: 44.2 to 59.5]), producing an OR of 2.55 (p<0.001).[8]

These results suggest that patients treated with ABE-FUL were more likely to exhibit a partial or complete tumour response and/or stable disease for at least 6 months than patients treated with PBO-FUL. By prolonging the response of the tumour to treatment and inducing shrinkage, symptoms such as pain may be relieved, and the burden of disease in later lines of therapy will be lower (supported by clinical expert opinion sourced by Lilly).

Table 12. Summary of best overall response by investigator assessment in MONARCH 2 at the final analysis for ABE-FUL vs PBO-FUL, ITT population

	ABE-FUL (N=446)		PBO-FUL (N=223)		Difference	OR	P-value
	n (%)	95% CI	n (%)	95%CI			
Complete response	14 (3.1)	1.5, 4.8	1 (0.4)	−0.4, 1.3	NA	NA	NA
Partial response	143 (32.1)	27.7, 36.4	35 (15.7)	10.9, 20.5	NA	NA	NA
Stable disease	213 (47.8)	43.1, 52.4	133 (59.6)	53.2, 66.1	NA	NA	NA
≥6 months	165 (37.0)	32.5, 41.5	89 (39.9)	33.5, 46.3	NA	NA	NA
Progressive disease	40 (9.0)	6.3, 11.6	45 (20.2)	14.9, 25.4	NA	NA	NA
Not evaluable	36 (8.1)	5.5, 10.6	9 (4.0)	1.5, 6.6	NA	NA	NA
Overall response rate (CR + PR)	157 (35.2)	30.8, 39.6	36 (16.1)	11.3, 21.0	19.1	2.82	<0.001
Disease control rate (CR + PR + SD)	370 (83.0)	79.5, 86.4	169 (75.8)	70.2, 81.4	7.2	1.56	0.025
Clinical benefit rate (CR + PR + SD ≥6 months)	322 (72.2)	68.0, 76.4	125 (56.1)	49.5, 62.6	16.1	2.04	<0.001

Abbreviations: CR: complete response; NA: not applicable; PR: partial response; SD: stable disease.
Source: Sledge et al. 2017[8]

B.2.6.4 Duration of response

For the 157 patients in the ABE-FUL arm with a CR or PR as assessed by the investigator, the median DoR had not been reached ([redacted]; 95% CI: [redacted] to [redacted]) at the time of analysis, with 90 responders (57.3%) continuing on treatment (Figure 8). Of the 157 patients who responded to ABE-FUL, [redacted] progression events and [redacted] deaths were observed. For the 36 patients in the PBO-FUL arm with a CR or PR as assessed by the investigator, median DoR in was [redacted] months (95% CI: [redacted] to [redacted]. [redacted] progression events and [redacted] death had been observed, with [redacted] responders ([redacted]) continuing on treatment at the time of the analysis. Responses in both arms were durable, with 67.8% of the responding patient's progression-free at 12 months in the ABE-FUL arm compared with 66.9% in the PBO-FUL arm.[8]

Figure 8. Kaplan-Meier plot of DoR in MONARCH 2 at the final analysis for ABE-FUL vs PBO-FUL

Abbreviations: ABE: abemaciclib; DoR: duration of response; FUL: fulvestrant; PBO: placebo; NR: not reached
Source: Lilly Data on File (Clinical Study Report P115). 2017[35]

B.2.6.5 Pain intensity

Pain intensity and pain assessments were assessed in terms of individual modified Brief Pain Inventory-Short Form (mBPI-sf) pain items. The baseline pain mean score for each pain severity

item (worst, least, average, now) was low (<3 on a 0 to 10 numeric rating scale) and similar between treatment arms. A summary of mBPI-sf in the safety population is presented in Table 13.

ABE-FUL demonstrated a numeric reduction from baseline of mBPI-sf-reported “worst pain” on a per- PRO-measurement cycle basis. Between-group differences versus PBO-FUL did not reach clinical or statistical significance. A pre-specified analysis of time to pain worsening showed a numerical but not significant benefit for ABE-FUL compared with PBO-FUL. The mixed effect repeated measures models showed the least square (LS) mean difference in score from baseline across all scheduled post-baseline measures demonstrated a numerical improvement within the ABE-FUL arm. The LS mean differences between treatment arms of the mean change from baseline for mBPI-sf items numerically favoured ABE-FUL but did not reach clinical or statistical significance.

[redacted] percent ([redacted]/441) of patients in the ABE-FUL arm and [redacted] ([redacted]/223) of patients in the PBO-FUL arm experienced at least one pain-worsening event. A difference of [redacted] months in median time to pain worsening numerically favoured those receiving ABE-FUL versus PBO-FUL ([redacted] vs [redacted] months; HR 0.900, p=0.4005). At 12 months, the percentage of patients without pain worsening was [redacted] for patients treated with ABE-FUL, compared with [redacted] of patients treated with PBO-FUL. Overall, a small benefit of pain reduction from baseline can be observed in the ABE-FUL arm, in comparison with the PBO-FUL arm.

Table 13. Summary of mBPI-sf at the final analysis MONARCH 2, safety population

	Baseline Score Mean (SD)		Within-treatment Group Change from Baseline[a] LS Mean (SE)		Between-treatment Group Difference[a,b,c]	
	ABE-FUL (N=441)	PBO-FUL (N=223)	ABE-FUL (N=441)	PBO-FUL (N=223)	LS Mean (SE)	p-value
Worst Pain in 24 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Least Pain in 24 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain on average	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain right now	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean interference Score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Across all postbaseline visits (ABE-FUL – PBO-FUL change difference). [b] p-values are from Type 3 sums of squares mixed models repeated measures model: Change from baseline = Treatment + Visit + Treatment*Visit + Baseline. [c] A negative between-treatment difference favours ABE-FUL.
Abbreviations: LS: least squares; mBPI-sf: Modified Brief Pain Inventory- short form; SD: standard deviation; SE: standard error.
Source: Lilly Data on File (Global Health Outcomes Clinical Study Report Addendum, P11). 2017[73]

B.2.6.6 EORTC QLQ-C30

The method of EORTC QCL-C30 administration and scoring is provided in Table 5, and a summary of EORTC QLQ-C30 results in the safety population is presented in Table 14. Patients on ABE-FUL received a median of [redacted] overall.

Baseline mean scores for the five functional scales (physical, role, emotional, cognitive and social functioning) were all [redacted] and the baseline mean score for global QoL was [redacted], indicating relatively high levels of functioning and QoL, although there was notable variation evident by the standard errors (approximately [redacted] to [redacted]). The mixed effect repeated measures models showed the LS mean differences between treatment arms of the mean change from baseline were similar for physical, role, cognitive, emotional, and social functioning, indicating that treatment with ABE-FUL did not adversely affect functioning and HRQoL.

Baseline mean scores were similar between treatment arms and for most symptom scales were [redacted], indicating a relatively low symptom burden, but were highest for fatigue and pain with mean scores of approximately [redacted]. For multi-item scales and single-item measures, baseline scores were similar between treatment arms.

Most of the symptom scores and emotional function score were stable and similar between the two treatment arms during the on-therapy and short-term follow-up study periods. Small reductions in pain and insomnia symptom scores were seen in both treatment arms, with the between-treatment differences numerically favouring ABE-FUL. The median time to pain worsening numerically favouring ABE-FUL relative to PBO-FUL ([redacted] versus [redacted] months; HR = [redacted], [redacted]). Conversely, dyspnoea scores on average increased numerically more in the ABE-FUL arm.

A significant increase in mean diarrhoea symptom score from baseline was observed in the ABE-FUL arm. Across all post-baseline on-therapy visits, a between-treatment group difference of [redacted] points was observed in the ABE-FUL arm, whereas there was no increase in diarrhoea observed in the PBO-FUL arm. This was seen as early as the first scheduled post-baseline assessment at Cycle 2. The mean between-treatment arm difference for diarrhoea score was at its highest over the first two scheduled visits ([redacted] points at Cycles 2 and 3), then gradually decreased during the later on-treatment cycles, but remained above [redacted] points. The LS mean change from baseline in diarrhoea score within the ABE-FUL arm decreased to [redacted] points at the 30-day safety follow-up visit, similar to that observed in the PBO-FUL arm ([redacted]), showing that the symptom of diarrhoea returned to baseline upon treatment discontinuation. The symptoms of appetite loss and nausea/vomiting were also reported at a higher frequency for the ABE-FUL arm compared with the PBO-FUL arm, but these were transient, reducing close to baseline levels after Cycle 5.

Table 14. Summary of EORTC QLQ-C30 at the final analysis in MONARCH 2, safety population

	Baseline Score Mean (SD)		Within-treatment Group Change from Baseline[a] LS Mean (SE)		Between treatment Group Difference[a,b, c]	
	ABE-FUL (N=441)	PBO-FUL (N=223)	ABE-FUL (N=441)	PBO-FUL (N=223)	LS Mean(SE)	p-value
Global health status						
Functional scales						
Physical functioning						
Role functioning						
Emotional functioning						
Cognitive functioning						
Social functioning						
Symptom scale items						
Fatigue						
Nausea and vomiting						
Pain						
Dyspnoea						
Insomnia						
Appetite loss						
Constipation						
Diarrhoea						
Financial difficulties						

Abbreviations: EORTC QLQ-C30: European Organization for the Research and Treatment of Cancer, Quality of Life Questionnaire Core 30; LS: least squares; N: number of patients in the population; SD: standard deviation; SE: standard error

[a] Across all postbaseline visits (ABE-FUL – PBO-FUL for change difference).[b] p-values are from Type 3 sums of squares mixed models repeated measures model: Change from baseline = Treatment + Visit + Treatment*Visit + Baseline. [c] A positive difference between treatments favours ABE-FUL for Global Health Status and Functional Scales. A negative difference between treatments favours ABE-FUL for Symptom scale items.
Source: Lilly Data on File (Global Health Outcomes Clinical Study Report Addendum P13)[73]

B.2.6.7 EQ-5D-5L

The method of administration and scoring of the EQ-5D-5L instrument is described in Table 5. EQ-5D-5L index values were similar between arms for all baseline and post-baseline assessments (Table 15). Overall, index values in most post-baseline assessments were stable and similar to baseline values for both treatment arms. The VAS demonstrated similar results as the index value; scores were similar between the two treatment arms for all baseline and post-baseline visits. These data support that the overall health status of patients was maintained throughout the study in both treatment arms.

It is further important to note that the HRQoL data observed in MONARCH 2 do not capture the delay in the detriment to QoL associated with initiating post-discontinuation chemotherapy treatment.

Table 15. Summary of EQ-5D-5L Index and Visual Analogue Scale by visit in MONARCH 2, safety population

	Baseline Score Mean (SD)		Within-treatment Group Change from Baseline[a] LS Mean (SE)		Between- treatment Group Change Difference (Abemaciclib vs Placebo)[a]	
	ABE-FUL	PBO-FUL	ABE-FUL	PBO-FUL	LS Mean (SE)[c]	p-Value[b]
Index value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visual analogue scale	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D 5L: EuroQol 5-Dimension 5-Level; LS: least squares; SE: standard error; SD: standard deviation
[a] Across all postbaseline visits. [b] p-Values are from Type 3 sums of squares mixed models repeated measures model: Change from baseline = Treatment + Visit + Treatment*Visit + Baseline. [c] A positive between treatment difference favours ABE-FUL.
Source: Lilly Data on File (Global Health Outcomes Clinical Study Report Addendum, P17) 2017[73]

B.2.7 *Subgroup analysis*

In order to evaluate the robustness of the analyses presented, subgroup analyses were performed for PFS and OS for each of the following potential prognostic factors:

- All baseline stratification factors:
    - Nature of disease (visceral metastases vs bone-only metastases vs other)
    - Sensitivity to endocrine therapy (primary resistance vs secondary resistance)

- Starting dose (200 mg vs 150 mg)
- Measurable disease at baseline (yes vs no)
- Number of organs involved (1 vs 2 vs 3+)
- Age (<65 years vs ≥65 years)
- Region (North America, Europe, Asia)
- Race (Caucasian, Asian, and Other)
- PgR status (positive vs negative)

The OS results for each pre-planned subgroup are not presented due to the immaturity of the data. The treatment effect of ABE-FUL on PFS was consistent across each pre-planned subgroup (detailed results for the subgroup analyses for PFS are provided in Appendix E).

B.2.8 *Meta-analysis*

Due to the identification of only one study evaluating the efficacy and safety of abemaciclib in the relevant patient population, no meta-analysis was performed.

B.2.9 *Indirect and mixed treatment comparisons*

Summary of indirect and mixed treatment comparisons

- A network meta-analysis (NMA) was conducted to compare the efficacy of interventions evaluated in patients comparable to the MONARCH 2 population using available data from randomised controlled trials (RCTs) identified in the SLR
- The reference treatment chosen for the analysis was fulvestrant 500 mg (FUL 500) and results are presented for ABE-FUL, exemestane (EXE) and everolimus plus exemestane (EVE-EXE), relative to FUL
- With regards to tamoxifen (TMX), a further relevant comparator, it was not possible to include this treatment in the NMA due to a lack of suitable evidence identified in the SLR. Evidence identified in the SLR for the MONARCH 3 indication for abemaciclib (in combination with an aromatase inhibitor), was therefore explored, which resulted in the identification of Milla-Santos (2001), which compared TMX to toremifene (TOR). An adjusted indirect comparison was subsequently conducted using Milla-Santos (2001) and the principal NMA to estimate relative treatment effects for TMX vs FUL 500
- The endpoints chosen for analysis were PFS, OS, ORR and CBR. For the NMA, CBR was defined as CR+PR+SD ≥6 months (the network included studies reporting CBR based on this definition)
- The hazard ratios (HRs) representing the treatment effects were synthesised using methodology obtained from Woods (2010)[56] for the NMA of survival endpoints (PFS and OS) and a logit link function for the binary endpoints (ORR and CBR)
- For PFS, ABE-FUL (HR [redacted]; 95% credible interval (CrI) [redacted]) and EVE-EXE (HR [redacted]; 95% CrI [redacted]) had lower hazard rates of progression or death compared to FUL 500. This treatment effect was significant for ABE-FUL compared to FUL 500 only. EXE (HR [redacted]; 95% CrI [redacted]) had a significantly higher hazard rate of progression or death compared to FUL 500
- ABE-FUL (HR [redacted]; 95% CrI [redacted]) had a lower hazard rate of death compared to FUL 500 but this treatment effect was not significant. No comparators showed a significant

treatment benefit compared to FUL 500. Due to the inclusion of immature OS data from the MONARCH 2 trial, uncertainty is introduced around the associated treatment effects

- For ORR, both ABE-FUL (OR [redacted]; 95% CrI [redacted]) and EVE-EXE (OR [redacted]; 95% CrI [redacted]) showed significantly higher odds of achieving an objective response compared to the reference treatment (FUL 500). There were no other significant differences between the treatments compared with FUL 500
- For CBR, ABE-FUL showed significantly higher odds (OR [redacted]; 95% CrI [redacted]) of achieving a clinical benefit compared to FUL 500. The OR for EVE-EXE was similar to ABE-FUL but did not reach significance (OR [redacted]; 95% CrI [redacted]). The OR for CBR was significantly lower for EXE (OR [redacted]; [redacted]) in comparison with FUL 500
- It was possible to generate treatment effects for TMX vs FUL 500 for OS and PFS/TTP (with equivalence assumed between these two endpoints) through the adjusted indirect comparison. For PFS/TTP, the HR for TMX vs FUL was [redacted] (95% CrI [redacted] to [redacted]). For OS, the HR for TMX vs FUL was [redacted] (95% CrI [redacted]).
- The results of the NMA support that the efficacy of ABE-FUL is at a minimum comparable to that of EVE-EXE, which is recommended by NICE as a post-ET treatment option. The results of the NMA and adjusted indirect comparison additionally support that ABE-FUL is more efficacious than EXE and TMX, which may be used for a small number of endocrine-resistant patients in the UK
- These results should be considered in light of heterogeneity across the included trials. The patient populations included in the NMA were broadly similar for a number of characteristics such as age, post-menopausal status and performance status. The MONARCH 2 trial addressed a very specific population, which differed from the majority of clinical trials evaluating treatments for advanced breast cancer patients that have progressed on or after ET. In all other comparator trials, prior chemotherapy and multiple rounds of prior ET were permitted. These patient populations may have been more heavily pre-treated than those in MONARCH 2. These factors could not be adjusted for in the analysis due to unavailability of subgroup data. Furthermore, due to the use of MONARCH 3 eligibility criteria to identify RCTs evaluating TMX, there is also likely to be heterogeneity between Milla-Santos (2001) and the other studies included in the NMA

B.2.9.1 Overview of the network meta-analysis

A SLR was conducted to identify relevant clinical evidence describing the efficacy and safety of abemaciclib plus fulvestrant [500 mg] (ABE-FUL) for locally advanced or metastatic HR+/HER2− breast cancer in patients who have progressed on or after prior ET, *i.e.* who are endocrine-resistant. It was known, and confirmed by the SLR, that there would be little published data available in a population directly comparable to MONARCH 2. The eligibility criteria for the SLR were broadened and allowed mixed populations to be included with regards to certain baseline characteristics (e.g. HR+ status, any number of ET and ≤1 chemotherapy in the advanced setting); increasing the variability across identified studies. The methodology and findings of the SLR are presented in Appendix D.

A NMA was conducted to synthesise efficacy estimates for relevant treatments used in patients comparable to the MONARCH 2 population for which data from RCTs were available, based on the studies identified by the SLR. Based on the requirements of the cost-effectiveness (CE) model and the findings of the NMA feasibility assessment, the following endpoints were analysed: PFS, OS, ORR and CBR. The NMA included all studies that met the inclusion criteria for the SLR, reported endpoint data for at least one endpoint assessed and connected to the

MONARCH 2 trial via common comparators between studies. As such, a broader network of treatments than required for this appraisal was constructed; the full network is presented in Figure 2, Appendix D1.3. For conciseness, only results for UK comparators relevant to this appraisal are presented here:

- ABE-FUL
- Exemestane (EXE)
- Everolimus plus exemestane (EVE-EXE)
- FUL 500

The reference treatment chosen for the analysis was FUL 500 as it is the comparator arm in the MONARCH 2 trial and allowed for the connection to other treatments in the network.

With regards to tamoxifen (TMX), another relevant UK comparator, it was not possible to include this treatment in the NMA. The only study identified in the SLR that investigated TMX and was aligned with the MONARCH 2 population was Stenbygaard (1993).[74] This study allowed for crossover of patients progressing on first-line toremifene (TOR) or TMX to second-line TMX or TOR, respectively. In order to align with the MONARCH 2 patient population, only efficacy data for second-line patients were extracted. PFS and OS data were not reported for the post-crossover period from this study. No data from the MONARCH 2 aligned review were identified to inform these clinical outcomes for TMX.

A SLR conducted for clinical evidence of the MONARCH 3 indication of abemaciclib (in combination with a non-steroidal aromatase inhibitor, for patients with HR+/HER2− locoregionally recurrent or metastatic breast cancer) had broad eligibility criteria, allowing for some potential overlap with the MONARCH 2 population. This allowed identification of studies investigating TMX, including Milla-Santos (2001), which compared TMX to TOR.[75] The patient population for this study included postmenopausal women with advanced breast cancer, and reported OS and time-to-progression (TTP). Patients were excluded if they had received previous systemic therapy for advanced breast cancer. The study permitted prior adjuvant ET. All other studies identified from the MONARCH 3 aligned SLR were either not considered to be comparable to the MONARCH 2 population or did not report OS and PFS/TTP. An adjusted indirect comparison was conducted using Milla-Santos (2001) and the principal NMA to estimate relative treatment effects for TMX vs FUL 500 mg for OS and PFS/TTP (assuming equivalence between the PFS and TTP endpoints). The results of the adjusted indirect comparison for the PFS and OS treatment effect between TMX and FUL 500 mg are provided in Table 16 in Section B.2.9.5.

Palbociclib plus FUL (PAL-FUL), anastrozole 1 mg (ANAS 1), anastrozole 10 mg (ANAS 10), letrozole 0.5 mg (LTZ 0.5) and letrozole 2.5 mg (LTZ 2.5) were included in the SLR and the NMA, as their respective trials met the inclusion criteria of the SLR and presented data for the chosen efficacy endpoints. However, as PAL-FUL has not yet been appraised by NICE, and anastrozole/letrozole are not considered to be relevant UK comparators for the MONARCH 2 patient population, results for PAL-FUL and ANAS/LTZ are not presented and these treatments were not included in the cost-effectiveness model. Megestrol 160 mg (MGA 160), MGA 800 mg (MGA 800) and TOR were similarly considered by clinicians not to be relevant UK comparators. FUL 250 is not a licensed dose in the UK but was included in the NMA to help connect the full network of comparators.

The NMA was conducted in accordance with International Society for Pharmacoeconomics and Outcomes Research Taskforce[76] using methodologies from or based on the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 2.[77] The time-to-event endpoints, OS and PFS, are traditionally analysed using a proportional hazards (PH) approach where the HR reported in the study is synthesised; using methodology obtained from Woods (2010).[56] The PH assumption was found to be upheld across the majority of the included studies, but violations in the assumption for OS were evident for the MONARCH 2 trial due to the immaturity of the data. The binary endpoints (ORR and CBR) were analysed using a logit link function as per the NICE DSU TSD.[77] Fixed and random effects models were conducted for each endpoint.

B.2.9.2 Results of the network meta-analysis

Nineteen studies met all of the criteria for inclusion in the NMA (eligibility criteria for the SLR, i.e. population, endpoints and study design) and were connected to the MONARCH 2 trial through FUL 500 (Table 20; Appendix D1.3). The base case results of the NMA are presented by endpoint: PFS, OS, ORR and CBR. Network diagrams for each endpoint are presented in Appendix D.

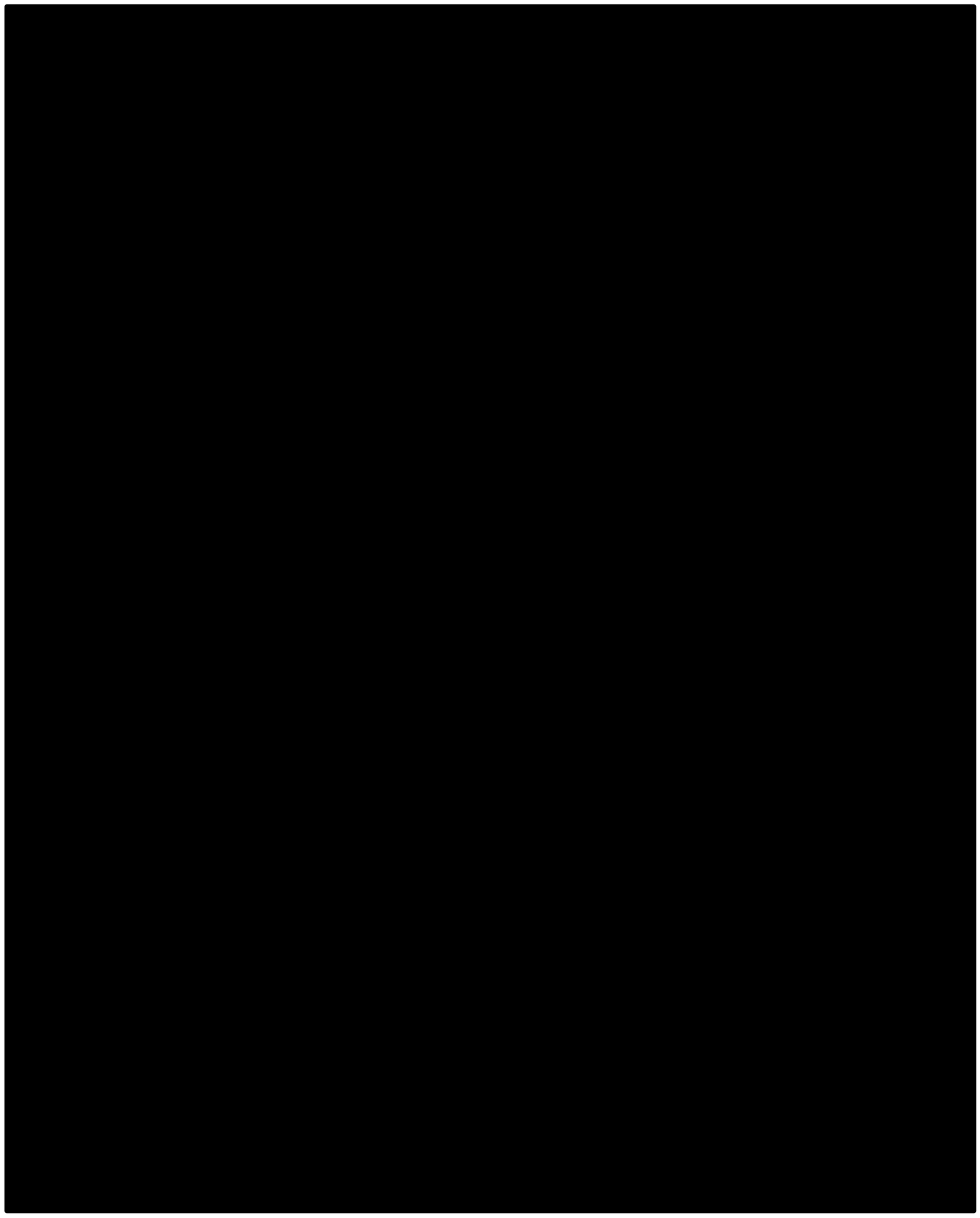
Both fixed effect (FE) and random effects (RE) models converged and there was no evidence of one model fitting better than another. For PFS, ORR and CBR endpoints, all results are presented for the RE model as this model can account for some heterogeneity between studies and provides a more conservative estimate of the relative treatment effect. For OS, FE model results are presented. Although the RE model converged for OS, there was evidence of the prior around the RE standard deviation dominating the posterior estimates. From a Bayesian analysis, the posterior estimates for each parameter are the model results, corresponding to a combination of the likelihood (data) and prior information. As per the NICE DSU guidance,[77] vague priors were used for the parameters and in this case the results were less informed by the study data compared to the prior distributions used.

PFS

Fourteen trials connected to form a network of evidence for PFS.

Figure 9 presents the forest plot for all treatments of interest to the submission compared to the reference treatment, FUL 500. HRs are presented with 95% credible intervals (CrI). ABE-FUL (HR [redacted]; 95% CrI [redacted]) and EVE-EXE (HR [redacted]; 95% CrI [redacted]) had lower hazard rates of progression or death compared to FUL 500. Only the treatment effect for ABE-FUL vs FUL 500 was significant. EXE (HR [redacted]; 95% CrI [redacted]) had a significantly higher hazard rate of progression or death compared to FUL 500.

Figure 9. Forest plot of treatment effects relative to FUL 500 mg for PFS using random-effects model

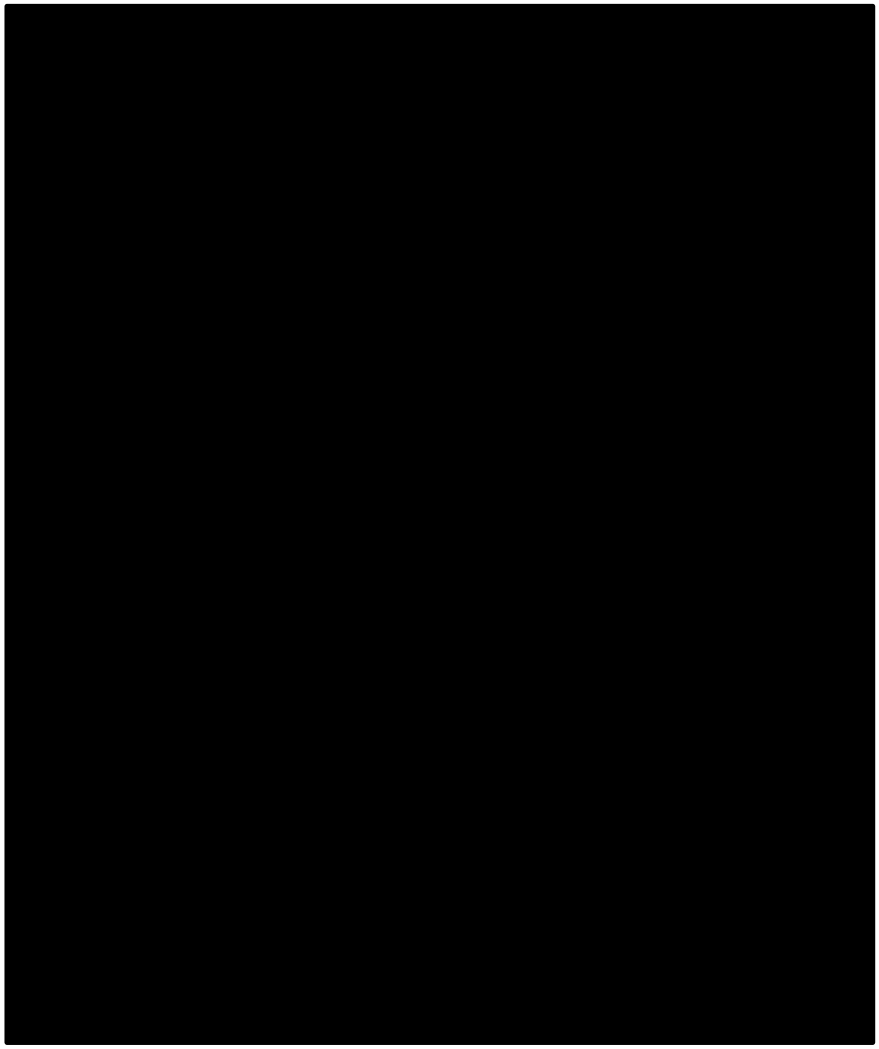


Footnotes: The results presented give the median of the posterior distributions as these are less skewed by outlying observations compared to the mean. FUL 250 is not a licensed dose in the UK but was included in the NMA to help connect the full network of comparators.
Abbreviations: ABE: abemaciclib; CrI: credible interval; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; mg: milligram; PFS: progression-free survival.

OS

Seventeen trials formed an evidence network for OS. Figure 10 presents the forest plot for all treatments of interest to this submission being compared to the reference treatment, FUL 500. No HR showed a significant treatment benefit compared to FUL 500. ABE-FUL (HR [redacted]; 95% CrI [redacted]) had a lower hazard rate of death compared to FUL 500 but this treatment effect was not significant. These results should be interpreted with caution as data from the MONARCH 2 trial were immature (i.e. less than 50% of the patients had died).

Figure 10. Forest plot of treatment effects relative to FUL 500 for OS using a fixed-effects model



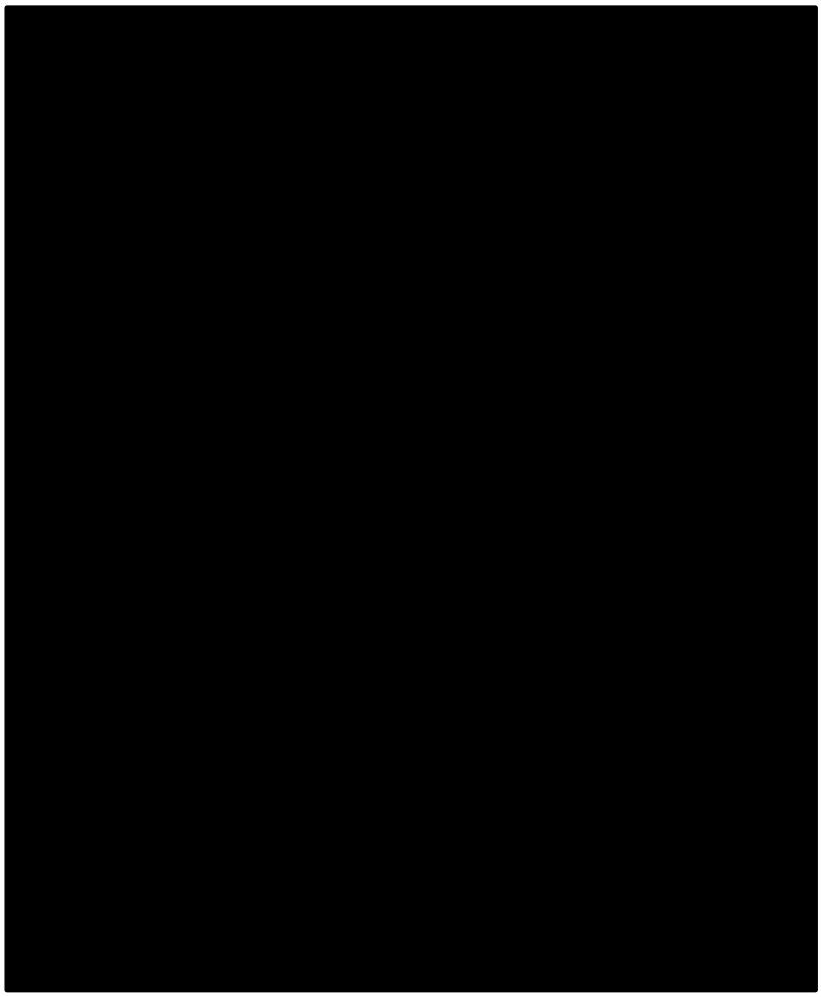
Footnotes: The results presented give the median of the posterior distributions as these are less skewed by outlying observations compared to the mean. FUL 250 is not a licensed dose in the UK but was included in the NMA to help connect the full network of comparators.
Abbreviations: ABE: abemaciclib; CrI: credible interval; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; OS: overall survival; PFS: progression-free survival.

ORR

Eighteen studies connected in a network of evidence for ORR. The results are presented as ORs (with 95% CrIs) in a forest plot (Figure 11). Only EVE-EXE (OR [redacted]; 95% CrI [redacted])

and ABE-FUL (OR [redacted]; 95% CrI [redacted]) showed significantly higher odds of achieving an objective response compared to the reference treatment (FUL 500). There were no other significant differences between the treatments compared to FUL 500.

Figure 11. Forest plot of treatment effects relative to FUL 500 for ORR using random-effects model

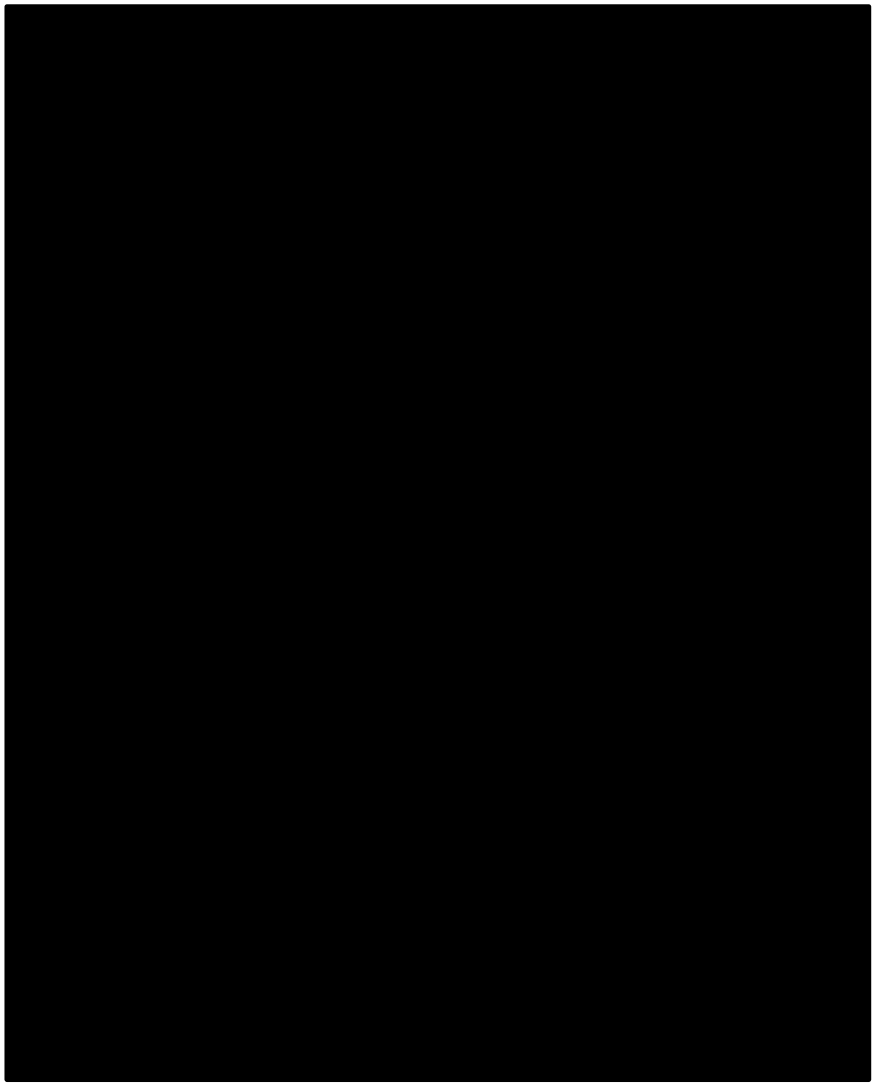


Footnotes: The results presented give the median of the posterior distributions as these are less skewed by outlying observations compared to the mean. FUL 250 is not a licensed dose in the UK but was included in the NMA to help connect the full network of comparators.
Abbreviations: ABE: abemaciclib; CrI: credible interval; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; PFS: progression-free survival.

CBR

Seventeen studies formed a connected network of evidence for CBR. A forest plot summarising the relative treatment effects compared to FUL 500 is presented in Figure 12. ABE-FUL (OR [redacted]; 95% CrI [redacted]) showed significantly higher odds of achieving a clinical benefit compared to FUL 500. The median OR for EVE-EXE was similar to ABE-FUL but did not reach significance (OR [redacted]; 95% CrI [redacted]). The OR of CBR for EXE (OR [redacted]; [redacted]) was significantly lower than FUL 500.

Figure 12. Forest plot of treatment effects relative to FUL 500 for CBR using random-effects model



Footnotes: The results presented give the median of the posterior distributions as these are less skewed by outlying observations compared to the mean. FUL 250 is not a licensed dose in the UK but was included in the NMA to help connect the full network of comparators.
Abbreviations: ABE: abemaciclib; CBR: clinical benefit rate; CrI: credible interval; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; PFS: progression-free survival.

Adjusted indirect comparison

The results of the adjusted indirect analysis comparing to TMX to FUL 500 is presented in Table 16.

Table 16. Adjusted indirect comparison results for TMX vs FUL 500 mg based on Milla-Santos 2001 and the NMA

	OS, HR (CrI)	PFS/TTP, HR (CrI)	Source
TOR vs TMX	[redacted]	[redacted]	Milla-Santos 2001[75]
TOR vs FUL 500 mg	[redacted]	[redacted]	NMA

	OS, HR (CrI)	PFS/TTP, HR (CrI)	Source
Adjusted indirect comparison TMX vs FUL 500 mg	[redacted]	[redacted]	

Abbreviations: CrI: credible interval; FUL: fulvestrant; HR: hazard ratio; NMA: network meta-analysis; OS: overall survival; PFS: progression-free survival; TOR: toremifene; TMX: tamoxifen.

B.2.9.3 Heterogeneity in the network meta-analysis

Overview

The patient populations were broadly similar for a number of characteristics, such as age, post-menopausal status and performance status. The MONARCH 2 trial assessed a very specific population (i.e. HR+/HER2− disease that progressed on [neo]adjuvant ET, ≤12 months after adjuvant ET or while receiving ET for ABC, and no prior chemotherapy permitted in the advanced setting), resulting in a degree of heterogeneity relative to other trials included in the analysis, as described below.

Methods and results of the assessment of heterogeneity

Prior to conducting the analyses, it was assessed whether there was any evidence of heterogeneity between trials based on differences in eligibility criteria and baseline characteristics. This involved a qualitative comparison of the criteria and baseline characteristics across the included studies. Clinical opinion was sought on the comparability of included studies and to identify potential treatment effect modifiers in the MONARCH 2 aligned population.

The eligibility criteria for studies included in the analysis (connected to the MONARCH 2 trial via common comparators) are presented in Table 17 of Appendix D1.2. The following characteristics were considered to be similar across studies:

- **Age**: mean and median age reported by arm ranged from 53.1 years to 66 years (mean) and 55 to 66.5 years (median) across the included studies.
- **Performance status**: >80% of patients in the study arms of the included studies were PS stage 0 or 1.
- **Post-menopausal status**: All studies included post-menopausal patients, except for Muss (1990) for which this was not reported.

A number of areas of heterogeneity were identified from a consideration of baseline characteristics in the studies:

- **Proportion of patients with visceral involvement**
    - Ranged from 13.5% to 100% of patients in each study arm of the included studies, where reported.
    - This characteristic was often not reported in the studies, and, where reported, the definitions were not consistent. Adjustments for differences in this characteristic were not considered feasible.

- **Number of prior chemotherapies and endocrine therapies received in the advanced setting**
    - MONARCH 2 included patients who received ≤ 1 prior endocrine therapy and no prior chemotherapy in the advanced setting.
    - In contrast, all of the included trials allowed for prior chemotherapy in the advanced setting and some studies allowed for more than one prior ET in the advanced setting.
    - Adjustments for these differences were considered:
        - Prior ET: no adjustment was considered feasible for the number of prior ETs in the advanced setting, as: i) the categories reported in the eligibility criteria (e.g. ≤1, ≤2, 'any' or not specified across the studies); ii) the proportions of patients reported to have received an ET in the advanced setting. Patients included in MONARCH 2 may have received prior ET in the (neo)adjuvant setting (with a DFI ≤12 months), therefore only considering the advanced setting does not provide a complete picture of the differences in prior ET exposure.
        - Prior chemotherapy: It was assessed whether subgroup data were available for patients who had received no prior chemotherapy in the advanced setting from the included studies. PALOMA 3 was the only study to report this with a connection to the MONARCH 2 trial, but this is not a relevant comparison.
- **HR+/HER2− status**
    - MONARCH 2 included patients with a HR+/HER2− status.
    - Details of the HR status were reported in all ET studies, and molecular subtype was commonly reported. However, there was considerable heterogeneity in how this was presented, such as percentage of participants with: "ER+ and PgR+", "ER+ or PgR+", or more vague descriptions denoted by "ER+ and/or PgR+" or simply grouping as ER+ with no details of whether the patients are ER+PgR+ or ER+PgR−.
    - HER2 status was not commonly reported prior to ASCO recommendations for HER2 testing in 2007 and, as such, studies where HER2 status was not reported were not excluded. Two studies that met the inclusion criteria also specified the inclusion of a small proportion of participants with HER2+ status: Yamamoto (2013; 2.2%) and Johnston (2013; 7.7%).
    - It was also assessed whether subgroup data for a HR+/HER2− population were available from the included studies. With the exception of PALOMA 3 which is not a relevant comparison, this was not identified in any other study.

B.2.9.4 Sensitivity Analyses

No sensitivity analyses were deemed feasible to perform due to lack of available subgroup data for the relevant comparators.

B.2.9.5 Uncertainties in the indirect and mixed treatment comparisons

The following factors are considered to be uncertainties in the NMA:

- There was substantial heterogeneity in the patient populations of the included trials, particularly in regard to treatment with prior chemotherapy or prior ET

- Data for OS were immature (i.e. less than 50% of the patients had died) in the MONARCH 2 study
- The BOLERO-2 trial included patients that were refractory to either LTZ or ANAS (i.e. patients had previously received an aromatase inhibitor), and based on clinical opinion this could have overestimated the benefit of EVE-EXE relative to EXE by potentially biasing against the control arm
- To generate a relative treatment effect for TMX vs FUL 500, an adjusted indirect comparison using Milla-Santos (2001) and NMA was performed. Milla-Santos (2001) was identified through use of the eligibility criteria for the MONARCH 3 SLR of RCTs, and, whilst Milla-Santos (2001) did permit patients who had received prior ET, it is likely that there was some heterogeneity between this study and other trials included in the NMA. This heterogeneity should be considered upon interpreting the results.

B.2.9.6 Conclusions

ABE-FUL was the only relevant comparator that had a significantly lower hazard rate of disease progression or death relative to FUL 500. EXE had a significantly higher hazard rate of progression or death compared with FUL 500 (HR [redacted]; 95% CrI [redacted]) suggesting that this treatment is not beneficial for endocrine-resistant patients over treatment with FUL. In terms of OS, no comparators showed a significant treatment benefit compared to FUL 500. Due to the inclusion of immature OS data from the MONARCH 2 trial, uncertainty is introduced around the associated treatment effects. For ORR, only ABE-FUL and EVE-EXE showed significantly higher odds of a response compared to FUL 500, and for CBR, the treatment effect was significantly favourable for ABE-FUL only. The CBR was significantly lower than FUL 500 for all other comparators. The adjusted indirect comparison identified that TMX was associated with a greater risk of progression or death versus FUL 500 (as assessed through PFS/TTP), and a lower risk of death (as assessed through OS); neither result was statistically significant.

These results support that the efficacy of ABE-FUL is at a minimum comparable to EVE-EXE, which is recommended by NICE specifically as an option for patients after ET.[78] The findings of the NMA and adjusted indirect comparison also suggest that ABE-FUL has superior efficacy compared to other treatments that may be used for a small number of endocrine-resistant patients in the UK, including EXE, FUL and TMX.

B.2.10 *Adverse reactions*

Summary of safety and tolerability of abemaciclib

- Safety was assessed in the safety population, which included all 664 randomised and treated patients who received at least one dose of study drug
- In the safety population, most patients (98.6%) in the ABE-FUL arm (N=441) and 89.2% of patients in the PBO-FUL arm (N=223) had ≥1 TEAE during the study, with [redacted] and [redacted] considered to be related to study treatment, respectively
- The incidence of Grade ≥3 TEAEs was higher in the ABE-FUL arm ([redacted]) than in the control arm ([redacted])
- The most frequent TEAEs reported by the investigator in the ABE-FUL arm were diarrhoea, neutropenia, nausea, fatigue and abdominal pain
- In the ABE-FUL arm, 86.4% of patients experienced diarrhoea, although the majority of events were mild in severity ([redacted] at Grade 1, [redacted] at Grade 2)
- A smaller proportion of patients experienced Grade 3 diarrhoea (13.4%), with no patients reporting Grade 4 events in the ABE-FUL arm
- Diarrhoea was manageable with anti-diarrhoeal medications in the majority of cases, most commonly using loperamide ([redacted]). Higher-grade diarrhoea occurred in the first few treatment cycles and was manageable with standard doses of anti-diarrhoeal agents, dose omissions, and/or dose reductions. The majority of patients (70.1%) with diarrhoea did not require any treatment modification
- A small proportion of patients (2.9%) in the ABE-FUL arm discontinued study treatment because of diarrhoea ([redacted] discontinued ABE but continued to receive FUL, and [redacted] of patients discontinued treatment with ABE-FUL), suggesting that this TEAE was manageable and acceptable[8]
- The incidence of diarrhoea and the proportion of patients who discontinued treatment due to diarrhoea, were higher in patients who received the starting dose ABE 200 mg than those who started treatment on 150 mg ABE
- Grade 3 neutropenia was reported for 23.6% of patients in the ABE-FUL arm compared to 1.3% of patients in the PBO-FUL arm. A small proportion of patients had Grade 4 neutropenia (2.9%) in the ABE-FUL arm, with 0.4% of patients reporting grade 4 neutropenia in the PBO-FUL arm. Febrile neutropenia was uncommon in patients treated with ABE-FUL (1.4%) and was not associated with severe infection
- Only [redacted] of patients discontinued treatment with ABE due to neutropenia, indicating that this was manageable
- TEAEs in the infection and infestations system organ class (SOC) were experienced by 42.6% of patients in the ABE-FUL arm and 24.7% of patients in the PBO-FUL arm
- SAEs were more frequent in the ABE-FUL group than in the PBO-FUL group (22.4 vs 10.8%, respectively). The most common SAEs were embolism (2.0%; ABE-FUL) and pleural effusion ([redacted]; PBO-FUL arm)
- The discontinuation rate for all study treatment due to AEs was [redacted] (ABE-FUL) and [redacted] (PBO-FUL arm). Of the patients who received a starting dose of 200 mg (N=121), a higher proportion discontinued any study drug due to an AE ([redacted]), compared with patients who received a starting dose of 150 mg abemaciclib ([redacted], N=320), demonstrating that ABE-FUL is more tolerable at the 150 mg dose of abemaciclib
- Deaths due to TEAEs during the study or within 30 days of treatment discontinuation were reported for nine patients in the ABE-FUL arm and two patients in the PBO-FUL arm. Of these, three deaths in the ABE arm were determined to be related to the study treatment

- Overall, ABE-FUL demonstrated a tolerable safety profile

B.2.10.1 Safety results informing the decision problem

The safety of ABE-FUL in women with HR+/HER2− locally advanced or metastatic breast cancer was evaluated in the MONARCH 2 trial. All 664 randomised and treated patients who received at least one dose of study drug were included in the safety analyses as the safety population (n = 441 [ABE] and n = 223 [PBO]). All patients in the safety population received ABE or PBO daily on a continuous schedule, plus FUL (on Days 1 and 15 of Cycle 1, then on Day 1 from Cycle 2 and beyond). In the ABE-treated safety population, the majority of the patients (320 of 441 patients, 72.5%) received ABE at the 150-mg starting dose. The remaining 121 patients (27.5%) were enrolled prior to the dose amendment and received ABE at the 200-mg starting dose. Of these 121 patients, [redacted] patients discontinued prior to having their dose reduced to 150 mg, which represents approximately [redacted] of the ABE population. The remaining [redacted] patients had their dose reduced to 150 mg due to treatment-emergent adverse events (TEAEs) or dose amendment. Patients enrolled prior to the dose amendment received a median of [redacted] days of 200 mg ABE.

In terms of exposure, the median number of cycles of ABE received per patient was 15 cycles, with a median dose intensity of 273.1 mg/day (relative median dose intensity, 91%). Median duration of therapy was [redacted] weeks in the ABE-FUL arm and [redacted] weeks in the PBO-FUL arm.

The safety of ABE-FUL was evaluated through the assessment of TEAEs; TEAEs leading to dose adjustments, omissions, or discontinuation of ABE; TEAEs leading to deaths; or adverse events of special interest. Clinical laboratory results, vital signs, and electrocardiograms (ECGs) were also performed to assess safety.

TEAEs were classified and graded for severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. For TEAEs without matching terminology within the National Cancer Institute CTCAE version 4.0 criteria, the investigator was responsible for selecting the appropriate system organ class (SOC) and assessing severity grade based on the intensity of the event.

B.2.10.2 Treatment-emergent adverse events

Summary

A summary of TEAEs reported in the safety population during the study is available in Table 17. During the study period, a total of 634 patients (95.5%) experienced at least one TEAE, including 435 patients (98.6%) in the ABE-FUL arm and 199 patients (89.2%) of patients in the PBO-FUL arm, with [redacted] and [redacted] considered to be related to study treatment, respectively.

The incidence of treatment-related Grade ≥3 TEAEs (as judged by the investigator) was greater in the ABE-FUL arm than in the PBO-FUL arm (Table 17).

Table 17. Overall summary of adverse events in each arm of MONARCH 2, safety population

Number of Patients	ABE-FUL N=441	PBO-FUL N=223
Patients with ≥1 TEAE	435 (98.6)	199 (89.2)
Related to study treatment	[redacted]	[redacted]
Patients with ≥1 CTCAE ≥ Grade 3 TEAE	[redacted]	[redacted]
Related to study treatment	[redacted]	[redacted]
Patients with ≥1 SAE	99 (22.4)	24 (10.8)
Related to study treatment	[redacted]	[redacted]
Patients who discontinued study treatment due to an AE	[redacted]	[redacted]
Related to study treatment	[redacted]	[redacted]
Patients who discontinued study treatment due to an SAE	[redacted]	[redacted]
Related to study treatment	[redacted]	[redacted]
Patients who died due to an AE on study treatment	[redacted]	[redacted]
Related to study treatment	[redacted]	[redacted]
Patients who died due to an AE within 30 days of discontinuation from study treatment	[redacted]	[redacted]
Related to study treatment	[redacted]	[redacted]

Abbreviations: AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; N: number of patients in the safety population; n: number of patients in the specified category; SAE serious adverse events;
Source: Lilly Data on File (Clinical Study Report). 2017[35]

Most frequent TEAEs

A summary of TEAEs experienced by ≥10% of patients by CTCAE Grade in order of decreasing frequency is presented in Table 18. In the ABE-FUL arm, the most frequently reported TEAEs of any grade were diarrhoea (86.4%), neutropenia (46.0%), nausea (45.1%) and fatigue (39.9%) (Table 18). Except for neutropenia (grade 3; 23.6%), these were predominately low-grade in severity. A summary of key safety data regarding the TEAEs of diarrhoea and neutropenia for patients by starting dose of abemaciclib is presented in Table 19. In the PBO-FUL arm, the most frequently reported TEAEs of any grade were diarrhoea (24.7%), nausea (22.9%) and fatigue (26.9%).

Diarrhoea was the most common TEAE reported for patients in the ABE-FUL arm. Diarrhoea was predominantly of low grade in the ABE-FUL arm, experienced by 13.4% and 0% of patients at grades 3 and 4, respectively.[8] The median time to onset of the first diarrhoea was 6 days and the median duration was [redacted] days for Grade 2 and [redacted] days for Grade 3 events. Diarrhoea was manageable with anti-diarrhoeal medications; [redacted] patients ([redacted]) with Grade 1, [redacted] patients ([redacted]) with Grade 2, and [redacted] patients ([redacted]) with Grade 3 diarrhoea reported anti-diarrhoeal medication use, most commonly loperamide ([redacted]). Higher-grade diarrhoea occurred in the first few treatment cycles and in addition to anti-diarrhoeal use, was manageable with dose omissions, and/or dose reductions, however the majority of patients (70.1%) with diarrhoea did not require any treatment modification. A small proportion of patients (2.9%) in the ABE-FUL arm discontinued study treatment because of diarrhoea ([redacted] discontinued ABE but continued to receive FUL, and [redacted] of patients discontinued treatment with ABE-FUL), suggesting that this TEAE was manageable and acceptable.[8] Of those receiving PBO-FUL, 24.7% of patients experienced diarrhoea; [redacted] of cases were defined as grade 1 or 2, with only one patient (0.4%) experiencing Grade 3 diarrhoea (Table 18).

With regards to starting dose of abemaciclib in the ABE-FUL arm, the incidence of Grade 2 or 3 diarrhoea was higher in patients who received the 200 mg abemaciclib starting dose (Grade 2 [redacted]; Grade 3 [redacted]), compared with patients who started on 150 mg abemaciclib (Grade 2 [redacted], Grade 3 [redacted]). Furthermore, a higher proportion of patients who received the abemaciclib 200 mg starting dose discontinued study treatment due to diarrhoea ([redacted]) compared with patients who received a starting dose of 150 mg ([redacted]).

Neutropenia was experienced as a TEAE by 203 patients (46.0%) treated with ABE-FUL and nine patients (4.0%) treated with PBO-FUL. Of the patients in the ABE-FUL arm who experienced neutropenia, 23.6% and 2.9% reported Grade 3 and Grade 4 events, respectively. A small number of patients treated with ABE-FUL ([redacted] patients, [redacted]) discontinued any study drug due to neutropenia. The median time to onset of Grade 3 or 4 neutropenia was [redacted] days for ABE-FUL and [redacted] days for PBO-FUL. For patients in the ABE-FUL arm who were still on treatment and had not experienced Grade 3 or 4 neutropenia within the first three treatment cycles, few patients ([redacted] patients; [redacted]) experienced a Grade 3 or 4 event during the rest of the study. Furthermore, only [redacted] of patients discontinued treatment with ABE due to neutropenia, indicating that this TEAE was manageable. Febrile neutropenia was reported in only six patients treated with ABE-FUL (1.4%). [redacted] patients ([redacted]) experienced grade 3 febrile neutropenia although these events were not associated with severe infection, and one patient (0.2%) experienced Grade 4 febrile neutropenia during the long-term follow-up period after discontinuation of ABE (and had received post-discontinuation therapy with paclitaxel [PAC]).[8] Only [redacted] of the febrile neutropenia events were SAEs. Afebrile neutropenia was miscoded as febrile neutropenia for one patient in the ABE-FUL arm.[8] In regard to starting dose of ABE, as shown in Table 19, the incidence of neutropenia and the proportion of patients who discontinued treatment due to neutropenia, were higher in the pre-amendment population (starting dose ABE 200 mg) than the post-amendment population (starting dose 150 mg ABE).

Nausea in both treatment arms was primarily low grade, with only 2.7% and 0.9% of patients experiencing Grade 3 nausea in the ABE-FUL and PBO-FUL arms, respectively. Fatigue was also predominantly mild in severity and was similar between patients treated with ABE-FUL (2.7% at Grade 3) and PBO-FUL (0.4% at Grade 3).

TEAEs in the infection/infestations SOC were experienced by 42.6% of patients in the ABE-FUL arm and 24.7% of patients in the PBO-FUL arm. These events were predominantly of grade 1 to 2 severity; 6.6% of patients in the ABE-FUL arm and 3.6% of patients in the PBO-FUL arm experienced grade ≥3 events.[8] The most frequent (>5%) TEAEs in the infection and infestations SOC were upper respiratory tract infection ([redacted]) and urinary tract infection ([redacted]) in the ABE-FUL arm, and upper respiratory tract infection ([redacted]) in the PBO-FUL arm. There does not appear to be a relationship between severe neutropenia and the occurrence of infection in the MONARCH 2 study.[8]

Table 18. Treatment-emergent adverse events by maximum CTCAE grade experienced by ≥10% of population of either arm of MONARCH 2, safety population

Preferred Term	ABE-FUL N=441					PBO-FUL N=223				
	CTCAE Grade									
	Grade 1	Grade 2	Grade 3	Grade 4	All	Grade 1	Grade 2	Grade 3	Grade 4	All
Patients with ≥1 TEAE, n (%)	[redacted]	[redacted]	241 (54.6)	26 (5.9)	435 (98.6)	[redacted]	[redacted]	46 (20.6)	5 (2.2)	199 (89.2)
Diarrhoea	[redacted]	[redacted]	59 (13.4)	0	381 (86.4)	[redacted]	[redacted]	1 (0.4)	0	55 (24.7)
Neutropenia	[redacted]	[redacted]	104 (23.6)	13 (2.9)	203 (46.0)	[redacted]	[redacted]	3 (1.3)	1 (0.4)	9 (4.0)
Nausea	[redacted]	[redacted]	12 (2.7)	NA	199 (45.1)	[redacted]	[redacted]	2 (0.9)	NA	51 (22.9)
Fatigue	[redacted]	[redacted]	12 (2.7)	NA	176 (39.9)	[redacted]	[redacted]	1 (0.4)	NA	60 (26.9)
Abdominal pain	[redacted]	[redacted]	11 (2.5)	0	156 (35.4)	[redacted]	[redacted]	2 (0.9)	0	35 (15.7)
Anaemia	[redacted]	[redacted]	31 (7.0)	1 (0.2)	128 (29.0)	[redacted]	[redacted]	2 (0.9)	0	8 (3.6)
Leukopenia	[redacted]	[redacted]	38 (8.6)	1 (0.2)	125 (28.3)	[redacted]	[redacted]	0	0	4 (1.8)
Decreased appetite	[redacted]	[redacted]	5 (1.1)	0	117 (26.5)	[redacted]	[redacted]	1 (0.4)	0	27 (12.1)
Vomiting	[redacted]	[redacted]	4 (0.9)	0	114 (25.9)	[redacted]	[redacted]	4 (1.8)	0	23 (10.3)
Headache	[redacted]	[redacted]	3 (0.7)	NA	89 (20.2)	[redacted]	[redacted]	1 (0.4)	NA	34 (15.2)
Dysgeusia	[redacted]	[redacted]	0	0	79 (17.9)	[redacted]	[redacted]	0	0	6 (2.7)
Alopecia	[redacted]	[redacted]	NA	NA	69 (15.9)	[redacted]	[redacted]	NA	NA	4 (1.8)
Thrombocytopenia	[redacted]	[redacted]	9 (2.0)	6 (1.4)	69 (15.6)	[redacted]	[redacted]	0	1 (0.4)	6 (2.7)

Preferred Term	ABE-FUL N=441					PBO-FUL N=223				
	CTCAE Grade									
	Grade 1	Grade 2	Grade 3	Grade 4	All	Grade 1	Grade 2	Grade 3	Grade 4	All
Stomatitis	[redacted]	[redacted]	2 (0.5)	0	67 (15.2)	[redacted]	[redacted]	0	0	23 (10.3)
Constipation	[redacted]	[redacted]	3 (0.7)	0	60 (13.6)	[redacted]	[redacted]	1 (0.4)	0	30 (13.5)
ALT increased	[redacted]	[redacted]	17 (3.9)	1 (0.2)	59 (13.4)	[redacted]	[redacted]	4 (1.8)	0	12 (5.4)
Cough	[redacted]	[redacted]	0	0	59 (13.4)	[redacted]	[redacted]	0	0	25 (11.2)
Pruritus	[redacted]	[redacted]	0	0	57 (12.9)	[redacted]	[redacted]	0	0	13 (5.8)
Dizziness	[redacted]	[redacted]	3 (0.7)	0	55 (12.5)	[redacted]	[redacted]	0	0	13 (5.8)
AST increased	[redacted]	[redacted]	10 (2.3)	0	54 (12.2)	[redacted]	[redacted]	6 (2.7)	0	15 (6.7)
Blood creatinine increased	[redacted]	[redacted]	4 (0.9)	0	52 (11.8)	[redacted]	[redacted]	0	0	1 (0.4)

Abbreviations: ABE-FUL: abemaciclib plus fulvestrant; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CTCAE: Common Terminology Criteria for Adverse Events; NA: not applicable per CTCAE; N: number of patients in the safety population; n: number of patients in the specified category; PBO-FUL: placebo plus fulvestrant; TEAE: treatment-emergent adverse event.
Source: Sledge et al. 2017,[8] Lilly Data on File (Clinical Study Report P142). 2017[35]

Table 19. Key safety results by pre-amendment and post-amendment populations

	Pre-amendment Population	Post-amendment Population	Intent-to-treat Population	
	ABE 200 mg (N=121)	ABE 150 mg (N=320)	ABE-FUL (N=441)	PBO-FUL (N=223)
Incidence of diarrhoea				
Grade 2, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Incidence of neutropenia				
Grade 3, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Grade 4, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Dose reductions due to TEAEs (%)	[redacted]	[redacted]	[redacted]	[redacted]
Dose reduced due to diarrhoea (%)	[redacted]	[redacted]	[redacted]	[redacted]
Dose reduced due to neutropenia (%)	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued any study drug due to AE (%)	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued due to diarrhoea (%)	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued due to neutropenia (%)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABE: abemaciclib; ABE-FUL: abemaciclib plus fulvestrant; AE: adverse event; mg: milligram; PBO-FUL: placebo plus fulvestrant.
Source: Lilly Data on File (Clinical Study Report P218). 2017.[35]

Serious adverse events

The incidence of SAEs was higher in the ABE-FUL arm (22.4%) compared to the PBO-FUL arm (10.8%; Table 20). The most frequently reported SAEs for ABE-FUL-treated patients were embolism (9 patients [2%]) and diarrhoea ([redacted] [redacted]/441], whilst pleural effusion ([redacted] [redacted]/223]) and dyspnea ([redacted] [redacted]/223]) were most common for PBO-FUL-treated patients. In the ABE-FUL arm, 39 patients (8.8%) experienced SAEs relating to study treatment as assessed by the investigator, compared with three patients (1.3%) in the PBO-FUL arm. The most frequent treatment-related SAE was diarrhoea (1.4% in the ABE-FUL arm vs 0% in the PBO-FUL arm).[8]

Table 20. Treatment-emergent serious adverse events occurring in ≥1% of patients in either arm of MONARCH 2, safety population

Preferred Term Reported Term	ABE-FUL N=441 n (%)	PBO-FUL N=223 n (%)
Patients with ≥1 serious adverse event	99 (22.4)	24 (10.8)
Embolism	9 (2.0)	1 (0.4)
Pulmonary embolism	[redacted]	[redacted]
DVT	[redacted]	[redacted]
Acute DVT of inferior vena cava	[redacted]	[redacted]
Pulmonary thromboembolism	[redacted]	[redacted]
Cerebral venous sinus thrombosis	[redacted]	[redacted]
Cerebral infarction	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Lung infection	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Lung infection	[redacted]	[redacted]
Bilateral pneumonia	[redacted]	[redacted]
Community-acquired bacterial pneumonia	[redacted]	[redacted]
Cryptogenic organizing pneumonia	[redacted]	[redacted]
Dyspnea	[redacted]	[redacted]
Dyspnea[a]	[redacted]	[redacted]
Shortness of breath[a]	[redacted]	[redacted]
Persistent cough	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Septic shock	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Intra-abdominal sepsis	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Abdominal pain secondary to cecal volvulus	[redacted]	[redacted]
Pain: abdominal	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]
Large left pleural effusion	[redacted]	[redacted]
Left hydrothorax	[redacted]	[redacted]
Bilateral pleural effusions	[redacted]	[redacted]

Abbreviations: ABE-FUL: abemaciclib plus fulvestrant; DVT: deep vein thrombosis; N: number of patients in the population; n: number of patients with a serious adverse event; PBO-FUL: placebo plus fulvestrant.
Source: Lilly Data on File (Clinical Study Report P153). 2017[35]

AEs leading to discontinuation of study treatment

In the ABE-FUL arm, [redacted] of patients discontinued all study treatment due to an AE, compared to [redacted] in the PBO-FUL arm. The TEAEs that led to discontinuation of treatment in the ABE-FUL arm were diarrhoea ([redacted]), sepsis ([redacted]), lung infection, drug-induced liver injury, muscular weakness and pneumonitis (each [redacted]). TEAEs leading to discontinuation in the PBO-FUL arm included an increase in blood markers, such as alanine aminotransferase ([redacted]) and aspartate

aminotransferase ([redacted]). Approximately [redacted] percent ([redacted]) of ABE-FUL treated patients discontinued study treatment due to an SAE, compared with [redacted] in the PBO-FUL arm.

The proportion of patients who discontinued any study treatment (ABE, FUL, or both) due to an AE in the ABE-FUL arm was [redacted] (n=[redacted]), in comparison with [redacted] of patients in the PBO-FUL arm (n=[redacted]) (Table 19). For patients whose starting dose of ABE was 150 mg (N=320), [redacted] discontinued any study treatment due to an AE, compared with [redacted] of those who received a starting dose of 200 mg ABE before the mandatory dose-reduction amendment (N=121).

Patient deaths

Overall, there were 14 deaths (3.2%) in the ABE-FUL arm and 10 deaths (4.5%) in the PBO-FUL arm that occurred during treatment or within 30 days of treatment discontinuation.[8] Of these, nine and two patient deaths were reported to be due to TEAEs in the ABE-FUL and PBO-FUL arms, respectively.[8] Of these patient deaths, [redacted] deaths ([redacted]) in the ABE-FUL arm and [redacted] ([redacted]) in the PBO-FUL arm were reported to be due to TEAEs whilst on study treatment, whilst three patients (0.7%) and [redacted] patient ([redacted]) died due to an TEAE within 30 days of treatment discontinuation, respectively.[8] Of these, three deaths (0.7%) in the ABE-FUL arm were determined to be related to study treatment; two resulted from sepsis in patients in whom guidance regarding granulocyte colony-stimulating factor administration and dose reduction was not followed, and one death was due to viral pneumonia in a patient receiving steroids for spinal stenosis.[8]

B.2.11 *Ongoing studies*

- JPBL (MONARCH 2): Follow-up for overall survival is still ongoing, and the estimated data cut-off is April 2019. The estimated study completion date is February 2020.
- JPBM (MONARCH 3): A phase III, randomised, double-blinded, placebo-controlled study evaluating the efficacy and safety of abemaciclib plus NSAI (anastrozole or letrozole) against placebo plus NSAI in postmenopausal women with HR+/HER2− locoregionally recurrent or metastatic breast cancer who have not received prior systematic therapy in the advanced setting. The primary outcome measure is PFS, with OS, ORR, DoR, CBR and HRQoL as secondary outcomes. Follow-up for overall survival is still ongoing, and the estimated data cut-off is May 2020. The estimated study completion date is July 2021. Abemaciclib for this indication is being evaluated as part of a separate NICE appraisal.[1]
- JPBN (MONARCH 1): A phase II, single arm study evaluating abemaciclib as a monotherapy in patients with previously treated HR+/HER2− metastatic breast cancer. The primary outcome measure is ORR, with OS, DOR, PFS, DCR, CBR, pain intensity, pharmacokinetics and HRQoL (EORTC QLQ-C30) as secondary outcomes. The estimated study completion date is October 2018.
- JPBZ (monarcHER): A phase II, randomised, three-arm, open-label study, evaluating the effectiveness of abemaciclib plus trastuzumab with or without fulvestrant or chemotherapy in women with HR+/HER2+ locally advanced or metastatic breast cancer, after prior exposure to at least two HER2-directed therapies for advanced disease. The primary endpoint is PFS, with OS, ORR, DoR, CBR and HRQoL measures as secondary outcomes. The study is active but not recruiting, with 225 participants. The expected study completion date is February 2021.[79]

- JPCF (monarchE): A Phase III, randomised, open-label study, evaluating the safety and efficacy of abemaciclib combined with standard adjuvant ET versus standard adjuvant ET alone, in patients with high risk, node positive, early stage, HR+, HER2− breast cancer. The study is currently recruiting with an estimated study complete date of June 28th 2027.[80]

B.2.12 *Innovation*

As HR+/HER2− locally advanced or metastatic breast cancer remains incurable, there remains a need to continue to improve patient survival and maintain HRQoL. These goals of treatment can be addressed by delaying disease progression and the need for treatment with chemotherapy. ABE-FUL has proven to be an efficacious treatment with a tolerable safety profile in the MONARCH 2 study. ABE addresses the need for alternative treatment options for ET resistant patients whose treatment options would otherwise often included toxic chemotherapy regimens, offering considerable improvements in PFS to those that progress on or after the completion of ET.

ABE-FUL is effective, significantly improving PFS and ORR in women with HR+/HER2− advanced breast cancer who have progressed on or after ET

The median PFS of 16.4 months and the 7.2-month improvement over control therapy observed in patients who received ABE-FUL represents the longest PFS reported in a population with advanced breast cancer whose disease had progressed on or after ET.[8]

Improved PFS delays the need for chemotherapy, which is the recommended treatment following failure of options for ET resistance. ABE-FUL was found to significantly delay the time to post-discontinuation chemotherapy compared with PBO-FUL in a *post hoc* exploratory analysis of MONARCH 2 (HR 0.65; p<0.01). This delay is an important benefit to clinicians and patients, as chemotherapy regimens are associated with high toxicity, often requiring regular clinical review and blood monitoring, which may negatively affect the HRQoL of patients and has additional health economic implications.[81] An adverse effect on HRQoL was demonstrated in a cross-sectional study of women with breast cancer in which a significant difference in depression, unmet sexual needs, breast-cancer specific concerns, and physical and mental well-being was observed among breast cancer patients receiving chemotherapy compared with those not receiving chemotherapy.[82] The burden of chemotherapy treatment that extends beyond the patient to caregivers should also be considered. Compared with patients receiving ET, significantly more patients receiving chemotherapy needed someone to accompany them to and from treatment, and provide additional care due to the potential toxicity burden.[30]

The addition of ABE to FUL significantly improved ORR (48.1% vs 21.3%), which included 14 patients in the ABE-FUL arm experiencing a CR, compared to one in the PBO-FUL arm. Tumour size reduction was more pronounced in the abemaciclib arm, and tumour response was durable.[8] Considering currently available knowledge, the ORR achieved in patients who received ABE-FUL is the highest observed in a phase III study of patients whose disease had progressed while they were receiving prior ET.[8] It is not common for ET-based treatment to promote tumour shrinkage following progression on prior ET, for example fulvestrant and anastrozole offered no advantage over anastrozole alone in patients previously exposed to ET.[83] Clinical opinion sought by Lilly reported that improved tumour response rate and reductions in tumour size allows for the relief of symptoms such as poor energy levels and pain, and may additionally reduce the need for health interventions such as analgesia, helping patients to maintain their QOL. Furthermore, by

prolonging the response of the tumour to treatment and inducing shrinkage, the burden of disease in later lines of therapy will be lower.

The addition of abemaciclib to the fulvestrant backbone offers novel potential for preventing disease progression in women with HR+/HER2− advanced breast cancer, who have previously progressed on or after ET. For these patients there are few treatment alternatives, most with high toxicity.

ABE-FUL was able to address prior ET resistance, demonstrated through improvements in PFS without adversely affecting HRQoL

Patients included in the MONARCH 2 study had received prior endocrine therapy and had either relapsed or progressed with primary or secondary ET. Approximately a quarter of enrolled patients (25.3%) had primary resistance (24.9% for ABE-FUL, 26.0% for PBO-FUL), defined as relapse in the first two years of adjuvant ET or progression whilst receiving the first 6 months of ET in the locally advanced or metastatic setting. Most (73.1%) patients entered the study with secondary ET resistance (those who relapsed on adjuvant therapy after the first two years or within 12 months of completion, or progressed after ≥6 months of ET for metastatic BC). Abemaciclib and fulvestrant in combination provide two novel mechanisms of action for the treatment of ET-resistant disease; other treatment options for these patients include at least one drug which has a mechanism previously deployed in the breast cancer treatment pathway. For example, switching from letrozole to exemestane (with everolimus), involves the use of another aromatase inhibitor. In contrast, a switch to abemaciclib (selective CDK4 inhibitor) and fulvestrant (SERD) provides a novel mechanism for delaying the evolution of drug-resistant disease, thereby extending the interval of clinical drug sensitivity.

ABE-FUL was efficacious in this patient population by offering a significant improvement to PFS with 7.2 additional months over treatment with PBO-FUL, with little detriment to HRQoL; EORTC QLQ-C30 scores were similar for most function and symptom scales, and there was no significant difference in EQ-5D-5L between treatment arms.[8]

ABE-FUL has a tolerable safety profile

The safety profile of ABE-FUL was acceptable and manageable. The most common adverse events reported were diarrhoea, neutropenia, nausea, fatigue and abdominal pain; these were predominantly grade 1 or 2 in severity. The majority of diarrhoea events occurred early in the first treatment cycle, and were managed with dose adjustment and standard anti-diarrhoeal medication. A small proportion (2.9%) of patients in the ABE-FUL arm of patients discontinued any study drug as a result of diarrhoea, indicating that this was managable.[8] The incidence of febrile neutropenia was very low, reported by only 1.4% of patients (n=6) receiving ABE-FUL, and was managed with dose reductions.[8] *Post hoc* multivariate analyses demonstrated that the efficacy of ABE-FUL was similar between patients who underwent dose reductions and patients who did not undergo any dose reductions, suggesting that the safety profile of abemaciclib is manageable and does not adversely affect efficacy.

Clinical opinion sought by Lilly reported that existing treatment options for patients who have progressed on or after ET have poor tolerability profiles, particularly the most commonly used comparator regimen in this setting, EVE-EXE, which is associated with significant toxicity. Whilst clinicians advised that exemestane is generally well-tolerated, everolimus is associated with mucositis, pneumonitis and rash, which may potentially warrant additional monitoring.[84, 85] The

poor tolerability profile of everolimus may consequently necessitate a dose reduction or even discontinuation, meaning patients do not experience the full treatment effect. In the BOLERO-2 trial, 62% of patients treated with EVE-EXE required dose interruptions or reductions (in comparison to 12% with placebo), and 26% and 9% of patients discontinued treatment with EVE or EXE due to TEAEs, respectively.[85] The provision of ABE-FUL will these provide ET-resistant patients with an efficacious alternative that is well-tolerated and has a manageable safety profile, for which there is a significant unmet need in current clinical practice.

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

B.2.13.1 Principal findings from the clinical evidence base

ABE-FUL provided clinically meaningful improvements in progression-free survival and objective response rate in patients with HR+/HER2− locally advanced or metastatic breast cancer.

The MONARCH 2 trial enrolled 669 patients across 19 countries, with a median follow-up period of 19.5 months. Results from the MONARCH 2 study demonstrated that treatment with ABE-FUL was associated with a significantly extended PFS and an improved ORR, in comparison with PBO-FUL.

The MONARCH 2 study achieved its primary endpoint by demonstrating a statistically significant improvement in PFS for ABE-FUL compared to PBO-FUL, corresponding to a risk reduction of 45% of progression or death for patients treated with abemaciclib. These results indicate that ABE-FUL can provide a clinically meaningful reduction in the risk of disease progression or death for patients whose disease has progressed on or after ET. By prolonging PFS, the need for patients to try alternative therapies with poorer tolerability or efficacy (such as EVE-EXE or TMX) followed by chemotherapy regimens once all other treatment options are exhausted, will be delayed, allowing for a longer period of effective treatment and maintained HRQoL. PFS results were consistent between the investigator and independent assessments, indicating their reliability. In addition, the benefit in PFS of adding abemaciclib to fulvestrant was demonstrated across all pre-specified subgroups. An improvement in PFS is likely to translate to improved OS,[70] however the extent of this is currently uncertain.

It is not typical for ET-based treatments to induce substantial tumour shrinkage, especially in patients whose disease has progressed on or after ET.[83] Treatment with ABE-FUL was associated with a significantly higher ORR relative to PBO-FUL; patients treated with ABE-FUL had 2.82 times greater odds of achieving a complete or partial response (measured by RECIST version 1.1[59]) than patients who were treated with PBO-FUL. Other measures of tumour response including CBR (PR, CR or stable disease ≥6 months) were also significantly higher in the ABE-FUL arm relative to PBO-FUL. Significantly higher ORR and CBR highlights the therapeutic potential of ABE-FUL, by increasing the likelihood of partial or complete tumour response (ORR), and/or stable disease for at least 6 months (CBR), relative to PBO-FUL.

Treatment with ABE-FUL maintained the HRQoL of patients

Pain intensity scores, in terms of individual mBPI-sf pain items, were similar between the ABE-FUL and PBO-FUL arms, but tended to numerically favour treatment with abemaciclib. This suggests that the addition of abemaciclib may confer a small benefit in pain reduction compared

with fulvestrant alone. HRQoL was measured by the EORTC QLQ-C30 and EQ-5D-5L questionnaires. A decrease of [redacted] points in diarrhoea symptom score was observed in the ABE-FUL arm relative to PBO-FUL. The highest symptom burden for diarrhoea was reported during early visits, and returned close to baseline upon treatment discontinuation. All other function and symptom EORTC QLQ-C30 scores were similar over the course of the study, and there was no significant difference in global health status between treatment arms. EQ-5D-5L index values and VAS scores were similar between treatment arms for all baseline and post-baseline visits, supporting that the overall health status of patients was maintained throughout the study in both treatment arms. It is further important to note that the HRQoL data observed in MONARCH 2 do not capture the delay in the detriment to quality of life associated with initiating chemotherapy treatment. The ability of ABE-FUL to extend PFS and OS without adversely affecting HRQoL makes this treatment a highly useful addition to the oncologist's armamentarium.

The results of the indirect treatment comparison support that the efficacy of ABE-FUL is at a minimum comparable with that of EVE-EXE. The results also support that ABE-FUL is more efficacious than other treatments that may be used in patients with HR+/HER2− locally advanced or metastatic breast cancer on or after ET in the UK

ABE-FUL was the only relevant comparator that had a significantly lower hazard rate of disease progression or death relative to fulvestrant (500 mg).

ABE-FUL had a lower hazard rate of death compared to FUL 500 but this treatment effect was not significant. EXE had a significantly higher hazard rate of progression or death compared with FUL 500, suggesting that this treatment is not beneficial for endocrine-resistant patients over treatment with fulvestrant. In terms of OS, no comparators showed a significant treatment benefit compared to FUL 500. Due to the inclusion of immature OS data from the MONARCH 2 trial, uncertainty is introduced around the associated treatment effects. For ORR, only ABE-FUL and EVE-EXE showed significantly higher odds of achieving a response compared to FUL 500, and for CBR, the treatment effect was significantly in favour of ABE-FUL only. The CBR for EXE was significantly lower compared to FUL 500.

The adjusted indirect comparison identified that TMX was associated with a greater risk of progression or death versus FUL 500 (as assessed through PFS/TTP), and a lower risk of death (as assessed through OS), however, neither result was statistically significant.

The results of the indirect comparison support that the efficacy of ABE-FUL is at a minimum comparable to EVE-EXE, which is recommended by NICE specifically as an option for patients after progression on or after ET.[26, 50] The findings of the NMA and adjusted indirect comparison also suggest that ABE-FUL has superior efficacy compared to other treatments that may be used for a small number of endocrine-resistant patients in the UK, including exemestane alone, fulvestrant (500 mg) alone and tamoxifen.

The MONARCH 2 trial addressed a very specific population (i.e. HR+/HER2− disease that progressed on (neo)adjuvant ET, ≤12 months after adjuvant ET or while receiving ET for ABC, and no prior chemotherapy permitted in the advanced setting), resulting in heterogeneity in certain patient characteristics relative to other comparator trials included in the analysis. The patient populations were broadly similar with regards to age, post-menopausal status and performance status. However, in all comparator trials, prior chemotherapy and multiple rounds of ET were permitted. These patient populations may therefore have been more heavily pre-treated than in MONARCH 2, which may have overestimated their benefit. The adjusted indirect

comparison performed to generate a treatment effect estimate for TMX vs FUL 500 necessitated identification of studies evaluating TMX in the MONARCH 3 aligned SLR, which had broader patient population criteria compared to the MONARCH 2 aligned SLR. Whilst Milla-Santos (2001) did permit patients who had received prior ET, it is likely that there was some heterogeneity between this study and other trials included in the NMA. This heterogeneity should be considered upon interpreting the results of the indirect comparisons.

ABE-FUL is associated with a manageable safety profile

The evidence for ABE-FUL demonstrates a tolerable safety profile. The most common TEAEs experienced by patients were diarrhoea (13.4% at Grade ≥3) and neutropenia (26.5% at Grade ≥3), although they were less frequently of high severity. Another Phase III study which evaluated abemaciclib for treatment of women with HR+/HER2− advanced breast cancer supports this finding, where the most frequent adverse events were diarrhoea and neutropenia, also predominantly of low severity.[42]

Whilst the majority of patients treated with abemaciclib experienced diarrhoea, most cases of diarrhoea were effectively managed using anti-diarrhoeal medications and with dose adjustments. The majority (70.1%) of patients did not require any treatment modification. A small proportion of patients (2.9%) in the ABE-FUL arm discontinued study treatment because of diarrhoea ([redacted] discontinued ABE but continued to receive FUL, and [redacted] of patients discontinued treatment with ABE-FUL), suggesting that this TEAE was manageable and acceptable.

Clinical opinion supports that ABE-FUL is of lower toxicity with a substantially improved tolerability profile in comparison with EVE-EXE; the use of EVE-EXE in clinical practice is limited by the risk of unpleasant side effects associated with everolimus which may be dose-limiting and require additional monitoring, such as stomatitis, mucositis, pneumonitis and rash.[26, 57, 58]

Further supported by the results of the NMA, which indicate that ABE-FUL is associated with at least similar clinical outcomes to EVE-EXE, the results demonstrate that ABE-FUL therefore will meet an unmet need for an efficacious and tolerable treatment option for women with HR+/HER2− locally advanced or metastatic breast cancer, who have previously progressed on or after ET. Based on the clinical and patient-reported findings, clinical opinion sought by Lilly strongly supports the use of abemaciclib in clinical practice.

B.2.13.2 Strengths and limitations of the evidence base

Internal validity

As described in Section B.2.5, the MONARCH 2 trial was methodologically robust and well-reported. The trial results were considered to be at low risk of bias:

- Participants were appropriately randomised using an IWRS, treatment allocation was concealed, and participants and care providers were blinded.
- The sample size was sufficient to detect a difference in the primary objective of PFS between the two treatment groups, yielding approximately 90% statistical power.[35]
- Participant flow through the study was well reported, and all treatment discontinuations and loss-to-follow up events were accounted for.

- All randomised patients were included in the efficacy analyses, thereby maintaining the principle of ITT analysis and preserving randomisation.
- PFS was also assessed independently in MONARCH 2 to minimise bias, as INV-assessed response rates are frequently overestimated due to PFS being inherently subjective, and knowledge of adverse events may potentially influence the investigator's assessment. Variability in investigator and independent assessment is commonly due to the influence of a patient's clinical status and information censoring.[86] However, independent review is also prone to bias given that information may be censored, for example the exclusion of unconfirmed local progressions.[87]

External validity

The results of the MONARCH 2 study are relevant to the decision problem specified by the NICE scope, which proposes the use of ABE-FUL in people with advanced HR+/HER2− locally advanced or metastatic breast cancer that has progressed on or after endocrine therapy.[88, 89] The external validity of the MONARCH 2 study is supported by the following:

- **Population** – [redacted] were confirmed to have HR+/HER2− locally advanced or metastatic breast cancer, and over 98% of the MONARCH 2 study population had previously progressed on or after endocrine therapy, including patients with both primary (25.3%) or secondary (73.1%) endocrine resistance. The results of the MONARCH 2 trial thus provide supportive evidence for the use of ABE-FUL in the patient population specified in the decision problem. With regards to the generalisability of the MONARCH 2 trial to the UK, the majority ([redacted]) of patients were post-menopausal at study entry which is in line with the epidemiology of breast cancer in the UK, where more than 80% of breast cancer cases in the UK occur in women over the age of 50,[14] of which, it is anticipated that the majority are likely to be postmenopausal.[90] Whilst no UK clinical trial sites were included in the MONARCH 2 study, 41.7% of patients were from clinical trial sites across Europe, and 55.8% were of white ethnicity, maintaining relevance to the UK population where 86% of the population are white.[91]
- **Intervention** – Abemaciclib was directly evaluated in combination with FUL as a treatment option for women with HR+/HER2− advanced breast cancer
- **Comparator** – The efficacy and safety of ABE-FUL was directly compared with that of PBO-FUL in the MONARCH 2 trial.[8] The evidence allowed for an indirect comparison to other relevant UK treatment comparators for women with locally advanced or metastatic breast cancer, in particular everolimus plus exemestane, which is recommended by NICE as a post-ET treatment option for women with locally advanced or metastatic breast cancer, and other UK comparators (although with limited use): fulvestrant alone, exemestane alone and tamoxifen.
- **Outcomes** – The efficacy and safety profile of ABE-FUL in HR+/HER2− locally advanced or metastatic disease was demonstrated in a well-defined, homogenous population. A wide range of outcomes were evaluated, including all outcomes outlined in the scope that are relevant to clinicians and to patients (PFS, ORR, OS, adverse events, HRQoL). The delay to chemotherapy was also assessed in an exploratory analysis to demonstrate the direct benefit of prolonging PFS for this patient population. Advanced breast cancer is incurable. For this reason, PFS is considered to be a particularly valuable endpoint for comparing treatment regimens in these patients, for whom achieving disease control and thus

maintenance of quality of life for as long as possible is the primary goal of treatment. Unlike OS, PFS is not confounded by the inevitable use of subsequent therapies, with results therefore reflecting the efficacy of the study treatment alone,[92, 93] and measurement of PFS provides a higher event frequency at an earlier time point in comparison to OS, and may be considered as an indicator of OS benefits, though the relationship between these two measures has not been fully elucidated.[92]

Limitations

- The impact of abemaciclib on the OS of patients with HR+/HER2− locally advanced or metastatic breast cancer has not yet been determined, as these data were immature at the time of data cut off. Mature OS data are not expected within the timeframe of this appraisal.
- The clinical evidence base for the use of ABE-FUL for women with advanced HR+/HER2− advanced breast cancer who have progressed on or after ET, comes from the MONARCH 2 trial, in which the only comparator was PBO-FUL. Everolimus in combination with exemestane (TA421) is recommended by NICE for postmenopausal women with HR+/HER2− advanced breast cancer following ET (TA421),[26] which would provide an alternative treatment option to allow the delay of chemotherapy.[26] Further treatment options exist which some patients with ET resistance may be offered locally. These include: exemestane alone, tamoxifen, or fulvestrant alone. Although they have limited use in UK practice, clinical expert opinion sourced by Lilly advised that these options are used substantially more frequently than proceeding to chemotherapy upon disease progression on or after ET. There has been no direct comparison between the efficacy and safety of ABE-FUL and these comparators in a clinical trial setting, and it was therefore necessary to perform an indirect comparison to generate relative efficacy estimates.
- There was substantial heterogeneity in the patient populations of the included trials, particularly in regard to treatment with prior chemotherapy or prior ET. In addition, to generate a relative treatment effect for TMX vs FUL 500, an adjusted indirect comparison using Milla-Santos (2001) and NMA was performed. Milla-Santos (2001) was identified through use of the eligibility criteria for the MONARCH 3 SLR of RCTs, and, whilst the study did permit patients who had received prior ET, it is likely that there was some heterogeneity between this study and other trials included in the NMA. This heterogeneity should be considered upon interpreting the results.

Conclusion

The evidence for the clinical effectiveness and safety of ABE-FUL for the management of HR+/HER2− locally advanced or metastatic breast cancer that has progressed on or after ET comes from the MONARCH 2 study, which demonstrated that ABE-FUL significantly improved PFS, ORR, DCR and CBR, with a tolerable safety profile and whilst maintaining HRQoL.

The quality of the evidence provided by the MONARCH 2 study is supported by robust and well-reported methodology. The results of MONARCH 2 highlight the key benefits of treatment with ABE-FUL for patients with HR+/HER2− locally advanced or metastatic breast cancer. ABE-FUL represents a treatment option with a novel mechanism of action (CDK 4/6 inhibitor in combination with a SERD) that effectively delays disease progression in patients whose disease has progressed on or after ET, thereby providing a therapy that can address the obstacle of endocrine resistance. The provision of a safe and tolerable treatment option for people with endocrine therapy resistance means that the worsening of symptoms associated with disease

progression, and the need for toxic chemotherapy regimens, can be delayed, helping to maintain the HRQoL of patients and their caregivers.

B.3 Cost effectiveness

Summary of the cost-effectiveness evaluation

- An SLR of cost-effectiveness evidence evaluating endocrine therapy (with or without a targeted agent) and chemotherapy (with or without a targeted agent) for the management of HR+/HER2− locally advanced or metastatic breast cancer identified 31 relevant studies
- A *de novo* partitioned survival analysis with three health states (PFS, post-progression survival [PPS] and death) was undertaken to investigate the cost-effectiveness of ABE-FUL in patients with HR+/HER2− locally advanced or metastatic breast cancer, as part of the MONARCH 2-relevant patient population for abemaciclib
- The analysis was consistent with the NICE reference case: a cost-utility analysis with an NHS and Personal Social Services (PSS) perspective. Costs and benefits were discounted at a rate of 3.5% and a lifetime-equivalent time horizon of 25 years was used
- The comparators deemed as relevant for the cost-effectiveness analysis were FUL, EXE, EXE-EVE and TMX
- Clinical outcomes (PFS and OS) for ABE-FUL were based on the ITT population of the MONARCH 2 trial, using the final PFS data cut (14th February 2017). Clinical outcomes for the comparators were estimated based on data from a SLR of RCTs synthesised in an NMA and adjusted indirect treatment comparison
- Health-state utilities for pre-progression were informed by EQ-5D-5L data collected in the MONARCH 2 trial, cross-walked to the 3L scale. Due to immaturity of the post-progression data from MONARCH 2, data from the comparable population in Lloyd (2006)[94] was used for post-progression utility values
- Costs and healthcare resource use were captured in the analysis for drug acquisition and administration, best supportive care, follow-up care, hospitalisations, post-progression therapy, terminal care, and AE management
- ABE-FUL accrued a greater number of life years (LYs, 3.64) over all comparators (EXE, FUL and EXE-EVE), except for TMX, which accrued a marginally greater amount ([redacted]). ABE-FUL accrued a greater number of quality-adjusted life years (QALYs) over all comparators ([redacted]). ABE-FUL (with the proposed Patient Access Scheme) was associated with a higher total cost (£[redacted]) compared to EXE, TMX and FUL (at list price). This was predominantly driven by the higher costs of acquisition and follow-up care for ABE-FUL relative to the other comparators, owing to its improved PFS
- ABE-FUL (with the proposed PAS) was associated with a lower total cost compared to EXE-EVE at list price (£[redacted]), which is the key comparator for ABE-FUL at its specific position in the treatment pathway for HR+/HER2− advanced breast cancer
- Based on the price of ABE with the proposed PAS, the base case fully incremental analysis produced a pairwise ICER for ABE-FUL of £108,789 per QALY gained compared to TMX, the reference comparator.
- The probabilistic sensitivity analyses demonstrated that there was a [redacted] chance of ABE-FUL being cost-effective at a threshold of £30,000 per QALY
- In the deterministic scenario analyses, the net monetary benefit for ABE-FUL vs TMX changed by less than 10% in 20/24 scenarios, demonstrating the robustness of the model
- In conclusion, the economic analysis found ABE-FUL to be associated with a clinical benefit, as measured by LYs and QALYs, relative to EXE-EVE, EXE, TMX and FUL

B.3.1 *Published cost-effectiveness studies*

A SLR was conducted in April 2016, and updated in November 2017, to identify cost-effectiveness evidence relevant to the treatment options for the management of HR+/HER2− locally advanced or metastatic breast cancer.

In the original SLR, a total of 4,612 articles were identified from the searches, which also includes those relevant to the cost and resource use component of the SLR, of which 93 papers relevant to cost-effectiveness, and cost and resource use were identified for full text review. Ultimately, ten publications, five conference proceedings, and five NICE technology appraisals relevant to the cost-effectiveness eligibility criteria were included in the review.

Subsequently, the November 2017 SLR update retrieved 1,962 references in total, of which 28 were determined to be relevant to the cost-effectiveness component. After the review process, three publications were ultimately included. Two additional conference proceedings, two NICE TAs and three Canadian Agency for Drugs and Technologies in Health (CADTH) submissions were also included.

The results of the cost-effectiveness SLR for studies relevant to the UK setting are presented in Table 21; full details of the search strategy and the complete results are presented in Appendix G.

Table 21: Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population	QALYs/LYs	Costs	ICER
Endocrine therapy or combination endocrine and a targeted agent						
Das[95]	2013	Partitioned survival methodology* Health states: First-line therapy of advanced ER+/HER2- advanced breast cancer, no disease progression, disease progression, chemotherapy and palliative care, death. Time horizon: lifetime (13.5 years) and cycle length: 1 month. 3.5% discount rate applied to costs and outcomes.	Postmenopausal women with ABC, who had "recurrence of first progression on or after anti-oestrogen treatment or recurred on or within 1 year of adjuvant anti-oestrogen therapy or progressed on anti-oestrogen therapy as first advanced therapy."	Total discounted QALYs: LTZ: 1.211 ANAS: 1.334 FUL: 1.638	Total discounted costs: LTZ: £23,841 ANAS: £28,976 FUL: £38,224	FUL 500 vs LTZ: £34,528 ANAS: extended dominance Pairwise: ANAS vs LTZ: £41,862 FUL 500 vs ANAS: £31,468
Polanyi (ISPOR)[96]	2014b	Partitioned survival methodology. Health states: NR. Time horizon: 10 years and cycle length NR. Discount rate applied to costs and outcomes NR	Postmenopausal women with HR+/HER2– MBC, prior therapy not reported	Incremental LYs: EVE + EXE vs EXE: 0.20 vs FUL: 0.19 Incremental QALYs EVE + EXE vs EXE: 0.31 vs FUL: 0.27	Total costs of productivity loss: EVE + EXE: £66,163 EXE: £75,067 FUL: £73,434	EXE-EVE vs EXE: £27,664 vs FUL: £14,030
NICE TA239[97]	2011	Partitioned survival methodology. Health states: Pre-progression, post-progression and death. Time horizon: lifetime (13 years) and cycle length: 1 month. 3.5% discount rate applied to costs and outcomes.	Postmenopausal women with HR+ locally advanced or metastatic BC, whose cancer has relapsed during on within 12 months of completing adjuvant hormone therapy (with anti-	Total QALYs: FUL 500mg: 1.487 FUL 250mg: 1.256 ANAS: 1.214 LTZ: 1.105	Total costs: FUL 500mg: £31,075 FUL 250mg: £25,603 ANAS: £22,467 LTZ: £18,836	FUL 500 vs LTZ: £31,982 ANAS and FUL 250 were extendedly dominated by FUL 500 and LTZ

Study	Year	Summary of model	Patient population	QALYs/LYs	Costs	ICER
			oestrogen or NSAI) for early breast cancer; or after progression on anti-oestrogen or NSAI therapy for ABC providing that this hormone therapy was started more than 12 months after completion of adjuvant hormone therapy; or after progression while on first-line hormone therapy for ABC.			
NICE TA421[26]	2016	Unclear; assume partitioned survival methodology as per TA295. Health states: Unclear; assume stable disease, progressed disease and death as per TA295. Time horizon: 15 years and cycle length NR. Discount rate applied to costs and outcomes NR.	Postmenopausal women with HR+/HER2- ABC cancer, without symptomatic visceral disease after recurrence or progression following treatment with a NSAI (LTZ or ANAS).	Total QALYs: EXE-EVE: 1.58 EXE: 1.37	Total costs: EXE-EVE: £49,748 EXE: £36,677	EXE-EVE vs EXE: £61,046 (without PAS)
Chemotherapy or combination chemotherapy and a targeted agent						
NICE TA214[98]	2011	Markov model. Health states: Progression-free survival, progressed and death. Time horizon: 10 years and cycle length 1 month. Discount rate applied to costs and outcomes NR.	Women with MBC who had not received treatment for metastatic disease	Incremental QALYs: BEV + PAC vs PAC: 0.259 vs DOC: 0.273 vs GEM + PAC: 0.259	Incremental costs: BEV + PAC vs PAC: £30,469 vs DOC: £31,416 vs GEM + PAC: £27,358	PAC-BEV vs PAC: £117,803 PAC-BEV vs DOC: £115,059 PAC-BEV vs GEM + PAC: £105,777;

Study	Year	Summary of model	Patient population	QALYs/LYs	Costs	ICER
				Prior taxane-treated subgroup: Incremental QALYs: BEV + PAC vs PAC: 0.501 vs DOC: 0.502	Prior taxane-treated subgroup: Incremental costs: BEV + PAC vs PAC: £37,358 vs DOC: £36,951	PAC-BEV vs DOC: £84,740; Prior taxane-treated subgroup: PAC-BEV vs PAC: £74,640; PAC-BEV vs DOC: £73,605
NICE TA250[99]	2012	Semi-Markov model. Health states: Treated, progressive and dead. Time horizon: lifetime (2.89 years) and cycle length: 21 days. 3.5% discount rate applied to costs and outcomes.	Women with locally advanced or metastatic BC, who had progressed after at least two chemotherapeutic regimens for locally advanced or metastatic disease. Prior therapy should have included an anthracycline and a taxane for eligible patients	Incremental QALYs: eribulin vs TPC: 0.1213 vs GEM: 0.1904 vs VNB: 0.1136 vs CAP: 0.2683	Incremental costs: eribulin vs TPC: £5,586 vs GEM: £5,177 vs VNB: £4,041 vs CAP: £12,779	Eribulin vs TPC: £46,050 vs GEM: £27,183 vs VNB: £35,602 vs CAP: £47,631
NICE TA263[100]	2012	Markov model* Health states: Progression-free survival, progressed disease and death. Time horizon: 15 years and cycle length: 1 month. 3.5% discount rate applied to costs and outcomes.	Women with HER2– locally recurrent or metastatic BC who had not received treatment for locally recurrent or metastatic disease. The economic analysis was based on a subgroup of patients from the	Incremental QALYs: BEV + CAP vs CAP: 0.5034	Incremental costs: BEV + CAP vs CAP: £38,924	BEV + CAP vs CAP: £77,318

Study	Year	Summary of model	Patient population	QALYs/LYs	Costs	ICER
			RIBBON-1 trial, who had previously received a taxane as part of adjuvant treatment.			
NICE TA423[52]	2016	Partitioned survival methodology. Health states: Stable disease, progressive disease and death. Time horizon: Stable disease, progressive disease and death and cycle length: 30.42 days (1 month). 3.5% discount rate applied to costs and outcomes.	Women with locally advanced or metastatic BC, who had progressed after at least two chemotherapeutic regimens for locally advanced or metastatic disease which includes CAP.	Not disclosed.	Not disclosed.	ERI vs TPC: £35,624
Combination endocrine therapy with a targeted agent where comparison includes chemotherapy						
Polanyi (ISPOR)[96]	2014a	Partitioned survival methodology. Health states: Stable disease, progressed disease and death. Time horizon: 10 years and cycle length: 1 month. 3.5% discount rate applied to costs and outcomes.	Women with HR+/HER2– locally advanced or metastatic BC, prior therapies not reported	Total LYs: EVE + EXE: 3.55 DOC: 1.88 VNB: 1.88 DOX: 1.88 CAP: 1.88 Total QALYs: EVE + EXE: 2.06 DOC: 0.95 VNB: 0.95 DOX: 0.95 CAP: 0.95	Total costs: EVE + EXE: £48,085 DOC: £31,835 VNB: £25,021 DOX: £23,743 CAP: £21,851	EXE-EVE vs DOC: £14,550 vs VNB: £20,653 vs DOX: £21,797 vs CAP: £23,491
NICE TA295[78]	2013	Partitioned survival methodology* Health states: Stable disease, progressed disease and death.	Postmenopausal women with HR+/HER2- MBC,	Incremental QALYs: EXE-EVE vs EXE: 0.84; EXE-EVE vs	Incremental costs: EXE-EVE vs EXE: £27,086	EXE-EVE vs EXE: £32,417 vs TMX: £29,109

Study	Year	Summary of model	Patient population	QALYs/LYs	Costs	ICER
		Time horizon: lifetime (10 years) and cycle length: 1 month. 3.5% discount rate applied to costs and outcomes.	who must have experienced progression or recurrence following treatment with a NSAI (LTZ or ANAS).	TMX: 1.18; EXE-EVE vs FUL: 0.77; EXE-EVE vs DOC: 1.21; EXE-EVE vs DOX: 1.25; EXE-EVE vs CAP: 1.21	vs TMX: £34,256 vs FUL: £20,937 vs DOC: £13,364 vs DOX: £25,227 vs CAP: £29,597	vs FUL: £27,147 vs DOC: £11,000 vs DOX: £20,253 vs CAP: £24,362

Abbreviations: ABC: advanced breast cancer; AE: adverse events; AI: aromatase inhibitor; ANAS; anastrazole; BEV: bevacizumab; BSC: best supportive care; CADTH: Canadian Agency for Drugs and Technologies in Health; CAP: capecitabine; CI: confidence interval; DOX: doxorubicin; ER: oestrogen receptor; ERI: eribulin; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; GEM: gemcitabine; ICER: incremental cost-effectiveness ratio; ISPOR: International Society for Pharmacoeconomics and Outcomes Research; IXA: ixabepilone; HER2−: human epidermal growth factor receptor 2 negative; HR+: hormone receptor positive; LTZ: letrozole; LY: life years; MBC: metastatic breast cancer; NA: not applicable; Nab: nanoparticle albumin-bound; NR: not reported; NSAI: non-steroidal aromatase inhibitor; PAC: paclitaxel; PAS: patient access scheme; QALYs: quality-adjusted life years; QAPFW: quality-adjusted progression free weeks; QAPFY: quality-adjusted progression free years; sb: solvent-based; TMX: tamoxifen; TPC: treatment of physician's choice; DOC: docetaxel; VNB: vinorelbine.

*Modelling approach adopted was unclear, so extractions were based on reviewer's interpretation of the paper. †ICERs calculated manually based on total costs and QALYs reported. ‡The authors conducted analyses with data from two separate studies (301 and 305), with results presented in one poster. §Based on reported total or median survival time/overall survival from trial.

B.3.2 *Economic analysis*

B.3.2.1 Patient population

In line with the final NICE scope for this appraisal, and in line with the MONARCH 2 trial, the cost-effectiveness analysis presented here considers patients with HR+/HER2− locally advanced or metastatic breast cancer who had progressed according to at least one of the following criteria:

- While receiving (neo)adjuvant ET
- ≤12 months from the end of adjuvant ET
- While receiving first-line ET for metastatic disease

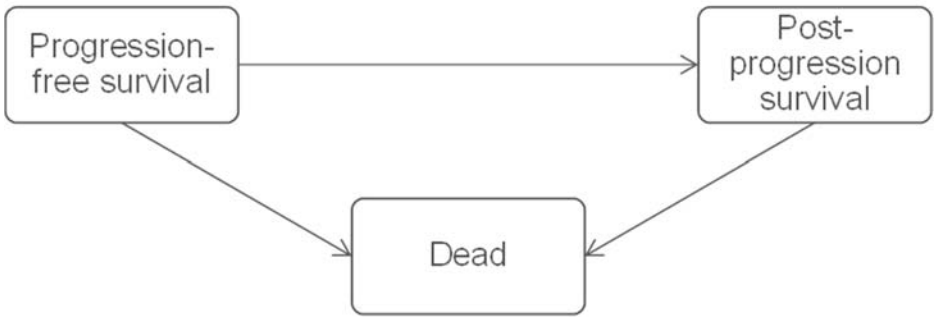
Patients eligible for the MONARCH 2 trial were not allowed to have received more than one line of ET or any chemotherapy for their locally advanced or metastatic disease.

B.3.2.2 Model structure

A *de novo* model was developed, as no economic evaluations assessing ABE-FUL were captured in the SLR.

A partitioned survival analysis was deemed appropriate for this decision problem. This choice aligns with the model structures adopted in the cost-effectiveness studies captured in the SLR, and is consistent with prior relevant NICE appraisals.[52, 78, 97] The partitioned survival analysis presented below (Figure 13) has three health states, progression-free survival, disease progression/post-progression survival (PPS), and death.

Figure 13. Model structure

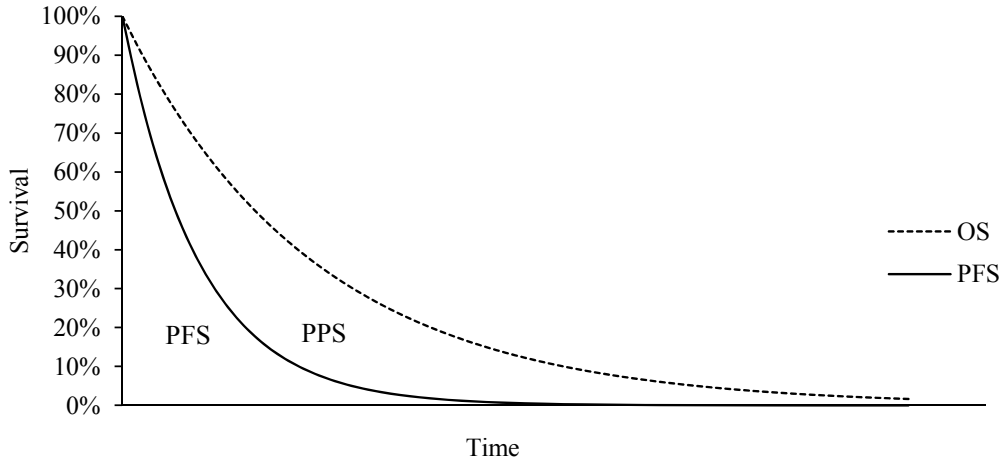


A partitioned survival approach was used to estimate health state occupancy at any given time. The proportion of patients in the PFS state over time was estimated directly from a parametric survival curve of PFS, with the proportion of patients in the PPS state estimated as the difference between parametric survival curves for PFS and OS. Costs, LYs and QALYs were accrued according to the proportion of patients in the PFS and PPS states over time. An illustrative example of the partitioned survival analysis undertaken is presented in Figure 14.

PFS and OS curves were modelled independently using different parametric functions (Section B.3.3.4 and Section B.3.3.5). It was possible for the PFS curve to lie above the OS curve, yielding negative occupancy of the 'post-progression' health state, and this outcome was

considered in the process of selecting parametric models, with distributions that avoided this outcome selected in the base case.

Figure 14. Illustration of partitioned survival methodology



Model characteristics

The model utilised weekly cycles over which transitions are modelled and costs and outcomes accrued. This was appropriate given the rate at which relevant clinical events may occur, and the frequency at which treatment regimens are administered in this patient population. A half-cycle correction was applied in all calculations to reduce the potential for bias in the cost-effectiveness estimates. Discount rates of 3.5% per annum were applied to both costs and benefits in the base case.[101] A summary of the model characteristics is provided in Table 22.

Table 22: Features of the economic analysis

	Previous appraisals	Current appraisal	
Factor	**TA421[26]**	**Chosen values**	**Justification**
Modelling approach	Markov state-transition	Partitioned survival analysis	A partitioned survival analysis was deemed appropriate for this decision problem. This choice aligns with the model structures adopted in the cost-effectiveness studies captured in the SLR, and is consistent with prior relevant NICE appraisals.[52, 78, 97]
Perspective	NHS	NHS and PPS	In accordance with the NICE reference case.[101]
Cycle length	1 month	1 week	A weekly cycle was appropriate given the rate at which clinical events may occur in this patient population, and the frequency at which treatment regimens are administered in this patient population.
Time horizon	Lifetime (10 years)	Lifetime (25 years)	A 25-year time horizon corresponds to the length of time in which survival in all arms fell to <0.1% for the base case extrapolations. Hence this can be considered equivalent to lifetime.
Outcome measures	QALYs	QALYs (base case), LYs (scenario)	In accordance with the NICE reference case[101]
Discount rate	3.5% per annum	3.5% per annum	In accordance with the NICE reference case[101]
Source of utilities	EQ-5D data from Lloyd (2006)[94]	For pre-progression utilities, EQ-5D data were collected as part of the MONARCH 2 trial and cross-walked to the EQ-5D-3L. For post-progression utilities, data from the comparable population in Lloyd (2006)[94], due	In accordance with the NICE reference case[101]

		to immaturity of MONARCH 2 post-progression data.	
Source of costs	BNF; NHS Reference costs; PSSRU (all updated to relevant year for the appraisal)	NHS Reference costs (2016−17); PSSRU (2017)	In accordance with the NICE reference case[101]

Abbreviations: BNF: British National Formulary; EQ-5D: EuroQol 5-Dimension; NHS: national health service; QALYs: quality-adjusted life years; PSS: personal social services; PSSRU: personal social services research unit; TA: technology appraisal.

B.3.2.3 Intervention technology and comparators

The following sources were reviewed to inform the comparator set for this analysis: NICE clinical guidelines, post-study therapies received by patients in the MONARCH 2 trial, clinical expert opinion, NICE EXE-EVE submission (TA421),[26] and European Society for Medical Oncology (ESMO) clinical guidelines 2016.

From this list, the following were deemed as relevant for the cost-effectiveness analysis:

- Fulvestrant 500 mg (FUL)
- Exemestane 25 mg (EXE)
- Exemestane 25 mg + everolimus 10 mg (EXE-EVE)
- Tamoxifen 40 mg (TMX)

B.3.3 *Clinical parameters and variables*

B.3.3.1 Clinical outcomes

The model structure necessitated identification of PFS and OS data for each comparator. The following sections describe the data sources for each comparator (Section B.3.3.2), patient characteristics (Section B.3.3.3) and the process for estimating long-term PFS (Section B.3.3.4) and OS (Section B.3.3.5).

B.3.3.2 Data sources

A summary of the clinical data sources used for the comparators are provided in Table 23.

Table 23. Summary of clinical effectiveness data sources

Treatment	Endpoint data source	
	PFS	OS
ABE (150 mg)-FUL (500 mg)	MONARCH 2; NMA (scenario)	MONARCH 2; NMA (scenario)
FUL (500 mg)	MONARCH 2*	MONARCH 2*
EXE (25 mg)	NMA; BOLERO 2,[57] Campos et al. (2009),[102] SoFEA,[103] Yamamoto et al. (2013)[104]	NMA; BOLERO 2,[57] Campos et al. (2009),[102] Kaufman et al. (2000), SoFEA,[103] Yamamoto et al. (2013)[104]
EXE (25 mg)-EVE (10 mg)	NMA; BOLERO 2[57]	NMA; BOLERO 2[57]
TMX (40 mg)	Adjusted indirect comparison; Milla-Santos (2001),[75] NMA	Adjusted indirect comparison; Milla-Santos (2001),[75] NMA

Footnotes: *FUL was the reference treatment in the NMA and was modelled using MONARCH 2 data.
Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; NMA: network meta-analysis; OS: overall survival; PFS: progression-free survival; TMX: tamoxifen.

Comparators included in the NMA

PFS and OS for ABE-FUL and FUL were based on the ITT population of the MONARCH 2 trial. The data-cut corresponding to the final PFS analysis from the MONARCH 2 trial were used (database lock 14th February 2017).

PFS and OS for the comparators presented in Section B.3.3.2 were estimated based on data from a SLR of RCTs (studies listed in Table 23) synthesised in an NMA (Section B.2.1 and Section B.2.9). The NMA provided relative efficacy estimates for each treatment vs FUL 500 (chosen as the reference treatment) in the form of HRs representing the instantaneous risk of an event (i.e. death for OS, disease progression or death for PFS). The corresponding PFS and OS HR estimates for each of the comparators vs the reference treatment are presented in Table 26 for PFS (Section B.3.3.4) and Table 28 for OS (Section B.3.3.5).

Comparators not included in the NMA

As described in Section B.2.9, it was not possible to include TMX in the NMA due to a lack of evidence identified for this treatment in the NMA of RCTs. The eligibility criteria for the SLR were broadened to align with the MONARCH 3 indication for abemaciclib, which resulted in the identification of Milla-Santos (2001), which compared TMX to TOR.[75] An adjusted indirect comparison was subsequently conducted using Milla-Santos (2001) and the NMA conducted in the MONARCH 2 aligned population to estimate relative treatment effects for TMX vs FUL 500 mg for OS and PFS/TTP (assuming equivalence between the PFS and TTP endpoints). The treatment effect estimates from this analysis were applied in the model. The PFS/TTP and OS HR estimates for TMX vs the reference treatment are presented in Table 27 for TTP/PFS (Section B.3.3.4) and Table 29 (Section B.3.3.5) for OS.

B.3.3.3 Patient characteristics

Body weight and body surface area (BSA) were required to calculate drug doses (where relevant). BSA data were not collected in the MONARCH 2 trial; as such, height and body weight data were collected and used to estimate BSA using the DuBois formula:[105]

$$BSA(m^2) = 0.20247 \times height(m)^{0.725} \times weight(kg)^{0.425}$$

These data are presented in Table 24.

Table 24. Model patient characteristics

Parameter	Mean	Source
Height (cm)	[redacted]	MONARCH 2 CSR (ITT population)
Weight (kg)	[redacted]	MONARCH 2 CSR (ITT population)
BSA (m^2)	[redacted]	Calculation (Du Bois, 1916)

Abbreviations: BSA: body surface area.

B.3.3.4 Progression-free survival

PFS for ABE-FUL and FUL were estimated based on the ITT population of the MONARCH 2 trial.

Two assessments of disease progression were conducted in the MONARCH 2 trial; per investigator (INV) and per independent review committee (IRC). The INV-assessed PFS data for MONARCH 2 were used in the base case to align with the primary endpoint in the MONARCH 2 trial. The majority of publications used to source data for the comparators also reported INV-assessed PFS data. Use of INV therefore allowed the model to align with the MONARCH 2 trial and comparator trial data. IRC-assessed PFS is a blinded outcome, and it is thus relevant to include as well as INV-assessed PFS data. The IRC-assessed data was therefore included as a scenario analysis.

The methods to estimate PFS for ABE-FUL and the comparators are presented in the sections that follow.

ABE-FUL and FUL

The observed KM PFS data for MONARCH 2 based on INV assessment are presented in Figure 15.

Figure 15. INV assessed KM curves for ABE-FUL and FUL PFS from MONARCH 2

Abbreviations: ABE: abemaciclib; FUL: fulvestrant; INV: investigator; KM: Kaplan-Meier; PFS: progression-free survival.

PFS data were collected in the MONARCH 2 trial at specific intervals (every 8 weeks after cycle 3), which does not necessarily reflect the underlying TTP for patients. Direct modelling of the KM data in this case can provide biased estimates of PFS without adjustment. Consequently, two parametric analyses were conducted; one assuming dates of progression were exact, and a second incorporating the potential for interval censoring (referred to as the 'interval censored adjusted' analysis). The interval censored adjusted analysis was used in the base case. The non-interval censored adjusted analysis was explored in a scenario analysis.

The interval censored adjusted analysis was performed using the dates of tumour assessments to form the intervals for patients that progressed. The time-to-event and event/censoring inputs for the survival analysis were based on the following cases:

- For patients that progressed:
    - Progression was considered as an event
    - Time-to-event was constructed as an interval from the tumour assessment prior to the progression event (or randomisation date for patients that progressed before their first assessment) and the tumour assessment in which progression was recorded
- For patients that died before progression:
    - Death was considered as an event
    - Time-to-event was time to death
- For patients that withdrew from the study prior to progression:
    - Withdrawal was considered as censored
    - Time-to-event was the time to withdrawal

Standard joint parametric models (including a covariate for treatment to estimate the treatment effect of ABE-FUL vs FUL) were fitted to the INV PFS data from the MONARCH 2 trial. Exponential, Weibull and Gompertz distributions (parameterised as proportional hazards models); and lognormal, log-logistic and gamma distributions (parameterised as accelerated failure time [AFT] models), were fitted in Stata using the streg command. Models both adjusted and unadjusted for interval censoring were fitted to the MONARCH 2 data.

The process for selecting the most appropriate parametric model was based on an assessment of the within-trial and extrapolation predictions. It is essential to consider both of these criteria as any given model may provide a suitable fit to the observed data yet generate long-term estimates which are clinically implausible. It is equally likely that a parametric model may provide accurate long-term estimates for an endpoint but poorly fit the within-trial data. The methods used for assessing the suitability of each distribution are summarised in Table 25 and were based on those described in the NICE DSU Technical Support Document 14.[106]

Cumulative hazard and log-log plots for PFS are presented in Appendix M1.1, Figure 17 and Figure 18, respectively. The cumulative hazard and log-log plots indicated no evidence of violation of the proportional hazards assumption in the MONARCH 2 PFS data, indicating that a proportional hazards model may be appropriate for these data.

An overlay of the KM curves for ABE-FUL and FUL, and corresponding parametric extrapolations based on the fitted joint models are presented in Figure 16 and Figure 17, respectively. Equivalent plots based on the unadjusted ITT analysis are presented in Figure 28 and Figure 29 in Appendix M2.2 for ABE-FUL and FUL, respectively.

Table 25. Methods for assessing the suitability of parametric survival models

Criteria	Method	Description
Within-trial period	Log-cumulative hazard plot (log cumulative hazards against time)	Assess the behaviour of the hazard function over time and the plausibility of the proportional hazards assumption
	Log-log plot (log cumulative hazards against log time)	As above

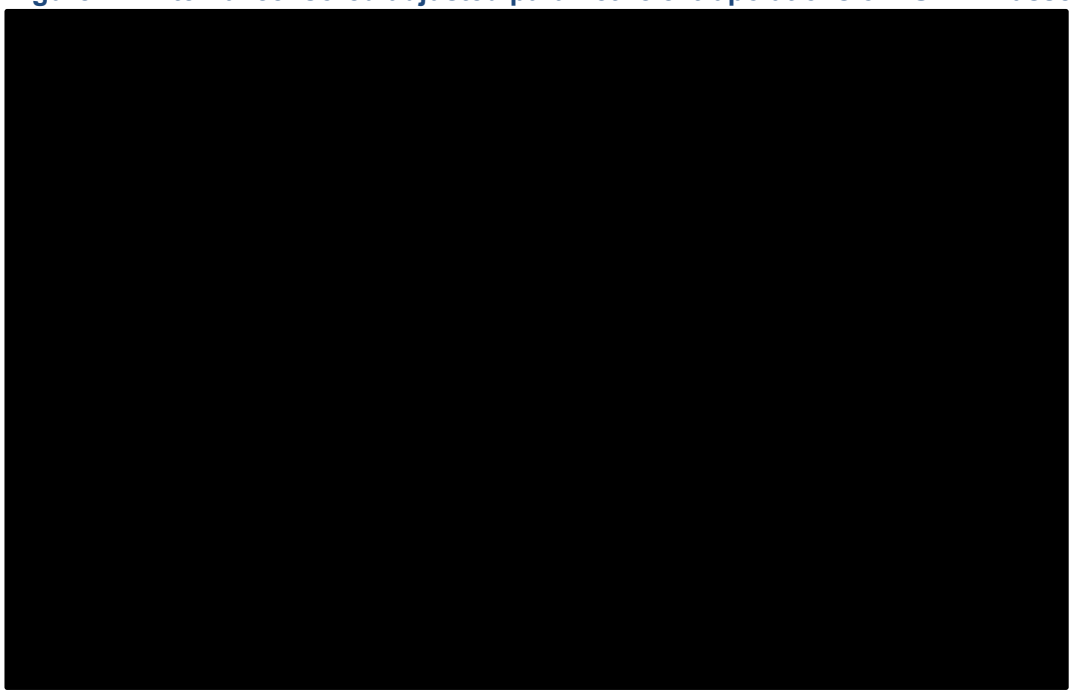
Criteria	Method	Description
	AIC and BIC statistics	Assess the relative fit of parametric models whilst accounting for the number of parameters
	Cox-Snell residuals	Assess how closely a parametric function follows the KM function
	Visual inspection	Assess how closely a parametric function follows the KM function and the clinical plausibility of the prediction in relation to other endpoints
Extrapolation period	Visual inspection	Assess how closely the tail of a parametric function fitted to the active treatment arm(s) concur with external longer term observational KM data

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; KM: Kaplan-Meier
Source: Latimer NR. NICE DSU Technical Support Document 14, 2013.[106]

Figure 16. Interval censored adjusted parametric extrapolations of ABE-FUL INV assessed PFS

Abbreviations: ABE: abemaciclib; FUL: fulvestrant; INV: investigator; PFS: progression-free survival.

Figure 17. Interval censored adjusted parametric extrapolations of FUL INV assessed PFS



Abbreviations: FUL: fulvestrant; INV: investigator; PFS: progression-free survival.

The corresponding AIC and BIC statistics, and long-term PFS estimates for the interval censored adjusted models are presented in Appendix M2.1, Table 58 and Table 60, respectively. Given the objective of the adjustment for interval censoring was not to fit to the observed data as it was, and instead account for the intervals in which progression events could occur, Cox-Snell residual plots were not considered to be informative for selecting parametric models. However, AIC and BIC statistics were assessed to explore the relative fit of distributions.

Of all models assessed, the Weibull, Gompertz and gamma models provided the best fit based on AIC and BIC statistics. Of these, the Weibull model provided the best fit based on both AIC and BIC. The exponential, Weibull, Gompertz and gamma models appeared to fit well to the observed data. In contrast, the lognormal and log-logistic models appeared to underestimate PFS for ABE-FUL between approximately 3 and 15 months, and potentially overestimate PFS after 22 months. A comparison of the extrapolated PFS from these distributions and external PFS data for FUL, identified from studies in the SLR, was made to assess the plausibility of the long-term extrapolations (Figure 18). The CONFIRM,[64] PALOMA-3[107, 108] and Zhang (2016)[109] studies all included PFS data for FUL 500 mg, with the CONFIRM study providing the longest follow-up (approximately 45 months). The extrapolations based on the exponential and Weibull distributions aligned more closely with the CONFIRM trial data. The extrapolations based on the log-normal, log-logistic and gamma distributions appeared to overestimate PFS compared to all of the external study data.

Figure 18. Interval censored adjusted parametric extrapolations of FUL INV assessed PFS with KMs from studies identified investigating FUL 500 mg

Abbreviations: FUL: fulvestrant; INV: investigator; KM: Kaplan-Meier; PFS: progression-free survival.

Based on this assessment, a Weibull distribution was selected to model PFS for ABE-FUL and FUL in the base case. A gamma distribution was used in a scenario analysis to explore the impact of employing an AFT model on mean PFS.

Parameter estimates for the selected distributions from modelling the INV assessed PFS data from MONARCH 2 are presented in Appendix M2.1, Table 59 for interval censored adjusted models and Appendix M2.1, Table 62 for models without adjustment for interval censoring.

Results of the PFS analysis based on the IRC-assessed data (adjusted and unadjusted for interval censoring) are presented in Appendix M2.2. Applying the same model selection process as described for the INV-assessed PFS data, Weibull and exponential distributions were included as scenario analysis to model the IRC- assessed PFS data for ABE-FUL and FUL.

Comparators

PFS for EXE and EXE-EVE was estimated by applying the relative treatment effects generated by the NMA (Table 26) to the FUL PFS curve based on the MONARCH 2 trial. The relative treatment effect generated for TMX vs FUL from the adjusted indirect comparison (Table 27) was similarly applied to the FUL PFS curve.

Table 26. Hazard ratios estimated by the NMA (95% credible interval) for PFS

Comparator	PFS HR (CrI)
EXE (25 mg)	[redacted]
EXE (25 mg)-EVE (10 mg)	[redacted]
FUL (500 mg)	Reference

Abbreviations: ABE: abemaciclib; CrI: credible interval; EVE: everolimus; EXE: exemestane; FUL: fulvestrant.

Table 27. Hazard ratio for TMX vs FUL 500 estimated by the adjusted indirect comparison (95% credible interval) for TTP/PFS

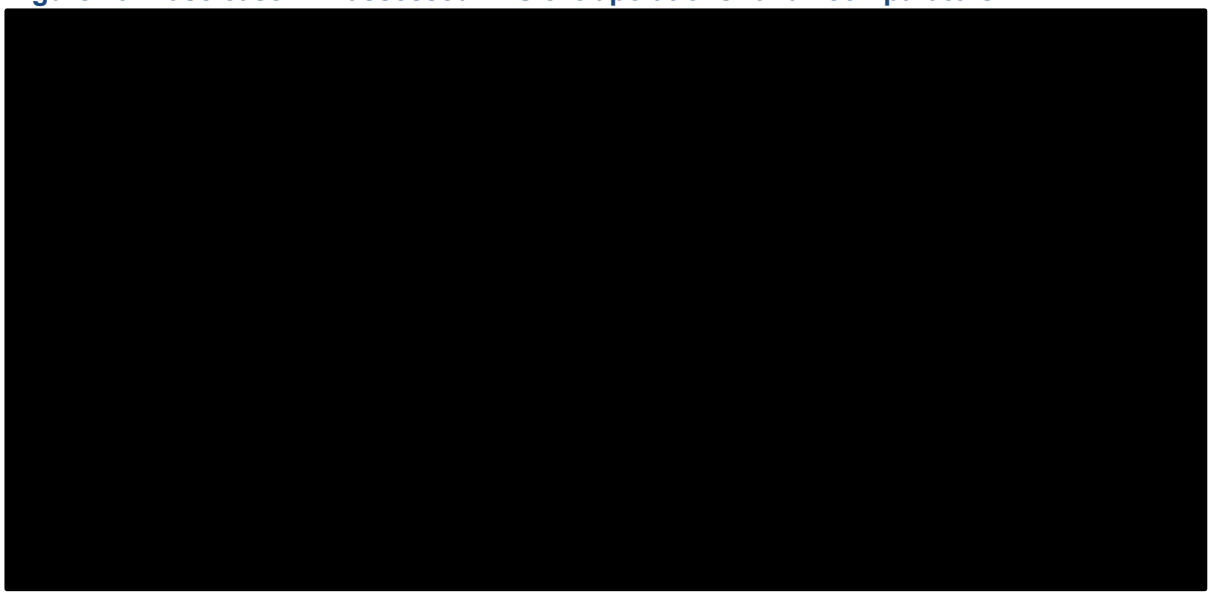
Comparator	TTP/PFS[a] HR (CrI)
TMX	[redacted]
FUL (500 mg)	Reference

Footnote: [a] Equivalence was assumed between TTP and PFS in the adjusted indirect comparison
Abbreviations: CrI: credible interval; FUL: fulvestrant; TMX: tamoxifen

Base case extrapolations

The base case extrapolations for PFS for all treatments are presented in Figure 19.

Figure 19. Base case INV assessed PFS extrapolations for all comparators



Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; INV: investigator; PFS: progression-free survival; TMX: tamoxifen.

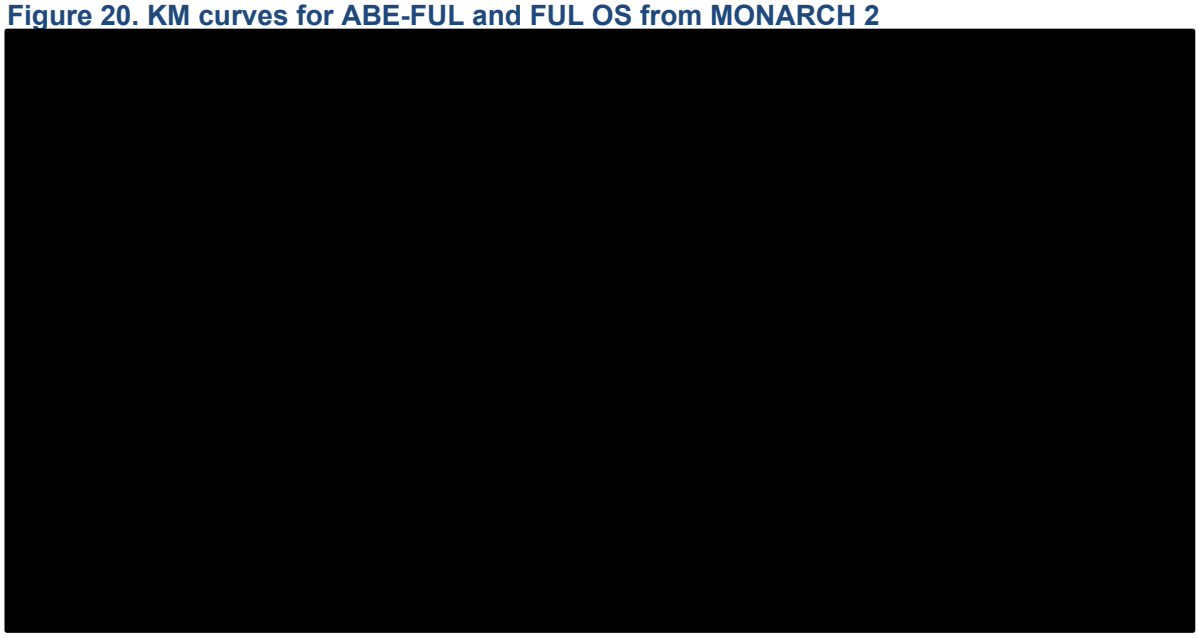
B.3.3.5 Overall survival

OS for ABE-FUL and FUL were estimated based on the ITT population of the MONARCH 2 trial and external data to inform long-term extrapolations.

ABE-FUL and FUL

The observed KM data for OS in MONARCH 2 are presented in Figure 20.

Figure 20. KM curves for ABE-FUL and FUL OS from MONARCH 2

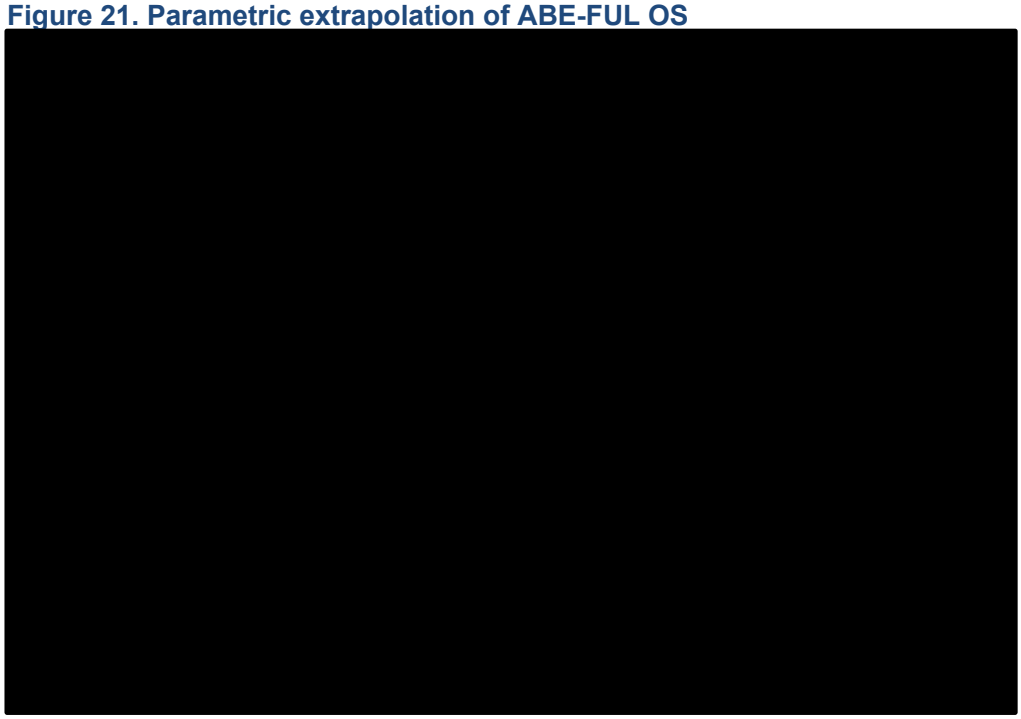


Abbreviations: ABEMA: abemaciclib; FUL: fulvestrant; KM: Kaplan-Meier; OS: overall survival.

Cumulative hazard and log-log plots for OS are presented in Appendix M1.2, Figure 21 and Figure 22, respectively. The cumulative hazard and log-log plots indicated no evidence of violation of the proportional hazards assumption, indicating a proportional hazards model may be appropriate for these data.

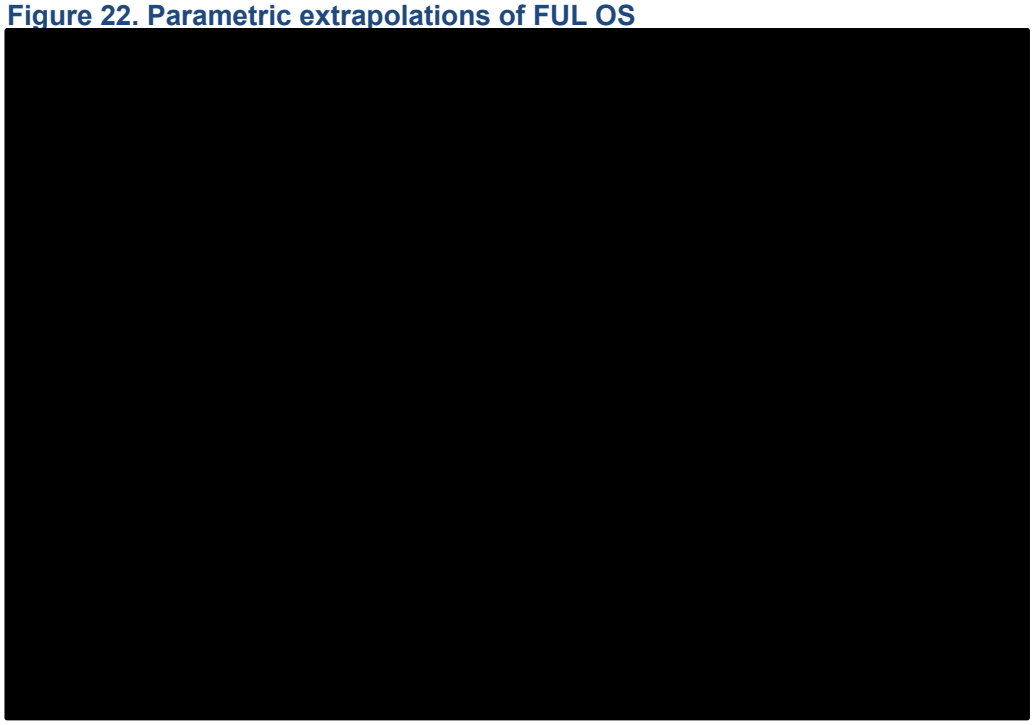
Standard parametric distributions were fitted to the MONARCH 2 data using the same approach as applied for PFS. An overlay of the OS KM plots for ABE-FUL and FUL with the parametric extrapolations based on the fitted joint models are presented in Figure 21 and Figure 22, respectively. The corresponding AIC and BIC statistics and long-term OS estimates are presented in Appendix M2.3, Table 69 and Table 70, respectively. Cox-Snell residual plots are presented in Appendix M2.3, Figure 32 and Figure 33. All-cause mortality was not incorporated into the model, since it was expected to have limited impact on the incremental results given the limited life expectancy in this population.

Figure 21. Parametric extrapolation of ABE-FUL OS



Abbreviations: ABE: abemaciclib; FUL: fulvestrant; KM: Kaplan-Meier; OS: overall survival.

Figure 22. Parametric extrapolations of FUL OS



Abbreviations: FUL: fulvestrant; KM: Kaplan-Meier; OS: overall survival.

The Gompertz, Weibull and gamma models provided the best fit based on AIC and BIC statistics and Cox-Snell residual plots. The Gompertz model provided the best fit based on both AIC and BIC. All models with the exception of the exponential distribution appeared to fit well to the observed data; the exponential model appeared to slightly underestimate OS between 6 and 18 months for both arms.

A comparison of the extrapolated OS from these distributions and external OS data for FUL was made to assess the plausibility of the long-term extrapolations (Figure 23). The CONFIRM trial,[64, 110] identified in the SLR, was the only study that provided long-term OS data for FUL 500 mg and FUL 250 mg (maximum OS follow-up for FUL 500 mg was approximately 80 months, corresponding to around 20% of patients remaining in the trial). The extrapolations based on the Gompertz, gamma and Weibull distributions aligned more closely with the CONFIRM trial data after approximately 40 months than the other distributions (exponential, log-normal, log-logistic); the Weibull distribution provided the closest alignment. Given that the CONFIRM trial population was a more pre-treated population than the MONARCH 2 population, clinical outcomes from this trial were expected to be worse for patients and the OS data were not expected to fully align. The extrapolations based on the log-normal, log-logistic and exponential distributions appeared to overestimate OS compared to the CONFIRM data.

Figure 23. Parametric extrapolations of FUL OS with KM data for FUL 500mg from CONFIRM

Abbreviations: FUL: fulvestrant; KM: Kaplan-Meier; OS: overall survival

Considering this, a Weibull distribution using data from the MONARCH 2 trial was selected to model OS for ABE-FUL and FUL in the base case. However, estimates of OS from the Weibull distribution were considered to be uncertain regarding:

- Long-term extrapolation for FUL
- Long-term treatment effect for ABE-FUL vs FUL

Therefore, an alternative approach was conducted whereby the extrapolations of OS for both arms were informed using long-term external data.

The FUL 500 mg data from the CONFIRM study were used to inform the long-term survival extrapolations in the base case. The process for selecting distributions, described for PFS, was applied to re-constructed individual patient data (IPD) from the CONFIRM trial for the FUL 500 mg arm. The re-constructed IPD was estimated by digitising the published KM graph and using a published algorithm (Guyot 2012).[111] A Weibull distribution was selected. The hazard rate from the Weibull distribution fitted to the CONFIRM data was applied to the Weibull distribution fitted to the MONARCH 2 data at a selected time point to extrapolate OS based on the estimated hazard from the CONFIRM study. This approach assumed that the hazard rate was equivalent in both ABE-FUL and FUL arms when the CONFIRM hazard was applied. This assumption was considered to be appropriate due to the lack of a treatment difference observed in the tail of the KM and the immaturity of the MONARCH 2 data at the time of the analysis.

In the base case, the time point at which the extrapolation was informed by the CONFIRM data was chosen to be [redacted] months, in line with the maximum follow-up on the ABE-FUL arm of the MONARCH 2 trial.

In addition, the treatment effect for ABE-FUL vs FUL was tapered between two time points, which involved increasing the HR gradually to reach 1 at the time point of extrapolation ([redacted] months). The time point at which the tapering started was chosen to be [redacted] months based on a Cox-Snell residual plot for the fitted Weibull distribution to the MONARCH 2 data (Appendix M.2.3, Figure 32). This represented the point after which the parametric model was shown to provide a poor fit to the MONARCH 2 data. Scenarios were conducted to explore the impact of using alternative time points for the tapering and of applying no tapering.

Clinical opinion was sought on the plausibility of the OS extrapolations for the approaches assessed. The base case approach to apply both tapering and use the CONFIRM data was considered to provide plausible extrapolations for FUL and apply conservative assumptions for the ABE-FUL treatment effect in the absence of further evidence.

As a scenario, a Gompertz distribution was used for the MONARCH 2 trial period as this represented the next best fitting distribution to the data. To explore the impact of using the external data, a scenario was conducted using the extrapolations based on the joint Weibull distribution fitted to the MONARCH 2 data.

Parameter estimates for the selected distributions from modelling the OS data from MONARCH 2 are presented in Appendix M2.3, Table 71.

Results for the models fitted to the CONFIRM data are presented in Appendix M2.4.

Comparators

OS estimates for EXE and EXE-EVE were estimated by applying the relative treatment effects generated by the NMA (Table 28) to the FUL OS curve based on the MONARCH 2 trial up until [redacted] months. As described in Section B.3.3.2, the results from the adjusted indirect comparison were used to inform the relative effect of TMX vs FUL in terms of OS (Table 29). As for EXE and EXE-EVE, the TMX treatment effect was applied to the FUL OS curve based on the MONARCH 2 trial up until [redacted] months.

Table 28. Hazard ratios estimated by the NMA (95% credible interval) for OS

Comparator	OS
EXE (25 mg)	[redacted]
EXE (25 mg)-EVE (10 mg)	[redacted]
FUL (500 mg)	Reference

Abbreviations: ABE: abemaciclib; EXE: exemestane; FUL: fulvestrant; OS: overall survival.

Table 29. Hazard ratio for TMX vs FUL 500 estimated by the adjusted indirect comparison (95% credible interval) for OS

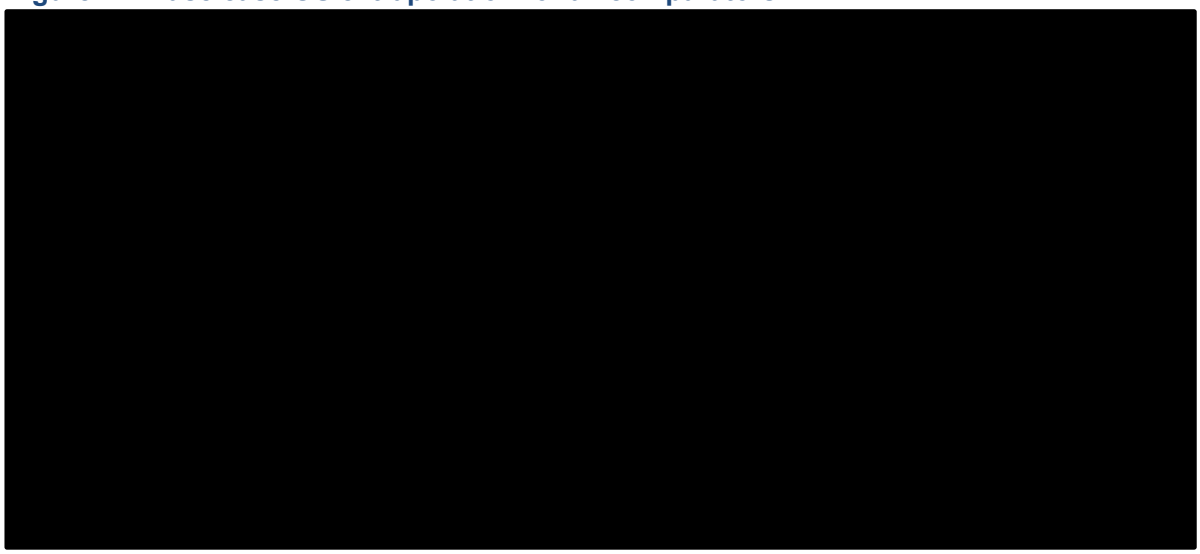
Comparator	OS HR (CrI)
TMX	[redacted]
FUL (500 mg)	Reference

Abbreviations: CrI: credible interval; FUL: fulvestrant; TMX: tamoxifen

Base case extrapolations

The base case extrapolations for all treatments are presented in Figure 24. Extrapolations based on various scenarios assessed for modelling OS have been provided in the Appendix 2.5, Figures 35 to Figure 40.

Figure 24. Base case OS extrapolation for all comparators



Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; OS: overall survival; TMX: tamoxifen.

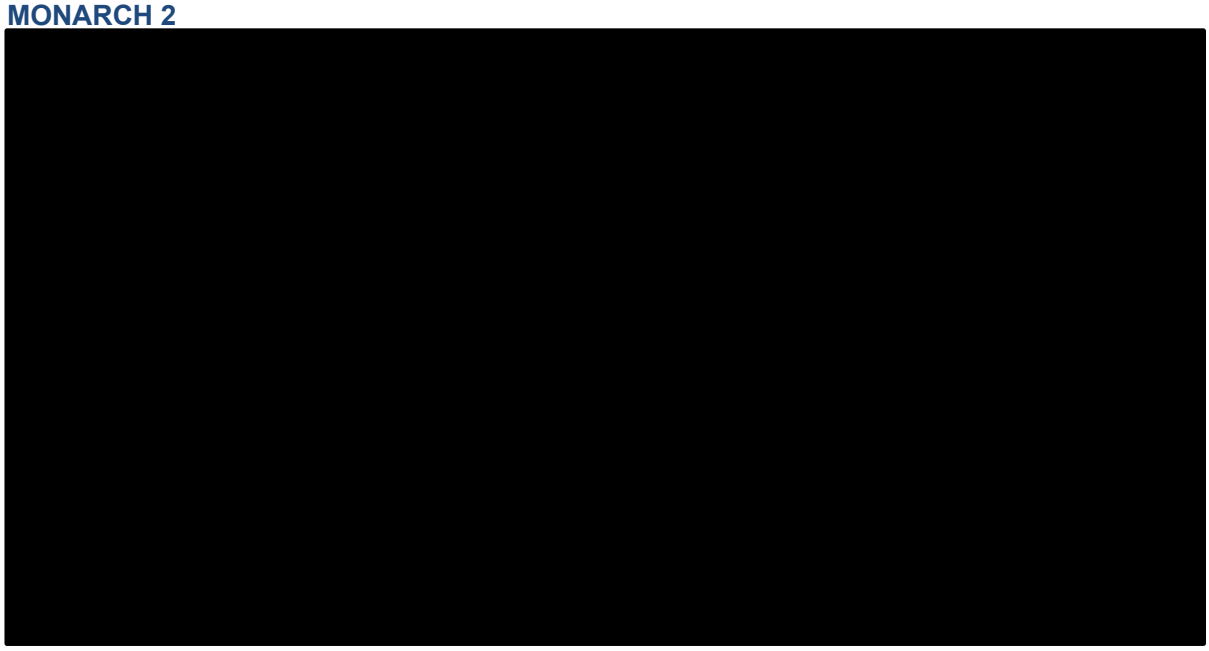
B.3.3.6 Duration of therapy

An analysis of duration of therapy (i.e. time-on-treatment) was conducted to model the rate of treatment discontinuation and allow a more accurate estimation of drug acquisition costs for ABE-FUL and the comparators.

ABE-FUL and FUL

Duration of therapy for ABE-FUL and FUL were estimated based on data from the MONARCH 2 trial. The observed KM data for time to discontinuation of the investigated treatment (i.e. ABE in the ABE-FUL arm or PBO in the PBO-FUL) are presented in Figure 25.

Figure 25. KM curve of time to discontinuation for ABE-FUL and PBO-FUL from MONARCH 2



Abbreviations: ABE: abemaciclib; FUL: fulvestrant; KM: Kaplan-Meier; PBO: placebo; ToT: time on treatment.

The modelling approach and the process for selecting the most appropriate parametric model for this endpoint replicated that of PFS. Consideration was also given to the distributions used to estimate PFS, given the anticipated correlation between the two endpoints.

An overlay of the KM for time to discontinuation for ABE-FUL and PBO-FUL with the parametric extrapolations based on the fitted joint models is presented in Figure 26 and Figure 27, respectively. The proportional hazards were tested, and the assumption appeared to hold, with the lines for ABE-FUL and PBO-FUL being close to those for PFS with no sign of violation. The corresponding AIC and BIC statistics, and long-term duration of therapy estimates are presented in Appendix M.3, Table 74 and Table 75, respectively. Cox-Snell residual plots are presented in Appendix M.3, Figure 41.

Figure 26. Parametric extrapolations of ABE-FUL duration of therapy

Abbreviations: ABE: abemaciclib; FUL: fulvestrant; KM: Kaplan-Meier.

Figure 27. Parametric extrapolations of PBO-FUL duration of therapy

Abbreviations: FUL: fulvestrant; KM: Kaplan-Meier.

The Gompertz, log-normal and gamma models provided the best fit based on AIC and BIC statistics and Cox-Snell residual plots; the Gompertz model provided the best fit based on BIC. The exponential distribution provided the poorest fit in comparison to the other models based on the AIC and BIC criteria. The Weibull distribution provided the second poorest fit based on the AIC and BIC criteria.

The lognormal, log-logistic, Gompertz and gamma distributions appeared to fit well to the observed data. However, the lognormal, log-logistic and Gompertz distributions appeared to overestimate duration of therapy compared to the tails of the KM data after approximately 15 months. In the PBO-FUL arm, the exponential distribution appeared to overestimate duration of therapy between approximately 3 and 9 months. For the FUL data, the Weibull distribution appeared to fit well, and for ABE-FUL the Weibull distribution showed similar over- or under-estimates as the exponential distribution.

In addition to model fit, consideration was given to the distribution chosen for modelling PFS for ABE-FUL and FUL and the associated relationship between PFS and duration of therapy, given both therapies are both treat-to-progression regimens. Using AFT distributions led to higher proportions of patients estimated to remain on treatment in both arms than those who had progressed or died (i.e. duration of therapy curves were higher than the PFS curves in the extrapolations), compared to proportional hazards distributions.

Considering this, and to keep the distributions consistent with those chosen for PFS, a joint Weibull distribution was selected to model duration of therapy for ABE-FUL and FUL in the base case. A joint gamma distribution was used in scenario analyses to explore the impact of a better fitting distribution.

Parameter estimates for the selected distributions for modelling duration of therapy from MONARCH 2 are presented in Appendix M.3, Table 76.

Comparators

KM estimates of duration of therapy for the comparators not included in the MONARCH 2 trial were unavailable from the primary publications. Considering this, duration of therapy for all other comparators were estimated based on the median duration of therapy estimates reported in the publications used to inform PFS and OS. Two approaches were assessed:

- Approach 1: Using the median duration of therapy and median PFS from the trial publications, a HR was estimated to reflect the difference in the medians. This hazard ratio was then applied to the PFS distribution in the CE model to attain relative estimates of duration of therapy for the comparators.
- Approach 2: Using the median duration of therapy from the trial publications, a HR was estimated to reflect the difference between this and the median PFS from the CE model. This hazard ratio was then applied to the PFS distribution in the CE model to attain relative estimates of duration of therapy for the comparators.

Approach 1 was considered as the base case when including all comparators, as it used the within trial difference between PFS and duration of therapy. Therefore, it was considered to more accurately reflect the relative difference between these outcomes. Approach 2 was assessed in scenario analysis as an alternative approach.

Data for both approaches are included in Appendix M.3, Table 77. For Approach 1, sources for duration of therapy were chosen based on median PFS data being available to calculate the relative difference. For Approach 2, sources for duration of therapy were chosen based on maturity of the data and sample size.

Base case extrapolations

The base case extrapolations for duration of therapy for all treatments are presented in Figure 28.

Figure 28. Base case duration of therapy extrapolations for all comparators

Abbreviations: ABE: abemaciclib; FUL: fulvestrant; EVE: everolimus; EXE: exemestane; TMX: tamoxifen.

B.3.3.7 Subgroup analyses

The initial trial design for MONARCH 2 involved patients receiving ABE at a starting dose of 200 mg every 12 hours (Q12H). A protocol amendment for the MONARCH 2 trial (protocol amendment (a)) was made in January 2015 (the original protocol was approved in April 2014) to change the starting dose of ABE to 150 mg Q12H and mandated that all patients receiving the 200 mg dose have their dose reduced to 150 mg.

In the trial, of those randomised to receive ABE, 121 patients were given the 200 mg starting dose (pre-amendment population) and 320 patients were given the 150 mg starting dose (post-amendment population). The pre- and post-amendment populations were comparable with respect to age, menopausal status and prior sensitivity to ET. Small differences in nature of disease and race were observed. The median dose intensity for patients randomised to the ABE arm pre- and post-amendment was observed to be similar ([redacted] mg/day versus [redacted] mg/day for the 200 mg and 150 mg starting dose populations, respectively). Furthermore, efficacy was consistent with respect to INV assessed PFS and ORR. These observations support the use of the ITT study population, which included all randomised patients from the 200 mg and 150 mg starting doses, as the base case.

The proposed licensed dose for ABE in combination with FUL is 150 mg Q12H. As such a scenario exploring the subgroup of patients who were randomised to receive ABE at the 150 mg starting dose was conducted in the model using data from the MONARCH 2 trial.

Approach for the subgroup analyses

For the outcomes described in Sections B.3.3.4, B.3.3.5 and B.3.3.6 (PFS, OS and duration of therapy), additional parametric survival models were fitted, including the following:

- Main effect for treatment (ABE-FUL vs FUL)
- Interaction effect between treatment and starting dose (150 mg starting dose ABE vs 200 mg starting dose for ABE and FUL)

The main effect for treatment is the same as in the previously described regression models. The interaction effect adjusts for the differences in starting dose for the ABE arm.

Typically when including interaction terms to assess subgroup effects in regression models, a main effect is also incorporated for the subgroup (i.e. a covariate for starting dose corresponding to the effect on FUL). Patients randomised to receive PBO instead of ABE, in combination with FUL, received a matching dose to those randomised to receive ABE. Clinical outcomes between patients receiving the different starting doses for PBO were not expected to be due to the dose of PBO given. In addition, including a main effect for starting dose could impact on the relative treatment effect estimate for ABE-FUL vs FUL. As the difference in starting dose is only expected to influence the clinical outcomes for patients who received ABE, a main effect for starting dose was not included and only an interaction term was included as described above.

The model fitting process as described for PFS based on the ITT population was repeated including the subgroup terms. The selected distributions were included in the CE model to predict clinical outcomes for ABE-FUL based on the 150 mg starting dose and FUL. The estimates for ABE-FUL based on the 200 mg starting dose, which could also be obtained from the model, were not required.

Subgroup analysis for PFS

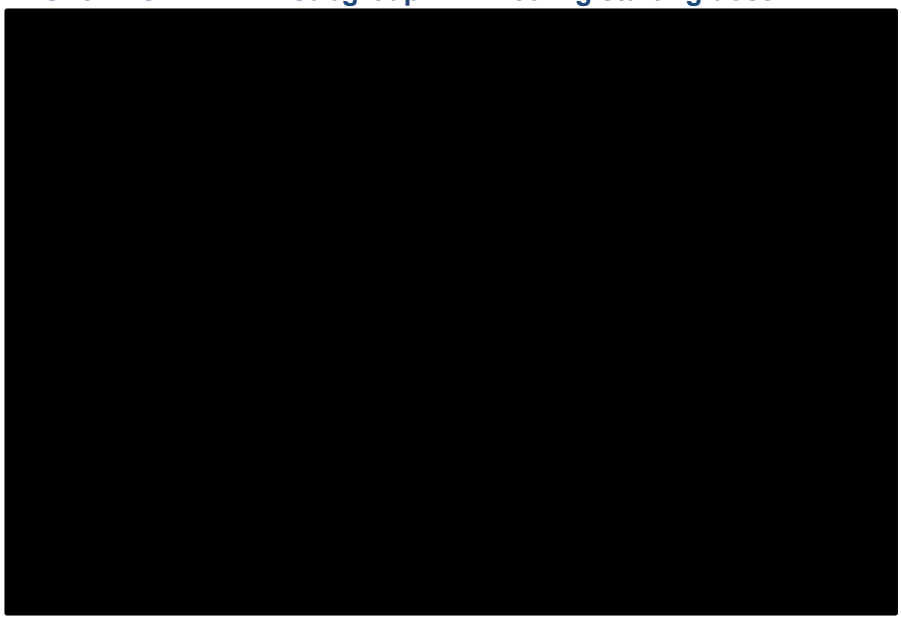
The observed KM data for MONARCH 2 based on the INV assessment and stratified by starting dose are presented in Figure 29.

Figure 29. KM curves for ABE-FUL and FUL INV assessed PFS stratified by starting dose for ABE

Abbreviations: ABE: abemaciclib; FUL: fulvestrant; INV: investigator; KM: Kaplan-Meier; PFS: progression-free survival.

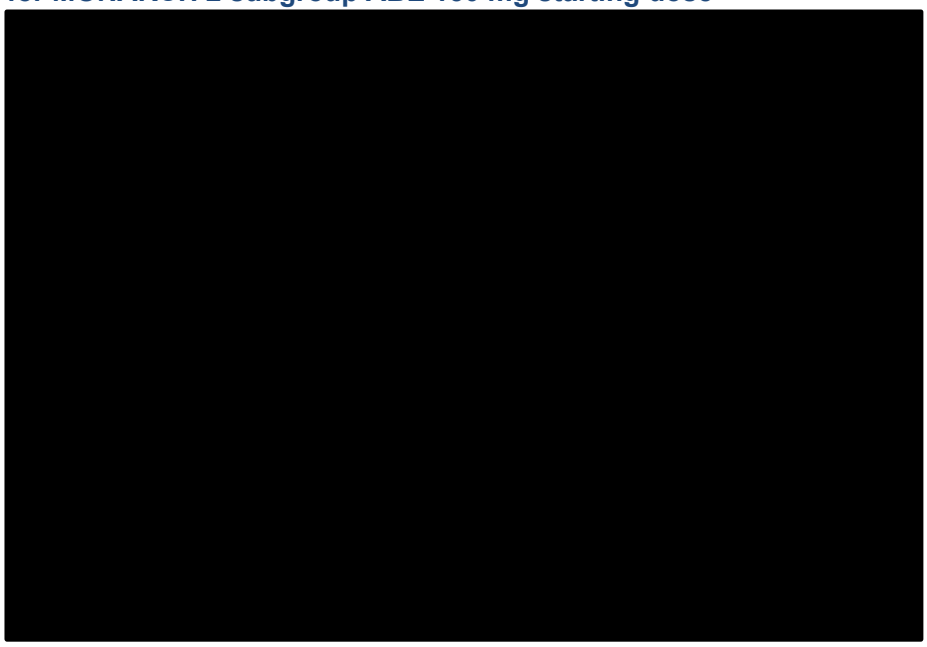
Standard parametric distributions were fitted to the MONARCH 2 data, with and without adjustment for interval censoring, using the same approach as applied for PFS using the ITT population data. An overlay of the KM for ABE-FUL and FUL with the parametric extrapolations based on the fitted joint models is presented in Figure 30 and Figure 31, respectively, for the models adjusted for interval censoring. The parametric extrapolations for the non-interval censored analysis are presented in Appendix M.4.2, Figure 42 and Figure 43. The corresponding AIC and BIC statistics, and long-term PFS estimates are presented in Appendix M.4.2, Table 81 and Table 82, respectively.

Figure 30. Interval censored adjusted parametric extrapolations of ABE-FUL INV assessed PFS for MONARCH 2 subgroup ABE 150 mg starting dose



Abbreviations: ABE: abemaciclib; FUL: fulvestrant; INV: investigator; KM: Kaplan-Meier; PFS: progression-free survival.

Figure 31. Interval censored adjusted parametric extrapolations of FUL INV assessed PFS for MONARCH 2 subgroup ABE 150 mg starting dose



Abbreviations: ABE: abemaciclib; FUL: fulvestrant; IA: investigator-assessed; INV: investigator; KM: Kaplan-Meier; PFS: progression-free survival.

The Weibull and Gompertz models provided the best fit after adjusting for interval censoring based on AIC and BIC statistics. The Weibull model provided the best fit based on both AIC and BIC. The Weibull, Gompertz and gamma models appeared to fit well to the observed data. In contrast, the lognormal and log-logistic models appeared to overestimate PFS after 22 months in the ABE 150 mg arm, as per the ITT analysis. Considering this, the Weibull distribution was included as the base case for the scenario based on starting dose.

The comparators outside the MONARCH 2 trial were incorporated using the same approach as for the ITT population (HRs applied to the FUL survival distributions).

The base case extrapolations for all treatments are presented in Figure 32.

Figure 32. Interval censored adjusted parametric extrapolations of INV assessed PFS for MONARCH 2 subgroup ABE 150 mg starting dose for all comparators

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; INV: investigator; PFS: progression-free survival; TMX: tamoxifen.

Subgroup analysis for OS

The observed KM data for MONARCH 2 for OS and stratified by starting dose are presented in Figure 33.

Figure 33. KM curves for ABE-FUL and FUL OS stratified by starting dose for ABE

Abbreviations: ABE: abemaciclib; FUL: fulvestrant; KM: Kaplan-Meier; OS: overall survival.

Standard parametric distributions were fitted to the MONARCH 2 data using the same approach as applied for PFS using the ITT population data. An overlay of the KM for ABE-FUL and FUL with the parametric extrapolations based on the fitted joint models is presented in Figure 34 and Figure 35, respectively. The corresponding AIC and BIC statistics, and long-term OS estimates are presented in Appendix M.4.4, Table 86 and Table 87 respectively. Cox-Snell residual plots are presented in Appendix M.4.4, Figure 45.

Figure 34. Parametric extrapolations for ABE-FUL OS for MONARCH 2 subgroup ABE 150 mg starting dose

Abbreviations: ABE: abemaciclib; FUL: fulvestrant; IA: investigator-assessed; KM: Kaplan-Meier; OS: overall survival; PFS: progression-free survival.

Figure 35. Parametric extrapolations of FUL OS for MONARCH 2 subgroup ABE 150 mg starting dose

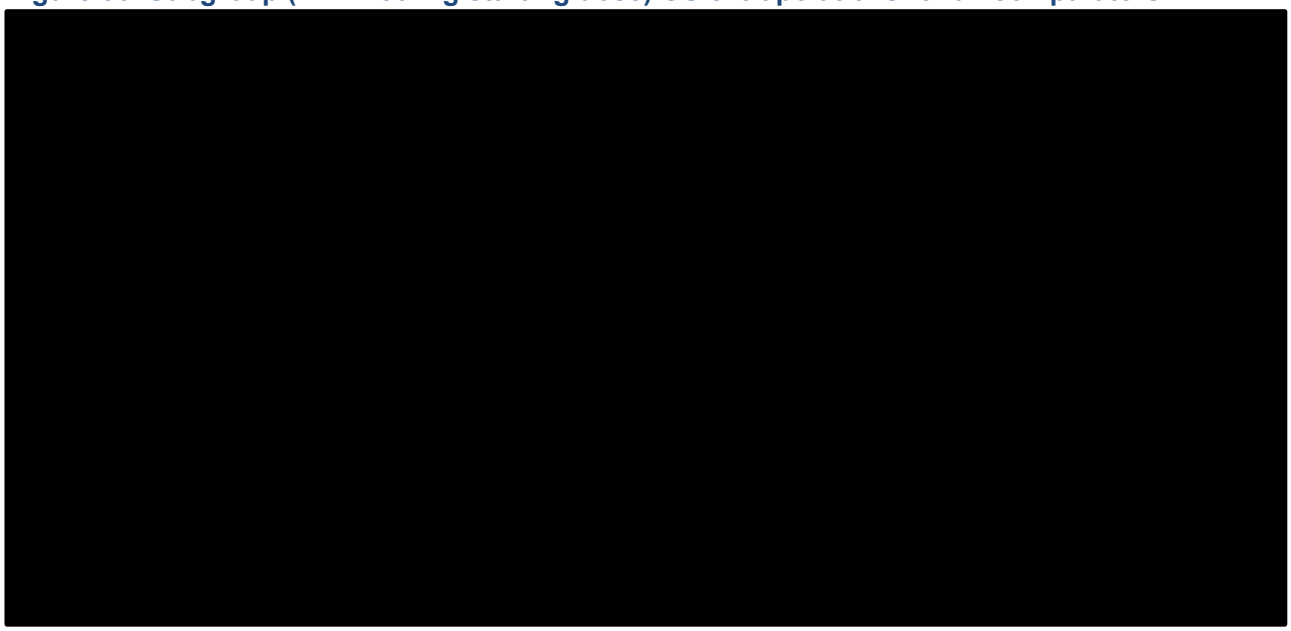
Abbreviations: ABE: abemaciclib; FUL: fulvestrant; IA: investigator-assessed; KM: Kaplan-Meier; OS: overall survival; PFS: progression-free survival.

The Weibull and Gompertz models provided the best fit based on AIC and BIC statistics. The Weibull model provided the best fit based on both AIC and BIC, as in the ITT analysis. Considering this, the Weibull distribution was included as the base case for the scenario based on starting dose, and the Gompertz distribution was included as an alternative scenario. The extrapolation approach described in Section B.3.3.4 was applied in the same way in the subgroup scenario.

The comparators outside the MONARCH 2 trial were incorporated using the same approach as for the ITT population (HRs applied to the FUL survival distributions).

The base case extrapolations for all treatments are presented in Figure 36.

Figure 36. Subgroup (ABE 150 mg starting dose) OS extrapolations for all comparators

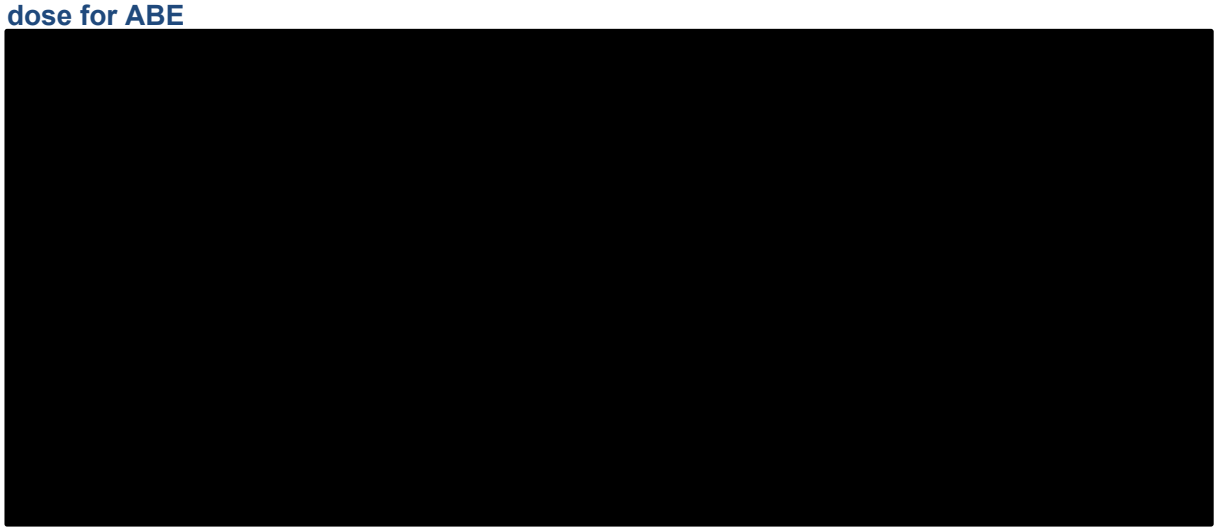


Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; IA: investigator-assessed; KM: Kaplan-Meier; OS: overall survival; PFS: progression-free survival; TMX: tamoxifen.

Subgroup analysis for duration of therapy

The observed KM data for MONARCH 2 based on duration of therapy and stratified by starting dose are presented in Figure 37.

Figure 37. KM curves for ABE-FUL and PBO-FUL duration of therapy stratified by starting dose for ABE



Abbreviations: ABE: abemaciclib; FUL: fulvestrant; KM: Kaplan-Meier; PBO: placebo.

In order to keep the distributions consistent with those chosen for PFS for the subgroup scenario, the Weibull and Gompertz distributions were included in the model, with the Weibull considered as the base case and Gompertz in a scenario.

The comparators outside the MONARCH 2 trial were incorporated using the same approach as for the ITT population (described in Section B.3.3.6).

The base case extrapolations for all treatments are presented in Figure 38.

Figure 38. Subgroup (ABE 150 mg starting dose) duration of therapy extrapolations for all comparators

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; KM: Kaplan-Meier.

The corresponding plots, assessment statistics and regression models for those fitted to the duration of therapy data are provided in Appendix M.4.5.

B.3.4 *Measurement and valuation of health effects*

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

The model necessitated estimates of HRQoL for both the pre- and post-progression health states. In the base case analysis, the EQ-5D-5L data collected in the MONARCH 2 trial was cross-walked to the 3L scale using the Van Hout (2012) approach.[63] The results of the cross-walk were subsequently valued using the Dolan (1997) publication, which provides the standard UK EQ-5D-3L weights.[112]

Two repeated measures regression models were fitted to the cross-walked data to estimate utility, including the following covariates as main effects:

- Model 1: Baseline utility and post- vs pre-progression
- Model 2: Baseline utility, post- vs pre-progression, and treatment

Model 1 allowed for pre- and post-progression utility to be estimated across treatments. Model 2 allowed for treatment specific utility for pre- and post-progression to be estimated. Analyses were conducted using data obtained from all of the safety population patients who completed at least one post-baseline assessment.

The health state utilities estimated by these regressions are presented in Table 30.

Table 30. Health state utilities predicted from the MONARCH 2 regression model

Health state	Utilities Model 1 – without treatment covariate	Utilities Model 2 – with treatment covariate
Pre-progression	[redacted]	N/A
Post-progression	[redacted]	N/A
Pre-progression (ABE-FUL)	N/A	[redacted]
Pre-progression (FUL)	N/A	[redacted]
Post-progression (ABE-FUL)	N/A	[redacted]
Post-progression (FUL)	N/A	[redacted]

Abbreviations: ABE: abemaciclib; FUL: fulvestrant.

As a conservative approach, Model 1 was used in the base case for estimating pre-progression utility, given there was no significant difference identified when adjusting for treatment. This model estimated a pre-progression utility value of [redacted].

Due to the immaturity of the post-progression data from MONARCH 2, an alternative utility estimate for post-progression was used in the base case. The FUL NICE submission (TA239)[97] used data from Lloyd (2006)[94] for informing post-progression utilities (0.44), and the population assessed in this submission was comparable to MONARCH 2. Similarly to the TA495 and TA496 appraisals for locally advanced or metastatic breast cancer, it was therefore considered appropriate to include the post-progression utility value from Lloyd (2006) instead of MONARCH

2. The ERG made a correction to the post-progression utility value for TA239 and estimated this as 0.505 instead of 0.44, which was used in this cost-effectiveness analysis in the base case.

As a scenario, the utility values based on the EQ-5D-5L data without the crosswalk were included. The regression models for estimating utility in the base case and scenario are provided in Appendix M.5, including the baseline utility values.

B.3.4.2 Mapping

No mapping was performed in this analysis, as EQ-5D data were sourced directly from the MONARCH 2 trial.

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

A SLR and update was conducted to identify utility studies relevant to treatment options in the management of HR+/HER2− locally advanced or metastatic breast cancer. The original utility SLR identified eight full publications and one conference proceeding, of which, six used generic preference-based measures of health valuation (EQ-5D). The updated utility SLR identified two full publications and five conference proceedings, all of which used generic preference-based measures of health valuation (EQ-5D). Twelve of these studies evaluated patients with advanced or metastatic breast cancer, one of which specified HER2− patients.

The heterogeneity of populations across studies hindered direct comparisons of HRQoL among individuals with advanced HR+/HER2− locally advanced or metastatic breast cancer. However, all estimates of utility reported in the studies were noticeably different from an estimate of perfect health (equivalent to 1), with HRQoL decreasing with increased disease severity. HRQoL was mapped from the cancer-specific measure EORTC-QLQ-C30 to EQ-5D in three studies.

Appendix H details the methods and results of the SLR conducted to identify utility studies relevant to treatment options for the management of HR+/HER2− locally advanced or metastatic breast cancer. Due to the lack of studies identified evaluating patients representative of the patient population under consideration in this analysis, EQ-5D-5L data collected in MONARCH 2 were preferred, as described above.

B.3.4.4 Adverse reactions

The rates of AEs for patients on ABE-FUL and FUL in the model were based on the TEAEs which occurred in the ITT population of the MONARCH 2 trial. AEs were selected for inclusion if they were grade 3–4 events occurring in more than 5% of patients for at least one comparator. AE rates for the comparators were based on the primary publications used in the NMA (Table 31). BOLERO-2[113] was used to parameterise AE rates for EXE and EXE-EVE, as this was the only study identified by the SLR which reported the AE rates. AE rates for TMX were assumed the same as FUL based on expected similarity between the therapy classes. This assumption was required due to the lack of available AE data that aligned with the AE inclusion criteria, and the assumption validated with a clinical expert.

Table 31. Adverse event probabilities, by comparator

Adverse event	ABE-FUL[35]	EXE[113]	EXE-EVE[113]	FUL[35]	TMX[35]
Anaemia	7.26%	0.00%	7.05%	0.90%	0.90%
Diarrhoea	13.38%	0.00%	2.07%	0.45%	0.45%
Dyspnoea	2.72%	0.00%	4.98%	1.35%	1.35%
Gamma-glutamyltransferase (GGT) increase	[redacted]	2.94%	7.05%	[redacted]	[redacted]
Hyperglycaemia	[redacted]	0.00%	4.98%	[redacted]	[redacted]
Leukopenia	8.84%	0.00%	0.00%	0.00%	0.00%
Neutropenia	26.53%	0.00%	0.00%	1.79%	1.79%
Stomatitis	0.45%	0.00%	8.09%	0.00%	0.00%

Source: ABE-FUL, MONARCH 2;[35] EXE, BOLERO 2;[113] EXE-EVE, BOLERO 2; FUL, MONARCH 2;[35] TMX, assumed equal to FUL[35]
Abbreviations: ABE; abemaciclib; FUL; fulvestrant; EVE; everolimus; EXE; exemestane; TMX: tamoxifen.

The impact of AEs on HRQoL was incorporated by applying a QALY decrement for each event. The combination of the utility decrement for the event, the duration of the event, and the proportion of patients experiencing the event all determined the expected QALY decrement associated with each AE.

$$QALY\ decrement = \%\ patients\ experiencing\ AE\ \times AE\ utility\ decrement\ \times AE\ duration\ in\ years$$

A SLR of utilities was consulted to identify utility data and event durations for each of the AEs identified. However, no data were reported in the identified studies. Consequently, utility decrements were informed by Hudgens (2016),[114] where available. This study mapped EORTC QLQ-C30 data collected in Kaufman (2015)[115] – a large RCT comparing eribulin (ERI) to capecitabine (CAP) in patients with advanced breast cancer − onto the EQ-5D to estimate health state utilities and decrements associated with AEs. Utility decrements for AEs which were not reported in Hudgens (2016) were based on utility studies conducted in solid tumours. These data are presented in Table 32.

Table 32. Adverse event disutilities

Adverse event	Utility decrement	Source
Anaemia	−0.119	Swinburn 2010[116]
Diarrhoea	−0.006	Hudgens 2016[114]
Dyspnoea	−0.029	Hudgens 2016[114] (assumption: same as asthenia/fatigue)
GGT increase	0.000	Assumed to have no utility impact
Hyperglycaemia	−0.119	Swinburn 2010[116] (assumption: same as anaemia)
Leukopenia	−0.003	Hudgens 2016[114]
Neutropenia	−0.007	Hudgens 2016[114]
Stomatitis	−0.269	Swinburn 2010[116] (disutility for mucositis only)

Abbreviations: GGT: gamma-glutamyl transferase.

AE event durations were not reported in Hudgens (2016). Considering this, durations were derived from an STA of pixantrone (ID414) for the treatment of adults with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma, in which the manufacturer's submission summarised HRQoL data from a number of solid tumour studies.[117] The AE durations included in the model are presented in Table 33. For diarrhoea, the MONARCH 2 study data were used to inform the mean duration as no data were provided in ID414. This was considered to be more plausible than using an alternative AE reported in ID414 and making an assumption regarding equivalence.

Table 33. Adverse event durations

Adverse event	Duration (days)	Source
Anaemia	16.1	ID414 MS[117]
Diarrhoea	6.0	MONARCH 2 (Sledge 2017)[8]
Dyspnoea	12.7	ID414 MS (assumption: same as fatigue)[117]
GGT increase	0	Assumed to have no utility impact
Hyperglycemia	16.1	ID414 MS (assumption: same as anaemia)[117]
Leukopenia	14.0	ID414 MS[117]
Neutropenia	15.1	ID414 MS[117]
Stomatitis	4.0	ID414 MS (assumption: same as mucosal inflammation) [117]

Abbreviations: GGT: gamma-glutamyl transferase.

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

A summary of the utility values used in the cost-effectiveness analysis is provided below in Table 34.

Table 34. Summary of utility values for the base case cost-effectiveness analysis

State	Utility value: mean (standard error)	Reference in submission (section and page number)	Justification
Pre-progression (ABE-FUL)	[redacted] (derived from regression analysis)	B.3.4.1, page 125	MONARCH 2
Post-progression (ABE-FUL)	[redacted] (derived from regression analysis)	B.3.4.1, page 125	Utilities are aligned with those in TA239[97] and TA496[41]
Anaemia	−0.119	B.3.4.4, page 127	Rates of AEs for patients on ABE-FUL were based on TRAEs that occurred in the MONARCH 2 ITT population;
Diarrhoea	−0.006		
Dyspnoea	−0.029		
GGT increase	0.000		
Hyperglycaemia	−0.119		
Leukopenia	−0.003		

Neutropenia	−0.007		AE rates for comparators were based on the primary publications used in the NMA
Stomatitis	−0.269		

Abbreviations: ABE: abemaciclib; AE: adverse events; FUL: fulvestrant; GGT: gamma-glutamyl transferase; NMA: network meta-analysis; TRAE: treatment-related adverse events.

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

The following resource use categories were captured in the analysis:

- Section B.3.5.1: drug acquisition and administration costs
- Section B.3.5.2: best supportive care (BSC), follow-up care, hospitalisations, post-progression therapy, terminal care
- Section B.3.5.3: AE management and costs

Costs were sourced for the year 2017. Where these were not available for 2017, they were inflated accordingly using the HCHS index.[118] As per Section B.3.2.2, the perspective is that of the UK NHS and Personal Social Services (PSS). Drug costs for all pre-progression, post-progression and supportive care medications were primarily sourced from the electronic market information tool (eMIT)[119] national database and the Monthly Index of Medical Specialties (MIMS)[120] database of prescription and generic drugs, respectively.

A SLR was conducted to identify relevant cost and healthcare resource use studies in HR+/HER2– locally advanced or metastatic breast cancer. Full details pertaining to the methods and results of the SLR can be found in Appendix I. Forty-four studies were identified that reported data on resource use, whilst 49 studies reported data on the costs associated with breast cancer patients. Of these identified studies, 12 evaluated resource use, and 17 evaluated costs associated with HR+ and/ or HER2− locally advanced or metastatic breast cancer patients.

B.3.5.1 Intervention and comparators' costs and resource use

Drug acquisition

Drug acquisition costs were calculated by combining dosing regimens, relative dose intensity (RDI) adjustments and mean patient BSA data. Treatment regimens and RDI were based on the ABE-FUL and FUL regimens received in the MONARCH 2 trial (ABE-FUL: 150 mg twice daily/28 days; FUL: 500 mg every 28 days [day 1 and 15 of first cycle, day 1 of subsequent cycles]) and the primary publications used in the NMA. However, RDI was set to be 100% for all therapies in the base case setting.

Where only one source was available for a comparator, this was used to identify the treatment regimen for that comparator. For EXE, multiple sources were available. Data from BOLERO-2 (2003)[57] were used to parameterise EXE, as this was the trial with the longest follow-up identified from the SLR for EXE. The regimen from this study aligned with the other publications identified

from the SLR. Stenbygaard (1993)[74] was the only study identified in the SLR for TMX, and was therefore used to inform the TMX regimen.

Based on the study publications, all treatments were given to patients until discontinuation for reasons such as toxicity, withdrawal from the study and progression. Therefore, acquisition costs are assigned based on the duration of therapy distributions (described in Section B.3.3.6).

Unit costs were based on the eMIT and MIMS databases, depending on the availability of unit costs from eMIT. Treatment regimens and drug acquisition costs for each comparator are presented in Table 35 and Table 36, respectively. For FUL, which is administered intramuscularly, drug acquisition costs per patient were calculated by determining the number of vials needed to provide the required dose and multiplying by the unit price of the vial.

The following options for modelling vial wastage were incorporated in the CE model:

- Vial wastage: incorporate vial wastage (i.e. any leftover drug not used in a specific patient is wasted) based on selecting a single vial size that will provide the lowest acquisition cost based on cycle dosage (base case)
- Vial sharing: incorporate vial-sharing (i.e. any leftover drug is used for another patient) such that costs are accrued only for the actual amount of medication administered; the vial size with the lowest cost per mg is chosen.

This was used alongside the weekly dose delivered to calculate the acquisition cost per week.

For all scenarios described above, oral wastage was assumed whereby the acquisition costs would account for full packs being provided to patients. Nevertheless, in reality, patients may not consume all tablets in a full pack for each cycle, instead using them for a subsequent dose, meaning minimal wastage.

Table 35. Treatment regimens

Treatment	Study	Dose (mg)	Admins per cycle	Cycle length (days)	RDI	Comments
ABE-FUL	MONARCH 2[8]	ABE: 150 mg FUL: 500 mg	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
FUL	MONARCH 2[8]	500 mg	1 (2 in cycle 1 and 1 thereafter)	28	100%	RDI assumed to be 100% for IM treatment
EXE	BOLERO 2[57]	25 mg	28	28	100%	RDI assumed to be 100% for oral treatment
EXE-EVE	BOLERO 2[57]	EXE: 25 mg	EXE: 28 EVE: 28	28	EXE: 100% EVE: 100%	RDI assumed to be 100% for oral treatment

Treatment	Study	Dose (mg)	Admins per cycle	Cycle length (days)	RDI	Comments
		EVE: 10 mg				
TMX	Stenbygaard (1993)[74]	40 mg	28	28	100%	RDI assumed to be 100% for oral treatment

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; IM: intramuscular; RDI: relative dose intensity; TMX; tamoxifen.

Table 36. Drug acquisition costs

Treatment	Drug	Units	Vial/Pack size	Cost	Source
ABE-FUL	ABE	150	56	£[redacted]*	Eli Lilly Data on File
ABE-FUL	FUL	250	2	£522.41	BNF Online, accessed 13th March 2017[121]
FUL	FUL	250	2	£522.41	BNF Online, accessed 13th March 2017[121]
EXE	EXE	25	30	£3.69	eMIT, 12 month period to end June 2017[119]
EXE-EVE	EXE	25	30	£3.69	eMIT, 12 month period to end June 2017[119]
EXE-EVE	EVE	10	30	£2,673.00	BNF Online, accessed 13th March 2017[121]
TMX	TMX	20	30	£1.59	eMIT, 12 month period to end June 2017[119]

Footnotes: * Price for ABE with proposed PAS. List price of ABE is £[redacted].
Abbreviations: ABE: abemaciclib; BNF: British National Formulary; eMIT: electronic market information tool; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; TMX; tamoxifen.

Drug administration

Administration costs were sourced from the NHS Reference Costs 2016–17.[122] Administration costs were only applicable to FUL as all other pre-progression drugs were administered orally.

The administration costs for FUL were based on those used in the NICE technology appraisals for FUL (TA503 and TA239).[53, 97] The cost of administering the regular monthly dose of FUL was assumed to be captured in the cost of a consultation with an oncologist; therefore only the administration of the loading dose incurred an administration cost. A summary of the drug administration costs per cycle are provided in Table 37.

Table 37. Administration costs

Treatment	Drug	Administrations per cycle	Cost per administration	Source
FUL	FUL loading dose*	1	£172.67	NHS Reference costs, 2016-17, WF01A Non-admitted face-to-

Treatment	Drug	Administrations per cycle	Cost per administration	Source
				face attendance, First, Service Code 370 (Medical Oncology)[122]
FUL	FUL	1	£0.00†	Assumption

Footnotes: *Loading dose in first cycle only. †FUL administration costs are assumed to be captured within follow-up oncologist appointments in the FUL loading dose costs.
Abbreviations: FUL: fulvestrant; NHS: National Health Service.

B.3.5.2 Health-state unit costs and resource use

Best supportive care

Components of BSC were identified from clinical guidelines,[33, 123] the MONARCH 2 trial[35] for the pre-progression state and the MONARCH 1 trial[124] for the post-progression state. BSC is defined as treatment that patients would receive for the management of their disease. This includes costs of opioids, anti-emetics or anti-nauseants, medication for depression or anxiety, cancer-associated venous thromboembolic disease and growth factors for neutropenia.

It is possible that some of these BSC components may be included in the treatment of adverse events, which could result in the double-counting of costs. Given that the same BSC components are assigned to all treatment arms with the same associated frequencies and proportions of patients who receive them, the potential double-counting of costs is unlikely to have a material impact on incremental cost-effectiveness.

Specific treatments for each BSC component were identified from the MONARCH 2 CSR and selected based on the treatment with the highest utilisation in the trial. A summary of the BSC components and resource utilisation is provided in Table 38; BSC costs are provided in Table 39.

Table 38. BSC components and resource use

BSC component	Medication	Proportion (%)	Units per day	Duration in days	Frequency per unit	Resource use per week	Source	Comments
Pain management*	Oxycodone	9.49	200.00	Ongoing	Daily	1400.00	MONARCH 2 CSR; dose-BNF	Assumed half of daily max dose(mg) for immediate-release oxycodone
Anti-emesis or anti-nauseants	Ondansetron	9.79	16.00	5	Daily	112.00	MONARCH 2 CSR; dose-BNF	8 mg every 12 hours for up to 5 days
Depression or anxiety	Alprazolam	8.28	500.00	5	Daily	3500.00	MONARCH 2 CSR; dose-BNF	250 mg 2-3 times per day (short term use assumed)
Cancer-associated venous thromboembolic disease	Rivaroxaban	3.46	30.00	21	Daily	210.00	MONARCH 2 CSR; dose-BNF	15 mg twice daily. Recommended dosage is for initial treatment of deep-vein thrombosis
Growth factors	Filgrastim	4.22	333.50	14	Weekly	333.50	MONARCH 2 CSR; dose-BNF	5 mcg/kg daily for up to 14 days for the reduction of neutropenia and incidence of febrile neutropenia

Footnotes: *Non-opioids have not been included as they were deemed inconsequential for the cost-effectiveness model.
Abbreviations: BNF: British National Formulary; BSC: best supportive care; CSR: clinical study report.

Table 39. BSC component costs

BSC treatment	Unit cost	Frequency (units per day)	Source
Oxycodone	£0.12	200	BNF[121]
Ondansetron	£0.08	16	BNF[121]
Alprazolam	£0.05	500	BNF[121]
Rivaroxaban	£1.80	30	BNF[121]
Filgrastim	£0.09	334	BNF[121]

Abbreviations: BNF: British National Formulary; BSC: best supportive care.

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 3–4 AEs.

In the MONARCH 2 trial, hospitalisation data were collected during the study and through the 30-day follow-up period after discontinuation of study treatment. These data were used to inform the following parameters:

- Length of stay
- Rate of hospitalisations

In the base case, an assumption was made that there were no treatment specific differences in the length of stay and rate of hospitalisations between treatments. This was based on the lack of a difference in the rates between treatment arms of the MONARCH 2 trial. Hospitalisation data for the comparators outside of the MONARCH 2 trial were not reported in the primary publications used in the NMA. Assumptions were required to parameterise these data based on the MONARCH 2 data. As a scenario, treatment specific estimates are included in the model assuming the following:

- Combination therapies were equivalent i.e. EXE-EVE were equivalent to ABE-FUL
- Monotherapies were equivalent i.e. EXE and TMX were equivalent to FUL

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 FUL. These data are presented in Table 40.

Table 40. Length of stay for patients in MONARCH 2

Cohort	Treatment	Number of hospitalisations	Mean (days)	SD
Pre-progression	ABE-FUL and FUL	73	7.74	8.57
Post-progression	ABE-FUL and FUL	23	7.65	4.90

Abbreviations: ABE: abemaciclib; FUL: fulvestrant; SD: standard deviation.

The rate of hospitalisation was estimated based on an analysis of the MONARCH 2 data (Table 41). This involved estimating rates of hospitalisation by pre- and post-progression states based on the observed number of hospitalisations and total follow-up time.

The rate of hospitalisations was calculated based on the total number of hospitalisations and total follow-up days, and converted to weeks based on the MONARCH 2 trial as follows:

$$rate\ per\ week\ = \frac{total\ number\ of\ hospitalisations}{total\ follow\ up\ in\ weeks}$$

Follow-up data from the MONARCH 2 trial were collected 30 days post-discontinuation based on the study protocol. Given ABE-FUL and FUL are treat-to-progression regimens, estimates of hospitalisation in post-progression would be limited based on these data and potentially underestimate the probability of hospitalisation. Two scenarios were therefore explored using the MONARCH 2 data by estimating an overall weekly rate of hospitalisations and assuming this was the same in the pre- and post-progression health states. In the first scenario the probability of hospitalisation was the same for both arms, whilst in the second scenario probability of hospitalisation was estimated by treatment arm.

Table 41. Hospitalisation rate and probability data from MONARCH 2

Cohort	Treatment	Total hospitalisations	Total follow-up (days)	Rate of hospitalisations/ week	Probability of hospitalisations/ week
Base case:					
Pre-progression	ABE-FUL and FUL	86	214841	0.003	0.003
Post-progression	ABE-FUL and FUL	11	11393	0.007	0.007
Scenarios:					
Overall	ABE-FUL and FUL[a]	97	226234	0.003	0.003
Overall	ABE-FUL[b]	74	157199	0.003	0.003
Overall	FUL[b]	23	69035	0.002	0.002

Footnotes: [a] Data used in hospitalisation probabilities scenario in deterministic sensitivity analysis (Table 64).
[b] Data used in hospitalisation probabilities by treatment scenario in deterministic sensitivity analysis (Table 64).
Abbreviations: ABE: abemaciclib; FUL: fulvestrant.

The unit cost per day was sourced from the NHS Reference costs and converted to a cost per hospitalisation based on a mean length of stay (Table 42).

Table 42. Hospitalisation cost

	Estimated cost per hospitalisation	Mean length of stay (days)	Cost per inpatient day	Source
Hospitalisation	£3,481.54	7.78	£447.35	NHS Reference costs 2016−17, JD12D-L, Malignant breast disorders with / without interventions, non-elective long stay

Follow-up care

Components of follow-up care were identified from the MONARCH 2 trial[35] for pre-progression, the MONARCH 1 trial[124] for post-progression and NICE clinical guidelines.[50] Follow-up care is defined as the routine monitoring of patients. Components include: scans, physical examination, electrocardiogram, complete blood counts, serum chemistry, consultations, GP visits, community nurse visits, clinical nurse specialist visits and therapist visits. Resource use was informed by the MONARCH 2 and 1 trials for the pre- and post-progression states, respectively. The follow-up care components, proportions and frequencies are listed in Table 43.

The proportions for scan modalities were sourced from the MONARCH 2 trial for the pre-progression state and MONARCH 1 trial for the post-progression state (Table 44 and Table 45, respectively). These proportions were re-scaled to sum to 100% to account for the patients who had multiple tests.

Unit costs were sourced from the NHS Reference Costs 2016–17[122, 125] and the PSSRU site[126] (Table 46).

Table 43. Follow-up care resource use

Health state	Component	Proportion	Frequency	Source
PFS	CT scan	89.6%	1 per alternate cycle	MONARCH 2 IPD[35]
	MRI scan	6.6%	1 per alternate cycle	MONARCH 2 IPD[35]
	PET scan	3.9%	1 per alternate cycle	MONARCH 2 IPD[35]
	X-ray	2.50%	1 per alternate cycle	MONARCH 2 IPD[35]
	Electrocardiogram	100%	1 per alternate cycle	MONARCH 2 CSR[35]
	Complete blood count	100%	1 per cycle	MONARCH 2 CSR[35]
	Serum chemistry	100%	1 per cycle	MONARCH 2 CSR[35]
	Oncologist consultation	100%	1 per cycle	MONARCH 2 CSR[35]
	GP visit	100%	1 per month	NICE clinical guideline 81 (package 1)[50]
	Community nurse	100%	1 per fortnight	NICE clinical guideline 81 (package 1)[50]
	Clinical nurse specialist	100%	1 per month	NICE clinical guideline 81 (package 1)

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

Abbreviations: CSR: clinical study report; CT: computerised tomography; GP: General Practitioner; IPD: individual patient data; MRI: magnetic resonance imaging; PET: positron emission tomography; PFS: progression-free survival; PPS: post-progression survival.

Table 44. Scan modalities received by patients in MONARCH 2

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

Abbreviations: CT: computerised tomography; MRI: magnetic resonance imaging; PET: positron emission tomography.

Table 45. Scan modalities received by patients in MONARCH 1

Scan modality	Number of patients	Proportion	Rescaled proportion	Comments
CT scan	50	27.6%	85.8%	Included in rescaled total, includes Spiral CT
MRI	15	8.3%	8.9%	Included in rescaled total

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

Abbreviations: CT: computerised tomography; MRI: magnetic resonance imaging; PET: positron emission tomography.

Table 46. Follow-up care costs

Component	Cost	Source
CT scan	£112.07	NHS Reference costs,[127] RD24Z, CT of 2 areas with contrast, outpatient setting
MRI scan	£204.57	NHS Reference costs,[127] RD05Z, MRI of 2 areas with contrast, outpatient setting
PET scan	£478.79	NHS Reference costs,[127] RN 07A, PET, 19 years and over outpatient setting
X-ray	£0.00	Assumed no cost
Electrocardiogram	£256.35	NHS Reference costs,[127] 2016-17, EY51Z, Electrocardiogram monitoring or stress testing, Service Code 370 (Medical Oncology)
Complete blood count	£3.06	NHS Reference costs,[127] 2016-17, DAPS05, Haematology
Serum chemistry	£1.13	NHS Reference costs,[127] 2016-17,DAPS04, Clinical biochemistry
Oncologist consultation	£172.67	NHS Reference costs, 2016-17, WF01A Non-admitted face-to-face attendance, Follow-up, Service Code 370 (Medical Oncology)
GP visit	£38.00	PSSRU,[118] 2017, Per patient contact lasting 9.22 minutes with qualifications
Community nurse	£36.00	PSSRU,[118] 2017, Community Nurse, Band 5, Cost per working hour
Clinical nurse specialist	£44.00	PSSRU,[118] 2017, Community Nurse, Band 6, Cost per working hour
Therapist	£42.00	PSSRU,[118] 2017, Community Occupational Therapist, cost per working hour

Abbreviations: CT: computerised tomography; GP: General Practitioner; MRI: magnetic resonance imaging; NHS: National Health Service; PET: positron emission tomography; PSSRU: Personal Social Services Research Unit.

Post-progression therapies

Post-progression therapies 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 CE estimates.

The average weighted cost of post-progression therapy was assigned to the proportion of patients who progressed in each cycle (per week) for each pre-progression treatment. The average weighted cost of post-progression therapy was calculated by combining the following:

- Weekly costs of acquisition and administration for each post-progression therapy
- Time on post-progression therapy in weeks
- Proportion of patients who received each post-progression therapy. The proportion of patients who received each post-progression therapy was dictated by what was received in pre-progression.

In the MONARCH 2 trial, [redacted]% of patients had some type of systemic therapy after discontinuation. Therapies were selected for inclusion in the model if they were received by ≥10% of patients in either the MONARCH 2 trial or the publications used in the NMA for the comparators. The following post-progression therapies were included: CAP, PAC, vinorelbine (VNB), ERI, FUL, LTZ, EXE, EVE, cyclophosphamide (CYC), gemcitabine (GEM) and bevacizumab (BEV).

The proportions of patients receiving each therapy were based on the MONARCH 2 trial, the primary publications used in the NMA and assumption based on clinical opinion. Post-progression therapy data were only found to be available from the MONARCH 2 and BOLERO-2 trials. Assumptions were made that the proportions for TMX were equivalent to FUL, based on data from the MONARCH 2 trial.

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. The probability of receiving the same treatment/drug component in post-progression as was received in pre-progression was therefore set to 0%. Similarly, the distribution was set to 0% for certain post-progression therapies if the combination was not used in clinical trials, for example the BOLERO 2 trial did not report use of ERI following EXE-EVE. The distributions were subsequently rescaled to sum to 100%. These data are presented in Table 47.

The rescaled subsequent therapy distribution was then multiplied by the proportion of patients expected to receive active therapy on disease progression ([redacted]%). The proportion of patients receiving active therapy after progression was assumed to be equal between treatment arms based on MONARCH 2 trial ([redacted]% in ABE-FUL vs. [redacted]% in FUL). The corresponding post-progression therapy distributions are presented in Table 48.

Table 47. Post-progression therapy distributions

	Pre-progression therapy				
Post-progression therapy	**ABE-FUL[35]**	**FUL[35]**	**EXE[113]**	**EXE-EVE[113]**	**TMX[35]**

	Pre-progression therapy				
CAP	19.55%	17.81%	38.36%	35.82%	17.81%
PAC	19.55%	17.81%	0.00%	0.00%	17.81%
VNB	5.13%	6.48%	17.81%	10.45%	6.48%
ERI	6.09%	4.86%	0.00%	0.00%	4.86%
FUL	0.00%	0.00%	24.66%	34.33%	0.00%
LTZ	7.05%	8.91%	0.00%	0.00%	8.91%
EXE	16.35%	19.84%	0.00%	0.00%	19.84%
EVE	12.82%	14.57%	0.00%	0.00%	14.57%
CYC	4.49%	2.83%	12.33%	13.43%	2.83%
GEM	2.56%	2.83%	6.85%	5.97%	2.83%
BEV	6.41%	4.05%	0.00%	0.00%	4.05%

Source: ABE-FUL, MONARCH 2;[35] TMX, assumed same as FUL;[35] FUL, MONARCH 2;[35] EXE and EXE-EVE, BOLERO 2.[113]
Abbreviations: ABE: abemaciclib; BEV: bevacizumab; CAP: capecitabine; CYC: cyclophosphamide; ERI: eribulin; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; GEM: gemcitabine; LTZ: letrozole; PAC: paclitaxel; TMX: tamoxifen; VNB: vinorelbine.

Table 48. Rescaled post-progression therapy distribution, by pre-progression therapy

	Pre-progression therapy				
Post-progression therapy	**ABE-FUL[35]**	**FUL[35]**	**EXE[113]**	**EXE-EVE[113]**	**TMX[35]**
CAP	17.59%	16.03%	34.51%	32.23%	16.03%
PAC	17.59%	16.03%	0.00%	0.00%	16.03%
VNB	4.61%	5.83%	16.02%	9.40%	5.83%
ERI	5.48%	4.37%	0.00%	0.00%	4.37%
FUL	0.00%	0.00%	22.19%	30.89%	0.00%
LTZ	6.34%	8.01%	0.00%	0.00%	8.01%
EXE	14.71%	17.85%	0.00%	0.00%	17.85%
EVE	11.54%	13.11%	0.00%	0.00%	13.11%
CYC	4.04%	2.55%	11.09%	12.09%	2.55%
GEM	2.31%	2.55%	6.16%	5.37%	2.55%
BEV	5.77%	3.64%	0.00%	0.00%	3.64%

Source: After excluding retreatment: ABE-FUL, MONARCH 2;[35] TMX, assumed same as FUL;[35] FUL, MONARCH 2;[35] EXE and EXE-EVE, BOLERO 2.[113]
Abbreviations: ABE: abemaciclib; BEV: bevacizumab; CAP: capecitabine; CYC: cyclophosphamide; ERI: eribulin; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; GEM: gemcitabine; LTZ: letrozole; PAC: paclitaxel; TMX: tamoxifen; VNB: vinorelbine.

Post-progression therapy costs comprised drug acquisition and drug administration. These were assigned to the proportion of patients experiencing disease progression in each cycle. This was based on the PFS curve for each comparator adjusted by the proportion of PFS events which

were progressive disease rather than death (Table 49). The proportion of PFS events which were progressive disease for ABE-FUL was estimated based on the MONARCH 2 trial. Data were unavailable from the primary publications for the comparators. In light of this, this proportion was assumed to be equivalent across all comparators (i.e. equivalent to ABE-FUL).

Table 49. PFS events

Comparator	Number of PFS events	Number of deaths	Proportion of PFS events which are death
ABE-FUL	379	[redacted]	[redacted]

Abbreviations: ABE: abemaciclib; FUL: fulvestrant; PFS: progression-free survival.

Post-progression therapies: drug acquisition

Post-progression therapy acquisition costs were calculated as per the pre-progression drug acquisition costs. Treatment regimens and RDI were assumed equivalent to pre-progression where available. Regimens and RDI for CYC, GEM and BEV were based on publications cited by the NCCN guidelines[123] (Table 50). Acquisition costs for all post-progression therapies are presented in Table 51.

Table 50. Post-progression treatment regimens

Treatment	Drug	Study	Dose (mg)	Admins per cycle	Cycle length	Number of cycles	RDI	Comments
CAP	CAP	Kaufman (2015)	1250 mg/m^2	28	21 days	TD	100%	RDI assumed to be 100% for oral treatment
PAC	PAC	Perez (2001)	80 mg/m^2	4	28 days	TD	100%	From Beuselinck (2010), RDI was 78% in initial 8 weeks then 71% from 8 weeks to TD
VNB	VNB	Meier (2008)	30 mg/m^2	6	56 days	TD - only 4 consecutive cycles allowed	100%	RDI assumed to be 100%, NR in Meier (2008)
ERI	ERI	Kaufman (2015)	1.4 mg/m^2	2	21 days	TD	100%	-
FUL	FUL	MONARCH 2	500 mg	1 (2 in cycle 1 and 1 thereafter)	28 days	TD	100%	Assumed equal to PFS
LTZ	LTZ	Rose (2003)	2.5 mg	28	28 days	TD	100%	Assumed equal to PFS
EXE	EXE	BOLERO 2	25 mg	28	28 days	TD	100%	Assumed equal to PFS

Treatment	Drug	Study	Dose (mg)	Admins per cycle	Cycle length	Number of cycles	RDI	Comments
EVE	EVE	BOLERO 2	10 mg	28	28 days	TD	100%	Assumed equal to PFS
CYC	CYC	Ackland (2001)	400 mg/m^2	2	28	TD – max of 6-9 cycles depending on response	100%	Median estimate of RDI in Ackland (2001)
CYC	EPI	Ackland (2001)	50 mg/m^2	2	28	TD – max of 6-9 cycles depending on response	100%	Median estimate of RDI in Ackland (2001)
CYC	FLU	Ackland (2001)	500 mg/m^2	2	28	TD – max of 6-9 cycles depending on response	100%	Median estimate of RDI in Ackland (2001)
GEM	GEM	Brodowicz (2000)	1250 mg/m^2	3	28	TD	100%	Assumed to be 100% RDI, no data reported in Brodowicz (2000)
BEV	BEV	Miller (2007)	10 mg/kg	2	28	TD	100%	Assumed to be 100% RDI, no data reported in Miller (2007)

Abbreviations: BEV: bevacizumab; CAP: capecitabine; CYC: cyclophosphamide; EPI: epirubicin; ERI: eribulin; EVE: everolimus; EXE: exemestane; FLU: fluorouracil; FUL: fulvestrant; GEM: gemcitabine; LTZ: letrozole; NR: not reported; PAC: paclitaxel; PFS: progression-free survival; RDI: relative dose intensity; TD: treatment discontinuation; VNB: vinorelbine.

Table 51. Post-progression drug acquisition costs

Treatment	Drug	Units (mg/ml)	Vial size (ml)	Price	Source
CAP	CAP	150	60	£3.97	eMIT, 12 month period to end June 2017
CAP	CAP	500	120	£21.76	eMIT, 12 month period to end June 2017
PAC	PAC	300	50	£19.68	eMIT, 12 month period to end June 2017
VNB	VNB	50	5	£22.58	eMIT, 12 month period to end June 2017
ERI	ERI	0.44	2	£361.00	BNF Online, accessed 13th March 2017
FUL	FUL	250	2	£522.41	BNF Online, accessed 13th March 2017
LTZ	LTZ	2.5	28	£2.71	eMIT, 12 month period to end June 2017

Treatment	Drug	Units (mg/ml)	Vial size (ml)	Price	Source
EXE	EXE	25	30	£3.69	eMIT, 12 month period to end June 2017
EVE	EVE	10	30	£2,673.00	BNF Online, accessed 13th March 2017
CYC	CYC	2000	1	£25.99	eMIT, 12 month period to end June 2017
CYC	EPI	50	25	£5.62	eMIT, 12 month period to end June 2017
CYC	FLU	2500	100	£3.59	eMIT, 12 month period to end June 2017
GEM	GEM	2000	52.6	£15.92	eMIT, 12 month period to end June 2017
BEV	BEV	100	1	£242.66	BNF Online, accessed May 2017

Abbreviations: BEV: bevacizumab; BNF: British National Formulary; CAP: capecitabine; CYC: cyclophosphamide; eMIT: Electronic market information tool; EPI: epirubicin; ERI: eribulin; EVE: everolimus; EXE: exemestane; FLU: fluorouracil; FUL: fulvestrant; GEM: gemcitabine; LTZ: letrozole; NR: not reported; PAC: paclitaxel; VNB: vinorelbine.

Post-progression therapies: drug administration

Post-progression therapy administration costs were calculated as per the pre-progression drug acquisition costs. Infusion times were based on the publications used to inform the treatment regimens. Infusion times were not a direct input into the model, however were used to inform the number of administration and type of administration. These data are presented in Table 52.

Table 52. Post-progression therapy infusion times

Treatment	Drug	Study	Infusion time
CAP	CAP	Kaufman (2015)[115]	N/A
PAC	PAC	Beuselinck (2010)[128]	1 hour
VNB	VNB	Meier (2008)[129]	NR
ERI	ERI	Kaufman (2015)[115]	2–5 minutes
FUL	FUL	MONARCH 2[8]	N/A
LTZ	LTZ	Rose (2003)[130]	N/A
EXE	EXE	BOLERO 2[113]	N/A
EVE	EVE	BOLERO 2[113]	N/A
CYC	CYC	Ackland (2001)[131]	NR
CYC	EPI	Ackland (2001)[131]	NR
CYC	FLU	Ackland (2001)[131]	NR
GEM	GEM	Brodowicz (2000)[132]	NR
BEV	BEV	Miller (2007)[133]	N/A

Abbreviations: BEV: bevacizumab; CAP: capecitabine; CYC: cyclophosphamide; EPI: epirubicin; ERI: eribulin; EVE: everolimus; EXE: exemestane; FLU: fluorouracil; FUL: fulvestrant; GEM: gemcitabine; LTZ: letrozole; N/A: not applicable; NR: not reported; PAC: paclitaxel; VNB: vinorelbine.

The drug administration costs for each comparator are presented in Table 53.

Table 53. Summary of drug administration costs for post-progression therapies

Line	Treatment	Drug	Cost per administration	Cost per cycle	Source
PPS	CAP	CAP	£163.82	£4,586.84	NHS reference costs 2016–17, SB11Z Deliver exclusively oral chemotherapy (outpatient only based no activity)
PPS	PAC	PAC	£259.76	£1,039.05	NHS reference costs 2016–17, SB12Z Deliver simple parenteral chemotherapy at first attendance (day case only based on activity)
PPS	VNB	VNB	£163.82	£982.89	NHS reference costs 2016–17, SB12Z Deliver simple parenteral chemotherapy at first attendance (day case only based on activity)
PPS	ERI	ERI	£259.76	£519.52	NHS reference costs 2016–17, SB12Z Deliver simple parenteral chemotherapy at first attendance (day case only based on activity)
PPS	FUL	FUL	£172.67	£172.67	As per pre-progression with loading dose of £172.67
PPS	LTZ	LTZ	£0.00	£0.00	As per pre-progression
PPS	EXE	EXE	£0.00	£0.00	As per pre-progression
PPS	EVE	EVE	£0.00	£0.00	As per pre-progression
PPS	CYC	CYC	£310.00	£619.99	NHS reference costs 2016–17, SB13Z, Deliver complex chemotherapy at first attendance, day case based on activity
PPS	CYC	EPI	£0.00	£0.00	Assumed to be captured in cost for CYC
PPS	CYC	FLU	£0.00	£0.00	Assumed to be captured in cost for CYC
PPS	GEM	GEM	£259.76	£779.28	NHS reference costs 2016–17, SB12Z Deliver simple parenteral chemotherapy at first attendance (day case only based on activity)
PPS	BEV	BEV	£205.09	£410.18	NHS reference costs 2016–17, Subsequent treatment cycles: SB15Z - delivery subsequent elements of a chemotherapy cycle (chemotherapy outpatient)

Abbreviations: BEV: bevacizumab; CAP: capecitabine; CYC: cyclophosphamide; EPI: epirubicin; ERI: eribulin; EVE: everolimus; EXE: exemestane; FLU: fluorouracil; FUL: fulvestrant; GEM: gemcitabine; LTZ: letrozole; N/A: not applicable; NR: not reported; PAC: paclitaxel; PPS: post-progression survival; VNB: vinorelbine.

Summary of post-progression costs

A summary of the weekly post-progression costs associated with each pre-progression comparator is provided in Table 54.

Table 54. Summary of post-progression costs by pre-progression intervention

Intervention (pre-progression)	Post-progression cost
ABE-FUL	£15,193.84
EXE	£34,563.38
EXE-EVE	£21,187.51
FUL	£22,708.57
TMX	£25,505.97

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; TMX: tamoxifen.

Terminal care

Terminal care costs were assigned to all patients who died in the model. Patients could receive care in a hospital, hospice or at home with community support. The proportion of patients receiving each type of care was based on NICE CG81[50] (Table 55).

Table 55. Terminal care

Setting of care	Proportion of patients	Source
Hospital	40.00%	NICE CG81 clinical guidelines[50]
Hospice	10.00%	NICE CG81 clinical guidelines[50]
At home with community support	50.00%	NICE CG81 clinical guidelines[50]

The unit costs of terminal care are presented in Table 56.

Table 56. Terminal care unit costs

Setting of care	Mean cost	Source
Hospital	£5,695.20	NICE CG81 package 3 inflated to 2016/17 prices using PSSRU HCHS index[118]
Hospice	£7,100.06	NICE CG81 package 3 inflated to 2016/17 prices using PSSRU HCHS index[118]
At home with community support	£2,938.29	NICE CG81 package 3 inflated to 2016/17 prices using PSSRU HCHS index[118]

Abbreviations: PSSRU: personal social services research unit.

B.3.5.3 Adverse reaction unit costs and resource use

The cost impact of AEs was captured in the CE analysis. As described in Section B.3.4.4, the rates of AEs for patients on ABE-FUL were based on TEAEs which occurred in the ITT

population of the MONARCH 2 trial. AEs were selected for inclusion if they were grade 3–4 events occurring in more than 5% of patients for at least one comparator. AE rates for comparators were based on the primary publications used in the NMA.

For included AEs, counts were entered into the model and converted to probabilities. Where counts were not reported, these were calculated based on the percentage of patients experiencing each event, and the total number of patients included in the AE analysis. The AE rates included in the model are provided in Table 31.

Unit costs were based on NHS Reference Costs 2016−17 for managing AEs (Table 57)[125]

Table 57. Adverse event costs

Adverse event	Cost	Source	Notes
Anaemia	£270.00	NHS Reference Costs 2016−17 for AEs	SA44A, outpatient, service code 370, Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over
Diarrhoea	£2.93	BNF	Cost corresponds to one pack of loperamide
Dyspnoea	£389.64	NHS Reference Costs 2016−17 for AEs	DZ19L, DZ19M and DZ19N for Other Respiratory Disorders without Interventions
Gamma-glutamyltransferase (GGT) increase	£0.00	Assumed no cost	Laboratory abnormality test
Hyperglycaemia	£434.91	NHS Reference Costs 2016−17 for AEs	KB02G, KB02H, KB02J and KB02K for Diabetes with Hyperglycaemic Disorders
Leukopenia	£173.00	NHS Reference Costs 2016−17 for AEs	WF01A service code 370 Medical Oncology Non-Admitted Face to Face Attendance, Follow-up
Neutropenia	£173.00	NHS Reference Costs 2016−17 for AEs	WF01A service code 370 Medical Oncology Non-Admitted Face to Face Attendance, Follow-up
Stomatitis	£482.28	NHS Reference Costs 2016−17 for AEs	FD10J, FD10K, FD10L and FD10M for Non-Malignant Gastrointestinal Tract Disorders without Interventions

Abbreviations: AE: adverse event; BNF: British National Formulary.

B.3.5.4 Miscellaneous unit costs and resource use

No additional miscellaneous costs or resource use were included.

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

B.3.6.1 Summary of base-case analysis inputs

A summary of the base case settings for the model and scenario analyses conducted is provided in Table 58.

Table 58: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
Model settings			
Cycle length	1 week	Fixed	B.3.2.2, page 97
Time horizon	20 years	Fixed	
Discount rate (costs and outcomes)	3.5%	Fixed	
Willingness to pay threshold	£30,000	Fixed	B.3.8.1, page 156
Patient characteristics			
Height	[redacted]	Fixed	B.3.3.3, page 102
Weight	[redacted]	Fixed	
BSA	[redacted]	Fixed	
Clinical efficacy- first-line treatment			
PFS (ABE-FUL and FUL)	Weibull	Multivariate normal	B.3.3.4, page 102
Hazard ratio for EXE – PFS	[redacted]	Log-normal	
Hazard ratio for EXE-EVE − PFS	[redacted]	Log-normal	
Hazard ratio for TMX - PFS	[redacted]	Log-normal	B.3.3.2, page 101
Hazard ratio for EXE – OS	[redacted]	Log-normal	B.3.3.5, page 108
Hazard ratio for EXE-EVE - OS	[redacted]	Log-normal	
Hazard ratio for TMX − OS	[redacted]	Log-normal	B.3.3.2, page 101
Hazard ratio for EXE – duration of therapy	[redacted]	Gamma	B.3.3.6, page 113
Hazard ratio for EXE-EVE – duration of therapy	[redacted]	Gamma	
Hazard ratio for TMX - duration of therapy	[redacted]	Gamma	
Probability of hospitalisation			
Pre-progression	0.0028	Normal	B.3.5.2, page 136
Post-progression	0.0067	Normal	
Endocrine therapies	66.34%	Gamma	
Utility- PFS			
PFS	[redacted]	Cholesky decomposition	B.3.4.1, page 125
PPS	0.505	Normal	B.3.4.1, page 125
Adverse event disutility – Anaemia	-0.119	Gamma	B.3.4.5, page 128
Adverse event disutility - Diarrhoea	-0.006	Gamma	
Adverse event disutility - Dyspnoea	-0.029	Gamma	

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
Adverse event disutility - Gamma-glutamyltransferase (GGT) increase	0.000	Gamma	
Adverse event disutility - Hyperglycemia	-0.119	Gamma	
Adverse event disutility - Leukopenia	-0.003	Gamma	
Adverse event disutility - Neutropenia	-0.007	Gamma	
Adverse event disutility - Stomatitis	-0.269	Gamma	
Adverse event disutility - Anaemia	-0.119	Gamma	
Drug acquisition			
ABE (56x 150mg)	£[redacted] per pack*	Fixed	B.3.5.1, page 130
FUL (2x250mg)	522.41	Fixed	
EXE (30x 25mg)	£3.69 per pack	Fixed	
EVE (30x 10mg)	£2,673.00 per pack	Fixed	
VNB (5x 50mg)	£22.58 per pack	Fixed	B.3.5.2, page 142
CAP (60x 150mg)	£3.97 per pack	Fixed	
CAP (120x 500 mg)	£21.76 per pack	Fixed	
PAC (50x 300mg)	£19.68 per pack	Fixed	
BEV (1x 100mg)	£242.66 per pack	Fixed	
EPI (25 x 50mg)	£5.62 per pack	Fixed	
FLU (100x 2500mg)	£3.59 per pack	Fixed	
GEM (52.6x 2000mg)	£15.92 per pack	Fixed	
TMX (10x 30mg)	£7.02 per pack	Fixed	B.3.5.1, page 130
TMX (20x 30mg)	£1.59 per pack	Fixed	
ERI (2x 0.44mg)	£361.00 per pack	Fixed	B.3.5.2, page 142
All oral endocrine therapies and regular doses of FUL	£0	Fixed	B.3.5.2, page 144
Drug administration			
FUL loading dose	£172.67 per admin	Gamma	B.3.5.1, page 131
Oral chemotherapies (CAP, VNB)	£163.82 per admin	Gamma	B.3.5.2, page 144
Day case chemotherapies (PAC, GEM, ERI)	£259.76 per admin	Gamma	

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
Complex chemotherapies (CYC)	£310.00 per admin	Gamma	
Outpatient chemotherapies (BEV)	£205.09 per admin	Gamma	
Adverse event cost			
Adverse event cost - Anaemia	£270.00	Gamma	B.3.5.3, page 146
Adverse event cost - Diarrhoea	£2.93	Gamma	
Adverse event cost - Dyspnoea	£389.64	Gamma	
Adverse event cost - Gamma-glutamyltransferase (GGT) increase	£0.00	Gamma	
Adverse event cost - Hyperglycemia	£434.91	Gamma	
Adverse event cost - Leukopenia	£173.00	Gamma	
Adverse event cost - Neutropenia	£173.00	Gamma	
Adverse event cost - Stomatitis	£482.28	Gamma	
Follow-up care			
Follow-up care cost - CT scan	£112.07	Gamma	B.3.5.2, page 138
Follow-up care cost - MRI scan	£204.57	Gamma	
Follow-up care cost - PET scan	£478.79	Gamma	
Follow-up care cost - Electrocardiogram	£256.35	Gamma	
Follow-up care cost - Complete blood count	£3.06	Gamma	
Follow-up care cost - Serum chemistry	£1.13	Gamma	
Follow-up care cost - Oncologist consultation	£172.67	Gamma	
Follow-up care cost - GP visit	£38.00	Gamma	
Follow-up care cost - Community nurse	£36.00	Gamma	
Follow-up care cost - Clinical nurse specialist	£44.00	Gamma	
Follow-up care cost - Therapist	£42.00	Gamma	
Follow-up care cost – X-ray	£0	Gamma	
Terminal care			
Terminal care- in hospital	£5,695.05	Gamma	B.3.5.2, page 145
Terminal care- in a hospice	£7,100.06	Gamma	
Terminal care- at home with community support	£2,938.29	Gamma	
Hospital costs			

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
Hospitalisation (cost per day)	£447.35	Gamma	B.3.5.2, page 136
Resource use			
Pre-progression - CT scan	89.56%	Beta	B.3.5.2, page 136
Pre-progression – Proportion receiving MRI scan	6.57%	Beta	
Pre-progression - Proportion receiving PET scan	3.87%	Beta	
Pre-progression - Proportion receiving X-ray	2.50%	Beta	
Pre-progression - Proportion receiving Electrocardiogram	100.00%	Beta	
Pre-progression - Proportion receiving Complete blood count	100.00%	Beta	
Pre-progression - Proportion receiving Serum chemistry	100.00%	Beta	
Pre-progression - Proportion receiving Oncologist consultation	100.00%	Beta	
Pre-progression - Proportion receiving GP visit	100.00%	Beta	
Pre-progression - Proportion receiving Community nurse	100.00%	Beta	
Pre-progression - Proportion receiving Clinical nurse specialist	100.00%	Beta	
Post-progression - Proportion receiving CT scan	85.80%	Beta	
Post-progression - Proportion receiving MRI scan	8.88%	Beta	
Post-progression - Proportion receiving PET scan	5.33%	Beta	
Post-progression - Proportion receiving Electrocardiogram	100.00%	Beta	
Post-progression - Proportion receiving Complete blood count	100.00%	Beta	
Post-progression - Proportion receiving Serum chemistry	100.00%	Beta	
Post-progression - Proportion receiving Oncologist consultation	100.00%	Beta	
Post-progression - Proportion receiving GP visit	100.00%	Beta	

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
Post-progression - Proportion receiving Community nurse	100.00%	Beta	
Post-progression - Proportion receiving Clinical nurse specialist	100.00%	Beta	
Post-progression - Proportion receiving Therapist	100.00%	Beta	
Pre-progression - Frequency per unit CT scan	0.50	Beta	
Pre-progression – Frequency per unit MRI scan	0.50	Gamma	
Pre-progression - Frequency per unit PET scan	0.50	Gamma	
Pre-progression - Frequency per unit X-ray	0.50	Gamma	
Pre-progression - Frequency per unit Electrocardiogram	0.50	Gamma	
Pre-progression - Frequency per unit Complete blood count	1.00	Gamma	
Pre-progression - Frequency per unit Serum chemistry	1.00	Gamma	
Pre-progression - Frequency per unit Oncologist consultation	1.00	Gamma	
Pre-progression - Frequency per unit GP visit	0.23	Gamma	
Pre-progression - Frequency per unit Community nurse	0.50	Gamma	
Pre-progression - Frequency per unit Clinical nurse specialist	0.23	Gamma	
Post-progression - Frequency per unit CT scan	0.50	Gamma	
Post-progression - Frequency per unit MRI scan	0.50	Gamma	
Post-progression - Frequency per unit PET scan	0.50	Gamma	
Post-progression - Frequency per unit Electrocardiogram	1.00	Gamma	
Post-progression - Frequency per unit Complete blood count	1.00	Gamma	
Post-progression - Frequency per unit Serum chemistry	1.00	Gamma	

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
Post-progression - Frequency per unit Oncologist consultation	1.00	Gamma	
Post-progression - Frequency per unit GP visit	0.50	Gamma	
Post-progression - Frequency per unit Community nurse	1.00	Gamma	
Post-progression - Frequency per unit Clinical nurse specialist	1.00	Gamma	
Post-progression - Frequency per unit Therapist	0.50	Gamma	
Post progression therapy			
Proportion receiving active therapy (of those who progress)	[redacted]	Beta	B.3.5.2, page 140
Deaths as progression event - Proportion who die prior to progression	[redacted]	Beta	B.3.5.2, page 141
Post-progression therapy proportions (by prior therapy) – ABE-FUL, FUL, TMX	MONARCH 2	Dirichlet distribution	B.3.5.2, page 139
Post-progression therapy proportions (by prior therapy) – EXE, EXE-EVE	BOLERO-2	Dirichlet distribution	

Footnotes: * Price for ABE with proposed PAS. List price of ABE is £[redacted].
Abbreviations: ABE: abemaciclib; BEV: bevacizumab; BSA: body surface area; CAP: capecitabine; CT: computerised tomography; CYC: cyclophosphamide; EPI: epirubicin; ERI: eribulin; EVE: everolimus; EXE: exemestane; FLU: fluorouracil; FUL: fulvestrant; GEM: gemcitabine; GP: general practitioner; MRI: magnetic resonance imaging; OS: overall survival; PAC: paclitaxel; PET: positron emission tomography; PFS: progression-free survival; TMX: tamoxifen; VNB: vinorelbine;

B.3.6.2 Assumptions

Table 59 includes a summary of the key model assumptions.

Table 59. Summary of model assumptions

Component	Assumption	Justification
Modelling of OS	No treatment effect on OS between ABE-FUL and all comparators beyond the MONARCH 2 trial follow-up	The OS extrapolations were reviewed by a clinical expert who deemed the extrapolation to provide plausible extrapolations for FUL, and apply conservative assumptions that could be justified for estimation of the ABE-FUL treatment effect.
	Long-term OS from the CONFIRM study reflects long-term OS for patients from MONARCH 2 trial	This assumption was considered to be appropriate due to the lack of a treatment difference observed in the tail of the KM and the immaturity of the MONARCH 2 data at the time of the analysis.

Component	Assumption	Justification
Modelling of duration of therapy	Based on published median duration of therapy and median PFS	Required to generate discontinuation estimates for comparators
Treatment effects	HRs for OS from the NMA assumes the population data in the trials are similar	HR for OS from the NMA was deemed to be a reasonable assumption despite differences in inclusion criteria.
Adverse events	AE rates for TMX were assumed to be the same as FUL	Based on expected similarity between the therapy classes, this assumption was required due to the lack of available AE data that aligned with the AE inclusion criteria. This assumption was validated with a clinical expert.
Hospitalisation	No treatment specific differences in the length of stay and rate of hospitalisations between treatments	This is based on the lack of a difference in the rates between treatment arms of the MONARCH 2 trial. Hospitalisation data for the comparators outside of the MONARCH 2 trial were not reported in the primary publications used in the NMA. Assumptions were required to parameterise these data based on the MONARCH 2 data.
Subsequent therapy	Assumptions were made that the proportions for TMX were equivalent to FUL.	This assumption was required due to the lack of available evidence for TMX to populate the model.
	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)	Based on clinical input received
Drug acquisition	Unused drug in vial is discarded (vial wastage)	Assumption to reflect that in clinical practice vial sharing may not occur
	Unused tablets in a pack are discarded (oral wastage)	Assumption to reflect that the full cost of a pack is incurred whether patients take all the tablets or not
Drug administration	All oral therapies assigned zero cost for administration	These are taken in the patient's own home without need for clinician supervision

Abbreviations: ABE: abemaciclib; AE: adverse events; FUL: fulvestrant; HR: hazard ratio; KM: Kaplan-Meier; NMA: network meta-analysis; OS: overall survival; PFS: progression-free survival; TMX: tamoxifen.

B.3.7 *Base-case results*

Base-case results for the cost-effectiveness analysis are presented in the following subsections.

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

The base case cost-effectiveness results are presented in Table 60, using the with-PAS price for ABE, and list price for all other comparators. Based on the fully incremental analysis and outcome of cost/QALY, TMX was the referent comparator. FUL and EXE were dominated by TMX. ABE-FUL was associated with a pairwise ICER of £108,789 per QALY gained vs TMX. ABE-FUL dominated EXE-EVE, the key comparator for ABE-FUL at its specific position in the treatment pathway for HR+/HER2− advanced breast cancer.

Table 60: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY) (Incremental analysis)	ABE-FUL pairwise ICER vs comparator (£/QALY)
TMX	[redacted]	3.72	[redacted]	[redacted]	-	[redacted]	Referent	£108,789
FUL	[redacted]	3.50	[redacted]	[redacted]	−0.22	[redacted]	Dominated	£74,103
EXE	[redacted]	3.33	[redacted]	[redacted]	−0.17	[redacted]	Dominated	£39,615
ABE-FUL	[redacted]	3.64	[redacted]	[redacted]	0.31	[redacted]	£108,789	N/A
EXE-EVE	[redacted]	3.45	[redacted]	[redacted]	−0.19	[redacted]	Dominated	Dominated

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; TMX: tamoxifen.

B.3.8 *Sensitivity analyses*

B.3.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analyses (PSA) were generated by assigning distributions to all input parameters and randomly sampling from these distributions over 10,000 Monte Carlo simulations, in order to calculate the uncertainty in costs and outcomes. A summary of the distributions chosen for the probabilistic parameters in the model is provided in Table 61.

Table 61. PSA distributions

Parameter	Distribution	Justification
Hazard ratios for treatment effect	Lognormal	Ratio, additive on log scale
Survival model coefficients (PFS, OS, duration of therapy)	Multivariate normal	To capture correlation between normally distributed regression parameters
Utility model coefficients	Multivariate normal	To capture correlation between normally distributed regression parameters
Utility decrements	Normal	Normal distribution
Adverse events (probability)	Beta	Constrained on an interval of 0 to 1
Adverse event (duration)	Gamma	Constrained on an interval from 0 to positive infinity
Hospitalisation length of stay (duration)	Gamma	Constrained on an interval from 0 to positive infinity
Relative risk of hospitalisation (vs ABE-FUL or FUL)	Lognormal	Ratio, additive on log scale
Hospitalisations per week (rate)	Lognormal	Rate, additive on log scale
Relative dose intensity	Beta	Constrained on an interval of 0 to 1
Best supportive care (proportion)	Beta	Constrained on an interval of 0 to 1
Best supportive care (resource use per week)	Gamma	Constrained on an interval from 0 to positive infinity
Follow-up care (proportion)	Beta	Constrained on an interval of 0 to 1
Follow-up care (frequency)	Gamma	Constrained on an interval from 0 to positive infinity
Terminal care (frequency)	Gamma	Constrained on an interval from 0 to positive infinity
Post-progression therapy (proportion)	Beta	Constrained on an interval of 0 to 1
PFS events which are deaths (proportion)	Beta	Constrained on an interval of 0 to 1
Odds ratio of death as a progression event	Lognormal	Ratio, additive on log scale
Unit costs	Gamma	Constrained on an interval from 0 to positive infinity

Abbreviations: ABE: abemaciclib; FUL: fulvestrant; OS: overall survival; PFS: progression-free survival.

Results of the PSAs for the comparison of ABE-FUL (at PAS price) versus the comparators (at list price) are summarised in Table 62.

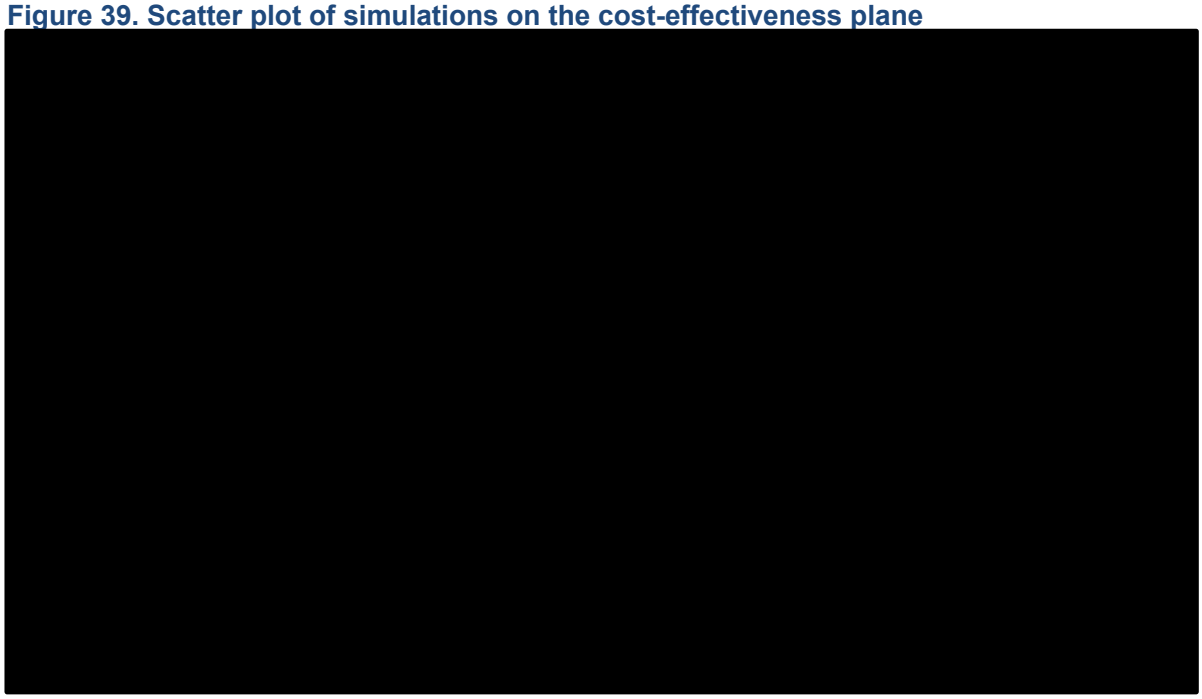
Table 62. Base case results (probabilistic)

Treatment	Costs	LYs	QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY) (Incremental analysis)	ABE-FUL pairwise ICER vs comparator (£/QALY)
TMX	[redacted]	3.70	[redacted]	[redacted]	-	[redacted]	Referent	£104,980
FUL	[redacted]	3.47	[redacted]	[redacted]	−0.23	[redacted]	Dominated	£71,714
EXE	[redacted]	3.30	[redacted]	[redacted]	−0.18	[redacted]	Dominated	£39,268
ABE-FUL	[redacted]	3.61	[redacted]	[redacted]	0.31	[redacted]	£104,980	N/A
EXE-EVE	[redacted]	3.42	[redacted]	[redacted]	−0.19	[redacted]	Dominated	Dominated

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; TMX: tamoxifen.

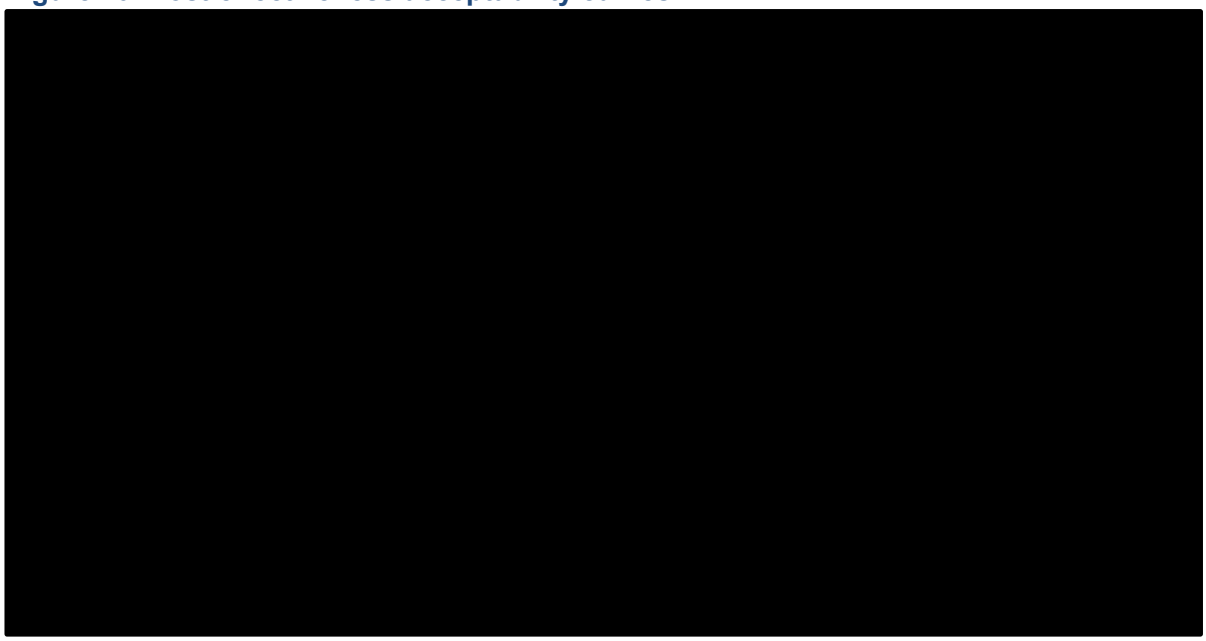
A scatter plot of the joint distribution of incremental costs and incremental QALYs from the PSA is shown in Figure 39, and the cost-effectiveness acceptability curves (CEAC) and frontier corresponding with the above outputs is presented in Figure 40 and Figure 41, respectively.

Figure 39. Scatter plot of simulations on the cost-effectiveness plane



Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; QALYs: quality-adjusted life years; TMX: tamoxifen.

Figure 40. Cost-effectiveness acceptability curves



Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; TMX: tamoxifen.

The probabilities of each comparator being cost-effective at a willingness-to-pay threshold of £30,000 per QALY is presented in Table 63. At a willingness-to-pay threshold of £30,000 per QALY, ABE-FUL at the with-PAS price had a [redacted] probability of being cost-effective.

Figure 41. Cost-effectiveness acceptability frontier

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; TMX: tamoxifen.

Table 63. Probability of cost-effectiveness, using with-PAS ABE price and list price for all other comparators

Comparator	Probability of cost-effectiveness at a £30,000 per QALY threshold
TMX	[redacted]
FUL	[redacted]
EXE	[redacted]
ABE-FUL	[redacted]
EXE-EVE	[redacted]

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; QALY: quality-adjusted life year; TMX: tamoxifen.

B.3.8.2 Deterministic scenario analysis

Extensive deterministic scenario analyses were conducted to evaluate the robustness of the CE estimates.

The scenario analyses involved replacing a parameter (or group of parameters) with another plausible value(s) in order to examine the impact of a new "scenario". This provided a single ICER estimate (for each comparator) associated with the new scenario.

The scenario analyses include:

- Alternative approaches to estimate PFS, OS and duration of therapy for ABE-FUL and the comparators;
- Use of relative treatment effects for ABE-FUL generated by the NMA for PFS and OS, the use of IRC assessed PFS data for ABE-FUL and FUL;

- Alternative discount rates for costs and benefits;
- Drug wastage assuming vial sharing;
- Excluding adjustment for relative dose intensity (RDI);
- Use of treatment-specific utilities;
- Use of overall probability for hospitalisation (i.e. same for PFS and PPS);
- Use of treatment specific probabilities for hospitalisations;
- Use of ABE 150 mg starting dose data from MONARCH 2;
- Use of alternative treatment cost for diarrhoea from TA215[134]

The results of the deterministic scenario analyses are presented in Table 64.

Table 64. Scenario sensitivity analysis results

Scenario	Base case value	Scenario value	Net monetary benefit versus TMX				
			ABE-FUL	TMX	EXE	EXE-EVE	FUL
Base Case	-	-	−£17,775	Referent	−£12,967	−£27,538	−£3,576
Discount rate costs and benefits	3.5%	0%	−£18,680	Referent	−£13,168	−£28,862	−£3,711
Discount rate costs and benefits	3.5%	6%	−£17,167	Referent	−£12,826	−£26,681	−£3,485
Source of ABE-FUL treatment effects for PFS	Joint model	NMA	−£17,689	Referent	−£12,967	−£27,538	−£3,576
Assessment of PFS	Investigator	Independent review centre	£1,079	Referent	−£14,762	−£30,612	−£3,054
Interval censored adjustment	Adjusted	Unadjusted	−£24,553	Referent	−£11,347	−£30,834	−£3,757
Distribution for extrapolating PFS	Weibull	Gamma	−£18,945	Referent	−£12,653	−£27,976	−£3,686
Distribution for extrapolating OS – treatment effect from NMA	Treatment effect tapering + CONFIRM hazard	HR from NMA applied throughout	−£16,749	Referent	−£7,415	−£23,555	−£778
Distribution for extrapolating OS – MONARCH 2 Weibull distribution only	Treatment effect tapering + CONFIRM hazard	Treatment effect from joint Weibull model	−£16,886	Referent	−£7,415	−£23,555	−£778
Distribution for extrapolating OS – No CONFIRM hazard	Treatment effect tapering + CONFIRM hazard	Treatment effect tapering	−£14,778	Referent	−£7,415	−£23,555	−£778
Distribution for extrapolating OS – No tapering	Treatment effect tapering + CONFIRM hazard	No tapering + CONFIRM hazard	−£17,905	Referent	−£12,967	−£27,538	−£3,576

Scenario	Base case value	Scenario value	Net monetary benefit versus TMX				
			ABE-FUL	TMX	EXE	EXE-EVE	FUL
Distribution for extrapolating OS – MONARCH 2 Gompertz distribution	Treatment effect tapering + CONFIRM hazard	Gompertz distribution in place of Weibull	−£17,602	Referent	−£12,245	−£27,043	−£3,440
OS treatment effect tapering in months	[redacted]	[redacted]	−£17,782	Referent	−£12,967	−£27,538	−£3,576
OS treatment effect tapering in months	[redacted]	[redacted]	−£17,426	Referent	−£12,967	−£27,538	−£3,576
OS time of extrapolation with CONFIRM in months	[redacted]	[redacted]	−£18,002	Referent	−£13,609	−£27,937	−£3,935
OS time of extrapolation with CONFIRM in months	[redacted]	[redacted]	−£17,996	Referent	−£13,575	−£27,916	−£3,915
Distribution for extrapolating duration of therapy	Weibull	Gamma	−£23,809	Referent	−£12,967	−£27,538	−£4,020
Drug acquisition	Vial wastage	Vial sharing	−£18,051	Referent	−£13,557	−£25,365	−£3,652
Utility model	Overall (non-treatment specific)	Treatment specific	−£17,511	Referent	−£12,928	−£27,295	−£3,584
Relative dose (RDI) adjustment	100%	Taken from trial data	−£17,873	Referent	−£13,260	−£27,830	−£3,609
Hospitalisation probabilities	By PFS and PPS	Overall	−£18,604	Referent	−£13,013	−£28,247	−£3,775
Hospitalisation probabilities by treatment	Overall	Treatment specific	−£18,147	Referent	−£13,015	−£27,890	−£3,571
Utility measure	EQ-5D-3L (cross-walked from EQ-5D-5L)	EQ-5D-5L	−£17,743	Referent	−£12,976	−£27,515	−£3,574

Scenario	Base case value	Scenario value	Net monetary benefit versus TMX				
			ABE-FUL	TMX	EXE	EXE-EVE	FUL
Adverse event cost of diarrhoea	2.93	752.24	−£17,872	Referent	−£12,964	−£27,550	−£3,576

Abbreviations: ABE: abemaciclib; D: dominated; ED: extendedly dominated; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; ICER: incremental cost-effectiveness ratio; ITT: intention-to-treat; NMA: network meta-analysis; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival; QALY: quality-adjusted life years; R: referent; TMX: tamoxifen.

B.3.8.3 Summary of sensitivity analyses results

The PSA demonstrated that there is a [redacted]% probability of ABE-FUL at the with-PAS price being cost-effective at a threshold of £30,000 per QALY.

Deterministic scenario analyses were conducted to explore uncertainty relating to both structural and parameter assumptions made in the modelling. In the scenario analyses, the economic results were largely stable when varying model assumptions, with net monetary benefit (NMB) for ABE-FUL vs TMX (the referent) changing by less than 10% versus the base case for 20/24 scenarios assessed, demonstrating the robustness of the model. Table 65 presents the scenarios for which the NMB varied by equal to or greater than 10% versus baseline, with further discussion provided below.

Table 65. Scenario analysis parameters influencing the base case NMB by ≥10%

Increase in ABE-FUL NMB of ≥10% vs base case	Decrease in ABE-FUL NMB of ≥10% vs base case
1. Assessment of PFS (base case: INV; scenario: IRC) 2. Distribution for extrapolating OS (base case: MONARCH 2 Weibull curve appended with CONFIRM data and treatment tapering; scenario: MONARCH 2 Weibull and treatment tapering)	3. Interval censored adjustment (base case: adjusted; scenario: unadjusted) 4. Distribution for extrapolating duration of therapy (base case: Weibull; scenario: gamma)

Abbreviations: ABE: abemaciclib; FUL: fulvestrant; INV: investigator; IRC: independent review commiteee; ITT: intent-to-treat; NMB: net monetary benefit; PFS: progression-free survival.
Footnote: ABE-FUL NMB is versus TMX

1. Use of IRC-assessed PFS data from MONARCH 2 in the model resulted in an increase in the ABE-FUL NMB, indicating a more cost-effective result. The IRC-assessed PFS data has potentially improved reliability and objectivity compared to INV-assessed PFS data used in the base case.

2. Using a Weibull distribution based on the MONARCH 2 data and treatment tapering between ABE-FUL and comparators (but no appendage with a distribution based on the CONFIRM trial FUL data, as in the base case) resulted in an increase to the ABE-FUL NMB, indicating a more cost-effective result. It is anticipated that the most plausible long-term OS extrapolation lies somewhere between the two distributions.

3. The scenario in which interval censored adjustment was not performed resulted in a decrease to the ABE-FUL NMB, indicating a less cost-effective result. As described in Section B.3.3.4, performing interval censored adjustment for PFS enables the analysis to more closely reflect the underlying time to progression for patients, and may therefore be more reflective of real life.

4. Use of the gamma parametric curve instead of a Weibull model to extrapolate duration of therapy for ABE-FUL and FUL resulted in a decrease to the ABE-FUL NMB, indicating a less cost-effective result. However, as described in Section B.3.3.6, given that ABE-FUL and FUL are both treat-to-progression therapies, the Weibull was considered the most

appropriate model for duration of therapy due to alignment with the parametric curve selected for PFS.

B.3.9 *Subgroup analysis*

A scenario exploring the subgroup of patients who were randomised to receive ABE at the 150 mg starting dose was conducted in the model using data from the MONARCH 2 trial. The methodology of this subgroup analysis is described in Section B.3.3.7. Incremental results for the subgroup analyses are shown in Table 66.

Table 66. Incremental results for subgroup analysis (150 mg starting dose)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY) (Incremental analysis)	ABE-FUL pairwise ICER vs comparator (£/QALY)
TMX	[redacted]	3.72	[redacted]	[redacted]	-	[redacted]	Referent	£123,116
FUL	[redacted]	3.49	[redacted]	[redacted]	-0.22	[redacted]	Dominated	£82,369
EXE	[redacted]	3.32	[redacted]	[redacted]	-0.17	[redacted]	Dominated	£43,792
ABE-FUL	[redacted]	3.64	[redacted]	[redacted]	0.31	[redacted]	£123,116	N/A
EXE-EVE	[redacted]	3.44	[redacted]	[redacted]	-0.19	[redacted]	Dominated	Dominated

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; TMX: tamoxifen.

As expected, the results from this analysis remained comparable to the base case in terms of both the clinical and cost-effectiveness outcomes. This is likely due to the relatively short duration of time on treatment (median 37 days) for the pre-amendment population in the trial, and the clinical outcome results for the pre- and post-amendment populations, which showed no statistically significant difference.

B.3.10 *Validation*

B.3.10.1 Validation of cost-effectiveness analysis

In alignment with best practice, a validation of the conceptual model was conducted by an external senior analyst not previously involved in the model conceptualisation or programming.[135] A technical validation of the CE model was conducted by two analysts: 1) a senior analyst not involved in the original programming and 2) an independent, external consultant. This allowed the approach to be validated, and permitted areas of disagreement to be resolved prior to generation of model results. It also enabled any issues which might be raised by reimbursement authorities or model critics to be pre-empted and addressed in advance. The OS extrapolations were reviewed by a clinical expert.

Clinical outcomes

Where possible, the results from the model were compared to the clinical trial data to assess how closely they were aligned, as presented in Table 67 and discussed below.

In the base case analysis, ABE-FUL was associated with superior mean PFS outcomes vs all comparators (28.02 months) and OS outcomes vs all comparators expect for TMX, which was slightly higher (48.42 vs 49.55 months, respectively). The median PFS estimates for ABE-FUL and FUL were similar to the trial publication, though slightly lower in both arms, due to the adjustment for interval censoring in the analysis of this outcome. As described in Section B.3.3.4, the adjustment for interval censoring produces parametric curves for PFS that fit closely to the steps of the KM plots, where tumour assessments occur as part of the clinical trial program. The model PFS values for the comparators were closely aligned with the publications, with the most substantial difference seen with EXE-EVE showed (13.34 months in model, 7.8 months in publication). The OS values were similar between the model and publication values for all comparators. Values for median time on treatment from the model were similarly close to the publication values, however the model estimated a greater time on treatment for EXE versus the publication (8.05 months vs 3.2−3.0, respectively).

Table 67. Comparison of clinical outcomes generated by the model with clinical trial data

Comparator	PFS (months)				OS (months)				Duration of therapy (months)			
	Mean	Median	Median from source	Publication source	Mean	Median	Median from source	Publication source	Mean	Median	Median from source	Publication source
ABE-FUL	[redacted]	[redacted]	16.4	MONARCH 2 CSR	[redacted]	[redacted]	-	-	[redacted]	[redacted]	[redacted]	MONARCH 2 CSR
EXE	[redacted]	[redacted]	4.1 3.71 3.4 3.7	BOLERO-2 Campos (2009) SoFEA Yamamoto (2013)	[redacted]	[redacted]	26.6 30.5 21.6 21.9	BOLERO-2 Campos (2009) SoFEA Yamamoto (2013)	[redacted]	[redacted]	3.2* 3.9* 3.8*	BOLERO-2 Campos (2009) Kaufman (2000)
EXE-EVE	[redacted]	[redacted]	7.8	BOLERO-2	[redacted]	[redacted]	31.0	BOLERO-2	[redacted]	[redacted]	6.8* 7.8*	BOLERO-2 (EXE)‡ BOLERO-2 (EVE)‡
FUL	[redacted]	[redacted]	6.5 8 7.5 9.3	CONFIRM Zhang 2016 Hi-FAIR fx MONARCH 2 CSR	[redacted]	[redacted]	26.4 33.4	CONFIRM Hi-FAIR fx	[redacted]	[redacted]	[redacted]	MONARCH 2 CSR
TMX	[redacted]	[redacted]	-	-	[redacted]	[redacted]	-	-	[redacted]	[redacted]	-	-

Abbreviations: ABE: abemaciclib; CSR: clinical study report; EXE: exemestane; EVE: everolimus; FUL: fulvestrant; OS: overall survival; PFS: progression-free survival; OS: overall survival.
Footnotes: * Calculated from weeks to months; † Calculated from days to months; ‡ Duration of therapy in BOLERO-2 reported by component of the combination treatment (indicated in brackets).

B.3.11 *Interpretation and conclusions of economic evidence*

Summary of economic evidence for ABE-FUL

In this analysis, ABE-FUL was found to have the highest estimate of mean PFS (28.02 months) relative to all comparators. Mean OS was similar between the comparators, though highest for TMX (49.55 months) and second highest for ABE-FUL (48.42 months). Greater LY and QALY gains were observed for ABE-FUL (3.64 and [redacted], respectively) compared to EXE, FUL and EXE-EVE. OS estimates were uncertain due to the immaturity of the MONARCH 2 data. These results indicate that ABE-FUL may potentially provide greater clinical benefit than the comparators.

ABE-FUL at the with-PAS price was associated with a higher total cost (£[redacted]) compared to EXE, TMX and FUL. This was predominantly driven by the higher cost of drug acquisition and follow-up care for ABE-FUL relative to the other comparators. For acquisition costs, this is in part due to the higher drug costs per weekly cycle, but also due to improvements in PFS, as patients incur treatment costs over longer periods of time compared to the other comparators. ABE-FUL (with the proposed PAS) was associated with a lower total cost and dominated EXE-EVE at list price (£[redacted]), which is the key comparator for ABE-FUL at its specific position in the treatment pathway for HR+/HER2− advanced breast cancer.

Based price of ABE with the proposed PAS, the base case fully incremental analysis produced a pairwise ICER for ABE-FUL of £108,789 per QALY gained compared to TMX, the reference comparator.

The probability that ABE-FUL is cost-effective at the with-PAS price at a £30,000 ICER threshold is [redacted].

Generalisability of the analysis

The economic evaluation is based on the patient population from the MONARCH 2 trial, which may be considered representative of advanced HR+/HER2− ABC patients who have progressed while receiving or after (neo)adjuvant ET in the UK. The model included comparators deemed to be relevant to the UK, and the key comparator for ABE-FUL at is specific position in the treatment pathway was EXE-EVE. As per the NICE reference case, the analysis was conducted from an NHS and PSS perspective.

Strengths of the economic evaluation

The partitioned survival analysis was deemed appropriate for this decision problem, as it aligned with the model structures adopted in the cost-effectiveness studies captured in the SLR, and is consistent with prior relevant NICE appraisals.[52, 78, 97] Learnings from previous similar appraisals, (including EXE-EVE [TA421]), such as assumptions and inputs preferred by the committee, were incorporated.[26, 52, 78, 97]

A large number of model inputs (clinical utility and resource use) were taken from the methodologically robust MONARCH 2 trial, and parameter uncertainty was thoroughly explored through a PSA and a range of DSAs. Given the lack of post-progression follow-up in the MONARCH 2 trial, estimates of utility and hospitalisation rates in the post-progression state of the model were uncertain. Where possible, alternative data were used to supplement these

estimates, for example the use of data from Lloyd (2006) to inform the post-progression utility for patients.

Other strengths of the evaluation are that the analysis meets all aspects of the NICE reference case, including performance of a cost-utility analysis from an NHS/PSS perspective, assessment of HRQoL using the EQ-5D, and discounting of costs and benefits at 3.5%. The analysis has similarly taken into account NICE's position statement regarding use of EQ-5D-5L data.[136] The 5L data captured in MONARCH 2 was mapped to the EQ-5D-3L value set.

Limitations of the economic evaluation

OS estimates were uncertain due to the immaturity of the MONARCH 2 data. A number of trials included in the NMA had immature data (median OS not reached in at least one arm): Buzdar (1997), Howell (2002), Jonat (1996), Hi-FAIR fx, Kaufmann (2000), MONARCH 2 and Trial 0021. In these cases, the long-term OS predictions from the model could not be compared to the study publications. Longer follow-up data from the MONARCH 2 trial will help to predict OS estimates more accurately. In order to reduce this uncertainty, OS estimates from a study with mature OS data (CONFIRM[64, 110]), were used to inform long-term extrapolations. Furthermore, a conservative assumption was made in the model of no treatment effect between ABE-FUL and the comparators in the long-term extrapolations.

Comparing ABE-FUL to treatments outside the MONARCH 2 trial in terms of clinical outcomes required an assumption to be made that the baseline characteristics across the trials including these comparators were comparable. Differences in prior therapy received and HR+/HER2− status were identified between the MONARCH 2 trial and trials for the other comparators. These differences may impact the relative effects estimated from the NMA, and subsequently included in the model. However, the NMA only synthesised relative treatment differences and assumed that there were no imbalances in treatment effect modifiers between populations. Differences in prognostic variables alone would not affect the results of the NMA and as such, the use of results from a NMA can be considered more appropriate to estimate relative clinical outcomes than published data alone.

Due to the lack of data on clinical outcomes for TMX in the MONARCH 2-aligned patient population, an adjusted indirect comparison was conducted using data from Milla-Santos (2001)[75] to provide a comparison between TMX and FUL. It was assumed that the relative treatment effects in Milla-Santos (2001) for TOR vs TMX reflected the effect that would have been observed in a MONARCH 2-aligned population. However, Milla-Santos (2001) did not include patients who have received prior ET in the metastatic setting, meaning the study corresponds to an earlier, and potentially less severe line of patients.

Acquisition costs were a main driver of CE in the model and required estimation of the duration of therapy for each of the comparators. Duration of therapy for the comparators outside the MONARCH 2 trial was informed by the relative difference in median values of this endpoint and PFS in trial publications for the comparators, and calibration of the PFS curves to reflect this difference. Therefore, this is dependent on the trial data used and required an assumption to be made that the relative difference between the two endpoints is constant over time. Without further data on the duration of therapy for the comparator trials, it is difficult to test the validity of this assumption.

Summary of the cost-effectiveness evaluation of abemaciclib plus fulvestrant

- A *de novo* partitioned survival analysis with three health states (PFS, PPS and death) was undertaken to investigate the cost-effectiveness of ABE in combination with FUL (ABE-FUL) in patients with HR+/HER2− locally advanced or metastatic breast cancer, as part of the MONARCH 2-relevant patient population for abemaciclib.
- ABE-FUL accrued a greater number of life years (LYs, 3.64) over all comparators (EXE, FUL and EXE-EVE), except for TMX, which accrued a marginally greater amount (3.72). ABE-FUL accrued a greater number of QALYs over all comparators ([redacted]). ABE-FUL (with the proposed PAS) was associated with a higher total cost (£[redacted]) compared to EXE, TMX and FUL (at list price). This was predominantly driven by the higher costs of acquisition and follow-up care for ABE-FUL relative to the other comparators, owing to its improved PFS.
- ABE-FUL (with the proposed PAS) was associated with a lower total cost compared to EXE-EVE at list price (£[redacted]), which is the key comparator for ABE-FUL at its specific position in the treatment pathway for HR+/HER2− advanced breast cancer.
- Based on the price of ABE with the proposed PAS, the base case fully incremental analysis produced a pairwise ICER for ABE-FUL of £108,789 per QALY gained compared to TMX, the reference comparator.
- The probabilistic sensitivity analyses demonstrated that there was a [redacted] chance of ABE-FUL being cost-effective at a threshold of £30,000 per QALY.
- In the deterministic scenario analyses, the economic results were largely stable when varying model assumptions, demonstrating the robustness of the model
- In conclusion, the economic analysis found ABE-FUL to be associated with a clinical benefit, as measured by LYs and QALYs, relative to EXE, TMX, FUL and EXE-EVE.

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Single technology appraisal

Abemaciclib with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer after endocrine therapy [ID1339]

Dear James,

The Evidence Review Group, BMJ Group, and the technical team at NICE have looked at the submission received on 9 October 2018 from Eli Lilly and Company Ltd. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **30th October 2018**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals [embed NICE DOCS LINK on 'NICE Docs/Appraisals'].

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Marcela Haasova, Technical Lead (Marcela.Haasova@nice.org.uk). Any procedural questions should be addressed to Gemma barnacle, Project Manager (Gemma.Barnacle@nice.org.uk).

Yours sincerely

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Section A: Clarification on effectiveness data

A1. **Priority question**: Please confirm that unadjusted PFS data, rather than data adjusted for interval censoring, were used for MONARCH-2 in the NMA. If not, please justify why data adjusted for interval censoring is comparable to the PFS results provided by other studies in the network. If this cannot be justified, please use the unadjusted PFS results.

A2. **Priority question:** Given that the PFS data from BOLERO-2 does not support the PHs assumption (based on a significant global test p-value), and that the best fitting parametric models to the unadjusted PFS KM data from MONARCH are not PH models (Section M.2.1. of the Appendix indicates that the lognormal, loglogistic and Gamma distributions are the best fitting models), please:

a. Provide the Log(survival function / (1-survival function)) plots versus Log(time), and assess the proportional odds (PO) assumption across all of the trials in the network (See question A3) for PFS and OS;
b. If proportional odds hold across all trials for each outcome, please carry out NMAs for OS and PFS using parametric curves (Ouwens *et al.* Research Synthesis Methods 2010, 1 258-271), exploring both random and fixed effect models, and reporting model fitting statistics (e.g. DIC) for all analyses.
c. If proportional odds do not hold, please carry out NMAs for OS and PFS using a method such as fractional polynomials (Jansen. BMC Medical Research Methodology 2011, 11:61), exploring both random and fixed effect models, and reporting model fitting statistics (e.g. DIC) for all analyses.
d. Please use investigator assessed PFS for trials which are double blind and independently assessed PFS for trials which are open label or single blind, where possible. Please provide a table with the available PFS data for all included studies (investigator, BICR, not specified) and indicate what measure was used in the NMA.
e. Please use the results of the OS and PFS analyses in the economic model.

A3. Priority question: The network proposed by the company included several interventions which are not relevant to the NICE final scope and do not add any data (direct or indirectly) to the comparisons of the interventions of interest and can therefore be excluded. Some additional

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studies can also be excluded to minimise the heterogeneity between the included trials. In addition, neither tamoxifen nor chemotherapy, both key comparators listed in the NICE final scope, were included in the network proposed by the company. The ERG appreciates the company's comment that, "Chemotherapy is reserved for patients in whom initial or second-line ET has failed, and is therefore positioned after ABE-FUL in the treatment pathway", but the ERG considers patients in whom initial ET has failed to be in line with the relevant population, as described by the company. The ERG considers that chemotherapy is a comparator of relevance to the decision problem and an NMA could be carried out. According to the ERG's clinical experts, capecitabine is one of the most relevant chemotherapies in this setting and the ERG is aware of the trial BOLERO-6 (Jerusalem *et al*. JAMA Oncol. 2018 doi:10.1001/jamaoncol.2018.2262), which may inform the comparison with chemotherapy in the relevant setting.

a. As the company considers it appropriate to do an adjusted indirect comparison between abemaciclib+fulvestrant and tamoxifen using Milla-Santos 2001, please provide the methods and a justification for these methods for the adjusted indirect comparison of abemaciclib+fulvestrant versus tamoxifen.
b. Please conduct the PFS and OS NMAs including the following trials:
    1. BOLERO-2
    2. Yamamoto 2013
    3. Hi-FAIR fx
    4. MONARCH 2
    5. CONFIRM
    6. Zhang 2016
    7. SoFEA
    8. Milla-Santos 2001
    9. BOLERO-6
c. As a sensitivity analysis please conduct the PFS and OS NMAs including the trials above as well as the following trials:
    1. Zhang 2016
    2. Howell 2002
    3. Campos 2009

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A4. **Priority Question**: Please provide description and critique of all trials included in the NMAs, as suggested in A3, including:

a. inclusion/exclusion criteria,
b. number of lines and type of subsequent therapies,
c. outcome assessment (investigator assessed or independent review of progression),
d. definition of PFS/TTP,
e. a quality assessment of each trial,
f. baseline and disease characteristics as listed below,
    1. age
    2. menopausal status
    3. ECOG performance status
    4. HR+ status
    5. HER2 status
    6. Prior chemotherapy in advanced setting
    7. Prior chemotherapy in (neo)adjuvant setting
    8. Prior AI
    9. Most recent ET ([neo]adjuvant or metastatic)
    10. ET resistance (primary/secondary)
    11. Metastatic site
    12. Measurable disease at baseline

A5. Please confirm that the definition of TTP for trials included in the PFS NMA was TTP or death and that trials with a definition of TTP not including or mentioning death were excluded from the NMA of PFS.

A6. The PRISMA diagram outlining the systematic literature review (SLR) indicates that 29 independent studies were included in the review. In Appendix D.1.3, Table 20 and 21, showing reasons for exclusion, only 27 studies are listed. Please provide a reason for exclusion for all studies not used in the NMAs for any of the outcomes.

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A7. On page 34 in the submission it is mentioned that, "If either abemaciclib or placebo was discontinued, patients were permitted to continue receiving fulvestrant. If fulvestrant required discontinuation, patients were permitted to continue receiving abemaciclib or placebo". As patients could continue with abemaciclib or fulvestrant and discontinue the other, please provide a summary of the extent of exposure to study treatments in MONARCH 2 in line with the table below:

	Abemaciclib + fulvestrant		Fulvestrant monotherapy
	Abemaciclib	Fulvestrant	
Duration of treatment (weeks)			
Mean (SD)			
Median			
Range			
Daily dose per subject (mg/day)	Abemaciclib	Fulvestrant	Fulvestrant monotherapy
Mean (SD)			
Median			
Range			

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Percent intended dose (%)			
Mean (SD)			
Median			
Range			

A8. As stated in the method of administration and dosage, dose adjustment and/or dose interruption are recommended for the management of some adverse reactions of abemaciclib. Please provide a summary of the dose reductions and omissions of the study treatments in MONARCH 2 in line with the table below:

	Abemaciclib + fulvestrant		Fulvestrant monotherapy
Number of subjects with, n (%)	Abemaciclib	Fulvestrant	
Dose reduction			
Dose interruption/omission			
Drug discontinuation due to AEs			

A9. Please clarify how many people from England were enrolled into MONARCH 2, and how many were randomised to each treatment group

A10. Please clarify the inclusion criteria reported in Table 4 of the submission:

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a. "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 AI as first-line ET for metastatic disease (patients may not have received more than 1 line of ET or any prior chemotherapy for metastatic disease)" and
b. "Presented de novo with metastatic disease and then relapsed with radiologic evidence of progression after treatment with an anti-oestrogen or an aromatase inhibitor as first-line ET for metastatic disease (patients may not have received >1 line of ET or any prior chemotherapy for metastatic disease)"

Do these includes both patients who progressed while receiving first line ET treatment for ABC as well as patients who progressed after receiving first line ET treatment for ABC?

A11. Please provide PFS (investigator and BICR) and OS results (including participants numbers and 95% CI) for the subgroup analyses based on line of therapy (first and second line) in the advanced setting).

A12. Please clarify the difference between the sample size reported on page 41 (630 patients) and the number of randomised patients (669), as reported for the ITT population on page 48.

Section B: Clarification on cost-effectiveness data

B1. **Priority question**: Please provide a detailed justification for why it was necessary to adjust PFS data for interval censoring and describe the method used to adjust the data. Please discuss the potential biases associated with the approach chosen (NICE TSD 14, Panageas *et al*. 2007).

B2. **Priority question**: Please clarify if the INV PFS KM data provided in the "KM" tab of the economic model are the adjusted or unadjusted KM data. Please provide the missing dataset (i.e. either the adjusted or the unadjusted) INV PFS KM data for ABE-FUL and FUL, separately (in the same format as the KM reported in the "KM" tab of the economic model).

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B3. **Priority question**: For both the adjusted and unadjusted INV PFS KM for the ABE-FUL and FUL arms of MONARCH please provide the log(inverse standard normal distribution function(1-survival function)) plots versus Log(time) and assess the assumption of accelerated failure time effects.

B4. **Priority question**: Based on your assessment of fit of different parametric models to the unadjusted INV PFS KM data for the FUL and ABE-FUL arms of MONARCH, reported in Section M.2.1. of the Appendix, the lognormal, loglogistic and Gamma distributions seem to provide the best statistical fit to the KM data. Therefore, could you please:

a. Justify why the exponential and Gompertz distributions (the worst fitting distributions to the data) were chosen as the two possible options to model the unadjusted INV PFS FUL curve in the model;
b. Consider using the best-fitting curves (also taking into account the clinical plusability of the curve's tails) to model the unadjusted INV PFS FUL curve in the model, and if not, please justify why;
c. Please apply the outputs obtained from the NMA (with the method deemed appropriate in question A2) to derive the survival curves for the different comparator treatments, and if not, please justify why;
d. If alternatively, you decide it is appropriate to apply the original NMA HRs to the fitted INV PFS arm of FUL in the model, to obtain PFS curves for ABE-FUL, TMX, EVE-EXE and EXE and chemotherapy (requested in question A3), please justify your choice and include the Weibull distribution as an option to model the baseline FUL PFS curve in the model. Please used the unadjusted data to run this analysis.

B5. **Priority question:** Please provide a plot in Excel (with the corresponding underlying data) of the unadjusted INV PFS KM data along with superimposed fitted curves for both arms of the MONARCH trial for all of the parametric models discussed above (Weibull, lognormal, Gamma, log-logistic, exponential and Gompertz). Please discuss the clinical plausibility of the tails.

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B6. **Priority question**: Similar to the option given for the Weibull model, please provide an option in the economic analysis to estimate OS with a Gompertz distribution fitted to MONARCH data only (i.e. not using CONFIRM data), to the FUL arm of the trial. In order to estimate the ABE-FUL OS curve please:

a. Depending on your assessment resulting from A2, either apply the NMA OS HR to the FUL curve to estimate the ABE-FUL OS curve (without using CONFIRM data); or use the best fitting curve derived from the NMA for ABE-FUL (taking into consideration the clinical plausibility of long-term extrapolations);
b. Similarly, please derive the OS curves for comparator treatments with either the NMA OS HR to the FUL curve; or use the best fitting curve derived from the NMA for each treatment;

B7. **Priority question**: Please provide an option in the economic analysis to estimate the baseline OS and PFS FUL curves with the OS and PFS data from the 500mg FUL arm of CONFIRM (ITT population). Please undertake the same steps described in A2, B3 and B4c and B4d to fit survival curves to the OS and PFS KM data from CONFIRM and justify your choice of model. Please include the three best-fitting curves as an option to model OS and PFS for the FUL arm of the model.

B8. **Priority question:** Please provide a plot in Excel (with the corresponding data) of the OS and PFS KM data along with superimposed fitted curves for the 500mg FUL arm of the ITT CONFIRM trial for all of the parametric models considered above (Weibull, lognormal, Gamma, log-logistic, exponential and Gompertz).

B9. **Priority question:** Please provide the plots used to assess the PH assumption for time to treatment discontinuation (TTD) in MONARCH, referred to in page 114 of the CS.

B10. **Priority question:** The CS states that, "*If either abemaciclib or placebo was discontinued, patients were permitted to continue receiving fulvestrant. If fulvestrant required discontinuation, patients were permitted to continue receiving abemaciclib or placebo*".

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Therefore, could you please provide the following KM data in Excel, with the respective number of patients at risk:

a. The TTD KM curves for the ABE-FUL arm of MONARCH for patients receiving ABE-FUL for the entire duration of the trial (i.e. excluding patients who discontinued one of the two drugs during the trial);
b. The TTD KM curves for the ABE-FUL arm of MONARCH for patients discontinuing ABE, from beginning of treatment with ABE-FUL until the event of interest or death (and indicating when treatment with ABE was discontinued);
c. The TTD KM curves for the ABE-FUL arm of MONARCH for patients discontinuing FUL, from beginning of treatment with ABE-FUL until the event of interest or death (and indicating when treatment with FUL was discontinued);
d. The OS and PFS KM curves for the same patient groups described in question b and c above.

B11. **Priority question:** Please run a scenario analysis that includes an option in the economic model (as a drop-down menu in Excel) assuming TTD curves to be the same as PFS curves for each of the following comparator treatments: EXE; EVE-EXE; TMX; and chemotherapy.

B12. **Priority question:** Please run a scenario analysis that includes an option in the economic model (as a drop-down menu in Excel) to independently or jointly (depending on your assessment of PHs, POs or AFT) fit the best-fitting distributions to the TTD KM MONARCH data for both ABE-FUL and FUL (Gamma, Gompertz and lognormal according to Table 74 in Appendix M3) to estimate TTD for FUL and ABE-FUL. Use the minimum function in Excel to prevent the TTD and the PFS fitted curves from crossing in the model, for each treatment arm (as currently done in the company's base case).

B13. **Priority question:** Please include an option in the economic model (as a drop-down menu in Excel) allowing the analyses requested in B11 and B12 to be run together as a single scenario.

B14. **Priority question:** Please explain why the pairwise results of the economic analysis (i.e. ICERs for ABE-FUL vs FUL; ABE-FUL vs TMX; ABE-FUL vs EXE-EVE; ABE-FUL vs EXE) increase,

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considerably for some comparators, when the 150mg baseline population is chosen to run the model, instead of the base case ITT population.

B15. **Priority question:** Please provide pairwise ICERs in the Excel model tab "Dashboard" for all the ABE-FUL relevant comparisons (ABE-FUL vs FUL; ABE-FUL vs TMX; ABE-FUL vs EXE-EVE; ABE-FUL vs EXE; and ABE-FUL vs chemotherapy).

B16. **Priority question:** For HRs obtained from the NMA, please use the CODA output from WinBUGs to inform each PSA simulation. Please ensure that HRs are sampled from the same Bayesian Markov chain Monte Carlo iteration. When the CODA output is stored as separate columns for each treatment with iteration values along the rows, this corresponds to sampling all the output in one row, for each PSA simulation.

B17. The model includes an option to fit the adjusted INV PFS KM data with a Weibull and a gamma function. Given that the Gamma function is not a PHs model, please justify your decision to include it is an option to model PFS outcomes.

B18. Please provide in Excel format, the underlying data for all the fitted curves and KM (with numbers at risk) data for:

a. Figure 16 (CS, page 105);
b. Figure 17 (CS, page 106);
c. Figure 18 (CS, page 107);
d. Figure 21 (CS, page 110);
e. Figure 22 (CS, page 110);
f. Figure 26 (CS, page 115);
g. Figure 27 (CS, page 115);
h. Figure 29 (for the ABE-FUL 150mg and the 200mg curves, CS page 119);
i. Figure 33 (for the ABE-FUL 150mg and the 200mg curves, CS page 121);
j. Figure 37 (for the ABE-FUL 150mg and the 200mg curves, CS page 124);
k. Figure 34 (Appendix M.2.4 to the CS, page 237).

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B19. Please confirm if the life-years reported in the Excel model tab "Results" and "Dashboard" are undiscounted. If not, please provide the undiscounted life-years.

B20. Given follow-up visits in MONARCH were conducted every 8 weeks, and clinical expert opinion indicated that disease progression cannot be measured in less than 4 week-intervals, please explain the need to have weekly model cycles.

B21. The ERG found some discrepancies between the values reported in the CS and in the Excel model results. Please clarify what are the correct values in Table 1 below.

Table 1. Discrepancies between the economic model and the company submission

Outcomes/Analysis	Reference in the model	Company submission	Correct values
HR TMX FUL	'HR'J25	Table 29	
RDI values	'Resource'J54:J76	Table 50	
Distribution used	'Resource'AN181	Table 58	

B22. Please explain the difference in the Cox-Snell plots in Figure 32 and Figure 33.

B23. Please clarify if the eight one-way sensitivity analyses (OWSA) presented in the model represent the key eight drivers in the model (resulting from varying all the model parameters). If not, please consider varying all parameters included in PSA to identify the key drivers in the model. If the company decides not to undertake additional OWSA analysis, please justify this decision.

Adverse events

B24. **Priority question:** On page 126 of the CS it states, "The rates of AEs for patients on ABE-FUL and FUL in the model were based on the TEAEs". Please clarify if the AE rates obtained from BOLERO 2 for exemestane and everolimus represent treatment-emergent or treatment-related AEs. For consistency, please use the same type of AE for all comparators, and if available please use treatment-related AEs.

B25. Please amend the cost to treat grade 3-4 diarrhoea from one pack of loperamide to the resource use accepted in TA496 (NHS Reference Costs: Gastrointestinal Infections, non-elective short stay, weighted average FZ36G to FZ36Q).

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B26. Please explain why grade 5 AEs were not considered in terms of impact on quality of life and costs.

B27. Please clarify how sources of AE disutilities (Hudgens 2016 and Swinburn 2010) were chosen and identified to inform the model and why the AE disutilities (stomatitis and vomiting) reported by Lloyd et al. 2006 were not considered.

B28. Please clarify how ID414 was chosen and identified to inform the duration of AEs (Table 33 of the CS).

Resource and cost use

B29. **Priority question:** Please correct the number of PFS events in the model ('Resource'F177) from 379 to 364, as to exclude the 15 deaths without progressive disease.

B30. **Priority question:** Please provide a scenario analysis where 100% of patients receive active therapy on progression.

B31. **Priority question:** In Table 77 of Appendix M.3, only one source is provided for each comparator, please clarify how many additional sources from the NMA could be used to inform either of the two approaches.

B32. **Priority question:** Please clarify why the median duration of treatment for EVE-EXE reported in Table 77 of Appendix M.3 is different in approach 1 (5.5) ('ToT'AB44)and 2 (6.8) ('ToT'AS44), when both approaches were informed by BOLERO-2.

B33. **Priority question:** Please explain if the follow-up care resources received in MONARCH 1 for pre-progression and MONARCH 2 for post-progression (Tables 43, 44 and 45 of the CS) are considered to reflect current clinical practice. Please provide a scenario analysis (as a drop down menu in the Excel model) using the follow-up resource use for PFS and PPS accepted in TA496.

B34. **Priority question:** To reflect the assumptions accepted in TA503 and TA496, please provide a scenario analysis where 32.3% of subsequent fulvestrant administrations are delivered in the

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primary care setting (PSSRU: band 6 community nurse specialist, 15 minutes) and 67.7% are delivered in the outpatient setting (NHS Reference Costs: Non-Consultant Led: Follow up Attendance, Non-Admitted Face to Face, Medical Oncology Code 370).

B35. **Priority question:** In the model, the weekly cost of fulvestrant (£43.17) is applied in the first cycle ('Trace'AH14) when FUL or ABE-FUL is chosen as the comparator ('Trace'E6). Please correct the model so that the full cost of the first administration is also included (£172.67).

B36. **Priority question:** Please clarify where hospitalisation data (length of stay, total hospitalisations and follow-up) used to inform 'Hosp'AA8:AG101 can be found in the CSR.

B37. **Priority question:** Please clarify why the number of hospitalisations reported in Table 40 of the CS (pre-progression 73, post-progression 23), is different to the base case numbers in Table 41 of the CS (pre-progression 86, post-progression 11).

B38. **Priority question:** Please justify the assumption that the proportion of post-progression survival on-treatment is 37% ('Dashboard'J45) for each treatment arm.

B39. **Priority question:** Please provide a scenario where patients receive post-progression treatment for 100% of the time during post-progression survival.

B40. **Priority question:** Please provide a scenario analysis (as a drop-down menu in Excel) including radiotherapy in the post-progression "pack of care" for 80% of progressed patients, allowing this scenario to be compatible with the scenario requested in B30 (i.e 100% of progressed patients receive subsequent treatment and out of those, 80% receive additional radiotherapy).

B41. Where bevacizumab is used as a post-progression therapy (Table 47 of the CS), please provide a scenario analysis replacing the cost of bevacizumab with the cost of tamoxifen. As for the patient distributions, please reweight the distributions to the following:

a. TMX patients receiving subsequent TMX to zero instead of the number receiving bevacizumab (10) ('Resource'AS216);

b. EVE-EXE patients who received subsequent TMX in BOLERO-2, instead of the number of patients who received bevacizumab in BOLERO-2 ('Resource'AQ216:AR216);

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c. ABE-FUL and FUL patients who received subsequent TMX in MONARCH-2 (11 and 11, respectively) instead of the number of patients who received bevacizumab in MONARCH-2 (20 and 10, respectively) ('Resource'AO216:AP216).

B42. Based on your response to B24, please explain how costing hospitalisations is not considered double-counting if TEAEs rather than TRAEs have been modelled. Please provide a scenario analysis excluding the cost of hospitalisations.

B43. The ERG is unable to identify the currency code (JD12D) reported in Table 42 of the CS, in NHS Reference Costs. The ERG is also unclear why the mean length of stay (7.78) in Table 42 of the CS does not reflect the mean lengths of stay in Table 40 of the CS. Please clarify both issues.

B44. Please explain why scan modalities in Tables 44 and 45 of the CS are considered separate to the scans received in follow-up care (Table 43). Also provide a scenario analysis excluding the cost of scan modalities.

B45. Please replace the cost of an x-ray (£0) with a cost of £29.78 (NHS reference costs 2016/17: Direct Access Plain Film, currency code DAPF).

B46. Please incorporate vial wastage into the cost of Filgrastim ('OtherCosts'AU14).

B47. Please amend the regimen for Capecitabine from 21 days of treatment to 14 days, to reflect recommendations in the BNF (1,25 g/m2 twice daily for 14 days, subsequent courses repeated after a 7-day interval).

Health-related quality of life

B48. **Priority question:** Please explain why age-related utility decrements were not included in the economic model. Also provide a scenario analysis including age-related utility decrements, using the published algorithm by Ara and Brazier 2010. (Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health 2010; 13: 509-18.)

B49. **Priority question:** Please clarify why Lloyd *et al.* 2005 was not identified in the search for HRQoL evidence. As advised by the NICE DSU (Technical Support Document 12) (http://nicedsu.org.uk/wp-content/uploads/2016/03/ TSD12-Utilities-in-modelling-FINAL.pdf) please compare the population and methods in Lloyd *et al.* 2005 with MONARCH 2.

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B50. Please provide descriptive statistics for the crosswalked EQ-5D-3L data captured in MONARCH 2 including the mean age of respondents, mean utility value, standard deviation and number of observations collected at each time point of data collection.

B51. For each regression model reported in Appendix M.5, please add the p-value and 95% confidence interval for each coefficient.

B52. Please run a scenario analysis (as a drop-down menu in Excel) removing the AE-related disutilities. Please discuss the implications of including them in the economic analysis, with regards to double counting given that PFS utility values are likely to have implicitly captured these.

B53. Please explain how the coefficients in Table 92 of Appendix M.5 result in the utility values reported in Table 30 of the CS. Also clarify if the regression model in Table 92 was ran independently of the baseline utility values reported in Table 91.

B54. Please clarify if the probability of hospitalisation input for endocrine therapies reported in Table 58 of the CS (66.34%) is used in the economic model.

B55. Please clarify why the administration cost code for bevacizumab relates to subsequent elements of a chemotherapy cycle.

Section C: Textual clarifications and additional points

C1. Please clarify why relevant NICE TAs in adults with locally advanced or metastatic breast cancer such as TA239, TA495, TA421 and TA496 were not identified in searches for HRQoL and resource and cost use evidence.

C2. Please clarify why NHS EED was not searched from 2015 using the database maintained in the Centre for Reviews and Dissemination (https://www.crd.york.ac.uk/CRDWeb/).

C3. Please provide the original search strategies for cost-effectiveness evidence, HRQoL evidence and cost and healthcare resource use evidence.

C4. Please clarify why 66 studies were included in the search for cost and healthcare resource evidence if only 20 reported results relating to this patient population.

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C5. Please provide the full reference and full-text for Kurosky 2015, Mitra 2016 and Wood 2017 included in the search for cost and healthcare resource evidence.

C6. Please explain why the searches for cost-effectiveness evidence, HRQoL evidence and cost and healthcare resource use evidence have not been updated since June 2017.

C7. Please provide a definition of the EP stratum, mentioned in the company submission page 43.

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18th December 2018

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Single technology appraisal

Abemaciclib with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer after endocrine therapy [ID1339]

Dear Kirsty,

This is the updated version of the clarifications response dated 12th November. Tables 12, 13, 17, 18, 20, 21, 22, 23, 24, 25, 26, 27, 29, 30, 33 and 34 have all been corrected.

The base case setting with the updated PAS results are presented in the table 0 below, these values are aligned with the submitted base case, but reflect the updated PAS, therefore the costs for the other treatments have remained the same along with the clinical outcomes.

Table 0. Base-case results (as per submission base case with revised PAS)

Comparator	Costs	LYs	QALYs	ICER (per QALY)	ICER (per QALY) for ABE-FUL vs comparator
TMX	[redacted]	3.72	[redacted]	Referent	£62,548
FUL	[redacted]	3.50	[redacted]	Dominated	£41,702
EXE	[redacted]	3.33	[redacted]	Dominated	£18,754
ABE-FUL	[redacted]	3.64	[redacted]	£62,548	N/A
EXE-EVE	[redacted]	3.45	[redacted]	Dominated	Dominant

Thank you for the opportunity to respond to the clarification questions posed by the Evidence Review Group, BMJ Group, regarding the Eli Lilly and Company Limited (Lilly) submission for Verzenios (abemaciclib) [ID1339]. Please see below a summary of Lilly's responses:

- Lilly has provided a response to the **priority** clarification questions posed; responses for non-priority clarification questions are not provided due to time limitations (except for questions A7 and A8 and those specifically requested by NICE, including B19, B20, B23, B41, B43, B50, and B53).

- Responses to the 35 priority questions have been provided in separate waves. The responses to the majority of the priority clarification questions were submitted on Tuesday 30th October and Monday 5th November, however are also presented again below together with additional responses for the third and final wave.

- Responses which are new or updated since the 5th November submission include clarification questions A2 parts c) d) and e), A3 parts b) and c), B4 part c), B16 and revised responses for B4 parts a) b) and d), B6 parts a) and b), B11, B14, B16, B30, B33 and B53 (revised AIC marking).

- Please note that results are presented in questions B11, B14, B30 and B33 that incorporate the revised patient access scheme (PAS) discount provided to NICE in correspondence on 8th November.

Lilly would also like to highlight the following:

- Additional data provided within the responses which are AIC or CIC have been highlighted using underlining and [redacted] or [redacted] highlighting. Any figures that are AIC/CIC are indicated by a yellow or blue outline. A checklist for confidential information of all clarification question responses and a redacted version of this document have also been submitted.

- The EPAR for abemaciclib has become available since submission of ID1339, and has been provided with this document. ACIC marking has been updated accordingly, however please note, ACIC marking in the full submission will be updated to align with EPAR at a later date.

- An updated economic model dated 20181113 will also be provided tomorrow, 13th November, due to file size.

- The code for the final NMA performed has been provided.

If you require any further information, please let me know.

Yours sincerely,

James
James Parnham BPharm (Hons)
Head of HOHTA, Lilly UK

Section A: Clarification on effectiveness data

A1. **Priority question**: Please confirm that unadjusted PFS data, rather than data adjusted for interval censoring, were used for MONARCH-2 in the NMA. If not, please justify why data adjusted for interval censoring is comparable to the PFS results provided by other studies in the network. If this cannot be justified, please use the unadjusted PFS results.

The NMA used the unadjusted PFS data for MONARCH 2 as reported in the trial publication.[1]

A2. **Priority question:** Given that the PFS data from BOLERO-2 does not support the PHs assumption (based on a significant global test p-value), and that the best fitting parametric models to the unadjusted PFS KM data from MONARCH are not PH models (Section M.2.1. of the Appendix indicates that the lognormal, loglogistic and Gamma distributions are the best fitting models), please:

a. Provide the Log(survival function / (1-survival function)) plots versus Log(time), and assess the proportional odds (PO) assumption across all of the trials in the network (See question A3) for PFS and OS;

Ordinal logistic regression is usually conducted to assess the impact of one or several explanatory variables on a response on the ordinal scale. In survival analysis, individual-level data on PFS and OS can be categorised into intervals of a specific duration (e.g. 5 months), and the impact of treatment on each of the categories can be assessed. The analysis is only valid if the proportional odds assumption holds. The proportional odds assumption implies that the relationship between each pair of outcome groups is the same; the coefficients that describe the relationship between the lowest versus all higher categories of the response are the same as those that describe the relationship between the next lowest category and all higher categories etc. Therefore, only one set of coefficients is necessary. Since tests such as the likelihood ratio test often find that the proportional odds assumption is violated even if it is not, a more reliable approach to assess this is given through graphical display, following the approach from Harrell (2001),[2] as described by the UCLA Institute for Digital Research and Education.[3]

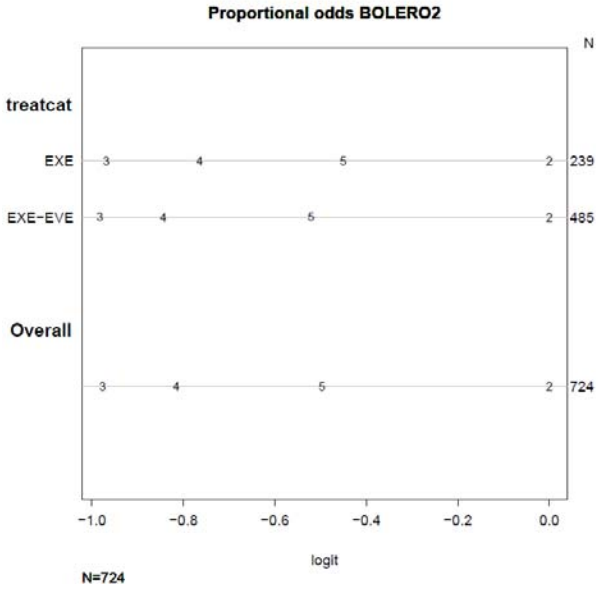
The values shown in the graphs are predictions from a logit model used to model the probability that the response is greater than or equal to a given value for each level of the response considering the explanatory variable treatment. For each treatment category considered, the difference between a level of the response and the next highest level of the response is calculated. The differences in logits between levels of the response are then compared over the treatments. If these are similar (with a tolerance level of +/- 0.3), the proportional odds assumption holds.

In order to conduct a logistic regression of categorised survival data, the time interval of death and disease progression of censored individuals has to be estimated. This can be conducted through an imputation approach, for example. The categories of the events of death and disease progression are evaluated in intervals of 5 months. For example, if an individual was censored in month 7, this individual could have died in category 2 (death at >5 and <=10 months), category 3 (death at >10 and <=15 months), category 4 (death at >15 and <=20 months) or category 5 (death at >20 months). Since we have a lack of information, we assume that death in any of the

categories occurs with equal probability. We use a random number generator of a uniform distribution to assign a value ranging between 2 and 5 to the censored individual. Examples of the proportional odds assumption holding and not holding are presented in Figure 1 and Figure 2, respectively.

We assessed graphs of differences in logits for all studies in the network for the outcomes OS and PFS. For OS, the proportional odds assumption holds for BOLERO-2, Buzdar 2001, SoFEA and is violated for Buzdar 1997, CONFIRM, Dombernowsky 1998, Jonat 1996, Kaufmann 2000, Muss 1990 and Yamamoto 2013. For PFS, the proportional odds assumption holds for CONFIRM, Howell 2002, PALOMA 3, SoFEA, Trial 0021, Zhang 2016 and is violated for BOLERO-2, Buzdar 1997, Buzdar 2001, Dombernowsky 1998, Jonat 1996, Yamamoto 2013. Since the proportional odds assumption does not hold for all studies of interest for the two outcomes, evidence synthesis will be conducted through a fractional polynomial approach. More details on the proportional odds assessment are shown below.

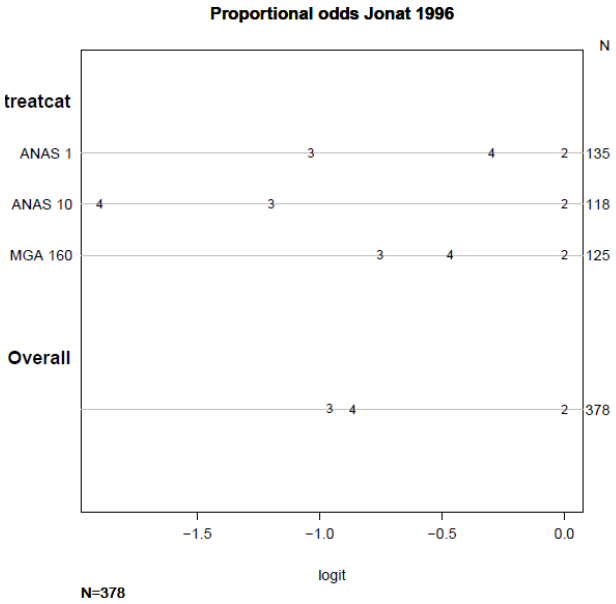
Figure 1. Proportional odds assumption holds for the BOLERO-2 study (OS)



Abbreviations: EXE: exemestane; EVE: everolimus; OS: overall survival.

Figure 1 shows the difference in logit of each category of the response to the next lower category, displayed by the number corresponding to the higher category. For example, the number 3 indicates the difference in logit of category 3 of the response (OS >=15 months) and category 2 of the response (OS >=10 months). These numbers are displayed for the treatment categories EXE and EXE-EVE. The number 2 is 0 for both treatment categories since it was normalized as a reference. The differences in logit are similar over the two treatment categories and at most 0.1; therefore we can conclude that the proportional odds assumption holds.

Figure 2. Proportional odds assumption does not hold for the Jonat 1996 study (OS)



Abbreviations: ANAS: anastrozole; MGA: megestrol; OS: overall survival.

Figure 2 shows the differences in logit between next highest and lower categories of the response for the three treatments of interest (ANAS1, ANAS10 and MGA160). The distances in differences between categories 3 (OS>=15 months) and 2 (OS>=10 months) are around 0.5 for the treatments ANAS10 and MGA160. The distances between categories 4 (OS>=20 months) and 3 are even higher for ANAS10 and MGA160. Therefore, the proportional odds assumption is clearly violated.

b. If proportional odds hold across all trials for each outcome, please carry out NMAs for OS and PFS using parametric curves (Ouwens *et al.* Research Synthesis Methods 2010, 1 258-271), exploring both random and fixed effect models, and reporting model fitting statistics (e.g. DIC) for all analyses.

Following the above response for part a), this part b) is no longer applicable.

c. If proportional odds do not hold, please carry out NMAs for OS and PFS using a method such as fractional polynomials (Jansen. BMC Medical Research Methodology 2011, 11:61), exploring both random and fixed effect models, and reporting model fitting statistics (e.g. DIC) for all analyses.

The approach as described by Jansen 2011 has been used for the updated NMA,[4] which is presented in response to Question A3b.

d. Please use investigator assessed PFS for trials which are double blind and independently assessed PFS for trials which are open label or single blind, where possible. Please provide a table with the available PFS data for all included studies (investigator, BICR, not specified) and indicate what measure was used in the NMA.

The data used in the NMA along with the available data for each of the trials requested in A3b has been presented in Table 1.

Table 1. Eligibility criteria for the trials included in the revised NMA

Trial	Design	Data available	Data used in NMA
BOLERO-2 (Yardley 2013)	Double blind	Local investigator Central review	Local investigator from Yardley 2013
Yamamoto 2013	Open label	NR	Figure 2a from Yamamoto 2017
Hi-FAIR fx	Open label	NR	Figure 2 from Nishimura 2017
MONARCH 2	Double blind	IA IRC	Investigator
CONFIRM	Double blind	NR	Figure 2b from Di Leo 2013
Zhang 2016	Double blind	NR	Figure 2 from Zhang 2016
SoFEA	Partially blinded - Participants and investigators were aware of assignment to FUL or EXE, but not of assignment to ANAS or placebo for patients in the groups assigned FUL	NR	Figure 2 from Johnston 2013
Milla-Santos 2001	Double blind	NR	NR
BOLERO-6	Open label	Local Investigator	Figure 2 from Jerusalem 2018

Abbreviations: IA: investigator assessed; IRC: independent review centre; NR: not reported

Due to the lack of reporting it is unclear how the data aligns with the requested PFS definition. The MONARCH 2 and BOLERO 2 trials reported both investigator review and independent review. Local investigator (BOLERO-2) and investigator (MONARCH 2)-assessed PFS were utilised in the NMA. The only know violation of the required data is BOLERO 6, which was partially blinded but only reported local investigator.

e. Please use the results of the OS and PFS analyses in the economic model.

The updated NMA has been incorporated into the model, via the page 'A3'. This page overrides the previous NMA inputs on the HR page and the selected data parametric curve fits for OS and PFS.

A3. Priority question: The network proposed by the company included several interventions which are not relevant to the NICE final scope and do not add any data (direct or indirectly) to the comparisons of the interventions of interest and can therefore be excluded. Some additional studies can also be excluded to minimise the heterogeneity between the included trials. In addition, neither tamoxifen nor chemotherapy, both key comparators listed in the NICE final scope, were included in the network proposed by the company. The ERG appreciates the company's comment that, "Chemotherapy is reserved for patients in whom initial or second-line

ET has failed, and is therefore positioned after ABE-FUL in the treatment pathway", but the ERG considers patients in whom initial ET has failed to be in line with the relevant population, as described by the company. The ERG considers that chemotherapy is a comparator of relevance to the decision problem and an NMA could be carried out. According to the ERG's clinical experts, capecitabine is one of the most relevant chemotherapies in this setting and the ERG is aware of the trial BOLERO-6 (Jerusalem *et al*. JAMA Oncol. 2018 doi:10.1001/jamaoncol.2018.2262), which may inform the comparison with chemotherapy in the relevant setting.

a. As the company considers it appropriate to do an adjusted indirect comparison between abemaciclib+fulvestrant and tamoxifen using Milla-Santos 2001, please provide the methods and a justification for these methods for the adjusted indirect comparison of abemaciclib+fulvestrant versus tamoxifen.

The adjusted indirect comparison between abemaciclib plus fulvestrant and tamoxifen was conducted using the Bucher Indirect Treatment Comparison (ITC) method.[5] Bucher ITC is a statistical approach used to compare interventions (which have not been directly compared in a head-to-head trial) via a common comparator in an indirect way, based on simple equations. The equations of the Bucher method for binary data can be applied to count outcomes (e.g. exacerbation rates) in terms of incidence rate ratio (IRR) as well, resulting in:

$$\ln(\mathrm{HR}_{\mathrm{AB}}) = \ln(\mathrm{HR}_{\mathrm{AC}}) - \ln(\mathrm{HR}_{\mathrm{BC}})$$

Which is equivalent to the following:

$$\mathrm{HR}_{\mathrm{AB}} = (\mathrm{HR}_{\mathrm{AC}})/(\mathrm{HR}_{\mathrm{BC}})$$

For the treatment effect, as well as

$$\mathrm{Var}(\mathrm{HR}_{\mathrm{AB}}) = \mathrm{Var}(\mathrm{HR}_{\mathrm{AC}}) + \mathrm{Var}(\mathrm{HR}_{\mathrm{BC}})$$

and

$$\mathrm{SE}(\mathrm{HR}_{\mathrm{AB}}) = \sqrt{\mathrm{SE}(\mathrm{HR}_{\mathrm{AC}})^2 + \mathrm{SE}(\mathrm{HR}_{\mathrm{BC}})^2}.$$

for corresponding variance and standard error, respectively.

Bucher ITC is a frequentist approach to evidence synthesis and is a requirement for several health technology assessment (HTA) bodies. However, the method has several shortcomings. It assumes that the trials included in the ITC are similar with regards to the study population, study design, outcome measurements, and the distribution of treatment effect-modifiers (i.e. study and patient characteristics that have an independent influence on treatment outcome).[5]

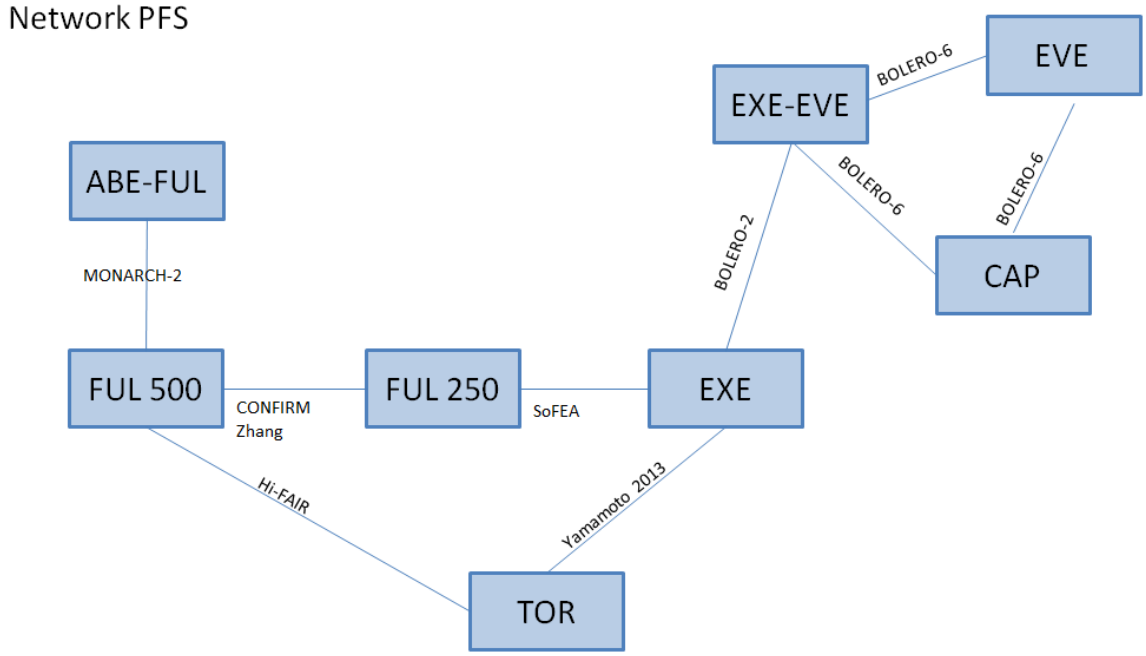
b. Please conduct the PFS and OS NMAs including the following trials:

1. BOLERO-2

2. Yamamoto 2013
3. Hi-FAIR fx
4. MONARCH 2
5. CONFIRM
6. Zhang 2016
7. SoFEA
8. Milla-Santos 2001
9. BOLERO-6

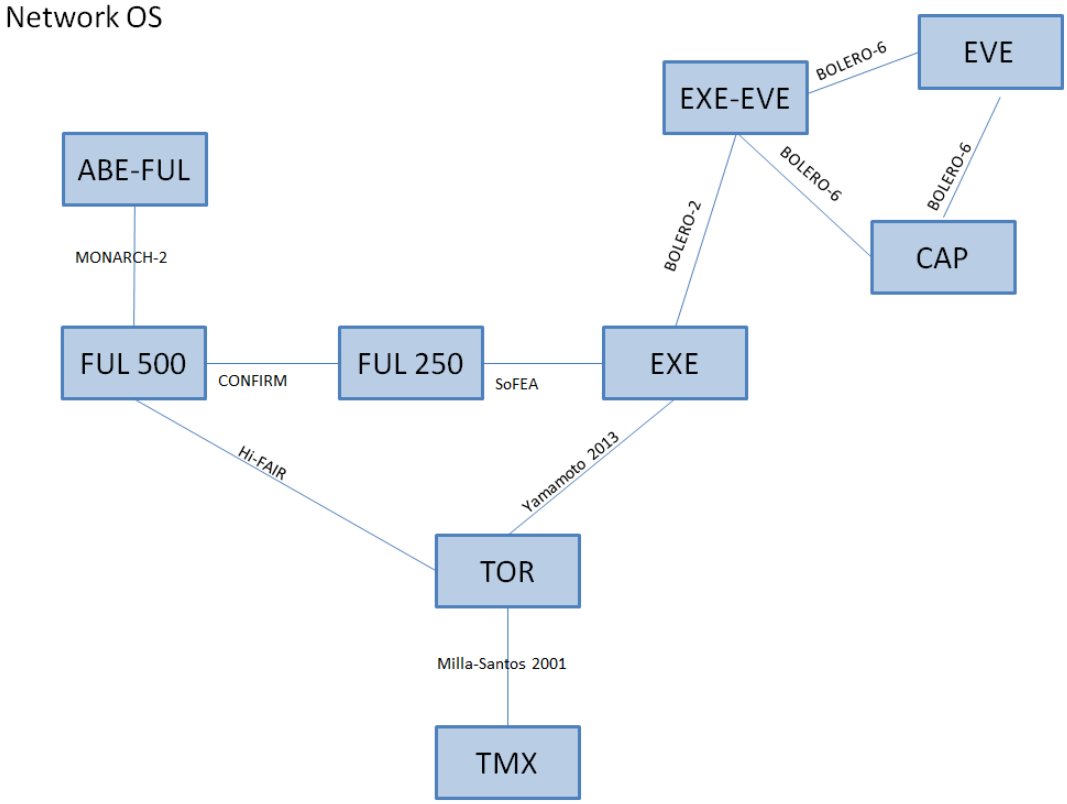
Based on the above trials, the networks presented in Figure 3 and Figure 4 were used for PFS and OS, respectively.

Figure 3. Network for PFS (updated NMA)



Abbreviations: ABE: abemaciclib; CAP: capecitabine; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; PFS: progression-free survival; TOR: toremifene.

Figure 4. Network for overall survival (updated NMA)



Abbreviations: ABE: abemaciclib; CAP: capecitabine; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; OS: overall survival; TMX: tamoxifen; TOR: toremifene.

For the PFS network (output shown in Figure 5), it was not possible to include Milla-Santos 2001 as this trial only reports a hazard ratio for toremifene and tamoxifen (which was used in the ITC analysis). Milla-Santos 2001 reports median duration of response in a Kaplan Meier chart, however, as these data are non-randomised, it was not possible to include this study within the network. For the OS network (output shown in Figure 6), Zhang 2016 was not included as this trial only reported PFS.

A fractional polynomial approach was taken to account for violation in the proportional hazards assumption. Unlike the standard NMA approach to time-to-event data considering HR data, the fractional polynomials approach (FP) does not require that the proportional hazards assumption holds.

A FP function of first or second order can be utilised to estimate the natural logarithm of the hazard function per treatment arm in each study, defined as $\ln(h(t)) = \beta_0 + \beta_1 t^{p1}$ and $\ln(h(t)) = \beta_0 + \beta_1 t^{p1} + \beta_2 t^{p2}$ with t0=log t. If p1=p2=p, the model becomes a repeated powers model, defined as $y = \beta_0 + \beta_1 t^{p} + \beta_2 t^{p} \log t$.

The power of the linear predictors p1 and p2 are chosen from a set; different choices correspond to different hazard functions, allowing a range of different shapes. In oncology, usually values in the set {-2,-1,-0.5,0,0.5,1,2,3} are considered to result in best fit to time-to-event data.

An NMA is then performed on the parameters of the fractional polynomials from each study to obtain an overall set of estimated parameters for each treatment. The survival curves can then be generated from these parameters.

For the purposes of the analysis of overall survival (OS) and progression-free survival (PFS) the following models were fitted:

- First order (β2=0) and second order fractional polynomials fixed effects (FE) and random effects (RE) models with powers p1 and p2 from the set {-2,-1,-0.5,0,0.5,1,2,3}.
- The RE models accounted for heterogeneity for d0 (treatment effect under the proportional hazard model) only (constant heterogeneity of log HR over time).

If various FP models showed similar DIC values (e.g. within 5 points), the selection was further informed by visual inspection of the fit of the observed data, carefully examining the tails of the distributions and plausibility of long-term extrapolation. Second-order models showed better fit than first-order models throughout, both in terms of DIC and visual inspection of the curves. For OS, the FE second-order model with p1=0, p2=1 showed best fit, whereas for PFS, the RE second-order model with p1=0.5, p2=1 fitted best. The corresponding time-to-event curves are displayed in Figure 5 for OS and Figure 6 for PFS, respectively.

For a number of combinations of p1 and p2 in the second-order FP models, we experienced issues with convergence and autocorrelation. This may occur due to the data being in conflict with the structural form implied by these combinations. As a consequence, the Gibbs sampler is unable to visit the relevant areas of the parametric space and cannot converge to the corresponding posteriors, even if the number of simulations is increased to 200,000 or more.

Analyses were conducted using OpenBUGS version 3.2.3, and R version 3.4.4. The package 'R2OpenBUGS' was used to run OpenBUGS from within R. Analyses were run with 30,000 iterations of which 12,000 were discarded as burn in, and a thinning parameter of 4, with 2 chains, to identify the parameter combinations with best fit. Once identified, the best-fitting models were rerun with 200,000 iterations of which 50,000 were discarded as burn in, with the same thinning parameter and number of chains as described above.

Minimally informative priors were used for all parameters, corresponding to a multivariate normal distribution with zero mean and covariance and 10,000 variance for d and μ parameters and a uniform distribution in the range of [0,2] for σ.

Figure 5. PFS output

Abbreviations: ABE: abemaciclib; CAP: capecitabine; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; PFS: progression-free survival; TOR: toremifene.

Figure 6. OS output

Abbreviations: ABE: abemaciclib; CAP: capecitabine; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; OS: overall survival; TOR: toremifene.

c. As a sensitivity analysis please conduct the PFS and OS NMAs including the trials above as well as the following trials:

1. Zhang 2016
2. Howell 2002
3. Campos 2009

The Zhang 2016 trial was included in the main analysis, listed in part b. The remaining two studies mentioned above were not included in the updated analysis with the following rationale:

- Campos 2009: This study did not report Kaplan Meier data that would be required for a fractional polynomial NMA.
- Howell 2002: This trial would add anastrozole to the PFS network, which is not a comparator of interest to this trial. In addition, this study did not include OS outcomes in Kaplan Meier form. Therefore, this trial would not benefit the model.

A4. Priority Question: Please provide description and critique of all trials included in the NMAs, as suggested in A3, including:

a. inclusion/exclusion criteria,
b. number of lines and type of subsequent therapies,
c. outcome assessment (investigator assessed or independent review of progression),
d. definition of PFS/TTP,
e. a quality assessment of each trial,
f. baseline and disease characteristics as listed below,

1. age
2. menopausal status
3. ECOG performance status
4. HR+ status
5. HER2 status
6. Prior chemotherapy in advanced setting
7. Prior chemotherapy in (neo)adjuvant setting
8. Prior AI
9. Most recent ET ([neo]adjuvant or metastatic)
10. ET resistance (primary/secondary)
11. Metastatic site
12. Measurable disease at baseline

Inclusion/exclusion criteria

The inclusion/exclusion criteria for all trials included in the NMA (as advised in question A3) are presented in Table 2. Across all studies, participants were required to have advanced breast cancer defined as advanced, locally advanced, locoregionally recurrent or metastatic disease.

The MONARCH 2 and BOLERO-2 trials recruited women with HR+/HER2− breast cancer. Details of the HR status were reported in all ET studies, and molecular subtype was commonly reported. HER2 status was not commonly reported prior to ASCO recommendations for HER2 testing in 2007 and, as such, studies where HER2 status was not reported were not excluded. Two studies that met the inclusion criteria also specified the inclusion of a small proportion of participants with HER2+ status: Yamamoto (2013; 2.2%) and the SoFEA trial (2013; 7.7%).

MONARCH 2 included patients who received ≤1 prior endocrine therapy and no prior chemotherapy in the advanced setting. Milla-Santos 2001 excluded patients who had received prior chemotherapy or endocrine therapy for advanced disease. In contrast, all other included trials allowed for prior chemotherapy in the advanced setting.

Number of lines and type of subsequent therapies

The subsequent therapies received by patients were not reported in eight out of the 11 trials included in the NMA and sensitivity analyses, and so it is unclear whether the subsequent therapies received by patients differed between MONARCH 2 and the comparator trials. Available data for subsequent therapies for MONARCH 2, BOLERO-6 and CONFIRM are presented in Table 3. Rates of subsequent chemotherapy and endocrine therapy were similar between the intervention arms of the MONARCH 2 and CONFIRM trials, whereas a larger proportion of patients from MONARCH 2 received subsequent radiotherapy. A smaller proportion the BOLERO-6 patient population received subsequent chemotherapy or ET, in comparison to the MONARCH 2 and CONFIRM patient populations (Table 3).

Outcome assessment (investigator assessed or independent review of progression)

There is a considerable risk of heterogeneity in the assessment of disease progression across the trials included in the NMA; the method of outcome assessment was not reported in all trials except for MONARCH 2, BOLERO-2 and BOLERO-6. PFS was evaluated through both investigator-assessment and a central, independent review in the MONARCH 2 and BOLERO-2 trials,[1, 6] while in BOLERO-6, PFS was assessed by the investigator only.[7, 8] Investigator-assessed PFS was the outcome used in the NMA.

Definition of PFS/TTP

All trials included in the NMA defined PFS or time to progression (TTP) as the time from randomisation until progressive disease or death, except for the Yamamoto 2013 and Johnston 2013 (SoFEA) studies in which the definition of PFS has not been reported.

Quality assessment of each trial

The quality assessment for each trial included in the NMA analyses is presented in Table 5.

Risk of bias assessments were not carried out for the Hi-FAIR fx (2013) study, as data for this study were reported in conference proceedings only. Due to the text restrictions in conference proceedings, assessment of risk of bias based on this information alone is not appropriate.

Due to insufficient reporting, Yamamoto (2013) was assessed as unclear or high risk across all modules. BOLERO-2 was the only study to be assessed as low risk across all modules, with MONARCH 2 assessed as mostly low-risk. In MONARCH 2, the module: "Is there any evidence to suggest that the authors measured more outcomes than they reported?" was assessed as unclear risk, because not all outcomes listed in the methodology were reported in Sledge (2017).[1] However, it is anticipated that these outcomes will be reported in future publications.

All included studies except from Yamamoto (2013) were assessed as having no apparent differences in the baseline prognostic factors of participants in each study arm and therefore had a low risk of bias assigned. High risk for the domain of blinding of treatment allocation was assigned in four of the studies: BOLERO-6, Campos (2009), Howell (2002), and Yamamoto (2013). This was due to the open label study design and a subjective primary endpoint. The majority of studies assessed analysed the ITT population. However, only MONARCH 2,[9] and BOLERO-2 appropriately detailed the methods used to account for missing data.

Baseline and disease characteristics

The baseline characteristics of patients in the trials included in the revised NMA are presented in Table 6. Age, performance status and post-menopausal status of patients were similar across the included studies.

The mean and median age reported by treatment arm ranged from 53.1 years[10] to 66 years (mean) and 55[10] to 66 years (median).[11] Over 80% of patients in the study arms of the included studies had a performance status of 0 or 1, thereby aligning with the MONARCH 2 eligibility criteria. All studies included post-menopausal patients; however, MONARCH 2 included 114 (17%) pre- or peri-menopausal patients, who were treated with a luteinising hormone-releasing hormone agonist to induce menopause.[1]

Details of the HR status were reported in all ET studies, and molecular subtype was commonly reported. However, there was considerable heterogeneity in how this was presented, such as percentage of participants with: "ER+ and PgR+", "ER+ or PgR+", or more vague descriptions denoted by "ER+ and/or PgR+" or simply grouping as ER+ with no details of whether the patients are ER+PgR+ or ER+PgR−.

The proportion of patients with primary or secondary endocrine resistance were reported in only two trials, MONARCH 2 and CONFIRM. In both trials, the majority of patients had secondary endocrine resistance, although this proportion was larger in the MONARCH 2 trial (75%)[12] compared with CONFIRM (approximately 65%).[13]

Where reported in five studies (Table 9), the majority of patients in each trial had measurable disease at baseline although this ranged from 59% to 100%.[14, 15] The reporting of metastatic site varied across the included trials, with trials reporting the proportion of patients with visceral disease, bone-only disease, or the dominant metastatic site. The proportion of patients with bone-only disease at baseline was reported in the MONARCH 2 and BOLERO-6 trials; slightly less patients enrolled in BOLERO-6 had bone-only disease, in comparison with the MONARCH 2 population (Table 9). The majority of patients enrolled in MONARCH 2 had visceral disease

(ABE-FUL: 54.9%, FUL: 57.4%),[1] which was similar with the patient populations of the BOLERO-6, Hi-FAIR fx, CONFIRM and SoFEA trials. Notably, in BOLERO-2, a larger proportion of patients had bone metastasis (EXE-EVE; 76%, EXE: 77%).[6]

Prior therapy

Only [redacted]% of patients enrolled in the MONARCH 2 trial and no patients in the Milla-Santos 2001 study[16] had received prior chemotherapy for advanced disease, whereas this ranged from 15%[7] to 37.5%[15] across the other included trials, where reported. The proportion of patients who had received prior adjuvant chemotherapy ranged from 34.2%[11] to 85.5%.[10] Prior chemotherapy therefore represents a considerable source of heterogeneity between the patient populations of MONARCH 2 and the comparator trials.

A similar proportion of the patient populations of MONARCH 2 and BOLERO-2 had been previously treated with an aromatase inhibitor (AI), as presented in Table 8. Prior treatment with an AI otherwise ranged from 42.7%[10] to 100%[17] of patients in the Zhang 2016 and Yamamoto 2013 trials, and was not reported in six trials.[7, 11, 13, 16, 18, 19] The lack of reporting for most recent ET in the [neo]adjuvant or advanced setting makes it difficult to assess the heterogeneity across the included trials. A higher proportion of patients from MONARCH 2 had received ET in the (neo)adjuvant or metastatic setting compared with in the Zhang 2016 study (Table 8).[1, 10]

Table 2. Eligibility criteria for the trials included in the revised NMA

Study ID	Stage	CNS/ brain metastases permitted?	Visceral crisis permitted ?	HR/HER2 status	Number of prior endocrine therapies for advanced BC as stated in eligibility criteria‡	Number of prior chemotherapies for advanced BC as stated in eligibility criteria‡
Endocrine therapy with or without targeted therapy						
BOLERO-2 2012	Advanced	No	-	HR+, HER2–	Not specified	≤1
BOLERO-6 2018	Advanced	<2% of patients	-	HR+, HER2−	Not specified	Not specified
Campos 2009	Advanced breast cancer with visceral metastases	-	-	HR+, HER2 not reported	≤1	≤1
CONFIRM 2010	Locally advanced or metastatic	No	-	HR+, HER2 not reported	≤1	≤1
Hi-FAIR fx 2017	Advanced or metastatic	-	-	HR+, HER2 not reported	Not specified	Not specified
Howell 2002	Locally advanced or metastatic	No	No	-	≤1	Not specified
Milla-Santos 2001	Advanced	-	-	HR+, HER2 not reported	Not specified	Not specified
MONARCH 2 2017	Advanced	No	No	HR+, HER2–	≤1	None
SoFEA 2013	Locally advanced or metastatic	-	No	HR+, HER2 not reported	Not specified	≤1
Yamamoto 2013	Metastatic	No	-	HR+, HER2 not reported	Not specified	≤1
Zhang 2016	Locally advanced or metastatic	-	No	HR+, HER2 not reported	≤1	≤1

Abbreviations: BC: breast cancer; CNS: central nervous system; HER2: human epidermal growth receptor-2; HR: hormone receptor.

Table 3. Subsequent therapies received across the trials included in the revised NMA, where reported

Study	Intervention	N	Chemotherapy, n (%)	Endocrine Therapy, n (%)	Radiotherapy, n (%)	Targeted, n (%)	HER2 directed therapy, n (%)	Other, n (%)
BOLERO-6	EXE-EVE	104	19	5	NR	NR	NR	NR
	EVE	103	19	10	NR	NR	NR	NR
	CAP	102	8	10	NR	NR	NR	NR
	TMX	111	NR	NR	NR	NR	NR	NR
MONARCH 2	ABE-FUL	446	Overall: [redacted] First subsequent line: [redacted]	Overall: [redacted] ([redacted]) First subsequent line: [redacted] ([redacted])	[redacted]	Overall: [redacted] ([redacted]) First subsequent line: [redacted] ([redacted])	NR	Overall: [redacted] ([redacted]) First subsequent line: [redacted] ([redacted])
	FUL	223	Overall: [redacted] First subsequent line: [redacted]	Overall: [redacted] First subsequent line: [redacted]	[redacted]	Overall: [redacted] First subsequent line: [redacted]	NR	Overall: [redacted] First subsequent line: [redacted]
CONFIRM	FUL500	362	135 (37.3)	80 (22.1)	8 (2.2)	NR	0	4 (1.1)
	FUL250	374	142 (38.0)	74 (19.8)	8 (2.1)	NR	1 (0.3)	5 (1.3)

Abbreviations: ABE: abemaciclib; CAP: capecitabine; FUL: fulvestrant; EVE: everolimus; EXE: exemestane; HER2: human epidermal growth factor receptor-2; TOR: toremifene; TMX: tamoxifen.

Table 4. Outcome assessment and definitions used for PFS/TTP across the trials included in the revised NMA

	BOLERO-2	BOLERO-6	Yamamoto 2013	Hi-FAIRfx	Milla-Santos 2001	MONARCH 2	CONFIRM	Zhang 2016	SoFEA	Howell 2002	Campos 2009
Outcome assessment of progression	Investigator assessment and independent review	Local assessment	NR	NR	NR	Investigator assessment and independent review	NR	NR	NR	NR	NR
Definition of PFS/TTP	PFS: date of randomisation to the date of first documented tumour progression or death from any cause, whichever occurs first	PFS: time from randomisation to first documented progression or death due to any cause	NR	NR	TTP: NR	PFS: time from random assignment until objective PD or death for any reason	PFS: time elapsing between the date of random assignment and the date of the earliest evidence of objective disease progression or death from any cause before documented disease progression	PFS: time from the first study visit (randomisation) to earliest objective disease progression, including death from any cause	PFS: time from randomisation to progression of existing disease, new sites of disease, secondary primary cancer or death from	TTP: time from randomisation until objective disease progression. Death was regarded as a progression event in those who died before	TTP: Time between the first day of treatment and the date of documented PD or death

	BOLERO -2	BOLERO-6	Yamamoto 2013	Hi-FAIR fx	Milla-Santos 2001	MONARCH 2	CONFIRM	Zhang 2016	SoFEA	Howell 2002	Campos 2009
									any cause	disease progression	

Abbreviations: NMA: network meta-analysis; NR: not reported; PFS: progression-free survival; TTP: time to progression.

Table 5. Quality assessment of all included trials in the revised NMA

	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors e.g. severity of disease?	Blinding of care providers, participants and outcome assessors to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Other potential risks noted?
	Level of risk	**Level of risk**	**Level of risk**	**Level of risk**	**Level of risk**	**Level of risk**	**Level of risk**	
BOLERO 2 (2012)	Low	Low	Low	Low	Low	Low	Low	Yes
BOLERO 6 (2018)	Low	High	Low	High	Low	Low	Low	No
Campos 2009	Unclear	Unclear	Low	High	Unclear	Low	Unclear	No
CONFIRM (2010)	Low	Low	Low	Low	Low	Low	Unclear	No
Howell 2002	Unclear	Unclear	Low	High	Unclear	Low	Unclear	No
Milla-Santos 2001	Low	Low	Low	Low	Unclear	Low	Unclear	No
MONARCH 2 2017	Low	Low	Low	Low	Low	Unclear	Low	No

SoFEA (2013)	Low	High	Low	Unclear	Unclear	Unclear	Unclear	No
Trial 0021 (2002)	Unclear	Low	Low	Low	Unclear	Low	Unclear	No
Yamamoto 2013	Unclear	Unclear	Unclear	High	Unclear	Unclear	Unclear	No
Zhang 2016	Unclear	Unclear	Low	Low	Low	Low	Unclear	No

Table 6. Baseline characteristics for all trials included in the revised NMA

Study ID	Interventions	N	Age (years)			Range		Menopausal status				ECOG/WHO performance status									
								Pre-menopausal		Post-menopausal		0		1		2		3		4	
			Mean	Median	SD	Min	Max	n	%	n	%	n	%	n	%	n	%	n	%	n	%
BOLERO-2 2012	EXE-EVE	485	-	62	-	34	93	-	-	485	100	-	60	-	36	-	2	-	-	-	-
	EXE	239	-	61	-	28	90	-	-	239	100	-	59	-	35	-	3	-	-	-	-
BOLERO-6 2018	EXE-EVE	104	-	61	-	32	86	-	-	104	100	54	52	42	40	5	5	-	-	-	-
	EVE	103	-	61	-	38	88	-	-	103	100	48	47	50	49	3	3	-	-	-	-
	CAP	102	-	60	-	35	84	-	-	102	100	57	56	39	38	4	4	-	-	-	-
Campos 2009	EXE	64	61.4	61	10.5	43	88	-	-	64	100	41	64.1	17	26.6	6	9.4	-	-	-	-
	ANAS 1 mg	64	64.2	64.5	10.1	42	84	-	-	64	100	31	48.4	30	46.9	3	4.7	-	-	-	-
CONFIRM 2010	FUL 500 mg	362	-	61	-	-	-	-	-	362	100	-	-	-	-	-	-	-	-	-	-
	FUL 250 mg	374	-	61	-	-	-	-	-	374	100	-	-	-	-	-	-	-	-	-	-
Hi-FAIR fx 2017	TOR	53	-	64	-	44	83	-	-	53	100	46	86.8	-	-	-	-	-	-	-	-
	FUL 500 mg	52	-	65	-	44	91	-	-	52	100	44	84.6	-	-	-	-	-	-	-	-

Howell 2002	FUL 250 mg	222	63	-	-	35	86	0	0	174	100	-	-	-	-	-	-	-	-	-	-
	ANAS 1 mg	229	64	-	-	33	89	0	0	222	100	-	-	-	-	-	-	-	-	-	-
Milla-Santos 2001	TOR	106	61.3	-	-	56	75	-	-	106	100	74	70	19	20	7	10	-	-	-	-
	TMX	111	60.8	-	-	55	75	-	-	111	100	77	69	26	23	8	8	-	-	-	-
MONARCH 2 2017	ABE-FUL 500 mg	446	[redacted]	59	[redacted]	[redacted]	[redacted]	72	16.1	371	83.2	264	59.2	176	39.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	FUL 500 mg	223	[redacted]	62	[redacted]	[redacted]	[redacted]	42	18.8	180	80.7	136	61	87	39	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoFEA 2013	FUL 250 mg	231	-	63.4	-	57	73.5	-	-	231	100	-	-	-	-	-	-	-	-	-	-
	EXE	249	-	66	-	59.2	75	-	-	249	100	-	-	-	-	-	-	-	-	-	-
Yamamoto 2013	TOR	46	-	63	-	51	87	-	-	46	100	-	-	-	-	1	-	0	0	0	0
	EXE	45	-	62	-	49	87	-	-	45	100	-	-	-	-	1	-	0	0	0	0
Zhang 2016	FUL 500 mg	111	53.6	55	10.1	26	80	0	0	111	100	-	-	-	-	-	-	0	0	0	0
	FUL 250 mg	110	53.1	55	10.2	31	76	0	0	110	100	-	-	-	-	-	-	0	0	0	0

Abbreviations: ABE: abemaciclib; ANAS: anastrozole; CAP: capecitabine; ER: oestrogen receptor; FUL: fulvestrant; EVE: everolimus; EXE: exemestane; TOR: toremifene; TMX: tamoxifen.

Table 7. Hormone receptor status for the trials included in the revised NMA

Study ID	Interventions	N	ER+ and PgR+ %	ER+ and PgR– %	ER– and PgR+ %	ER– and PgR– %	ER+ %	PgR+ %	ER+ or PgR+ %	Description provided
BOLERO-2 2012	EXE-EVE	485	-	-	-	-	100	-	-	-
	EXE	239	-	-	-	-	100	-	-	-
BOLERO-6 2018	EXE-EVE	104	-	-	-	-	-	-	-	-
	EVE	103	-	-	-	-	-	-	-	-
	CAP	102	-	-	-	-	-	-	-	-
Campos 2009	EXE	64	-	-	-	-	95.3	73.4	-	-
	ANAS 1 mg	64	-	-	-	-	93.8	62.5	-	-
CONFIRM 2010	FUL 500 mg	362	-	-	-	-	100	66.6	-	-
	FUL 250 mg	374	-	-	-	-	100	71.1	-	-
Hi-FAIR fx 2017	TOR	53	-	-	-	-	-	71.7	100	All patients required to be HR+
	FUL	52	-	-	-	-	-	86.5	100	All patients required to be HR+
Howell 2002	FUL 250 mg	222	-	-	-	3.6	-	-	73.4	ER+ and/or PgR+
	ANAS 1 mg	229	-	-	-	3.9	-	-	79.9	ER+ and/or PgR+
Milla-Santos 2001	TOR	106	-	-	-	-	-	-	-	-
	TMX	111	-	-	-	-	-	-	-	-
MONARCH 2 2017	ABE-FUL 500 mg	446	[redacted]	21.5	[redacted]	-	-	76	-	
	FUL 500 mg	223	[redacted]	[redacted]	[redacted]	-	-	76.7	-	
SoFEA 2013	FUL 250 mg	231	54	14	-	-	-	-	-	-
	EXE	249	53	9	-	-	-	-	-	-
Yamamoto 2013	TOR	46	-	-	-	-	98*	59*	-	-
	EXE	45	-	-	-	-	93*	69*	-	-
Zhang 2016	FUL 500 mg	111	82.0	18.0	0	0	100	82.0	100	ER+
	FUL 250 mg	110	80.9	19.1	0	0	100	80.9	100	ER+

Abbreviations: ABE: abemaciclib; ANAS: anastrozole; CAP: capeitabine; ER: oestrogen receptor; FUL: fulvestrant; EVE: everolimus; EXE: exemestane; mg: milligram; PgR: progesterone receptor; TOR: toremifene; TMX: tamoxifen.

Table 8. Prior therapy received by the patient populations of the trials included in the NMA

Study	Intervention	N	Prior chemotherapy in the (neo)adjuvant setting, n (%)	Prior chemotherapy in the advanced setting, n (%)	Prior AI, n (%)	Most recent ET ([neo]adjuvant or metastatic), n (%)
BOLERO-2	EXE-EVE	485	NR	26	74[a]	TMX as prior therapy: 47
	EXE	239	NR	26	75[a]	TMX as prior therapy: 50
BOLERO-6	EXE-EVE	104	45	15	NR	NR
	EVE	103	42	19	NR	NR
	CAP	102	54	16	NR	NR
Yamamoto 2013	TOR	46	NR	NR	100 (ANAS: 48 LTZ: 52)	TMX as prior therapy: 21
	EXE	45	NR	NR	100 (ANAS: 47 LTZ: 53	TMX as prior therapy: 24
Hi-FAIR fx	TOR	53	42.8	13.2	100	NR
	FUL	52	34.2	11.5	100	NR
Milla-Santos 2001	TOR	106	55.4	0	NR	NR
	TMX	111	61.3	0	NR	NR
MONARCH 2	ABE-FUL	446	59.9	0.7	70.9	(Neo)adjuvant ET: 59 ET for metastatic disease: 38.3
	FUL	223	60.1	1.8	66.8	(Neo)adjuvant ET: 59.6 ET for metastatic disease: 38.1
	FUL500	362	51.1	22	NR	NR

CONFIRM	FUL250	374	53.5	18	NR	NR
Zhang 2016	FUL500	111	88.3	22.5	47.7	Adjuvant ET: 45.0 ET for advanced disease: 25.2
	FUL250	110	85.5	18.2	42.7	Adjuvant ET: 38.2 ET for advanced disease: 20.9
SoFEA	FUL250	231	NR	NR	NR	NR
	EXE	249	NR	NR	NR	NR
Howell 2002	FUL250	222	NR	NR	NR	NR
	ANAS	229	NR	NR	NR	NR
Campos 2009	EXE	64	40.6	29.7	NR	NR
	ANAS	64	53.1	37.5	NR	NR

[a] Most recent treatment was anastrozole or letrozole. **Abbreviations**: ABE: abemaciclib; AI: aromatase inhibitor; ANAS: anastrozole; CAP: capecitabine; ET: endocrine therapy; FUL: fulvestrant; EXE: exemestane: EVE: everolimus; NR: not reported.

Table 9. Disease characteristics for the trials included in the revised NMA

Study	Intervention	N	ET resistance, %	Metastatic site, %			Measurable disease at baseline, %
				Bone	Visceral	Other	
BOLERO-2	EXE-EVE	485	NR	76	56	Liver: 30	70
	EXE	239	NR	77	56	Liver: 33	68
BOLERO-6	EXE-EVE	104	NR	13*	66	64	NR
	EVE	103	NR	16*	64	59	NR
	CAP	102	NR	24*	62	59	NR
Yamamoto 2013	TOR	46	NR	20	NR	Liver: 15.2	NR
	EXE	45	NR	31	NR	Liver: 13.3	NR
Hi-FAIR fx	TOR	53	NR	NR	66	NR	NR
	FUL	52	NR	NR	55.6	NR	NR
Milla-Santos 2001	TOR	106	NR	37.70	36.8	NR	NR
	TMX	111	NR	47	28	NR	NR

MONARCH 2	ABE-FUL	446	Primary: 24.9 Secondary: 73.1	27.6*	54.9	16.8	71.3
	FUL	223	Primary: 26 Secondary: 73.1	25.6*	57.4	17	73.5
CONFIRM	FUL500	362	NR	NR	52.9	NR	NR
	FUL250	374	NR	NR	56.6	NR	NR
Zhang 2016	FUL500	111	NR	NR	39	NR	51
	FUL250	110	NR	NR	47	NR	60
SoFEA	FUL	231	NR	16	62	NR	NR
	EXE	249	NR	13	58	NR	NR
Howell 2002	FUL	222	NR	17.1	NR	Liver: 21.6	59
	ANAS	229	NR	17.5	NR	Liver: 24.5	62
Campos 2009	EXE	64	NR	57.8	NR	Liver: 62.5	100
	ANAS	64	NR	65.6	NR	Liver: 54.7	100

* Bone-only disease

Abbreviations: ABE: abemaciclib; AI: aromatase inhibitor; ANAS: anastrozole; CAP: capecitabine; ET: endocrine therapy; FUL: fulvestrant; EXE: exemestane: EVE: everolimus; NR: not reported.

A5. Please confirm that the definition of TTP for trials included in the PFS NMA was TTP or death and that trials with a definition of TTP not including or mentioning death were excluded from the NMA of PFS.

A6. The PRISMA diagram outlining the systematic literature review (SLR) indicates that 29 independent studies were included in the review. In Appendix D.1.3, Table 20 and 21, showing reasons for exclusion, only 27 studies are listed. Please provide a reason for exclusion for all studies not used in the NMAs for any of the outcomes.

A7. On page 34 in the submission it is mentioned that, "If either abemaciclib or placebo was discontinued, patients were permitted to continue receiving fulvestrant. If fulvestrant required discontinuation, patients were permitted to continue receiving abemaciclib or placebo". As patients could continue with abemaciclib or fulvestrant and discontinue the other, please provide a summary of the extent of exposure to study treatments in MONARCH 2 in line with the table below:

A summary of the extent of exposure to the study treatments of abemaciclib, fulvestrant and placebo in the ABE-FUL and PBO-FUL treatment arms in MONARCH 2 is presented in Table 10.

The mean duration of treatment in the ABE-FUL arm (n=441) was [redacted] weeks for abemaciclib and [redacted] weeks for fulvestrant. The mean percent intended daily dose was [redacted]% for abemaciclib and [redacted]% for fulvestrant. In the ABE-FUL arm, 8.6% of patients discontinued abemaciclib due to adverse events whereas there were no discontinuations of fulvestrant due to adverse events.

Lilly interpret that there is no meaningful difference, in the mean duration and range(s) of treatment between abemaciclib and fulvestrant, to suggest that exposure to one drug was significantly greater than the other. Lilly also note that median duration of treatment (weeks) incorporates time off treatment due to dose omissions. In the ABE-FUL arm there were 58.0% dose interruptions or omissions of abemaciclib to successfully manage toxicities, versus [redacted]% in the PBO-FUL arm (Table 11). Following the first month, fulvestrant is given in a 28-day cycle which may also account for the difference in mean duration of treatment.

The mean duration of treatment in the PBO-FUL arm (n=223) was [redacted] weeks for placebo and [redacted] for fulvestrant. Standard deviation is similar in both arms and the mean is approximately one week greater in the fulvestrant arm. The mean percent daily dose is similar in the placebo ([redacted]%) and fulvestrant groups ([redacted]%).

Similarly to the ABE-FUL arm, Lilly interpret there is no meaningful difference in exposure between the placebo and fulvestrant groups.

Table 10. Exposure to study treatment in MONARCH 2

	Abemaciclib + Fulvestrant		Placebo + Fulvestrant	
	Abemaciclib (N = 441)	Fulvestrant (N = 441)	Placebo (N = 223)	Fulvestrant (N = 223)
Duration of treatment (weeks)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range Q1 – Q3 Min - Max	[redacted]	[redacted]	[redacted]	[redacted]
Daily dose per subject (mg/day)				
Mean (SD)	260.80 [redacted]	[redacted]	309.26 ([redacted]	[redacted]
Median	273.06	[redacted]	298.22	[redacted]
Range Q1 – Q3 Min - Max	[redacted]	[redacted]	[redacted]	[redacted]
Percent intended dose (%)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range Q1 – Q3 Min - Max	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SD: standard deviation.

A8. As stated in the method of administration and dosage, dose adjustment and/or dose interruption are recommended for the management of some adverse reactions of abemaciclib. Please provide a summary of the dose reductions and omissions of the study treatments in MONARCH 2 in line with the table below:

A summary of the dose reductions and omission of study treatment in the ABE-FUL and PBO-FUL treatment arms of the MONARCH 2 trial is presented in Table 11. In the ABE-FUL arm, 189 patients (42.9%) had abemaciclib dose reductions due to AEs. AEs leading to abemaciclib dose reductions that were experienced by ≥5% of patients included diarrhoea (83 patients [18.8%]) and neutropenia (44 patients [10.0%]). In the ABE-FUL arm, 256 patients (58.0%) had at least one abemaciclib dose omission. For patients with a dose omission due to AE, the median percentage of abemaciclib doses omitted due to AEs was low ([redacted]%), which still corresponded to a high dose intensity.

Table 11. Dose reductions and omission of study treatment in MONARCH 2

	Abemaciclib + Fulvestrant		Placebo + Fulvestrant	
Number of subjects with, n (%)	**Abemaciclib N=441**	**Fulvestrant N=441**	**Placebo N=223**	**Fulvestrant N=223**
Dose reduction	218 (49.4)	[redacted]	[redacted]	[redacted]
Dose interruption/omission	256 (58.0)	[redacted]	[redacted]	[redacted]
Drug discontinuation due to AEs*	[redacted]	-	[redacted]	-

Footnote: *Patients who died on study treatment with primary cause as AE or SAE are also included as discontinuation.
Abbreviation: AE: adverse event; SAE: serious adverse event.

A9. Please clarify how many people from England were enrolled into MONARCH 2, and how many were randomised to each treatment group

A10. Please clarify the inclusion criteria reported in Table 4 of the submission:

a. "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 AI as first-line ET for metastatic disease (patients may not have received more than 1 line of ET or any prior chemotherapy for metastatic disease)" and

b. "Presented de novo with metastatic disease and then relapsed with radiologic evidence of progression after treatment with an anti-oestrogen or an aromatase inhibitor as first-line ET for metastatic disease (patients may not have received >1 line of ET or any prior chemotherapy for metastatic disease)"

Do these includes both patients who progressed while receiving first line ET treatment for ABC as well as patients who progressed after receiving first line ET treatment for ABC?

A11. Please provide PFS (investigator and BICR) and OS results (including participants numbers and 95% CI) for the subgroup analyses based on line of therapy (first and second line) in the advanced setting).

A12. Please clarify the difference between the sample size reported on page 41 (630 patients) and the number of randomised patients (669), as reported for the ITT population on page 48.

Section B: Clarification on cost-effectiveness data

B1. **Priority question**: Please provide a detailed justification for why it was necessary to adjust PFS data for interval censoring and describe the method used to adjust the data. Please discuss the potential biases associated with the approach chosen (NICE TSD 14, Panageas *et al*. 2007).

The MONARCH 2 trial collected tumour assessment/PFS data at specific intervals − approximately every 8 weeks for the first 12 months and every 12 weeks thereafter.[1] This frequency of radiographic assessments of disease status may not accurately reflect the underlying TTP for patients, as progression events would have only been observed at pre-specified timepoints, yet may have occurred at any time between the two assessment intervals.[20, 21] This introduced the need to adjust for interval censoring to avoid any bias from the direct modelling of KM data, which could have resulted in an overestimation of median PFS.[21]

The method used for interval censoring was based on Griffin 2005 and the INTCENS Stata package.[22] The interval censored adjusted analysis was used in the base case, and non-interval censored adjusted analysis explored in a scenario analysis.

The key advantage of the Griffin 2005 methodology is the simplicity of the approach and consistency with the survival curve fitting. Nevertheless, biases are associated with any interval censoring approach, due to the limited amount of prior information available.

B2. **Priority question**: Please clarify if the INV PFS KM data provided in the "KM" tab of the economic model are the adjusted or unadjusted KM data. Please provide the missing dataset (i.e. either the adjusted or the unadjusted) INV PFS KM data for ABE-FUL and FUL, separately (in the same format as the KM reported in the "KM" tab of the economic model).

The KM data on the "KM" tab of the model is adjusted data. The unadjusted data is presented in Figure 7 and has been added to the updated version of the model.

Figure 7. Unadjusted INV PFS KM data

Abbreviations: ABE-FUL: abemaciclib plus fulvestrant; FUL: fulvestrant; INV: investigator; KM: Kaplan-Meier; PFS: progression-free survival.

B3. **Priority question**: For both the adjusted and unadjusted INV PFS KM for the ABE-FUL and FUL arms of MONARCH please provide the log(inverse standard normal distribution function(1-survival function)) plots versus Log(time) and assess the assumption of accelerated failure time effects.

The log(inverse standard normal distribution function(1-survival function)) plots versus Log(time) have been added to the model, and are presented in Figure 8 (adjusted INV PFS) and Figure 9 (unadjusted INV PFS).

Figure 8. Inverse standard normal distribution function(1-survival function) plots versus Log(time) – adjusted INV PFS

Abbreviations: ABE-FUL: abemaciclib plus fulvestrant; INV: investigator; KM: Kaplan-Meier; PBO-FUL: placebo plus fulvestrant; PFS: progression-free survival.

Figure 9. Inverse standard normal distribution function(1-survival function) plots versus Log(time) – unadjusted INV PFS

Abbreviations: ABE-FUL: abemaciclib plus fulvestrant; INV: investigator; KM: Kaplan-Meier; PBO-FUL: placebo plus fulvestrant; PFS: progression-free survival.

B4. **Priority question**: Based on your assessment of fit of different parametric models to the unadjusted INV PFS KM data for the FUL and ABE-FUL arms of MONARCH, reported in Section

M.2.1. of the Appendix, the lognormal, loglogistic and Gamma distributions seem to provide the best statistical fit to the KM data. Therefore, could you please:

a. Justify why the exponential and Gompertz distributions (the worst fitting distributions to the data) were chosen as the two possible options to model the unadjusted INV PFS FUL curve in the model;

This was an error with regards to which curves were programmed into the model. The lognormal appears to be the best fit based on the goodness of fit statistics provided in the CS Appendices. However, please note, this selection is overridden when using the updated fractional polynomial NMA (see response B4b).

b. Consider using the best-fitting curves (also taking into account the clinical plausability of the curve's tails) to model the unadjusted INV PFS FUL curve in the model, and if not, please justify why;

The model can now use any of the parametric curves for unadjusted PFS FUL on the page 'B4.' of the model. To use this switch, the model needs to be set to use the unadjusted data on the 'Dashboard' page. Please note that if selected (see B4c response), the fractional polynomial NMA approach provides a survival curve as an output.

c. Please apply the outputs obtained from the NMA (with the method deemed appropriate in question A2) to derive the survival curves for the different comparator treatments, and if not, please justify why;

This option has been included in the model and can be selected on the model page 'A3'. As discussed in response A3, the Milla-Santos trial was not included in the PFS network and therefore TMX cannot be used in the model with the updated NMA.

The updated NMA produced survival curves that had a long flat tail. Therefore, in the model it is recommended that PFS is set to being less than or equal to OS (set on J32 on the Dashboard page). Additionally, there is now a disconnect between PFS and ToT, with one being from the data and one being from NMA. Therefore an option has been included to allow ToT to be equal to PFS for ABE-FUL and FUL; this option is on page 'A3.'.The updated base case results incorporating the revised NMA results are shown in Table 12.

Table 12. Updated base case (revised NMA, revised PAS for abemaciclib)

Comparator	Costs	LYs	QALYs	ICER (per QALY)	ICER (per QALY) for ABE-FUL vs comparator
CAP	[redacted]	2.55	[redacted]	Referent	£59,441
EXE	[redacted]	2.55	[redacted]	Dominated	£41,452
EXE-EVE	[redacted]	2.34	[redacted]	Dominated	£23,374
FUL	[redacted]	4.38	[redacted]	Ext. dominated	£47,763
ABE-FUL	[redacted]	4.57	[redacted]	£59,441	N/A

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; ICER: incremental cost-effectiveness ratio; LY: life year; PFS: progression-free survival; QALY: quality-adjusted life year; TMX: tamoxifen; TTD: time to discontinuation.

If we test a scenario where ToT is calculated from MONARCH-2 the total cost for ABE-FUL is significantly lower as the drug cost is not based on the flat PFS curve (Table 13).

Table 13. Updated base case with ToT from MONARCH (revised NMA, revised PAS for abemaciclib)

Comparator	Costs	LYs	QALYs	ICER (per QALY)	ICER (per QALY) for ABE-FUL vs comparator
CAP	[redacted]	2.55	[redacted]	Referent	£31,921
EXE	[redacted]	2.55	[redacted]	Dominated	£17,172
EXE-EVE	[redacted]	2.34	[redacted]	Dominated	£8,133
ABE-FUL	[redacted]	4.57	[redacted]	£31,921	N/A
FUL	[redacted]	4.38	[redacted]	Dominated	Dominant

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; ICER: incremental cost-effectiveness ratio; LY: life year; PFS: progression-free survival; QALY: quality-adjusted life year; TMX: tamoxifen; TTD: time to discontinuation.

d. If alternatively, you decide it is appropriate to apply the original NMA HRs to the fitted INV PFS arm of FUL in the model, to obtain PFS curves for ABE-FUL, TMX, EVE-EXE and EXE and chemotherapy (requested in question A3), please justify your choice and include the Weibull distribution as an option to model the baseline FUL PFS curve in the model. Please used the unadjusted data to run this analysis.

The Weibull curve is available in the model – please see the B4b response. The default parametric curve is the lognormal curve based on the goodness of fit statistics presented in the CS Appendices.

As discussed above, the updated NMA has been programmed into the model using the fractional polynomial approach.

B5. Priority question: Please provide a plot in Excel (with the corresponding underlying data) of the unadjusted INV PFS KM data along with superimposed fitted curves for both arms of the MONARCH trial for all of the parametric models discussed above (Weibull, lognormal, Gamma, log-logistic, exponential and Gompertz). Please discuss the clinical plausibility of the tails.

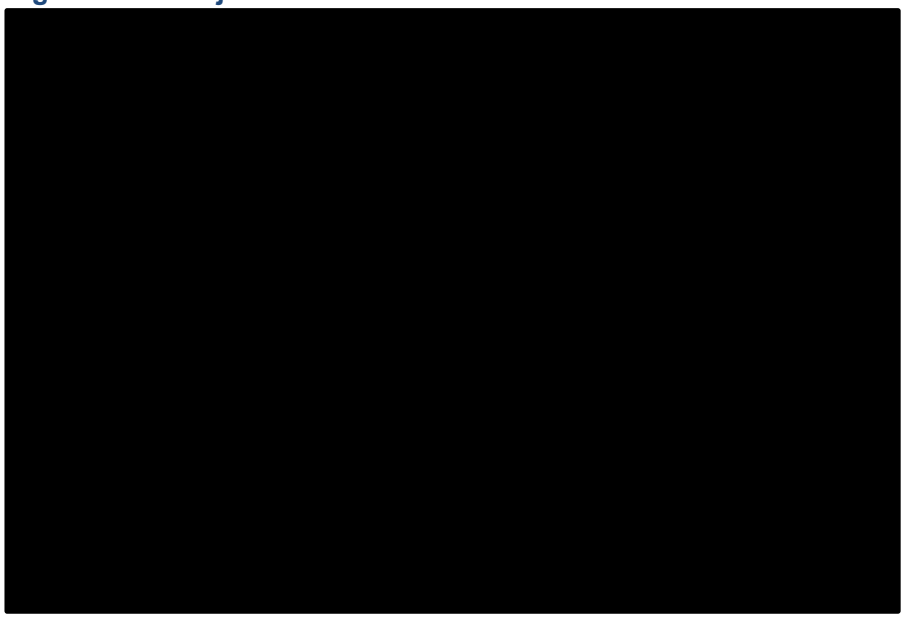
These plots have been added to the updated model, and are presented in Figure 10 (ABE-FUL) and Figure 11 (FUL).

In Figure 10 for ABE-FUL, the Log-Normal, Log-Logistic and Gamma curves present approximately [redacted]% of patients surviving to five years (60 months) and approximately [redacted]% of patients surviving to 20 years (i.e. 240 months). These percentages are relatively high, and Lilly medical opinion considers these to be clinically implausible. However, the exponential, Weibull and Gompertz curves appear to present more clinically plausible survival rates.

In Figure 5 for FUL, PFS from the MONARCH 2 trial (FUL KM) appears to provide slightly higher rates of PFS compared to the CONFIRM trial. However, it should be noted that the CONFIRM

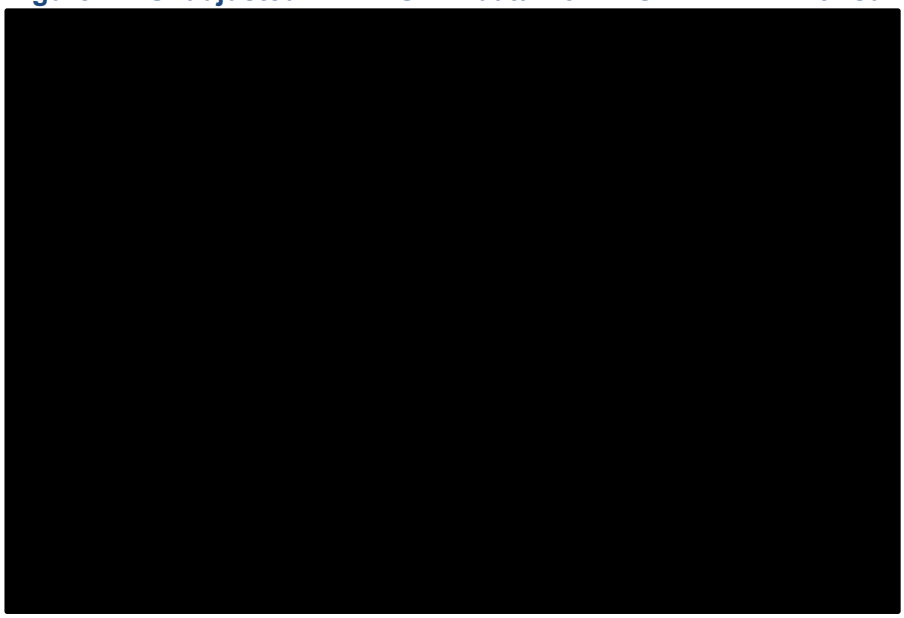
trial included both 500 mg and 250 mg doses of FUL, and showed that the 500 mg dose was superior in terms of PFS and OS, whereas the MONARCH 2 trial only included 500 mg doses of FUL. Similarly to ABE-FUL, the Log-Logistic, Log-Normal, and Gamma curves may be clinically implausible, with [redacted]% of patients surviving to 100 months (>8 years), however the exponential, Weibull and Gompertz present more clinically plausible survival rates.

Figure 10. Unadjusted INV PFS KM data from MONARCH 2 with survival curves – ABE-FUL



Abbreviations: ABE-FUL: abemaciclib plus fulvestrant; INV: investigator; KM: Kaplan-Meier; PFS: progression-free survival.

Figure 11. Unadjusted INV PFS KM data from MONARCH 2 with survival curves - FUL



Abbreviations: FUL: fulvestrant; INV: investigator; KM: Kaplan-Meier; PFS: progression-free survival.

B6. Priority question: Similar to the option given for the Weibull model, please provide an option in the economic analysis to estimate OS with a Gompertz distribution fitted to MONARCH data

only (i.e. not using CONFIRM data), to the FUL arm of the trial. In order to estimate the ABE-FUL OS curve please:

a. Depending on your assessment resulting from A2, either apply the NMA OS HR to the FUL curve to estimate the ABE-FUL OS curve (without using CONFIRM data); or use the best fitting curve derived from the NMA for ABE-FUL (taking into consideration the clinical plausibility of long-term extrapolations);

For FUL this option has been included in the existing drop-down menu on the Dashboard page, on cell J35.

When using the fractional polynomial NMA is used, the survival curves for ABE-FUL are based on the NMA output.

b. Similarly, please derive the OS curves for comparator treatments with either the NMA OS HR to the FUL curve; or use the best fitting curve derived from the NMA for each treatment;

Using the original NMA, the chart presented in Figure 12 has been produced.

When using the fractional polynomial NMA, the survival curve for FUL is taken from the NMA, which incorporates the CONFIRM trial. The option to choose between CONFIRM and MONARCH 2 data does not work when the fractional polynomial is used.

Figure 12. Overall survival for comparator treatments

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; TMX: tamoxifen.

B7. Priority question: Please provide an option in the economic analysis to estimate the baseline OS and PFS FUL curves with the OS and PFS data from the 500mg FUL arm of CONFIRM (ITT population). Please undertake the same steps described in A2, B3 and B4c and B4d to fit

survival curves to the OS and PFS KM data from CONFIRM and justify your choice of model. Please include the three best-fitting curves as an option to model OS and PFS for the FUL arm of the model.

The six curves fitted to the PFS and OS data from CONFIRM have been added to the model. The sheet 'B7.' can be used to switch between the different curve options.

The log(inverse standard normal distribution function(1-survival function)) plots versus Log(time) for PFS and OS from CONFIRM are presented in Figure 13 and Figure 14, respectively, whilst the model fit statistics for PFS and OS from CONFIRM are presented in Table 14 and Table 15, respectively.

For both PFS and OS, the three best-fitting curves were the Log-normal, Log-logistic and Gamma. For PFS, Gamma was the best fit, however, it had the highest tail. Log normal is set as the default for PFS, however this is amendable in the model. For OS, Log-normal and log logistic were very close, with OS estimates within 1% at all-time points. Log-logistic is set as the default due to marginally better goodness of fit tests.

Figure 13. Inverse standard normal distribution function(1-survival function) plots versus Log(time) – CONFIRM PFS FUL

Abbreviations: FUL: fulvestrant; PFS: progression-free survival.

Table 14. AIC and BIC − CONFIRM PFS FUL

	AIC	BIC
Weibull	1086.14	1093.92
Log-Normal	1029.72	1037.501
Log-Logistic	1045.31	1053.089
Gompertz	1076.67	1084.45
Exponential	1084.17	1088.057
Gamma	1017.22	1028.899

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; FUL: fulvestrant; PFS: progression-free survival.

Figure 14. Inverse standard normal distribution function(1-survival function) plots versus Log(time) – CONFIRM OS FUL

Abbreviations: FUL: fulvestrant; OS: overall survival.

Table 15. AIC and BIC − CONFIRM OS FUL

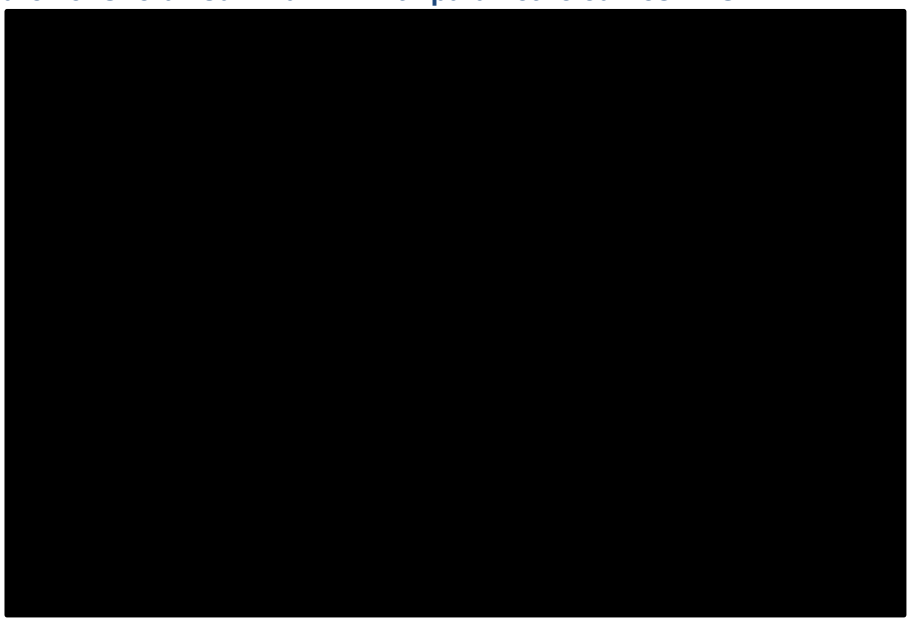
	AIC	BIC
Weibull	964.2378	972.021
Log-Normal	955.19	962.9684
Log-Logistic	955.1649	962.9482
Gompertz	969.0268	976.81
Exponential	967.192	971.0837
Gamma	955.5838	967.2588

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; FUL: fulvestrant; OS: overall survival.

B8. Priority question: Please provide a plot in Excel (with the corresponding data) of the OS and PFS KM data along with superimposed fitted curves for the 500mg FUL arm of the ITT CONFIRM trial for all of the parametric models considered above (Weibull, lognormal, Gamma, log-logistic, exponential and Gompertz).

The chart has been added to the model and is presented below in Figure 15 for OS and Figure 16 for PFS.

Figure 15. Overall survival KM with parametric curves - CONFIRM



Abbreviations: FUL: fulvestrant; KM: Kaplan-Meier; OS: overall survival.

Figure 16. PFS KM data from CONFIRM with survival curves − FUL

Abbreviations: FUL: fulvestrant; KM: Kaplan-Meier; PFS: progression-free survival.

B9. Priority question: Please provide the plots used to assess the PH assumption for time to treatment discontinuation (TTD) in MONARCH, referred to in page 114 of the CS.

The Log-log plot and cumulative hazard plot for time to treatment discontinuation are presented in the model and in Figure 17 and Figure 18 below, respectively.

Figure 17. Log-log plot for time on treatment

Abbreviations: ABE-FUL: abemaciclib plus fulvestrant; PBO-FUL: placebo plus fulvestrant; ToT: time on treatment.

Figure 18. Cumulative hazard plot for time on treatment

Abbreviations: ABE-FUL: abemaciclib plus fulvestrant; PBO-FUL: placebo plus fulvestrant; ToT: time on treatment.

B10. **Priority question:** The CS states that, "*If either abemaciclib or placebo was discontinued, patients were permitted to continue receiving fulvestrant. If fulvestrant required discontinuation, patients were permitted to continue receiving abemaciclib or placebo*". Therefore, could you please provide the following KM data in Excel, with the respective number of patients at risk:

a. The TTD KM curves for the ABE-FUL arm of MONARCH for patients receiving ABE-FUL for the entire duration of the trial (i.e. excluding patients who discontinued one of the two drugs during the trial);

b. The TTD KM curves for the ABE-FUL arm of MONARCH for patients discontinuing ABE, from beginning of treatment with ABE-FUL until the event of interest or death (and indicating when treatment with ABE was discontinued);

c. The TTD KM curves for the ABE-FUL arm of MONARCH for patients discontinuing FUL, from beginning of treatment with ABE-FUL until the event of interest or death (and indicating when treatment with FUL was discontinued);

d. The OS and PFS KM curves for the same patient groups described in question b and c above.

The numbers of patients discontinuing ABE, PBO, or FUL in either treatment arm are shown in Table 16.

- For B10 part a, [redacted] patients received ABE-FUL for the entire duration of the trial, however provision of the TTD KM curve would break randomisation. OS and PFS KM curves would similarly require extrapolation of these non-randomised data for part d.
- For B10 part b, only [redacted] patients discontinued ABE prior to discontinuation of FUL. KM curves have not been provided due to this low number of patients.
- For B10 part c, [redacted] patients discontinued ABE/PBO following discontinuation of FUL, meaning KM curves cannot be provided.

As discussed in the response to A7, the mean and median durations of treatment, and dose intensity, are similar for both PBO and FUL in the PBO-FUL arm (Table 10). The slightly shorter mean duration of treatment for ABE ([redacted] weeks) compared to FUL ([redacted] weeks) in the ABE-FUL arm is explained by the small number of patients ([redacted]) discontinuing ABE prior to FUL.

Table 16. Treatment discontinuations in MONARCH 2

	ABE-FUL, N=446 n (%)	PBO-FUL, N=223 n (%)
Discontinued study treatment	271 (60.8)	178 (79.8)
Discontinued ABE/PBO and FUL at the same time	[redacted] ([redacted])	[redacted] ([redacted])
Discontinued ABE/PBO prior to FUL	[redacted] ([redacted])	[redacted] ([redacted])

Abbreviations: ABE: abemaciclib; FUL: fulvestrant; PBO: placebo.

B11. Priority question: Please run a scenario analysis that includes an option in the economic model (as a drop-down menu in Excel) assuming TTD curves to be the same as PFS curves for each of the following comparator treatments: EXE; EVE-EXE; TMX; and chemotherapy.

This scenario has been implemented into the model. The scenario results are presented in Table 17 (original NMA, revised PAS for abemaciclib), Table 18 (revised NMA, revised PAS for abemaciclib) and Table 19 (original NMA, original PAS for abemaciclib).

Table 17. Scenario analysis assuming TTD is equivalent to PFS (original NMA, revised PAS for abemaciclib)

Comparator	Costs	LYs	QALYs	ICER (per QALY)	ICER (per QALY) for ABE-FUL vs comparator
TMX	[redacted]	3.72	[redacted]	Referent	£62,548
FUL	[redacted]	3.50	[redacted]	Dominated	£41,702
EXE	[redacted]	3.33	[redacted]	Dominated	£18,754
ABE-FUL	[redacted]	3.64	[redacted]	£62,548	N/A
EXE-EVE	[redacted]	3.45	[redacted]	Dominated	Dominant

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; ICER: incremental cost-effectiveness ratio; LY: life year; PFS: progression-free survival; QALY: quality-adjusted life year; TMX: tamoxifen; TTD: time to discontinuation.

Table 18. Scenario analysis assuming TTD is equivalent to PFS (revised NMA, revised PAS for abemaciclib)

Comparator	Costs	LYs	QALYs	ICER (per QALY)	ICER (per QALY) for ABE-FUL vs comparator
CAP	[redacted]	2.55	[redacted]	Referent	£59,441
EXE	[redacted]	2.55	[redacted]	Dominated	£41,452
EXE-EVE	[redacted]	2.34	[redacted]	Dominated	£23,374
FUL	[redacted]	4.38	[redacted]	Ext. dominated	£47,763
ABE-FUL	[redacted]	4.57	[redacted]	£59,441	N/A

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; ICER: incremental cost-effectiveness ratio; LY: life year; PFS: progression-free survival; QALY: quality-adjusted life year; TMX: tamoxifen; TTD: time to discontinuation.

Table 19. Scenario analysis assuming TTD is equivalent to PFS (original NMA, original PAS for abemaciclib)

Comparator	Costs	LYs	QALYs	ICER (per QALY)	ICER (per QALY) for ABE-FUL vs comparator
TMX	[redacted]	3.72	[redacted]	Referent	£108,789
FUL	[redacted]	3.50	[redacted]	Dominated	£74,103
EXE	[redacted]	3.33	[redacted]	Dominated	£39,615
ABE-FUL	[redacted]	3.64	[redacted]	£108,789	N/A
EXE-EVE	[redacted]	3.45	[redacted]	Dominated	Dominant

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; ICER: incremental cost-effectiveness ratio; LY: life year; PFS: progression-free survival; QALY: quality-adjusted life year; TMX: tamoxifen; TTD: time to discontinuation.

B12. **Priority question:** Please run a scenario analysis that includes an option in the economic model (as a drop-down menu in Excel) to independently or jointly (depending on your assessment of PHs, POs or AFT) fit the best-fitting distributions to the TTD KM MONARCH data for both ABE-FUL and FUL (Gamma, Gompertz and lognormal according to Table 74 in Appendix M3) to estimate TTD for FUL and ABE-FUL. Use the minimum function in Excel to prevent the TTD and the PFS fitted curves from crossing in the model, for each treatment arm (as currently done in the company's base case).

This has been programmed into the model. The minimum function is already included to prevent TTD exceeding the PFS curve.

B13. **Priority question:** Please include an option in the economic model (as a drop-down menu in Excel) allowing the analyses requested in B11 and B12 to be run together as a single scenario.

This will not be implemented by Lilly due to time limitations. This can be conducted by switching the two options on the model pages "B11." and "B12." to the required settings.

B14. **Priority question:** Please explain why the pairwise results of the economic analysis (i.e. ICERs for ABE-FUL vs FUL; ABE-FUL vs TMX; ABE-FUL vs EXE-EVE; ABE-FUL vs EXE) increase,

considerably for some comparators, when the 150mg baseline population is chosen to run the model, instead of the base case ITT population.

Pairwise cost-effectiveness results for ABE-FUL for the intent-to-treat (ITT) (base case) and 150 mg subpopulation from the original model and previous PAS for abemaciclib are presented in Table 20 and Table 21, respectively. The numerical differences between the two sets of results are presented in Table 22.

The difference between the pairwise ICER values between the populations is driven by different clinical outcomes between the two populations for ABE-FUL, with a slightly improved mean PFS for ABE-FUL in ITT population versus the 150 mg subgroup ([redacted] vs [redacted] months, respectively), but slightly reduced mean ToT ([redacted] vs [redacted] months, respectively). As a result, patients in the 150 mg subgroup accumulate slightly more drug acquisitions costs for ABE-FUL, and also spend a greater amount of time in the post-progression health state, thus accumulating a greater quantity of post-progression costs, specifically PPS follow-up care and third-line treatment costs, as illustrated in Table 23. An increase in hospitalisation costs is also observed in the 150 mg subgroup compared to the ITT population; this is due to differences in length of stay and frequency of hospitalisation between the groups. The number of hospitalisations in the 150 mg subgroup was extremely small, therefore there is uncertainty around these parameters in the subgroup. The 150 mg subgroup hospitalisation data should therefore not be used due to small sample size. In addition to the above, it should be considered that less PFS follow-up care costs are accumulated in the ITT population compared to the 150 mg subpopulation.

Following initiation of the study, the protocol was amended reducing the ABE start dose from 200 mg to 150 mg. In the trial, of those randomised to receive ABE, 121 patients were given the 200mg starting dose (pre-amendment population) and 325 patients were given the 150mg starting dose (post-amendment population). The initial protocol planned to enrol 450 patients in the ITT population. However, after the dose reduction from 200 mg to 150 mg the sample size was increased to 630 patients to ensure that at least 450 patients were enrolled at the 150 mg start dose. The pre- and post-amendment populations were comparable with respect to age, menopausal status and prior sensitivity to endocrine therapy. Small differences in nature of disease and race were observed.[12]

Patients in the ABE-FUL arm received a median of 34 days of treatment at the 200 mg start dose prior to dose reduction or discontinuation. Due to the early implementation of the starting dose change and the required reduction of all ongoing patients to 150 mg, the median dose intensity for patients randomised to the ABE arm pre- and post-amendment was observed to be similar ([redacted] mg/day versus [redacted] mg/day for the 200 mg and 150 mg starting dose populations, respectively). Furthermore, efficacy was consistent with respect to investigator-assessed PFS and overall response rate. The stratified hazard ratio for PFS was [redacted] in the pre-amendment population (ABE-FUL n=121, PBO-FUL, n=57) and 0.588 in the post-amendment population (ABE-FUL n=325, PBO-FUL, n=166) − an interaction test revealed no significant difference between the HR values ([redacted]). Furthermore, in the subgroup analysis of patients (n = 491) who only received the 150 mg dose, the HR was [redacted] (95% CI [redacted], [redacted]). These data indicate that the reduction in starting dose does not affect the outcome of the primary endpoint and confirm the efficacy of the 150 mg dose.[12]

Overall, the ITT population is considered the most appropriate population to utilise in the base case, due to the increased sample size and thus greater statistical power to detect differences in clinical outcomes between arms.

Table 20. ABE-FUL pairwise cost-effectiveness results (ITT population) (base case; original NMA, original PAS for abemaciclib)

Comparator	Costs	Lys	QALYs	Incremental Costs	Incremental QALYs	ICER (ABE-FUL vs Comparator)
TMX	[redacted]	3.72	[redacted]	[redacted]	[redacted]	[redacted]
FUL	[redacted]	3.50	[redacted]	[redacted]	[redacted]	[redacted]
EXE	[redacted]	3.33	[redacted]	[redacted]	[redacted]	[redacted]
ABE-FUL	[redacted]	3.64	[redacted]	[redacted]	[redacted]	[redacted]
EXE-EVE	[redacted]	3.45	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABE-FUL: abemaciclib plus fulvestrant; EXE-EVE: exemestane plus everolimus; FUL: fulvestrant; ICER: incremental cost-effectiveness ratio; ITT: intention-to-treat; LY: life year; PFS: progression-free survival; QALY: quality-adjusted life year; TMX: tamoxifen; TTD: time to discontinuation.

Table 21. ABE-FUL pairwise cost-effectiveness results (150 mg Subpopulation; original NMA; original PAS for abemaciclib)

Comparator	Costs	Lys	QALYs	Incremental Costs	Incremental QALYs	ICER (ABE-FUL vs Comparator)
TMX	[redacted]	3.72	[redacted]	[redacted]	[redacted]	[redacted]
FUL	[redacted]	3.49	[redacted]	[redacted]	[redacted]	[redacted]
EXE	[redacted]	3.32	[redacted]	[redacted]	[redacted]	[redacted]
ABE-FUL	[redacted]	3.64	[redacted]	[redacted]	[redacted]	[redacted]
EXE-EVE	[redacted]	3.44	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABE-FUL: abemaciclib plus fulvestrant; EXE-EVE: exemestane plus everolimus; FUL: fulvestrant; ICER: incremental cost-effectiveness ratio; LY: life year; PFS: progression-free survival; QALY: quality-adjusted life year; TMX: tamoxifen; TTD: time to discontinuation.

Table 22. Difference between ABE-FUL pairwise cost-effectiveness results (ITT vs 150 mg subpopulation; original NMA, original PAS for abemaciclib)

Comparator	Costs	Lys	QALYs	Incremental Costs	Incremental QALYs	ICER (ABE-FUL vs Comparator)
TMX	[redacted]	0.00	[redacted]	[redacted]	[redacted]	[redacted]
FUL	[redacted]	0.01	[redacted]	[redacted]	[redacted]	[redacted]
EXE	[redacted]	0.01	[redacted]	[redacted]	[redacted]	[redacted]
ABE-FUL	[redacted]	0.00	[redacted]	[redacted]	[redacted]	[redacted]
EXE-EVE	[redacted]	0.01	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABE-FUL: abemaciclib plus fulvestrant; EXE-EVE: exemestane plus everolimus; FUL: fulvestrant; ICER: incremental cost-effectiveness ratio; ITT: intention-to-treat; LY: life year; PFS: progression-free survival; QALY: quality-adjusted life year; TMX: tamoxifen; TTD: time to discontinuation.

Table 23. Differences in costs accumulated between the ITT and 150 mg subpopulation (original NMA, original PAS for abemaciclib)

Comparator	Acquisition	Admin	Pre-medication	Follow-up care (PFS)	Follow-up care (PPS)	BSC	AEs	Hosp	Third-line	Terminal care	Total costs
ABE-FUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EXE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EXE-EVE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TMX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnote: Costs are calculated as 150 mg subgroup cost – ITT population costs

Abbreviations: ABE-FUL: abemaciclib plus fulvestrant; AEs: adverse events; BSC: best supportive care; EXE: exemestane; EXE-EVE: exemestane-everolimus; FUL: fulvestrant; ITT: intention-to-treat; PFS: progression-free survival; PPS: post-progression survival; TMX: tamoxifen.

Please note, the fractional polynomial NMA has not been conducted for the 150 mg subgroup, therefore the survival curves for OS and PFS are equal between the ITT population and 150 mg subgroup. Therefore, in the revised model, any differences between the two groups are driven by differences in hospitalisation rates and length of stay.

For the ERG's information, the cost-effectiveness results for ABE-FUL from the new model with the revised PAS for abemaciclib are presented in Table 24 to Table 27.s

Table 24. ABE-FUL pairwise cost-effectiveness results (ITT population) (base case; revised NMA, revised PAS for abemaciclib)

Comparator	Costs	Lys	QALYs	Incremental Costs	Incremental QALYs	ICER (ABE-FUL vs Comparator)
CAP	[redacted]	2.55	[redacted]	[redacted]	[redacted]	£59,441
EXE	[redacted]	2.55	[redacted]	[redacted]	[redacted]	£41,452
EXE-EVE	[redacted]	2.34	[redacted]	[redacted]	[redacted]	£23,374
FUL	[redacted]	4.38	[redacted]	[redacted]	[redacted]	£47,763
ABE-FUL	[redacted]	4.57	[redacted]	[redacted]	[redacted]	N/A

Abbreviations: ABE-FUL: abemaciclib plus fulvestrant; EXE-EVE: exemestane plus everolimus; FUL: fulvestrant; ICER: incremental cost-effectiveness ratio; ITT: intention-to-treat; LY: life year; PFS: progression-free survival; QALY: quality-adjusted life year; TMX: tamoxifen; TTD: time to discontinuation.

Table 25. ABE-FUL pairwise cost-effectiveness results (150 mg Subpopulation; revised NMA, revised PAS for abemaciclib)

Comparator	Costs	Lys	QALYs	Incremental Costs	Incremental QALYs	ICER (ABE-FUL vs Comparator)
CAP	[redacted]	2.55	[redacted]	[redacted]	[redacted]	£59,456
EXE	[redacted]	2.55	[redacted]	[redacted]	[redacted]	£41,330
EXE-EVE	[redacted]	2.34	[redacted]	[redacted]	[redacted]	£23,363
FUL	[redacted]	4.38	[redacted]	[redacted]	[redacted]	£46,990
ABE-FUL	[redacted]	4.57	[redacted]	[redacted]	[redacted]	N/A

Abbreviations: ABE-FUL: abemaciclib plus fulvestrant; EXE-EVE: exemestane plus everolimus; FUL: fulvestrant; ICER: incremental cost-effectiveness ratio; LY: life year; PFS: progression-free survival; QALY: quality-adjusted life year; TMX: tamoxifen; TTD: time to discontinuation.

Table 26. Difference between ABE-FUL pairwise cost-effectiveness results (ITT vs 150 mg subpopulation; revised NMA, revised PAS for abemaciclib)

Comparator	Costs	Lys	QALYs	Incremental Costs	Incremental QALYs	ICER (ABE-FUL vs Comparator)
CAP	[redacted]	0.00	[redacted]	[redacted]	[redacted]	-£15
EXE	[redacted]	0.00	[redacted]	[redacted]	[redacted]	£122
EXE-EVE	[redacted]	0.00	[redacted]	[redacted]	[redacted]	£11
FUL	[redacted]	0.00	[redacted]	[redacted]	[redacted]	£773
ABE-FUL	[redacted]	0.00	[redacted]	[redacted]	[redacted]	-£15

Abbreviations: ABE-FUL: abemaciclib plus fulvestrant; EXE-EVE: exemestane plus everolimus; FUL: fulvestrant; ICER: incremental cost-effectiveness ratio; ITT: intention-to-treat; LY: life year; PFS: progression-free survival; QALY: quality-adjusted life year; TMX: tamoxifen; TTD: time to discontinuation.

Table 27. Differences in costs accumulated between the ITT and 150 mg subpopulation (revised NMA, revised PAS for abemaciclib)

Comparator	Acquisition	Admin	Pre-medication	Follow-up care (PFS)	Follow-up care (PPS)	BSC	AEs	Hosp	Third-line	Terminal care	Total costs
ABE-FUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CAP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EXE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EXE-EVE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnote: Costs are calculated as 150 mg subgroup cost – ITT population costs

Abbreviations: ABE-FUL: abemaciclib plus fulvestrant; AEs: adverse events; BSC: best supportive care; EXE: exemestane; EXE-EVE: exemestane-everolimus; FUL: fulvestrant; ITT: intention-to-treat; PFS: progression-free survival; PPS: post-progression survival; TMX: tamoxifen.

B15. **Priority question:** Please provide pairwise ICERs in the Excel model tab "Dashboard" for all the ABE-FUL relevant comparisons (ABE-FUL vs FUL; ABE-FUL vs TMX; ABE-FUL vs EXE-EVE; ABE-FUL vs EXE; and ABE-FUL vs chemotherapy).

This has been added to the model.

B16. **Priority question:** For HRs obtained from the NMA, please use the CODA output from WinBUGs to inform each PSA simulation. Please ensure that HRs are sampled from the same Bayesian Markov chain Monte Carlo iteration. When the CODA output is stored as separate columns for each treatment with iteration values along the rows, this corresponds to sampling all the output in one row, for each PSA simulation.

Based on the fractional polynomial approach being undertaken, it was not possible to incorporate the CODA output into the model. The CODA output would have required the model to store 6 million cells of data (10,000 PSA iterations with 1000 rows of data for the survival function and 6 treatments. The text file which stores this data is 700 megabytes.

B17. The model includes an option to fit the adjusted INV PFS KM data with a Weibull and a gamma function. Given that the Gamma function is not a PHs model, please justify your decision to include it is an option to model PFS outcomes.

B18. Please provide in Excel format, the underlying data for all the fitted curves and KM (with numbers at risk) data for:

a. Figure 16 (CS, page 105);
b. Figure 17 (CS, page 106);
c. Figure 18 (CS, page 107);
d. Figure 21 (CS, page 110);
e. Figure 22 (CS, page 110);
f. Figure 26 (CS, page 115);
g. Figure 27 (CS, page 115);
h. Figure 29 (for the ABE-FUL 150mg and the 200mg curves, CS page 119);
i. Figure 33 (for the ABE-FUL 150mg and the 200mg curves, CS page 121);
j. Figure 37 (for the ABE-FUL 150mg and the 200mg curves, CS page 124);
k. Figure 34 (Appendix M.2.4 to the CS, page 237).

B19. Please confirm if the life-years reported in the Excel model tab "Results" and "Dashboard" are undiscounted. If not, please provide the undiscounted life-years.

The values presented in the model and company submission are discounted life-years. Undiscounted life-years have not been provided in this response due to time limitations, however can be obtained from the model by adjusting the discount rate from 3.5% to 0%.

B20. Given follow-up visits in MONARCH were conducted every 8 weeks, and clinical expert opinion indicated that disease progression cannot be measured in less than 4 week-intervals, please explain the need to have weekly model cycles.

A weekly cycle was convenient for modelling and also deemed appropriate given the frequency at which treatment regimens are administered in this patient population, in the MONARCH 2 trial for abemaciclib and also the comparator trials included in the model. In the MONARCH 2 trial, abemaciclib or placebo were administered twice daily, and fulvestrant administered on days 1 and 15 of the first 28-day cycle, and on day 1 of subsequent cycles. Furthermore, a weekly cycle was appropriate given the rate at which clinical events beyond progression, such as adverse events, may occur in this patient population.

B21. The ERG found some discrepancies between the values reported in the CS and in the Excel model results. Please clarify what are the correct values in Table 1 below.

Table 28. Discrepancies between the economic model and the company submission

Outcomes/Analysis	Reference in the model	Company submission	Correct values
HR TMX FUL	'HR'J25	Table 29	
RDI values	'Resource'J54:J76	Table 50	
Distribution used	'Resource'AN181	Table 58	

Abbreviations: FUL: fulvestrant; HR: hazard ratio; RDI: relative dose intensity.

B22. Please explain the difference in the Cox-Snell plots in Figure 32 and Figure 33.

B23. Please clarify if the eight one-way sensitivity analyses (OWSA) presented in the model represent the key eight drivers in the model (resulting from varying all the model parameters). If not, please consider varying all parameters included in PSA to identify the key drivers in the model. If the company decides not to undertake additional OWSA analysis, please justify this decision.

The eight one-way sensitivity analyses (OWSA) listed in the model and below represent the key drivers in the model specifically relating to abemaciclib plus fulvestrant:

1. ABE-FUL PFS treatment effect (coefficient) (Lower/Upper 95% CI)
2. ABE-FUL OS treatment effect (coefficient) (Lower/Upper 95% CI)
3. ABE-FUL time-on-treatment treatment effect (coefficient) (Lower/Upper 95% CI)
4. Pre-progression state utility coefficient (Lower/Upper 95% CI)
5. Post-progression state utility coefficient (Lower/Upper 95% CI)
6. Drug price ABE-FUL (+/- 20%)

7. Discount rates for costs

8. Discount rates for benefits

Additional OWSA have not been conducted due to time constraints. However, the deterministic sensitivity analysis programmed into the model tests a number of scenarios to help address uncertainty around different model parameters and assumptions. Parameters influencing the base case NMB by ≥10% included assessment of PFS, distribution for extrapolating OS, interval censored adjustment, and distribution for extrapolating time on treatment. We believe these are key areas of uncertainty and the results of the scenarios show the magnitude of this uncertainty.

We do not believe additional OWSA which vary the input by an arbitrary ±x% will help the committee understand the uncertainty around the decision problem. As highlighted by the ISPOR best practice guidelines about model parameter estimation and uncertainty, this approach can be used as a measure of sensitivity but should not be used to represent uncertainty.[23] This approach to not provide additional OWSA was also followed for the recent submission for abemaciclib in combination with an aromatase inhibitor (MONARCH 3 indication; ID1227; submitted June 2018).

Adverse events

B24. **Priority question:** On page 126 of the CS it states, "The rates of AEs for patients on ABE-FUL and FUL in the model were based on the TEAEs". Please clarify if the AE rates obtained from BOLERO 2 for exemestane and everolimus represent treatment-emergent or treatment-related AEs. For consistency, please use the same type of AE for all comparators, and if available please use treatment-related AEs.

The BOLERO 2 trial reports treatment-emergent AEs,[24] and was used to parameterise AE rates for EXE and EXE-EVE, since it provided the most granular data for AEs across all trials captured in the SLR.

B25. Please amend the cost to treat grade 3-4 diarrhoea from one pack of loperamide to the resource use accepted in TA496 (NHS Reference Costs: Gastrointestinal Infections, non-elective short stay, weighted average FZ36G to FZ36Q).

B26. Please explain why grade 5 AEs were not considered in terms of impact on quality of life and costs.

B27. Please clarify how sources of AE disutilities (Hudgens 2016 and Swinburn 2010) were chosen and identified to inform the model and why the AE disutilities (stomatitis and vomiting) reported by Lloyd et al. 2006 were not considered.

B28. Please clarify how ID414 was chosen and identified to inform the duration of AEs (Table 33 of the CS).

Resource and cost use

B29. Priority question: Please correct the number of PFS events in the model ('Resource'F177) from 379 to 364, as to exclude the 15 deaths without progressive disease.

The number of PFS events in the model has been corrected from 379 to 364, to exclude the 15 deaths without progressive disease.

B30. Priority question: Please provide a scenario analysis where 100% of patients receive active therapy on progression.

This scenario has been implemented into the model. The scenario results are presented in Table 29 (original NMA, revised PAS for abemaciclib), Table 30 (revised NMA, revised PAS for abemaciclib), and Table 31 (original NMA, original PAS for abemaciclib).

Table 29. Results of the scenario analysis with 100% of patients receiving active therapy on PD (original NMA, revised PAS for abemaciclib)

Comparator	Costs	LYs	QALYs	ICER (per QALY)	ICER (per QALY) for ABE-FUL vs comparator
TMX	[redacted]	3.50	[redacted]	Referent	£35,441
FUL	[redacted]	3.72	[redacted]	£92	£50,539
EXE	[redacted]	3.33	[redacted]	Dominated	£11,609
ABE-FUL	[redacted]	3.64	[redacted]	£50,539	N/A
EXE-EVE	[redacted]	3.45	[redacted]	Dominated	Dominant

Abbreviations: ABE-FUL: abemaciclib plus fulvestrant; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; ICER: incremental cost-effectiveness ratio; LY: life year; PD: progressive disease; QALY: quality-adjusted life year; TMX: tamoxifen.

For the ERG's information, the results of the scenario incorporating the revised NMA into the model are provided in Table 30.

Table 30. Results of the scenario analysis with 100% of patients receiving active therapy on PD (revised NMA, revised PAS for abemaciclib)

Comparator	Costs	LYs	QALYs	ICER (per QALY)	ICER (per QALY) for ABE-FUL vs comparator
CAP	[redacted]	2.55	[redacted]	Referent	£59,550
EXE	[redacted]	2.55	[redacted]	Dominated	£39,799
EXE-EVE	[redacted]	2.34	[redacted]	Dominated	£23,250
FUL	[redacted]	4.38	[redacted]	Ext. dominated	£39,819
ABE-FUL	[redacted]	4.57	[redacted]	£59,550	N/A

Abbreviations: ABE-FUL: abemaciclib plus fulvestrant; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; ICER: incremental cost-effectiveness ratio; LY: life year; NMA: network meta-analysis; PD: progressive disease; QALY: quality-adjusted life year; TMX: tamoxifen.

Table 31. Results of the scenario analysis with 100% of patients receive active therapy on PD (original NMA, original PAS for abemaciclib)

Comparator	Costs	LYs	QALYs	ICER (per QALY)	ICER (per QALY) for ABE-FUL vs comparator
TMX	[redacted]	3.50	[redacted]	Referent	£67,842
FUL	[redacted]	3.72	[redacted]	£92	£96,780
EXE	[redacted]	3.33	[redacted]	Dominated	£32,470
ABE-FUL	[redacted]	3.64	[redacted]	£96,780	N/A
EXE-EVE	[redacted]	3.45	[redacted]	Dominated	Dominant

Abbreviations: ABE-FUL: abemaciclib plus fulvestrant; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; ICER: incremental cost-effectiveness ratio; LY: life year; PD: progressive disease; PFS: progression-free survival; QALY: quality-adjusted life year; TMX: tamoxifen.

B31. **Priority question:** In Table 77 of Appendix M.3, only one source is provided for each comparator, please clarify how many additional sources from the NMA could be used to inform either of the two approaches.

Based on the response to A4, the available time on treatment information was also reviewed, and available information from the studies is presented in Table 32.

Table 32. Time on treatment information available from study publications

Study	Comparator	Text relating to time on treatment	Use in the model
Yamamoto 2013[17]	EXE	*'Duration of response has not yet been analyzed, because twelve patients (27.9%) of the TOR120 arm and 6 patients (13.3%) of the EXE arm were still being treated at the median observation period of 72 weeks.'*	The publication does not provide sufficient information for the time on treatment to be implemented.
Zhang 2016[10]	FUL	*'There were no discontinuations due to an AE in the fulvestrant 500 mg group. 7 patients discontinued FUL500 (n=109).'*	This publication presents a smaller and therefore less robust study than MONARCH 2. Since patient-level data are available from MONARCH 2, the Zhang 2016 study was not used.
Campos 2009[19]	EXE	*'The median duration of treatment was similar in the exemestane and anastrozole groups (17 weeks versus 18.5 weeks, respectively).'*	These data are closely aligned with the data from the model used in the company submission i.e. 3.8 months for exemestane.

Abbreviations: AE: adverse event; EXE: exemestane; FUL: fulvestrant; TOR: toremifene.

B32. **Priority question:** Please clarify why the median duration of treatment for EVE-EXE reported in Table 77 of Appendix M.3 is different in approach 1 (5.5) ('ToT'AB44)and 2 (6.8) ('ToT'AS44), when both approaches were informed by BOLERO-2.

The 5.5 and 6.8 values for median duration of treatment were both taken BOLERO 2 trial (Yardley 2013).[25] The median duration of exposure reported for EXE is 29.5 weeks, which is equivalent to 6.8 months. The median duration of exposure reported for EVE is 23.9 weeks, which is equivalent to 5.5 months.

The base case (approach 1) used the lower value of 5.5 months as a conservative assumption and the higher value was considered in the scenario analysis as part of approach 2.

B33. **Priority question:** Please explain if the follow-up care resources received in MONARCH 1 for pre-progression and MONARCH 2 for post-progression (Tables 43, 44 and 45 of the CS) are considered to reflect current clinical practice. Please provide a scenario analysis (as a drop-down menu in the Excel model) using the follow-up resource use for PFS and PPS accepted in TA496.

Please note that data from MONARCH 2 were used to inform pre-progression follow-up care resource use in the model, whilst data from MONARCH 1 were used to inform resource use for post-progression follow-up care.

MONARCH 2 was a phase III, double-blind, randomised controlled trial in patients with advanced, HR+/HER2− breast cancer who had progressed while receiving neoadjuvant or adjuvant endocrine therapy (ET), ≤ 12 months from the end of adjuvant ET, or while receiving first-line ET for metastatic disease,[1] and is thus aligned with the population specified in the decision problem for this appraisal. MONARCH 2 was conducted recently (2014–2018), with a large proportion of centres ([redacted]%) located in Europe.[12, 26] Due to the existence of European wide guidelines such as the European Society for Medical Oncology (ESMO) consensus guidelines for advanced breast cancer,[27] it is considered likely that the pre-progression resource use adopted in the model is representative of advanced breast cancer follow-up care in the UK.

MONARCH 1 was a single-arm, open-label, phase 2 study of abemaciclib as a single agent in patients with refractory HR+/HER2− metastatic breast cancer in which patients were required to have progressed on or after endocrine therapy and have received at least one, but no more than two chemotherapy treatment regimens in the metastatic setting.[28] One chemotherapy regimen must have included a taxane, either in the adjuvant or metastatic setting. Patients included in MONARCH 1 are considered representative of patients from the MONARCH 2 population whose disease has subsequently progressed, and similarly to MONARCH 2, a large proportion of centres ([redacted]%), were located in Europe.[29] MONARCH 1 was conducted between 2014 and 2016, and can thus be considered to provide a representative estimation of resource use in progressed HR+/HER2− advanced breast cancer patients.

A scenario has been tested in the model using the value of £1,200 per month (programmed as £300 per week) for follow-up care in PPS and third-line treatment costs. This has been programmed into the model as option, and the results of this scenario are presented in Table 33 (original NMA, revised PAS for abemaciclib), Table 34 (revised NMA, revised PAS for abemaciclib) and Table 35 (original NMA, original PAS for abemaciclib).

Table 33. Results of the scenario analysis using the follow-up resource use for PFS and PPS accepted in TA496 (original NMA, revised PAS for abemaciclib)

Comparator	Costs	LYs	QALYs	ICER (per QALY)	ICER (per QALY) for ABE-FUL vs comparator
EXE	[redacted]	3.33	[redacted]	Referent	£48,546
TMX	[redacted]	3.72	[redacted]	£15,865	£88,305
FUL	[redacted]	3.50	[redacted]	Dominated	£54,746
ABE-FUL	[redacted]	3.64	[redacted]	£88,305	N/A
EXE-EVE	[redacted]	3.45	[redacted]	Dominated	Dominant

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; ICER: incremental cost-effectiveness ratio; LY: life year; QALY: quality-adjusted life year; TMX: tamoxifen

For the ERG's information, with the updated NMA, the scenario provides the results in Table 34.

Table 34. Results of the scenario analysis using the follow-up resource use for PFS and PPS accepted in TA496 (revised NMA, revised PAS for abemaciclib)

Comparator	Costs	LYs	QALYs	ICER (per QALY)	ICER (per QALY) for ABE-FUL vs comparator
CAP	[redacted]	2.55	[redacted]	Referent	£57,507
EXE	[redacted]	2.55	[redacted]	Dominated	£47,881
FUL	[redacted]	4.38	[redacted]	£49,140	£68,347
EXE-EVE	[redacted]	2.34	[redacted]	Dominated	£24,734
ABE-FUL	[redacted]	4.57	[redacted]	£68,347	N/A

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; ICER: incremental cost-effectiveness ratio; LY: life year; NMA: network meta-analysis; QALY: quality-adjusted life year; TMX: tamoxifen

Table 35. Results of the scenario analysis using the follow-up resource use for PFS and PPS accepted in TA496 (original NMA, original PAS for abemaciclib)

Comparator	Costs	LYs	QALYs	ICER (per QALY)	ICER (per QALY) for ABE-FUL vs comparator
EXE	[redacted]	3.33	[redacted]	Referent	£69,407
TMX	[redacted]	3.72	[redacted]	£15,865	£134,545
FUL	[redacted]	3.50	[redacted]	Dominated	£87,147
EXE-EVE	[redacted]	3.45	[redacted]	Ext. dominated	£3,607
ABE-FUL	[redacted]	3.64	[redacted]	£134,545	N/A

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; ICER: incremental cost-effectiveness ratio; LY: life year; QALY: quality-adjusted life year; TMX: tamoxifen

B34. **Priority question:** To reflect the assumptions accepted in TA503 and TA496, please provide a scenario analysis where 32.3% of subsequent fulvestrant administrations are delivered in the primary care setting (PSSRU: band 6 community nurse specialist, 15 minutes) and 67.7% are delivered in the outpatient setting (NHS Reference Costs: Non-Consultant Led: Follow up Attendance, Non-Admitted Face to Face, Medical Oncology Code 370).

The economic models used in TA503 and TA496 differ from the model used in the company submission in how they structure the input of follow up, monitoring and administrations costs. The model used in the company submission applies follow up costs separately to the

administration costs, unlike other models which have combined them (such as the TA503 appraisal)

Therefore, FUL (and ABE-FUL) patients are already modelled to incur the following costs on average, described in the model as follow up costs rather than administration costs:

- Oncologist consultation – once per 4-week cycle
- GP visit – approximately once per 4-week cycle
- Community nurse – twice per 4-week cycle
- Clinical nurse specialist – approximately once per 4-week cycle

Having noted the resource use above, Lilly note that FUL is an intramuscular injection given once a month.

Lilly consider that this pattern of resource use for follow-up already represents a considerable amount of patient contact in both primary and secondary care and easily captures the administration cost of FUL, given that this is a simple injection. The addition of the suggested cost to the administration costs in the model would undoubtedly represent double-counting of the resource use as any administration requirement for FUL has been met within the already-modelled visits.

To avoid double-counting, Lilly have not made the requested adjustment to the model. Furthermore, Lilly reject the suggestion that the cost of administration alone (as opposed to a monitoring visit wherein administration may occur) of a simple intramuscular injection has a cost to the NHS of £101, as suggested by the ERG.

B35. **Priority question:** In the model, the weekly cost of fulvestrant (£43.17) is applied in the first cycle ('Trace'AH14) when FUL or ABE-FUL is chosen as the comparator ('Trace'E6). Please correct the model so that the full cost of the first administration is also included (£172.67).

Lilly thank the ERG for bringing to our attention that an additional administration cost of £172.67 (the NHS reference cost for a consultant outpatient appointment) was incorrectly included in the model in the first cycle of FUL treatment; the administration of an additional intramuscular injection does not incur the cost of a consultant visit.

Lilly agree with the ERG that the model programming has applied the incorrect £172.67 cost inaccurately by applying a cost of £43.17 (one-quarter of the cost representing one week out of a four-week cycle) instead of £172.67 and thank the ERG for bringing this to our attention.

Lilly consider that the administration of the additional loading dose (which occurs two weeks after the first dose) is likely to be captured adequately within the package of follow up care listed in the response to clarification question B34 and have therefore removed the administration cost of the loading dose from the model entirely. If the ERG were to desire a scenario analysis wherein this one-off injection did incur a separate cost, Lilly would propose that 15 min of Band 5 nurse time represents a realistic cost to the NHS and would strongly reject the suggestion in question B34 that a single inject incurs an administration cost of £101.

To ensure internal consistency, this cost has also been removed from the PPS inputs for FUL.

B36. **Priority question:** Please clarify where hospitalisation data (length of stay, total hospitalisations and follow-up) used to inform 'Hosp'AA8:AG101 can be found in the CSR.

The hospitalisation data used to inform 'Hosp'AA8:AG101 is based on a bespoke analysis of the patient level data for the economic model and not presented in the CSR. The closest the CSR comes to reporting these numbers can be found in 'Table JPBL.14.40. Summary of All Hospitalizations (On Therapy or within 30 Days of Treatment Discontinuation) Safety Population'.

B37. **Priority question:** Please clarify why the number of hospitalisations reported in Table 40 of the CS (pre-progression 73, post-progression 23), is different to the base case numbers in Table 41 of the CS (pre-progression 86, post-progression 11).

The hospitalisation numbers in Table 40 of the company submission were incorrect, as they presented treatment-specific hospitalisation rates and combined pre-progression and post-progression health states. An updated version of Table 40 that aligns with Table 41 of the company submission is presented below in Table 36. The updated values show a wider difference between PFS and OS.

These values have been implemented into the model as a switch to allow the model to test the impact of this change.

Table 36. Update for Table 40 of company submission: Hospitalisation rate and probability data from MONARCH 2

Cohort	Treatment	Number of hospitalisations	Mean (days)	SD
Pre-progression	ABE-FUL and FUL	86	7.26	7.30
Post-progression	ABE-FUL and FUL	11	11.27	10.85

Abbreviations: ABE: abemaciclib; FUL: fulvestrant; SD: standard deviation.

B38. **Priority question:** Please justify the assumption that the proportion of post-progression survival on-treatment is 37% ('Dashboard'J45) for each treatment arm.

The assumption that 37% of patients in the post-progression stage were on treatment was based on clinical expert opinion, with the rationale that not all patients would wish to receive further treatment at this late stage of breast cancer.

B39. **Priority question:** Please provide a scenario where patients receive post-progression treatment for 100% of the time during post-progression survival.

This question is duplicative of B30. Please see above.

B40. **Priority question:** Please provide a scenario analysis (as a drop-down menu in Excel) including radiotherapy in the post-progression "pack of care" for 80% of progressed patients, allowing

this scenario to be compatible with the scenario requested in B30 (i.e 100% of progressed patients receive subsequent treatment and out of those, 80% receive additional radiotherapy).

During discussion with NICE and the ERG on 18th October, we stated that this response would result in minimal difference to the model outcomes. Although radiotherapy use may vary, the impact on the model outcomes would be minimal since the effect is applied to all arms. This question will therefore not be addressed by the company due to time limitations.

B41. Where bevacizumab is used as a post-progression therapy (Table 47 of the CS), please provide a scenario analysis replacing the cost of bevacizumab with the cost of tamoxifen. As for the patient distributions, please reweight the distributions to the following:

a. TMX patients receiving subsequent TMX to zero instead of the number receiving bevacizumab (10) ('Resource'AS216);

This has been added to the updated model.

b. EVE-EXE patients who received subsequent TMX in BOLERO-2, instead of the number of patients who received bevacizumab in BOLERO-2 ('Resource'AQ216:AR216);

No data were identified for this input from BOLERO-2, however an input cell has been added to the 'B40.' page of the model that can test this.

c. ABE-FUL and FUL patient who received subsequent TMX in MONARCH-2 (11 and 11, respectively) instead of the number of patients who received bevacizumab in MONARCH-2 (20 and 10, respectively) ('Resource'AO216:AP216).

This has been added to the updated model.

B42. Based on your response to B24, please explain how costing hospitalisations is not considered double-counting if TEAEs rather than TRAEs have been modelled. Please provide a scenario analysis excluding the cost of hospitalisations.

B43. The ERG is unable to identify the currency code (JD12D) reported in Table 42 of the CS, in NHS Reference Costs. The ERG is also unclear why the mean length of stay (7.78) in Table 42 of the CS does not reflect the mean lengths of stay in Table 40 of the CS. Please clarify both issues.

We apologise for the error − the currency code for hospitalisation should be **JA12D-L** (malignant breast disorders with CC Score 7+, non-elective long stay).

For the mean length of stay values, the value in Table 42 reflects the average length of stay from the NHS reference costs. This is used to create a cost per day (also reported in Table 42) which is multiplied by the length of stay in the model, reported in Table 40.

B44. Please explain why scan modalities in Tables 44 and 45 of the CS are considered separate to the scans received in follow-up care (Table 43). Also provide a scenario analysis excluding the cost of scan modalities.

B45. Please replace the cost of an x-ray (£0) with a cost of £29.78 (NHS reference costs 2016/17: Direct Access Plain Film, currency code DAPF).

B46. Please incorporate vial wastage into the cost of Filgrastim ('OtherCosts'AU14).

B47. Please amend the regimen for Capecitabine from 21 days of treatment to 14 days, to reflect recommendations in the BNF (1,25 g/m2 twice daily for 14 days, subsequent courses repeated after a 7-day interval).

Health-related quality of life

B48. **Priority question:** Please explain why age-related utility decrements were not included in the economic model. Also provide a scenario analysis including age-related utility decrements, using the published algorithm by Ara and Brazier 2010. (Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health 2010; 13: 509-18.)

During discussion with NICE and the ERG on 18th October, we explained that this response would likely result in minimal difference to the model outcomes. Although age-related utility decrements are valuable to include in models assessing patients with a long life expectancy, the population relevant to this submission are stated in the literature to have a median overall survival of 2−3 years.[30] The company model similarly demonstrates survival of <5 years. The approach to not provide age-related decrements is consistent with other appraisals for advanced breast cancer, including TA495[31] and TA496[32] and ID1227 (abemaciclib with an aromatase inhibitor; submitted June 2018). This question will therefore not be addressed by the company due to time limitations.

B49. **Priority question:** Please clarify why Lloyd *et al.* 2005 was not identified in the search for HRQoL evidence. As advised by the NICE DSU (Technical Support Document 12) (http://nicedsu.org.uk/wp-content/uploads/2016/03/ TSD12-Utilities-in-modelling-FINAL.pdf) please compare the population and methods in Lloyd *et al.* 2005 with MONARCH 2.

The Lloyd et al. study[33] (published in 2006) commonly utilised by cost-effectiveness studies in this disease setting was not captured in the searches for the utilities SLR. This is because the study did not report utilities or scores for a standardised, generic, preference-based measure (i.e. the EQ-5D, SF-36 or HUI3), nor did it map from a condition-specific measure (e.g. the EORTC-QLQ-BR23) to a standard, generic, preference-based measure in the patient population of interest, as per the eligibility criteria for the SLR (reported in Table 41 of the CS appendices). Lloyd 2006[33] was identified from the TA421[34] appraisal (which assessed the key competitor to ABE-FUL in this appraisal, EVE-EXE) in which Lloyd 2006 was used as a source of utility for progressive disease, in addition to other NICE appraisals of advanced breast cancer, namely TA495, TA496 and TA239. Lloyd 2006[33] was therefore considered to be an appropriate source of utility for progressive disease in this appraisal.

The Lloyd 2006[33] study was conducted to identify societal preferences for distinct stages of metastatic breast cancer, utilising members of the UK general public. As discussed in the CS, MONARCH 2 was a Phase III, double-blind, RCT of women with advanced or metastatic breast cancer who had progressed on or after endocrine therapy.

Due to the immaturity of post-progression data from MONARCH 2, an alternative utility source was sought to inform the post-progression utility. Lloyd 2006[33] was considered an appropriate study to inform the utility of UK-based, MONARCH 2-aligned advanced breast cancer patients whose disease has progressed following treatment with ABE-FUL or a comparator treatment.

In line with the NICE reference case, members of the UK general public provided their preferences on health states. The set of vignettes developed to represent health states of different stages of metastatic breast cancer for patients treated in the UK was informed by a literature review, exploratory interviews with expert physicians, a focus group with oncology specialist nurses and additional content validation interviews. Through these methods the authors gained a thorough understanding of the symptom burden, toxicity of treatments and areas of functioning (social, sexual, cognitive, physical and emotional), to fully understand the impact of metastatic breast cancer on HRQoL in patients in the UK.

B50. Please provide descriptive statistics for the crosswalked EQ-5D-3L data captured in MONARCH 2 including the mean age of respondents, mean utility value, standard deviation and number of observations collected at each time point of data collection.

The EQ-5D-5L data were scored as described by van Hout et al (2012) (EQ-5D-5L to EQ-5D-3L crosswalk). EQ-5D-5L data presented in the company submission are from the safety population of MONARCH 2. EQ-5D-5L data were collected at baseline (Day −14 to Day −1), Cycle 2 Day 1, and then on Day 1 of every second cycle beginning with Cycle 3 and continuing through Cycle 13, on Day 1 of every third cycle after Cycle 13, and at Short-Term Follow-Up. Short-Term Follow-Up began the day after the patient and the investigator agreed that the patient would no longer continue study treatment and lasted approximately 30 days.

The compliance rate (i.e. number of observations collected at each time point) for EQ-5D-5L is included in Table 37. A summary of EQ-5D-5L data is provided in Table 38.

Table 37. Compliance rate for ED-5D-5L (safety population)

Planned visit	Abemaciclib plus fulvestrant (N=441) n (%)	Placebo plus fulvestant (N=223) n (%)
Baseline, n	441	223
Compliant with Questionnaire	[redacted]	[redacted]
Cycle 2, n	[redacted]	[redacted]
Compliant with Questionnaire	[redacted]	[redacted]
Cycle 3, n	[redacted]	[redacted]
Compliant with Questionnaire	[redacted]	[redacted]
Cycle 5, n	[redacted]	[redacted]
Compliant with Questionnaire	[redacted]	[redacted]
Cycle 7, n	[redacted]	[redacted]
Compliant with Questionnaire	[redacted]	[redacted]
Cycle 9, n	[redacted]	[redacted]
Compliant with Questionnaire	[redacted]	[redacted]
Cycle 11, n	[redacted]	[redacted]
Compliant with Questionnaire	[redacted]	[redacted]
Cycle 13, n	[redacted]	[redacted]
Compliant with Questionnaire	[redacted]	[redacted]
Cycle 16, n	[redacted]	[redacted]
Compliant with Questionnaire	[redacted]	[redacted]
Cycle 19, n	[redacted]	[redacted]
Compliant with Questionnaire	[redacted]	[redacted]
Cycle 22, n	[redacted]	[redacted]
Compliant with Questionnaire	[redacted]	[redacted]
Cycle 25, n	[redacted]	[redacted]
Compliant with Questionnaire	[redacted]	[redacted]
Cycle 28, n	[redacted]	[redacted]
Compliant with Questionnaire	[redacted]	[redacted]
Follow Up, n	[redacted]	[redacted]
Compliant with Questionnaire	[redacted]	[redacted]

Source: Lilly Data on File. MONARCH 2 CSR Health Outcomes Addendum.[35]

Table 38. Summary of EQ-5D-5L index by visit (safety population)

Visit	Treatment	N	Mean (SD) Score	Change from Baseline LSMean (SE)	p-value Within Group*b	LS Mean Change Difference (SE)	95% CI for Difference	p-value*c
EQ 5D-5L EQ-5D-5L Index Value								
Baseline	Abemaciclib	[redacted]	[redacted]	-	-	-	-	-
	Placebo	[redacted]	[redacted]	-	-	-	-	-
Cycle 2	Abemaciclib	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
	Abemaciclib vs Placebo	-	-	-	-	[redacted]	[redacted]	[redacted]
Cycle 3	Abemaciclib	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
	Abemaciclib vs Placebo	-	-	-	-	[redacted]	[redacted]	[redacted]
Cycle 5	Abemaciclib	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
	Abemaciclib vs Placebo	-	-	-	-	[redacted]	[redacted]	[redacted]
Cycle 7	Abemaciclib	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
	Abemaciclib vs Placebo	-	-	-	-	[redacted]	[redacted]	[redacted]
Cycle 9	Abemaciclib	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
	Abemaciclib vs Placebo		-	-	-	[redacted]	[redacted]	[redacted]
Cycle 11	Abemaciclib	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
	Abemaciclib vs Placebo	-	-	-	-	[redacted]	[redacted]	[redacted]
Cycle 13	Abemaciclib	223	[redacted]	[redacted]	[redacted]	-	-	-
	Placebo	88	[redacted]	[redacted]	[redacted]	-	-	-

Visit	Treatment	N	Mean (SD) Score	Change from Baseline LSMean (SE)	p-value Within Group*b	LS Mean Change Difference (SE)	95% CI for Difference	p-value*c
EQ 5D-5L **EQ-5D-5L Index Value**								
	Abemaciclib vs Placebo	-	-	-	-	[redacted]	[redacted]	[redacted]
Cycle 16	Abemaciclib	185	[redacted]	[redacted]	[redacted]	-	-	-
	Placebo	67	[redacted]	[redacted]	[redacted]	-	-	-
	Abemaciclib vs Placebo	-	-	-	-	[redacted]	[redacted]	[redacted]
Follow-up	Abemaciclib	177	[redacted]	[redacted]	[redacted]	-	-	-
	Placebo	123	[redacted]	[redacted]	[redacted]	-	-	-
	Abemaciclib vs Placebo	-	-	-	-	[redacted]	[redacted]	[redacted]
All Post-baseline	Abemaciclib	-	-	[redacted]	[redacted]	-	-	-
	Placebo	-	-	[redacted]	[redacted]	-	-	-
	Abemaciclib vs Placebo	-	-	-	-	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; EQ-5D-5L: EuroQol 5-Dimension 5-Level; SD: standard deviation; SE: standard error.
Source: Lilly Data on File. MONARCH 2 CSR Health Outcomes Addendum.[35]

ED-5D-5L data are from the safety population, for which mean age is not available. However, the safety population includes just five fewer participants in the abemaciclib plus fulvestrant arm compared to the ITT population (i.e. N=441 compared to N=446 for ITT), and the same number of patients in the placebo plus fulvestrant arm (N=223). The mean age for the safety population is likely very similar to the ITT, for which the mean age was [redacted] years in the abemaciclib plus fulvestrant arm and [redacted] in the placebo plus fulvestrant arm.

B51. For each regression model reported in Appendix M.5, please add the p-value and 95% confidence interval for each coefficient.

These data are unfortunately not readily available, and this question will therefore not be addressed by the company due to time limitations.

B52. Please run a scenario analysis (as a drop-down menu in Excel) removing the AE-related disutilities. Please discuss the implications of including them in the economic analysis, with regards to double counting given that PFS utility values are likely to have implicitly captured these.

B53. Please explain how the coefficients in Table 92 of Appendix M.5 result in the utility values reported in Table 30 of the CS. Also clarify if the regression model in Table 92 was ran independently of the baseline utility values reported in Table 91.

Using the parameters in Table 92 from the Appendix M.5:

[redacted] = [redacted] (baseline utility from Table 91)

[redacted] = [redacted] (baseline utility from Table 91) + -[redacted](progression variable)

For the utility values that are treatment specific, the coefficients from Model 2 were used:

[redacted] = [redacted] (treatment effect)

[redacted]

[redacted](treatment effect) + [redacted] (progression variable)

[redacted](progression variable)

The regression model in Table 92 was run independently of the baseline utility values.

B54. Please clarify if the probability of hospitalisation input for endocrine therapies reported in Table 58 of the CS (66.34%) is used in the economic model.

B55. Please clarify why the administration cost code for bevacizumab relates to subsequent elements of a chemotherapy cycle.

Section C: Textual clarifications and additional points

C1. Please clarify why relevant NICE TAs in adults with locally advanced or metastatic breast/ cancer such as TA239, TA495, TA421 and TA496 were not identified in searches for HRQoL and resource and cost use evidence.

C2. Please clarify why NHS EED was not searched from 2015 using the database maintained in the Centre for Reviews and Dissemination (https://www.crd.york.ac.uk/CRDWeb/).

C3. Please provide the original search strategies for cost-effectiveness evidence, HRQoL evidence and cost and healthcare resource use evidence.

C4. Please clarify why 66 studies were included in the search for cost and healthcare resource evidence if only 20 reported results relating to this patient population.

C5. Please provide the full reference and full-text for Kurosky 2015, Mitra 2016 and Wood 2017 included in the search for cost and healthcare resource evidence.

C6. Please explain why the searches for cost-effectiveness evidence, HRQoL evidence and cost and healthcare resource use evidence have not been updated since June 2017.

C7. Please provide a definition of the EP stratum, mentioned in the company submission page 43.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Abemaciclib with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer after endocrine therapy [ID1339]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Breast Cancer Care
3. Job title or position	Policy and Campaigns Officer
4a. Brief description of the organisation (including who funds it). How many members does it have?	Breast Cancer Care is the only specialist UK-wide charity providing support for women, men, families and friends affected by breast cancer. Our free services include support over the phone with a nurse or someone who's been there, our welcoming online forums, reliable information and local group support. Every day, our care, support and information help thousands of people to find a way to live with, through and beyond breast cancer. We are funded by entirely by voluntary donations, this includes individual and corporate donations, corporate sponsorships, project grants and income generated from events.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None to declare.
5. How did you gather information about the experiences of patients and carers to include in your submission?	This submission reflects the views of Breast Cancer Care, based on our experiences of working with people who have personal experience of, or who are concerned about, breast cancer, as well as our experiences of supporting people living with metastatic breast cancer.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Breast Cancer Care offers support to people living with or affected by advanced (also referred to as metastatic or secondary) breast cancer. We hear from many people about their experiences of living with the condition, as well as their hopes for new treatments. Uncertainty is a key element of living with metastatic breast cancer. On average, people live with the disease for two to three years after diagnosis. However, this can vary considerably from person to person, with some only living for months after their diagnosis, while others live for many years longer. As a result, many people tell us that they live from “scan to scan”, and feel unable to plan their lives in any long-term way. Many are keen to reach a personal milestone, such as seeing their child go to secondary school, or attending a family wedding. The physical impact of metastatic breast cancer differs greatly, depending on where a person’s breast cancer has spread (for example, the lungs or brain), the extent of this progression, and treatment received. Broadly, physical effects include but aren’t limited to: pain, fatigue, nausea, poor appetite, and sleep difficulties. However, if symptoms and side effects can be managed successfully, metastatic breast cancer can, for some, become more like a chronic condition, with people experiencing a good quality of life for some time. One person living with metastatic (also known as secondary) breast cancer told us: *"My diagnosis of secondary breast cancer has changed my life in so many ways. I live in pain despite being on morphine constantly. I live with the fear of my death. I live knowing that I will not be able to see my son grow to adulthood. I live knowing he will have no parent to help him in his life. I live knowing that my life is a series of treatments, scans, appointments.* *"I know that in the near future my career will be taken from me as the pain and treatments, fatigue and side effects take a grip. Cancer frightens other people: they don’t know what to say; they don’t know how*

	they can help. My friends disappeared. My family also disappeared. I have had to keep my fears to myself: how can I tell anyone the truth and reality of living with incurable breast cancer? I have gone from being the person that was there to help other people, to being an ill, disabled person; a condition, a diagnosis."
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	People with hormone receptor positive, HER2 negative metastatic breast cancer face limited treatment options. Current treatment options for this patient group include hormone (endocrine) therapies and chemotherapy. Endocrine therapies provide an alternative or additional option to chemotherapy. Where applicable, they may be preferable for many people, helping to defer the use of chemotherapy and its side effects which often impact heavily on quality of life. Chemotherapy may be used in cases where the use of endocrine therapy is clinically unsuitable, or when it has become ineffective. However, chemotherapy has increased side effects and requires frequent trips to hospital to receive treatment. The combination of abemaciclib alongside fulvestrant offers a treatment modality which can provide extended progression free survival, delaying the time to the disease becoming resistant to endocrine therapy and the possible need to use chemotherapy.
8. Is there an unmet need for patients with this condition?	The combination offers a new treatment option for those with disease which has progressed on one previous line of endocrine therapy.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The potential for an extended period of PFS with a good quality of life and additional time to spend with family means that the use of abemaciclib in combination with endocrine therapy such as fulvestrant is an advantage to endocrine therapy alone. Additionally postponing or avoiding the need for chemotherapy is a significant benefit to patients and their carers. Abemaciclib is taken in tablet form, continually. Fulvestrant is administered via intramuscular injections. It's usually given every two weeks for the first three doses, then once a month for as long as the treatment combination has effect. These methods of administration are hugely likely to be preferable for some patients over treatments which require more time in a hospital setting, such as chemotherapy. Both drugs are well tolerated with a lower burden of side effects in comparison to most chemotherapy regimes. This is likely to have a positive effect on both the physical and psychological quality of life for those with a diagnosis of metastatic breast cancer.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	<u>Abemaciclib</u> A common side effect of abemaciclib is diarrhoea, which can be very severe in some cases. Patient education and preparation is recommended and healthcare professionals should monitor patients to ensure these adverse effects are identified swiftly and managed appropriately. Other side effects for abemaciclib include risk of infection, nausea, fatigue, diarrhoea and hair thinning. The administration method of abemaciclib (tablet) is convenient, but some people may find remembering to take tablets problematic. <u>Fulvestrant</u> Many people treated with fulvestrant experience only mild side effects, which are tolerable. These include

	nausea and hot flushes. Some people may find the method of administration problematic. Additionally, fulvestrant would require more frequent trips to hospital or primary care for the injections, which may be a disadvantage of the treatment for some people.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Current use of CDK 4/6 inhibitors has only been approved for first line use. This combination offers an additional treatment option for those whose disease has progressed on prior endocrine therapy with the potential for significant benefit for this particular patient group.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages
14. In up to 5 bullet points, please summarise the key messages of your submission: • The combination of Abemaciclib and Fulvestrant presents a significant leap forward in treatment options for people with hormone receptor positive HER2 negative advanced breast cancer and in particular those whose disease has progressed on prior endocrine therapy. • The key benefit of this drug combination is a prolonged period of PFS, compared with endocrine therapy alone. • It can allow people to delay having chemotherapy and its potential debilitating side effects for a substantial amount of time • It has the potential to allow people to live with a good quality of life, with limited side effects, meaning they can continue with their day-to-day activities and provide invaluable additional time with those closest to them.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Abemaciclib with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer after endocrine therapy [ID1339]

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Breast Cancer Now
3. Job title or position	Senior Research and Policy Officer
4a. Brief description of the organisation (including who funds it). How many members does it have?	Breast Cancer Now is the UK's largest breast cancer charity, dedicated to funding ground-breaking research into the disease. Our ambition is that by 2050, everyone who develops breast cancer will live. We're bringing together all those affected by the disease to improve the way we prevent, detect, treat and stop breast cancer. We're committed to working with the NHS and governments across the UK to ensure that breast cancer services are as good as they can be, and that breast cancer patients benefit from advances in research as quickly as possible. Our main sources of income are individual giving and corporate partnerships. In particular, in 2016/17 we received £2.7 million of income from Pfizer for our Catalyst programme, which provides grants for research. Further details about our income are set out in our annual report, which is available on our website at http://breastcancernow.org/about-us/what-we-do/annual-report-and-accounts Our work on access to drugs is independent of any funding we may receive from the pharmaceutical industry and is based on the evidence of the clinical effectiveness of drugs.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and	Information about the experiences of patients and carers is drawn from Breast Cancer Now's extensive network of supporters.

carers to include in your submission?	
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Metastatic (also known as advanced, secondary or stage 4) breast cancer is when cancer originating in the breast has spread to other parts of the body; most commonly the lungs, brain, bones or liver. There is no cure for metastatic breast cancer, so the aim of treatment is to extend the length of life and to improve quality of life for patients. A patient can be diagnosed with metastatic cancer initially, or they can develop the condition years after treatment for their primary breast cancer has ended. Being diagnosed with metastatic breast cancer is extremely difficult to come to terms with both for patients and their family and friends and it can affect patients in different ways. Some people may feel upset and shocked or anxious, as well as angry and alone. These common feelings can have a huge impact on people's mental health. As well as the huge emotional toll of living with metastatic breast cancer, patients often have to cope with numerous practical concerns, such as managing their day to day activities, including working, household responsibilities and travelling to and from hospital appointments. Patients are keen to find treatments that will halt progression and extend life for as long as possible. As patients' time is limited, people tell us that quality of life is just as important to take into account as length of life, as this enables them to spend quality time with their loved ones. Therefore, the type and severity of treatment side effects are also important for patients.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	This appraisal is considering abemaciclib in combination with fulvestrant for two population groups. In responding to this question, we will look at the current treatments available on the NHS for both groups. 1) For people with untreated advanced hormone-receptor positive HER2-negative breast cancer: In November 2017, NICE approved two CDK 4/6 inhibitors palbociclib and ribociclib with an aromatase inhibitor as first-line treatments for women with HR positive, HER2 negative locally advanced or metastatic breast cancer. This was a significant step forward and welcomed by patients, as these treatment options provide patients with around 10 additional months of progression free survival. We know that being progression free – and being able to continue with normal activities – are highly valued by patients and their families. These drugs are also taken orally, which is convenient for many patients. The criteria outlines that these treatments are only available to patients as long as they have had a disease-free interval of 12 months or more since completing treatment with anastrazole or letrozole either as neoadjuvant or adjuvant therapy. Also whilst these CDK 4/6 inhibitors have recently been established as standard of care on the NHS, there will be some existing patients who are still receiving only endocrine therapy (such as aromatase inhibitors or tamoxifen) which was the standard of care prior to the approval of the CDK 4/6 inhibitors. Chemotherapy can be offered as a first line treatment for patients whose disease is imminently life-threatening or if they require early relief of symptoms because of significant visceral organ involvement. 2) For people with advanced hormone-receptor positive HER2 negative breast cancer that has progressed after one line of prior endocrine therapy: Currently, once patients progress on either an aromatase inhibitor, or a CDK4/6 inhibitor with an aromatase inhibitor, they may start treatment on exemestane, everolimus in combination with exemestane or start treatment on systemic (non-targeted) chemotherapies. Chemotherapies are associated with

	gruelling side effects and can have a huge impact on people's quality of life. As a result of this, patients would prefer other targeted treatment options in order to delay the negative impact that chemotherapy can have on their quality of life. In some parts of England, fulvestrant is available as a second line treatment for women that have already had hormone therapy, although we believe it is not available in the majority of England.
8. Is there an unmet need for patients with this condition?	Yes, this treatment at first line would provide an important option for women who have progressed early, and relapsed on or within 12 months from completion of neoadjuvant or adjuvant endocrine therapy. As a second line treatment, it would also provide an important option for women who have already received endocrine therapy.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	For patients, the advantages of abemaciclib in combination with fulvestrant are: • The MONARCH 2 study demonstrated that abemaciclib plus fulvestrant improves progression free survival (PFS) compared with fulvestrant alone, with a median PFS of 16.4 months compared to 9.3 months. We know patients value this extra time, as delaying disease progression means more quality time to spend with their relatives and friends. Maintaining a high quality of life for as long as possible is currently the best outcome for this patient group. • Delaying progression can also have a positive impact on patients' emotional wellbeing and mental health, as it may mean that the patient can continue doing the activities they enjoy and leading a more or less normal daily life. • Increasing the time until a patient's disease progresses is also likely to bring some comfort to their relatives and friends, as this is the best possible outcome for an incurable disease. This in turn could help to reduce any stress the patient is experiencing as a result of worrying about any burden on their friends and family. • The use of this technology could also delay patients having to start on systemic (non-targeted) chemotherapy. Chemotherapy is traditionally associated with more severe and gruelling side

	effects which can result in a poorer quality of life for patients and people are often particularly fearful and anxious about being moved onto chemotherapy.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Abemaciclib plus fulvestrant is associated with some increased side effects compared to fulvestrant alone. MONARCH 2 reported that the most common adverse events of any grade were diarrhoea, neutropenia, nausea, fatigue and abdominal pain. Apart from neutropenia, these side effects occurred mostly at grade 1 or 2 severity. Although diarrhoea was the most common side effect of abemaciclib in combination with fulvestrant, it is noted that diarrhoea events typically occurred in the first treatment cycle and that in most cases, it was effectively managed using antidiarrheal medications and with dose adjustments. Every treatment for breast cancer has some side effects and each patient's situation will be different and the side effects will affect some patients more than others. Patients' willingness to take treatments will vary, however, as long as all the side effects are clearly discussed with the patient, they will be able to make their own choice as to the level of risk they will be willing to take. Patients would also need to attend hospital or in some places a GP surgery for fulvestrant to be administered, as this is given as an injection. However, for many patients, any inconvenience caused by attending hospital or GP appointments for the administration of fulvestrant will be outweighed by an increase in progression free survival.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	This treatment was tested in women with any menopausal status (pre or peri menopausal women received ovarian suppression), who had hormone positive, HER2-negative advanced breast cancer and whose disease progressed while receiving prior endocrine therapy. Patients were excluded from the trial if prior treatment included CDK4/6 inhibitors, or fulvestrant or everolimus. MONARCH 2 reported that the addition of abemaciclib to fulvestrant improved progression free survival across all patient subgroups.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None that we are aware of.

Other issues	
13. Are there any other issues that you would like the committee to consider?	N/A.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- In the MONARCH 2 trial, abemaciclib in combination with fulvestrant showed promise in improving progression-free survival compared to fulvestrant alone.
- This delay in disease progression is important as it enables patients to spend quality time with their friends and families as well as continue with their daily activities, which can improve the emotional wellbeing of both patients and their loved ones.
- There are some increased side effects from abemaciclib in combination with fulvestrant, compared to fulvestrant alone. However, not all patients will experience side effects. As long as the benefits and risks of a treatment are clearly discussed with the patient, they can make the decision that is right for them.
- This treatment adds to the drug options available for patients with this type of breast cancer which cannot be cured. Any new treatments that can delay the need to start on chemotherapy which is generally associated with more severe side effects and a poorer quality of life is welcomed by patients.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Abemaciclib with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer after endocrine therapy [ID1339]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Professor Andrew M. Wardley**
2. Name of organisation	**The Christie**

3. Job title or position	**Consultant and Honorary Professor in Breast medical Oncology**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of treatment in metastatic breast cancer is to improve overall survival and maintain quality of life. In hormone receptor positive breast cancer this is best achieved with endocrine therapy and CDK4/6 inhibitors of which there are 3 namely palbociclib, ribociclib and abemaciclib. They also extend the time until traditional cytotoxic chemotherapy is required. This is also considered to be an important outcome
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Improvement of 6 months or more in pfs are certainty considered to be clinically meaningful. Abemaciclib plus fulvestrant significantly extended PFS versus fulvestrant alone (median, 16.4 v 9.3 months; hazard ratio, 0.553; 95% CI, 0.449 to 0.681; P < .001). Response to treatment is also an important consideration especially in patients with symptoms from the metastatic breast cancer. In patients with measurable disease, abemaciclib plus fulvestrant achieved an ORR of 48.1% (95% CI, 42.6% to 53.6%) compared with 21.3% (95% CI, 15.1% to 27.6%) in the control arm. This is as good a response as one might expect with combination chemotherapy but without the considerable toxicity of chemotherapy.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes patients progressing/relapsing on an aromatase inhibitor are excluded from treatment with a CDK4/6 inhibitor in combination with an aromatase inhibitor as first line treatment for there metastatic breast cancer Recently presented data for palbociclib in combination with fulvestrant showed that median overall survival improved by 6.9 months with palbociclib plus fulvestrant (median overall survival = 34.9 months, 95% confidence interval [CI] = 28.8–40.0) compared to placebo plus fulvestrant (median overall survival = 28.0 months, 95% CI = 23.6–34.6, *P* = .043).

	In view of the remarkable similarity of the datasets from the 3 CDK4/6 inhibitors in first line (in combination with an aromatase inhibitor) and in second line treatment (in combination with fulvestrant) it is likely that similar improvement in overall survival will be seen with abemaciclib in combination with fulvestrant The improvement was even greater in patients with sensitivity to prior endocrine therapy, with an absolute improvement in median overall survival of 10.0 months. Median overall survival improved significantly by 11.5 months in patients without visceral disease. No new safety signals were observed with longer follow-up
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Patients who relapse on an aromatase inhibitor are currently excluded form treatment with CDK4/6 inhibitors and receive either endocrine therapy alone or chemotherapy Patients who don't relapse on an aromatase inhibitor receive treatment with CDK4/6 inhibitor in combination with aromatase inhibitor. Although many of these patients would be eligible for treatment with an aromatase inhibitor alone the absence of available CDK4/6 inhibitors in second line means that these patients currently receive CDK4/6 inhibitors as first line as otherwise they would be deprived access to these very effective and well tolerated treatments. Unfortunately there is variable access to fulvestrant in UK
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	ESMO ASCO NCCN

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway is well defined from an evidence and guideline perspective. There is variable access to some treatments across UK (and across England and wales). Opinion outside England in Europe and N America is reflected in ESMO and ASCO guidelines
• What impact would the technology have on the current pathway of care?	Improve treatment for patients currently denied CDK4/6 inhibitors Reduce first line use of CDK4/6 inhibitors in patients with more indolent metastatic breast cancer
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Abemaciclib is not currently available in NHs The other 2 CDK4/6 inhibitors are. Their funding requires use as first line therapy and therefore artificially changes the pathway for many patients as otherwise access is denied
• How does healthcare resource use differ between the technology and current care?	As above
• In what clinical setting should the technology be used? (For example,	Under supervision of systemic anti-cancer therapy specialist in breast cancer

primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The ever increasing number of treatments in metastatic breast cancer extends life and the burden of care in organisations there is already a shortage of oncologists to manage the burden of care for metastatic breast cancer
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes improved pfs and probably overall survival Reduced toxicity of treatment compared to chemotherapy Delay in need for chemotherapy
• Do you expect the technology to increase length of life more than current care?	Yes as above
• Do you expect the technology to increase health-related quality of life more than current care?	Yes as above

13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No sub-groups fared less well than others
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Generally easier as many of these patients would be receiving chemotherapy

15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Reduced in patient episodes as less chemotherapy required
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes A large number of patients will benefit from CDK4/6 inhibitor therapy that are currently denied these very effective drugs

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes No access to CDK4/6 inhibitors at the moment for a large proportion of patients with metastatic breast cancer
• Does the use of the technology address any particular unmet need of the patient population?	Yes as above
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The most common adverse events in the abemaciclib versus placebo arms were diarrhea (86.4% v 24.7%), neutropenia (46.0% v 4.0%), nausea (45.1% v 22.9%), and fatigue (39.9% v 26.9%). These are usually mild or moderate and easily managed with supportive measures and dose reduction They are side-effects that oncologists are familiar with
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes A sizeable proportion of patients have access to fulvestrant

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	PFS OVERALL SURVIVAL quality of life Objective response rate
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	PFS is a recognised important outcome for metastatic breast cancer Time to chemotherapy is also recognised as an important outcome quality of life is an impy outcome
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
20. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TTA503, TA496, TA495, TA421, TA239, TA116]?	Other CDK4/6 inhibitors have similar data
22. How do data on real-world experience compare with the trial data?	
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

23b. Consider whether these issues are different from issues with current care and why.	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your statement.

- Meaningful and clinically important improvement in progression free survival likely to improve overall survival
- Access to a ground breaking class of treatment currently denied to many patients with metastatic breast cancer
- Improved quality of life
- Easily managed side-effects
- Further strain on metastatic breast cancer services (workforce issues in NHS)

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Abemaciclib with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer after endocrine therapy [ID1339]

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- Your response should not be longer than 13 pages.

About you	
1. Your name	Prof Carlo Palmieri
2. Name of organisation	University of Liverpool and Clatterbridge Cancer Centre NHS Foundation Trust

3. Job title or position	Professor of Translational Oncology and Consultant Medical Oncologist
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To delay the time to disease progression.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	An increased in disease progression by at least 3-4 months would be considered clinically significant. Within MONARCH 2 the improvement in progression free survival seen with the addition of abemaciclib to fulvestrant as compared to placebo plus fulvestrant was 7.1 months and therefore in excess of this threshold.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there is a clear unmet need for both patients and healthcare professionals. ER-positive recurrent breast cancer when treated with endocrine therapy will eventually become resistant to such therapy. There is a clear need for the development and introduction of treatments which augment the efficacy of current endocrine therapies. Disease progression results in morbidity both physical and psychological, impacts the family and society, leads to a decline in functionality and quality of life as well as the use of chemotherapy which is more toxic and burdensome. Therefore, treatments which extend the period of time advanced breast cancer is controlled and which delays the need for chemotherapy would clinically be useful and relevant for patients, their family and society in general.

What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	ER-positive, HER-negative breast cancer (herein ER+ BC) is the most common subtype of breast cancer, representing around 70-80% of all cases diagnosed. Patients with metastatic ER+ BC are not curable and treatment would normally consist of sequential lines of endocrine therapy with or without targeted therapy and when the disease becomes resistant to endocrine therapy (with or without targeted therapy) would be followed by sequential single agent chemotherapy. Such treatments normally results in women living for many years and enables them to continue to contribute to society in an active and positive way despite their disease. Endocrine or hormone therapy is a cornerstone treatment of ER+ BC and such treatment aim to inhibit ER activity. Endocrine therapy includes SERMs (tamoxifen), which blocks the estrogen receptor; aromatase inhbitors (letrozole, anastraozole and exemestane) which lowers the levels of circulating estradiol and SERDs (fulvestrant) which increases the degradation of the oestrogen receptor. Bone metastasis are very common in patients with ER+ secondary BC and in such circumstances, patients would receive treatment with a bisphosphonates or a RANK ligand inhibitor to reduce the risk of skeletal related events. Palliative radiotherapy and other measures may also be used to ameliorate symptoms related to their disease. A holistic approach is key to the management of patients with secondary BC and such an approached should meet the physical, psychological and spiritual needs of the patient. Endocrine therapy would be the treatment of choice for women diagnosed with de novo metastatic ER+ BC as well as women who have been previously treated with adjuvant endocrine therapy. The choice of endocrine therapy for those women who have had early breast cancer, received adjuvant endocrine therapy and subsequently development recurrent disease would be defined by the period of time from cessation of their adjuvant endocrine therapy and the diagnosis of locally advanced/metastatic breast cancer. In the presence of so called ‘visceral crisis’ chemotherapy would normally be considered the treatment of choice which would then be followed by endocrine therapy. For women who relapse after one year from cessation of adjuvant endocrine therapy they would receive treatment with an aromatase inhibitor in combination with a CDK4/6 inhibitor in the form of palbociclib or ribociclib. Aromatase inhibitors can only be given to women who are post-menopausal. Therefore pre-menopausal women would have to be rendered post-menopausal

	either by oophorectomy or the administration of a gonadotropin-releasing hormone analogue (goeserlin) before they could be commenced on an aromatase inhibitor. Currently, in England a CDK4/6 inhibitor in combination with endocrine therapy is not available to patients who relapse on or within a year of neoadjuvant/adjuvant endocrine therapy with a non-steroidal aromatase inhibitor or who have received prior endocrine therapy for their locally advanced or metastatic breast cancer (Blueteq Approval Criteria, National Cancer Drugs Fund List, Ver1.110, 22nd Nov 2018). Currently, these patients would be treated with one of the following treatment options (1) Single agent endocrine therapy, options would include: exemestane, fulvestrant or tamoxifen; (2) Exemestane plus everolimus; (3) Single agent chemotherapy options would include weekly paclitaxel or capecitabine. However, recent publication of the PALOMA 3, MONARCH 2 and MONALEESA-3 studies supports the use of endocrine therapy with a CDK4/6 inhibitor for patients who relapse on or shortly after (neo)adjuvant endocrine therapy or on first line endocrine therapy. **MONARCH 2** MONARCH 2 (Sledge et al., J Clin Oncol 35:2875-2884) recruited postmenopausal women with ER+ BC who developed recurrent disease while receiving neoadjuvant or adjuvant endocrine therapy or ≤12 months after adjuvant ET or who were receiving first line endocrine therapy for their recurrent disease. Women were randomised to abemaciclib with fulvestrant or placebo plus fulvestrant. The addition of abemaciclib to fulvestrant significantly improved the progression free survival in patients with hormone positive recurrent breast cancer (hazard ratio, 0.553; 95% CI, 0.449 to 0.681; P <0.001), with the PFS increasing from 9.3 months with placebo plus fulvestrant to 16.4 months with abemaciclib plus fulvestrant.. The most common adverse events (any grade) in the abemaciclib versus placebo arms were diarrhoea (86.4% v 24.7%), neutropenia (46.0% v 4.0%), nausea (45.1% v 22.9%), and fatigue (39.9% v 26.9%). In contrast to other CDK4/6 inhibitors, the most common adverse event in MONARCH 3 was diarrhoea. At study initiation, abemaciclib was administered at a dose of 200 mg twice daily. After a review of safety data and dose reduction rates, the protocol was amended to reduce the starting dose to 150 mg for new trial participants and all participants who were receiving 200 mg underwent a mandatory dose reduction to 150 mg. This change led to a reduction in discontinuation rates (pre-/post-amendment: 6.6% vs 1.6%) as well

	as grade 2 and 3 diarrhoea (pre-/post-amendment: 62.8% vs 38.5%). Diarrhoea occurred early and was managed with dose adjustments and antidiarrheal medication (Sledge et al., ASCO 2018). Neutropenia is a class effect and seen with all CDK4/6 inhibitors however severe neutropenia is more infrequent with abemaciclib as compared to palbociclib and ribociclib. As with the others this neutropenia rarely manifested clinically within MONARCH 2 febrile neutropenia was very rare observed in only 6 of 441 cases. It was reported of these six cases that one patient had grade 2 afebrile neutropenia which was miscoded as febrile neutropenia, and another patient had febrile neutropenia 53 days after discontinuing abemaciclib and had received paclitaxel before the reported event. **PALOMA 3** The PALOMA 3 trial (Turner et al., NEJM 2015; 373:209-219) recruited women who had progressed during or within 12 months after the completion/discontinuation of adjuvant endocrine therapy or had disease progression in the advanced disease setting during prior aromatase inhibitor therapy. Study participants were randomised women to palbociclib in combination with fulvestrant versus placebo plus fulvestrant. A significant improvement in progression-free survival was demonstrated with the addition of palbociclib (9.2 versus 3.8 months, P < 0.001). There are differences between PALOMA-3 and MONARCH-2 which should be noted. MONARCH-2 did not allow prior chemotherapy for advanced disease while PALOMA-3 allowed up to one line. Only one prior line of endocrine therapy was allowed within MONARCH-2 but any number were allowed within PALOMA-3. Of note, in both studies pre- or perimenopausal women were recruited and received a gonadotropin-releasing hormone agonist. **MONALEESA 3** The MONALEESA 3 (J Clin Oncol 2018; 36:2465-2472) randomised patients to ribociclib plus fulvestrant versus placebo plus fulvestrant. The was a significant improvement in progression-free survival with the addition of ribociclib to fulvestrant (20.5 versus 12.8 months; P <0.001). of note, inclusion criteria of MONALEESA 3 were more broader as compared to MONARCH 2 and PALOMA 3 with regard to prior adjavunt endocrine therapy with women who had relapsed on or within 12 months of adjuvant endocrine as

	well women who had relapsed >12 months since completion of adjuvant endocrine therapy being eligible for study entry. MONARCH 2, PALOMA 3 and MONALEESA-3 demonstrate the clinical benefit of adding a CDK4/6 inhibitor to a fulvestrant in the treatment of ER+ advanced breast cancer. This use of abemaciclib would be consistent with current UK based practice iwhere fulvestrant is currently funded and available.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes. These include NICE guidance on advanced breast cancer: diagnosis and treatment (CG81), which recommends first-line treatment with endocrine therapy for most people with advanced hormone receptor-positive breast cancer. More recently, NICE technology appraisals 495 and 496 recommended palbociclib and ribociclib with an aromatase inhibitor for treating hormone receptor positive, HER2-negative, locally advanced or metastatic breast cancer as initial endocrine based therapy. Fulvestrant was not recommended by NICE, within its marketing authorisation, for treating locally advanced or metastatic oestrogen-receptor positive breast cancer in postmenopausal women who have not had endocrine therapy before (technology appraisal 503) or for postmenopausal women whose cancer has relapsed on or after adjuvant anti-oestrogen therapy, or who have disease progression on anti-oestrogen therapy (technology appraisal 239). International guidelines are also available and often referred to such as Breast cancer 4th ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4) (Cardoso et al., Ann Oncol 2018; 29: 1634–1657).
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	In general the pathway of care is well defined and in practice relatively uniform across the UK. However, patients with locally advanced and metastatic breast cancer are widely distributed between secondary and tertiary units and in some centres treating clinicians are treating multiple tumour types. Opinions can vary amongst oncologists in some cases with regard to the use of endocrine therapy with or without a targeted agent versus chemotherapy. There is some variability in the pathway of care given the access to fulvestrant is not uniform.

• What impact would the technology have on the current pathway of care?	The introduction of abemaciclib would have a positive impact on the current pathway of care for patients who develop recurrent disease on or within 12 months of (neo)adjuvant or who progress on first line single agent AI. These patients currently do not have access to a CDK4/6 inhibitor. If the current technical appraisal were to be positive it would result in CDK4/6 inhibitors being available as a treatment option in the first or second line setting for ER+ locally advanced/metastatic breast cancer and may lead to an evolution of the current pathway of care and a more nuanced approach to how CDK4/6 inhibitors are used by the clinical community.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	The use of healthcare resource with abemaciclib plus fulvestrant would be more involved than using endocrine therapy alone, less than chemotherapy and on balance similar to exemestane and everolimus.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Abemaciclib should be administered in secondary/tertiary care by an oncologist who has expertise in the management of breast cancer, experienced in the use of CDK4/6 inhibitors, and in managing their side effects with dose delays, interruptions or reductions as required.
• What investment is needed to introduce the technology? (For	Investment would be needed in terms of the provision of fulvestrant where it is not currently available. The clinical community has had access to CDK4/6 inhibitors for a while now via clinical trials, open access schemes and more widely since the positive appraisal by NICE of palbociclib and ribociclib (NICE technology appraisals 495 and 496), and therefore the necessary expertise exists with regard to managing the common

example, for facilities, equipment, or training.)	side effects seen with these agents such as neutropenia. Some additional training would be needed with regard to the diarrhoea seen with abemaciclib, however this is not a significant issue and will not be a barrier to its use. The clinical community is already use to managing diarrhoea seen with systemic anticancer agents eg capecitabine.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes given the significant improvement in progression free survival seen within MONARCH 2.
• Do you expect the technology to increase length of life more than current care?	Sequential improvements in treatments in this patient group are likely to be translated into increase in the length of life for this patient group. Although there is no published data as yet with regard to overall survival from MONARCH 2. Recent data from PALOMA 3 has shown an absolute increase in overall survival by 6 months although this did not reach statistical significance (34.9 months (95% CI]: 28.8 to 40.0) palbociclib–fulvestrant group and 28.0 months (95% CI, 23.6 to 34.6) placebo–fulvestrant group (HR, 0.81; 95% CI, 0.64 to 1.03; P=0.09) (Turner et al., N Engl J Med 2018; 379:1926-1936).
• Do you expect the technology to increase health-related quality of life more than current care?	Although the initial presentation of health related quality of life data within MONARCH-2 showed no significant differences as measured by EORTC QLQ-C30 and BR23 subscales and mBPI-sf within MONARCH2 (Kaufman et al., JCO 36, no.15 suppl (May 2018) 1049-1049), it is anticipated that delaying progression and the need for chemotherapy will lead to an improvement in quality of life.
13. Are there any groups of people for whom the technology would be more or	This treatment has been tested in both pre- and post-menopausal women with advanced hormone positive, HER2-negative breast cancer. In particular MONARCH 2 included two groups of patients (1) those progressing while receiving first-line ET for metastatic disease and (2) those who progressed while receiving neoadjuvant or adjuvant endocrine therapy (ET), <12 months from the end of adjuvant ET. Therefore, treatment with abemaciclib plus fulvestrant could be a second-line metastatic treatment option (after first-

less effective (or appropriate) than the general population?	line metastatic endocrine therapy) or a first-line metastatic treatment option (directly after adjuvant or neoadjuvant endocrine therapy). This treatment is likely to benefit a significant number of metastatic breast cancer patients given ER-positive, HER2 negative breast cancer is the largest group within the breast cancer population.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The use of abemaciclib in terms will be more involved than using endocrine therapy alone, less involved than chemotherapy and on balance similar of complexity to exemestane and everolimus. In common with palbociclib and ribociclib the use of abemaciclib would need closer monitoring with blood tests (as compared to endocrine therapy alone) particularly with regard to neutropenia. Blood tests are required 2 weekly for the first two months and monthly thereafter and would entail some extra visits. For the first month this would align with fulvestrant injections and thereafter monthly. Bone metastasis are common in ER-positive metastatic breast cancer and these patients would be seen on day unit or within clinic on a monthly basis for denosumab or a bisphosphonate with blood tests,. Therefore, after the initial two months of treatment the addition of abemaciclib would not involve additional visits. As indicted the clinical community is now well versed in managing issues related to neutropenia this issue. While neutropenia is frequent, the sequela of febrile neutropenia is rare within MONARCH 2 (6 cases in 446 patients). Supportive treatment with G-CSF is not used for neutropenia related to CDK4/6 inhibition. This should be contrasted with the febrile neutropenia seen with chemotherapy induced neutropenia. Patients on abemaciclib also require ALT and AST monitoring prior to starting abemaciclib therapy, every two weeks for the first two months, monthly for the next two months, and then as clinically indicated (similar to ribociclib). No ECG monitoring is required as with ribociclib. Diarrhoea is associated with abemaciclib and requires monitoring and management with the use of loperamide, dose delay or dose reduction.

	Given abemaciclib will be being utilised in centres using chemotherapy there should be not be any practical issues with regard to its prescribing or handing.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The initiation of abemaciclib plus fulvestrant treatment would be based on the population included in the pivotal phase III trial, MONARCH 2. There are well recognised criteria for managing toxicity with CDK4/6 inhibitors including abemaciclib and these include stopping if there are unmanageable toxicity or ongoing issues despite dose reductions In addition, disease progression would result in the treatment being stopped.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Abemaciclib is an inhibitor of cyclin-dependent kinases 4 and 6. This class of agent is an innovative therapy both in terms of its mechanism of action and the significant improvement in progression free survival which provides clear evidence that targeting this pathway in combination with fulvestrant is effective in controlling disease. The introduction of these agents into the management of ER-positive breast cancer has been the biggest recent innovation in the management of this patient group. CDK4/6 inhibitors have been made available to a patients with recurrent ER-positive breast cancer in the first line setting as per NICE technology appraisals 495 and 496. However, the population included with MONARCH2 are unable to access CDK4/6 inhibitor.

improve the way that current need is met?	Abemaciclib is currently the only CDK 4/6 inhibitor to allow continuous dosing. This may present some advantages to patients with regard to ease of use of and compliance. At the recommend initiation dose abemaciclib has a similar pill burden per dose to palbociclib (one tablet) and lower as compared to ribociclib (three tablets). Although abemaciclib is twice daily dosing compared to the once daily dosing with palbociclib and ribociclib.
• Is the technology a 'step-change' in the management of the condition?	Yes the introduction of abemaciclib would be a significant step change.
• Does the use of the technology address any particular unmet need of the patient population?	Yes it does. Resistance to endocrine therapy in the advanced disease setting is a major clinical issue. Abemaciclib extends the period of time that disease is controlled as compared to endocrine therapy alone and as such will delay the need/initiation of chemotherapy. This is important for patients given all the squeal associated with chemotherapy.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	As described above in section 14.
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Fulvestrant was not recommended by NICE, within its marketing authorisation, for treating locally advanced or metastatic oestrogen-receptor positive breast cancer in postmenopausal women who have not had endocrine therapy before (technology appraisal 503) or for postmenopausal women whose cancer has relapsed on or after adjuvant anti-oestrogen therapy, or who have disease progression on anti-oestrogen therapy (technology appraisal 239). However, in the UK some units do have access to fulvestrant and therefore access is not equitable. This inequitable access is well known but difficult to accuracy quantify. Therefore, the control arm within MONARCH 2 is in part reflective of current UK clinical practice. Clinicians within those centres where fulvestrant is not available would consider fulvestrant an appropriate treatment option as utilised within MONARCH 2. In those centres where fulvestrant is not available therapeutic options would include single agent endocrine therapy such as exemestane or tamoxifen, exemestane in combination with everolimus or single agent chemotherapy such as capecitabine.
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important finding within MONARCH 2 is the significant improvement in progression free survival which increased from a median of 9.3 months (placebo arm) to 16.4 months (Abemaciclib arm).
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not	No

apparent in clinical trials but have come to light subsequently?	
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TTA503, TA496, TA495, TA421, TA239, TA116]?	No
22. How do data on real-world experience compare with the trial data?	Im not aware of any real world experience data.
Equality	

23a. Are there any potential equality issues that should be taken into account when considering this treatment?	Currently, there is an equity issue given some patients can access fulvestrant while other can not depending on the centre where they receive their care. Therefore, if the current technical appraisal was positive and both agents were made available it would in part help end this inequity.
23b. Consider whether these issues are different from issues with current care and why.	As noted above there is an equity issue in the accessing of fulvestrant.

Key messages

24. In up to 5 bullet points, please summarise the key messages of your statement.

- Abemaciclib is an innovative agent with a significant improvement in progression free survival data based on MONARCH 2
- The introduction of abemacilib in combination with fulvestrant would benefit a large proportion of patients given ER-positive breast cancer forms 70-80% of the breast cancer population.
- In the treatment of patients who recur on or very shortly after adjuvant endocrine therapy or on first line endocrine therapy it would help delay the time to initiation of chemotherapy and all its concomitant issue.
- .Abemaciclib is given orally, and is simple for patients to take given its daily dosing. It is arelatively easy to use medication. There would be no major implementation issues.
- There are some additional side effects as compared to fulvestrant alone but these are manageable.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Patient expert statement

Abemaciclib with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer after endocrine therapy [1339]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Holly Heath**
2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ a carer of a patient with the condition?

	☒ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	Breast Cancer Now
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☒ yes

Thank you for your time.

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NICE National Institute for Health and Care Excellence

National Institute for Health and Care Excellence

Cancer Drugs Fund Clinical Lead statement

Abemaciclib plus fulvestrant in ER pos HER-2 neg advanced breast cancer [ID1339]

Background

1. The aim of palliative treatment for hormone receptor positive HER-2 receptor negative patients with advanced (and thus incurable) breast cancer is to maximise quality of life and length of life for as long as possible. Hormone therapies for such patients are generally used in sequence and are worked as hard as possible to extract the maximal benefit to patients before various types of chemotherapy then come into consideration. The exception to this rule would be those patients with potentially life-threatening metastatic visceral disease (eg bulky liver secondaries, symptomatic pulmonary spread) in whom chemotherapy is used first as it works more quickly; patients then commence hormone therapy after completion of chemotherapy in an effort to prolong the progression free interval. One of the bonuses to patients of responding to sequential hormone therapies is that the consideration of chemotherapy is delayed for as long as possible.

2. As a general rule, the longer a previous hormone treatment has worked in advanced breast cancer or the longer the time since adjuvant hormone therapy was discontinued before subsequent relapse, the higher the chance of responding and the greater the likely duration of response will be for subsequent hormone therapy.

3. Any new hormone treatment or any combination which increases the efficacy of hormone treatment is welcome as this is likely to increase the duration of maintained quality of life and also delay the consideration of chemotherapy.

The treatment pathway

4. In the current advanced breast cancer treatment pathway, various CDK4/6 inhibitors (eg palbociclib, ribociclib, potentially abemaciclib) have been recommended by NICE as treatment options for use in combination with an aromatase inhibitor. The evidence base for these recommendations and thus adoption by NHS England is in hormone receptor positive HER-2 receptor negative advanced breast cancer patients who are either completely hormone therapy naïve (ie first presentation with breast cancer was with advanced disease) or have relapsed after previous adjuvant aromatase inhibitor therapy as long as there has been a disease-free interval of ≥12 months since completion of adjuvant aromatase inhibitor therapy.

5. This appraisal is centred on the use of abemaciclib plus fulvestrant in hormone receptor positive HER-2 receptor negative advanced breast cancer patients who have progressed either on first line aromatase inhibitor therapy for advanced disease or within 12 months of neoadjuvant/adjuvant therapy with hormone therapy. It thus complements the above use of CDK4/6 inhibitors in combination with an aromatase inhibitor in the treatment pathway as it offers an additional option for patients who currently cannot access a CDK4/6 inhibitor plus aromatase inhibitor combination.

Comparators for abemaciclib plus fulvestrant

6. NHS England agrees that the comparators for abemaciclib plus fulvestrant in this appraisal are everolimus plus exemestane, exemestane monotherapy and tamoxifen monotherapy.

7. NICE did not recommend fulvestrant monotherapy as an alternative to aromatase inhibitors in postmenopausal women whose cancer had relapsed on or after anti-oestrogen therapy or whose advanced breast cancer had progressed on anti-oestrogen therapy (TA 239). (Nor did

NICE recommend fulvestrant as 1st line therapy for advanced breast cancer in TA503). The breast cancer pathway has changed substantially since the TA239 appraisal with much greater and earlier use of aromatase inhibitors than tamoxifen. One could therefore argue that the outcome of this TA239 appraisal does not rule out fulvestrant monotherapy as a comparator at least for patients who are naïve to anti-oestrogen agents. Nevertheless, the outcome of TA239 is such that in most parts of England, the use of fulvestrant monotherapy is not commissioned for patients failing hormone therapy for advanced breast cancer and this non-commissioning of such fulvestrant use is increasing as commissioners focus on ensuring that NICE negative recommendations are not commissioned. NHS England does not therefore regard fulvestrant monotherapy as a comparator in this appraisal of abemaciclib plus fulvestrant.

Commissioning of hormonal therapy for breast cancer and administration of fulvestrant

8. A complication of any funding for fulvestrant is that it is funded by CCGs and not by NHS England Specialised Commissioning (unlike the funding of abemaciclib which comes from Specialised Commissioning). This CCG funding of hormonal therapies has contributed to the variability in access to fulvestrant monotherapy in advanced breast cancer patients who have failed other hormone therapies.

9. A further issue is that fulvestrant is an hormonal therapy and thus is not excluded from tariff (unlike all chemotherapy and other systemic therapies for cancer). This means that if Trusts administer fulvestrant they have to fund the fulvestrant injections themselves (£522 for every month bar the first month when the cost is £1044) yet they would only be paid the appropriate tariff fee for an attendance for an injection

(<£100 for every month bar the first month). The income from this tariff is thus much less than the cost of fulvestrant and hence prescribers such as hospitals have to bear the majority of the drug cost of fulvestrant. Trusts are thus increasingly wary of doing so given the financial pressures in secondary care. In addition, fulvestrant monotherapy for progressed advanced breast cancer is currently not given for most patients for very long periods as such monotherapy is not very effective and hence the additional unrecovered cost of fulvestrant to hospitals is modest in this indication. However this would not be the case for fulvestrant in combination with abemaciclib as the duration of treatment with fulvestrant is so much greater (mean [redacted] months as stated in the NICE pre-meeting briefing).

10. Primary care is unlikely to accept the responsibility for prescribing fulvestrant without a shared care agreement in place and after appropriate training and also without an additional payment as it would be considered an enhanced service. If NICE recommends abemaciclib in combination with fulvestrant, the hospital or GP prescribing of fulvestrant would need to be discussed at Area Prescribing Committees as to whether it would be most appropriate to administer fulvestrant in primary or secondary care. Most secondary care providers will be content to commence fulvestrant but not to continue it for reasons outlined above.

11. Fulvestrant administration requires two slow 5 ml injections to be given as deep intramuscular injections, one into each buttock on a 4-weekly basis (apart from an additional treatment after 2 weeks in the first month of treatment). Care therefore needs to be taken when injecting fulvestrant at the dorsogluteal site due to the proximity of the sciatic nerve. Although fulvestrant is tolerated well by patients from the side effect point of view, it does have this disadvantage as to how it is administered. Nevertheless, in a treatment pathway in which chemotherapy may not be very far away for some patients, the vast

majority of patients would accept the inconvenience and discomfort of a pair of monthly intramuscular injections in their buttocks as the price for delaying the onset of chemotherapy.

12. NHS England notes that at least one generic fulvestrant formulation has received CHMP approval although the timing of availability of these has been the subject of recent legal action in Europe. It seems that generic availability of fulvestrant will not occur in Europe until 2020/21.

Clinical trial data for the use of abemaciclib plus fulvestrant

13. NHS England notes that the efficacy data presented by Lilly for this appraisal is from a data cut in February 2017. NHS England is disappointed that there are no more up to date results for overall survival for NICE to consider especially since despite the clear difference in progression free survival, the data cut in February 2017 showed no significant difference in survival, albeit with only 20% of patient events in the survival analysis. NHS England is surprised that there have not been more recent data analyses for overall survival.

14. NHS England notes that a post hoc analysis of the time to chemotherapy was longer in the abemaciclib plus fulvestrant arm as compared to placebo plus fulvestrant . The hazard ratio was 0.61 but medians were not presented. Although this is a post hoc analysis, it is still very clinically relevant and hence NHS England is disappointed that no further data is provided other than this hazard ratio.

15. NHS England notes that even at the 150mg twice daily dose of abemaciclib, [redacted] of patients had to reduce the dose of abemaciclib and [redacted] had dose reductions due to neutropenia although there were few discontinuations of treatment for these toxicities. These are clinically relevant dose reductions especially as regards the degree of clinical monitoring that is involved in order to ensure that the

treatment is safe. NHS England notes that the monthly cost of abemaciclib medication remains the same even on significant dose reductions ie lower doses cost just the same as starting doses.

Specific issues in this appraisal of clinical and cost effectiveness of abemaciclib plus fulvestrant

16. NHS England agrees with the ERG that the company's network meta-analysis suffers from very great heterogeneity as a consequence of inclusion of trials carried out over a wide time frame and in which differing patients were treated with differing previous hormonal treatments, differing previous chemotherapies and differing adjuvant therapies. NHS England also agrees with the ERG that the outputs of the company's polynomial network meta-analysis produce some wholly implausible consequences eg a very significant proportion of patients with advanced breast cancer being cured with abemaciclib plus fulvestrant in terms of never progressing, eg the PFS curve crossing the OS curve in some scenarios. The ERG's fractional polynomial method produces much more clinically plausible results.

17. NHS England shares the ERG's assessment of treatments used post abemaciclib in that there will be significant use of tamoxifen, no bevacizumab use but greater paclitaxel use.

18. NHS England notes that the ERG assumed that 32% of fulvestrant would be given in primary care and 68% in hospitals. For reasons outlined above, hospitals may be reluctant to do anything but start treatment with fulvestrant. As has been stated above too, it may take a considerable time for any widespread prescribing and administration of fulvestrant to occur in primary care.

19. NHS England notes the high weekly costs used in the economic models for administering abemaciclib plus fulvestrant as well as the weekly costs of the various comparators. The administration of

abemaciclib or of everolimus would attract the monthly chemotherapy SB11Z 2018/19 tariff which is £120 but no other comparator would attract this payment. The 2018/19 tariff for a medical oncology outpatient attendance on a monthly basis is £105. All patients would attract this tariff but few patients would require monthly attendance after the first few visits. However these two tariffs are combined, they do not match the high weekly costs used for all the treatment options in the economic models.

Commissioning perspective

20. If NICE was to recommend the combination of abemaciclib and fulvestrant in this indication, this would be an additional option to the current treatment pathway as fulvestrant monotherapy is not recommended by NICE and is not commissioned in most of and increasing parts of England. Since many patients with progressing advanced breast cancer who are at the place in the treatment pathway sought by Lilly do not have life-threatening visceral disease, these patients will still have sequential hormonal therapies after failure of abemaciclib and fulvestrant ie the options of everolimus plus exemestane, exemestane monotherapy and tamoxifen remain in the treatment pathway. The same applies to any comparison of abemaciclib plus fulvestrant with capecitabine chemotherapy as capecitabine would be a valuable treatment option after disease progression in a patient pathway that included previous abemaciclib plus fulvestrant.

21. If NICE was to recommend the option of the combination of abemaciclib plus fulvestrant in patients who have progressed either after 1st line endocrine therapy for advanced breast cancer or progressed during adjuvant hormone therapy or within 12 months of completing adjuvant hormone therapy, NHS England will not

commission this combination in patients who have previously received CDK4/6 inhibitors in combination with aromatase inhibitors. This is because there is no evidence base for such use and there is strong biological plausibility that the clinical effectiveness of such use would be much less than seen in the MONARCH 2 trial and thus the cost effectiveness would be much worse.

Generalisability of the MONARCH 2 trial to NHS practice

22. NHS England notes that the difference in median progression free survival with abemaciclib plus fulvestrant versus fulvestrant (16.4 vs 9.3 months) is very clinically worthwhile. The median values seen in the palbociclib plus fulvestrant versus fulvestrant trial (9.2 vs 3.8 months) are less whereas those in the ribociclib plus fulvestrant versus fulvestrant trial (20.5 vs 12.8 months) are similar/slightly greater than those observed in MONARCH 2. Breast cancer clinicians consider abemaciclib, palbociclib and ribociclib to be equally efficacious. These apparent differences in the above trials are most likely to be related to the inclusion/exclusion criteria of the trials concerned. For example, the abemaciclib trial excluded patients previously treated with chemotherapy for advanced breast cancer and also excluded patients treated with more than 1 line of endocrine therapy for advanced disease whereas the palbociclib trial did neither. The ribocilib trial included patients more in keeping with the abemaciclib trial. The consequence of these cross trial comparisons and the evidence base for abemaciclib plus fulvestrant is that the degree of benefit in the trial is only likely to be achieved in the NHS if access in NHS England mirrors the key inclusion criteria of the abemaciclib trial: patients who have progressed on (neo)adjuvant hormone therapy or progressed within 12 months of completing

adjuvant therapy or progressed on 1st line endocrine treatment for advanced breast cancer.

23. NHS England also notes that MONARCH 2 only included patients of ECOG performance status 0 or 1 whereas in clinical practice in this place in the treatment pathway there will be a significant proportion of patients who are of performance status 2. NHS England currently commissions CDF4/6 inhibitors in combination with an aromatase inhibitor in patients of performance status 0-2 and would plan to do the same for abemaciclib plus fulvestrant. NHS England considers it likely that abemaciclib plus fulvestrant would be reasonably tolerated by patients of ECOG performance status 2.

Implementing a positive NICE recommendation

NICE recognises that in the event of a positive recommendation, more prescriptive clinical commissioning criteria for treatments commissioned via Specialised Services will be implemented by NHS England to ensure appropriate use within the NHS.

NHS England is responsible for ensuring that the final clinical commissioning criteria are aligned with final guidance (section 1 – recommendation and section 3 – committee discussion).

Draft commissioning criteria

24. If abemaciclib in combination with fulvestrant for treating patients with hormone receptor positive HER-2 receptor negative advanced/metastatic breast is recommended for use within its marketing authorisation, NHS England proposes to use the following commissioning treatment criteria:

- Patients must have hormone receptor positive and HER-2 negative advanced/metastatic breast cancer
- Use of abemaciclib plus fulvestrant is in patients who have progressed on neoadjuvant or adjuvant hormone therapy for early breast cancer with no subsequent endocrine therapy received following progression **or** progressed within 12 months of completing adjuvant hormone therapy for early breast cancer with no subsequent endocrine therapy received following progression **or** progressed on 1st line hormone therapy (with anti-oestrogen or aromatase inhibitor therapy) for advanced/metastatic breast cancer with no subsequent endocrine therapy received following progression
- If patients are female, then they must be functionally postmenopausal
- Patients must have an ECOG performance status of 0 or 1 or 2
- No prior treatment with any CDK4/6 inhibitor
- No prior treatment with everolimus
- No prior treatment with fulvestrant
- Abemaciclib must only be given in combination with fulvestrant
- Patients will continue treatment until loss of clinical benefit or excessive toxicity or patient choice to discontinue treatment, whichever is the sooner

If this technology is recommended for routine commissioning in a subpopulation or with certain specifications (for example, a treatment continuation rule), the final commissioning criteria will reflect these conditions.

Issues for discussion

25. The 4.1 SPC wording for the marketing authorisation for abemaciclib is broad and is phrased thus: abemaciclib is indicated for the treatment of women with hormone receptor positive, HER-2 receptor negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy or in women who have received prior endocrine therapy. This wording is despite the fact that the only evidence base 'for initial endocrine-based therapy' is with abemaciclib in combination with an aromatase inhibitor and the only evidence base for use in people 'who have received prior endocrine therapy' is with abemaciclib in combination with fulvestrant. The company has recognised this patient pathway issue, applied the distinction between these two evidence bases and two wordings in the marketing authorisation and chosen the appropriate comparators relevant to the treatment pathway. If NICE recommends the combination of abemaciclib plus fulvestrant, NHS England would wish to see this recommendation optimised to patients who have progressed on neoadjuvant or adjuvant hormone therapy with no subsequent endocrine therapy received following progression or progressed within 12 months of completing adjuvant therapy with no subsequent endocrine therapy received following progression or progressed on 1st line endocrine treatment for advanced breast cancer with no subsequent endocrine therapy received following progression.

26. Men can get breast cancer yet the marketing authorisation states that it is only licensed in women. Fulvestrant is known to be active in male breast cancer and there is no biologically plausible reason why men would not benefit from the combination of abemaciclib plus fulvestrant. NHS England would wish that that any NICE recommendation for abemaciclib plus fulvestrant resulted in access to men as well as women.

Equality

27. The issue of equality of access to both women and men of any positive NICE recommendation has been dealt with in paragraph 26..

Author

Professor Peter Clark, NHS England Chair of Chemotherapy Clinical Reference Group and National Clinical Lead for the Cancer Drugs Fund

January 2019

Abemaciclib with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer after endocrine therapy

STA REPORT

This report was commissioned by the NIHR HTA Programme as project number 17/141/03

BMJ Technology Assessment Group

Title: Abemaciclib with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer after endocrine therapy

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Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Charlotta Karner	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, background and clinical results sections
Kayleigh Kew	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and assisted with drafting the clinical results sections
Mariana Bacelar	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Gemma Marceniuk	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

All authors read and commented on draft versions of the ERG report.

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TABLE OF ABBREVIATIONS

Abbreviation	In full	Abbreviation	In full
aBC	Advanced breast cancer	IA	Investigator-assessed
ABE	Abemaciclib	ICER	Incremental cost-effectiveness ratio
AE	Adverse event	IHC	Immunohistochemistry
AFT	Accelerated failure time	IM	Intramuscular
AI	Aromatase Inhibitor	INV	Investigator
ALT	Alanine aminotransferase	IPD	Individual patient data
ANAS	Anastrozole	IQR	Interquartile range
ASCO	American Society of Clinical Oncology	IRC	Independent review committee
AST	Aspartate aminotransferase	ISH	In-situ hybridisation
BEV	Bevacizumab	ITT	Intent-to-treat
BIM	Budget Impact Model	IWRS	Interactive web-based randomisation scheme
BNF	British National Formulary	IXA	Ixabepilone
BOR	Best overall response	KM	Kaplan-Meier
BPI	Brief pain inventory	LHRH	Luteinising hormone-releasing hormone
BSA	Body surface area	LS	Least squares
BSC	Best supportive care	LTZ	Letrozole
CAP	Capecitabine	LY	Life year
CBR	Clinical benefit rate	LYG	Life years gain
CDK	Cyclin-dependent kinase	MAA	Marketing Authorisation Applications
CE	Cost-effectiveness	mBC	Metastatic breast cancer
CI	Confidence interval	mBPI-sf	Modified Brief Pain Inventory- short form
CONSORT	Consolidated Standards of Reporting Trials	MGA	Megestrol acetate
CRD	Centre for Reviews and Dissemination	MRI	Magnetic resonance imaging
CrI	Credible interval	NA	Not available/applicable
CSF	Colony stimulating factor	Nab	Nanoparticle albumin-bound
CSR	Clinical study report	NCCN	National Comprehensive Cancer Network
CTCAE	Common Terminology Criteria for Adverse Events	NMA	Network meta-analysis
CYC	Cyclophosphamide	NMB	Net monetary benefit
CYP3A4	Cytochrome P4503A	NR	Not reported
DCR	Disease control rate	NSAI	Non-steroidal aromatase inhibitor
DFI	Disease-free interval	OR	Odds ratio
DNA	Deoxyribonucleic acid	ORR	Objective response rate
DOC	Docetaxel	OS	Overall survival
DoR	Duration of response	PAC	Paclitaxel
DOX	Doxorubicin	PBO	Placebo
DSA	Deterministic sensitivity analysis	PD	Progressive disease
DSU	Decision Support Unit	PET	Positron emission tomography
DVT	Deep vein thrombosis	PFS	Progression-free survival
ECG	Electrocardiogram	PgR	Progesterone receptor
ECOG	Eastern Cooperative Oncology Group	PH	Proportional hazards
EMA	European Medicines Agency	PPS	Post-progression survival
eMIT	Electronic market share information tool	PR	Partial response
EORTC	European Organisation for Research and Treatment of Cancer	PROs	Patient-reported outcomes
EPAR	European Public Assessment Reports	PS	Performance status
EPI	Epirubicin	PSA	Probabilistic sensitivity analysis
EQ-5D-5L	EuroQol 5-Dimension 5-Level	PSS	Personal Social Services
ER	Oestrogen receptor	PSSRU	Personal Social Services Research Unit
ERI	Eribulin	Q12H	Every 12 hours
ESMO	European Society of Medical Oncology	QALY	Quality adjusted life year
ESO	European School of Oncology	QAPFW	Quality-adjusted progression free weeks
ET	Endocrine therapy	QAPFY	Quality-adjusted progression free years
EVE	Everolimus	RB	Retinoblastoma
FACT-B	Functional Assessment of Cancer Therapy - Breast Cancer	RCT	Randomised controlled trial
FE	Fixed effect	RDI	Relative dose intensity
FLU	fluorouracil	RE	Random effects
FSH	Follicle stimulating hormone	RECIST	Response Evaluation Criteria in Solid Tumors
FUL	Fulvestrant	SAE	Serious adverse event
G-CSF	Granulocyte-colony stimulating factor	sb	Solvent-based
GEM	Gemcitabine	SERD	Selective oestrogen receptor degrader
GP	General Practitioner	SERM	Selective oestrogen receptor modulator

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company of abemaciclib (Verzenios©; Eli Lilly & Company Limited [Lilly]) submitted to the National Institute for Health and Care Excellence (NICE) clinical and economic evidence in support of the effectiveness of abemaciclib in combination with fulvestrant (ABE-FUL) in the treatment of women with hormone-receptor positive (HR+) and human epidermal growth factor receptor 2 negative (HER2–) advanced breast cancer (aBC).

Abemaciclib, is a small molecule inhibitor of cyclin-dependent kinase (CDK)4 and CDK6. It was granted marketing authorisation in October 2018 for the treatment of women with HR+/HER2– aBC in combination with an aromatase inhibitor (AI) or fulvestrant as initial endocrine therapy (ET), or in women who have received prior ET.

The final scope issued by NICE specifies two population of interest to this appraisal: people with HR+/HER2- aBC who are either 1) untreated in the advanced setting, or 2) who have progressed after prior ET. The populations in the scope are in line with the population specified in the marketing authorisation for abemaciclib but these are slightly different from the population in the clinical evidence presented in the company's submission (CS). The clinical evidence presented is derived from the key trial, MONARCH 2, designed to evaluate the efficacy and safety of ABE-FUL in women with HR+/HER2− aBC who had progressed while receiving (neo)adjuvant ET, ≤ 12 months from the end of adjuvant therapy, or while receiving first-line ET in the advanced setting, that is, people who are defined as having ET-resistant disease. The trial population of MONARCH 2, therefore, falls into the second population specified in the scope (people who have had prior ET) as well as being a subset of the first population in the scope (people untreated in the advanced setting). However, it does not include people with ET-naïve or ET-sensitive aBC, that is, *de novo* advanced disease and people who progressed > 12 months from completion of ET in the (neo)adjuvant setting, who also form part of the first population in the scope. The ERG's clinical experts agree with the company that ABE-FUL would be used for people who have progressed after prior ET and that it isn't relevant for people in the advanced setting who are ET-naïve or ET-sensitive. Thus, the ERG agrees with the company to focus on ABE-FUL for people with ET-resistant HR+/HER2− aBC.

At the initiation of MONARCH 2, patients in the ABE-FUL group received a daily dose of 400 mg abemaciclib. After a review of preliminary safety data and dose reduction rates, the protocol was amended to reduce the daily dose of abemaciclib to 300 mg. Following this, the recommended dose of abemaciclib is one 150 mg oral tablet twice daily on a 28-day cycle. The recommended dose of fulvestrant is 500 mg given as an intramuscular injection at intervals of one month, with an additional

500 mg dose given two weeks after the initial dose. Abemaciclib in combination with fulvestrant should be taken continuously as long as the patient is deriving clinical benefit or until unacceptable toxicity.

The comparators listed in the NICE final scope as relevant for this appraisal of ABE-FUL differed for the two populations specified in the scope. For people with untreated HR+/HER2– aBC the comparators are: palbociclib in combination with an aromatase inhibitor (AI), ribociclib in combination with an AI, and tamoxifen. For people with HR+/HER2– aBC that has progressed after one line of prior ET the comparators are: exemestane, everolimus in combination with exemestane, tamoxifen, fulvestrant, and chemotherapy. The ERG's clinical experts agree with the company that the comparators for the first population in the NICE final scope are only relevant for those who have ET-sensitive disease. That is, people with *de novo* advanced disease and people who progressed > 12 months from completion of ET in the (neo)adjuvant setting would be offered palbociclib or ribociclib in combination with an AI, or tamoxifen for men and pre- and peri-menopausal women as first-line treatment. However, the submission is focused on ET-resistant aBC, whether it's first or second line in the advanced setting. For people with ET-resistant aBC, the relevant comparators are the same as those specified for the second population (progressed after one line of ET) in the NICE scope, irrespective of if they are untreated in the advanced setting or progressed after one line of ET. What guides suitability of the different treatments is the degree of resistance, that is, depending on where on the ET-resistance spectrum the patient is.

The clinical outcomes listed in the final scope issued by NICE are: overall survival (OS), progression-free survival (PFS), response rate, adverse effects of treatment and health-related quality of life (HRQoL). All the outcomes listed in the NICE final scope were captured in MONARCH 2. The primary outcome in MONARCH 2 was investigator assessed PFS, though, results of sensitivity analyses based on independent review of PFS were also provided. The outcome data presented by the company are based on the primary analysis data cut-off of 14 February 2017 at which point OS data were immature with only around 20% of patients having died in each of the trial arms. The long-term efficacy of ABE-FUL is therefore currently uncertain. The estimated data cut-off for the final OS analysis for MONARCH 2 is anticipated to be April 2019, and the estimated study completion date is February 2020.

To assess the relative efficacy and safety of ABE-FUL compared with the comparators in the NICE final scope for which there were no head-to-head data available, the company performed network meta-analyses (NMAs) for PFS, OS, objective response rate (ORR), and clinical benefit rate (CBR).

1.2 Summary of clinical effectiveness evidence submitted by the company

1.2.1 Literature review

The company conducted a systematic review of various sources for clinical evidence relevant to the decision problem and the ERG is confident that the search strategies will have retrieved all relevant records up until the last search date in January 2018. However, the ERG is aware that at least one trial (BOLERO-6), relevant to the indirect treatment comparison, was not identified due to being published after the search date. The trial inclusion criteria, in terms of the population, were relaxed compared with the key trial, MONARCH 2, to enable identification of clinical efficacy RCTs that were relevant to the decision problem outlined in the CS. The ERG is confident that all key RCTs are used to inform the analysis of the clinical efficacy and safety of ABE-FUL versus the comparators in the NICE final scope. However, there may be relevant NRSs with populations more aligned to that of MONARCH 2, which haven't been identified.

1.2.2 Trial design and conduct

Direct evidence on the clinical effectiveness of ABE-FUL versus PBO-FUL in the treatment of aBC is derived from a well-designed and well-conducted RCT, MONARCH 2, which is a multicentre, international, double-blind study. MONARCH 2 enrolled women with HR+/HER2− aBC who had relapsed while receiving neo(adjuvant) ET, ≤ 12 months from completion of adjuvant ET, or relapsed while receiving first-line ET for metastatic disease. That is, both people who were treatment naïve and those who had received one prior line of ET in the advanced setting were eligible for enrolment if they had primary or acquired ET resistant disease.

The trial only enrolled women of whom the vast majority (> 99%) had metastatic disease with visceral metastases present in just under 60% of people. Of the women enrolled, 80% were post-menopausal and 20% were pre- or peri-menopausal. Three quarters of people had acquired ET resistance and the remaining quarter primary ET resistance. Approximately 60% had received their most recent ET in the (neo)adjuvant setting, and the remaining 40% had received their most recent ET for aBC. Baseline characteristics of people enrolled in MONARCH 2 were well balanced across the treatment groups. Although no patients from the UK were enrolled in MONARCH 2, the ERG's clinical experts consider the baseline characteristics of those enrolled in the trial to be representative of people in England who are likely to be eligible for treatment with ABE-FUL either as first- or second-line treatment for aBC.

People were randomised 2:1 to receive ABE-FUL (n=446) or PBO-FUL (n=223). Randomisation was stratified by metastatic site and ET resistance. Fulvestrant was administered as an intramuscular injection (500 mg) on days 1 and 15 of the first cycle and on day 1 of subsequent cycles (every 28 days). Abemaciclib was given twice daily during each 28-day cycle. At study initiation, patients in the ABE-FUL group received a daily dose of 400 mg abemaciclib. After a review of preliminary safety data and dose reduction rates, the protocol was amended to reduce the dose of abemaciclib to 150 mg. A total of

178 patients (26.6%) were enrolled prior to the protocol amendment. Treatment was continued until progression, death, or patient withdrawal. Patients could discontinue either of the treatments in the combination but permitted to continue the other. Abemaciclib dose modifications, including interruption and up to two dose reductions, were permitted to manage adverse events. Fulvestrant dose reductions were also allowed.

The primary efficacy measure was investigator-assessed PFS as per RECIST version 1.1 criteria. PFS was calculated from the date of randomisation to the date of objective disease progression or death due to any cause. Tumour assessments were undertaken at baseline and approximately every 8 weeks for the first 12 months following randomisation and approximately every 12 weeks thereafter until the patient had objective disease progression, or until the primary analysis of PFS.

1.2.3 Clinical effectiveness

- Median PFS was 16.4 months on ABE-FUL and 9.3 months on PBO-FUL, corresponding to a HR of 0.553 (95% CI: 0.449 to 0.681), and a statistically significant difference between groups ($p < 0.001$). The sensitivity analysis of blinded central analysis of PFS showed similar results with a slightly larger relative difference between ABE-FUL and PBO-FUL. A subgroup analysis of starting dose showed that although the interaction between the 200 mg and the 150mg subgroups was [redacted], the mean relative treatment effect in favour of ABE-FUL was [redacted] in the 200 mg subgroup compared with the 150mg subgroup.

- OS data were immature at the primary analysis with only 19.1% of patients who had died in the ABE-FUL group and 21.5% in the PBO-FUL group; median OS was not reached in either treatment group and there was no statistically significant difference between the treatment arms (HR [redacted], 95% CI: [redacted], p-value [redacted]).

- More patients treated with ABE-FUL achieved a complete or partial response than patients treated with PBO-FUL, the difference being statistically significant (OR 2.82, $p<0.001$). Similarly, there was a statistically significant difference in DCR (OR 1.56, $p=0.025$) and CBR (OR 2.04, $p<0.001$) between the ABE-FUL group and PBO-FUL group.

- HRQoL and disease-related symptoms were assessed using mBPI-sf, EQRTC QLQ-C30 and EQ-5D-5L. Between-group differences in pain intensity (mBPI-sf) generally favoured ABE-FUL over PBO-FUL but the differences did not reach clinical or statistical significance. Mean change from baseline within each treatment group and the mean differences between treatment groups were similar for the EQRTC QLQ-C30 global health status and the functional scales and for EQ-5D-5L, indicating that neither ABE-FUL or

PBO-FUL treatment adversely affect functioning, HRQoL or the overall health status of patients. However, a [redacted] increase in mean symptom score with ABE-FUL compared with PBO-FUL was observed for diarrhoea, appetite loss, and nausea and vomiting.

- At the start of MONARCH 2 abemaciclib was administered at a daily dose of 400 mg. However, because of a large number of dose reductions due to adverse events, the protocol was amended lowering the daily dose to 300 mg. 178 patients (26.6%) were enrolled on the 400 mg dose. Of these 121 patients in the ABE-FUL group who started on the 200 mg dose, [redacted] ([redacted]) of patients discontinued treatment prior to having their dose reduced to 150 mg. The remaining [redacted] patients had their dose reduced to 150 mg due to treatment-emergent adverse events (TEAEs) ([redacted]) or the protocol amendment ([redacted]). Patients enrolled prior to the dose amendment received a median of [redacted] days of 200 mg abemaciclib before either having their dose reduced to 150 mg or discontinued treatment.

- The duration of treatment (of abemaciclib/placebo or fulvestrant) was [redacted] longer in the ABE-FUL group compared with the PBO-FUL group. The company reports conflicting figures of the proportion of patients who discontinued treatment due to AEs. [redacted] patients discontinued ABE-FUL compared with PBO-FUL.

- The most frequently reported AEs in the ABE-FUL group were diarrhoea (86.4%), neutropenia (46.0%), nausea (45.1%) and fatigue (39.9%). In the PBO-FUL group, the most frequently reported AEs were diarrhoea (24.7%), nausea (22.9%) and fatigue (26.9%).

- The incidence of SAEs was higher in the ABE-FUL group (22.4%) compared with the PBO-FUL group (10.8%). The most frequently reported SAEs for patients who received ABE-FUL were embolism (2%) and diarrhoea ([redacted]). For patients who received PBO-FUL the most common SAE was dyspnoea ([redacted]).

- Higher-grade diarrhoea occurred in the first few treatment cycles and was managed with dose omissions and/or dose reductions ([redacted] in ABE-FUL group), in addition to anti-diarrhoeal therapy. Most cases of neutropenia were Grade 3 AEs in both treatment groups. The median time to onset of Grade 3 or 4 neutropenia was [redacted] days for ABE-FUL and [redacted] days for PBO-FUL. The incidence of higher-Grade diarrhoea and neutropenia was higher in patients who received the 200 mg abemaciclib starting dose compared with patients who started on 150 mg abemaciclib.

- Due to the absence of head-to-head trials comparing ABE-FUL with everolimus plus exemestane, exemestane monotherapy, tamoxifen, or chemotherapy in the relevant population, the company conducted NMAs.

- The PH assumption is not fulfilled for PFS or OS for some of the included trials. Despite this, these results of the HR NMA inform the company's base case is in the economic model. The ERG would like to emphasise the difficulty in deriving a meaningful interpretation of these results.

- The HR NMA for PFS indicate that the ranking in terms of efficacy from highest to lowest is [redacted]. Although, the 95% CrI were relatively wide for each of the comparisons. For OS the uncertainty was even more pronounced with even wider 95% credible intervals. The ranking was also slightly different starting at the most effective treatment: [redacted]. TMX may be ranked as the [redacted] treatment for OS but [redacted] for PFS.

- The company's analysis of ORR showed that the best treatment is [redacted] followed by [redacted]. The ranking of best to worst treatment for CBR was slightly different with [redacted] being the best followed by [redacted], in decreasing efficacy.

- For FP NMA OS, the company concluded that the FE second-order model with p1=0, p2=1 showed the best fit, whereas for PFS, the company's preferred choice was the FE second-order model with p1=0.5, p2=1. The curves reported in the clarification response for PFS and OS differ from the curves used in the economic model. For PFS and OS the chosen curves all lack clinical plausibility as the curves plateau for several of the treatments, which is not in line with the clinical trial data underpinning the analyses or the experience of those therapies used in clinical practice.

1.3 Summary of cost effectiveness evidence submitted by the company

The company developed a *de novo* model in Microsoft Excel® to assess the cost-effectiveness of ABE-FUL in comparison with FUL; EXE; EXE-EVE and TMX in patients with HR+/HER2– locally advanced or metastatic breast cancer (aBC) with progressive disease. Following the clarification stage, the company included chemotherapy as a comparator in a scenario analysis.

The cohort-based partitioned survival model includes three health states: progression-free survival (PFS), progressed disease (PD), and death. The cohort is allocated to the PFS state at the beginning of

the economic analysis and is assumed to initiate treatment with ABE-FUL or with one of the comparators. Patients occupying the PFS state are at risk of disease progression or death and can also discontinue treatment before disease progression, even though the latter was not explicitly modelled, but estimated to capture treatment costs. Patients occupying the PD state are also at risk of death and can receive further treatment lines in the model. After entering the PD state patients cannot enter remission.

The company reports that a life time horizon of 25 years is adopted in the model, however, upon inspection of the company's economic model the ERG concluded that a 20-year time horizon was used instead. Time is discretised into weekly cycles with a half-cycle correction applied. The analysis was carried out from an NHS and Personal Social Services (PSS) perspective. Costs and health effects are discounted at an annual rate of 3.5%, in line with the NICE Reference Case.

The company's base case HR NMA approach relied on the assumption that PH hold across the studies included in the network for PFS and OS outcomes. Therefore, the company fitted a variety of parametric models to MONARCH 2 Kaplan-Meier (KM) data and applied the HRs estimated through the NMA to the fitted MONARCH 2 FUL curves for OS and PFS. This allowed the estimation of OS and PFS curves for EXE; and EXE-EVE. However, the company did not use the HR obtained in the NMA to estimate the ABE-FUL curves, but instead used the fitted curves to the ABE-FUL KM data. The company carried out an adjusted indirect comparison (using the Bucher method) using Milla-Santos 2001 and the results from the HR NMA to estimate the relative treatment effect for TMX vs FUL 500mg for OS and PFS/time to progression (assuming equivalence between the PFS and time to progression endpoints).

The parametric models fitted to MONARCH 2 data were jointly fitted to the ABE-FUL and FUL KM curves for PFS, TTD and OS, as the company concluded that the PH assumption was valid between treatment arms in MONARCH 2, for all clinical outcomes. The company reports fitting clinical data with exponential, Weibull, log-logistic, lognormal and generalised gamma models, and assessing the fit of each parametric model compared with the observed KM using the AIC and Bayesian Information Criterion (BIC), in accordance with guidance from NICE Technical Support Document (TSD) 14.

As a result of the clarification stage, the company undertook a FP NMA (using the method described by Jansen. 2011) to estimate relative treatment effectiveness. However, the company decided to use the original HR-based NMA to run their base case analysis and provided FP-based NMA survival models as a scenario analysis.

The company's base case model uses the adjusted, investigator (INV)-assessed PFS data from MONARCH 2. The company used a joint Weibull model to fit the ABE-FUL and FUL KM curves from MONARCH 2, and then applied the HR NMA-derived HR to estimate the EXE and EXE-EVE PFS

curves, while the HR derived through the adjusted indirect comparison (Bucher method) was used to estimate PFS for TMX (all HRs reported in Table 20).

The company used TTD data to estimate time on treatment in their base case model, and thus the cost of every treatment regimen. TTD curves were jointly fitted to ABE-FUL and FUL KM data from MONARCH 2. The company chose the Weibull distribution to model TTD in their base case analysis and a gamma distribution for sensitivity analysis. In order to estimate TTD for the remaining treatments (EXE; EXE-EVE; TMX and chemotherapy), the company used estimates of median duration of treatment from different publications and divided the median PFS by the median TTD for the specific treatment, to then apply a ratio to the respective PFS curve, thus obtaining a TTD curve.

The company used a joint Weibull model to fit the ABE-FUL and FUL OS KM data from MONARCH 2 but reported that due to the uncertainty around long-term extrapolation of the FUL curve, and around the long-term relative treatment effect of ABE-FUL vs FUL, data from CONFIRM were used to inform long-term survival estimates. The CONFIRM trial compared the effectiveness of FUL 500mg with FUL 250mg and had a long follow-up period of nearly seven years.

To estimate OS curves for the remaining treatments, the company applied the HR NMA-derived HRs to the fitted FUL curve and obtained the EXE and EXE-EVE OS curves. The HR derived through the adjusted indirect comparison (Bucher method) was used to estimate OS for TMX.

The EQ-5D-5L data collected in MONARCH 2, mapped to EQ-5D-3L, were used in the economic analysis. The company also reported that PD utility data from MONARCH 2 were immature and therefore, considered that the PD utility value accepted in previous NICE TAs for locally advanced or metastatic breast cancer (TA239, TA496, TA495), obtained from Lloyd *et al.* 2006 (and updated in TA495) was more appropriate to inform the base case analysis. Following this decision, estimates of [redacted] and 0.505 (Lloyd *et al.* 2006 and TA495) were used to inform the utility values in the model for PFS and PPS, respectively.

The economic model included pre- and post - progression treatment costs; health state (follow-up) costs; best supportive care costs; hospitalisation and terminal care costs; and costs of managing adverse events.

1.4 ERG commentary on the robustness of evidence submitted by the company

1.4.1 Strengths

Clinical

- MONARCH 2, which provides the only direct evidence of the efficacy and safety of ABE-FUL in women with HR+/HER2− aBC who had progressed on or after ET, is a well-designed and well-conducted RCT with mature data for the primary outcome, PFS.

- The trial population in MONARCH 2 is representative of women with HR+/HER2− aBC in UK clinical practice, even though no patients were recruited in the UK.

Economic

The economic model was partially based on MONARCH 2 data, which is a well-designed RCT. The partitioned survival approach employed by the company is appropriate and the formulae within the economic model are generally sound, although the structure of the model is somewhat inflexible.

1.4.2 Weaknesses and areas of uncertainty

Clinical

- The available OS data for MONARCH 2 were immature, with only 19.1% of patients who had died in the ABE-FUL group and 21.5% in the PBO-FUL group, which introduces substantial uncertainty in the relative effectiveness of ABE-FUL versus all of the comparators of interest for this outcome.

- Due to the specificity of the MONARCH 2 population the eligibility criteria for identifying comparable studies for the NMAs were relaxed which resulted in some heterogeneity between the included studies; some studies were double blind and some were open-label, HER2- status was not consistently reported, some study populations were more heavily pre-treated than others, both in terms of prior chemotherapy and number of lines of ET in the advanced setting, and baseline characteristics such as visceral involvement varied substantially.

- The PFS and OS results for capecitabine compared with EVE+EXE in BOLERO-6 and versus the other comparators in the FP NMA, may be overestimated due to imbalances in baseline characteristics of patients in the trial and potentially due to informative censoring of PFS.

- No reliable comparison between ABE-FUL and tamoxifen was possible. In the trial informing the efficacy of tamoxifen, Milla-Santos 2001, an unknown proportion of patients may have progressed on or after adjuvant ET. In addition, the trials linking Milla-Santos 2001 to the network, Hi-FAIR fx and Yamamoto 2013, administered the common comparator, toremifene, at double the dose of that in Milla-Santos 2001, and both were of a cross-over design likely to confound any estimate of OS.

- The PH assumption is not fulfilled for PFS or OS for some of the trials included in the NMA. Despite this, the results of the HR NMA, which relies on the PH assumption holding, inform the company's base case in the economic model. The ERG emphasises the difficulty in deriving a meaningful interpretation of these results.

- The company's results from the FP NMA lack clinical plausibility as the curves plateau for several of the treatments, which is not in line with the clinical trial data underpinning the analyses or the experience of using those therapies in clinical practice. In addition, the PFS curve crosses the OS curve for several of the treatments, which is not biologically plausible.

Economic

The ERG disagrees with the company's decision to use the HR NMA in their base case analysis, given that PHs are unlikely to hold across the network of studies included in the relative effectiveness analysis. Furthermore, the ERG considers that the company's base case analysis relied even further on the PH/PO/AFT assumptions, as the company decided to jointly fit curves to the ABE-FUL and FUL KM data from MONARCH 2, and only apply the HR NMA results to the FUL arm to estimate EXE, EXE-EVE and TMX curves in the model. In summary, the ERG considers that the company's base case analysis relies on weak assumptions and has methodological flaws.

In their clarification response, the company states that, "*A fractional polynomial approach was taken to account for violation in the proportional hazards assumption. Unlike the standard NMA approach to time-to-event data considering HR data, the fractional polynomials approach (FP) does not require that the proportional hazards assumption holds.*" Therefore, the ERG does not understand why the company decided to use the HR-based NMA to run their base case analysis, and decided to include their FP NMA only as a scenario analysis.

The ERG considers the company's method employed to run the FP NMA to have considerable limitations. The company used OpenBUGS to directly estimate survival curves from the FP NMA analysis. Therefore, the beta estimates were not explicitly obtained from the NMA, and the ERG was only provided with survival curves, hard-wired into the economic model (and the OpenBUGS coda). This considerably limited the ERG's capability of incorporating different survival curves (using different power estimates and varying between first and second order equations) in the analysis. Firstly, the computational burden of running the NMA with survival curves as outputs is paramount. To this, added the fact that the company chose weekly cycles for their analysis, and the considerable number of comparator treatments included. Secondly, this method rendered probabilistic sensitivity analysis (PSA) impossible to run from a computational power point of view.

Instead, the company could have ran the FP NMA so the output of the latter were the beta estimates associated with the best fitting powers. This would have drastically decreased the computational burden of running the analysis. The second necessary step would have been to build survival curves in the Excel economic model using beta estimates. This would have allowed curves to change automatically when beta estimates were varied, and more importantly, it would have allowed for PSA to be computed based on the beta values.

The ERG was able to adapt the code and re-run the NMA so that the output of the analysis were beta estimates. However, the ERG could not alter the structure of the survival model in order to incorporate the beta estimates into the model survival curves. Instead, the ERG varied the betas, in order to obtain different survival curves, and directly estimated the survival curves in R. Unfortunately, while this approach overcame the computational challenge of producing different FP-based survival curves (3 hours using the company's approach compared to 20 mins using the ERG's approach), the inflexibility in the economic model still meant that the different beta parameters could not be used in the model to run PSA.

The ERG finds the company's FP NMA's results clinically implausible as ~35% of ABE-FUL patients were considered cured at 30 months in the company's FP NMA-derived PFS curve. The plateau on all the PFS curves suggests that patients on all treatments are cured (albeit at different rates and in different percentages, according to treatment received). The FP-NMA-derived OS curves selected by the company also produce clinically implausible results, with approximately 15% of ABE-FUL, FUL and TMX patients living forever. The plateau of the OS curves is clearly implausible, and given that it occurs at ~15%, compared to the plateau in PFS curves at ~35%, it also means that PFS and OS curves cross quite markedly. Therefore, the ERG ran its own analysis of relative treatment effectiveness, using the FP NMA approach.

The ERG is concerned with the high degree of uncertainty embedded in the OS analysis of relative treatment effectiveness of ABE-FUL compared with all other treatments. Given the immaturity of OS data in MONARCH 2, the ERG advises caution when interpreting all analysis undertaken involving these data. Furthermore, the costs of ABE-FUL are likely to be considerably underestimated in the economic analysis, given the discrepancy in the ITT TTD and the 150mg TTD data in MONARCH 2. This uncertainty is propagated through the economic analysis and thus, all the final ICERs. Unfortunately, the company's model does not capture this uncertainty, given that the PSA ran for the HR NMA base cases analysis is flawed, and that the FP NMA analyses did not include PSA.

The key drivers of the economic analysis are: the method used to estimate relative treatment effectiveness in the model (i.e. HR NMA vs FP NMA); the assumptions made around the estimation of TTD curves (and the consequent separation of TTD and PFS curves for ABE-FUL); the assumptions

around subsequent treatments received and duration of the latter; the follow-up and CAP cost assumptions; and finally, the PPS-related utility value used in the analysis. These issues are discussed below in more detail:

1. *PFS and OS*: Given the clinical implausibility of the company's FP NMA-derived PFS and OS curves, the ERG used its FP NMA curves to estimate treatment effectiveness in the model. Figure A and Figure B report the ERG's FP NMA-derived survival curves. The ERG used a first-order FP NMA, which produced more clinically plausible long-term extrapolations of PFS and OS, with less than 10% of patients being free from progression at 5 years and virtually all patients being dead at approximately 13 years (160 months). As explained in Section 4, the ERG used the simplified FP NMA which excluded TMX from the network and thus, from the economic analysis. Results for CAP should be interpreted with caution, as the relative treatment effectiveness for CAP is likely to have been overestimated in BOLERO-6, and thus in the FP NMA.

Figure A. ERG's FP NMA-derived survival curves and MONARCH 2 KM data (p=0)

Figure B. ERG's FP-NMA derived survival curves (p = -0.5)

Comparison of the company's base case OS curves with the company's FP NMA-based curves and the ERG's FP NMA-based curves reveals that the ERG's NMA provides a better approximation of the estimated OS FUL curve in the model to the FUL 500mg KM curve from CONFIRM (Figure C). This is not unexpected as CONFIRM had the richer, more complete dataset for OS therefore, it "overwhelmed" the OS NMA analysis for FUL (Figure D).

The CS reports that the CONFIRM population was more pre-treated and thus expected to be at a more advanced stage of the disease compared with the MONARCH 2 population. Clinical expert opinion sought by the ERG agreed that the CONFIRM population was more pre-treated and thus clinical outcomes could be expected to be worse relatively to outcomes in MONARCH 2. Nonetheless, the company used the CONFIRM data to adjust the extrapolated tails of the FUL and ABE-FUL curves in their base case analysis.

Furthermore, the CONFIRM data are considerably rich and complete, with a follow-up period close to seven years, whereas the MONARCH 2 OS data are very immature (with median OS not reached for either treatment arms at the end of the follow-up period of two years and four months). Interestingly, OS for the FUL arm of MONARCH 2 reached 54% at 28 months, while CONFIRM median survival was approximately 27 months (Figure D). An earlier data cut-off analysis of the CONFIRM data showed a median survival of 25 months. Although the numbers at risk at 28 months in the FUL arm of MONARCH 2 (one patient) require caution when interpreting the OS curve, the 54% survival estimate is not dissimilar to the median OS for the shorter and longer follow-up analysis of the CONFIRM OS data.

Even though CONFIRM patients are expected to have worse outcomes than MONARCH 2 patients, it is not clear to what extent (given the relatively similar median OS across studies). Furthermore, the PFS KM curve for the FUL arm of MONARCH 2 and CONFIRM are relatively similar (Figure E), with CONFIRM patients doing only slightly worse than MONARCH 2 patients. Moreover, it could be hypothesised that the similarity between the PFS FUL 500mg arms of CONFIRM and MONARCH 2, would have also been observed for OS curves, had the latter been more mature in MONARCH 2.

The immaturity of the of OS data in MONARCH 2 means that the shape and relative positioning of the KM OS curves need to be interpreted with caution. While using CONFIRM data in the economic analysis helps mitigating some of the uncertainty around the OS FUL curve, the impact of the uncertainty in the OS data from MONARCH 2 on the relative treatment effectiveness of ABE-FUL vs FUL is less easy to circumscribe, as there are no other, more mature data sources for the effectiveness of ABE-FUL in the relevant population.

Figure C. OS curves obtained with the ERG's FP NMA and company's HR NMA

Figure D. OS data from MONARCH 2 and CONFIRM

Figure E. PFS KM data from MONARCH 2 and CONFIRM

To note is that even though using the ERG's FP NMA curves brings all the OS curves down (as these are mainly driven by the baseline treatment in the NMA, which is FUL, and the latter is mainly driven by CONFIRM data), this does not mean that the relative treatment effectiveness for ABE-FUL vs FUL is penalised. In fact, the separation between the ABE-FUL and the FUL curves in the ERG's analysis is greater than that in the company's base case, therefore attributing a greater difference in survival benefit to ABE-FUL.

2. *TTD*: The company chose the Weibull distribution to model TTD in their base case analysis, however this was the second-worst fitting model to TTD data, according to the company's AIC

and BIC statistics. The ERG considers that a Gompertz curve should have been used to model TTD curves, as it was the first and second best-fitting curve according to the BIC and AIC criteria, respectively. Nonetheless, the ERG notes that the AIC and BIC statistics provided are for a joint fit of the curves, which is not appropriate given that the PH assumption is unlikely to hold for TTD data in MONARCH 2.

Both the ABE-FUL and FUL ERG's FP NMA-based PFS curves stand above the company's respective TTD curves fitted with a Weibull or a Gompertz model. This is clinically implausible as both treatments were discontinued upon disease progression. Therefore, in order to use the PFS curves obtained through the ERG's FP NMA, some assumptions had to be made to estimate TTD curves. The ERG used the same method as the one proposed by the company to estimate TTD curves for comparator treatments in a scenario analysis, with some adjustments. The company's approach consisted on dividing the cumulative hazard for median TTD [i.e. log(0.5)] by the cumulative hazard for the HR NMA-estimated PFS curve at the time of median TTD. Using the median TTD and median PFS for EXE-EVE (reported in Table A) as an illustrative example, the company took the median TTD of 6.8 months from BOLERO 2 and looked up what the probability of survival in the PFS curve of the NMA-derived EXE-EVE curve was at that point in time. The company then used the cumulative hazard in the PFS curve at that point in time, relative to median TTD, to estimate a HR to apply to the same PFS curve in order to estimate the TTD curve for EXE-EVE.

From a methodological point of view, the ERG disagrees with using the HR NMA-estimated PFS curve for comparison with median TTD. The ERG considers that using the PFS curve from BOLERO 2 would have been more appropriate to estimate survival in the PFS curve at the point of median TTD, given that the median TTD estimate was taken from BOLERO 2. Given that the point of this adjustment exercise is to assess if PFS and TTD curves (or medians) are similar within treatments, using the PFS and TTD curves from BOLERO 2 (and all the other respective trial sources) is more appropriate.

Furthermore, the company did not consider BOLERO 6, which is a relevant study, given it was included in all NMAs and compared EXE-EVE with CAP. The data from BOLERO 6 shows a much higher separation in median TTD and median PFS estimates than BOLERO 2, however the company did not include BOLERO 6 in the discussion and therefore did not discuss the differences in median survival estimates. Nonetheless, BOLERO 6 is likely to be a less robust data source when compared to BOLERO 2, as the latter was a phase 3, double-blind study (while BOLERO 6 was a phase 2, open-label study), with a considerably bigger sample size.

Table A. Median TTD and PFS across comparator treatments

	PFS	TTD	Source
ABE-FUL	16.4	[redacted]	MONARCH 2
FUL	9.3	[redacted]	MONARCH 2
EXE	3.2	3.2	BOLERO 2
EXE-EVE	7.8	EXE:6.8 EVE:5.5	BOLERO 2
EXE-EVE	8.4	Overall: 6.3	BOLERO 6
TMX	9.2	9.2	Milla-Santos, 2001[1]
Chemotherapy	9.6	9.6	BOLERO 6

Most importantly, the estimates shown in Table A indicate that the only treatments where there might be a difference (as far as medians are concerned) between PFS and TTD curves is ABE-FUL, FUL, and EXE-EVE. Therefore, the PFS curves for EXE, TMX and chemotherapy can be used as proxies to estimate TTD in the economic analysis. To estimate TTD for ABE-FUL, FUL, and EXE-EVE, the ERG used the company's proposed methodological approach, but used the MONARCH 2 and BOLERO 2 PFS curves instead of the HR NMA-derived ones. Table B reports the calculations undertaken by the ERG and the resulting HRs used to estimate TTD curves in the economic analysis.

Table B. ERG's HRs to estimate TTD curves

	PFS	TTD	PFS % at median TTD	HR
ABE-FUL	16.4	[redacted]	[redacted]	[log(0.5) / log([redacted])] = [redacted]
FUL	9.3	[redacted]	[redacted]	[log(0.5) / log([redacted])] = [redacted]
EXE-EVE (BOLERO 2)	7.8	EXE:6.8 EVE:5.5	PFS (6.8) = 0.55	[log(0.5) / log(0.55)] = 1.16
EXE-EVE (BOLERO 6)	8.4	6.3	PFS (6.3) = 0.59	[log(0.5) / log(0.59)] = 1.31

Figure F shows the TTD curves when the ERG's HRs were applied to the ERG's FP NMA PFS curves. The TTD curve for ABE-FUL has a considerable separation from the ABE-FUL PFS curve. This is a direct translation of the separation in TTD and PFS KM curves in the ITT analysis of MONARCH 2 data (Figure G and Figure H). However, when compared with the TTD curves by starting dose of abemaciclib (i.e. 150mg vs 200mg populations) shown in Figure I, the ABE-FUL curve for the ITT population is considerably underestimating the time on treatment for patients receiving 150mg of abemaciclib. Given that abemaciclib will be given in 150mg regimens in clinical practice, and that the 150mg population sample size in MONARCH 2 was considerably bigger than the 200mg population, the ERG considers that the 150mg TTD data would have been a more appropriate choice to model TTD for ABE-FUL. In fact, using the ITT TTD data leads to considerable underestimation of the ABE-FUL costs in the economic

analysis. During the clarification stage, the ERG asked the company to provide the TTD data for the 150mg and the 200mg populations, however the company did not provide these.

Furthermore, the HRs for the TTD and PFS curves for ABE-FUL and EXE-EVE in BOLERO 2 ([redacted] vs 1.16) suggest that patients in ABE-FUL discontinue treatment before progression at higher rates that EXE-EVE patients.

Given that the HR used to estimate TTD curves in the economic analysis is one of the key model drivers, the ERG advises that the Committee considers the clinical plausibility of the assumptions underlying these clinical data. The ERG also recommends that the 150mg TTD data are used by the company to generate a more robust estimation of the costs of ABE-FUL in the economic analysis.

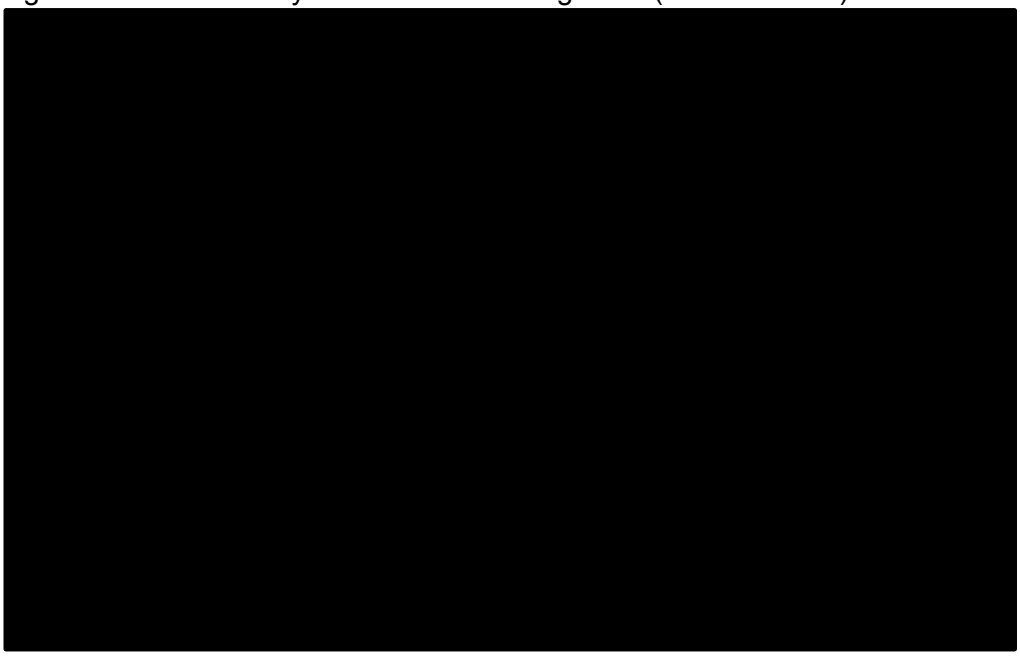
Finally, the ERG notes the caveat in the approach undertaken to estimate HRs to derive TTD curves. The basis of this approach is on comparing median TTD with median PFS values. However, comparison of medians is a reasonably weak approach, as equivalence (or difference) in median survival estimates does not inform the difference in the curves' shape and doesn't necessarily translate an accurate picture of differences in mean survival times. Nonetheless, given that TTD data were not available for the comparator treatments, the use of median TTD estimates is necessary.

Figure F. PFS and TTD in ERG's anaysis

Figure G. TTD and PFS curves for ITT population (MONARCH 2)

Figure H. TTD curves in ITT population (MONARCH 2)

Figure I. TTD curves by abemaciclib starting dose (MONARCH 2)



3. *Post-progression utility*: During the clarification stage, the company reported that the p-values and 95% confidence intervals associated with the coefficients obtained in the regression models used to estimate utility values from MONARCH 2 were not available, and therefore did not provide these. The ERG cannot see a reason as to why p-values and confidence intervals would not be available, as these are an output of the regression analysis ran by the company, for which regression coefficients were provided. As a result of not having access to these estimates, the ERG cannot validate the company's statement that no statistically significant differences were found between utility estimates in the treatment arms in MONARCH 2. More importantly, if the difference between pre-and post-progression utility coefficients in the regression model are statistically significant, the PPS utility value predicted from MONARCH 2 could have been used by the company, rather than the utility estimate from Lloyd *et al*. 2006. The company used the PPS utility value from Lloyd *et al*. 2006 as it considered that PPS data from MONARCH 2 were immature. However, the ERG is unclear as to why the company considered PPS utility data from MONARCH 2 to be immature. During the trial period, [redacted] patients in the ABE-FUL arm and [redacted] patients in the FUL arm had a progression event (excluding death). During follow-up (lasted approximately 30 days after the patient stopped study treatment), 185 (79.7%) patients in the ABE-FUL arm and 129 (82.7%) patients in the FUL arm provided EQ-5D data. Furthermore, if the pre- and post-progression utility data from MONARCH show a statistically significant difference, this could help mitigate the company's concerns around data immaturity.

   The ERG is also concerned that the population and methods in Lloyd *et al*. 2006 are not comparable to those in MONARCH 2. For example, Lloyd *et al*. 2006 elicited utilities using

vignettes describing health states related with metastatic BC, which were valued by the general public using the standard gamble approach. Contrastingly, MONARCH 2 patients with HR+/HER2- aBC replied to the EQ-5D questionnaire.

However, the PFS utility in Lloyd *et al*. 2006 (0.762) was only [redacted] than the PFS utility predicted from MONARCH 2 ([redacted]). Therefore, and considering the ERG has little evidence to suggest that the PPS utility value from MONARCH 2 is not a robust estimate, the substantial difference in HRQoL between PFS and PPS in Lloyd *et al*. 2006 (0.762 vs 0.505), compared to that in MONARCH 2 ([redacted] vs. [redacted]) is not easily explained. As a scenario analysis, the ERG used both the PFS and PPS-related utility values from MONARCH 2 in the economic analysis.

One of the studies identified in the company' systematic literature review for HRQoL evidence (Mitra *et al*. 2016) included HR+/HER2- patients and elicited utility values using the preferred EQ-5D technique, in five major European countries (N= 613) and the USA (N= 126). However, Mitra *et al*. 2016 is a conference abstract, therefore providing a limited description of methods and results. Moreover, utility estimates for progression status were not reported in Mitra *et al*. 2016. Instead Mitra et al. 2016 reported index utility values according to the number of lines of therapy (first, second and third or greater) received by patients. Despite this, utility estimates for patients on second or later line of therapy in Mitra *et al*. 2016 were [redacted] to those derived in MONARCH 2 for PPS (0.69 vs. [redacted], respectively). The utility related to first-line therapy in Mitra et al. 2016 was 0.77, which compares to [redacted] in MONARCH 2 for PFS. Comparisons with the Mitra et al. 2016 study need to be interpreted with caution as the latter is a cross-sectional study, with no statistical analysis of changes in patients' utility over time. Nonetheless, the ERG considers the values in Mitra *et al*. 2016 to be informative as a scenario analysis. Therefore, the ERG applied a relative decrement of –11% (calculated as the difference between the utility value for first-line therapy in Mitra *et al*. 2016 [0.77] and the second, third or later line utility in Mitra *et al*. 2016 [0.69]) to the PFS utility value obtained from MONARCH 2 ([redacted]) to estimate the PPS utility ([redacted]).

4. *Subsequent treatments*: The company included bevacizumab (BEV) as a subsequent treatment in the model, which clinical experts advising the ERG indicated would not be available to patients in UK NHS. Clinical experts also pointed out that TMX should be included as a post-progression therapy. To address these issues, the ERG asked the company to remove BEV as a subsequent treatment option and add treatment with TMX. In a scenario analysis, the company removed BEV as a subsequent treatment option following all treatments in the model. The company subsequently looked in BOLERO-2 to inform the proportion of patients receiving TMX as a post-progression therapy after EXE and EXE-EVE, however found no data and thus

did not include TMX as a subsequent treatment option for these treatments. Patients in the TMX arm also did not receive re-treatment with the same drug. For ABE-FUL and FUL, the company used the proportion of patients who received TMX in MONARCH 2.

Although removing BEV and adding TMX to the list of possible subsequent treatments illustrates the UK clinical practice more closely, the ERG still considers that some caution should be taken when interpreting these. For example, clinical experts advised the ERG that they would expect the proportion of patients receiving subsequent paclitaxel to be larger. Moreover, as noted in Section 2, access to FUL is patchy in the UK and therefore the proportions taken from BOLERO 2 (24.66% and 34.33% following EXE and EXE-EVE, respectively) could be higher than those seen in the UK. To address these issues, the ERG applied a set of alternative distributions which have been validated by its clinical experts.

Furthermore, the company did not justify the model assumption that the proportion of time spent on subsequent treatment during PPS would be 37% of PPS time. More importantly, clinical experts advised the ERG that the company's assumption was too low as patients would usually spend all but the last 3 months of their life on treatment. To reflect clinical expert opinion, the ERG ran a scenario using the time on post progression treatment reported in Table C.

When the ERG used its FP NMA to estimate treatment effectiveness in the model, the change in PFS and OS curves also impacted the time patients spent on the PPS state (as the latter is calculated as OS minus PFS). Overall, ABE-FUL remained the treatment for which patients spent [redacted] on PPS ([redacted] months). The ERG's approach needs to be caveated by the fact that in clinical practice, patients would not remain on the same subsequent treatment until 3 months before death. Clinical experts advising the ERG explained that patients are likely to receive several rounds of chemotherapy before death, and so the ERG made some simplifying assumptions in order to estimate the costs of subsequent treatments. Given that the costs of chemotherapy regimens, TMX and EXE are considerably low and broadly similar, the ERG did not differentiate between these as further lines of treatment. However, FUL and EVE are expensive treatments, and so the assumption that patients would remain on these for the entire period of their subsequent therapy was likely to bias the costs of subsequent treatments upwards in the analysis. Therefore, the ERG assumed that patients receiving FUL or EXE-EVE as subsequent treatments in the model would do so for a limited amount of time, which was assumed to be the same as the time spent in the PFS state when given these treatments first. So, for example, if a patient received ABE-FUL in the model, the time spent on EXE-EVE as a subsequent therapy was set to be the same as the time spent in the PFS state by patients who receive EXE-EVE as their first treatment in the model. This is an optimistic assumption, given

that as patients progress (and move to subsequent lines of therapy) they become less likely to tolerate treatments for long, and treatments are unlikely to be as effective as they would be in a first-line setting, so the ERG's assumption might result in an overestimation of EXE-EVE (and FUL) costs as a subsequent treatment. Decreasing the costs associated with subsequent treatments in the model increases the final ICERs for ABE-FUL vs all comparators. This is because ABE-FUL patients receive subsequent treatments for [redacted] than any other patients in the analysis. The ERG assumed that after subsequent treatment with FUL or EXE-EVE, patients would receive chemotherapy regimens (specifically CAP) until 3 months before dead.

Time spent on subsequent treatments is one of the model's key drivers, therefore, the ERG advises that the Committee discusses the clinical plausibility of ABE-FUL patients receiving subsequent treatments for shorter periods than other patients in the model. To note, is that ABE-FUL patients spend less time on subsequent treatments due to their PFS period being longer. However, this has not been translated into a proportional increase in OS with ABE-FUL, thus patients spend less time of subsequent treatments before they die. Given the sensitivity of the model's results to the assumption of time spent on subsequent treatments, the ERG also conducted a deterministic sensitivity analysis around these parameters.

Table C. Time on treatment during PPS, ERG scenario

Treatment	Time on treatment (months)		Total time in PPS (months)
	Base case	ERG scenario	
ABE-FUL	[redacted]	[redacted]	[redacted]
FUL	[redacted]	[redacted]	[redacted]
EXE	[redacted]	[redacted]	[redacted]
EXE-EVE	[redacted]	[redacted]	[redacted]
TMX	[redacted]	[redacted]	[redacted]
CAP*	[redacted]	[redacted]	[redacted]

Abbreviations: ABE, abemaciclib; BEV, bevacizumab; CAP, capecitabine; EVE, everolimus; EXE, exemestane; FUL, fulvestrant; NA, not applicable; TMX, tamoxifen; ToT, time on treatment
*Included in scenario analysis

5. *Other issues related with the estimation of costs in the model:*

Health state (follow-up costs): Clinical experts advised the ERG that the health state (follow-up) costs used by the company and taken from the MONARCH 2 and MONARCH 1 trials, are likely to overestimate the resource use in UK's clinical practice. Specifically, patients would not receive ECGs, and the frequency of CT scans, community nurse visits and oncologist consultations would be lower (i.e. every three months rather than every few weeks). Following this, the ERG considered the follow-up costs in TA496 for PFS and PPS to be more appropriate and therefore requested the company to provide a scenario analysis using those resources.

However, instead of employing the follow-up costs in TA496 for PFS and PPS, the company extracted the drug acquisition cost for third and subsequent lines of treatment (£1,200 per month). Then, the company replaced the cost of PPS follow-up with a cost of £1,200 per month (£300 per weekly cycle) and removed third-line treatment costs from the economic model. As a result, the company replaced follow-up costs with drug acquisition costs. The ERG considers this to be an uninformative scenario given that drug acquisition costs are not equivalent to follow-up costs. To address this issue, the ERG explored a scenario using the follow-up costs (Table D) accepted in TA496. The impact of changing follow-up costs in the model has a considerable impact on the final ICERs.

Table D. Follow-up costs estimated from TA496

Component	**Frequency (per week*)**	
	PFS	**PPS**
GP visits	Once a month (0.23)	Once a month (0.23)
Oncology consultant	Every 6 months (0.04)	Every 6 months (0.04)
Community nurse	Every 3 months (0.08)	Every 3 months (0.08)
Clinical nurse specialist	Once a month (0.23)	Once a month (0.23)
CT scan	Every 3 months (0.08)	Every 3 months (0.08)
Social worker	-	Every 2 months (0.11)

*4.348 weeks per month
Abbreviations: CT, computerised tomography; GP, General Practitioner; PFS, progression free survival; PPS, post-progression survival; PSSRU, Personal Social Services Research Unit

Inconsistencies associated with CAP administrations: During the clarification stage, the company included CAP as a treatment option. However, the company only applied administration costs to CAP when it was received as a post-progression treatment. In addition, the company applied different regimens for CAP as a pre- and post-progression treatment: 14 administrations per 21- day cycle (i.e. one per day) and 28 administrations per cycle (i.e. two per day), respectively. Clinical experts advised the ERG that the same dose would be used during pre-progression and post-progression thus, the ERG amended the company's scenario analysis and included administration costs during pre- and post-progression treatment and 28 treatment administrations. Furthermore, the company had assumed that during PPS, treatment with CAP would incur a daily administration cost, for every day of treatment with CAP. Given that CAP is an oral treatment, this assumption is not clinically plausible and led to a considerable overestimation of CAP costs as a subsequent treatment. As mentioned above in this section, the higher the costs associated with subsequent treatments, the lower the ICERs for ABE-FUL vs all other treatments, thus, the company's assumption resulted in an underestimation of the final ICERs. The ERG corrected this in the model, so that CAP

administration costs were incurred once per treatment cycle (i.e. once every 21 days, as per TA296).

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

Clinical

Due to proportional hazards not holding for at least some of the studies in the company's network of RCTs, the ERG's preferred approach would be using a methodology not requiring PH to hold. Unfortunately, the FP NMAs chosen by the company, lack face validity and so proved to be unhelpful. As such, the ERG explored other powers for the FP NMA, to identify ones which were more clinically plausible to inform PFS and OS used in the economic model. Due to time constraints, the ERG only explored first-order FP NMAs. The ERG's general approach was to assess the different powers explored for statistical fit before then choosing its preferred FP NMAs based on clinical plausibility of the curves produced. The ERG chose a FE first-order NMA for both PFS and OS. For PFS, the FP NMA for two different powers (p=0 and p=0.5) had the same statistical fit but p=0 produced more plausible tails, with most curves indicating all patients had progressed by 140 months, whereas for p=0.5 some patients were still progression free on some treatments at this timepoint. The power, p=0, was therefore chosen to inform the ERG base case for PFS, and p=0.5 was used for a scenario analysis. For OS, there were three FP powers available for consideration of which the ERG chose p=–0.5 for its base case. All the treatment curves in the p=–0.5 NMA had all patients dying earlier than the other two powers (p=–1 and p=–1.5) and while the individual treatment curves converged there were no extreme crossing of curves. The curves for the FP model with p=–1 and p=–1.5 were very similar, however, the results of the PF model with p=–1.5, which had the best statistical fit of the two, was used as an alternative scenario for the ERG base case. The FP NMAs chosen by the ERG all produced curves that seemed consistent in terms of the relative order of the treatments compared with the underlying trial data and which produced plausible tails.

Economic

The ERG ran two analyses reflecting two different scenarios for treatment effectiveness. One scenario assumes a bigger survival benefit for ABE-FUL compared with the other treatments, while the other portrays a more conservative scenario. The ERG caveats the analysis presented with the very high degree of uncertainty embedded in the analysis of OS through the HR or FP NMA. This is mainly related with the lack of maturity of the MONARCH 2 OS data and thus on the survival benefit related with ABE-FUL when compared with FUL (and therefore, the other comparators included in the NMAs). The ERG's analysis is also caveated by the fact the TTD curve for ABE-FUL was estimated based on a HR derived from the comparison of PFS and TTD data in the ITT population of MONARCH 2.

Nonetheless, as discussed throughout the report, using the ITT TTD data underestimates the costs of ABE-FUL in the model. Alternatively, the ERG recommends that the company provides the 150mg TTD data so that these can be used in the economic analysis.

The ERG's assumptions included in the analysis (and listed in the previous section) are the following:

1. The ERG replaced the company's OS and PFS FP NMA-derived curves by the ones estimated by the ERG using the first-order FP NMA approach (PFS power of 0; OS power of –1.5). This also includes the TTD curves estimated by the ERG;

3. The ERG used the utility value for first-line therapy in Mitra *et al.* 2016 [0.77] and the second, third or later line utility in Mitra *et al*. 2016 [0.69]) to estimate a relative decrement to be applied to the PFS utility value from MONARCH 2 ([redacted]), in order to estimate the PPS utility ([redacted]);

4. The ERG removed AE-related disutilities from the model;

5. The ERG ran a scenario analysis including age-related utility decrements, using the published algorithm by Ara and Brazier 2010;

6. The ERG used a set of alternative distributions for subsequent treatments received in the model, which have been validated by its clinical experts;

7. The ERG assumed that patients would receive subsequent treatments for the entire time spent on PPS, with the exception of the last 3 months;

8. The ERG caped the time patients could spend on FUL and EXE-EVE as subsequent treatments;

9. The ERG ran a scenario analysis including the resource use associated with follow-up care accepted in TA496;

10. The ERG ran a scenario analysis including the resource use associated with FUL administration costs accepted in TA496, and applied it for every cycle of FUL treatment in the model;

11. The ERG ran a scenario analysis excluding the cost of non-AE-related hospitalisations from the analysis;

12. The ERG removed the half-cycle correction from the model;

13. The ERG included the first-order FP OS curve with a power of –0.5, which portrays a more conservative analysis of the relative survival benefit for ABE-FUL. This scenario includes the ERG's FP NMA for PFS and the ERG's estimated TTD curves.

The ERG used Mitra *et al.* 2016 data to estimate the PPS-related utility in the base case analysis. However, the ERG provides all the relevant permutations of the ERG's base case ICERs using the alternative PPS utility value from MONARCH 2 in the economic analysis. Furthermore, given the uncertainty around the estimation of the PFS vs TTD HRs for ABE-FUL, the ERG ran a deterministic scenario analysis, with the aim of exploring the sensitivity of the final ICERs to variations in the parameter. The ERG also conducted deterministic sensitivity analysis on the assumption made for the time patients spend on FUL and EXE-EVE subsequent treatments. A confidential appendix is provided incorporating the EVE PAS, which includes the results of all of these analyses.

Results of the ERG analysis are reported in Table E. The final ABE-FUL ICERs, compared with FUL and EXE are [redacted] and [redacted] per QALY gained, respectively, with the ICER against EXE-EVE being [redacted] and the ICER against CAP being [redacted] for the more conservative OS analysis (i.e. using the OS FP with p=–0.5). The corresponding values using the FP OS curve with p=–1.5 are [redacted] and [redacted] for ABE-FUL compared with FUL and EXE. The ICER against EXE-EVE remained [redacted] (with ABE-FUL being associated [redacted] than EXE-EVE) and the ICER against CAP remained [redacted] (with ABE-FUL being associated [redacted] than CAP). However, the FP NMA results for CAP are likely to be an overestimation of the drug's effectiveness, and so all ICERs against CAP should be interpreted with caution.

The ERG ran two alternative analyses with the PFS and PPS-related utility values from MONARCH 2 ([redacted] vs [redacted]), respectively, instead of using the Mitra *et al*. 2016 [0.69] value. The final ABE-FUL ICERs, compared with FUL and EXE are [redacted] and [redacted] per QALY gained, respectively, with the ICER against EXE-EVE being [redacted], and the ICER against CAP remaining [redacted], for the more conservative OS analysis (i.e. using the OS FP with p=–0.5). The corresponding values using the FP OS curve with p=–1.5 are [redacted] and [redacted] for ABE-FUL compared with FUL and EXE. The ICERs against EXE-EVE and CAP remained [redacted] and dominated, [redacted].

Table F and Table G present the results for the ERG's deterministic sensitivity analysis. Table F shows the impact on the final ICER when the HR used to estimate TTD curves (from the PFS curves) for ABE-FUL is varied. The ERG decreased the HR by 5%, 10% and finally assumed that the TTD and PFS curves for ABE-FUL would be the same (HR=1). The 5% and 10% reduction in the ERG's base case ICER ([redacted]) represents using HRs of [redacted] and, [redacted] respectively.

Varying the HR by 5% led to an increase in ICERs from [redacted] and [redacted] vs FUL and EXE, respectively to from [redacted] and [redacted] per QALY gained. The ICER against EXE-EVE remained [redacted] and the ICER against CAP [redacted] for the more conservative OS analysis (i.e. using the OS FP with p=–0.5), and using the Mitra *et al*, 2016 PPS utility. This shows that the model results are

highly sensitive to small changes in the HR used to derive the ABE-FUL TTD curve in the model. When the HR was assumed to be 1, the ICERs for ABE-FUL vs FUL and EXE, rose to [redacted] and [redacted], respectively, per QALY gained.

The ABE-FUL ICER seem less sensitive to varying the time spent with FUL and EXE-EVE as subsequent treatments. When the ERG's decreased the time spent in FUL and EXE-EVE by 25% of the time used in the ERG's base case (Table G), the ICER for ABE-FUL vs FUL increased from [redacted] to [redacted], and it decreased from [redacted] vs EXE to [redacted] per QALY gained. The ICER against EXE-EVE remained [redacted] and the ICER against CAP [redacted] for the more conservative OS analysis (i.e. using the OS FP with p=–0.5) and using the Mitra *et al*. 2016 PPS utility.

Table E. ERG's exploratory analysis with all changes incorporated

	Results per patient	ABE-FUL (1)	FUL (2)	EXE (3)	EXE-EVE (4)	CAP* (5)	Incremental value			
							(1-2)	(1-3)	(1-4)	(1-5)
0	**Corrected base case**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	-					£50,687	£57,247	Dominant	£82,621**
1	**Using the ERG's FP NMA results for OS and PFS and adjusting TTD curves**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	-					£41,719	£44,089	Dominant	Dominated
3	**PPS utility using a -11% relative decrement (Mitra *et al*. 2016) on PFS utility**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	-					£92,990	£89,733	Dominant	£611,615**
	ICER with all changes incorporated	-					£52,288	£51,578	Dominant	Dominated
4	**Removed AE-related disutilities**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	-					£50,614	£57,183	Dominant	£82,451**
	ICER with all changes incorporated	-					£52,210	£51,525	Dominant	Dominated
5	**Age-related utility decrements included**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	ICER (compared with base case)	**-**					£51,757	£58,360	Dominant	£84,299**
	ICER with all changes incorporated	-					£53,668	£52,778	Dominant	Dominated
6+7 +8	**Post-progression treatment in PPS from 37% to up to 3 months before death**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	[redacted]					£29,786	£53,150	Dominan	£99,317**
	ICER with all changes incorporated	**-**					£45,168	£46,116	Dominant	Dominated
9	**TA496 health state costs**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	-					£62,737	£65,459	Dominant	£111,549**
	ICER with all changes incorporated	-					£47,885	£45,994	Dominant	Dominated
10	**TA496 FUL administration costs**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	**-**					£52,348	£59,546	Dominant	£88,566**
	ICER with all changes incorporated	**-**					£49,254	£47,637	Dominant	Dominated
11	**Removing non-AE-related hospitalisation costs**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	**-**					£54,054	£59,797	Dominant	£89,595**

	ICER with all changes incorporated	**-**					£50,725	£48,406	Dominant	Dominated
12	**Remove half-cycle correction**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	-					£51,432	£57,790	Dominant	£84,139**
	ICER with all changes incorporated	-					£52,351	£52,002	Dominant	Dominated
13	**Using first-order FP OS curve with a power of -0.5 (compared to p = -1.5)**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	**-**					£42,065	£44,258	Dominant	Dominated
	ICER with all changes incorporated	**-**					£70,634	£63,436	Dominant	Dominated

Abbreviations: ABE, abemaciclib; AE, adverse event; BEV, bevacizumab; CAP, capecitabine; EVE, everolimus; EXE, exemestane; FUL, fulvestrant; FP, fractional polynomial; ICER, incremental cost-effectiveness ratio; LD, loading dose; LY, life years; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; PPS, post-progression survival; QALYs, quality-adjusted life years; TMX, tamoxifen; TTD, time to treatment discontinuation.
*This refers to TMX instead of CAP for the scenario using the company's corrected base case (0)
**ABE-FUL is compared to TMX instead of CAP when the ICER is compared with the base case

Table F. Using alternative HRs to estimate TTD curve for ABE-FUL (with FP OS power of –0.5, and Mitra *et al.* 2016 PPS utility)

	Results per patient	**ABE-FUL (1)**	**FUL (2)**	**EXE (3)**	**EVE-EXE (4)**	**CAP (5)**	**Incremental value**			
							(1-2)	**(1-3)**	**(1-4)**	**(1-5)**
0	**ERG base case**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-	-	-	-	-	£70,634	£63,436	Dominant	Dominated
a	**HR=1 for PFS vs TTD curve**									

	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-	-	-	-	-	£120,775	£87,152	Dominant	Dominated
b	**Reduce HR by 5% ([redacted])**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-	-	-	-	-	£78,996	£67,391	Dominant	Dominated
c	**Reduce HR by 10% ([redacted])**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-	-	-	-	-	£88,353	£71,817	Dominant	Dominated

Table G. Varying the time patients spend on FUL and EXE-EVE as subsequent treatments (with FP OS power of –0.5, and Mitra *et al.* 2016 PPS utility)

	Results per patient	**ABE-FUL (1)**	**FUL (2)**	**EXE (3)**	**EVE-EXE (4)**	**CAP (5)**	**Incremental value**			
							(1-2)	**(1-3)**	**(1-4)**	**(1-5)**
0	**ERG base case**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-	-	-	-	-	£70,634	£63,436	Dominant	Dominated
d	**Decreasing time spent in FUL and EXE-EVE as subsequent treatments by 5%**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-	-	-	-	-	£70,634	£63,477	Dominant	Dominated
e	**Decreasing time spent in FUL and EXE-EVE as subsequent treatments by 10%**									

	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-	-	-	-	-	£72,634	£63,518	Dominant	Dominated
f	**Decreasing time spent in FUL and EXE-EVE as subsequent treatments by 25%**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-	-	-	-	-	£74,448	£60,649	Dominant	Dominated

Abbreviations: ABE, abemaciclib CAP, capecitabine; EVE, everolimus; EXE, exemestane; FUL, fulvestrant; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; ToT, time on treatment

2 BACKGROUND

2.1 Critique of company's description of underlying health problems

Section B.1.3.1 of the company submission (CS) provides an overview of the key aspects of breast cancer including: incidence and prevalence, breast cancer classification, prognosis, endocrine therapy (ET), ET resistance, and the impact of breast cancer on patients and carers. The final scope issued by the National Institute for Health and Care Excellence (NICE) for this Single Technology Appraisal (STA) indicates two populations of interest to the decision problem:[2]

- People with untreated advanced breast cancer (aBC) that is hormone-receptor positive ((HR+) and human epidermal growth factor receptor 2 negative (HER2–);
- People with HR+/HER2– aBC that has progressed after prior ET.
- The company has chosen to define the population of interest in terms of resistance to ET rather than prior treatment, the implications of this are discussed in Section 3.1.
- The Evidence Review Group (ERG) considers the CS to present an appropriate overview of breast cancer that is relevant to the decision problem. Below, the ERG presents a summary of information from the CS. As highlighted by the company:
- Breast cancer is the most common cancer amongst women in the UK.[3]
- Approximately 46,000 women in England are diagnosed with breast cancer each year.[4]
- The main risk factors of breast cancer are female gender, family history of breast cancer and increasing age, with more than 80% of cases occurring in women over the age of 50.[5]
- As with many cancers, severity of breast cancer is determined based on the staging of the disease:
- Early breast cancer comprises cancer only in the breast and lymph nodes nearby.[6]
- Locally aBC involves cancer in a large part of the breast and lymph nodes.[6]
- Metastatic breast cancer where the disease has spread to other parts of the body such as the bones, liver, and lungs.[6]
- The majority of early and locally aBC cases are amenable to curative surgical treatment, however, around 35% will progress to aBC.[7]

- aBC refers to locally advanced disease that is not amenable to curative treatment by surgery, or metastatic cancer.[8] aBC is incurable and has a poor prognosis, with a median overall survival (OS) of two to three years.

- Treatment of aBC is predominantly given with the goal of prolonging life, managing pain and symptoms and improving quality of life.

- Breast cancers are classified according to the characteristics of the tumour cells and are described in terms of oestrogen receptor (ER) status and progesterone receptor status (PgR), which are referred to as hormone receptors (HR), and Human epidermal growth factor receptor-2 (HER2) status.

- HR positive and HER2 negative (HR+/HER2−) breast cancer, which is specified as the population of interest in the NICE final scope, is the most common type (64% of women with metastatic breast cancer in the UK).[9, 10]

- For HR+ breast cancer, which is the focus of this STA, the treatment strategy comprises interventions that disrupt hormone production or otherwise interfere with intracellular oestrogen signalling, such as the ETs tamoxifen, fulvestrant and aromatase inhibitors (AIs), which are the mainstay of treatments.[11, 12]

- Some HR+ tumours do not respond to initial ET or develop resistance to ET over time. HR+/HER2− aBC can therefore be subdivided into patients with sensitivity, or primary or acquired resistance to ET. The ERG notes that resistance is a continuum and the following definitions are mainly used in clinical trials and not necessarily clinical practice.

- ET-sensitive patients include those with no prior treatment with ET (*de novo* advanced), and those who have relapsed more than one year after completion of adjuvant ET with curative intent.

- Primary endocrine resistance is defined as relapse during the first two years of treatment with adjuvant endocrine therapy, or progressive disease within the first six months of initial ET for aBC.[8]

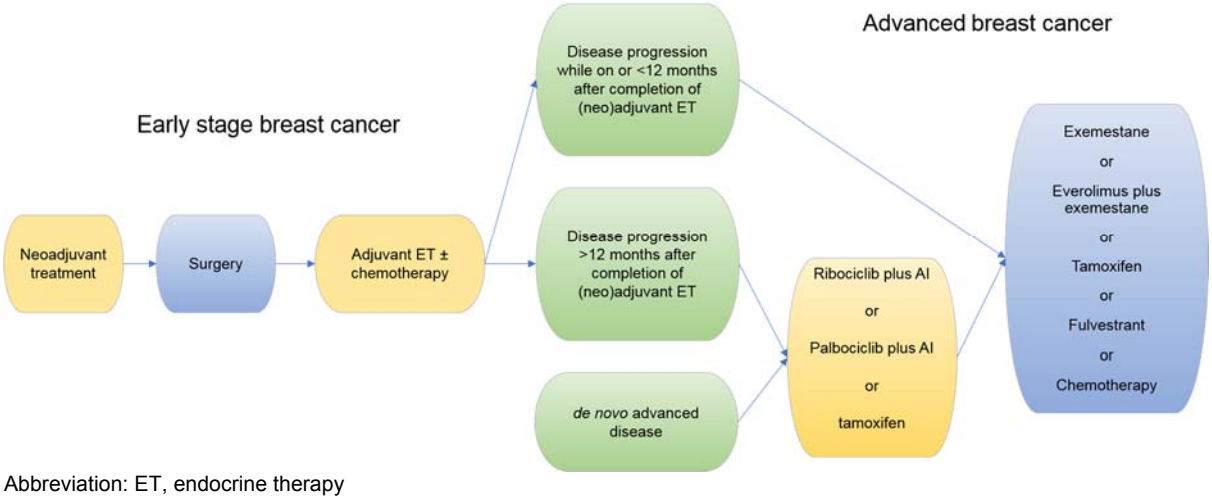
- Secondary or acquired resistance is defined as patients who initially respond to ET, yet later become unresponsive: relapse while on adjuvant ET but after the first 2 years, or relapse within 12 months of completing adjuvant ET, or progressive disease while on ET for metastatic BC, but more than 6 months after initiating therapy.[8]

- Of the HR+/HER2− breast cancer patients eligible for ET, approximately 53% progress or relapse whilst receiving, or following ET therapy,[13] and it is this ET-resistant breast cancer population the company is focusing on in their submission.

2.2 Critique of company's overview of current service provision

The company provides a summary of the current clinical pathway for early and advanced breast cancer (CS Section B.1.3.3). Although the focus of this STA is on abemaciclib plus fulvestrant (ABE-FUL) as a treatment option for people with HR+/HER2− ET-resistant aBC, the ERG considers an outline of the treatment pathway for early disease and ET-sensitive disease important as the choice of treatment at these stages in the treatment pathway has an impact on the treatment options for patients in the advanced setting who have progressed on or after ET (Figure 1).

Figure 1. Treatment pathway for early and advanced HR+/HER2- breast cancer



Abbreviation: ET, endocrine therapy

2.2.1 Early breast cancer

As highlighted by the company, NICE Guideline 101 (NG101) recommend patients with early and locally aBC undergo surgery and appropriate adjuvant therapy (Figure 1).[14] People with tumours deemed to be operable will undergo either breast-conserving surgery (removal of the tumour) or mastectomy (removal of the breast). In cases in which the cancer is judged to be inoperable at presentation, or unsuitable for breast conservation surgery, neoadjuvant therapy might be given before surgery with the goal of reducing tumour size to ensure maximal removal of cancerous cells and potentially facilitate breast conservation.[14] For people with HR+ disease, recommended neoadjuvant therapies include chemotherapy or an ET: an aromatase inhibitor (AI) such as anastrozole or letrozole, or occasionally tamoxifen. Surgery is typically followed by adjuvant therapy to reduce the risk of disease recurrence. The choice of adjuvant therapy, which includes radiotherapy, chemotherapy, biological therapy, bisphosphonates and endocrine therapy, is based on prognostic and predictive factors and the type of surgery performed (radiotherapy only).[14, 15] NICE Guideline 101 recommends

using the PREDICT tool to estimate prognosis and the absolute benefits of different adjuvant therapies for women with invasive breast cancer.[14] Most people with HR+ breast cancer will receive adjuvant ET.[16] NICE recommends that tamoxifen should be offered to men and premenopausal women, and to postmenopausal women if they are at low risk of disease recurrence. Postmenopausal women at medium or high risk of disease recurrence should be offered an AI as the initial adjuvant ET.[14] The choice of AI is determined by marketing authorisation and tolerability profile. AIs should be given as initial adjuvant therapy for five years. Extended therapy (total duration of ET > 5 years) with an AI should be offered to postmenopausal women who are at medium or high risk of disease recurrence and who have been taking tamoxifen for two to five years. Extended therapy with tamoxifen for longer than five years should be considered for both pre- and postmenopausal women with HR+ breast cancer.

Around 65% of patients with early or localised breast cancer will not need any further therapy, however, the remaining 35% will go on to develop aBC.[7] Some of these patients will have relapsed soon after starting adjuvant ET, others will have progressed after completing adjuvant ET and therefore be considered to have different degrees of ET-resistance, which will have an impact on their prognosis and choice of treatment for their aBC.

2.2.2 Advanced breast cancer

Patients with aBC includes those who progress to locally advanced or metastatic disease after completing neoadjuvant or adjuvant therapy as well as people newly diagnosed with metastatic disease. The treatment options for aBC depend on prior treatment, menopausal status, disease severity, and HR and HER2 status (Figure 1). In the advanced setting patients are treated until progression and likely to go through multiple lines of treatment. At each new line of therapy the treatment choice will depend on additional factors including response to prior treatment, toxicity profile of the different treatments and patient preference. The company presents the treatment options for people with HR+/HER2- aBC based on ET sensitivity (CS Section B.1.3.3). The ERG's clinical experts agree with the company that people with ET-resistant disease, whether primary or acquired, are treated differently to patients who are ET-naïve or have ET-sensitive disease. However, the ERG notes that ET resistance is a continuum and that the ESMO definitions of ET-resistance may not be followed in clinical practice.[8] Below is a summary of the treatment pathway for ET-sensitive and ET-resistant aBC, as put forward by the company, together with details about at what line of therapy these treatment options are recommended and used.

Treatment options for ET-sensitive aBC

For people with HR+/HER2– cancer who progress to metastatic disease after completing neoadjuvant or adjuvant therapy, or newly diagnosed metastatic disease, NICE recommends an AI or tamoxifen as first-line endocrine-based treatment (Figure 1).[17] An AI is recommended for postmenopausal women with HR+ aBC who have not previously received ET, or who have been previously treated with

tamoxifen, and tamoxifen is recommended with ovarian suppression for pre- or peri-menopausal women.[17] According to the ERG's clinical experts, preferred first-line treatment for postmenopausal women and premenopausal women with ovarian suppression, is an AI in combination with a cyclin-dependent kinases (CDK) 4/6 inhibitor, that is, either palbociclib or ribociclib, both of which are recommended by NICE within their marketing authorisations.[18, 19]

In patients with aBC that is imminently life-threatening or with visceral organ involvement which requires early relief of symptoms, an anthracycline- or taxane-based chemotherapy regimen is the preferred treatment.[17] For patients who have received chemotherapy as first-line treatment, ET is recommended as second line treatment following the completion of chemotherapy.[17] Fulvestrant is not recommended by NICE in postmenopausal women who are ET-naïve (in ET sensitive category).[17]

Treatment options for ET-resistant aBC

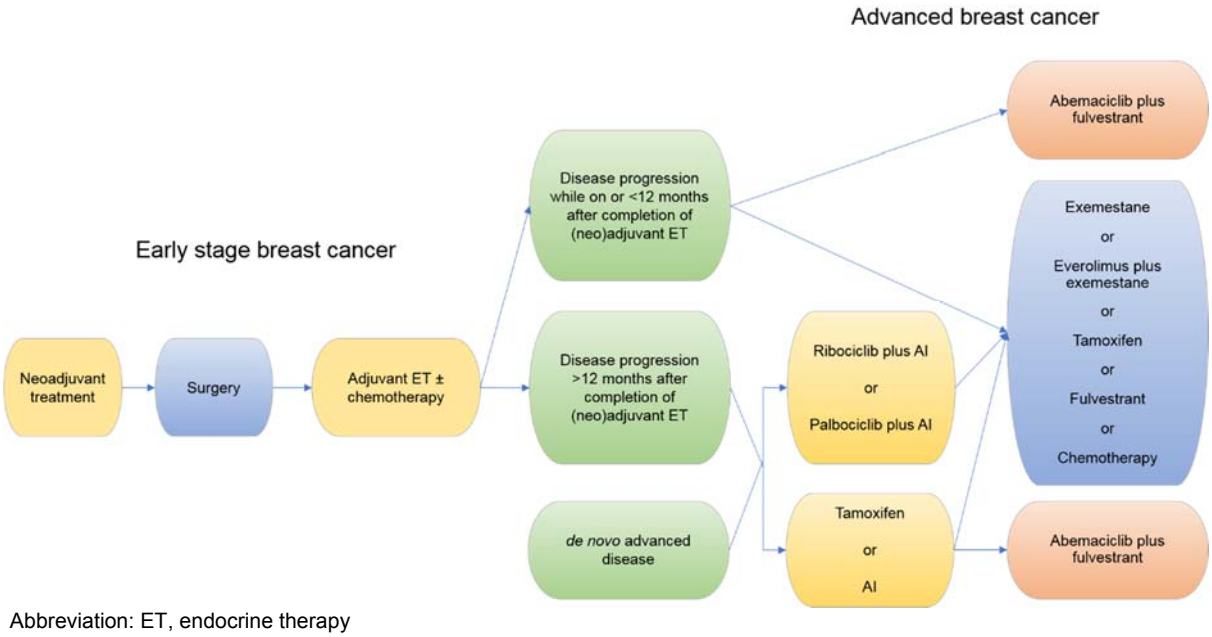
As outlined by the company, NICE recommends exemestane with or without everolimus or tamoxifen as treatment options for people experiencing disease progression after ET (Figure 1).[17] The ERG notes that NICE also recommends offering chemotherapy on disease progression. The ERG's clinical experts fed back that the choice of treatment would be determined on a patient-by-patient basis, based on prior treatment, age, performance status, disease severity and patient preference. According to the company's clinical experts, initiation of chemotherapy would be delayed as long as possible since chemotherapy is associated with a significant toxicity burden and impact on patients' health related quality of life (HRQoL), and that chemotherapy is therefore positioned after all other treatment options for ET-resistant disease have been exhausted. In contrast, the ERG's clinical experts fed back that chemotherapy is a relevant treatment alternative for some people in this patient group, who are progressively symptomatic but who are not in visceral crisis. Typically, capecitabine would be used in those whose disease is progressing slowly, and more aggressive chemotherapy regimens, such as taxanes, weekly paclitaxel or 3-weekly docetaxel, in those in whom a more rapid response is required. The ERG's clinical experts also advised that, as highlighted by the company, the predominant treatment of choice for ET-resistant aBC would be everolimus plus exemestane, but note that the combination is recommended specifically for postmenopausal women that have recurred or progressed after a non-steroidal AI. In clinical practice, this also includes pre- and peri-menopausal women who take ovarian suppression.

Despite not being recommended by NICE for use in the NHS, fulvestrant is included as a relevant comparator in the final scope for this STA.[10] The company and the ERG's clinical experts highlight that, fulvestrant is used in a small number of patients in the UK, either funded by NHS Trusts without reimbursement, or in private hospitals and is therefore considered a treatment option in this setting. CDK 4/6 inhibitors palbociclib and ribociclib, in combination with fulvestrant hold marketing

authorisations for this patient population, but neither have been appraised by NICE at the time of writing.

ABE-FUL is proposed within this STA as a treatment alternative for women who have relapsed or progressed on or after prior ET, that is, for women with primary or acquired ET-resistant breast cancer (Figure 2). The CS outlines that introduction of ABE-FUL would give greater treatment choice, and delay initiation of chemotherapy. The ERG's clinical experts commented that they would not consider using ABE-FUL after another CDK 4/6 inhibitor plus AI because of the intensity of following a combination treatment with another combined regimen, and because of the lack of evidence of reversal of ET resistance. If a CDK 4/6 inhibitor plus AI is used first-line, subsequent treatment would most likely be a monotherapy, typically fulvestrant (if available) or single agent chemotherapy. At this time, as CDK4/6 inhibitors plus AI is the preferred first-line choice of treatment, use of ABE-FUL second line would be limited. However, the ERG's clinical experts emphasised that should ABE-FUL be approved as a treatment option for people with ET-resistant aBC then, dependent on the patient, AI monotherapy might be given as a first-line treatment and ABE-FUL might be given subsequently at second-line, although the number of patients this applies to is likely to be small.

Figure 2. Treatment pathway for early and advanced HR+/HER2- breast cancer after introduction of abemaciclib



Abbreviation: ET, endocrine therapy

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

The company provided a summary of the final scope issued by the National Institute for Health and Care Excellence (NICE),[10] together with the rationale for any deviation from the scope (Table 1). The company highlights the submission differs from the final scope in terms of the population, which in the company submission (CS) is focused on women with endocrine therapy (ET) resistant breast cancer in the advanced setting. In addition, the decision problem addressed in the CS does not consider chemotherapy as a relevant comparator to abemaciclib plus fulvestrant (ABE-FUL). The differences between the decision problem addressed in the CS and the scope are discussed in greater detail in the sections that follow.

Table 1. Summary of decision problem as outlined in the company's submission. (reproduced from CS, Table 1, pg. 20)

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	• People with untreated advanced HR+/HER2− breast cancer • People with advanced HR+/HER2− breast cancer that has progressed on or after endocrine therapy	Women of any menopausal status[a] with locally advanced[b] or metastatic HR+/HER2− breast cancer who had progressed while receiving (neo)adjuvant ET, ≤ 12 months from the end of adjuvant therapy, or while receiving first-line ET for locally advanced[b] or metastatic disease	Patients who are untreated in the advanced setting and those who have progressed after ET in the advanced setting are considered to be part of one homogenous population for this submission. They share the ET-resistant characteristics,[c] having received prior ET as (neo)adjuvant therapy or therapy for advanced breast cancer. Patients have progressed whilst receiving or ≤ 12 months after ET, and therefore both populations represent a rapidly-progressing, hard-to-treat, ET-resistant patient population.
Intervention	Abemaciclib in combination with fulvestrant	Abemaciclib in combination with fulvestrant	N/A
Comparator(s)	For people with untreated advanced hormone-receptor positive HER2-negative breast cancer: • Palbociclib in combination with an aromatase inhibitor • Ribociclib in combination with an aromatase inhibitor • Tamoxifen (in accordance with NICE guidance CG81) For people with advanced hormone-receptor positive HER2-negative breast cancer that has progressed after one line of prior endocrine therapy:	• Exemestane • Everolimus and exemestane • Tamoxifen • Fulvestrant	Palbociclib or ribociclib in combination with an aromatase inhibitor are not used in clinical practice for the patients in this Decision Problem, who are ET-resistant,[c] and have progressed whilst receiving or ≤ 12 months after ET, as described above. Palbociclib and ribociclib in combination with an aromatase inhibitor are utilised in endocrine-sensitive patients, defined as patients who have received treatment with ET in the (neo)adjuvant setting with a disease-free interval >12 months from completion of ET in PALOMA-1 and MONALEESA-2, respectively.[20, 21]

	• Exemestane • Everolimus and exemestane • Tamoxifen • Fulvestrant • Chemotherapy (in accordance with NICE guidance)		Chemotherapy is reserved for patients in whom initial or second-line ET has failed, and is therefore positioned after ABE-FUL in the treatment pathway
Outcomes	• OS • PFS • Response rate • Adverse effects of treatment • HRQoL	• OS and OS rated • PFS • Response rates • ORR o DCR o CBR o DoR • Safety and tolerability (adverse effects of treatment) • PROs: o Pain intensity (BPI) o Change in symptom burden from baseline using the EORTC QLQ-C30 and EQ-5D-5L	N/A
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY). If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective. The availability of any patient access schemes for the comparator technologies will be taken into account.	As per NICE reference case, cost-effectiveness is expressed in terms of incremental cost QALY, and costs considered from the perspective of the NHS and PSS.	The patient access scheme for abemaciclib has been incorporated into the cost-effectiveness analysis. A patient access scheme is available everolimus. However, this is confidential and therefore cannot be considered in this submission.

a In pre- or peri-menopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone agonist to induce menopause.
b Locally advanced disease was not amenable to curative treatment by surgery.
c ET-resistant patients are those whose disease does not respond to ET. Relapse during the first two years of treatment with adjuvant therapy, or progressive disease within the first six months of initial ET for aBC is known as primary resistance.

Secondary acquired resistance refers to patients who initially respond to ET, yet later become unresponsive (patients relapse whilst being treated with adjuvant ET but after the first 2 years of treatment, relapse within 12 months of completing adjuvant ET, or progress ≥6 months after initiating ET for aBC , while on ET).[8]
d At the time of cut-off for the MONARCH 2 trial, OS data were still immature and data are not expected within the appraisal timelines.

Abbreviations: BPI: brief pain inventory; CBR: clinical benefit rate; DCR: disease control rate; DoR: duration of response; EORTC QLQ-C: European organisation for research and treatment of cancer quality of life questionnaires-core; ET: endocrine therapy; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; HRQoL: health-related quality of life; N/A: not applicable; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PROs: patient-reported outcomes; PSS: Personal Social Services; QALY: quality-adjusted life year.

3.1 Population

The final scope issued by NICE specifies two population of interest for this appraisal:

People with HR+/HER2- aBC who are either:

1. untreated in the advanced setting; or

2. who have progressed after prior ET.

The populations in the scope are in line with the population specified in the marketing authorisation for abemaciclib: women with HR+/HER2- aBC as initial ET in the advanced setting, or in women who have received prior ET.[22]

The decision problem as addressed by the company in the CS is based on the key trial, MONARCH 2, designed to evaluate the efficacy and safety of ABE-FUL in women with HR+/HER2− aBC who had progressed while receiving (neo)adjuvant ET, ≤ 12 months from the end of adjuvant therapy, or while receiving first-line ET in the advanced setting. The population that the company is focusing on in their submission therefore falls into the second population in the scope, people who have had prior ET, as well as being a subset of the first population in the scope, people untreated in the advanced setting. However, the decision problem, as addressed by the company, does not include people with ET-naïve or ET-sensitive aBC, that is, *de novo* advanced disease and people who progressed > 12 months from completion of ET in the (neo)adjuvant setting, who also form part of the first population in the scope. According to the company, this ET-sensitive population is not relevant for the appraisal of ABE-FUL but is relevant for the appraisal of abemaciclib plus an AI (GID-TA10262), which looks at people with HR+/HER2− aBC that has not been previously treated with ET in the advanced setting. As mentioned previously, the marketing authorisation for abemaciclib is in line with the scope of this STA, though, the wording of the licence does not mention ET-resistance or specify any limitation of who would be eligible for ABE-FUL versus abemaciclib plus an AI.

The ERG's clinical experts agree with the company that ABE-FUL would be used for people who have progressed after prior ET and that it isn't relevant for people in the advanced setting who are ET-naïve

or ET-sensitive. Thus, the ERG agrees with the company to focus on ABE-FUL for people with ET-resistant HR+/HER2− aBC.

The key trial, MONARCH 2, is limited to women of any menopausal status, which is consistent with the marketing authorisation for abemaciclib, but only partly consistent with the marketing authorisation for fulvestrant and the final scope. The indication for fulvestrant is limited to post-menopausal women, although in clinical practice fulvestrant is also used for pre-and peri-menopausal women receiving ovarian suppression. The scope for this appraisal does not specify sex or menopausal status, that is, the proposed indication for abemaciclib is narrower than the scope, although the number of men who have breast cancer is very low.

MONARCH 2 is a multicentre trial conducted in 142 centres across 19 countries; around 40% of patients were from Europe, but the trial did not include any UK centres. Nonetheless, the baseline characteristics of patients in MONARCH 2 are generally in keeping with those expected in women with HR+/HER2− aBC in UK clinical practice, according to the ERG's clinical experts. Further patient and disease characteristics of those enrolled in MONARCH 2 are discussed in greater detail in Section 4.2.2.

In summary, the ERG considers the data presented within the submission to be representative of women with HR+/HER2− aBC in England and Wales who would be eligible for treatment with ABE-FUL, and therefore to be relevant to the decision problem the company has focused on for this STA.

3.2 Intervention

The focus of this STA is abemaciclib in combination with fulvestrant. Abemaciclib, brand name Verzenios©, is a small molecule inhibitor of cyclin-dependent kinase (CDK)4 and CDK6.[23] CDKs are a family of enzymes regulating the cell cycle by promoting cell division and proliferation.[24, 25] CDK 4/6 inhibitors such as abemaciclib inhibit DNA synthesis and cell proliferation leading to suppression of tumour growth. Fulvestrant is a competitive oestrogen receptor (ER) antagonist that acts by down-regulation of ERs.[26]

Abemaciclib was granted marketing authorisation in October 2018.[22] The indication for abemaciclib is for the treatment of women with HR+/HER2– aBC in combination with an AI or fulvestrant as initial ET, or in women who have received prior ET. In pre- or perimenopausal women, the ET should be combined with a luteinising hormone-releasing hormone (LHRH) agonist. Thus, the license is broader in terms of both the population (as discussed in Section 3.1) and the intervention compared to the scope of this STA, which is only focused on abemaciclib in combination with fulvestrant. Abemaciclib in combination with an AI is being assessed in a separate appraisal (GID-TA10262).[10]

Fulvestrant was granted European marketing authorisation in 2004 for the treatment of ER+, aBC in postmenopausal women not previously treated with endocrine therapy, or with disease relapse on or after adjuvant ET, or disease progression on ET.

At initiation of MONARCH 2, patients in the ABE-FUL group received a daily dose of 400 mg abemaciclib. After a review of preliminary safety data and dose reduction rates, the protocol was amended to reduce the daily dose of abemaciclib to 300 mg. The impact of the protocol amendment is discussed in Section 4.2 and 4.3.6. Following this, the recommended dose of abemaciclib is one 150 mg oral tablet twice daily on a 28-day cycle. The recommended dose of fulvestrant is 500 mg given as an intramuscular injection at intervals of one month, with an additional 500 mg dose given two weeks after the initial dose.[26] Abemaciclib in combination with fulvestrant should be taken continuously as long as the patient is deriving clinical benefit or until unacceptable toxicity occurs.[22] In MONARCH 2, people were treated until progression, death or patient withdrawal.[27] Management of some adverse reactions of abemaciclib may require dose interruption and/or dose reduction (such as haematological toxicities, diarrhoea, increased alanine aminotransferase [ALT]). Abemaciclib is available as 50 mg, 100mg and 150mg tablets; for a first dose adjustment 100 mg twice daily is recommended for abemaciclib, the recommended dose for a second dose adjustment is 50 mg twice daily.[22]

3.3 Comparators

The comparators listed in the NICE final scope as relevant for this appraisal of ABE-FUL are listed below.

1. Comparators for people with untreated HR+/HER2– aBC:
    - palbociclib in combination with an aromatase inhibitor (AI);
    - ribociclib in combination with an AI;
    - tamoxifen.
2. Comparators for people with HR+/HER2– aBC that has progressed after one line of prior endocrine therapy:
    - exemestane;
    - everolimus and exemestane;
    - tamoxifen;
    - fulvestrant;

- chemotherapy.

The ERG's clinical experts agree with the company that the comparators for the first population in the NICE final scope are only relevant for those which are ET-sensitive. That is, people with *de novo* advanced disease and people who progressed > 12 months from completion of ET in the (neo)adjuvant setting would be offered palbociclib or ribociclib in combination with an AI, or tamoxifen for men and pre- and peri-menopausal women as first-line treatment. However, the decision problem is focused on ET-resistant aBC, whether it's first or second line in the advanced setting, as discussed in Section 3.1 (Figure 2). For people with ET-resistant aBC, the relevant comparators are the same as those specified for the 2nd population (progressed after one line of ET) in the NICE scope, irrespective of if they are untreated in the advanced setting or progressed after one line of ET. The ERG's clinical experts went on to comment that, what guides suitability of the different treatments is the degree of resistance, that is, depending on where on the ET-resistance spectrum the patient is; ET-sensitive disease, primary or acquired resistance or somewhere in between.

Exemestane is a steroidal AI. As a monotherapy it has limited use; it is only used for patients who have shown a relatively good response to prior AI, or are medically unfit to receive exemestane in combination with everolimus, or chemotherapy. Currently the main treatment for people with ET-resistant aBC is exemestane in combination with everolimus, an inhibitor of mammalian target of rapamycin (mTOR). Tamoxifen, a selective oestrogen receptor modulator (SERM),[28] has some use for ET-resistant aBC. Similar to ET-sensitive disease it is mainly used for pre- and peri-menopausal women, and mainly for people who has progressed while receiving (neo)adjuvant ET. Fulvestrant monotherapy is used for people who have responded to AI monotherapy, but show signs of acquired or secondary resistance. As mentioned previously, fulvestrant is not recommended by NICE, and is only available through trusts who choose to fund it without reimbursement.

Chemotherapy is associated with a significant toxicity burden and impact on patients' HRQoL compared with ETs. According to the company's clinical experts, clinicians aim to delay initiation of chemotherapy for as long as possible and would therefore exhaust all other treatment options for ET-resistant aBC before commencing chemotherapy. Chemotherapy would therefore be positioned after ABE-FUL in the treatment pathway and not be a relevant comparator. The ERG notes that NICE recommends offering chemotherapy for patients whose disease is imminently life-threatening or requires early relief of symptoms because of significant visceral organ involvement, and that in MONARCH 2 more than half of patients had visceral metastases (Section 4.2.2). This is supported by the ERG's clinical experts who commented that, because CDK4/6 inhibitors, such as abemaciclib, have shown favourable response rates in clinical trials, these are likely to be used in people with progressively symptomatic disease, but who are not in visceral crisis, for whom chemotherapy would otherwise be the most suitable alternative.

MONARCH 2, the key trial assessing the efficacy and safety of ABE-FUL, provides direct evidence for ABE-FUL versus fulvestrant monotherapy. To assess the relative efficacy and safety of ABE-FUL compared with the other comparators in the NICE final scope, the company performed network meta-analyses (NMAs). In the initial CS, the company did not include chemotherapy as a comparator in the NMA, for the reasons described above. However, at the request of the ERG this was addressed at the clarification stage. The ERG's critique on the appropriateness of the trials included in the NMA and the methods used by the company is presented in Section 4.

3.4 Outcomes

The clinical outcomes listed in the final scope issued by NICE[10] are:

- overall survival (OS);
- progression-free survival (PFS);
- response rate;
- adverse effects of treatment;
- health related quality of life (HRQoL).

The company presents direct evidence for ABE-FUL versus fulvestrant monotherapy for all the outcomes listed in the NICE final scope, which were all captured in the key trial MONARCH 2. The primary outcome in MONARCH 2 was investigator assessed PFS, though, results of sensitivity analyses based on independent review of PFS were also provided (Section 4.2.1 and 4.3.1). The data presented in the CS are based on the primary analysis data cut-off of 14 February 2017 at which point the median follow-up was just over 19 months in both trial arms. At this timepoint OS data were immature with only around 20% of patients having died in each of the trial arms, and therefore the long-term efficacy of ABE-FUL is uncertain. The estimated data cut-off for the final OS analysis for MONARCH 2 is anticipated to be April 2019, and the estimated study completion date is February 2020.

Response rate was captured as objective response rate (ORR), disease control rate (DCR), and clinical benefit rate (CBR). The company also present data for duration of response (DoR). During MONARCH 2, all adverse events (AEs) were recorded at every visit according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. General HRQoL was measured using the EORTC QLQ-C30 and EQ-5D-5L, and symptom specific QoL, pain intensity, was assessed using the modified Brief Pain Inventory-Short Form (mBPI-sf).

The company presented evidence for ABE-FUL versus other relevant comparators through network meta-analyses (NMAs) for PFS, OS, ORR, and CBR. The company's original approach was based on the assumption of proportional hazards (PH), which was shown not to hold for some of the trials for some of the outcomes, but at the clarification stage the company provided NMAs based on fractional polynomials for PFS and OS, which does not depend on the PH assumption. This will be discussed in Section 4.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review

4.1.1 Searches

The company's review of the literature sought to identify all randomised controlled trials (RCTs) and non-randomised studies (NRSs) evaluating the clinical efficacy and safety of abemaciclib and comparators relevant to the MONARCH trial population. The search terms and strategies implemented in the company's literature review were provided as an Appendix (Appendix D.1.1.) of the company's submission (CS).

The company searched key electronic databases, including MEDLINE and Embase, via OVID SP, and The Cochrane Library, for RCT and NRS evidence. Databases were searched from inception. Searches were originally run in December 2015 with two update searches, the most recent in January 2018. The search strategies combined free text terms and exploded MESH terms for MEDLINE and The Cochrane Library, and Emtree terms for Embase. The search strategies included terms for breast cancer, interventions and study type (RCT and NRS filter). According to the company, an adequate number of RCTs were identified in the original search in 2015 and therefore NRSs were not considered in the search strategy for later updates. The company also searched relevant conference proceedings from 2014 to 2017 and clinical trial registries for additional relevant studies and ongoing trials. The company does not mention searching reference lists of identified systematic reviews or included studies.

The evidence review group (ERG) considers the company's search strategies to be substantially broader than what is required for the decision problem or the scope for this single technology appraisal (STA), but comprehensive, and likely to enable identification of studies to inform the indirect treatment comparison (ITC) of this STA. The ERG is confident that the search strategies will have retrieved all relevant records up until the last search date in January 2018. However, the ERG is aware that at least one trial (BOLERO-6[29]), relevant to the ITC, was not identified due to being published after the search date.

4.1.2 Inclusion criteria

Full eligibility criteria for the review of clinical effectiveness of abemaciclib plus fulvestrant in HR+/HER2– advanced breast cancer (aBC) compared with relevant comparators are presented in Appendix **10.1**. The eligibility criteria aimed to identify studies investigating populations comparable to that of the MONARCH 2 trial. However, it was anticipated that the volume of relevant literature would be low if the same eligibility criteria were used, due to the specificity of the MONARCH 2 population and heterogenous reporting in published studies. Therefore, the eligibility criteria for the population were relaxed. The deviations compared with the MONARCH trial population are

summarised below. The impact of these assumptions in terms of the heterogeneity of the trials included in the ITC will be discussed in Section 4.4.1.

HER2- status: the criterion of HER2- status was removed to prevent exclusion of potentially relevant trials performed before 2007, as HER2– status was not commonly reported prior to ASCO recommendations in 2007. The ERG notes that only one out of nine trials eventually included in the analysis were published before 2007 and five of the included studies did report HER2 status (Appendix 10.5,

Table 61. Summary of the methods of the included studies (adapted from CS Appendix D.1.2. Table 22)

Trial	Treatments	Study location	Primary endpoint	Phase	Blinded/ open-label
BOLERO-2[55]	EXE-EVE, EXE	Multicentre, International	PFS	III	Double-blind
BOLERO-6[28]	EXE-EVE, CAP	Multicentre, International	PFS	II	Open-label
CONFIRM[56]	FUL 500 mg, FUL 250 mg	Multicentre, international: 128 centres in 17 countries	PFS	III	Double-blind
Hi-FAIR fx[42]	TOR 120 mg, FUL 500 mg	NR	CBR	II	Open-label
Milla-Santos 2001[40]	TOR 60 mg, TMX	NR	CBR	III	Open-label
MONARCH 2[26]	ABE-FUL 500 mg, FUL 500 mg	Multicentre, International: in 19 countries	PFS	III	Double-blind
SoFEA[59]	FUL 250 mg, EXE	Multicentre: UK and South Korea	PFS	III	Open-label
Yamamoto 2013[43]	TOR 120 mg, EXE	Multicentre	CBR	II	Open-label
Zhang 2016[60]	FUL 500 mg, FUL 250 mg	China	PFS	III	Double-blind

Abbreviations: ABE, abemaciclib; ANAS, anastrozole; CBR, clinical benefit rate; EVE, everolimus; EXE, exemestane; FUL, fulvestrant; LTZ, letrozole; mg, milligrams; MGA, megestrol acetate; NMA, network meta-analysis; ORR, objective response rate; OS, overall survival; PAL, palbociclib; PFS, progression-free survival; SLR, systematic literature review; TOR, toremifene; TTP, time to progression.

- Table 62). In addition, the prognosis and treatment pathway, as recommended by the National Institute for Health and Care Excellence (NICE, CG81)[17], is markedly different for HR+/HER2- , which is the population of interest to this appraisal, compared with people with, e.g. HR+/HER2+ disease. The ERG considers relaxing the HER2 status criterion reasonable to enable comparisons of abemaciclib plus fulvestrant (ABE-FUL) with all the relevant comparators in the scope but notes that the potential heterogeneity in HER2- status should be kept in mind when interpreting the results of the ITCs.

- *HR+ status:* only studies reporting ≥50% of the population to be HR+ were included. If HR status was not reported the study was excluded.

- *Progression on prior endocrine therapy (ET):* studies were eligible for inclusion even if no information was reported about progression on prior ET. These studies were included under the company's assumption that the standard treatment for patients undergoing later lines of treatment in the advanced setting would require exhaustion of ET options prior to subsequent chemotherapy regimens. The ERG's clinical experts commented that chemotherapy can be used at any time in the treatment pathway and does not necessarily mean that a patient will have progressed on prior ET. However, the company's assumption is supported by NICE recommendations (CG81)[17], stating that ET should be offered as first line treatment for the majority patients with ER-positive aBC.

- *Menopausal status:* if a trial population was exclusively pre-menopausal, the study was not included, however, if menopausal status was not reported the study was still eligible for inclusion.

- *Prior chemotherapy:* studies were eligible for inclusion if patients were permitted to receive up to one line of chemotherapy in the advanced setting.

In addition to the comparators of interest to this appraisal, the company included a comprehensive list of treatments. The company states that the comparators listed in the inclusion criteria were based on treatment guidelines from the National Comprehensive Cancer Network (NCCN) in the USA[30], the European Society for Medical Oncology (ESMO)[8] and NICE in the UK[17]. The ERG notes that the comparators do not seem to be limited to those considered to be relevant for the treatment of the population of interest. However, the broad inclusion criteria are likely to capture all studies that could potentially inform networks for ITCs. The outcomes listed in the inclusion criteria are in line with those captured in MONARCH 2. No language limit was applied. Overall, the ERG considers the inclusion criteria to be appropriate to identify clinical efficacy studies that are relevant to the decision problem outlined in the CS.

4.1.3 Critique of screening process and data extraction

Although the company states that, at the screening stage, identified abstracts were reviewed against eligibility criteria that were specific to the MONARCH 2 population, the ERG assumes that all references were assessed against the relaxed eligibility criteria listed in Table 58. All titles and abstracts were reviewed independently by two systematic reviewers. Any disagreements in selection were referred to a third reviewer. The full paper was reviewed for all references that were considered potentially eligible. A phased approach was used in which RCTs were first identified, with the intention to investigate NRSs should the RCT evidence-base be limited. Following identification of an adequate number of RCTs in the initial review in 2015, NRSs were not considered further. The ERG notes the contradiction in terms of the eligibility criteria, that were relaxed because of the anticipated low volume

of relevant literature in the population of interest. In addition, the company failed to identify RCTs for one of the comparators in the scope, tamoxifen (Section 4.4.1), even using the relaxed eligibility criteria. There may, therefore, have been some value in continuing looking at NRSs which could potentially inform the efficacy and safety of treatments in the relevant population.

In total the systematic review included 29 independent studies, reported in 37 full-text articles, eight conference abstracts, and one CSR. No relevant studies of tamoxifen were identified in the systematic review, but the company included one trial, Milla-Santos 2001, with potential overlap with the relevant population, which was identified from the systematic review for the appraisal of abemaciclib plus AI.

Only 19 of the included studies informed the ITCs presented in the CS, for any of the outcomes analysed. The remaining studies could not be connected to the network for any of the required outcomes. During the clarification stage, at the ERG's recommendation, the company re-analysed PFS and OS concentrating the network to studies directly or indirectly informing the comparisons of interest by excluding some studies. In addition, at the request of the ERG, the company also included trials connecting tamoxifen and chemotherapy to the network (discussed in Section 4.4.1). The trial of chemotherapy, BOLERO-6, was not identified in the company's systematic literature review as it was published after the final search date. However, the company was aware of the trial, which is referenced in the CS. Nine trials were included in the company's updated analysis of PFS or OS. Data extraction of included studies was done by a single reviewer and independently validated by a second reviewer.

In summary, the data from key RCTs are used to inform the analysis of the clinical efficacy and safety of ABE-FUL versus the comparators in the NICE final scope. However, there may also be relevant NRSs with populations more aligned to that of MONARCH 2, which haven't been identified. The ERG considers it unlikely that any RCTs that are relevant to the decision problem were omitted from the analysis of clinical effectiveness evidence.

4.1.4 Quality assessment

The company assessed the quality of MONARCH 2, and the key trials included in the ITC, against criteria adapted from guidance for undertaking reviews in health care issued by the Centre for Reviews and Dissemination (CRD)[31], as provided in the NICE template for company submission of evidence to the STA process.[32] The ERG independently validated the company's assessment of MONARCH 2; the company's assessment, together with accompanying comments from the ERG, is presented in Section 4.2.4. The company's assessment of the key trials in the ITC is presented in Section 4.4.1.

4.1.5 Summary statement

The company conducted a comprehensive search of various sources for clinical evidence relevant to the decision problem and the ERG is confident that the search strategies will have retrieved all relevant

records up until the last search date in January 2018. However, the ERG is aware that at least one trial (BOLERO-6), relevant to the ITC, was not identified due to being published after the search date. The trial inclusion criteria, in terms of the population, were relaxed compared with the key trial, MONARCH 2, to enable identification of clinical efficacy RCTs that were relevant to the decision problem outlined in the CS. The ERG is confident that all key RCTs are used to inform the analysis of the clinical efficacy and safety of ABE-FUL versus the comparators in the NICE final scope. However, there may be relevant NRSs with populations more aligned to that of MONARCH 2, which haven't been identified.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

As discussed in Section 4.1, the company's systematic review of the literature on clinical effectiveness of ABE-FUL identified one RCT comparing ABE-FUL versus fulvestrant alone.[33] The methodology and conduct of the RCT, MONARCH 2, is summarised in Table 2.

Table 2. Clinical effectiveness evidence (reproduced from CS, Table 3, pg. 28)

Study	**MONARCH 2 (NCT02107703)**
Study design	Phase III, multicentre, randomised, placebo-controlled, double-blind trial
Population	Women with HR+ / HER− locally advanced or metastatic breast cancer. Patients must have relapsed with radiologic evidence of progression while receiving neo(adjuvant) ET, ≤ 12 months from completion of adjuvant ET, or relapsed while receiving first-line ET for metastatic disease.
Intervention(s)	Oral abemaciclib 150 mg twice daily (every 12 hours) on a continuous 28-day treatment cycle, in combination with IM fulvestrant 500 mg on Days 1 and 15 of Cycle 1, then on Day 1 of subsequent cycles (every 28 days)
Comparator(s)	Oral placebo twice daily (every 12 hours) on a continuous 28-day treatment cycle, in combination with IM fulvestrant 500 mg on Days 1 and 15 of Cycle 1, then on Day 1 of subsequent cycles (every 28 days)
Indicate if trial supports application for marketing authorisation	Yes — Indicate if trial used in the economic model: Yes
Rationale for use/non-use in the model	MONARCH 2 is the pivotal phase III study for ABE-FUL in women with HR+/HER2− locally advanced or metastatic breast cancer that had progressed on or after prior endocrine therapy. This trial informed the marketing authorisation application and considers a population directly relevant to the decision problem addressed in the submission

Reported outcomes specified in the decision problem	• PFS
	• OS
	• Response rate
	  o ORR (CR + PR)
	  o DCR (CR + PR + SD)
	  o CBR (CR + PR + SD ≥6 months)
	  o DoR (CR + PR)
	• Safety and tolerability
	• HRQoL
	  o Pain intensity (BPI)
	  o EORTC QLQ-C30
	  o EQ-5D-5L

All other reported outcomes	Resource utilisation (concomitant medications)

Abbreviations: AE: adverse event; BPI: Brief Pain Inventory; CBR: clinical benefit rate; CR: complete response; DCR: disease-control rate; DoR: duration of response; EORTC QLQ: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; ET: endocrine therapy; HER: human epidermal growth factor receptor; HR: hormone receptor; HRQoL: health-related quality of life; IM: intramuscular; mBC: metastatic breast cancer; ORR: objective response rate; OS: overall survival PR: partial response.

4.2.1 Trial conduct

MONARCH 2 is an international, randomised, double-blind, placebo-controlled phase III trial. The primary objective of MONARCH 2 was to assess the efficacy and safety of ABE-FUL compared with fulvestrant alone in people with advanced HR+/HER2− breast cancer that has progressed on or after prior ET.[27] MONARCH 2 was conducted in 142 centres across 19 countries in Europe, North and Central America, Asia and Australia; though no patients were recruited in the UK. Patients were randomly assigned, in a 2:1 ratio, to receive ABE-FUL (n=446) or PBO-FUL (n=223). The patient flow diagram for MONARCH 2 is presented in Appendix **10.3.**. Randomisation was stratified by metastatic site (visceral, bone only, or other) and ET resistance (primary or secondary).

- Primary ET resistance was defined as: patients whose disease relapsed while receiving the first 2 years of neoadjuvant or adjuvant ET or progressed while receiving the first 6 months of ET for advanced breast cancer;[8]

- Secondary ET resistance was defined as: everyone not defined as having primary ET resistance. The ERG notes that the definition of secondary ET resistance stated in the ESMO guideline[8] is, "relapse while on adjuvant ET but after the first 2 years, or relapse within 12 months of completing adjuvant ET, or progressive disease ≥6 months after initiating ET for metastatic breast cancer, while on ET" but that this definition includes everyone not defined as having primary ET resistance in MONARCH 2.

Patients were administered abemaciclib and fulvestrant as per the treatment schedule in Table 2. Treatment continued until disease progression, death, or patient withdrawal. At study initiation, patients in the ABE-FUL group received 200 mg abemaciclib twice daily. The protocol was then amended to reduce the starting dose of abemaciclib to 150 mg. A total of 178 patients (26.6%) were enrolled prior to the protocol amendment; 121 were randomized to abemaciclib at the 200 mg starting dose and 57 to matching placebo. The protocol amendment was based on a review of preliminary safety data and dose reduction rates from a Phase I study (I3Y-MC-JPBH), which prompted an early safety review of MONARCH 2. In study JPBH, several patients discontinued treatment early due to diarrhoea, and most patients did not complete one cycle of treatment at the 200 mg dose or either had a dose reduction or omission. During the blinded safety review in MONARCH 2, it was found that one third of patients required a dose modification in the first 28-day cycle. Based on the 2:1 randomisation ratio, this may have corresponded to up to half of the patients treated with abemaciclib. The protocol amendment reduced the starting dose of abemaciclib to 150 mg for new patients, and all patients randomised to

receive 200 mg abemaciclib had their dose reduced to 150 mg, if they had not already had a dose reduction to manage an adverse event. Dose modifications, including interruption and up to two dose reductions of abemaciclib, were permitted to manage adverse events. Fulvestrant dose reductions were also allowed. If either abemaciclib or placebo was discontinued, patients were permitted to continue receiving fulvestrant, and if fulvestrant required discontinuation, patients were permitted to continue receiving abemaciclib or placebo. However, patients were not permitted to switch treatment groups.

The primary efficacy measure was investigator-assessed PFS as defined by the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1.[34] A blinded review of imaging scans was performed by an independent panel of radiologists. Tumour response was assessed at baseline, approximately every 8 weeks for the first 18 months following randomisation, and approximately every 12 weeks thereafter until disease progression, death, withdrawal of consent, or loss to follow-up.

In summary, MONARCH 2 represents the only available direct comparative evidence on the clinical effectiveness and safety of ABE-FUL versus PBO-FUL. The ERG considers MONARCH 2 to be well-designed and well-conducted. The ERG highlights the potential impact of the protocol amendment reducing the starting dose from 200 mg to 150 mg, on efficacy and safety, which will be discussed in Section 4.3.6.

4.2.2 Baseline characteristics

Baseline characteristics of people enrolled in MONARCH 2 were well balanced across the treatment groups (Table 3). Although no patients from the UK were enrolled in MONARCH 2, the ERG's clinical experts fed back that the baseline characteristics of those enrolled in the trial are representative of people with aBC in England who are likely to be eligible for treatment with ABE-FUL either as first- or second-line treatment.

Almost all people (> 99%) had metastatic disease with visceral metastases present in just under 60% of people (Table 3). The trial only enrolled women of whom less than 20% were pre- or peri-menopausal and the majority post-menopausal. Three quarters of people had acquired ET resistance and the remaining quarter primary ET resistance. Approximately 60% had received their most recent ET in the (neo)adjuvant setting, and the remaining 40% had received their most recent ET for aBC.

Table 3. Baseline characteristics of participants in MONARCH 2 (reproduced from CS, Table 6, pgs 38-39)

Baseline Characteristic	ABE-FUL (N=446)	PBO-FUL (N=223)
Age		
Median (range)	59 (32 to 91)	62 (32 to 87)
Menopausal status, n (%)[a]		

Pre- or peri-menopause (ovarian suppression)	72 (16.1)	42 (18.8)
Post-menopause	371 (83.2)	180 (80.7)
Natural	[redacted]	[redacted]
Surgical	[redacted]	[redacted]
Race, n (%)b		
Asian	149 (33.4)	65 (29.1)
Caucasian	237 (53.1)	136 (61.0)
Other	29 (6.5)	13 (5.8)
ECOG performance statusc		
0	264 (59.2)	136 (61.0)
1	176 (39.5)	87 (39.0)
Region, n (%)		
Europe	[redacted]	[redacted]
Asia	[redacted]	[redacted]
North America	[redacted]	[redacted]
Hormone receptor status, n (%)d		
HR+	[redacted]	[redacted]
ER+/PgR+	[redacted]	[redacted]
ER+/PgR−	[redacted]	[redacted]
ER+/PgR unknown	[redacted]	[redacted]
ER-/PgR+	[redacted]	[redacted]
Missing	[redacted]	[redacted]
HER2 status, n (%)e		
Negative	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Duration of disease (months)		
Median (IQR)	[redacted]	[redacted]
Metastatic site, n (%)f		
Visceral	245 (54.9)	128 (57.4)
Bone only	123 (27.6)	57 (25.6)
Other	75 (16.8)	38 (17.0)
Measurable disease, n (%)		
Yes	318 (71.3)	164 (73.5)
No	128 (28.7)	59 (26.5)
ET resistance, n (%)g		
Primary	111 (24.9)	58 (26.0)
Secondary	326 (73.1)	163 (73.1)
Most recent ET, n (%)h		
(Neo)adjuvant	263 (59.0)	133 (59.6)
Metastatic	171 (38.3)	85 (38.1)
Prior AI, n (%)		
Yes	316 (70.9)	149 (66.8)
No	130 (29.1)	74 (33.2)
Prior chemotherapy for (neo)adjuvant treatment, n (%)		
Yes	267 (59.9)	134 (60.1)
No	179 (40.1)	89 (39.9)

[a] Menopausal status was not available for three patients in the abemaciclib arm and one in the placebo arm.
[b] A total of 31 patients in the abemaciclib arm and nine in the placebo arm had missing race information.

[c] One patient had ECOG performance status of 2 in the abemaciclib arm.
[d] For three patients in the ABE-FUL arm, hormone receptor status was unknown.
[e] For three patients in the ABE-FUL arm and two patients in the PBO-FUL arm, HER2 status was unknown.
[f] Metastatic site was not available for three patients in the abemaciclib arm
[g] ET history was not available for 12 patients in the ABE-FUL arm and five patients in the PBO-FUL;
[h] Six patients in the ABE-FUL arm and two patients in PBO-FUL had not received prior ETs
Abbreviations: AI: aromatase inhibitor; ECOG: Eastern Cooperative Oncology Group; ER: oestrogen receptor; ET: endocrine therapy; HER2: human epidermal growth factor receptor-2; HR: hormone receptor; PgR: progesterone receptor.

4.2.3 Description and critique of statistical approach used

MONARCH 2 was designed to compare PFS for ABE-FUL to that for PBO-FUL. PFS was calculated from the date of randomisation to the date of the first documented disease progression or death due to any cause. The study initially planned to enrol 450 patients, however, after a change in the starting dose of abemaciclib/placebo from 200 mg to 150 mg, the sample size was increased to 630 patients to ensure at least 450 patients were enrolled at the 150 mg dose. Approximately 180 patients were enrolled before the protocol amendment, at the 200 mg dose. The assumptions in the sample size calculation, and a summary of the other statistical analyses carried out in MONARCH 2 are presented in Table 4.

All efficacy analyses, including the primary outcome of PFS, were performed in the intention-to-treat (ITT) population (669 patients), which included all randomised patients who were analysed according to the treatment and stratum to which they were assigned at randomisation, regardless of starting dose. Safety analyses were carried out in the safety population (664 patients) which consisted of all patients who received at least one dose of study drug. Planned sensitivity analyses included (1) analysis of only patients enrolled after the change in starting dose, and (2) analysis of PFS based in assessment of progression by a blinded independent central review (BICR). The stratification factors for the primary and secondary analyses were (1) nature of disease (visceral metastases vs bone-only metastases vs other), and (2) sensitivity to ET (primary resistance vs secondary resistance).

In the economic model the company used PFS KM data from MONARCH 2 adjusted for interval censoring, despite the unadjusted data being the only result presented to show the clinical efficacy of ABE-FUL, and the data used to run the ITC informing the comparisons with the other relevant comparators (Section 4). The company states that the frequency of radiographic assessments in MONARCH 2 (every eight weeks for the first 12 months and every 12 weeks thereafter, Section 4.2.1) may not accurately reflect the underlying time to progression (TTP) for patients as the latter might have occurred at any time between assessments. The company concluded that using the unadjusted PFS KM data could result in an overestimation of median PFS. The ERG does not agree with the company's rationale for a difference in approach between the clinical effectiveness presented for PFS in Section 4.3.1 and the PFS data used in the economic model. This is discussed in more detail in Section 5.4.5.3.

At the time of data cut-off for the primary and final analysis of PFS (14 February 2017), data for PFS and response rate were mature and OS data were immature. The estimated data cut-off for the final OS

analysis for MONARCH 2 is anticipated to be April 2019, and the estimated study completion date is February 2020.

In summary, the ERG considers the methods applied for the design and statistical analysis of MONARCH 2 to be appropriate, including the adjustments to account for the change in dose of study treatment from 200 mg to 150 mg, but that an adjustment of PFS to account for interval censoring is not sufficiently justified.

Table 4. Summary of statistical analyses for MONARCH 2 (reproduced from CS, Table 8, pgs 42-43)

Hypothesis objective	The primary objective of MONARCH 2 was to compare ABE-FUL with PBO-FUL, with respect to PFS for women with HR+/HER2− locally advanced or metastatic breast cancer. The null and alternative hypotheses were defined as follows (letting SA(t) and SP(t) denote the PFS functions of ABE-FUL and PBO-FUL respectively): • Null hypothesis (H0): SA(t) = SP(t) i.e. no difference in PFS between treatment groups • Alternative hypothesis (H1): SA(t) > SP(t) i.e. superior PFS in ABE-FUL group compared with PBO-FUL group
Statistical analysis	**Primary outcome:** • All efficacy analyses, including the primary outcome of PFS, were performed on the ITT population which included all randomised patients regardless of starting dose, and were performed by treatment arm • PFS was defined as the time from the date of randomisation to the date of objective PD or death due to any cause, whichever was earlier • If it was not known whether a patient had progressed or died at the time of analysis, PFS was censored at the last known progression-free assessment • There was 1 planned interim analysis and 1 primary analysis to test the above hypotheses • The interim analysis was to be performed after approximately [redacted] (approximately [redacted] of the [redacted] planned) INV-assessed PFS events had occurred • The primary (final) PFS analysis was planned to be performed after [redacted] PFS events were observed, based on investigator assessment (corresponding to a [redacted] censoring rate, relative to the anticipated [redacted] patients enrolled in the EP stratum) • PFS was determined using a 1-sided log-rank test • PFS curves for each treatment arm were estimated using the Kaplan-Meier method[35]. PFS rates for each arm were compared at 3-month intervals up to 15 months for the difference between rates • A stratified Cox proportional hazard model[36] with treatment as a factor was used to estimate the HR between treatment arms and the corresponding CI and Wald p-value • To estimate an improvement in PFS with abemaciclib, the method of Irwin (1949)[37] detailed in Karrison (1997)[38] and Meier (2004)[39] for estimating the "difference in average PFS" was followed (and is hereafter referred to as the restricted mean difference in PFS) **Safety:** • All 664 randomised and treated patients who received at least one dose of study drug were included in the safety analyses as the safety population • Overall exposure to study drug, the numbers of patients completing each cycle, and the dose intensity were summarised using descriptive statistics. The number of patients with any dose adjustment was presented for the entire treatment period as well as for each cycle **Subgroup Analyses:** • Subgroup analyses of PFS and OS were performed for each of following potential prognostic subgroup variables: o All baseline stratification factors o Starting dose (200 mg vs 150 mg) o Measurable disease at baseline (yes vs no)

	○ Number of organs involved (1 vs 2 vs 3+) ○ Age (<65 years vs ≥65 years) ○ Region (North America, Europe, and Asia) ○ Race (Caucasian, Asian, and Other) ○ PgR status (positive vs negative) • Analyses were performed within subgroup and, separately, across subgroups with a test of interactions of subgroups with treatment. Estimated HRs and 95% CIs for the within subgroup analyses were presented as a forest plot along with p-values for tests of interactions between subgroup variables and treatment
Sample size, power calculation	• Assuming a hazard ratio of 0.703, 378 events PFS yielded approximately 90% statistical power to detect superiority of the ABE-FUL arm over the PBO-FUL arm with the use of a 1-sided log-rank test and a type I error of 0.025 • If the true median PFS for the PBO-FUL arm was 6.5 months, then the hazard ratio of 0.703 amounted to an approximate 2.75 month (42%) improvement in median PFS for the ABE-FUL arm; under an additional assumption of exponential survival distribution
Data management, patient withdrawals	• All patients were followed up for progression and survival information until death or study completion, whichever occurred first. This included those patients who were randomised and never received study treatment or discontinued study treatment without objectively measured PD • For randomised patients who did not receive or discontinued study treatment without objectively measured PD, tumour response was evaluated every 8 weeks for the first 18 months and thereafter approximately 12 weeks, until the patient had objective PD or until the final PFS analysis • All randomised patients were included in the efficacy analysis

Abbreviations: ABE-FUL: abemaciclib plus fulvestrant; BOR: best overall response; CBR: clinical benefit rate; CI: confidence interval; CR: complete response; DCR: disease control rate; DoR: duration of response; HER2: human epidermal growth factor receptor 2**;** HR: hormone receptor; INV: investigator; ITT: intent-to-treat; KM: Kaplan-Meier; mBC: metastatic breast cancer; ORR: objective response rate; OS: overall survival**;** PBO-FUL: placebo plus fulvestrant; PD: progressive disease; PFS: progression-free survival; PgR: progesterone receptor; PR: partial response; RECIST: Response Evaluation Criteria In Solid Tumors;[34] SD: stable disease.

4.2.4 Quality assessment of MONARCH 2

The company's assessment of the quality of MONARCH 2, together with accompanying comments from the ERG, is presented in Table 5. The ERG agrees with company's quality assessment of MONARCH 2; overall, the results of the MONARCH 2 trial can be considered to be at low risk of bias.

The study was double-blind with patients and investigators masked to treatment allocation and progression was assessed both by investigator and independent panel of radiologists. Investigator-assessed PFS was the primary endpoint and PFS assessed by independent review a sensitivity analysis. The ERG notes that there is a risk of informative censoring with the independent review as this was done retrospectively, which may bias the PFS result.

Table 5. Risk of bias assessment for MONARCH 2 (adapted from CS, Table 9, pg 45)

NCT02107703 (MONARCH 2)	Company's risk of bias assessment	ERG's risk of bias assessment
Was randomisation carried out appropriately?	Low; randomisation was performed using a computer-generated random sequence	Low. The ERG agrees with the company's assessment.
Was the concealment of treatment allocation adequate?	Low; treatment allocation was concealed using an interactive web-based scheme	Low. The ERG agrees with the company's assessment.

Were the groups similar at the outset of the study in terms of prognostic factors?	Low; patient baseline characteristics were well-balanced	Low. The ERG agrees with the company's assessment.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Low; double blind, placebo-controlled study	Low. The ERG agrees with the company's assessment. Additional note: progression was assessed both by blinded investigators and blinded independent review
Were there any unexpected imbalances in drop-outs between groups?	Low; loss to follow-up was similar between the two treatment arms	Low. The ERG agrees with the company's assessment. Additional note: Number lost to follow up and withdrawal by patients were low and balanced between groups.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Unclear; the data on OS and pharmacokinetics have not been presented in follow-up publications	Low. OS data have been presented in the CS and pharmacokinetics outcomes are reported in the CSR.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Low; ITT analysis was used and missing data were not imputed	Low. The ERG agrees with the company's assessment.
Abbreviations: ERG, evidence review group; ITT: intent-to-treat; OS: overall survival.		

4.2.5 Summary statement

Direct evidence on the clinical effectiveness of ABE-FUL versus PBO-FUL in the treatment of aBC is derived from a well-designed and well-conducted RCT, MONARCH 2, which is a multicentre, international, double-blind study. MONARCH 2 enrolled women with HR+/HER2− aBC who had relapsed while receiving neo(adjuvant) ET, ≤ 12 months from completion of adjuvant ET, or relapsed while receiving first-line ET for metastatic disease. That is, both people who were treatment naïve and those who had received one prior line of ET in the advanced setting were eligible for enrolment if they had primary or acquired ET resistant disease.

The trial only enrolled women of whom the vast majority (> 99%) had metastatic disease with visceral metastases present in just under 60% of people. Of the women enrolled, 80% were post-menopausal and 20% were pre- or peri-menopausal. Three quarters of people had acquired ET resistance and the remaining quarter primary ET resistance. Approximately 60% had received their most recent ET in the (neo)adjuvant setting, and the remaining 40% had received their most recent ET for aBC. Baseline characteristics of people enrolled in MONARCH 2 were well balanced across the treatment groups. Although no patients from the UK were enrolled in MONARCH 2, the ERG's clinical experts consider the baseline characteristics of those enrolled in the trial to be representative of people in England who are likely to be eligible for treatment with ABE-FUL either as first- or second-line treatment for aBC.

People were randomised 2:1 to receive ABE-FUL (n=446) or PBO-FUL (n=223). Randomisation was stratified by metastatic site and ET resistance. Fulvestrant was administered as an intramuscular

injection (500 mg) on days 1 and 15 of the first cycle and on day 1 of subsequent cycles (every 28 days). Abemaciclib was given twice daily during each 28-day cycle. At study initiation, patients in the ABE-FUL group received a daily dose of 400 mg abemaciclib. After a review of preliminary safety data and dose reduction rates, the protocol was amended to reduce the dose of abemaciclib to 150 mg. A total of 178 patients (26.6%) were enrolled prior to the protocol amendment. Treatment was continued until progression, death, or patient withdrawal. Patients could discontinue either of the treatments in the combination but permitted to continue the other. Abemaciclib dose modifications, including interruption and up to two dose reductions, were permitted to manage adverse events. Fulvestrant dose reductions were also allowed.

The primary efficacy measure was investigator-assessed PFS as per RECIST version 1.1 criteria. PFS was calculated from the date of randomisation to the date of objective disease progression or death due to any cause. Tumour assessments were undertaken at baseline and approximately every 8 weeks for the first 12 months following randomisation and approximately every 12 weeks thereafter until the patient had objective disease progression, or until the primary analysis of PFS.

4.3 Clinical effectiveness results

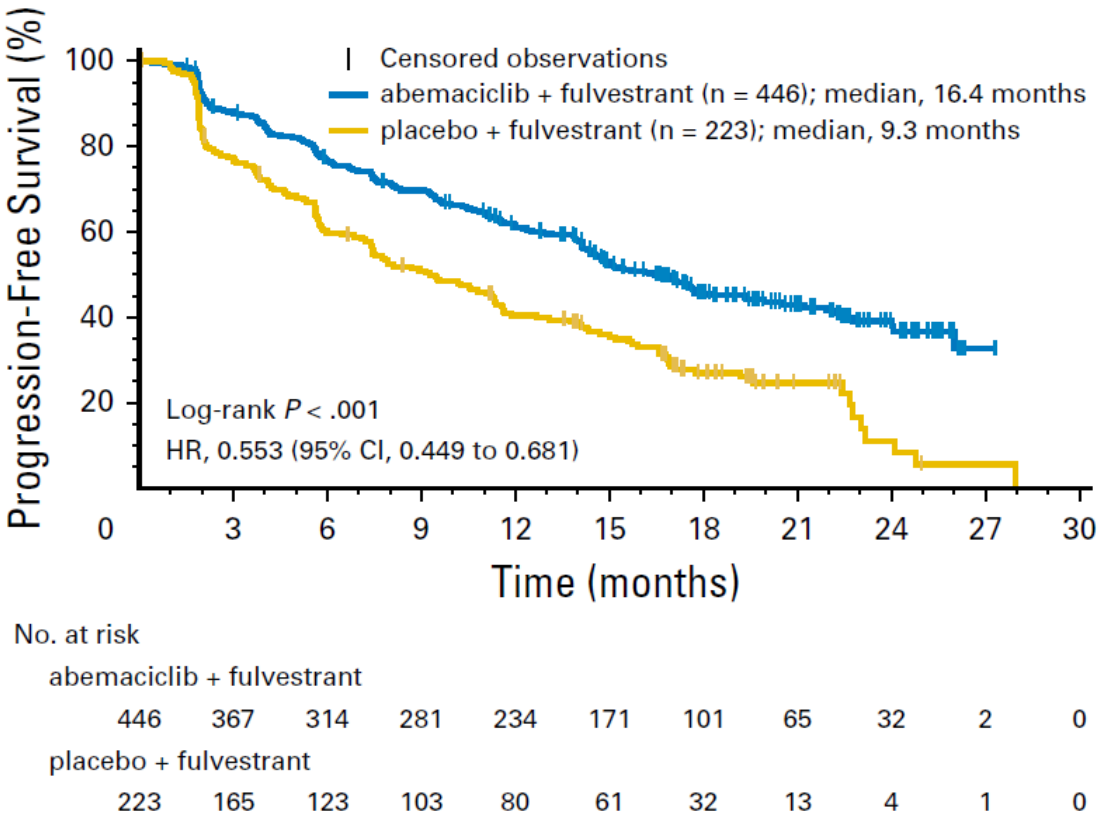
All outcome data presented in the CS for MONARCH 2 are based on the primary analysis data-cut off of 14 February 2017 at which time the median length of follow-up was 19.5 months. Efficacy outcomes are based on the ITT population, including a total of 669 patients: 446 in the ABE-FUL group and 223 in the PBO-FUL group.

4.3.1 Progression free survival

The primary outcome in MONARCH 2 was investigator-assessed PFS.[27] At the primary analysis 49.8% of patients had progressed in the ABE-FUL group and 70.4% in the PBO-FUL group. The Kaplan–Meier (KM) curves for PFS clearly show a benefit with ABE-FUL over PBO-FUL (Figure 3). Median PFS was 16.4 months on ABE-FUL and 9.3 months on PBO-FUL, corresponding to a difference of 7.1 months, a HR of 0.553 (95% CI: 0.449 to 0.681), and a statistically significant difference between groups ($p < 0.001$, Figure 3). The sensitivity analysis of blinded central analysis of PFS showed similar results with longer median PFS in both treatment groups and a slightly larger relative difference between ABE-FUL and PBO-FUL (HR 0.460, 95% CI: 0.363 to 0.584, $p < 0.001$, Figure 4). Another sensitivity analysis including only those patients enrolled after the change in starting dose was consistent with the ITT analysis (HR 0.588, 95% CI: 0.458 to 0.754).

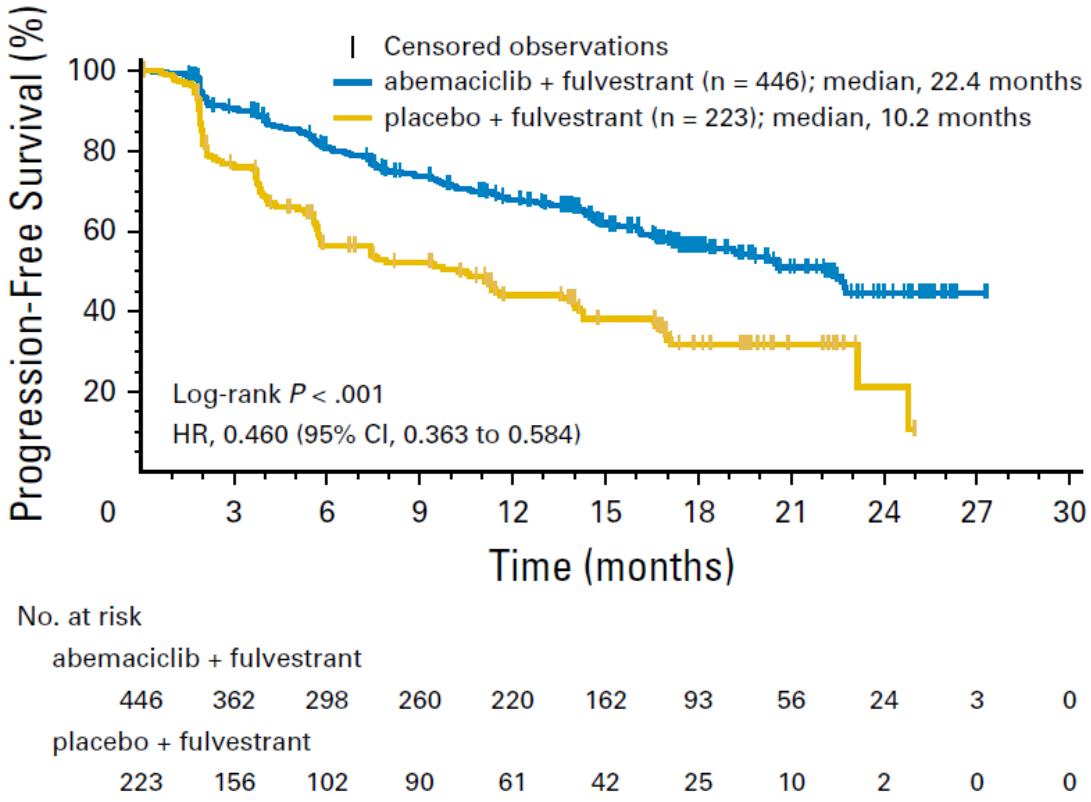
The ERG reiterates that, the company used PFS KM data adjusted for interval censoring for their base case, and that the ERG does not agree with the difference in approach between the clinical effectiveness presented here for PFS and the PFS data used in the economic model (Section 5.4.5.3.).

Figure 3. Kaplan-Meier plot of INV-assessed PFS at the final analysis in MONARCH 2 for ABE-FUL vs PBO-FUL, ITT population (reproduced from CS, Figure 4, pg 48)



Abbreviations: ABE-FUL: abemaciclib plus fulvestrant; CI: confidence interval; HR: hazard ratio; INV: investigator; ITT: intent-to-treat; PBO-FUL: placebo plus fulvestrant; PFS: progression-free survival.

Figure 4. Kaplan-Meier plot of progression-free survival by independent review in MONARCH 2 at the final PFS analysis, ITT population (reproduced from CS, Figure 5, pg 49)



Abbreviations: HR: hazard ratio; NR: not reached; ITT: intent-to-treat; PFS: progression-free survival.

4.3.2 Overall survival

The OS data were immature at the primary analysis with only 19.1% of patients who had died in the ABE-FUL group and 21.5% in the PBO-FUL group; median OS was not reached in either treatment group. At this timepoint there was no statistically significant difference between the treatment arms (HR [redacted], 95% CI: [redacted], p-value [redacted], Figure 5).

Figure 5. Kaplan-Meier plot of OS for ABE-FUL vs PBO-FUL at the final analysis, ITT population (reproduced from CS, Figure 7, pg 51)

Abbreviations: ABE-FUL: abemaciclib plus fulvestrant; HR: hazard ratio; ITT: intent-to-treat; NR: not reached; OS: overall survival; PBO-FUL: placebo plus fulvestrant.

4.3.3 Response rate

More patients treated with ABE-FUL achieved a complete or partial response (objective response rate [ORR] 35.2%, 95% CI: 30.8 to 39.6) than patients treated with PBO-FUL (ORR 16.1%, 95% CI: 11.3 to 21.0), the difference being statistically significant (odds ratio [OR] 2.82, $p<0.001$) in favour of the combination group (Table 6). The company also provided a sensitivity analysis comprising of the 72% of patients in the ITT population, with measurable disease at baseline. The results of the sensitivity analysis were in line with the analysis of the ITT population, showing a statistically significant difference in favour of ABE-FUL (OR 3.42, $p<0.001$).

Similarly, there was a statistically significant difference in disease control rate (DCR: patients with complete response, partial response, or stable disease) between the ABE-FUL group (DCR 83.0%, 95%

CI: 79.5 to 86.4) and PBO-FUL group (DCR 75.8%, 95% CI: 70.2 to 81.4, OR 1.56, p=0.025;Table 6). The equivalent clinical benefit rate (CBR: patients with complete response, partial response, or stable disease ≥6 months) were 72.2% (95% CI: 68.0 to 76.4) in the ABE-FUL group and 56.1% (95% CI: 49.5 to 62.6) in the PBO-FUL group. This equates to a statistically significant improvement in CBR with ABE-FUL treatment compared with PBO-FUL (OR 2.04, p<0.001,Table 6).

Table 6. Summary of best overall response by investigator assessment in MONARCH 2 at the final analysis for ABE-FUL vs PBO-FUL, ITT population (reproduced from CS, Table 12, pg 53)

	ABE-FUL (N=446)		PBO-FUL (N=223)		Difference	OR	P-value
	n (%)	95% CI	n (%)	95%CI			
Complete response	14 (3.1)	1.5, 4.8	1 (0.4)	−0.4, 1.3	NA	NA	NA
Partial response	143 (32.1)	27.7, 36.4	35 (15.7)	10.9, 20.5	NA	NA	NA
Stable disease	213 (47.8)	43.1, 52.4	133 (59.6)	53.2, 66.1	NA	NA	NA
≥6 months	165 (37.0)	32.5, 41.5	89 (39.9)	33.5, 46.3	NA	NA	NA
Progressive disease	40 (9.0)	6.3, 11.6	45 (20.2)	14.9, 25.4	NA	NA	NA
Not evaluable	36 (8.1)	5.5, 10.6	9 (4.0)	1.5, 6.6	NA	NA	NA
Objective response rate (CR + PR)	157 (35.2)	30.8, 39.6	36 (16.1)	11.3, 21.0	19.1	2.82	<0.001
Disease control rate (CR + PR + SD)	370 (83.0)	79.5, 86.4	169 (75.8)	70.2, 81.4	7.2	1.56	0.025
Clinical benefit rate (CR + PR + SD ≥6 months)	322 (72.2)	68.0, 76.4	125 (56.1)	49.5, 62.6	16.1	2.04	<0.001

Abbreviations: CR: complete response; NA: not applicable; PR: partial response; SD: stable disease.

The ERG notes that the median time to response was [redacted] the treatment groups with [redacted] for patients in the ABE-FUL group and [redacted] for patients in the PBO-FUL group.[23] For the 16.1% of patients in the PBO-FUL group median duration of response (DoR) was [redacted] months (95% CI: [redacted]), but had not been reached for the patients with a complete or partial response in the ABE-FUL group ([redacted], 95% CI: [redacted], Figure 6).

Figure 6. Kaplan-Meier plot of DoR in MONARCH 2 at the final analysis for ABE-FUL vs PBO-FUL (reproduced from CS, Figure 8, pg 54)

Abbreviations: ABE: abemaciclib; DoR: duration of response; FUL: fulvestrant; PBO: placebo; NR: not reached

4.3.4 Health related quality of life

In MONARCH 2, health related quality of life (HRQoL) and disease-related symptoms were assessed through

- modified Brief Pain Inventory-Short Form (mBPI-sf);
- EQRTC QLQ-C30;
- EQ-5D-5L.

According to the CSR for MONARCH 2, the analyses of HRQoL were based on the safety population rather than the ITT population.[40] Compliance rates were high and balanced between treatment groups

across questionnaires and time points; for patients in both groups, compliance rates were 95.5% or higher at baseline, 85.7% or higher on-therapy, and 77.1% or higher at follow-up.[40]

Pain intensity

The mean baseline pain score for each pain severity item (worst, least, average, now) was low (<3 on a 0 to 10 numeric rating scale) and similar between treatment arms, but with substantial variability within the groups as indicated by the size of the standard deviations (SDs, Table 7). Within treatment group change from baseline generally had a small numerical improvement in both treatment groups, though, none reached clinical or statistical significance. Similarly, between-group differences generally favoured ABE-FUL but the differences did not reach clinical or statistical significance (Table 7).

Table 7. Summary of mBPI-sf at the final analysis MONARCH 2, safety population (reproduced from CS, Table 13, pg 55)

	Baseline Score Mean (SD)		**Within-treatment Group Change from Baseline[a] LS Mean (SE)**		**Between-treatment Group Difference[a,b,c]**	
	ABE-FUL (N=441)	**PBO-FUL (N=223)**	**ABE-FUL (N=441)**	**PBO-FUL (N=223)**	**LS Mean (SE)**	**p-value**
Worst Pain in 24 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Least Pain in 24 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain on average	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain right now	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean interference Score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Across all postbaseline visits (ABE-FUL – PBO-FUL change difference). [b] p-values are from Type 3 sums of squares mixed models repeated measures model: Change from baseline = Treatment + Visit + Treatment*Visit + Baseline. [c] A negative between-treatment difference favours ABE-FUL.
Abbreviations: LS: least squares; mBPI-sf: Modified Brief Pain Inventory- short form; SD: standard deviation; SE: standard error.

EQRTC QLQ-C30

Baseline scores for the five functional scales (physical, role, emotional, cognitive and social functioning) were all [redacted] and the baseline score for global health status was [redacted], in both treatment groups, indicating relatively high levels of functioning and QoL at baseline. Mean change from baseline within each treatment group and the mean differences between treatment groups were similar for global health status and the five functional scales, indicating that neither ABE-FUL or PBO-FUL treatment adversely affect functioning or HRQoL.

Baseline scores for the symptom scales were also similar between treatment groups. The highest symptom burden at baseline was for fatigue and pain, which both scored more than [redacted]. A [redacted] increase in mean symptom score with ABE-FUL compared with PBO-FUL was observed for diarrhoea, appetite loss, and nausea and vomiting (Table 8). The company reports that the symptoms of appetite loss and nausea/vomiting were transient, reducing close to baseline levels

after Cycle 5. The company reports that the between-treatment group difference in mean diarrhoea symptom score was [redacted] points across all on-therapy visits. The increased diarrhoea symptom score was seen as early as the first scheduled post-baseline assessment at Cycle 2. The mean between-treatment arm difference for diarrhoea score was at its highest over the first two scheduled visits ([redacted] points at Cycles 2 and 3), then gradually decreased during the later on-treatment cycles but remained above [redacted] points. The symptom of diarrhoea returned to baseline upon treatment discontinuation. The remaining symptom scores were relatively stable and similar between the two treatment groups (Table 8).

Table 8. Summary of EORTC QLQ-C30 at the final analysis in MONARCH 2, safety population (reproduced from CS, Table 14, pg 57)

	Baseline Score Mean (SD)		**Within-treatment Group Change from Baseline LS Mean (SE)**		**Between treatment Group Difference[a] (Abemaciclib vs Placebo)**	
	ABE-FUL (N=441)	**PBO-FUL (N=223)**	**ABE-FUL (N=441)**	**PBO-FUL (N=223)**	**LS Mean(SE)**	**p-value**
Global health status	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Functional scales						
Physical functioning	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Role functioning	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Emotional functioning	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cognitive functioning	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Social functioning	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Symptom scale items						
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea and vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Appetite loss	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Financial difficulties	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EORTC QLQ-C30: European Organization for the Research and Treatment of Cancer, Quality of Life Questionnaire Core 30; LS: least squares; N: number of patients in the population; SD: standard deviation; SE: standard error
[a] A positive difference between treatments favours ABE-FUL for Global Health Status and Functional Scales. A negative difference between treatments favours ABE-FUL for Symptom scale items.

EQ-5D-5L

The VAS and EQ-5D-5L index values were similar between the treatment groups for both baseline and change from baseline assessments, indicating that the overall health status of patients was maintained throughout the study in both treatment arms.

Table 9. Summary of EQ-5D-5L Index and Visual Analogue Scale by visit in MONARCH 2, safety population (reproduced from CS, Table 15, pg 58)

	Baseline Score Mean (SD)		Within-treatment Group Change from Baseline LS Mean (SE)		Between- treatment Group Difference (Abemaciclib vs Placebo)	
	ABE-FUL	PBO-FUL	ABE-FUL	PBO-FUL	LS Mean (SE)[c]	p-Value
Index value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visual analogue scale	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D 5L: EuroQol 5-Dimension 5-Level; LS: least squares; SE: standard error; SD: standard deviation

4.3.5 Subgroup analyses

The NICE final scope for the appraisal of ABE-FUL does not specify any subgroups of interest to the appraisal, however, the company presents results from various pre-specified subgroup analyses from MONARCH 2 for the primary endpoint PFS. For most subgroup analyses the difference between ABE-FUL and PBO-FUL remained statistically significant, favouring ABE-FUL (Figure 7). The subgroup analyses included one of starting dose of abemaciclib, which was due to the protocol amendment changing the starting dose from 200 mg to 150 mg (Figure 7), with 121 patients received a starting dose of 200 mg and 320 patients received abemaciclib at the 150 mg starting dose. Although the interaction between the 200 mg and the 150mg subgroups was [redacted], the mean relative treatment effect in favour of ABE-FUL was [redacted] in the 200 mg subgroup compared with the 150mg subgroup (Figure 7). This is despite patients enrolled prior to the amendment only receiving a median of 34 days of treatment before all patients still at the 200 mg starting dose had their dose reduced to 150 mg.

Figure 7. Forest plot of summary of PFS by select subgroups (reproduced from CS Appendix E, Figure 13)

Abbreviations: CI: confidence interval; ECOG PS; Eastern Cooperative Oncology Group performance status; ET: endocrine therapy; mg: milligram; NR: not reached; PFS: progression-free survival

4.3.6 Adverse effects

Safety was assessed in the safety population, which included all 664 randomised patients who received at least one dose of study drug.

Treatment exposure

Patients were treated until progression or withdrawal in MONARCH 2. Two treatment interruption or dose reduction were allowed for managing adverse reactions such as diarrhoea. Also, if either abemaciclib or placebo was discontinued, patients were permitted to continue receiving fulvestrant, and if fulvestrant required discontinuation, patients were permitted to continue receiving abemaciclib or placebo.

Initially abemaciclib was administered at a daily dose of 400 mg (200 mg twice daily) in MONARCH 2. However, because of a large number of dose reductions due to adverse events (Section 4.2.1), a protocol amendment changed the administered daily dose to 300 mg (150 mg twice daily), which is the recommended dose in the final Summary of Product Characteristics (SmPC) for abemaciclib. A total of 178 patients (26.6%) were enrolled prior to the protocol amendment; 121 were randomised to abemaciclib at the 200 mg starting dose and 57 to matching placebo. Of these 121 patients who started on the 200 mg dose, [redacted] ([redacted]) of patients discontinued treatment prior to having their dose reduced to 150 mg. The remaining [redacted] patients had their dose reduced to 150 mg due to treatment-emergent adverse events (TEAEs) ([redacted]) or the protocol amendment ([redacted]). Patients enrolled prior to the dose amendment received a median of [redacted] days of 200 mg abemaciclib before either having their dose reduced to 150 mg or discontinued treatment.

The mean daily dose of abemaciclib received in MONARCH 2 was 261 mg or [redacted] of intended daily dose (Table 10). The mean dose of fulvestrant was [redacted] in the two treatment groups at [redacted] and [redacted] mg/week of fulvestrant, giving a relative dose intensity of [redacted] and [redacted] in the ABE-FUL and PBO-FUL groups, respectively (Table 10). Just under 50% of patients had a dose reduction of abemaciclib compared with [redacted] of patients on placebo and [redacted] of patients had a dose reduction of their fulvestrant treatment in either treatment group (Table 10). The numbers of dose interruptions and omissions were [redacted] but [redacted] to the dose reductions for both treatments in both groups.

The company reports conflicting figures of the proportion of patients who discontinued treatment due to AEs. [redacted] patients discontinued both study treatments in either treatment arm; [redacted] discontinued ABE-FUL compared with [redacted] on PBO-FUL (Table 10). However, [redacted] of patients in the ABE-FUL group discontinued one or both of the study treatments due to AEs, whereas the proportion in the PBO-FUL group was [redacted] as those discontinuing both treatments ([redacted], Table 10). According to the patient flow diagram (Appendix 10.3), the discontinuation rates due to AEs were

[redacted] and [redacted] in the ABE-FUL group and the PBO-FUL group, respectively. It is unclear from the CSR what proportion of patients who discontinued one drug or the other, was due to abemaciclib/placebo or fulvestrant. As such, the ERG is unable to adequately explain the reported figures. The ERG is concerned that the reported figures might mean that there is [redacted] discontinuation rate for abemaciclib of [redacted] due to AEs.

The duration of treatment (of abemaciclib/placebo or fulvestrant), or time to treatment discontinuation (TTD), was [redacted] longer in the ABE-FUL group compared with the PBO-FUL group (Table 10). This was despite [redacted] of patients discontinuing treatment in the ABE-FUL group compared with the PBO-FUL group (Table 10). Within both treatment groups the median duration of treatment with fulvestrant was [redacted] than with abemaciclib or placebo (Table 10). The median duration of treatment with abemaciclib was around [redacted] compared with [redacted] for placebo, and the median duration of fulvestrant treatment was around [redacted] in the ABE-FUL group but [redacted] in the PBO-FUL group.

Interestingly, patients in the ABE-FUL group had a longer gap between discontinuing treatment and progression, i.e. the difference between time to treatment discontinuation (TTD) and PFS, than in the PBO-FUL group. This difference was even more pronounced in the subgroup of patients who started on 200 mg abemaciclib compared with the 150 mg group. The impact of this is discussed in Section 5.4.5.5.

Table 10. Exposure to study treatment in MONARCH 2 (adapted from clarification response A7 and A8, Table 10 and 11)

	Abemaciclib + Fulvestrant		**Placebo + Fulvestrant**	
	Abemaciclib (N = 441)	**Fulvestrant (N = 441)**	**Placebo (N = 223)**	**Fulvestrant (N = 223)**
Duration of treatment (weeks)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range Q1 – Q3 Min - Max	[redacted]	[redacted]	[redacted]	[redacted]
Dose intensity	(mg/day)	(mg/week)	(mg/day)	(mg/week)
Mean (SD)	260.80 [redacted]	[redacted]	309.26 ([redacted]	[redacted]
Median	273.06	[redacted]	298.22	[redacted]

Range Q1 – Q3 Min - Max	[redacted]	[redacted]	[redacted]	[redacted]
Percent intended dose (%)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range Q1 – Q3 Min - Max	[redacted]	[redacted]	[redacted]	[redacted]
Number of subjects with, n (%)				
Dose reduction	218 (49.4)	[redacted]	[redacted]	[redacted]
Dose interruption/omission	256 (58.0)	[redacted]	[redacted]	[redacted]
Discontinuation of both study drugs due to AE*	[redacted]		[redacted]	
Discontinuation of any study drug due to AE	[redacted]		[redacted]	

Footnote: *discontinuation of study treatment was either whole regimen or the last component of the regimen
Abbreviations: AE; adverse event, SAE; serious adverse event, SD; standard deviation.

Safety profile

In the ABE-FUL group, 98.6% of patients, and 89.2% of patients in the PBO-FUL group, experienced at least one treatment emergent adverse event (TEAE, Table 11). In the ABE-FUL group [redacted] of patients were considered to have an AE related to the study treatment compared with [redacted] in the PBO-FUL group. A [redacted] of patients in the ABE-FUL group reported an AE of grade ≥3 or a serious adverse event (SAE), in comparison to the placebo group (Table 11). There were [redacted] on ABE-FUL and [redacted] on PBO-FUL whose death was attributed to an AE.

Table 11. Overall summary of adverse events in each arm of MONARCH 2, safety population (reproduced from CS, Table 17, pg 73)

Number of Patients	**ABE-FUL N=441**	**PBO-FUL N=223**
Patients with ≥1 TEAE	435 (98.6)	199 (89.2)
Related to study treatment	[redacted]	[redacted]
Patients with ≥1 CTCAE ≥ Grade 3 TEAE	[redacted]	[redacted]
Related to study treatment	[redacted]	[redacted]
Patients with ≥1 SAE	99 (22.4)	24 (10.8)
Related to study treatment	[redacted]	[redacted]

Patients who discontinued study treatment due to an AE	[redacted]	[redacted]
Related to study treatment	[redacted]	[redacted]
Patients who discontinued study treatment due to an SAE	[redacted]	[redacted]
Related to study treatment	[redacted]	[redacted]
Patients who died due to an AE on study treatment	[redacted]	[redacted]
Related to study treatment	[redacted]	[redacted]
Patients who died due to an AE within 30 days of discontinuation from study treatment	[redacted]	[redacted]
Related to study treatment	[redacted]	[redacted]
Abbreviations: AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; N: number of patients in the safety population; n: number of patients in the specified category; SAE serious adverse events;		

A summary of TEAEs experienced by ≥10% of patients by CTCAE Grade is presented in Table 12 and safety data regarding the TEAEs of diarrhoea and neutropenia by starting dose of abemaciclib is presented in Table 13. In the ABE-FUL group, the most frequently reported TEAEs of any Grade were diarrhoea (86.4%), neutropenia (46.0%), nausea (45.1%) and fatigue (39.9%) (Table 12). In the PBO-FUL group, the most frequently reported TEAEs of any Grade were diarrhoea (24.7%), nausea (22.9%) and fatigue (26.9%).

Diarrhoea was predominantly of Grade 1 or 2 in both treatment groups. In the ABE-FUL group 13.4% and 0% of patients had diarrhoea of Grade 3 and 4, respectively. The company reports that the median time to onset of the first diarrhoea was 6 days and the median duration was [redacted] days for Grade 2 and [redacted] days for Grade 3 events. Diarrhoea was manageable with anti-diarrhoeal medications, most commonly loperamide. Higher-Grade diarrhoea occurred in the first few treatment cycles and was managed with dose omissions and/or dose reductions ([redacted] in ABE-FUL group), in addition to anti-diarrhoeal therapy. A small proportion of patients in the ABE-FUL group discontinued abemaciclib but continued to receive fulvestrant ([redacted]) or discontinued both therapies ([redacted]) because of diarrhoea. However, the incidence of Grade 2 or 3 diarrhoea was higher in patients who received the 200 mg abemaciclib starting dose compared with patients who started on 150 mg abemaciclib (Table 13). Consequently, a higher proportion of patients who received the abemaciclib 200 mg starting dose discontinued study treatment or had a dose reduction due to diarrhoea compared with patients who received a starting dose of 150 mg (Table 13).

Most cases of neutropenia were Grade 3 AEs in both treatment groups. Of the patients in the ABE-FUL group who experienced neutropenia, 23.6% and 2.9% reported Grade 3 and Grade 4 events, respectively. The median time to onset of Grade 3 or 4 neutropenia was [redacted] days for ABE-FUL and [redacted] days for PBO-FUL. A small proportion of patients treated with ABE-FUL ([redacted]) discontinued treatment due to neutropenia, and [redacted] of patients had a dose reduction. As for diarrhoea, the incidence of neutropenia and the proportions of patients who had a dose reduction or discontinued treatment due to neutropenia, were higher in patients who received the abemaciclib 200 mg starting dose compared with patients who received a starting dose of 150 mg (Table 13).

Table 12. Treatment-emergent adverse events by maximum CTCAE Grade experienced by ≥10% of population of either arm of MONARCH 2, safety population (reproduced from CS, Table 18, pgs 76-77)

Preferred Term	ABE-FUL N=441					PBO-FUL N=223				
	CTCAE Grade									
	Grade 1	Grade 2	Grade 3	Grade 4	All	Grade 1	Grade 2	Grade 3	Grade 4	All
Patients with ≥1 TEAE, n (%)	[redacted]	[redacted]	241 (54.6)	26 (5.9)	435 (98.6)	[redacted]	[redacted]	46 (20.6)	5 (2.2)	199 (89.2)
Diarrhoea	[redacted]	[redacted]	59 (13.4)	0	381 (86.4)	[redacted]	[redacted]	1 (0.4)	0	55 (24.7)
Neutropenia	[redacted]	[redacted]	104 (23.6)	13 (2.9)	203 (46.0)	[redacted]	[redacted]	3 (1.3)	1 (0.4)	9 (4.0)
Nausea	[redacted]	[redacted]	12 (2.7)	NA	199 (45.1)	[redacted]	[redacted]	2 (0.9)	NA	51 (22.9)
Fatigue	[redacted]	[redacted]	12 (2.7)	NA	176 (39.9)	[redacted]	[redacted]	1 (0.4)	NA	60 (26.9)
Abdominal pain	[redacted]	[redacted]	11 (2.5)	0	156 (35.4)	[redacted]	[redacted]	2 (0.9)	0	35 (15.7)
Anaemia	[redacted]	[redacted]	31 (7.0)	1 (0.2)	128 (29.0)	[redacted]	[redacted]	2 (0.9)	0	8 (3.6)
Leukopenia	[redacted]	[redacted]	38 (8.6)	1 (0.2)	125 (28.3)	[redacted]	[redacted]	0	0	4 (1.8)
Decreased appetite	[redacted]	[redacted]	5 (1.1)	0	117 (26.5)	[redacted]	[redacted]	1 (0.4)	0	27 (12.1)
Vomiting	[redacted]	[redacted]	4 (0.9)	0	114 (25.9)	[redacted]	[redacted]	4 (1.8)	0	23 (10.3)
Headache	[redacted]	[redacted]	3 (0.7)	NA	89 (20.2)	[redacted]	[redacted]	1 (0.4)	NA	34 (15.2)
Dysgeusia	[redacted]	[redacted]	0	0	79 (17.9)	[redacted]	[redacted]	0	0	6 (2.7)
Alopecia	[redacted]	[redacted]	NA	NA	69 (15.9)	[redacted]	[redacted]	NA	NA	4 (1.8)
Thrombocytopenia	[redacted]	[redacted]	9 (2.0)	6 (1.4)	69 (15.6)	[redacted]	[redacted]	0	1 (0.4)	6 (2.7)
Stomatitis	[redacted]	[redacted]	2 (0.5)	0	67 (15.2)	[redacted]	[redacted]	0	0	23 (10.3)
Constipation	[redacted]	[redacted]	3 (0.7)	0	60 (13.6)	[redacted]	[redacted]	1 (0.4)	0	30 (13.5)
ALT increased	[redacted]	[redacted]	17 (3.9)	1 (0.2)	59 (13.4)	[redacted]	[redacted]	4 (1.8)	0	12 (5.4)
Cough	[redacted]	[redacted]	0	0	59 (13.4)	[redacted]	[redacted]	0	0	25 (11.2)
Pruritus	[redacted]	[redacted]	0	0	57 (12.9)	[redacted]	[redacted]	0	0	13 (5.8)
Dizziness	[redacted]	[redacted]	3 (0.7)	0	55 (12.5)	[redacted]	[redacted]	0	0	13 (5.8)
AST increased	[redacted]	[redacted]	10 (2.3)	0	54 (12.2)	[redacted]	[redacted]	6 (2.7)	0	15 (6.7)
Blood creatinine increased	[redacted]	[redacted]	4 (0.9)	0	52 (11.8)	[redacted]	[redacted]	0	0	1 (0.4)

Abbreviations: ABE-FUL: abemaciclib plus fulvestrant; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CTCAE: Common Terminology Criteria for Adverse Events; NA: not applicable per CTCAE; N: number of patients in the safety population; n: number of patients in the specified category; PBO-FUL: placebo plus fulvestrant; TEAE: treatment-emergent adverse event.

Table 13. Key safety results by pre-amendment and post-amendment populations (reproduced from CS, Table 19, pg 78)

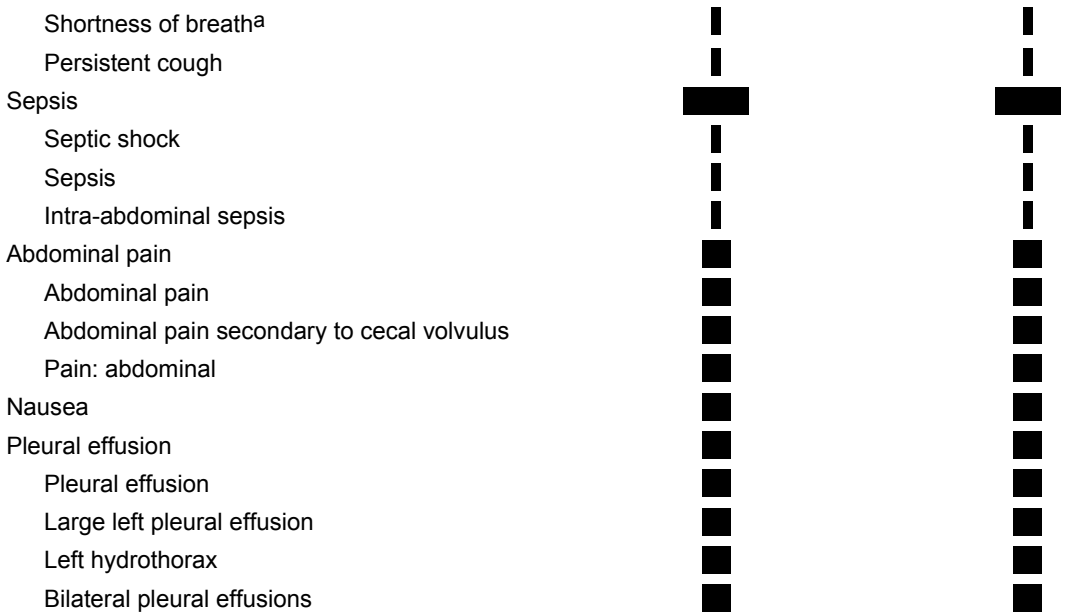
	Pre-amendment Population	Post-amendment Population	Intent-to-treat Population	
	ABE 200 mg (N=121)	ABE 150 mg (N=320)	ABE-FUL (N=441)	PBO-FUL (N=223)
Incidence of diarrhoea				
Grade 2, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Incidence of neutropenia				
Grade 3, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Grade 4, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Dose reductions due to TEAEs (%)	[redacted]	[redacted]	[redacted]	[redacted]
Dose reduced due to diarrhoea (%)	[redacted]	[redacted]	[redacted]	[redacted]
Dose reduced due to neutropenia (%)	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued any study drug due to AE (%)	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued due to diarrhoea (%)	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued due to neutropenia (%)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABE: abemaciclib; ABE-FUL: abemaciclib plus fulvestrant; AE: adverse event; mg: milligram; PBO-FUL: placebo plus fulvestrant.

The incidence of SAEs was higher in the ABE-FUL group (22.4%) compared with the PBO-FUL group (10.8%, Table 14). The most frequently reported SAEs for patients who received ABE-FUL were embolism (2%) and diarrhoea ([redacted]). For patients who received PBO-FUL the most common SAE was dyspnoea ([redacted]).

Table 14. Treatment-emergent serious adverse events occurring in ≥1% of patients in either arm of MONARCH 2, safety population (reproduced from CS, Table 20, pg 79)

Preferred Term Reported Term	ABE-FUL N=441 n (%)	PBO-FUL N=223 n (%)
Patients with ≥1 serious adverse event	99 (22.4)	24 (10.8)
Embolism	9 (2.0)	1 (0.4)
Pulmonary embolism	[redacted]	[redacted]
DVT	[redacted]	[redacted]
Acute DVT of inferior vena cava	[redacted]	[redacted]
Pulmonary thromboembolism	[redacted]	[redacted]
Cerebral venous sinus thrombosis	[redacted]	[redacted]
Cerebral infarction	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Lung infection	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Lung infection	[redacted]	[redacted]
Bilateral pneumonia	[redacted]	[redacted]
Community-acquired bacterial pneumonia	[redacted]	[redacted]
Cryptogenic organizing pneumonia	[redacted]	[redacted]
Dyspnea	[redacted]	[redacted]
Dyspnea[a]	[redacted]	[redacted]



Abbreviations: ABE-FUL: abemaciclib plus fulvestrant; DVT: deep vein thrombosis; N: number of patients in the population; n: number of patients with a serious adverse event; PBO-FUL: placebo plus fulvestrant.

4.4 Indirect treatment comparison

Due to the absence of head-to-head trials comparing ABE-FUL with everolimus plus exemestane, exemestane monotherapy, tamoxifen, or chemotherapy in the relevant population, the company conducted network meta-analysis (NMA). The company's original NMAs for OS and PFS were based on HRs (hereafter referred to as the HR NMA). However, the company assessed if the PH assumption held for PFS and OS within each study in the network and found that the PH assumption is violated for some of the studies in both the PFS and OS analysis (see Section 4.4.2). At the clarification stage the ERG therefore requested a re-analysis of both outcomes using fractional polynomials (FP), a method which can better account for a variable hazard over time (hereafter referred to as the FP NMA). Despite the lack of PH in some of the trials, the company decided to retain its base case using the results of the HR NMAs. A description and critique of both methods and their results are therefore presented in the following sections, but the ERG emphasises the challenge in deriving a meaningful interpretation of the results of the HR NMA.

4.4.1 Included studies

The studies included in the networks underpinning the NMAs were identified via a systematic literature review; the methods used to identify the studies included in the network and the quality assessment of the included studies are described in Section 4.1. Studies were excluded from the analyses if they could not be connected to the networks, if no data were available for the outcome, and for PFS, depending on endpoint definition (time to progression [TTP] was also accepted). The included studies therefore varied for the different outcomes and analyses (Table 15). The networks for the dichotomous outcomes, ORR and CBR, and for HR NMAs can be found in Appendix 10.3.

Tamoxifen was not included in the original HR NMAs for PFS and OS due to a lack of suitable evidence identified in the systematic literature review. However, the company identified Milla-Santos 2001,[1] a trial of tamoxifen versus TOR in a population with potential overlap with the relevant population. Milla-Santos 2001[1] was used in an adjusted indirect comparison with output from the HR NMA, using the Bucher method.[41] The company does not provide a rationale for why tamoxifen trial and the HR NMA results were analysed using the Bucher method rather than including Milla-Santos 2001[1] in the HR NMA.

To inform the decision problem, for the FP NMAs, the ERG requested two studies to be added to those in the networks for the HR NMAs of PFS and OS. As the company considered an adjusted indirect comparison between the tamoxifen trial Milla-Santos 2001[1] and the HR NMA appropriate, the ERG requested that this trial be included in the network rather than analysed separately. In addition to adding Milla-Santos 2001,[1] BOLERO-6,[29] a trial comparing capecitabine, EVE-EXE and everolimus, was also added. The addition of BOLERO-6 enabled the comparison of ABE-FUL with chemotherapy, one of the comparators listed in the NICE final scope.[2] The ERG emphasises that BOLERO-6 was not identified through a systematic review of the literature by the ERG. Therefore, there may be additional trials eligible to inform the comparison of ABE-FUL and chemotherapy, which have not been identified.

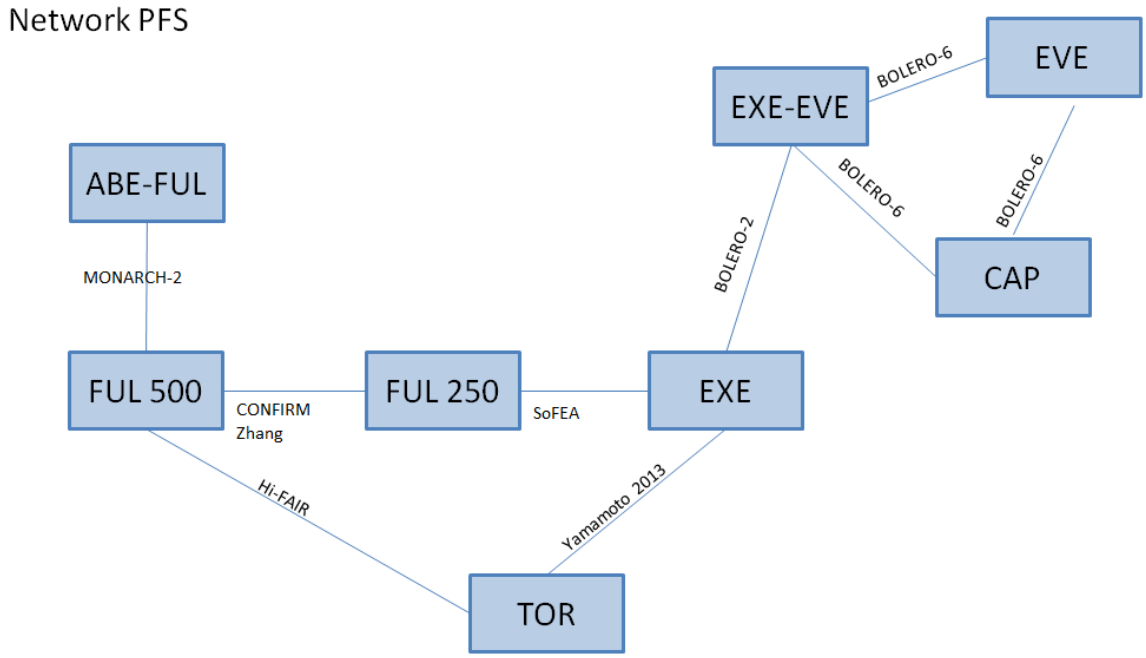
Several studies were also excluded from the network for the FP NMAs compared with the original network for the HR NMAs for both PFS and OS. The ERG suggested that the company simplify the network by removing studies not informing the decision problem. This meant excluding Buzdar 2001,[42] Buzdar 1997,[43] Jonat 1996,[44] and PALOMA 3[45] from both the PFS and OS networks. Additional studies removed from the OS network, for the same reason, were Muss 1990,[46] Kaufmann 2000,[47] Dombernowsky 1998,[48] and Rose 2003.[49] The ERG also suggested limiting studies that were deemed by the ERG to potentially introduce heterogeneity in terms of population or study design, from the primary analysis. These trial were therefore only requested to be included in sensitivity analyses: Howell 2002[50] and Trial 0021[51] in which only around 80% of patients had HR+ aBC, whereas HR+ disease was an eligibility criteria for all the other included studies (Appendix **10.6**, **Table 62**), and Campos 2009[52] which was limited to patients with visceral metastases. Visceral involvement was around 60% in the other included studies (Appendix **10.6**, **Table 65**). The ERG considers the avoidance of unnecessary clinical heterogeneity to outweigh the possible loss of precision. The full network, the company used for the FP NMAs for PFS and OS are presented in Figure 8 and Figure 9, respectively. The description and critique of the trials included in the indirect comparisons focus on the trials included in the FP NMAs for PFS and OS.

Table 15. Summary of trials used to inform the network meta-analysis (adapted from CS Appendix D.1.3. Table 19)

Trial	Treatment A (ITT n)	Treatment B (ITT n)	Treatment C (ITT n)	Dichotomous		HR NMA		FP NMA			
								Full network*		Limited network**	
				ORR	CBR	OS	PFS	OS	PFS	OS	PFS
BOLERO-2[53]	EXE-EVE (485)	EXE (239)	NA	✓	✓	✓	✓	✓	✓	✓	✓
BOLERO-6[29]	EXE-EVE (104)	EVE (103)	CAP (102)	×	×	×	×	✓	✓	✓	✓
Buzdar 1997[43]	ANAS 1 mg (128)	ANAS 10 mg (130)	MGA 160 mg (128)	✓	✓	✓	✓	×	×	×	×
Buzdar 2001[42]	LTZ 0.5 mg (202)	LTZ 2.5 mg (199)	MGA 160 mg (201)	✓	×	✓	✓	×	×	×	×
Campos 2009[52]	EXE (65)	ANAS 1 mg (65)	NA	×	✓	✓	✓	×	×	×	×
CONFIRM[54, 55]	FUL 500 mg (362)	FUL 250 mg (374)	NA	✓	✓	✓	✓	✓	✓	✓	✓
Dombernowsky 1998[48]	LTZ 0.5 mg (188)	LTZ 2.5 mg (174)	MGA 160 mg (189)	✓	✓	✓	×	×	×	×	×
EFECT[56]	FUL 250 mg (351)	EXE (342)	NA	✓	✓	×	×	×	×	×	×
Hi-FAIR fx[57]	FUL 500 mg (52)	TOR 120 mg (53)	NA	✓	✓	✓	✓	✓	✓	×	×
Howell 2002[50]	FUL 250 mg (222)	ANAS 1 mg (229)	NA	✓	✓	✓	✓	×	×	×	×
Jonat 1996[44]	ANAS 1 mg (135)	ANAS 10 mg (118)	MGA 160 mg (125)	✓	✓	✓	✓	×	×	×	×
Kaufmann 2000[47]	EXE (366)	MGA 160 mg (403)	NA	✓	✓	✓	×	×	×	×	×
Milla-Santos 2001[1]	TMX 40 mg (111)	TOR 60 mg (106)	NA	×	×	×	×	✓	×	×	×
MONARCH 2[27]	ABE-FUL (446)	FUL 500 mg (223)	NA	✓	✓	✓	✓	✓	✓	✓	✓
Muss 1990[46]	MGA 160 mg (86)	MGA 800 mg (84)	NA	✓	×	✓	×	×	×	×	×
PALOMA 3[45]	PAL-FUL (347)	FUL 500 mg (174)	NA	✓	✓	✓	✓	×	×	×	×
Rose 2003[49]	LTZ 2.5 mg (356)	ANAS 1 mg (357)	NA	✓	✓	✓	×	×	×	×	×
SoFEA[58]	FUL 250 mg (231)	EXE 25 mg (249)	NA	✓	✓	✓	✓	✓	✓	✓	✓
Trial 0021[51]	FUL 250 mg (206)	ANAS 1 mg (194)	NA	✓	✓	✓	✓	×	×	×	×
Yamamoto 2013[59]	TOR 120 mg (46)	EXE 25 mg (45)	NA	✓	✓	✓	✓	✓	✓	×	×
Zhang 2016[60]	FUL 500 mg (111)	FUL 250 mg (110)	NA	✓	✓	×	✓	×	✓	✓	✓

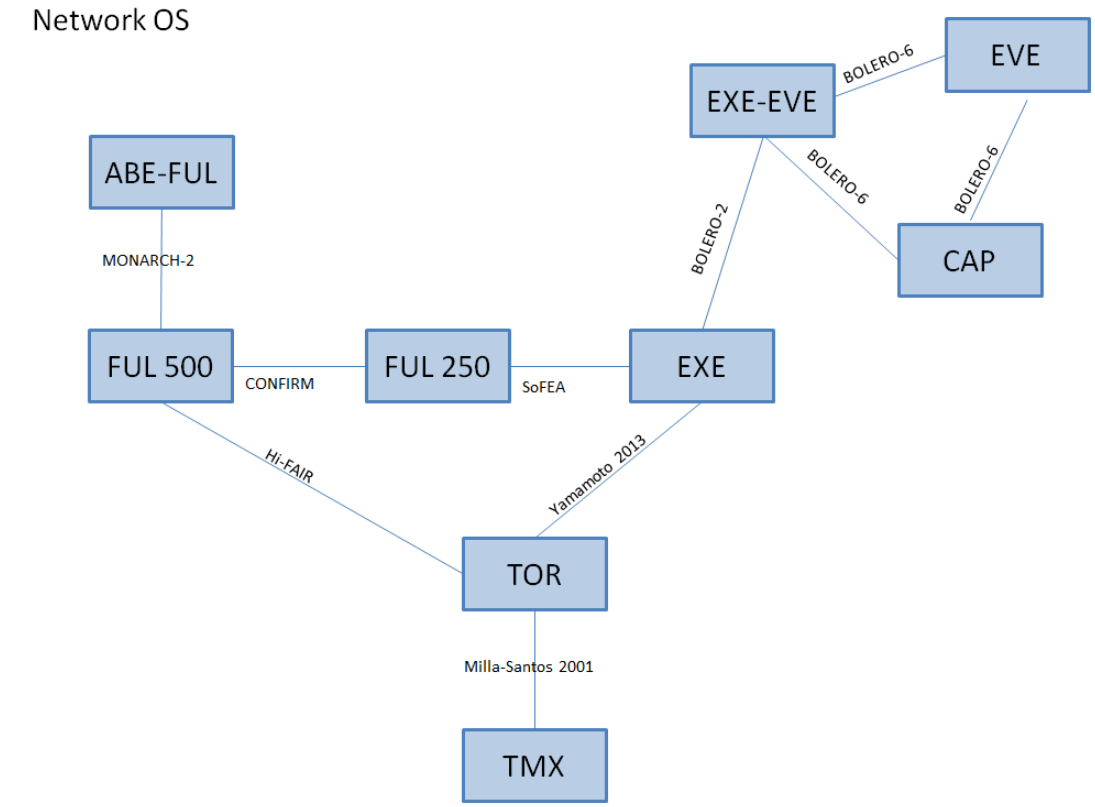
Abbreviations: ABE, abemaciclib; ANAS, anastrozole; CBR, clinical benefit rate; EVE, everolimus; EXE, exemestane; FUL, fulvestrant; LTZ, letrozole; mg, milligrams; MGA, megestrol acetate; NA, not applicable; NMA, network meta-analysis; ORR, objective response rate; OS, overall survival; PAL, palbociclib; PFS, progression-free survival; SLR, systematic literature review; TOR, toremifene.

Figure 8. Network for PFS (updated NMA) (reproduced from clarification response A3, Figure 3)



Abbreviations: ABE: abemaciclib; CAP: capecitabine; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; PFS: progression-free survival; TOR: toremifene.

Figure 9. Network for overall survival (updated NMA) (reproduced from clarification response A3, Figure 4)



Abbreviations: ABE: abemaciclib; CAP: capecitabine; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; OS: overall survival; TMX: tamoxifen; TOR: toremifene.

The eligibility criteria for the systematic literature review were broadened with regards to certain baseline characteristics, as discussed in Section 4.1.2, as there were little published data available in a population directly comparable to MONARCH 2.[27] This resulted in a degree of clinical heterogeneity, particularly for MONARCH 2 relative to other trials included in the analysis.

In the CS, the company presents limited details on the studies informing their original networks, reporting some baseline characteristics of the populations enrolled across the studies and some information on the study design as well as the extracted data (CS, Appendix D.1.4.). The company also provided a discussion around the heterogeneity between the studies in the original networks in Section B.3.9.3. of the CS, which will be expanded on in the section below. An assessment of the quality of the individual studies was not available in the CS or Appendices. As part of the clarification process, the company provided additional information on the conduct and quality of the studies informing the updated networks. The company's quality assessment together with the ERG's independent review is presented in Appendix 10.5.

BOLERO-2,[53] CONFIRM,[54] Milla-Santos 2001,[1] MONARCH 2,[27] SoFEA[58] and Zhang 2016[60] were all phase III trials, and the remaining trials (BOLERO-6,[29] Hi-FAIR fx,[57] and Yamamoto 2013[59]) had a phase II design (Appendix 10.6, Table 61). Four of the studies (BOLERO-2,[53] CONFIRM,[54] MONARCH 2,[27] and Zhang 2016[60]) were double-blind in design and five studies were open-label (BOLERO-6,[29] Hi-FAIR fx,[57] Milla-Santos 2001,[1] SoFEA,[58] and Yamamoto 2013,[59] Table 62). The majority of the trials were multicentre and international, though SoFEA[58] only enrolled patients in the UK and South Korea, and Zhang 2016[60] was a solely Chinese study (Table 62).

MONARCH 2[27] included pre- (<20%) and post-menopausal women, whereas all women were post-menopausal in the remaining trials (Table 64). With the exception of Milla-Santos 2001,[1] all studies included women who had aBC that had recurred or progressed during treatment with an ET, either as an adjuvant treatment or as a treatment for advanced disease. Milla-Santos 2001[1] may have included a proportion of patients who had progressed on or after adjuvant ET (but excluded patients previously treated with hormone therapy for aBC), and also women who were ET naïve. All studies required people to have HR+ aBC. HER2– status was only an eligibility criterion in BOLERO-2,[53] BOLERO-6[29] and MONARCH 2 (Table 62).[27] However, in SoFEA[58] and Yamamoto 2013[59] the proportion of patients with HER2– was 59% and 91%, respectively. The remaining studies (CONFIRM,[54] Hi-FAIR fx,[57] Milla-Santos 2001,[1] and Zhang 2016[60]) did not report HER2 status of the participants. HER2+ breast cancers tend to be more aggressive and faster growing than HER2– tumours and are also more likely to recur. The populations enrolled in CONFIRM,[54] Hi-FAIR fx,[57] Milla-Santos 2001,[1] SoFEA[58] and Zhang 2016[60] could have a worse prognosis than those recruited to the trials where all or almost all were HER2–.

Only MONARCH 2[27] reported primary or secondary ET resistance of patients enrolled (Table 65). The other studies informing the networks include a mix of patients with primary and secondary ET resistance as well as some patients with ET sensitive disease. Though, the proportion of patients who would be defined as having ET sensitive or ET resistant disease is not clearly reported across studies.

The company comments that the results of BOLERO-2[53] may have overestimated the benefit of EVE-EXE relative to EXE as the trial only enrolled patients that were refractory to aromatase inhibitors (letrozole or anastrozole). The ERG assumes that the company is referring to the full population in BOLERO-2 having primary rather than acquired resistance to ET. The ERG does not agree that this would necessarily bias the results of the trial. As shown in the subgroup analysis of MONARCH 2,[27] there was no statistically significant difference between the primary and acquired ET resistance subgroups in terms of relative efficacy of the two treatments.

MONARCH 2[27] only allowed patients with up to one prior ET and no prior chemotherapy in the advanced setting. The number of previous treatments is not consistently reported as a baseline characteristic across studies. CONFIRM[54] and Zhang 2016[60] enrolled patients with up to one prior ET for aBC, as in MONARCH 2.[27] Considering other lines of treatment, those receiving more than one prior line of therapy for aBC, including chemotherapy were eligible for inclusion in four studies (BOLERO-2,[53] CONFIRM,[54] SoFEA,[58] and Yamamoto 2013[59]). BOLERO-2[53] reports that about 50% of people had received three or more previous treatments, including treatment in the adjuvant setting.

PFS was the primary outcome reported across studies, with the exception of Milla-Santos 2001,[1] Hi-FAIR fx[57] and Yamamoto 2013,[59] and was measured from randomisation to disease progression or death from any cause, whichever was sooner (**Table 63**). The primary outcome in Hi-FAIR fx[57] and Yamamoto 2013,[59] was CBR. As in MONARCH 2,[27] most of the studies report that progression of disease was assessed against RECIST criteria: criteria for assessment of progression was not specified in BOLERO-2,[53] Hi-FAIR fx[57] and Milla-Santos 2001.[57] Only two trials (BOLERO-2[53] and MONARCH 2[27]) reported both investigator-assessed and independent review of progression. As for the HR NMA and FP NMA, the company and the ERG used investigator-assessed PFS as this was comparable across all studies.

All studies, except MONARCH 2,[27] had relatively mature OS data, with event rates of more than 50%. Subsequent therapies, which may impact OS, were only reported in four of the trials included in the network (BOLERO-6,[29] CONFIRM,[54] Hi-FAIR fx,[57] and MONARCH 2[27]). Hi-FAIR fx[57] and Yamamoto 2013[59] were of a cross-over design; after progression on the randomised treatment, patients would switch to the other treatment group, which is likely to confound OS estimates. Available data for subsequent therapies for MONARCH 2,[27] BOLERO-6[29] and CONFIRM[54] are presented in Appendix **10.5**, Table 67. Hi-FAIR fx[57] and Yamamoto 2013[59] administered toremifene at a daily dose of 120 mg,

which is double the dose recommended in the SmPC.[61] In Milla-Santos 2001,[1] on the other hand, patients were given 60 mg per day of toremifene. These doses may not be comparable and as the relative effectiveness of tamoxifen versus the other treatments in the network is reliant on the link via toremifene, this should be interpreted with caution.

The proportion of patients with visceral involvement ranged from 28% to 66% of patients between the included studies, where reported (Table 65). The baseline characteristics of patients were well balanced within each trial, with the potential exception of BOLERO-6.[29] The ERG notes that the authors of BOLERO-6[29] commented that the observed benefit in PFS noted for capecitabine over EXE-EVE was inconsistent with PFS reported for capecitabine from other studies in first-line treatment of aBC, in which a range of 4.1 to 7.9 months for PFS on treatment with capecitabine was reported.[29] The authors speculated that the difference in PFS could be attributed to informative censoring as a result of the open-label nature of the study, and imbalances in prognostic factors and baseline characteristics. A larger proportion of people were censored from the capecitabine group because of initiation of antineoplastic therapies (20% with capecitabine vs 9% with EXE-EVE). The authors commented that those starting antineoplastic therapies might not have the same PFS prognosis as those censored for other reasons and thus could bias the PFS estimate.

4.4.2 Statistical methods

The company ran NMAs to assess the relative efficacy of the interventions of interest for the following outcomes: PFS, OS, ORR and CBR. For PFS and OS the company used the published HRs and associated 95% CIs for each of the studies. HRs are conditional on the proportional hazards (PH) assumption being fulfilled and any NMA or ITC based on HRs would need to assume that the PH assumption holds within each of the trials included. The company therefore did an assessment of the PH assumption for OS and PFS for all the trials in the networks. Kaplan-Meier (KM) graphs for each outcome were digitised using WebPlotDigitizer® software. The digitised KM curves were used to estimate the underlying individual patient data (IPD) as described by Guyot 2012.[62] The PH assumption was then assessed by log–log plot (log cumulative hazard over log time),[63] Schoenfeld residual plots, and weighted residual test based on standardised Schoenfeld residuals.[64] The results of the company's assessment are reported in Section 4.4.2, showing that the PH assumption was upheld across the majority, but not all, of the included studies.

The NMAs were conducted based on the methodologies from the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 2.[65] The methodology described in Woods 2010[66] was also used to account for multi-arm trials of time-to-event data. The models were fitted using the OpenBUGS software package version 3.2.2. For all NMAs, whether for dichotomous or continuous outcomes, FUL 500 mg was chosen as the reference treatment, vague priors were used for all parameters, and fixed

effect (FE) and random effects (RE) models were conducted for each endpoint. The best fitting model was determined using the deviance information criterion (DIC).[67] The model with the lowest DIC provides the 'best' fit to the data. Where the DIC values were similar between the FE and RE models, the RE model results were presented. The binary outcomes ORR and CBR were analysed using a logit link function as per the NICE DSU TSD 2[65] and the results are presented as odds ratios (ORs) with 95% credible intervals (CrI). Results for the time-to-event outcomes OS and PFS are presented as HRs with 95% CrIs. Where there were closed loops in the network, the company tested for inconsistency between the direct and indirect evidence in accordance with NICE DSU TSD 4.[68]

To estimate the relative treatment effects of TMX versus FUL 500 for PFS and OS, the company performed an adjusted indirect comparison using the Bucher method.[41] The comparison of TMX and FUL 500 was based on Milla-Santos 2001[1] and the results of the HR NMA for TOR versus FUL 500, with TOR being the common comparator. Milla-Santos 2001[1] only reported TTP but did not report the definition of the outcome (Table 63). The company's analysis is therefore based on the assumption of equivalence between the PFS and TTP endpoints. The company did not provide a justification for why the comparison with TMX was run in a separate adjusted indirect treatment comparison rather than including it in the HR NMA.

To account for the lack of PH within some of the trials the company used a FP NMA, which better describes a variable hazard over time. This analysis was requested by the ERG at the clarification stage and was conducted by the company as a scenario analysis, however, the company's base case is based on the results of the HR NMAs.

Within a FP NMA, the treatment effect is represented by multiple parameters and the hazard is modelled over time which allows a wide family of survival functions to be estimated. Analyses were conducted using OpenBUGS version 3.2.3, and R version 3.4.4. The package 'R2OpenBUGS' was used to run OpenBUGS from within R. The 1st and 2nd order powers for the fractional polynomials were chosen from the set: -2, -1, -0.5, 0, 0.5, 1, 2, 3, although not all possible 2nd order models were considered. Analyses were run with 30,000 iterations of which 12,000 were discarded as burn in, and a thinning parameter of 4, with 2 chains, to identify the parameter combinations with best fit. The DIC was used to compare the goodness of fit. If several FP models showed similar DIC values (e.g. within 5 points), the selection was further informed by visual inspection of the fit of the observed data, carefully examining the tails of the distributions and plausibility of long-term extrapolation. Once identified, the best-fitting models were re-run with 200,000 iterations of which 50,000 were discarded as burn in, with the same thinning parameter and number of chains as described above. The ERG notes that if 200,000 iterations were required to get convergence on the posterior distribution, then it is likely that the results after 30,000 iterations would be different and potentially a bad predictor of statistical fit and clinical plausibility. In addition, the use of thinning is an inefficient and often unhelpful method for dealing

with problems with convergence and best practice advice would suggest simply increasing the number of iterations.

For all NMAs, whether for dichotomous or continuous outcomes and whether based on HRs or FPs, FUL 500 was chosen as the reference treatment, vague priors were used for all parameters, and fixed effect and random effects models were explored for each endpoint.

4.4.3 Results

For the NMAs presented in the CS, that is, the NMAs based on HRs for OS and PFS and for the dichotomous outcomes ORR and CBR, results were presented only for comparators regarded as relevant to this appraisal according to the company: ABE-FUL, exemestane (EXE), everolimus plus exemestane (EVE-EXE), and FUL 500. The efficacy of each of the comparators was presented in relation to the reference treatment (FUL 500) rather than ABE-FUL.

Assessment of proportional hazards

The company presented the results of their assessment of PH in the CS Appendix D.1.5. The assessment was done for studies included in the HR NMA (Appendix 10.4, Figure 46 and Figure 47). According to the company's assessment the log-log plots show clear violations in the PH assumption for Yamamoto 2013 and Zhang 2016 for PFS. In addition, for a number of the studies the hazards were not proportional for the initial time period although they became proportional at a later time point. The company states that the lack of PH in the beginning of the curves is due to interval censoring. For these cases, the company considered the PH assumption to hold as the curves do not reflect the true hazards for the treatment groups. The ERG does not agree with the company's assessment – if the hazards are truly proportional the interval in which they are assessed should have no bearing on whether or not the same proportional difference in events will have occurred. Based on the Schoenfeld residual plots for PFS the company found violations in PH for BOLERO-2,[53] CONFIRM,[54] PALOMA 3[45] and Yamamoto 2013.[59] The global test shows a statistically significant p-value only for Dombernowsky 1998[48] and BOLERO-2[53] (**Table 68**).

From the log-log plot for OS, the company identified violations in the PH assumption for the Dombernowsky 1998,[48] Muss 1990[46] and SoFEA[58] studies. Based on the Schoenfeld residual plots for OS the company found violations in the assumption for a number of studies including Buzdar 1997,[43] MONARCH 2[27] and Muss 1990.[46] Although, the global test showed a significant p-value only for Jonat 1996[44] and Muss 1990[46] (Table 68). The ERG notes that the results of the assessment were only reported for most, but not all of the studies included in the PFS and OS networks (**Table 68**). The company points out that the OS data are immature for a number of trials which introduces uncertainty into their assessment of the PH assumption.

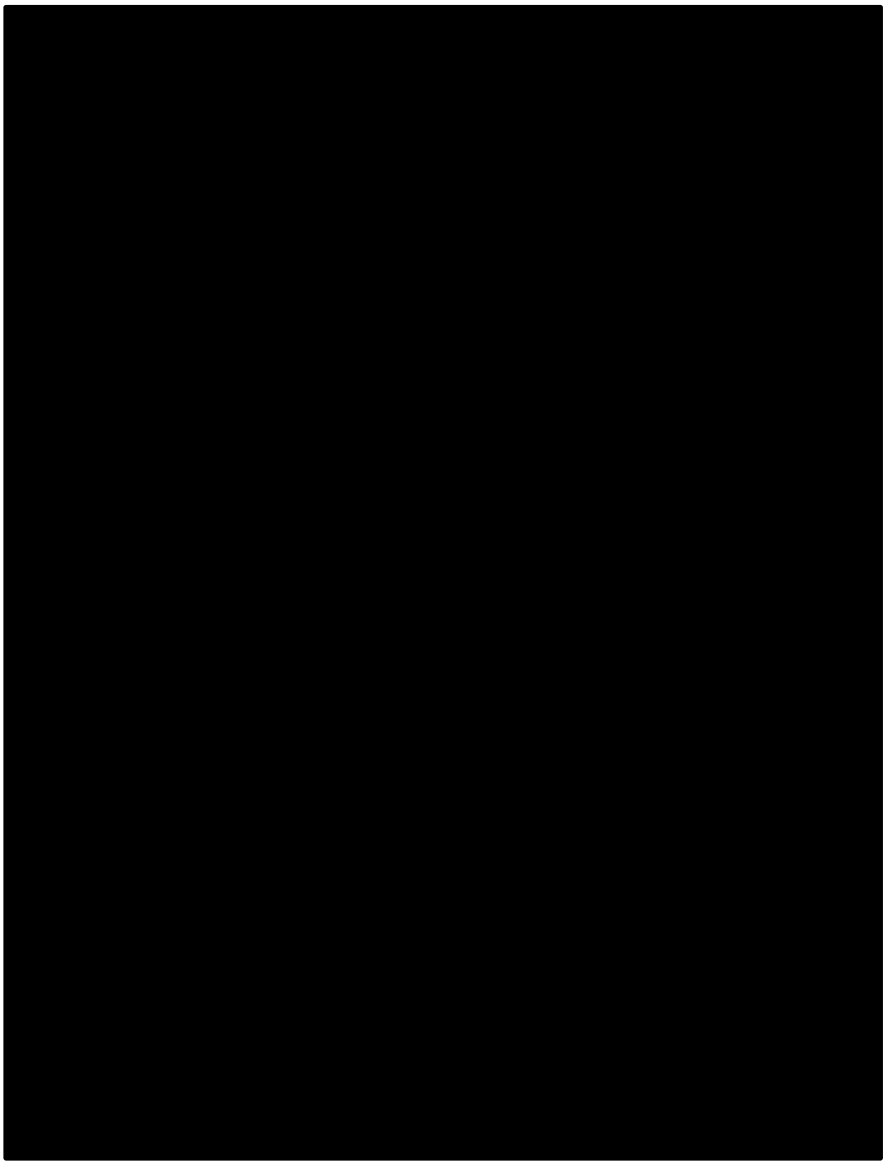
The company concludes that the assessment of PH for PFS and OS demonstrated that the assumption holds across the majority of studies, and that where there was evidence of non-PH, potential reasons for this could be identified, such as high levels of censoring in the tails due to immature survival data and interval censoring for PFS. As the PH assumption is not fulfilled for PFS or OS for some of the relevant trials, the ERG considers it inappropriate to base the analysis of these outcomes on any indirect comparison method which relies on the PHs assumption, even though the potential reasons for the lack of PH are identified. Despite this, these results inform the company's base case is in the economic model and are therefore presented in Section 4.4.2. However, the ERG would like to emphasise the difficulty in deriving a meaningful interpretation of these results.

Network meta-analysis based on Hazard Ratios

The company reported that there was no evidence of the fixed effect or random effects model fitting better than another. The results presented in the CS for PFS, ORR and CBR are all based on a random effects model to account for some heterogeneity between studies. For OS, however, the results are presented for a fixed effect model, the company states that as there was evidence of the prior around the random effects standard deviation dominating the posterior estimates. No results were presented for the company's assessment of potential inconsistence between the direct and indirect evidence within the closed loops within the networks.

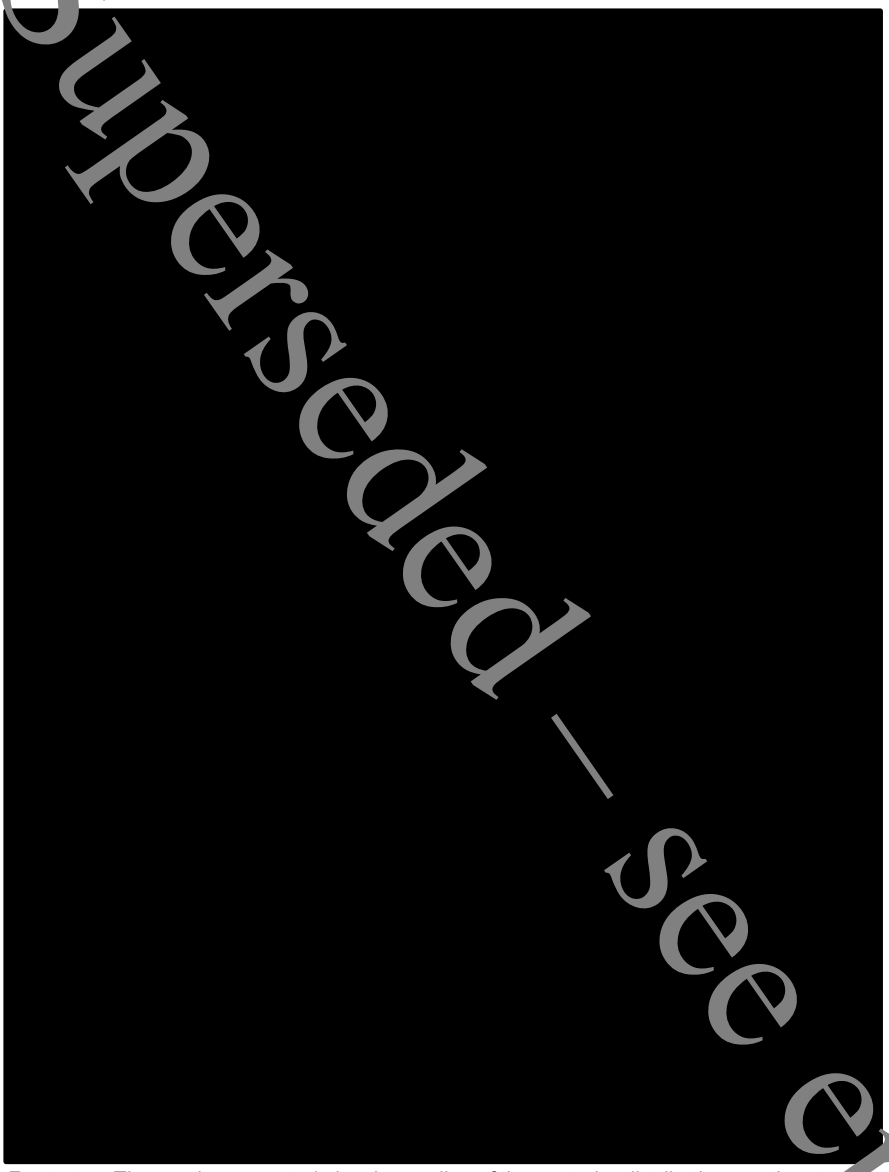
The HRs versus FUL 500 for each of the comparators in the PFS analysis indicate that the ranking in terms of efficacy from highest to lowest is [redacted] (Figure 10). However, the 95% credible intervals were relatively wide for each of the comparisons with ABE-FUL and EXE-EVE [redacted], and FUL 250 and EXE [redacted]. For OS the uncertainty was even more pronounced with even wider 95% credible intervals. The ranking was also slightly different starting at the most effective treatment: [redacted] (Figure 11). For the indirect treatment comparison of TMX and FUL 500, the point estimate indicates that TMX may be ranked as the [redacted] treatment for OS but [redacted] for PFS (Table 16). The ERG notes that there is considerable uncertainty around the point estimates for OS and PFS, which is calculated based on 95% confidence intervals for TMX versus TOR (Milla-Santos 2001), but the 95% credible intervals for FUL 500 versus TOR (HR NMA), and therefore unclear how it should be described.

Figure 10. Forest plot of treatment effects relative to FUL 500 mg for PFS using random-effects HR NMA



Footnotes: The results presented give the median of the posterior distributions as these are less skewed by outlying observations compared to the mean. FUL 250 is not a licensed dose in the UK but was included in the NMA to help connect the full network of comparators.
Abbreviations: ABE: abemaciclib; CrI: credible interval; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; mg: milligram; PFS: progression-free survival.

Figure 11. Forest plot of treatment effects relative to FUL 500 for OS using a fixed-effects HR NMA



Footnotes: The results presented give the median of the posterior distributions as these are less skewed by outlying observations compared to the mean. FUL 250 is not a licensed dose in the UK but was included in the NMA to help connect the full network of comparators.
Abbreviations: ABE: abemaciclib; CrI: credible interval; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; OS: overall survival; PFS: progression-free survival.

Table 16. Adjusted indirect comparison results for TMX vs FUL 500 mg based on Milla-Santos 2001 and the HR NMA (adapted from CS Table 23)

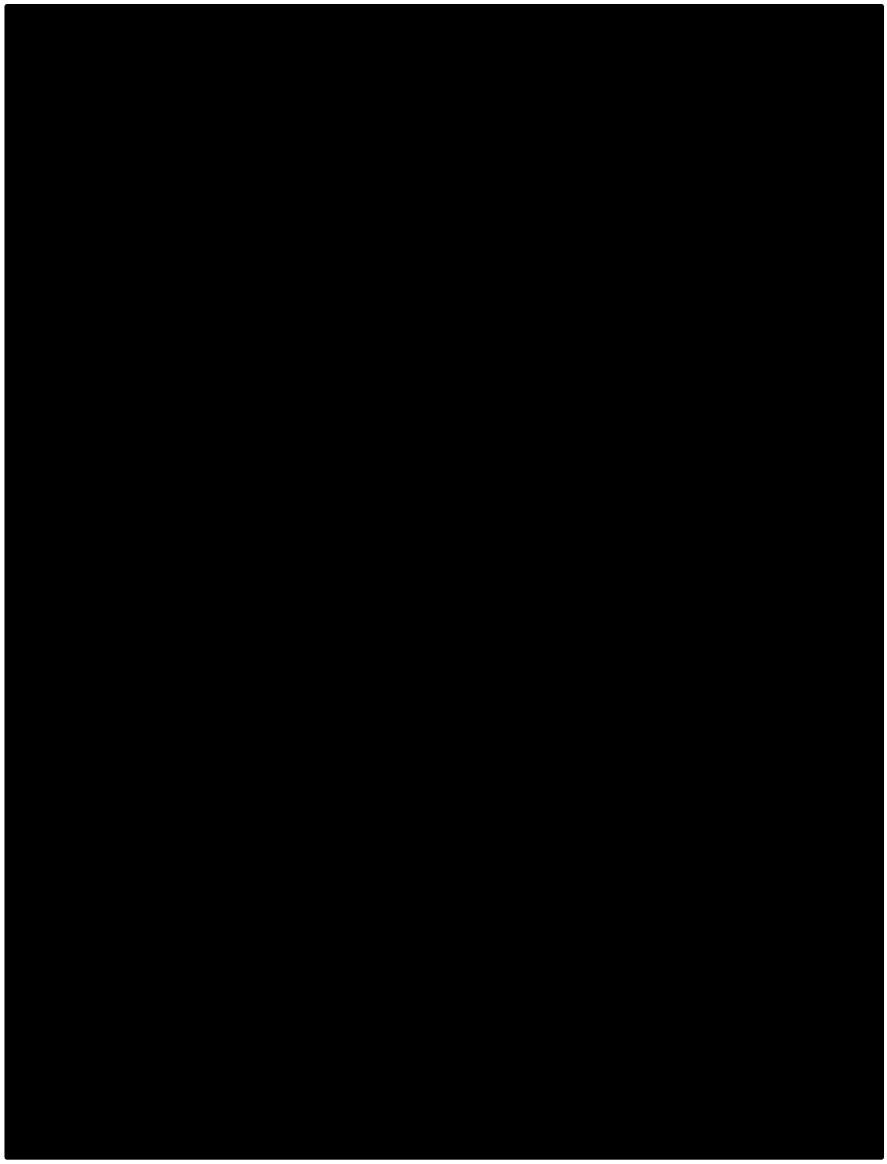
	OS, HR (95% CrI or CI)*	**PFS/TTP, HR (95% CrI or CI)***	**Source**
TOR vs TMX	[redacted]	[redacted]	Milla-Santos 2001[1]
TOR vs FUL 500 mg	[redacted]	[redacted]	NMA
Adjusted indirect comparison TMX vs FUL 500 mg	[redacted]	[redacted]	

*For TOR vs TMX the uncertainty is presented as 95% CI, for TOR vs FUL 500 mg the uncertainty is presented as 95% CrI, but for TMX vs FUL 500 mg the ERG is unsure of the unit of the interval quantifying the uncertainty as it is calculated based on a combination of CrI and CI
Abbreviations: CrI: credible interval; FUL: fulvestrant; HR: hazard ratio; NMA: network meta-analysis; OS: overall survival; PFS: progression-free survival; TOR: toremifene; TMX: tamoxifen.

Network meta-analysis dichotomous outcomes

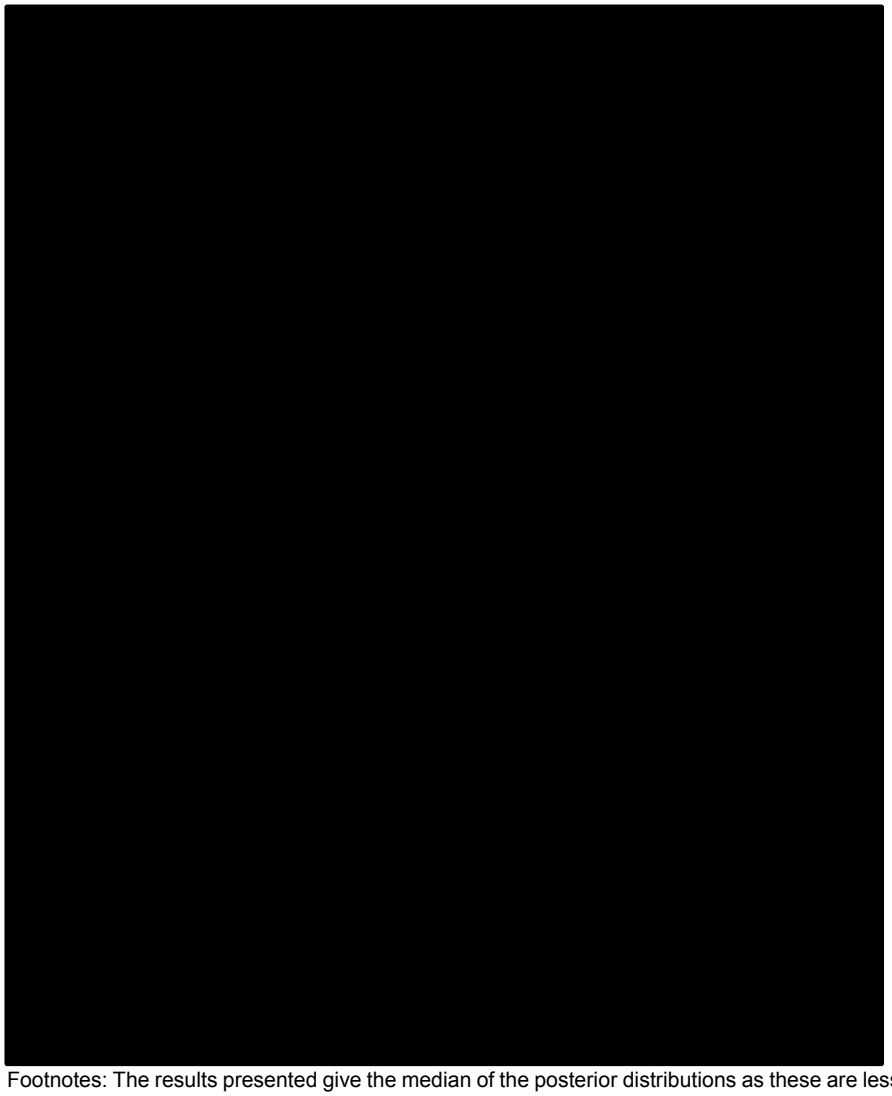
The company's analysis of ORR showed that based on the odds ratio versus the reference treatment FUL 500, the best treatment is [redacted] followed by [redacted] (Figure 12). The ranking of best to worst treatment for CBR was slightly different with [redacted] being the best followed by [redacted], in decreasing efficacy (Figure 13).

Figure 12. Forest plot of treatment effects relative to FUL 500 for ORR using random-effects model (reproduced from CS, Figure 11, pg 67)



Footnotes: The results presented give the median of the posterior distributions as these are less skewed by outlying observations compared to the mean. FUL 250 is not a licensed dose in the UK but was included in the NMA to help connect the full network of comparators.
Abbreviations: ABE: abemaciclib; CrI: credible interval; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; PFS: progression-free survival.

Figure 13. Forest plot of treatment effects relative to FUL 500 for CBR using random-effects model (reproduced from CS, Figure 12, pg 68)



Footnotes: The results presented give the median of the posterior distributions as these are less skewed by outlying observations compared to the mean. FUL 250 is not a licensed dose in the UK but was included in the NMA to help connect the full network of comparators.
Abbreviations: ABE: abemaciclib; CBR: clinical benefit rate; CrI: credible interval; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; PFS: progression-free survival.

Network meta-analysis based on Fractional Polynomials

According to the company, second-order FP models showed better fit than first-order models throughout, both in terms of DIC and visual inspection of the curves. However, for a number of second-order FP models the company experienced difficulties with convergence and autocorrelation even when the number of iterations was increased to 200,000 or more.

For OS, the company concluded that the FE second-order model with p1=0, p2=1 showed the best fit, whereas for PFS, the company's preferred choice was the FE second-order model with p1=0.5, p2=1. The corresponding time-to-event curves for these FP models are displayed in Figure 14 for OS and Figure 16 for PFS, respectively. However, the curves reported in the clarification response and reproduced below for PFS (Figure 14) and OS (Figure 16) differ from the curves used in the economic

model (Figure 15, Figure 17). In fact, the curves used in the economic model do not match the curves for any of the powers for PFS or OS that the company provided figures for. Therefore, the ERG has not been able to validate the FP model used in the economic model. However, for PFS and OS the curves presented in the clarification response and those used in the economic model all lack clinical plausibility as the curves plateau for several of the treatments, which is not in line with the clinical trial data underpinning the analyses or the experience of those therapies used in clinical practice. In addition, the PFS curve crosses the OS curve for several of the treatments, which is not biologically plausible. At the clarification stage the company kindly supplied the figures for all the assessed FP NMA results. Unfortunately, all curves with a relatively good statistical fit for PFS (Company's FP NMA statistics

Table 69) show a similar implausible plateau for most of the curves (data not shown).

Figure 14. PFS output* fixed effect 2nd order model (p1=0.5, p2=1) (reproduced from clarification response A3, Figure 5)

*According to the text in the company's clarification response the preferred FP NMA for PFS is p1=0.5 and p2=1 rather than p1=0 and p2=2 as presented in this figure. It is unclear if the figure or the text is miss-labelled or if the wrong figure has been presented.
Abbreviations: ABE: abemaciclib; CAP: capecitabine; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; PFS: progression-free survival; TOR: toremifene.

Figure 15. PFS output used in the economic model

Figure 16. OS output fixed effect 2nd order model (p1=0, p2=1) (reproduced from clarification response A3, Figure 6)

Abbreviations: ABE: abemaciclib; CAP: capecitabine; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; OS: overall survival; TOR: toremifene.

Figure 17. OS output used in the economic model

4.5 Summary of clinical effectiveness

- Median PFS was 16.4 months on ABE-FUL and 9.3 months on PBO-FUL, corresponding to a HR of 0.553 (95% CI: 0.449 to 0.681), and a statistically significant difference between groups ($p < 0.001$). The sensitivity analysis of blinded central analysis of PFS showed similar results with a slightly larger relative difference between ABE-FUL and PBO-FUL. A subgroup analysis of starting dose showed that although the interaction between the 200 mg and the 150mg subgroups was [redacted], the mean relative treatment effect in favour of ABE-FUL was [redacted] in the 200 mg subgroup compared with the 150mg subgroup.

- OS data were immature at the primary analysis with only 19.1% of patients who had died in the ABE-FUL group and 21.5% in the PBO-FUL group; median OS was not reached in either treatment group and there was no statistically significant difference between the treatment arms (HR [redacted], 95% CI: [redacted], p-value [redacted]).

- More patients treated with ABE-FUL achieved a complete or partial response than patients treated with PBO-FUL, the difference being statistically significant (OR 2.82, $p<0.001$). Similarly, there was a statistically significant difference in DCR (OR 1.56, $p=0.025$) and CBR (OR 2.04, $p<0.001$) between the ABE-FUL group and PBO-FUL group.

- HRQoL and disease-related symptoms were assessed using mBPI-sf, EQRTC QLQ-C30 and EQ-5D-5L. Between-group differences in pain intensity (mBPI-sf) generally favoured ABE-FUL over PBO-FUL but the differences did not reach clinical or statistical significance. Mean change from baseline within each treatment group and the mean differences between treatment groups were similar for the EQRTC QLQ-C30 global health status and the functional scales and for EQ-5D-5L, indicating that neither ABE-FUL or PBO-FUL treatment adversely affect functioning, HRQoL or the overall health status of patients. However, a [redacted] increase in mean symptom score with ABE-FUL compared with PBO-FUL was observed for diarrhoea, appetite loss, and nausea and vomiting.

- At the start of MONARCH 2 abemaciclib was administered at a daily dose of 400 mg. However, because of a large number of dose reductions due to adverse events, the protocol was amended lowering the daily dose to 300 mg. 178 patients (26.6%) were enrolled on the 400 mg dose. Of these 121 patients in the ABE-FUL group who started on the 200 mg dose, [redacted] ([redacted]) of patients discontinued treatment prior to having their dose reduced to 150 mg. The remaining [redacted] patients had their dose reduced to 150 mg due to treatment-emergent adverse events (TEAEs) ([redacted]) or the protocol amendment ([redacted]). Patients enrolled prior to the dose amendment received a median of [redacted] days of 200 mg abemaciclib before either having their dose reduced to 150 mg or discontinued treatment.

- The duration of treatment (of abemaciclib/placebo or fulvestrant) was [redacted] longer in the ABE-FUL group compared with the PBO-FUL group. The company reports conflicting figures of the proportion of patients who discontinued treatment due to AEs. [redacted] patients discontinued ABE-FUL compared with PBO-FUL.

- The most frequently reported AEs in the ABE-FUL group were diarrhoea (86.4%), neutropenia (46.0%), nausea (45.1%) and fatigue (39.9%). In the PBO-FUL group, the most frequently reported AEs were diarrhoea (24.7%), nausea (22.9%) and fatigue (26.9%).

- The incidence of SAEs was higher in the ABE-FUL group (22.4%) compared with the PBO-FUL group (10.8%). The most frequently reported SAEs for patients who received ABE-FUL were embolism (2%) and diarrhoea ([redacted]). For patients who received PBO-FUL the most common SAE was dyspnoea ([redacted]).

- Higher-grade diarrhoea occurred in the first few treatment cycles and was managed with dose omissions and/or dose reductions ([redacted] in ABE-FUL group), in addition to anti-diarrhoeal therapy. Most cases of neutropenia were Grade 3 AEs in both treatment groups. The median

time to onset of Grade 3 or 4 neutropenia was [redacted] days for ABE-FUL and [redacted] days for PBO-FUL. The incidence of higher-Grade diarrhoea and neutropenia was higher in patients who received the 200 mg abemaciclib starting dose compared with patients who started on 150 mg abemaciclib.

- Due to the absence of head-to-head trials comparing ABE-FUL with everolimus plus exemestane, exemestane monotherapy, tamoxifen, or chemotherapy in the relevant population, the company conducted NMAs.

- The PH assumption is not fulfilled for PFS or OS for some of the included trials. Despite this, these results of the HR NMA inform the company's base case is in the economic model. The ERG would like to emphasise the difficulty in deriving a meaningful interpretation of these results.

- The HR NMA for PFS indicate that the ranking in terms of efficacy from highest to lowest is [redacted]. Although, the 95% CrI were relatively wide for each of the comparisons. For OS the uncertainty was even more pronounced with even wider 95% credible intervals. The ranking was also slightly different starting at the most effective treatment: [redacted]. TMX may be ranked as the [redacted] treatment for OS but [redacted] for PFS.

- The company's analysis of ORR showed that the best treatment is [redacted] followed by [redacted]. The ranking of best to worst treatment for CBR was slightly different with [redacted] being the best followed by [redacted], in decreasing efficacy.

- For FP NMA OS, the company concluded that the FE second-order model with p1=0, p2=1 showed the best fit, whereas for PFS, the company's preferred choice was the FE second-order model with p1=0.5, p2=1. The curves reported in the clarification response for PFS and OS differ from the curves used in the economic model. For PFS and OS the chosen curves all lack clinical plausibility as the curves plateau for several of the treatments, which is not in line with the clinical trial data underpinning the analyses or the experience of those therapies used in clinical practice.

4.6 Additional work on clinical effectiveness undertaken by the ERG

The company kindly provided the OpenBUGS and R code (and datasets) they had analysed for the FP NMA of PFS and OS in response to a clarification request from the ERG. However, when the ERG

attempted to validate the company's assessed combination of powers and models it became apparent that this was computationally prohibitive taking around 3 hours to run each analysis. This is likely to be due to the number of iterations (for burn-in, sampling, and thinning) combined with the number of chains and number of data points analysed (when outputting the survival probabilities for either PFS and OS). The ERG, therefore, decided to run the FP NMA to estimate the beta parameters describing the FP curves produced by the NMA (two for first order and three for second order).

The ERGs FP NMAs were run using two-chains, with 300,000 iterations for burn-in followed by 300,000 iterations for sampling the posterior distribution, and with uninformed priors. Estimating the beta parameters for the FP curves produced by the NMA lowered the running time substantially to approximately 20 mins. As the ERG had concern around model selection (using DIC) based on a lower number of iterations to data collection, the same number was used consistently for all analyses.

The beta parameters estimated by the ERG's FP NMA were transformed in R into survival curves by firstly integrating the exponential of the FP up to the time point for each time period (e.g. monthly [or weekly in the economic model) to give the cumulative hazard at each time period, which was then used to estimate the survival probabilities as the exponential of the negative value of the cumulative hazard up to the time point.

The ERG attempted to validate the company's preferred fixed effects second order FP NMA powers for OS (p1=0, p2=1) and PFS (p1=0.5, p2=1), but the survival curves estimated bore no relationship to the either the company's curves presented in their clarification response document or those included in the model. However, they were similar in as much as they had clinically implausible tails that would be considered indicative of cure.

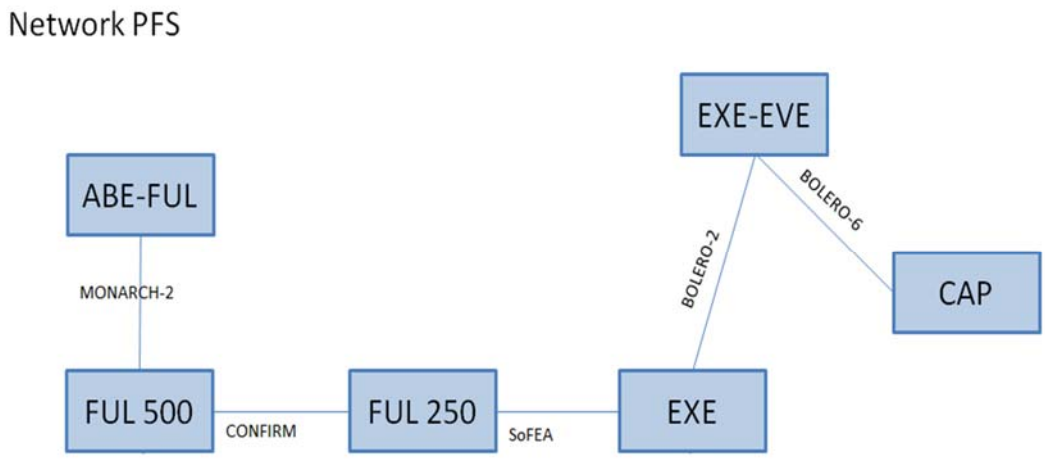
Similarly, the company's DIC statistics for other powers were also impossible for the ERG to replicate, as seen in Appendix 10.8.2. On visual inspection, most of the company's estimated curves presented in their clarification response document lacked clinical plausibility with implausibly long tails of the curves or even a plateau for one of more treatments, indicating that a substantial proportion of patients never relapse (data not shown). The FP models presented by the company with a more clinically plausible fit all had worse statistical fit (higher DIC), and several of them were first-order FP. As such, the ERG embarked upon its own exploration of FP NMA models to identify which would be considered the most appropriate to use. The DIC statistics for the powers explored by the ERG are presented in Appendix 10.3 with the ERG's findings described in Sections 4.6.1 and 4.6.2.

4.6.1 Progression free survival

For PFS the ERG simplified the network by excluding studies which were likely to introduce heterogeneity into the network and which were not required to connect the interventions of interest

(Figure 18). The network was simplified by excluding Hi-FAIR fx,[57] Yamamoto 2013[59] and the everolimus monotherapy arm from BOLERO-6.[29] Hi-FAIR fx[57] and Yamamoto 2013[59] were requested by the ERG to be included in the FP NMA network to enable the comparison with tamoxifen. However, the tamoxifen trial Milla-Santos 2001[1] could not be included in the FP NMA for PFS as the trial only reports a hazard ratio for toremifene and tamoxifen. Therefore, Hi-FAIR fx[57] and Yamamoto 2013[59], which could potentially increase additional heterogeneity within the network, were not required. Similarly, the everolimus monotherapy arm of BOLERO-6[59] was not required. As described in Section 4.4.1, Hi-FAIR fx and Yamamoto 2013 are both relatively small, open label, phase II trials in which the primary outcome was CBR rather than PFS, and with limited information on prior therapy.

Figure 18. Simplied PFS network – ERG analysis



Due to time constraints, the ERG only explored first-order FPs for the NMA of PFS, testing the following powers: -1, -0.5, 0, 0.5 and 1. Of the first-order FP NMAs tested, three had similar statistical fit (p=0.5, p=0, p=-0.5) and produced curves that seemed clinically plausible in terms of the relative order of the treatments compared with the underlying trial data. The ABE-FUL curve was above the FUL 500 curve in the KM-curves for MONARCH 2, the EXE-EVE curve was above the curve of EXE as in the KM-curves for BOLERO-2, and the capecitabine curve was above the EXE-EVE curve as in BOLERO-6. The FP NMAs for p=0 and p=-0.5 gave very similar curves but the FP NMA for p=0 had a slightly better statistical fit and therefore only the results of this power are presented here.

The FP NMAs for p=0 and p=0.5 had the same statistical fit but p=0 produced more clinically plausible tails, with most curves showing everyone had progressed by 140 months (Figure 19), whereas for p=0.5 some patients were still progression free on some treatments at this timepoint. The power, p=0, was therefore chosen to inform the ERG base case and p=0.5 used for a scenario analysis. The FP NMA with p=0 is equivalent to a Weibull curve, which is the curve chosen to inform the company's PFS analysis based on the HR NMA, informing their base case.

For the FP NMAs p=0.5 and p=0, capecitabine starts as the most effective treatment, but the curve crosses ABE-FUL at around 30 months (p=0.5) or converges with the ABE-FUL curve at around 45 months (p=0). That capecitabine is the most effective treatment for a considerable amount of time is consistent with the underlying trial data in the network. As mentioned in Section 4.4.1, the authors of BOLERO-6 consider the results of the trial to be potentially biased due to imbalances in prognostic factors and baseline characteristics, informative censoring of PFS, and because the findings were inconsistent with previous capecitabine studies. The PFS HR for EVE+EXE versus capecitabine in BOLERO-6 was 1.26 (90% CI: 0.96 to 1.66), however, the authors also presented the result of a stratified multivariate Cox regression model adjusted for the imbalances observed in prognostic factors and baseline characteristics. In the adjusted model, the difference between the treatments was smaller but treatment with capecitabine still seemed to lead to an improvement in PFS compared with EVE+EXE, and remained not statistically significant (HR 1.15, 90% CI: 0.86 to1.52). The ERG agrees that the efficacy of capecitabine is likely to be overestimated in the ERG's FP NMA and that the results for capecitabine should be interpreted with caution.

Figure 19. Simplified NMA PFS 1st order

As can be seen in Figure 20, where the results of the FP NMA have been overlaid on the underlying KM data for ABE-FUL and FUL from MONARCH 2,[27] the fit of the ABE-FUL and FUL curves to the KM data seems very poor. However, the fit of the resulting curves from the FP NMA to the original KM data is unlikely to be good due to the nature of "adjusting" the effectiveness of treatments to make them directly comparable as part of the NMA. In simplistic terms, the FUL curve resulting from the FP NMA is better thought of as a "weighted average" curve of all of the trials including FUL in the network as opposed to being a direct reflection of FUL in MONARCH 2.[27]

To help illustrate this further, a better assessment is how well the FP NMA estimates the individual trials as FP curves prior to the NMA. Due to limited time, the ERG only explored the visual fit of the estimated FP curves for MONARCH 2[27] and CONFIRM[54] with the KM data from MONARCH 2[27] and CONFIRM,[54] respectively. Figure 21 shows that the FP curves for ABE-FUL and FUL treatment arms in MONARCH 2[27] provide a reasonably good visual fit to the underlying KM data for both trial arms. However, the ERG notes that the model fit statistics are based on the average fit across the network; that is, the FP may not fit any individual treatment well but, on average, the family of curves is the best fit for the network. As can be seen in Figure 21, the FP curve for FUL in CONFIRM[54] fits less well and is underestimating the underlying KM data.

Figure 20. Simplified NMA PFS 1st order with MONARCH 2[27] KM curves

Figure 21. MONARCH 2[27] and CONFIRM FP versus KM curve validation

A. MONARCH 2 ABE-FUL and FUL arms

B. CONFIRM Fulvestrant 500 arm

4.6.1 Overall survival

For OS the ERG explored the same simplified network as used in the ERG analysis of PFS (Figure 18). For the analysis of OS, Hi-FAIR fx[57] and Yamamoto 2013[59] could have been included to enable the inclusion of tamoxifen in the network as OS KM data are available for Milla-Santos 2001,[1] the trial comparing tamoxifen with toremifene. However, because of the cross-over design of both Hi-FAIR fx[57] and Yamamoto 2013[59] and the different doses of toremifene used on Milla-Santos 2001[1] (60 mg/day) compared with Hi-FAIR fx[57] and Yamamoto 2013[59] (120 mg/day), the relative efficacy of tamoxifen is likely to be confounded and potentially misleading.

Due to time constraints, the ERG only explored first-order FP NMAs for OS. For a list of FP powers tested and the resulting DICs see Appendix 10.8.3. Of the FP NMAs tested, p=1 gave a very high DIC, indicating a poor fitting model, two powers (p=0 and p=0.5) produced an OS curve for ABE-FUL that crossed FUL 500, which was not deemed clinically plausible, and two powers (p=–2.5 and p=–2) produced curves for some but not all treatments. Due to time constraints the ERG was unable to resolve this issue, however, the treatment curves that were produced were broadly similar to the FP NMAs preferred by the ERG (described below).

The three remaining FP NMAs produced curves that seemed consistent in terms of the relative order of the treatments compared with the underlying trial data. As mentioned previously, the authors of BOLERO-6 consider the OS results of this trial to be potentially biased due to imbalances in baseline

characteristics. Similar to the analysis of PFS, the difference between EVE+EXE and capecitabine was smaller in the analysis adjusted for these differences but treatment with capecitabine still improved OS compared with EVE+EXE (HR 1.19, 90% CI: 0.88 to 1.62).

Of the three remaining clinically plausible FP NMAs, the ERG chose p=–0.5 for its base case. All the treatment curves in the p=–0.5 FP NMA indicate all patients died earlier than the p=–1.5 and p=–1 FP NMAs and while the individual treatment curves converge there were no extreme crossing of curves (Figure 22). The curves for the FP NMA with p=–1 and p=–1.5 were very similar (data not shown), however, the results of the FP NMA with p=–1.5, which had the best statistical fit and are presented below as an alternative scenario for the ERG's base case (Figure 22).

Figure 22. Simplied OS network – ERG analysis

The trial-based FP curves for ABE-FUL and FUL in MONARCH 2[27] for the chosen model (p=–1.5) overlaid on the underlying KM data show a relatively poor fit of the data for both trial arms (Figure 23). As discussed in the previous section for PFS, the model fit statistics are based on the average fit across the network; that is, the FP curves may not fit any individual treatment well but, on average, the family of curves is the best fit for the entire network. In addition, for MONARCH 2,[27] the poor fit may also be partly due to the immaturity of the OS data compared with the other trials in the network. Similar to MONARCH 2,[27] the FP curve for FUL in CONFIRM shows a relatively poor fit to the underlying KM data, but in contrast to the results for PFS, the FP curve for OS is a slight overestimate compared to the KM curve.

Figure 23. MONARCH 2[27] and CONFIRM[54] FP versus KM curve validation

A. MONARCH 2 ABE-FUL and FUL arms

B. CONFIRM Fulvestrant 500 arm

[redacted]

[redacted]

4.7 Conclusions of the clinical effectiveness section

Abemaciclib was granted marketing authorisation in October 2018 for the treatment of women with HR+/HER2– aBC in combination with an AI or fulvestrant as initial ET, or in women who have received prior ET. The submitted evidence from MONARCH 2 were used to inform the analysis of efficacy and safety of abemaciclib in combination with fulvestrant (ABE-FUL) versus fulvestrant monotherapy. MONARCH 2 is an international, randomised, double-blind, placebo-controlled phase

III trial. Around 40% of patients were from Europe, but the trial did not include any UK centres. Nonetheless, the patients in MONARCH 2 are representative of women with HR+/HER2− aBC in UK clinical practice.

Patients in MONARCH 2 were initially administered a daily dose of 400 mg abemaciclib. However, because of a large number of dose reductions due to adverse events, the protocol was amended lowering the daily dose to 300 mg. Before the protocol amendment, 178 patients (26.6%) were enrolled on the 400 mg dose.

The primary objective of MONARCH 2 was to assess the efficacy and safety of ABE-FUL compared with fulvestrant alone in people with advanced HR+/HER2− breast cancer that has progressed on or after prior ET. The primary outcome in MONARCH 2, investigator-assessed PFS, showed a statistically significant benefit with ABE-FUL compared with placebo+ fulvestrant (PBO-FUL). The sensitivity analysis of blinded central review of PFS and the subgroup analysis by starting dose were consistent with the primary analysis favouring ABE-FUL. As were the results of secondary outcomes, OS and response rates. OS data were immature and the difference in OS between ABE-FUL and PBO-FUL did not reach statistical significance.

At the start of MONARCH 2 abemaciclib was administered at a daily dose of 400 mg. However, because of a large number of dose reductions due to adverse events, the protocol was amended lowering the daily dose to 300 mg. Just over a quarter of the trial population were enrolled on the 400 mg dose.

Treatment discontinuations due to AEs were [redacted] with ABE-FUL compared with PBO-FUL and the incidence of SAEs was higher in the ABE-FUL group (22.4%) compared with the PBO-FUL group (10.8%). The incidence of higher-grade diarrhoea and neutropenia was higher in patients who received the 400 mg daily abemaciclib starting dose compared with patients who started on 300 mg abemaciclib per day.

Due to the absence of head-to-head trials comparing ABE-FUL with everolimus plus exemestane, exemestane monotherapy, tamoxifen, or chemotherapy in the relevant population, the company conducted network meta-analysis (NMA). The company's original NMAs for OS and PFS were based on HRs. However, the PH assumption is violated for some of the studies in both the PFS and OS analysis. Despite this, the results of the HR NMA inform the company's base case is in the economic model. OS and PFS were also analysed using FP NMA, which can better account for a variable hazard over time. However, for the company's preferred FP NMAs the resulting curves for PFS and OS all lack clinical plausibility as the curves plateau for several of the treatments, which is not in line with the clinical trial data underpinning the analyses or the experience of those therapies used in clinical practice. The ERG attempted to validate the company's FP NMA, but the survival curves estimated bore no

relationship to the company's curves. However, they were similar in as much as they had clinically implausible tails that would be considered indicative of cure. The ERG therefore explored other FP NMA models to identify which would be considered the most appropriate to use. Based on a combination of statistical fit and clinical plausibility the ERG chose a FE first-order model for both PFS and OS; p=0 was chosen to inform the ERG base case for PFS, and p=0.5 was used for a scenario analysis, for OS the ERG chose p=–0.5 for its base case and p=–1.5 as a scenario. The FP NMAs chosen all produced curves that seemed consistent in terms of the relative order of the treatments compared with the underlying trial data and which produced more clinically plausible tails, with all curves reaching the baseline and no crossing of the PFS and OS curves as seen in the company's analysis.

4.7.1 Clinical issues

- The available OS data for MONARCH 2 were immature, with only 19.1% of patients who had died in the ABE-FUL group and 21.5% in the PBO-FUL group, which introduces substantial uncertainty in the relative effectiveness of ABE-FUL versus all of the comparators of interest for this outcome.

- Due to the specificity of the MONARCH 2 population the eligibility criteria for identifying comparable studies for the ITCs were relaxed which resulted in some heterogeneity between the included studies; some studies were double blind and some were open-label, HER2- status was not consistently reported, some study populations were more heavily pre-treated than others, both in terms of prior chemotherapy and number of lines of ET in the advanced setting, and baseline characteristics such as visceral involvement varied substantially.

- The PFS and OS results for capecitabine compared with EVE+EXE in BOLERO-6 and versus the other comparators in the FP NMA, may be overestimated due to imbalances in baseline characteristics of patients in the trial and potentially due to informative censoring of PFS.

- No reliable comparison between ABE-FUL and tamoxifen was possible. In the trial informing the efficacy of tamoxifen, Milla-Santos 2001, an unknown proportion of patients may have progressed on or after adjuvant ET. In addition, the trials linking Milla-Santos 2001 to the network, Hi-FAIR fx and Yamamoto 2013, administered the common comparator, toremifene, at double the dose of that in Milla-Santos 2001, and both were of a cross-over design likely to confound any estimate of OS.

- The PH assumption is not fulfilled for PFS or OS for some of the trials included in the ITC. Despite this, the results of the HR NMA, which relies on the PH assumption holding, inform the company's base case in the economic model. The ERG emphasises the difficulty in deriving a meaningful interpretation of these results.

The company's results from the FP NMA lack clinical plausibility as the curves plateau for several of the treatments, which is not in line with the clinical trial data underpinning the analyses or the experience of using those therapies in clinical practice. In addition, the PFS curve crosses the OS curve for several of the treatments, which is not biologically plausible.

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured description and critique of the systematic literature review and *de novo* economic evaluation submitted by the company. The company provided a written submission of the economic evidence along with an electronic version of the Microsoft© EXCEL based economic model. As a result of the clarification stage, the company submitted an updated economic model. The company's updated base case results compared the cost-effectiveness of abemaciclib in combination with fulvestrant (ABE-FUL), with fulvestrant (FUL) monotherapy; exemestane (EXE); exemestane in combination with everolimus (EXE-EVE); and tamoxifen (TMX). The company's updated economic model also included capecitabine (CAP) as a comparator, however the latter was not included in the company's base case, but instead as a scenario analysis.

5.2 Summary of the company's key results

The company's updated deterministic base case results for ABE-FUL, compared with FUL; EXE; EXE-EVE and TMX are provided in Table 17, with the ABE-FUL's patient access scheme (PAS) included. The ERG has several concerns with the probabilistic sensitivity analysis undertaken by the company. This is discussed in Section 5.5.

Table 17. Company's base case results with PAS included

Comparator	Costs	LYs	QALYs	ICER (per QALY)	ICER (per QALY) for ABE-FUL vs comparator
TMX	[redacted]	3.72	[redacted]	[redacted]	£62,548
FUL	[redacted]	3.50	[redacted]	[redacted]	£41,702
EXE	[redacted]	3.33	[redacted]	[redacted]	£18,754
ABE-FUL	[redacted]	3.64	[redacted]	[redacted]	N/A
EXE-EVE	[redacted]	3.45	[redacted]	[redacted]	Dominant

5.3 ERG comment on company's review of cost-effectiveness evidence

The company carried out a systematic literature review (SLR) to identify economic, and health-related quality of life (HRQoL) evidence relevant to treatment options for the management of hormone-receptor positive (HR+) and human epidermal growth factor receptor 2 negative (HER2–), locally advanced or metastatic breast cancer (aBC). However, to ensure that all potentially relevant data were identified and included, the eligibility criteria were not restricted to HR+/HER2− patients. To identify cost and resource use evidence, the company searched the same sources identified for the economic evidence.

The company searched the following electronic databases: MEDLINE, EMBASE, EconLit, NHS Economic Evaluation Database (NHS EED), the NICE website and the Canadian Agency for Drugs and Technology in Healthcare (CADTH). In addition, conference proceedings at four key international conferences were searched through EMBASE. All searches were first run in April 2016 and updated in June 2017. However, the NHS EED stopped being maintained in 2015, therefore the search update was not relevant in that database.

The company applied a date limit to the electronic databases as it considered that studies published prior to 2010 are not representative of current cost and resource use, or cost-effectiveness modelling practice. As for conference proceedings, the company applied a date limit of 2013. The company did not justify a later date for conference proceedings, and the ERG is concerned that the company's approach lends to publication bias. Nonetheless, given that abstracts provide a limited description of methods and results, their ability to inform economic analysis is always restricted. Therefore, the ERG does not consider the publication bias to pose a significant concern in this case.

Search strategies are provided in Appendix G, H and I of the CS for economic evidence, HRQoL evidence, and cost and resource use evidence, respectively. In summary, search terms combined the population with economic and quality of life terms, which the ERG considers to be inclusive.

The SLR for economic evidence identified 13 publications, seven conference proceedings, seven NICE technology appraisals (TAs) and three CADTH submissions relevant to the eligibility criteria reported in Table 36, Appendix G of the CS. A summary of the seven studies relevant to the UK setting are presented in Table 21 of the CS. In brief, four of those studies[13, 69-71] considered endocrine therapy (ET) or combination endocrine and a targeted agent treatments, while three studies[72-74] considered chemotherapy, or combination chemotherapy and a targeted agent. Among those studies, the predominant model structure was a partitioned survival model with three health states: progression-free survival (or stable disease), progressed disease and death, most with a cycle length of one month.

With regards to the cost and resource use evidence, a total of 66 studies were identified based on the eligibility criteria reported in Table 50 of the CS, and 20 of those studies related to HR+/HER2− patients. Two of those studies[75, 76] were undertaken in the UK, however the company did not explain why the latter were not used to inform the economic model. Moreover, the ERG is unclear why the company did not include relevant NICE TAs in adults with aBC, such as those included in their search for economic evidence. During the clarification stage, the ERG asked the company to explain these issues, however the company did not provide a response, reporting time limitations as a justification. Nonetheless, the company considered NICE CG81[17] and the MONARCH 1 and MONARCH 2 trials to inform health state resource use inputs in their submission.

As for HRQoL evidence, a total of 13 publications and six conference proceedings met the eligibility criteria reported in Table 41 of Appendix H. Of those, 13 studies[76-88] used the EQ-5D to value patients' preferences and two of those studies[77, 78] also mapped values from cancer-specific instruments (FACT-B and EORTC QLQ-C30) to the EQ-5D. Another three studies mapped responses from cancer-specific instruments to generic preference-based measures.[89-91] A summary of those 13 studies reporting EQ-5D data, and five studies reporting mapping algorithms, are provided in Tables 44 and 46 of Appendix H, respectively. Finally, three further studies reported in Table 43 of Appendix G, reported SF-36 data.[92-94] As described in Section 5.4.8, the company did not incorporate data from any of the identified studies, given that EQ-5D data from the MONARCH 2 trial were available to populate the economic model.

Although the ERG considers the searches carried by the company to be appropriate, the ERG is concerned that the company might have missed important studies published since June 2017, and NICE TAs reporting resource and cost use data. During the clarification stage, the ERG asked the company to explain why searches had not been updated since June 2017, but the company did not provide a response. The ERG was also unable to replicate the company's search and appraisal of identified abstracts for all databases, due to time constraints. Instead, the ERG performed a non-systematic targeted search to identify potentially relevant studies. Following this, the ERG identified TA496[19], Harbeck *et al.* 2017[95], Hettle *et al.* 2017[96], Mistry *et al.* 2018[97], Rugo *et al.* 2018[98], Suri *et al*. 2017[99] and Wood *et al.* 2017[100] as potentially relevant sources of utility, resource or cost use data. As a result, the ERG considers the company's searches to be incomplete. Additional scenarios considering TA496 to inform resource use data are reported in Section 5.4.9.

5.4 Overview and critique of company's economic evaluation

5.4.1 NICE reference case checklist

Table 18 summarises the ERG's appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base case analysis, with reference to the NICE final scope outlined in Section 3.[101, 102]

Table 18. NICE reference checklist

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Decision problem	The final scope developed by NICE	Yes, although there is a considerable amount of heterogeneity across the study populations used in the NMA (see details in Section 4).
Comparator(s)	Alternative therapies routinely used in the NHS	Yes, although the modelled dose of TMX(40mg) is not reflective of NHS clinical practice, which is based on 20mg. Furthermore, the ABE-FUL cost did not include the initial loading cost for FUL.
Perspective costs	NHS and Personal Social Services	Yes.

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-utility analysis	Yes.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes, however the company reported the time horizon to be 25 years, when it was in fact 20 years in the analysis.
Synthesis of evidence on outcomes	Systematic review	Yes.
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	Yes.
Benefit valuation	Time-trade off or standard gamble	EQ-5D-5L data collected in the MONARCH 2 trial mapped to EQ-5D-3L values, using the mapping function developed by van Hout *et al.* 2012[103].
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Sensitivity analysis	Probabilistic sensitivity analysis	No – The ERG is concerned that the uncertainty in the company's analysis has not been appropriately accounted for, whether in the NMA HR base case analysis or in the FP NMA scenario.
Abbreviations used in the table: EQ-5D, EuroQoL 5-Dimension; HRQoL, health-related quality of life; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year; SF-36, 36-Item Short Form Survey; TTO, time trade-off.		

5.4.2 Population

The population considered by the company for this STA comprises women with HR+/HER2- aBC who had progressed according to at least one of the following criteria:

1. While receiving (neo)adjuvant ET;
2. Less than or equal to 12 months from the end of adjuvant ET;
3. While receiving first-line ET for metastatic disease.

In the company's base case, the modelled population was based on the FUL and ABE-FUL arms of MONARCH 2. Around 40% of patients in MONARCH 2 were from Europe, but the trial did not include any UK centres. Nonetheless, the baseline characteristics of patients in MONARCH 2 are generally in

keeping with those expected in women with HR+/HER2− aBC in UK clinical practice, according to the ERG's clinical experts.

Given that relative treatment effectiveness in the model was obtained through the NMA, the study populations included in the latter are also indirectly reflected in the economic model. Even though the modelled population is generally an appropriate reflection of the NICE final scope, there is a considerable amount of heterogeneity across the study populations used in the NMA. This issue is discussed in detail in Section 4.

5.4.3 Interventions and comparators

The intervention considered in the economic model reflects that set out in the NICE final scope. The recommended dose for abemaciclib is two 150mg capsules daily on a 28-day cycle while for FUL (in combination with abemaciclib) the recommended dose is 500mg given as an intramuscular injection at intervals of one month, with an additional 500mg dose given two weeks after the initial dose. The company modelled the cost of abemaciclib correctly, however did not include the additional 500mg loading dose of FUL in the economic model. This issue is further discussed in Section 5.4.9.

There are five comparators considered in the economic analysis. The latter consist on FUL 500mg; EXE 25mg; EXE 25mg + EVE 10mg; TMX 40mg; and chemotherapy. The company did not originally include chemotherapy as a comparator in the economic analysis, however the treatment was included as a scenario analysis following the clarification stage. The ERG's clinical experts advised that chemotherapy is a relevant treatment alternative for patients who are progressively symptomatic and that the choice of second-line chemotherapy regimen is determined on a patient-by-patient basis, based on prior treatment, disease severity and patient preference. Clinical experts added that CAP would be used in those whose disease is progressing slowly, and more aggressive chemotherapy regimens in those for whom a more rapid response is required. The company included CAP in their analysis.

Clinical experts advising the ERG confirmed that all the comparators included in the company's original analysis were relevant to the UK clinical practice, however, noted that the recommended daily dose for TMX in UK clinical practice is normally 20mg (compared with the 40mg modelled by the company) given that no additional clinical benefit has been demonstrated with higher doses.[61]

Despite not being recommended by NICE as a treatment option for this population, FUL was included as a relevant comparator in the final scope for this STA. The company and the ERG's clinical experts highlighted that FUL is used in a small number of patients in the UK, either funded by NHS Trusts without reimbursement, or in private hospitals and is therefore, considered a relevant treatment option in this setting. Palbociclib and ribociclib in combination with FUL are licensed in this patient

population, but neither have been appraised by NICE at the time of writing. If recommended, these treatments will become direct comparators to ABE-FUL.

The proportion of patients who received subsequent treatments in MONARCH 2 is reported in Table 19. The proportion of patients with disease progression who received subsequent treatments was [redacted] in the ABE-FUL and [redacted] in the FUL arm, respectively. The first subsequent line consisted mainly of [redacted] - overall, [redacted] of progressed patients received [redacted] as their first line of treatment, with [redacted]. A slightly higher percentage of patients received [redacted].

A considerable proportion of patients also received [redacted] as a first line option after they discontinued study drugs. The main [redacted]

Overall, the proportion of progressed patients who received subsequent treatments was [redacted] received first-line subsequent [redacted], compared with patients in the FUL arm. [redacted] the company's proposition that ABE-FUL will provide an additional treatment option for primary or secondary ET-resistant patients therefore, allowing the postponement of chemotherapy. Although MONARCH 2 data have demonstrated that ABE-FUL delays disease progression (47% of ABE-FUL patients progressed within the trial follow-up period, while 69% of FUL patients progressed in the same time interval), therefore, delaying the beginning of subsequent therapy, the observed subsequent treatment regimens [redacted]. This analysis needs to be caveated by the fact that the data on subsequent therapies in MONARCH 2 are incomplete (70% of patients in the ABE-FUL arm had progressed or left the study at the end of the follow-up period) and so it is unknown what treatments these patients would receive after they progressed on ABE-FUL.

Furthermore, it is unknown how subsequent treatments affect the OS estimates in MONARCH 2. Most treatments received after ABE-FUL and FUL are available through the NHS, except for a few treatments, however, the latter where not used very frequently. For example, [redacted] of patients in the ABE-FUL arm received bevacizumab, while [redacted] of FUL patients received the same treatment. About [redacted] of patients in both treatment arms received other treatments such as ribociclib and nivolumab, not available in the NHS for this indication. Thirteen percent of ABE-FUL patients received subsequent FUL, which is not recommended by NICE as a monotherapy for this population. Further lines of subsequent treatment also included treatments that would not be available in the NHS, however the main treatments received were chemotherapy, EXE or EXE-EVE.

Table 19. Subsequent treatments received in MONARCH 2

[redacted]

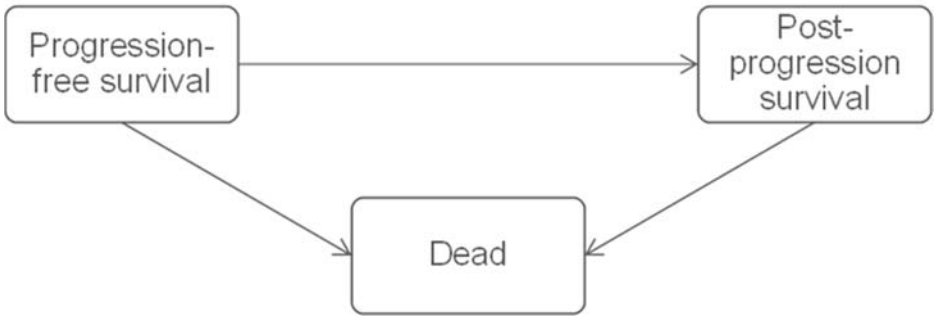
5.4.4 Modelling approach and model structure

The company developed a *de novo* model in Microsoft Excel® to assess the cost-effectiveness of ABE-FUL in comparison with FUL; EXE; EXE-EVE and TMX in patients with HR+/HER2- locally advanced or metastatic BC with progressive disease (as defined in Section 5.4.1). Following the clarification stage, the company included chemotherapy as a comparator in a scenario analysis.

The cohort-based partitioned survival model (presented in Figure 24) includes three health states: progression-free survival (PFS), progressed disease (PD), and death. The cohort is allocated to the PFS state at the beginning of the economic analysis and is assumed to initiate treatment with ABE-FUL or with one of the comparators. Patients occupying the PFS state are at risk of disease progression or death and can also discontinue treatment before disease progression, even though the latter was not explicitly modelled, but estimated to capture treatment costs. Patients occupying the PD state are also at risk of death and can receive further treatment lines in the model. After entering the PD state patients cannot enter remission.

The partitioned survival (or area under the curve [AUC]) approach means that the proportion of patients modelled in each health state is based on parametric survival curves for each clinical outcome. A description of how the survival curves were estimated and implemented in the model is provided in detail in Section 5.4.5.

Figure 24. Model structure



The company reports that a life time horizon of 25 years is adopted in the model, however, upon inspection of the company's economic model the ERG concluded that a 20-year time horizon was used instead. Time is discretised into weekly cycles with a half-cycle correction applied. The analysis was carried out from an NHS and Personal Social Services (PSS) perspective. Costs and health effects are discounted at an annual rate of 3.5%, in line with the NICE Reference Case.[104]

5.4.4.1 ERG critique

The ERG is generally satisfied with the model structure. Patients discontinuing treatment due to toxicity were captured through time to treatment discontinuation (TTD) data but not explicitly through the health states included in the economic model. Patients who have progressed are assumed to receive subsequent treatments, which is in line with clinical expert opinion provided to the ERG. Patients who progress are assumed to start subsequent treatment as soon as they enter the progression state.

The partitioned survival approach employed by the company is appropriate. A life time horizon of 20 years seems plausible considering the baseline mean age of MONARCH 2 patients was 60 years, and

median life expectancy for aBC is two to three years (Section 4). Nonetheless, the company's base case economic analysis estimates that 5% of ABE-FUL patients are still alive at 10 years, with 1% alive at 16 years. This might suggest an overestimation of long-term survival in the model, especially for patients with metastatic disease. This issue is further discussed in Section 5.4.8 of the ERG report.

As reported in Section 5.3, most of the relevant cost-effectiveness models identified in the SLR included monthly cycles. Weekly-cycles models can become unwieldy, particularly when the time horizon is long. Furthermore, due to the number of treatments included in the analysis, the use of weekly cycles considerably added to the computation burden of the analysis. During the clarification stage, the ERG asked the company to justify their choice of weekly model cycles. The company replied that, "*a weekly cycle was convenient for modelling and also deemed appropriate given the frequency at which treatment regimens are administered in this patient population*…". The company added that, "*In the MONARCH 2 trial, abemaciclib or placebo were administered twice daily, and fulvestrant administered on days 1 and 15 of the first 28-day cycle, and on day 1 of subsequent cycles*." It was also reported that, "…*a weekly cycle was appropriate given the rate at which clinical events beyond progression, such as adverse events, may occur in this patient population*.".

From a modelling point of view, the ERG does not understand the convenience of using weekly cycles, as shorter model cycles add to the computation burden of the analysis. With regards to clinical events, the ERG disagrees with the company's statement that weekly cycles are adequate to capture progression, as the ERG's clinical experts advised that the minimum time-period when observable disease progression could be identified would be four weeks. With respect to adverse events, these were estimated as an up-front cost, therefore the length of model cycles does not influence this. The only reasonably justifiable need for weekly cycles in the model is the fact that abemaciclib is given daily to patients. Nonetheless, given the computational disadvantages of using weekly cycles when compared to monthly intervals, the ERG does not consider the company's decision to be appropriate. To change this, would mean building a new economic model, thus the ERG did not carry out this analysis, nor did it ask the company to do so.

Considering the short duration of the model cycles (seven days), the ERG does not see the need for the half-cycle correction applied by the company. The ERG removed the half-cycle correction from the model as an exploratory analysis and presents the results of the analysis in Section 6.

5.4.5 Treatment effectiveness

The CS reports that ABE-FUL provides an additional treatment option for primary or secondary ET-resistant patients, allowing the postponement of chemotherapy and its additional toxicity.

Treatment effectiveness within the model was implemented through a partitioned survival method, which used OS, PFS and TTD data from MONARCH 2 and the other studies included in a network meta-analysis (NMA) to determine mortality, disease progression and time on treatment for each cycle of the economic model. The different methods employed by the company to compare treatment effectiveness for treatments not included in MONARCH 2 are explained below and more details are available in Section 4.

The company's original hazard ratio (HR) NMA approach relied on the assumption that proportional hazards (PH) hold across the studies included in the NMA for PFS and OS outcomes. Therefore, the company fitted a variety of parametric models to MONARCH 2 Kaplan-Meier (KM) data and applied the HRs estimated through the NMA to the fitted MONARCH 2 FUL curves for OS and PFS. This allowed the estimation of OS and PFS curves for EXE; and EXE-EVE. However, the company did not use the HR obtained in the NMA to estimate the ABE-FUL curves, but instead used the fitted curves to the ABE-FUL KM data. The company carried out an adjusted indirect comparison using Milla-Santos 2001 and the HR NMA to estimate the relative treatment effect for TMX vs FUL 500mg for OS and PFS/time to progression (assuming equivalence between the PFS and time to progression endpoints).[1]

The parametric models fitted to MONARCH 2 data were jointly fitted to the ABE-FUL and FUL KM curves for PFS, TTD and OS, as the company concluded that the PH assumption was valid between treatment arms in MONARCH 2, for all clinical outcomes. The company reports fitting clinical data with exponential, Weibull, log-logistic, lognormal and generalised gamma models, and assessing the fit of each parametric model compared with the observed KM using the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), in accordance with guidance from NICE Technical Support Document (TSD) 14.[105]

Nonetheless, during the clarification stage, the ERG raised some concerns with the validity of the PH assumption across PFS and OS outcomes in the NMA, and with the application of HRs to some of the parametric curves selected by the company to model the baseline FUL OS and PFS outcomes in the model. Therefore, the ERG suggested that the company undertake a parametric curve NMA (Ouwens *et al.* 2010)[106] or fractional polynomial (FP) NMA (Jansen *et al.* 2011)[107] to estimate relative treatment effectiveness. Section 4 provides a detailed description and discussion of the company's FP NMA after the ERG's clarification request.

However, the company decided to use the original HR-based NMA to run their base case analysis and provided FP-based survival models as a scenario analysis. Given the ERG's considerations that a HR-based analysis is unlikely to be appropriate in this case, the focus of the following sections is on the FP approach. Comparisons with the company's base case HR-based analysis are drawn when needed, and to explore the impact of using the ERG's suggested FP survival curves. The appropriateness of the

company's HR-based NMA, together with the company's approach to estimating FP and the ERG's alternative approach to the latter is also discussed in detail in Section 4.

5.4.5.1 ERG critique

The ERG disagrees with the company's decision to not use the HRs obtained from their original HR NMA to estimate the ABE-FUL OS and PFS curves in their base case analysis. Using the jointly fitted curves to the ABE-FUL and FUL KM data relies even further on the validity of the PH (or PO or AFT) assumption within treatments arms in MONARCH 2, which the ERG does not agree with. Moreover, the HRs obtained from the NMA should be used to estimate the relative treatment effectiveness of all treatments that are part of the network of trials informing the NMA. In summary, the ERG considers that the company's base case analysis relies on weak assumptions and has methodological flaws.

In their reply to the clarification document, the company states that, "*A fractional polynomial approach was taken to account for violation in the proportional hazards assumption. Unlike the standard NMA approach to time-to-event data considering HR data, the fractional polynomials approach (FP) does not require that the proportional hazards assumption holds."* Therefore, the ERG does not understand why the company decided to use the HR-based NMA to run their base case analysis. Moreover, the company has not provided any justification for this decision.

The key limitation of the FP NMA method is that goodness-of-fit is measured globally, and so the best fitting overall model may not provide individually well-fitted curves. Despite this, the ERG considers this method to have the potential to provide a more accurate estimation of survival for all comparators when a variable hazard has been identified and considered it a worthwhile route to explore.

The FP NMA method used was that described by Jansen *et al.* 2011, which estimated treatment effects on each of the parameters of a specified survival function in an NMA performed using OpenBUGS.[107] More specifically, the method defines the hazard function as a FP, and a range of variations of the polynomials with different powers were tested for optimal fit. A FP function of first or second order can be utilised to estimate the natural logarithm of the hazard function per treatment arm in each study, defined as $\ln(h(t)) = \beta_0 + \beta_1 t^{p1}$ and $\ln(h(t)) = \beta_0 + \beta_1 t^{p1} + \beta_2 t^{p2}$ with t0=log t, respectively. If p1=p2=p, the model becomes a repeated powers model, defined as $y = \beta_0 + \beta_1 t^{p} + \beta_2 t^{p} \log t$.

The ERG considers the company's method employed to run the FP NMA to have considerable limitations. The company used OpenBUGS to directly estimate survival curves from the FP NMA analysis. Therefore, the beta estimates (shown in the equations above) were not explicitly obtained from the NMA, and the ERG was only provided with survival curves, hard-wired into the economic model (and the OpenBUGS coda). This considerably limited the ERG's capability of incorporating different survival curves (using different power estimates and varying between first and second order equations)

in the analysis. Firstly, the computational burden of running the NMA with survival curves as outputs is paramount. To this, adds the fact that the company chose weekly cycles for their analysis, and the considerable number of comparator treatments included. Secondly, this method rendered probabilistic sensitivity analysis (PSA) impossible to run from a computational power point of view.

Instead, the company could have ran the FP NMA so the output of the latter were the beta estimates associated with the best fitting powers. This would have drastically decreased the computational burden of running the analysis. The second necessary step would have been to build survival curves in the Excel economic model using beta estimates. This would have allowed curves to change automatically when beta estimates were varied, and more importantly, it would have allowed for PSA to be computed based on the beta values.

The ERG was able to adapt the code and re-run the NMA so that the output of the analysis were beta estimates. However, the ERG could not alter the structure of the survival model in order to incorporate the beta estimates into the model survival curves. Instead, the ERG varied the betas, in order to obtain different survival curves, and directly estimated the survival curves in R. Unfortunately, while this approach overcame the computational challenge of producing different FP-based survival curves (3 hours using the company's approach and 20 mins using the ERG's approach), the inflexibility in the economic model still meant that the different beta parameters could not be used in the model nor to run PSA.

5.4.5.2 Progression-free survival

The company's original submission used the investigator (INV)-assessed PFS data from MONARCH 2 and from the studies included in the NMA. However, the company decided to adjust the PFS KM data from MONARCH 2 for interval censoring, in order to fit survival curves to the ABE-FUL and FUL KM adjusted data. The ERG asked the company to clarify the rationale behind this decision. The company replied that the frequency of radiographic assessments of disease status in MONARCH 2 (every eight weeks for the first 12 months and every 12 weeks thereafter) may not accurately reflect the underlying time to progression (TTP) for patients as the latter might have occurred at any time between assessments. The company concluded that using the unadjusted PFS KM data could have resulted in an overestimation of median PFS. Nonetheless, the company confirmed that the unadjusted data was used to run the NMA.

The company reports using the Griffin 2005 method to adjust for interval censoring, and the INTCENS Stata package.[108] The original and updated economic models used the interval-censored adjusted PFS analysis in their base case and included an option to use the non-interval-censored PFS in a scenario analysis. The FP NMA-based PFS curves included as a scenario analysis in the company's updated model used the non-interval-censored PFS data from MONARCH 2.

The company's base case PFS curves are reported in Figure 25. The company used a joint Weibull model to fit the ABE-FUL and FUL KM curves from MONARCH 2, and then applied the HR NMA-derived HR to estimate the EXE and EXE-EVE PFS curves, while the HR derived through the adjusted indirect comparison (Bucher method) was used to estimate PFS for TMX (all HRs reported in Table 20). The ERG notes that HRs>1 favours FUL while a HR<1 favours the comparator treatment. This seems to be the opposite when interpreting the adjusted indirect comparison HR carried out for TMX.

Figure 25. Company's base case PFS curves

Table 20. Hazard ratios (95% credible interval) for PFS

Comparator	PFS HR (CrI)
EXE (25 mg) (NMA)	[redacted]
EXE (25 mg)-EVE (10 mg) (NMA)	[redacted]
FUL (500 mg)	[redacted]
TMX (adjusted indirect comparison)	[redacted]

Abbreviations: ABE: abemaciclib; CrI: credible interval; EVE: everolimus; EXE: exemestane; FUL: fulvestrant.
*HRs above 1 indicate treatment is worse than FUL

5.4.5.3 ERG's critique

The ERG disagrees with the use of interval-censored PFS data in the economic analysis. The NICE DSU TSD 14 advises that when KM curves are too "steppy", the time intervals used to document disease progression in the underlying clinical study and the nature of the disease (i.e. actual disease progression) might be very disconnected, and so a bias in survival analysis can be created. In these cases, there might be a need for interval censoring methodology. TSD 14 advises that the use of this approach in the economic analysis should always be justified.[105]

The ERG requested the unadjusted INV PFS KM data for MONARCH 2 during the clarification process. The company provided the data reported in Figure 26. However, upon inspecting the reportedly

adjusted (Figure 27) and unadjusted (Figure 26) data in the company's model, the ERG concluded these are identical. Therefore, the ERG is not reassured that no mistakes were involved in the reporting of the data.

Given that the best-fitting curves to the adjusted and unadjusted data are not the same – according to the AIC and BIC criteria reported in Table 21 and Table 22, the best-fitting model to the unadjusted data is the lognormal, and the worst-fitting model is the Gompertz. Differently, the best-fitting model to the adjusted data is the Weibull, and the worst-fitting model is the lognormal – this implies that the underlying data are different. The ERG cannot be sure if the curves reported by the company are the adjusted or unadjusted curves.

Nonetheless, the curves reported are not particularly "steppy", with the exception of time 0 to 2.5 months approximately, for both treatment arms, and month 23 for the FUL arm. However, at 23 months, the number of patients at risk in the FUL arm is small (less than 13 patients). Overall, the ERG does not see an obvious need for adjusting PFS data for interval censoring, especially considering that all the studies informing the NMA, including MONARCH 2, were analysed using the unadjusted PFS KM data. Furthermore, clinical expert opinion provided to the ERG explained that the minimum time-period when observable disease progression could be identified for aBC is four weeks. Therefore, eight-week assessments for the first year and 12-week assessments after then, seem broadly reasonable for capturing progression events. Finally, interval censoring also carries associated biases, and validation analyses should be undertaken to assess the extent of the latter, depending on the interval censoring method used. The ERG asked the company which method had been used and if its associated biases had been explored. The company replied that, "…*biases are associated with any interval censoring approach, due to the limited amount of prior information available*." In conclusion, the ERG does not see enough reason for a non-standard approach to be taken in analysing PFS KM data, and further, the ERG is not confident that enough detail on the adjustment method and consequent biases have been explored by the company.

The company used the Weibull curve to model the adjusted PFS data, however, the company used the exponential and Gompertz distributions to fit the unadjusted PFS data (the worst fitting distributions to the data). During the clarification stage, the ERG asked the company to justify their choice. The company reported that this was an error as the lognormal appears to be the best fitting curve. Nonetheless, as per the ERG's request, the company included a wider selection of curves in their updated model, which included the lognormal and the Gamma for the unadjusted PFS KM data.

Figure 26. Unadjusted INV PFS KM data from MONARCH 2

Figure 27. Adjusted INV PFS KM data from MONARCH 2

Table 21. AIC and BIC statistics – Unadjusted INV PFS for MONARCH 2

[redacted]

Table 22. AIC and BIC statistics – Adjusted INV PFS for MONARCH 2

[redacted]

The PFS curves estimated with the company's FP NMA are reported in Figure 28. The company reports that second-order models showed better fit than first-order FP models throughout their analysis, both in terms of DIC and visual inspection of the curves. For PFS, the company chose the random effects, second-order FP model with p1=0.5 and p2=1. Nonetheless, the PFS curves in the model did not match the curves reported by the company in their clarification response, for p1=0.5 and p2=1. The curves reported in this section are based on the curves included in the company's model. A detailed discussion of the company's FP NMA and curve selection is provided in Section 4 of the ERG report.

However, looking at Figure 28 it is apparent that the curves selected by the company produce clinically implausible results, with approximately 35% of ABE-FUL patients considered cured at 30 months. The plateau of the PFS curves suggests that patients on all treatments are cured (albeit at different rates and in different percentages, according to treatment received). This is clinically implausible with aBC.

The company did not provide a discussion of the clinical plausibility of their FP-NMA curves. Instead, it clarified that PFS curves were capped by OS curves, so the former would not cross the latter. The company also included an option in the model to allow TTD to be equal to PFS for ABE-FUL and FUL. This issue is further discussed in the next subsection of the ERG report. Finally, to note, is that the company's FP NMA did not include TMX in the network for PFS outcomes, as explained in Section 4.

Table 23 shows the company's ICERs for ABE-FUL compared with EXE; EXE-EVE; FUL; and also CAP, which is included in the company's FP NMA. The company's results with the FP NMA do not include TMX as there were no PFS data available. Overall, using the company's FP NMA leads to a considerable increase in all ICERs, compared with the company's base case HR NMA. However, the ERG does not consider the results of the company's FP NMA to be clinical plausible, therefore the results of the ERG's FP NMA analysis is discussed below (with methods discussed in Section 4).

Table 23. Company's results with FP NMA (with PAS for abemaciclib)

Comparator	Costs	LYs	QALYs	ICER (per QALY)	ICER (per QALY) for ABE-FUL vs comparator
CAP	[redacted]	2.55	[redacted]	Referent	£59,441
EXE	[redacted]	2.55	[redacted]	Dominated	£41,452
EXE-EVE	[redacted]	2.34	[redacted]	Dominated	£23,374
FUL	[redacted]	4.38	[redacted]	Ext. dominated	£47,763
ABE-FUL	[redacted]	4.57	[redacted]	£59,441	N/A

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; ICER: incremental cost-effectiveness ratio; LY: life year; PFS: progression-free survival; QALY: quality-adjusted life year; TMX: tamoxifen; TTD: time to discontinuation.

Figure 28. Company's FP-derived PFS curves

Figure 29 reports the ERG's FP NMA-derived survival curves. The ERG used first-order FP, which produced more clinically plausible long-term extrapolations of PFS, with less than 10% of patients being free from progression at 5 years, and virtually all patients having progressed after 10 years.

Overall, the ERG PFS curves present more conservative tails than the company's HR and FP NMA-based curves.

As mention in Section 4, the results for CAP should be interpreted with caution as the relative treatment effectiveness for CAP is likely to have been overestimated in BOLERO-6. This issue is discussed in detail in Section 4.

Figure 29. ERG's FP-derived survival curves and MONARCH 2 KM data

5.4.5.4 Time to treatment discontinuation

The company used TTD data to estimate time on treatment in their base case model, and thus the cost of every treatment regimen. Time to treatment discontinuation curves were jointly fitted to ABE-FUL and FUL KM data from MONARCH 2. The company chose the Weibull distribution to model TTD in their base case analysis and a gamma distribution for sensitivity analysis. The company reports that consideration was given to the distribution chosen to model PFS for ABE-FUL and FUL, and the associated relationship between PFS and TTD curves, given both therapies are treat-to-progression regimens. The company reported that using accelerated failure time (AFT) models led to higher proportions of patients estimated to remain on treatment in both arms than those who had progressed or died (i.e. TTD curves were above the PFS curves in the extrapolations).

In order to estimate TTD for the remaining treatments (EXE; EXE-EVE; TMX and chemotherapy), the company used estimates of median duration of treatment from different publications, as the company concluded that TTD KM data were not available in the primary studies included in the original HR NMA. The company considered two possible approaches to estimate TTD for comparator treatments:

1. Dividing the median PFS by the median TTD for the specific treatment, and applying this ratio to the respective PFS curve, thus obtaining a TTD curve;

2. Diving the cumulative hazard for median TTD [i.e. log(0.5)] by the cumulative hazard for the HR NMA-estimated PFS curve at the time of median TTD.

The company used the first approach in their base case, while the second was included as a scenario analysis.

5.4.5.5 ERG critique

ABE-FUL and FUL curves

The ERG disagrees with the company's assessment of the validity of the PH assumption for TTD data in MONARCH 2. Following a clarification request from the ERG, the company provided the log-log plot for TTD data, reported in Figure 30. The [redacted] indicates that the PH assumption is unlikely to hold for TTD data between ABE-FUL and FUL arms.

Figure 30. Log-log plot for TTD data from MONARCH 2

The company chose the Weibull distribution to model TTD in their base case analysis, however this was the [redacted] to TTD data, according to the company's AIC and BIC statistics, reported in Table 24. The company reported that using AFT models led to TTD curves being above PFS curves, however this is also the case in the company's base case analysis using the Weibull model. Hence, the company has included a minimum function in Excel, to prevent PFS and TTD curves from crossing, as ABE-FUL and FUL are not supposed to be given beyond patients' progression.

The ERG considers that a Gompertz curve should have been used to model TTD curves, as it was the first and second best-fitting curve according to the BIC and AIC criteria, respectively. Nonetheless, the ERG notes that the AIC and BIC statistics provided are for a joint fit of the curves, which is not appropriate given that the PH assumption is unlikely to hold for TTD data. During the clarification stage, the ERG requested that the company included an option in the economic model to independently or jointly (depending on the company's assessment of PHs, POs or AFT) fit the best-fitting distributions to the TTD KM MONARCH 2 data, to estimate TTD curves for FUL and ABE-FUL. As a result, the company has provided an option in the model to estimate TTD curves with an exponential, Weibull, Gompertz, lognormal, loglogistic and gamma distributions. However, the company fitted these models jointly for treatments arms, with a treatment effect covariate, therefore indirectly implying that the PHs, POs or AFT assumptions hold.

Table 24. AIC and BIC statitistics for the jointly fitted ABE-FUL and FUL data

Figure 31 shows the Weibull and Gompertz curves fitted to the TTD KM data from MONARCH 2 for ABE-FUL and FUL, together with the company's base case PFS curves. Using the Weibull curve to model TTD for ABE-FUL considerably reduces the costs of ABE-FUL in the economic analysis, compared with using the Gompertz model. Even though the same could be argued for the FUL arm, the relative distance between curves is much smaller than with the ABE-FUL curves. Therefore, using the Weibull curves is likely to benefit ABE-FUL as it leads to a reduction in the costs associated with the treatment, compared with using the Gompertz curve.

Figure 31. Gompertz and Weibull TTD curves compared to company's base case PFS curves

The company's scenario analysis using the FP NMA-based survival curves included an option to allow TTD to be equal to PFS for the ABE-FUL and FUL treatment arms as the company considered there was a disconnect between PFS and TTD data, with, "*one being from the data and one being from NMA"*. While the ERG agrees that there is a disconnect, it does not consider this to be a problem, as the company's base case analysis should have used the HR NMA-derived HR to estimate the ABE-FUL PFS curve, and thus the same disconnect between the source of data to model PFS and TTD for ABE-FUL would have been observed. Furthermore, the same disconnection is observed for all the other comparators in the economic analysis, as TTD data were not available to run a HR or FP NMA.

Figure 32 compares the company's FP NMA-based PFS curves with the TTD curves fitted with a Weibull and Gompertz models. Due to plateau in the ABE-FUL curve, it is not surprising that the company's scenario assuming TTD=PFS considerably increases the costs associated with ABE-FUL. However, as mentioned in the previous section, the ERG finds the company's FP NMA-based PFS curves clinically implausible, and therefore disagrees with using these in the economic analysis.

Figure 33 compares the ERG's FP NMA-based PFS curves with the TTD curves fitted with a Weibull and Gompertz modes. Conversely to the company's FP NMA, both ABE-FUL and FUL TTD curves (fitted with a Weibull and Gompertz models) are above the treatments' respective PFS curves for the entire period of the analysis. This is also clinically implausible as both treatments were discontinued upon disease progression. Therefore, in order to use the PFS curves obtained through the ERG's FP NMA, some assumptions had to be made to estimate TTD curves. The ERG used the same method as the one proposed by the company to estimate TTD curves for comparator treatments, which is discussed in the subsection below.

Figure 32. Gompertz and Weibull TTD curves compared to company's FP NMA-based PFS curves

Figure 33. Gompertz and Weibull TTD curves compared to ERG's FP NMA-based PFS curves

Other comparators

Overall, there was not much clarity in the CS regarding the approach taken to estimate TTD curves for comparator treatments in the economic analysis. The ERG investigated the economic model and based its critique of the company's approach on its investigation.

The ERG disagrees with the company's approach to estimating TTD for EXE, EXE-EVE, TMX and chemotherapy. From a methodological point of view, the company's base case approach does not estimate a HR, but instead a ratio between median PFS and median TTD within each of the comparators'

relevant trials. For example, for EXE-EVE, the company took the median PFS and median TTD from BOLERO 2[109] (Table 25), obtained a ratio of 1.4 (7.8 divided by 5.5) and exponentiated the EXE-EVE PFS curve derived through the NMA in the economic model to 1.42. Nonetheless, the ratio of median survivals is not a HR, and therefore, should not be used as such. Furthermore, the company decided to use 5.5 months as the median TTD for EXE-EVE, however this was the median for EVE in the EXE-EVE arm in BOLERO 2. The company should have taken the longest median value as patients will not discontinue the intervention (i.e. the combination treatment) until both treatments are discontinued.

From a methodological point of view, while the second approach used by the company in a scenario analysis is more appropriate, as it estimates a HR that can be applied to a PFS curve, the ERG disagrees with using the HR NMA-estimated PFS curve for comparison with median TTD. Using EXE-EVE as an illustrative example, the company took the median TTD of 6.8 months from BOLERO 2 and looked up what the probability of survival in the PFS curve of the NMA-derived EXE-EVE curve was at that point in time. The company then used the cumulative hazard in the PFS curve at that point in time, relative to median TTD, to estimate a HR to apply to the same PFS curve in order to estimate the TTD curve for EXE-EVE.

The ERG considers that using the PFS curve from BOLERO 2 would have been more appropriate to estimate survival in the PFS curve at the point of median TTD, given that the median TTD estimate was taken from BOLERO 2. Given that the point of this adjustment exercise is to assess if PFS and TTD curves (or medians) are similar within treatments, using the PFS and TTD curves from BOLERO 2 (and all the other respective trial sources) is more appropriate.

Table 25. Median TTD and PFS across comparator treatments (in months)

[redacted]

The company used the Kaufman 2000 paper to estimate median PFS in their second approach (3.8 months), but used the BOLERO 2 source for estimating the same outcome in their base case approach (3.2 months).[47] No justification was provided for this, and the ERG cannot see a valid reason to use different data sources. Furthermore, the company did not consider the BOLERO 6 source, which is a relevant study given it was included in all NMAs and compared EXE-EVE with CAP. The data from

BOLERO 6 shows a much higher separation in median TTD and median PFS estimates than BOLERO 2, however the company did not include BOLERO 6 in the discussion and therefore did not discuss the difference in median survival estimates. Nonetheless, BOLERO 2 trial's design is superior than that of BOLERO 6, thus the former is likely to be a more robust source of data.

Most importantly, the estimates shown in Table 25 indicate that the only treatments where there might be a difference (as far as medians are concerned) between PFS and TTD curves is ABE-FUL, FUL, and EXE-EVE. Therefore, the PFS curves for EXE, TMX and chemotherapy can be used as proxies to estimate TTD in the economic analysis. To estimate TTD for ABE-FUL, FUL, and EXE-EVE, the ERG used the company's second proposed methodological approach, but used the MONARCH 2 and BOLERO 2 PFS curves instead of the HR NMA-derived ones. Table 26 reports the calculations undertaken by the ERG and the resulting HRs used to estimate TTD curves in the economic analysis.

Figure 34 shows the TTD curves when the ERG's HRs were applied to the ERG's FP NMA PFS curves. The TTD curve for ABE-FUL has a considerable separation from the ABE-FUL PFS curve. This is a direct translation of the separation in TTD and PFS KM curves in the ITT analysis of MONARCH 2 data (Figure 35 and Figure 36). However, when compared with the TTD curves by starting dose of abemaciclib (i.e. 150mg vs 200mg populations) shown in Figure 37, the ABE-FUL curve for the ITT population is considerably lower than the 150mg ABE-FUL TTD curve. Given that abemaciclib will be given in 150mg regimens in clinical practice, and that the 150mg population size in MONARCH 2 was considerably bigger than the 200mg population, it is the ERG's opinion that the 150mg TTD curve would have been a more appropriate choice to model TTD for ABE-FUL. In fact, using the ITT TTD curve leads to a considerable underestimation of the ABE-FUL costs in the economic analysis. During the clarification period, the ERG asked the company to provide the TTD data for the 150mg and the 200mg populations, however the company has not provided these.

Furthermore, the HRs for the TTD and PFS curves for ABE-FUL and EXE-EVE in BOLERO 2 ([redacted] vs 1.16) suggest that patients in ABE-FUL discontinue treatment before progression at higher rates that EXE-EVE patients.

Given that the HR used to estimate TTD curves in the economic analysis is one of the key model drivers, the ERG advises that the Committee considers the clinical plausibility of the assumptions underlying these clinical data. The ERG also recommends that the 150mg TTD data are used by the company to generate a more robust estimation of the costs of ABE-FUL in the economic analysis.

Finally, the ERG notes the caveat in the approach undertaken to estimate HRs in order to derive TTD curves. The starting point in this approach is to compare median TTD with median PFS values. However, comparison of medians is a reasonably weak approach, as equivalence (or difference) in

median survival estimates does not inform the difference in the curves' shape and doesn't necessarily translate an accurate picture of differences in mean survivals. Nonetheless, given that TTD data were not available for the comparator treatments, the use of median TTD estimates is necessary.

Table 26. ERG's HRs to estimate TTD curves (in months)

[redacted]

Figure 34. PFS and TTD in ERG's anaysis

[redacted]

Figure 35. TTD and PFS curves for ITT population in MONARCH 2

Figure 36. TTD curves for ITT population in MONARCH 2

Figure 37. TTD curves for 150mg and 200mg subgroups in MONARCH 2

5.4.6 Mortality

The company's base case OS curves are reported in Figure 38. The company used a joint Weibull model to fit the ABE-FUL and FUL KM data from MONARCH 2 but reported that due to the uncertainty around long-term extrapolation of the FUL curve, and around the long-term relative treatment effect for ABE-FUL vs FUL, data from CONFIRM were used to inform long-term survival estimates. The CONFIRM trial compared the effectiveness of FUL 500mg with FUL 250mg and had a long follow-up period of nearly seven years.

The company reports re-constructing individual patient data (IPD) from the CONFIRM trial for the FUL 500mg arm by digitising the published KM OS data and using the Guyot 2012 published algorithm.[62] The company then selected the best-fitting curve to the CONFIRM OS data and chose a Weibull distribution. The hazard rate from the Weibull distribution fitted to the CONFIRM data was then applied to the Weibull distribution fitted to the MONARCH 2 data at a selected time point to extrapolate OS based on the estimated hazard from the CONFIRM study. The company explained that this approach assumed that the hazard rate was equivalent in both ABE-FUL and FUL arms when the CONFIRM hazard was applied. This assumption was considered to be appropriate due to the lack of a treatment difference observed in the tail of the KM and the immaturity of the MONARCH 2 data at the time of the analysis.

The company chose [redacted] months as the time point from which the OS curve extrapolation was informed by the CONFIRM data, as this was the last data point on the ABE-FUL arm of the MONARCH 2 trial. The company also decided to taper the treatment effect for ABE-FUL vs FUL between two time points, which involved increasing the HR gradually to reach 1 at the time point of

extrapolation ([redacted] months). The time point at which the tapering started was chosen to be [redacted] months, based on a Cox-Snell residual plot for the fitted Weibull distribution to the MONARCH 2 data (CS Appendix M.2.3, Figure 32). The company reported that this represented the point after which the parametric model was shown to provide a poor fit to the MONARCH 2 data.

The company ran a scenario analysis including the Gompertz distribution to fit MONARCH 2 trial data as this represented the next best fitting distribution to the data. To explore the impact of using the external data, the company also conducted a scenario using only the jointly fitted Weibull (and alternatively Gompertz) curves to the MONARCH 2 data (i.e. without using CONFIRM data).

To estimate OS curves for the remaining treatments, the company applied the HR NMA-derived HRs to the fitted FUL curve and obtained the EXE and EXE-EVE OS curves. The HR derived through the adjusted indirect comparison (Bucher method) was used to estimate OS for TMX (all HRs reported in Table 27). The ERG notes that HRs>1 favour FUL and that a HRs<1 favour the comparator treatment. The company's estimation of relative treatment effectiveness suggests TMX is more effective than FUL and ABE-FUL in terms of its impact on survival. Interpretation and validation of the company's HR NMA OS outputs is provided in Section 4. In the company's base case the HRs were applied to the FUL curve up until [redacted] months.

Figure 38. Company's base case OS curves

Table 27. Hazard ratios (95% credible interval) for PFS

Comparator	PFS HR (CrI)
EXE (25 mg) (NMA)	[redacted]
EXE (25 mg)-EVE (10 mg) (NMA)	[redacted]
FUL (500 mg)	Reference
TMX (adjusted indirect comparison)	[redacted]

Abbreviations: ABE: abemaciclib; CrI: credible interval; EVE: everolimus; EXE: exemestane; FUL: fulvestrant.

5.4.6.1 ERG critique

The CS reports that the CONFIRM population was more pre-treated and thus expected to be at a more advanced stage of the disease compared with the MONARCH 2 population. Clinical expert opinion sought by the ERG agreed that the CONFIRM population was more pre-treated and thus clinical outcomes could be expected to be worse relatively to outcomes in MONARCH 2. Nonetheless, the company used the CONFIRM data to adjust the extrapolated tails of the FUL and ABE-FUL curves in their base case analysis.

The CONFIRM data are considerably rich and complete, with a follow-up period close to seven years, whereas the MONARCH 2 OS data are very immature (with median OS not reached for either treatment arms at the end of the follow-up period of two years and four months). Interestingly, OS for the FUL arm of MONARCH 2 reached 54% at 28 months, while CONFIRM median survival was approximately 27 months (Figure 39). An earlier data cut-off analysis of the CONFIRM data showed a median survival of 25 months.[54, 55] Although the numbers at risk at 28 months in the FUL arm of MONARCH 2 (one patient) require caution when interpreting the OS curve, the 54% survival estimate is not dissimilar to the median OS for the shorter and longer follow-up analysis of the CONFIRM OS data.

Given the immaturity of OS data in MONARCH 2, the ERG advises caution when interpreting all analysis undertaken involving these data. Furthermore, the ABE-FUL and FUL OS curves in the trial show a very small – if any – benefit for ABE-FUL (with the OS HR not being statistically significant), potentially due to data immaturity. Therefore, the ERG sees the additional value in using CONFIRM data in the economic analysis. Furthermore, CONFIRM was included in the HR (and ER) NMA, therefore it should, to a reasonable degree, provide a comparable source of effectiveness for FUL.

Similar to the company's PFS analysis, the ERG disagrees with the company's decision to jointly fit the OS curves to the ABE-FUL and FUL arms of MONARCH 2 instead of using the HR obtained in their base case NMA to estimate the ABE-FUL OS curve. Moreover, given the immaturity of OS data in MONARCH 2, the company could have also considered using the CONFIRM FUL 500mg curve as the baseline FUL curve in the model (rather than the MONARCH 2 FUL curve) to then apply the NMA

HR, and estimate the OS curve for ABE-FUL, EXE, EXE-EVE and TMX. This would have been a more robust method than choosing the last data point available in the FUL arm of MONARCH 2 (with only one patient at risk) to then apply the CONFIRM hazard, in order to adjust the tail of the FUL curve.

The impact of the uncertainty in the OS data from MONARCH 2 on the relative treatment effectiveness of ABE-FUL vs FUL is less easy to circumscribe, as there are no other, more mature data sources for the effectiveness of ABE-FUL in the relevant population. The standard way to quantify this uncertainty would have been to properly account for the latter through PSA, however, this analysis was not properly run for the company's base case HR NMA, and not run at all for the FP NMA approaches. In summary, the ERG is concerned with the imbedded uncertainty in the OS MONARCH 2 data and its impact on the NMA. This uncertainty is propagated through the economic analysis and thus, all the final ICERs. Unfortunately, the company's model does not capture this uncertainty, given the flaws in the PSA, discussed in Section 5.5.

Figure 39. OS data from MONARCH 2 and CONFIRM

The OS curves estimated by the company's FP NMA scenario analysis are reported in Figure 40. The company reports that second-order models showed better fit than first-order FP models throughout their analysis, both in terms of DIC and visual inspection of the curves. For OS, the company reported choosing the random effects, second-order FP model with p1=0 and p2=1. Nonetheless, the OS curves in the model did not match the curves reported by the company in their clarification reply, for p1=0 and p2=1. The curves reported in this section are based on the curves included in the company's model.

Similar to the company's FP NMA-based PFS curves, the OS curves selected by the company produce clinically implausible results, with approximately 15% of ABE-FUL, FUL and TMX patients living

forever. The plateau of the OS curves is clearly implausible, and given that it occurs at ~15%, compared to the plateau in PFS curves at ~35%, it also means that PFS and OS curves cross, which is equally implausible. Furthermore, the ABE-FUL and FUL curves cross, indicating that FUL patients might die at slower rates than ABE-FUL patients. This could be a result or the immature shape (and close tracking) of the ABE-FUL and FUL KM curves in MONARCH 2. The company did not provide a discussion of the clinical plausibility of their FP-NMA curves. Instead, it clarified that PFS curves were capped by OS curves so the former would not cross the latter.

Figure 40. Company's FP-derived OS curves

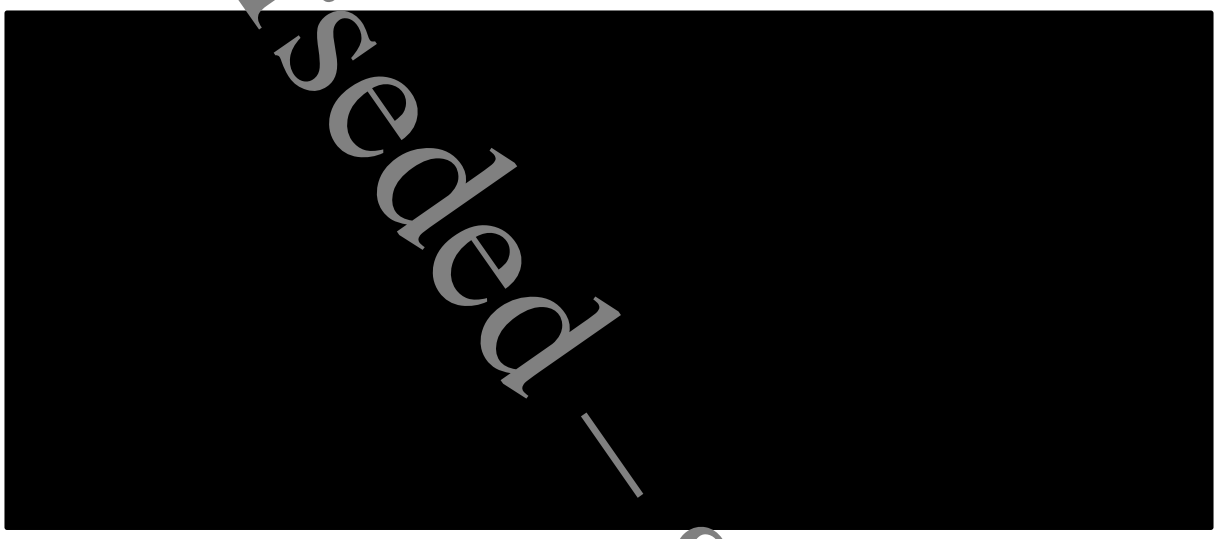


Figure 41 reports the ERG's FP NMA-derived survival curves. The ERG used a first-order FP NMA, which produced more clinically plausible long-term extrapolations of OS, with virtually all patients being dead at approximately 13 years (160 months). As explained in Section 4, the ERG used the simplified FP NMA which excluded TMX from the network. The CAP curve crosses the ABE-FUL curve at approximately 30 months; however, CAP results should be interpreted with caution, as mentioned in Section 5.4.5.2.

As a scenario analysis, the ERG included the first-order FP OS curve with a power of -0.5. As explained in Section 4, the FP curve for p = -0.5 has a higher DIC statistic, indicating a worse fit when compared to the ERG's base case of p = -1.5. Nonetheless, given the uncertainty around the relative treatment effect for ABE-FUL compared with the other treatments in the OS NMA, the ERG considered the p = -1.5 curves to be relevant for a scenario analysis as these show a smaller, and thus more conservative, relative treatment effect for ABE-FUL compared with other treatments (Figure 42). The curves also portray a more conservative scenario overall, as OS curves plateau close to zero much earlier than the

ERG's base case analysis, with the exception of CAP. Results of the ERG's analysis are reported in Section 6.

Figure 41. ERG's FP-NMAderived survival curves (p = -1.5)

Figure 42. ERG's FP-NMAderived survival curves (p = -0.5)

Comparison of the company's base case OS curves (Figure 38) with the company's FP NMA-based curves (Figure 40) and the ERG's FP NMA-based curves (Figure 41) reveals that the ERG's NMA provides a better approximation of the estimated FUL curve in the model to the FUL 500mg KM curve from CONFIRM. This is not unexpected as CONFIRM had the richer, more complete dataset for OS therefore, it "overwhelmed" the OS analysis for FUL. Even though CONFIRM patients are expected to have worse outcomes than MONARCH 2 patients, it is not clear to what extent (given the relatively similar median OS across studies). Furthermore, the PFS KM curve for the FUL arm of MONARCH 2

and CONFIRM are relatively similar (Figure 43), with CONFIRM patients doing only slightly worse than MONARCH 2 patients. Moreover, it could be hypothesised that the similarity between the PFS FUL 500mg arms of CONFIRM and MONARCH 2, would have also been observed for OS curves, had the latter been more mature in MONARCH 2.

In summary, the ERG considers that the ERG's FP NMA results for OS are not only based on a more robust methodology (in the case of the PHs assumption being unlikely to hold) than the company's base case approach, but also produce more plausible OS estimates, based on the more robust dataset of the CONFIRM trial. To note is that even though using the ERG's FP NMA curves brings all the OS curves down (as these are mainly driven by the baseline treatment in the NMA, which is FUL, and the latter is mainly driven by CONFIRM data), this does not mean that the relative treatment effectiveness for ABE-FUL vs FUL is penalised. In fact, assessment of Figure 44 indicates that the separation between the ABE-FUL and the FUL curves in the ERG's analysis is greater than that in the company's base case, therefore attributing a greater difference in survival benefit to ABE-FUL.

Figure 43. PFS KM data from MONARCH 2 and CONFIRM

Figure 44. OS curves obtained with the ERG's FP NMA and company's HR NMA

5.4.7 Adverse events

To estimate ABE-FUL and FUL-related adverse events (AEs) in the model, the company included grade 3 or 4 treatment-emergent adverse events (TEAEs) observed in ≥ 5% of patients in the ITT population of MONARCH 2. For EXE and EXE-EVE-related AEs, the company used the TEAEs rates from the BOLERO-2 trial. The company reported lack of available AE data for TMX that aligned with the AE inclusion criteria, and thus assumed that TMX has the same safety profile as FUL. The safety profile of CAP was also assumed to be the same as that of FUL. The TEAEs included in the economic analysis are summarised in Table 28. The costs of adverse events included in the model are discussed in Section 5.4.9. The impact of AEs in patients' quality of life is discussed in Section 5.4.8.

Table 28. TRAEs included in the economic model (adapted from Table 31 of the CS)

Adverse event	ABE-FUL (MONARCH 2)	EXE (BOLERO-2)	EXE-EVE (BOLERO-2)	FUL (MONARCH 2)	TMX (assumed the same as FUL)	Chemotherapy (CAP)
Anaemia	7.26%	0.00%	7.05%	0.90%	0.90%	0.90%
Diarrhoea	13.38%	0.00%	2.07%	0.45%	0.45%	0.45%
Dyspnoea	2.72%	0.00%	4.98%	1.35%	1.35%	1.35%
Gamma-glutamyltransferase (GGT) increase	[redacted]	2.94%	7.05%	[redacted]	[redacted]	[redacted]
Hyperglycaemia	[redacted]	0.00%	4.98%	[redacted]	[redacted]	[redacted]
Leukopenia	8.84%	0.00%	0.00%	0.00%	0.00%	0.00%

Neutropenia	26.53%	0.00%	0.00%	1.79%	1.79%	1.79%
Stomatitis	0.45%	0.00%	8.09%	0.00%	0.00%	0.00%

5.4.7.1 ERG critique

Clinical experts advising the ERG indicated that drugs' safety profiles are broadly as expected. Both clinical experts advised that diarrhoea grade II has a big impact on patients' QoL, although it would not require hospital admission. More importantly, both experts noticed that thrombolytic events were not included and that these can be observed with ABE-FUL, potentially leading to the need of regular anticoagulation. However, the ERG anticipates that the impact of including these in the model would be negligible, considering the low cost of anticoagulation therapy.

5.4.8 Health-related quality of life

As noted in Section 5.3, 13 studies included in the SLR for HRQoL evidence adopted a generic preference-based measure of health valuation (the EQ-5D), one of which (Mitra *et al*. 2016) specified HR+/HER2− aBC patients.[76] According to the company, the heterogeneity of populations across the included studies hindered comparisons of HRQoL measures, and therefore EQ-5D-5L data collected in MONARCH 2 were preferred for the economic analysis.

During the MONARCH 2 trial, patients completed the EQ-5D-5L questionnaire at baseline; day 1 of cycle 2; and then on day 1 of every second cycle beginning with cycle 3 and continuing through cycle 13. Following that, patients filled the questionnaires at day 1 of every third cycle (after cycle 13), and at follow-up (the day after the patient and the investigator agreed that the patient would no longer continue study treatment). Using these data, EQ-5D-3L utilities were derived by mapping the 5L descriptive system data onto the 3L valuation set using the algorithm published by van Hout *et al.* 2012.[103]

Two repeated-measures regression models were run on the EQ-5D-3L utility values obtained from MONARCH 2. One model allowed for PFS and post-progression survival (PPS) utilities to be estimated across treatments, and the other allowed for treatment specific utilities for PFS and PPS. The parameter estimates from the regression models are given in Table 29, while the resulting PFS and PPS utility values are reported in Table 30. The ERG requested the company to provide the p-values and 95% confidence intervals associated with the coefficients obtained in the regression models, however, the company reported that these statistics were not available, and therefore would not be provided. The company reported that as no statistically significant differences between the treatment arms were observed, model 1 was chosen to inform the base case analysis.

The company also reported that PPS data from MONARCH 2 were immature and therefore, considered that the PPS utility value accepted in previous NICE TAs for locally advanced or metastatic breast

cancer (TA239[71], TA496[19], TA495[18]), obtained from Lloyd *et al.* 2006 (and updated in TA495[110]) was more appropriate to inform the base case analysis. Following this decision, estimates of [redacted] and 0.505 (Lloyd *et al.* 2006 and TA495) were used to inform the utility values in the model for PFS and PPS, respectively.

Table 29. Parameter estimates from regression models fitted to MONARCH 2 data based on EQ-5D-5L data crosswalked to 3L (base case) (adapted from Table 92 of Appendix M)

Parameter	Coefficient	SE
Model 1 - baseline utility and pre/post-utility covariates		
Intercept	[redacted]	[redacted]
Baseline utility*	[redacted]	[redacted]
Post vs. pre-progression disutility	[redacted]	[redacted]
Model 2 - baseline utility, pre/post-utility and treatment effect covariates		
Intercept	[redacted]	[redacted]
Baseline utility*	[redacted]	[redacted]
Post vs. pre-progression utility	[redacted]	[redacted]
ABE-FUL vs. FUL	[redacted]	[redacted]
*Acts multiplicatively on the mean baseline utility observed in MONARCH 2 (0.739). Abbreviations: ABE, abemaciclib; FUL, fulvestrant; SE, standard error		

Table 30. Utilities predicted from the MONARCH 2 regression models (adapted from Table 30 of the CS)

Health state	Mean utility	
	Model 1 without treatment covariate	Model 2 with treatment covariate
PFS	[redacted]	N/A
PPS	[redacted]	N/A
PFS (ABE-FUL)	N/A	[redacted]
PFS (FUL)	N/A	[redacted]
PPS (ABE-FUL)	N/A	[redacted]
PPS (FUL)	N/A	[redacted]
Abbreviations: ABE, abemaciclib; FUL, fulvestrant; HSUV, health state utility value; PFS, post-progression survival; PPS, post-progression survival		

Adverse events

The company applied disutilities associated with AEs in the economic model. The proportions of patients experiencing each AE in the model have been previously reported in Section 5.4.7.

Given that AE-related utility decrements were not reported in the studies identified in the SLR, the company obtained utility decrements from Hudgens 2016.[111] This study mapped EORTC QLQ-C30 data collected in a large RCT (Kaufman *et al*. 2012) in patients with aBC, to the EQ-5D.[112] Utility decrements for AEs which were not reported in Hudgens 2016 were taken from Swimburn 2010 who asked members of the general public to rate the health states of patients with solid tumours using the TTO.[113] Durations of AEs were not reported in Hudgens 2016, so were derived from the CS for

pixantrone (ID414) which included HRQoL data from solid tumour studies.[114] These data are shown in Table 31.

The impact of AEs on HRQoL was incorporated by applying a one-off QALY decrement in the first model cycle. For each AE, the QALY decrement was calculated by multiplying the proportion of patients experiencing the AE, the duration of the AE and the utility decrement associated with the AE. The resulting QALY decrements applied in the model are given in Table 32.

Table 31. Impact of AEs on HRQoL (adapted from Tables 32 and 33 of the CS)

AE	Utility decrement	Utility decrement, source	Duration (days)	Duration, source
Anaemia	−0.119	Swinburn 2010[113]	16.1	ID414 [114]
Diarrhoea	−0.006	Hudgens 2016[111]	6.0	MONARCH 2 (Sledge 2017)[27]
Dyspnoea	−0.029	Hudgens 2016 (assumption: same as asthenia/fatigue) [111]	12.7	ID414 (assumption: same as fatigue) [114]
GGT increase	0.000	Assumed to have no utility impact	0	Assumed to have no utility impact
Hyperglycaemia	−0.119	Swinburn 2010 (assumption: same as anaemia)[113]	16.1	ID414 (assumption: same as anaemia) [114]
Leukopenia	−0.003	Hudgens 2016[111]	14.0	ID414[114]
Neutropenia	−0.007	Hudgens 2016[111]	15.1	ID414[114]
Stomatitis	−0.269	Swinburn 2010 (disutility for mucositis only)[113]	4.0	ID414 (assumption: same as mucosal inflammation) [114]

Abbreviations: AE, adverse event; GGT, gamma-glutamyl transferase; HRQoL, health-related quality of life

Table 32. QALY decrements associated with AEs by treatment arm (taken from the economic model)

Treatment arm	QALY decrement
ABE-FUL	-0.0006
EXE	0.0000
EXE-EVE	-0.0009
FUL	-0.0001
TMX	-0.0001

Abbreviations: ABE, abemaciclib; AE, adverse event; FUL, fulvestrant; EVE, everolimus; EXE, exemestane; QALY, quality-adjusted life year; TMX: tamoxifen;

5.4.8.1 ERG critique

The company measured changes in HRQoL directly from patients in the MONARCH 2 trial, using a generic preference-measured measure (EQ-5D), therefore, following the key components of the NICE reference case. Moreover, the company mapped EQ-5D-5L data collected in the MONARCH 2 trial to EQ-5D-3L values, using the mapping function developed by van Hout *et al.* 2012,[103] which is in line with the NICE recommendations for using EQ-5D-5L data in submissions for technology appraisals.[115]

During the clarification stage, the company provided descriptive statistics for the cross-walked EQ-5D-3L data captured in MONARCH 2 and clarified that EQ-5D data presented in the CS are from the safety,

rather that the ITT population. However, given that the safety population includes just five fewer participants in the ABE-FUL arm compared to the ITT population, the ERG considers the approach taken to be reasonable. In addition, the ERG notes that the compliance rates (number of EQ-5D questionnaires collected at each time point) were high enough to suggest against attrition bias. Compliance rates at each time point of EQ-5D data collection ranged from 78% to 100% with most compliance rates above 90% for each treatment arm.

The company reported that the p-values and 95% confidence intervals associated with the coefficients obtained in the regression models used to estimate utility values from MONARCH 2 were not available, and therefore did not provide these. The ERG cannot see a reason as to why p-values and confidence intervals would not be available, as these are an output of the regression analysis ran by the company, for which regression coefficients were provided. As a result of not having access to these estimates, the ERG cannot validate the company's statement that no statistically significant differences were found between utility estimates in the treatment arms in MONARCH 2. More importantly, if the difference between pre-and post-progression utility coefficients in the regression model are statistically significant, the PPS utility value predicted from MONARCH 2 could have been used by the company, rather than the utility estimate from Lloyd *et al.* 2006. As previously outlined, the company used the PPS utility value from Lloyd *et al.* 2006 as it considered that PPS data from MONARCH 2 were immature. However, the ERG is unclear as to why the company considered PPS utility data from MONARCH 2 to be immature. During the trial period, [redacted] patients in the ABE-FUL arm and [redacted] patients in the FUL arm had a progression event (excluding death). During follow-up (lasted approximately 30 days after the patient stopped study treatment), [redacted] patients in the ABE-FUL arm and [redacted] patients in the FUL arm provided EQ-5D data. Furthermore, if the pre- and post-progression utility data from MONARCH show a statistically significant difference, this could help mitigate the company's concerns around data immaturity.

The ERG is also concerned that the population and methods in Lloyd *et al*. 2006 are not comparable to those in MONARCH 2. For example, Lloyd *et al.* 2006 elicited utilities using vignettes describing health states related with metastatic BC, which were valued by the general public using, the standard gamble approach. Contrastingly, MONARCH 2 patients with HR+/HER2- aBC replied to the EQ-5D questionnaire.

However, the PFS utility in Lloyd *et al.* 2006 (0.762) was only [redacted] than the PFS utility predicted from MONARCH 2 ([redacted]). Therefore, and considering the ERG has little evidence to suggest that the PPS utility value from MONARCH is not a robust estimate, the substantial difference in HRQoL between PFS and PPS in Lloyd *et al.* 2006 (0.762 vs 0.505), compared to that in MONARCH 2 ([redacted] vs. [redacted]) is not easily explained. As a scenario analysis, the ERG used both the PFS and

PPS-related utility values from MONARCH 2 in the economic analysis. The result of this analysis can be found on Section 6.

One of the studies identified in the company' SLR for HRQoL evidence (Mitra *et al.* 2016 [76]) included HR+/HER2- patients and elicited utility values using the preferred EQ-5D technique, in five major European countries (N= 613) and the US (N= 126). However, Mitra *et al.* 2016 is a conference abstract, therefore providing a limited description of methods and results. Moreover, utility estimates for progression status were not reported in Mitra *et al*. 2016. Instead Mitra *et al.* 2016 reported index utility values according to the number of lines of therapy (first, second and third or greater) received by patients. Despite this, utility estimates for patients on second or later line of therapy in Mitra *et al.* 2016 were [redacted] to those derived in MONARCH 2 for PPS (0.69 vs. [redacted], respectively). The utility related to first-line therapy in Mitra *et al.* 2016 was 0.77, which compares to [redacted] in MONARCH 2 for PFS. Comparisons with the Mitra *et al.* 2016 study need to be interpreted with caution as the latter is a cross-sectional study, with no statistical analysis of changes in patients' utility over time. Nonetheless, the ERG considers the values in Mitra *et al.* 2016 to be informative as a scenario analysis. Therefore, the ERG applied a relative decrement of –11% (calculated as the difference between the utility value for first-line therapy in Mitra *et al.* 2016 [0.77] and the second, third or later line utility in Mitra *et al*. 2016 [0.69]) to the PFS utility value obtained from MONARCH 2 ([redacted]) to estimate the PPS utility ([redacted]). The result of this analysis can be found in Section 6.

During the clarification stage, the ERG requested that the company included age-related utility decrements in their QoL analysis. However, the company stated that the population relevant to this submission has a median OS of 2 to 3 years[8] and that the modelled survival was less than 5 years in the analysis. Therefore, the company concluded that including age-related utility decrements would likely result in minimal difference to the model outcomes. Nonetheless, inspection of the company's model indicated that there was still 1% of patients alive at about 16 years. Therefore, the ERG considers it important to include age-related utility decrements to accurately estimate the total QALYs accrued for each treatment. As a result, the ERG ran a scenario analysis including age-related utility decrements, using the published algorithm by Ara and Brazier 2010.[116] The result of this analysis can be found in Section 6.

Finally, the ERG notes that the PFS utility values obtained from MONARCH 2 are likely to capture the impact of AE-related disutilities and therefore, the company's decision to include the latter in the analysis potentially leads to double counting. During the clarification stage, the ERG asked the company to run a scenario analysis removing AE-related disutilities, but the company did not provide this due to time constraints. For completeness, the ERG ran this scenario analysis, but the impact was found to be minimal.

5.4.9 Resources and costs

The cost components included in the economic model are listed below and discussed in detail in the following subsections:

- Pre-progression treatments (Section 5.4.9.1);
- Health state (follow-up) costs, best supportive care (BSC) costs, hospitalisation and terminal care costs (Section 5.4.9.2);
- Post-progression treatment (Section 5.4.9.3);
- Costs of managing AEs (Section 0);

5.4.9.1 Pre-progression treatments

Drug acquisition costs

A patient access scheme (PAS) has been proposed for abemaciclib, therefore the results in the CS and the ERG report are based on the proposed PAS price. The current list price for ABE is [redacted] per 28-day cycle treatment with the proposed PAS price at [redacted]. When available, unit costs for all other treatments in the company's analysis were taken from eMIT, otherwise these were taken from the BNF.[117, 118] Details of the approved PAS for EVE, along with results of the economic analysis incorporating the latter, are reported in the confidential appendix produced by the ERG.

The proposed licensed dose for abemaciclib in this indication is one 150mg oral tablet twice daily (a total of 300mg daily) on a continuous 28-day cycle, in combination with fulvestrant (500mg on days 1 and 15 of the first cycle [loading dose, LD], and on day 1 of subsequent 28-day cycles). However, the initial trial design for MONARCH 2 involved patients receiving abemaciclib at a starting dose of 200mg every 12 hours (Q12H), before a protocol amendment for the trial was made to change the starting dose of abemaciclib to 150mg Q12H. All efficacy analyses were performed on the ITT population which included all randomised patients regardless of starting dose. The cost of abemaciclib was nonetheless, based on the 150mg dose for the entire period of the economic analysis.

Data from BOLERO-2 were used to inform the treatment regimens for EXE and EXE-EVE, as this was the trial with the longest follow-up period identified from the SLR for EXE. The regimens from this study also aligned with the other publications identified in the SLR. Stenbygaard *et al.* 1993 was the only study identified in the SLR for TMX and was therefore used to inform the drug's treatment regimen.[119] According to the ERG's clinical experts, CAP is one of the most relevant chemotherapies in this setting and therefore, following a clarification request from the ERG, the company included CAP

as a comparator treatment in a scenario analysis, using cost data from BOLERO-6. Treatment regimens and drug acquisition costs used in the model for each treatment are provided in Table 33.

Based on the study publications, all treatments (including ABE-FUL and FUL) were given until discontinuation for reasons such as toxicity, withdrawal from the study, or progression. The company used TTD curves to estimate treatment costs in the model, as described in Section 5.4.5.4.

In the base case, the relative dose intensity (RDI) was set to be [redacted] and in a scenario analysis the RDI was set to [redacted] for ABE and [redacted] for FUL (both for the combination arm and FUL as a monotherapy), according to the mean RDI seen in MONARCH 2. The company also included drug wastage (accounting for the cost of full packs) in the base case analysis and vial sharing in a scenario analysis.

Table 33. Treatment regimens and drug aquisition costs, pre-progression treatment (adapted from Tables 35 and 36 of the CS, and the economic model)

Treatment	Drug	Dose (mg)	Dose source	Admins per cycle	Cycle length (days)	Dose per cycle (mg)	Dose per week (mg)	Units (mg/mL)	Pack/vial size (mg/mL)	Price	Total size (mg)	Cost per treatment cycle	Cost per week
ABE-FUL	ABE	150	MONARCH 2	56	28	8400	2100	150	56	[redacted]	8400	[redacted]	[redacted]
	FUL	500	MONARCH 2	1	28	500	125	250	2	£522.41	500	£522.41	£130.60
	FUL.LD**	500	MONARCH 2, PALOMA3, Zhang 2016[60], CONFIRM	1	28	500	125	250	2	£522.41	500	£522.41	£130.60
FUL	FUL	500	MONARCH 2, PALOMA3, Zhang 2016[60], CONFIRM	1	28	500	125	250	2	£522.41	500	£522.41	£130.60
	FUL.LD**	500	MONARCH 2, PALOMA3, Zhang 2016[60], CONFIRM	1	28	500	125	250	2	£522.41	500	£522.41	£130.60
EXE	EXE	25	BOLERO 2	28	28	700	175	25	30	£3.69	750	£3.69	£0.92
EXE-EVE	EXE	25	BOLERO 2	28	28	700	175	25	30	£3.69	750	£3.69	£0.92
	EVE	10	BOLERO 2	28	28	280	70	10	30	£2,673.00	300	£2,673.00	£668.25
TMX	TMX	40	Stenbygaard 1993[119]	28	28	1120	280	20	30	£1.59	600	£3.18	£0.80
CAP*	CAP	1250	BOLERO 6	14	21	29610	9870	150	60	£3.97	9000	£15.88	£5.29

Abbreviations: ABE, abemaciclib; BEV, bevacizumab; EVE, everolimus; EXE, exemestane; CAP, capecitabine; FUL, fulvestrant; LD, loading dose; TMX, tamoxifen.

*Included in scenario analysis

**FUL requires an additional LD of 500mg on day 15 of the first cycle

Drug administration costs

In the company's initial analysis, administration costs were only applied to FUL as all other pre-progression treatments are administered orally. The company also assumed that the cost of regular monthly administration of FUL was captured in the cost of a consultation appointment with an oncologist; hence only the administration of the loading dose (the first administration) incurred a cost.

During the clarification stage, the ERG asked the company to correct a mistake related with the implementation of the administration cost of the LD of FUL in the model, however, as a result the company reported that it would remove the total FUL administration costs (instead of correcting the error) as the cost of administering any dose of FUL was already captured within the model package of follow-up care (described in the next subsection). Nonetheless, the company's updated economic model still included the wrongly implemented administration cost. Therefore, the ERG corrected the latter and reports the results in Section 6.

When the company added CAP (an oral chemotherapy) as a comparator it was also assumed this drug would not incur any administration costs during pre-progression, despite post-progression CAP administration having an administration cost in the analysis.

5.4.9.2 Health state (follow-up) costs, BSC costs, hospitalisation and terminal care costs

Health state (follow-up) costs

The company obtained the components of follow-up care from the MONARCH 2 trial for PFS and the MONARCH 1 trial for PPS, both complemented with NICE CG81.[17] The follow-up care components, proportions and frequencies are given in Table 34. Cycles in Table 34 refer to treatment cycles rather than model cycles. Treatment cycles lasted for 28 days for all treatments, except for CAP (21 days) (as pre- and post-progression treatment) and the following post-progression treatments: eribulin (21 days); and vinorelbine (56 days). The ERG has provided the frequency of follow-up care per week (to match the economic model cycle-length) for the components of follow-up care during PFS. All unit costs were sourced from NHS Reference Costs 2016-17 and the PSSRU, and can be found in Table 46 of the CS.[120, 121]

The total weekly cost of follow-up care during PFS and PPS is given in Table 35, per treatment arm. The weekly costs differ by treatment arm because some components of follow-up care (i.e. imaging, electrocardiograms [ECGs], blood tests and oncologist consultations) depend on the length of a treatment cycle.

Table 34. Follow-up care resource use (adapted from Table 43 of the CS and the economic model)

Component	Proportion	Frequency	Frequency per week (model cycle length) by treatment cycle			Source
			56-day[a]	28-day[b]	21-day[c]	
PFS						
CT scan (including spiral CT)	89.6%	1 per alternate cycle	NA	0.11	0.15	MONARCH 2 IPD
MRI scan	6.6%	1 per alternate cycle	NA	0.01	0.01	MONARCH 2 IPD
PET scan	3.9%	1 per alternate cycle	NA	0.00	0.01	MONARCH 2 IPD
X-ray	2.50%	1 per alternate cycle	NA	0.00	0.00	MONARCH 2 IPD
ECG	100%	1 per alternate cycle	NA	0.13	0.17	MONARCH 2 CSR
Complete blood count	100%	1 per cycle	NA	0.25	0.33	MONARCH 2 CSR
Serum chemistry	100%	1 per cycle	NA	0.25	0.33	MONARCH 2 CSR
Oncologist consultation	100%	1 per cycle	NA	0.25	0.33	MONARCH 2 CSR
GP visit	100%	1 per month	NA	0.23	0.23	NICE CG81 (package 1) [17]
Community nurse	100%	1 per fortnight	NA	0.50	0.50	NICE CG81 (package 1) [17]
Clinical nurse specialist	100%	1 per month	NA	0.23	0.23	NICE CG81 (package 1) [17]
PPS						
CT scan (including spiral CT)	85.8%	1 per alternate cycle	0.05	0.11	0.14	MONARCH 1 IPD
MRI scan	8.9%	1 per alternate cycle	0.01	0.01	0.01	MONARCH 1 IPD
PET scan	5.3%	1 per alternate cycle	0.00	0.01	0.01	MONARCH 1 IPD
ECG	100%	1 per cycle	0.13	0.25	0.33	MONARCH 1 IPD
Complete blood count	100%	1 per cycle	0.13	0.25	0.33	MONARCH 1 IPD
Serum chemistry	100%	1 per cycle	0.13	0.25	0.33	MONARCH 1 IPD
Oncologist consultation	100%	1 per cycle	0.13	0.25	0.33	MONARCH 1 IPD
GP visit	100%	1 every fortnight	0.50	0.50	0.50	NICE CG81 (package 2) [17]
Community nurse	100%	1 per week	1.00	1.00	1.00	NICE CG81 (package 2) [17]
Clinical nurse specialist	100%	1 per week	1.00	1.00	1.00	NICE CG81 (package 2) [17]
Therapist	100%	1 every fortnight	0.50	0.50	0.50	NICE CG81 (package 2) [17]

a Treatments with a 56-day treatment cycle: vinorelbine (PPS)
b Treatments with a 28-day treatment cycle: ABE-FUL (PFS), EXE-EVE (PFS), TMX (PFS), FUL (PFS and PPS), EXE (PFS and PPS), letrozole (PPS), EVE (PPS), CYC (PPS), GEM (PPS), BEV (PPS), PAC (PPS)
c Treatments with a 21-day treatment cycle: CAP (PFS and PPS) and eribulin (PPS)
Abbreviations: ABE, abemaciclib; BEV, bevacizumab; CAP, capecitabine; CG, clinical guideline; CSR, clinical study report; CT, computerised tomography; CYC, cyclophosphamide; ECG, electrocardiogram; ERI, eribulin; EVE, everolimus; EXE, exemestane; FUL, fulvestrant; GEM, gemcitabine; GP, General Practitioner; IPD, individual patient data; LTZ, letrozole; MRI, magnetic resonance imaging; NA, not applicable; PAC, paclitaxel; PET, positron emission tomography; PFS, progression-free survival; PPS, post-progression survival; TMX, tamoxifen; VNB, vinorelbine.

Table 35: Weekly cost of follow-up care (taken from the economic model)

Best supportive care costs

The company obtained the components of BSC from European Society for Medical Oncology (ESMO) guidelines for aBC[122], The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in BC[123], and the MONARCH 2 trial. In summary, BSC costs included opioids (oxycodone) for pain management; anti-emetics or anti-nauseants (ondansetron); alprazolam for depression or anxiety; rivaroxaban for cancer-associated venous thromboembolic disease; and growth factors (filgrastim) for neutropenia. Drug dosages and unit costs were taken from the BNF and can be found in Tables 38 and 39 of the CS, respectively.[117] Overall, the weekly cost of BSC totalled £34.30, and this was applied to each treatment arm during PFS and PPS.

Hospitalisation costs

The company costed hospitalisations by combining the probability of hospitalisation, length of stay and unit cost per day. Only hospitalisations due to non-treatment related AEs were included to avoid double counting costs that were captured through costing grade 3–4 AEs.

In the base case, the company assumed that there were no treatment-specific differences in the length of stay and rate of hospitalisations between treatments, based on the MONARCH 2 trial data. The company also performed a scenario analysis assuming combination therapies had equivalent hospitalisation costs (i.e. EXE-EVE equivalent to ABE-FUL), which differed from monotherapy regimens (i.e. EXE and TMX were equivalent to FUL).

The rate of hospitalisation was calculated based on the total number of hospitalisations and total follow-up days, converted to weeks. Then, the rate of hospitalisations per week was transformed into a weekly

probability to be used in the model. During the clarification stage, the company explained that the hospitalisation data reported in the CS were incorrect, thus the ERG reports the correct data in Table 36.

During the clarification stage, the company also provided corrected length of stay (LOS) data. However, the company has not included the corrected data in their base case, but as a scenario analysis, in their updated model. The LOS data used by the company in their base case analysis, together with the corrected data, are reported in Table 37.

Table 36. Hospitalisation data from MONARCH 2 (adapted from Table 40 and Table 41 of the CS, the company's response to clarification B37 and the economic model)

Health state	Treatment	Number of hospitalisations	Total follow-up (days)	Probability of hospitalisation per week
Base case, without treatment-specific assumptions				
PFS	ABE-FUL and FUL	86	214841	0.0028
PPS	ABE-FUL and FUL	11	11393	0.0067
Scenario analysis, with treatment-specific assumptions				
PFS	ABE-FUL	68	151079	0.0031
PPS	ABE-FUL	6	6120	0.0068
PFS	FUL	18	63762	0.0020
PPS	FUL	5	5273	0.0066
Abbreviations: ABE, abemaciclib; FUL, fulvestrant; PFS, post-progression survival; PPS, post-progression survival				

Table 37. Length of stay data from MONARCH 2 (adapted from the company's response to clarification B37 and the economic model)

Health state	Treatment	Mean LOS (days)	SD LOS (days)
Base case, without treatment-specific assumptions, incorrect data			
PFS	ABE-FUL and FUL	7.74	8.57
PPS	ABE-FUL and FUL	7.65	4.90
Scenario analysis, with treatment-specific assumptions, incorrect data			
PFS	ABE-FUL	7.05	7.19
PPS	ABE-FUL	6.50	4.56
PFS	FUL	12.10	14.36
PPS	FUL	10.29	4.96
Scenario analysis, without treatment-specific assumptions, correct data			
PFS	ABE-FUL and FUL	7.26	7.30
PPS	ABE-FUL and FUL	11.27	10.85
Scenario analysis, with treatment-specific assumptions, correct data			
PFS	ABE-FUL	7.45	7.93
PPS	ABE-FUL	11.00	14.57
PFS	FUL	6.56	4.30
PPS	FUL	11.60	5.37
Abbreviations: ABE, abemaciclib; FUL, fulvestrant; PFS, post-progression survival; PPS, post-progression survival; SD, standard deviation; LOS, length of stay			

The company estimated a cost per inpatient day of £447.35. This was based on the mean length of stay and cost per hospitalisation reported in NHS Reference Costs 2016-17 for malignant breast disorders (currency codes JA12D-L).[120] In the model, the cost per inpatient day was multiplied by the length of stay reported in Table 36.

Overall, the expected cost of hospitalisation based on the weekly probability of hospitalisation in the base case analysis (assuming no treatment-specific differences) was £9.69 during PFS and £23.06 during PPS. When the company applied the correct data, the expected cost of hospitalisation (assuming no treatment-specific differences) reduced to £9.09 during PFS and increased to £33.97 during PPS given that the LOS decreased from 7.74 to 7.26 during PFS and increased from 7.65 to 11.27 during PPS. The impact of using the correct data is reported for all treatment arms in Section 6.

Terminal care costs

A one-off terminal care cost (£4,457) was applied to patients who died in the model. Resource use comprised of care at home with community support (50%), terminal care in hospital (40%), and Marie Curie hospice care (10%), according to the package recommended in NICE CG81.[17]

5.4.9.3 Post-progression therapy

The company's choice of subsequent treatments to be included in the model was based on the therapies received by ≥10% of patients in either the MONARCH 2 or the BOLERO-2 trials. The company assumed that the post-progression therapies following TMX were equivalent to those following treatment with FUL. However, following a clarification request from the ERG, the company included CAP as a comparator in a scenario analysis using post-progression therapy data from BOLERO-6.

The probability of being re-treated in the post-progression state with the same drug received during pre-progression was set to 0%, based on the company's clinical experts' opinion. The company subsequently rescaled those distributions to add to 100% of treatment regimens (Table 38).

The rescaled subsequent therapy distributions were then multiplied by the proportion of patients expected to receive post-progression therapy in the model. In the MONARCH 2 trial, a total of 341 patients (51.0%) in the ITT population, including 200 patients (44.8%) in the ABE-FUL arm and 141 patients (63.2%) in the FUL arm, had some type of systemic therapy after discontinuation. Using these data and the number of events in the PFS KM curve of MONARCH 2 (Table 39), the company estimated the proportion of patients expected to receive active therapy on disease progression as [redacted]/379 = [redacted]. During the clarification stage the ERG requested the company corrected this estimate to exclude deaths from the events in the PFS dataset. Following this, the company estimated that [redacted] (previously [redacted]) of patients would receive post-progression treatment. However, the company has

not included this correction in their base case, but as a scenario analysis, in their updated model. The impact of using the correct data is reported for all treatment arms in Section 6.

Table 38. Rescaled post-progression therapy distribution, by pre-progression therapy (adapted from Table 47 of the CS)

Post-progression therapy	Pre-progression therapy					
	ABE-FUL (MONARCH 2)	FUL (MONARCH 2)	EXE (BOLERO 2)	EXE-EVE (BOLERO 2)	TMX (assumed equal to FUL)	CAP (BOLERO 6)*
CAP	19.55%	17.81%	38.36%	35.82%	17.81%	0.00%
PAC	19.55%	17.81%	0.00%	0.00%	17.81%	5.00%
VNB	5.13%	6.48%	17.81%	10.45%	6.48%	5.00%
ERI	6.09%	4.86%	0.00%	0.00%	4.86%	2.50%
FUL	0.00%	0.00%	24.66%	34.33%	0.00%	25.00%
LTZ	7.05%	8.91%	0.00%	0.00%	8.91%	2.50%
EXE	16.35%	19.84%	0.00%	0.00%	19.84%	25.00%
EVE	12.82%	14.57%	0.00%	0.00%	14.57%	30.00%
CYC	4.49%	2.83%	12.33%	13.43%	2.83%	2.50%
GEM	2.56%	2.83%	6.85%	5.97%	2.83%	2.50%
BEV	6.41%	4.05%	0.00%	0.00%	4.05%	0.00%
Total	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Abbreviations: ABE, abemaciclib; BEV, bevacizumab; CAP, capecitabine; CYC, cyclophosphamide; ERI, eribulin; EVE, everolimus; EXE, exemestane; FUL, fulvestrant; GEM, gemcitabine; LTZ, letrozole; PAC, paclitaxel; TMX, tamoxifen; VNB, vinorelbine.
*Included in scenario analysis

Table 39. Progression events in MONARCH 2, ITT population (taken from the economic model)

PFS	ABE-FUL n=446	FUL n=223	Total
Number of events	222 (49.8%)	157 (70.4%)	379
Death without PD	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]

Abbreviations: ABE, abemaciclib; FUL, fulvestrant; PD, progressive disease; PFS, progression-free survival

The company has assumed that patients in the model receive post-progression treatment for 37% of the time spent in the PPS state. To aid interpretation of this estimate, the ERG has provided the number of months patients receive post-progression treatment for, by treatment arm in Table 40. Patients on ABE-FUL spent the [redacted] on subsequent treatments, given the [redacted] time spent on the PFS state, compared with the other treatments. Time spent in the OS state was [redacted] across ABE-FUL and other treatments.

Table 40. Time on treatment during PPS (taken from the economic model)

Treatment	Total OS (months)	Total PFS (months)	Time on treatment [(OS – PFS)*37%]	Time off treatment [(OS – PFS)*63%]	Total time in PPS (months)
ABE-FUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EXE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EXE-EVE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TMX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CAP*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABE, abemaciclib; BEV, bevacizumab; EVE, everolimus; EXE, exemestane; FUL, fulvestrant; NA, not applicable; TMX, tamoxifen; ToT, time on treatment

*Included in scenario analysis

Treatment regimens and RDI were assumed equivalent to pre-progression regimens when available, except for CAP. Treatment regimens and RDI for cyclophosphamide (CYC) (including epirubicin [EPI] and fluorouracil [FLU]), gemcitabine (GEM) and bevacizumab (BEV) were based on publications cited by the NCCN guidelines.[123] The company did not explain how the sources for CAP, paclitaxel (PAC), vinorelbine (VNB), eribulin (ERI) and letrozole (LTZ) were chosen. In the base case, the RDI was set to be 100% for all treatments and in a scenario analysis, ranged from 74% to 100% for post-progression treatments according to the publications cited in Table 41.

When available, unit costs for all treatments were taken from eMIT, otherwise they were taken from the BNF.[117, 118] Treatment regimens and drug acquisition costs used in the model for each comparator are provided in Table 41. Based on the average weight (66.67g) and height (159.39cm) of patients included in MONARCH 2, and using the DuBois 1916 method, a body surface area of 1.69m^2 was assumed for patients in the model to calculate doses dependent on body surface area.[124] Drug administration costs are provided in Table 42.

Table 41. Treatment regimens and drug aqusition costs, post-progression treatment (adapted from Tables 50 and 51 of the CS, and the economic model)

Drug	Dose (mg)	Dose source	per unit	Admins per cycle	Treatment cycle (days)	Dose per cycle (mg)	Therapy type	Price	Units (mg/mL)	Pack/vial size (mg/mL)	Cost per cycle	Cost per week
CAP	1250	Kaufman 2015[125]	m2	28	21	59220	Oral	£21.76	500	120	£21.76	£7.25
PAC	80	Perez 2001[126]	m2	4	28	541	IV	£19.68	300	50	£19.68	£4.92
VNB	30	Meier 2008[127]	m2	6	56	305	IV	£22.58	50	5	£45.16	£5.65
ERI	1.4	Kaufman 2015[125]	m2	2	21	5	IV	£361.00	0.44	2	£2,166.00	£722.00
FUL	500	MONARCH 2	Fixed	1	28	500	IM	£522.41	250	2	£522.41	£130.60
FUL.LD*	500	MONARCH 2, PALOMA3, Zhang 2016[60], CONFIRM	Fixed	1	28	500	IM	£522.41	250	2	£522.41	£130.60
LTZ	2.5	Rose 2003[49]	Fixed	28	28	70	Oral	£2.71	2.5	28	£2.71	£0.68
EXE	25	BOLERO 2	Fixed	28	28	700	Oral	£3.69	25	30	£3.69	£0.92
EVE	10	BOLERO 2	Fixed	28	28	280	Oral	£2,673.00	10	30	£2,673.00	£668.25
CYC	400	Ackland 2001[128]	m2	2	28	1354	IV	£25.99	2000	1	£25.99	£6.50
EPI	50	Ackland 2001[128]	m2	2	28	169	IV	£5.62	50	25	£5.62	£1.41
FLU	500	Ackland 2001[128]	m2	2	28	1692	IV	£3.59	2500	100	£3.59	£0.90
GEM	1250	Brodowicz 2000[129]	m2	3	28	6345	IV	£15.92	2000	52.6	£15.92	£3.98
BEV	10	Miller 2007[130]	m2	2	28	34	IV	£242.66	100	1	£242.66	£60.67

Abbreviations: ABE, abemaciclib; BEV, bevacizumab; CAP, capecitabine; CYC, cyclophosphamide; EPI, epirubicin; ERI, eribulin; EVE, everolimus; EXE, exemestane; FLU, fluorouracil; FUL, fulvestrant; GEM, gemcitabine; IM, intramuscular; IV, intravenous; LD, loading dose; LTZ, letrozole; PAC, paclitaxel; TMX, tamoxifen; VNB, vinorelbine.

* FUL requires an additional LD of 500mg on day 15 of the first cycle

Table 42. Post-progression drug administration costs (adapted from Table 53 of the CS)

Treatment	Cost per administration	Source
Oral chemotherapies (CAP, VNB)	£163.82	NHS Reference Costs 2016–17: SB11Z Deliver exclusively oral chemotherapy (outpatient only based no activity)[120]
Day case chemotherapies (PAC, GEM, ERI)	£259.76	NHS Reference Costs 2016–17: SB12Z Deliver simple parenteral chemotherapy at first attendance (day case only based on activity)[120]
Complex chemotherapies (CYC)	£310.00	NHS Reference Costs 2016–17: SB13Z, Deliver complex chemotherapy at first attendance, day case based on activity[120]
Outpatient chemotherapies (BEV)	£205.09	NHS Reference Costs 2016–17: Subsequent treatment cycles: SB15Z - delivery subsequent elements of a chemotherapy cycle (chemotherapy outpatient)[120]

Abbreviations: BEV, bevacizumab; CAP, capecitabine; CYC, cyclophosphamide; ERI, eribulin; FUL, fulvestrant; GEM, gemcitabine; PAC, paclitaxel; VNB, vinorelbine.

In the model, post-progression treatment costs are assigned upon progression (i.e. not incurred weekly). Those costs are provided in Table 43 and combine the distribution of post-progression treatments (Table 38), the proportion of patients expected to receive active therapy on disease progression ([redacted] in the company's base case), the time on-treatment during PPS (37% of time in PPS), drug acquisition costs (Table 41) and drug administration costs (Table 42).

Table 43. Post-progression treatment cost by treatment arm in company's base case (taken from the economic model)

[redacted]

5.4.9.4 Costs of managing AEs

The model includes all grade 3 and 4 AEs with an incidence of ≥ 5% for at least one comparator. The proportions of patients experiencing each AE in the model have been previously reported in Section 5.4.6. In order to apply the costs of managing AEs in the model, the total cost was applied upfront in the first model cycle. The total cost per patient was calculated by weighting the cost to treat AEs (Table 44) by the probabilities observed in the trials (Table 28). The resulting one-off costs applied in the model are reported in Table 45.

Table 44. Adverse event costs (adapted from Table 57 of the CS)

Adverse event	Cost	Source
Anaemia	£270.00	NHS Reference Costs 2016−17: SA44A, outpatient, service code 370, Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over[120]
Diarrhoea	£2.93	BNF: one pack of loperamide[117]
Dyspnoea	£389.64	NHS Reference Costs 2016−17: DZ19L, DZ19M and DZ19N for Other Respiratory Disorders without Interventions[120]
GGT increase	£0.00	Laboratory abnormality test [assumption]
Hyperglycaemia	£434.91	NHS Reference Costs 2016−17: KB02G, KB02H, KB02J and KB02K for Diabetes with Hyperglycaemic Disorders[120]
Leukopenia	£173.00	NHS Reference Costs 2016−17: WF01A service code 370 Medical Oncology Non-Admitted Face to Face Attendance, Follow-up[120]
Neutropenia	£173.00	NHS Reference Costs 2016−17: WF01A service code 370 Medical Oncology Non-Admitted Face to Face Attendance, Follow-up[120]
Stomatitis	£482.28	NHS Reference Costs 2016−17: FD10J, FD10K, FD10L and FD10M for Non-Malignant Gastrointestinal Tract Disorders without Interventions[120]
Abbreviations: AE, adverse event; BNF: British National Formulary; GGT, gamma-glutamyltransferase		

Table 45. One-off costs to manage AEs, by treatment arm (taken from the economic model)

Treatment arm	AE cost
ABE-FUL	[redacted]
EXE	[redacted]
EXE-EVE	[redacted]
FUL	[redacted]
TMX	[redacted]
CAP*	[redacted]
Abbreviations: ABE, abemaciclib; AE, adverse event; CAP, capecitabine; EVE, everolimus; EXE, exemestane; FUL, fulvestrant; QALY, quality-adjusted life year; TMX: tamoxifen *Included in scenario analysis	

5.4.9.5 ERG critique

The estimates used are based on the 2016/17 price year, with unit costs obtained from published sources such as NHS Reference Costs, the PSSRU, the eMIT, and the BNF, which is in line with the NICE reference case.[117, 118, 120, 121, 131] The ERG validated the costs from the sources cited, and checked that prices are correctly inflated when necessary. Overall, the ERG's main concerns include: post-progression treatments modelled, FUL-related costs, health state costs, the dose for ABE and TMX, CAP-related administrations and finally, hospitalisation costs. Each of these is described in turn, below.

Post-progression treatments

The company only considered systemic post-progression treatments in the model. However, in the MONARCH 2 trial, a total of 63 patients (9.4%) in the ITT population, including 37 patients (8.3%) in the ABE-FUL arm, and 26 patients (11.7%) in the FUL arm, had radiotherapy after discontinuation. Moreover, clinical experts advised the ERG that radiotherapy is commonly used as a concomitant post-progression therapy. To address this issue, the ERG asked the company to include radiotherapy as a

post-progression treatment in the model. However, in response to the ERG's clarification question, the company stated that they would expect the impact of including radiotherapy to be minimal and therefore did not provide the requested scenario analysis.

Furthermore, the company included bevacizumab (BEV) as a subsequent treatment in the model, which clinical experts advising the ERG indicated would not be available to patients in UK NHS. Clinical experts also pointed out that TMX should be included as a post-progression therapy. To address these issues, the ERG asked the company to remove BEV as a subsequent treatment option and add treatment with TMX. In a scenario analysis, the company removed BEV as a subsequent treatment option following all treatments in the model. The company subsequently looked in BOLERO-2 to inform the proportion of patients receiving TMX as a post-progression therapy after EXE and EXE-EVE, however found no data and thus did not include TMX as a subsequent treatment option for these treatments. Patients in the TMX arm also did not receive re-treatment with the same drug. For ABE-FUL and FUL, the company used the proportion of patients who received TMX in MONARCH 2.

Although removing BEV and adding TMX to the list of possible subsequent treatments illustrates the UK clinical practice more closely, the ERG still considers that some caution should be taken when interpreting these. For example, clinical experts advised the ERG that they would expect the proportion of patients receiving subsequent PAC to be larger. Moreover, as noted in Section 2, access to FUL is patchy in the UK and therefore the proportions taken from BOLERO 2 (24.66% and 34.33% following EXE and EXE-EVE, respectively) could be higher than those seen in the UK. To address these issues, the ERG applied a set of alternative distributions which have been validated by its clinical experts (Table 46). The impact of the ERG's analysis on the results can be found in Section 6.

Table 46 Distribution of post-progression therapies, ERG scenario

Post-progression therapy	**Pre-progression therapy**					
	ABE-FUL	**FUL**	**EXE**	**EXE-EVE**	**TMX**	**CAP***
TMX	25%	25%	20%	20%	0%	10%
PAC	25%	25%	25%	20%	25%	50%
CAP	25%	25%	35%	40%	35%	0%
EXE-EVE	15%	15%	0%	0%	20%	20%
EXE	5%	5%	0%	0%	5%	5%
VNB	5%	5%	10%	10%	5%	5%
FUL	0%	0%	10%	10%	10%	10%
Total	100%	100%	100%	100%	100%	100%

ABE: abemaciclib; CAP: capecitabine; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; PAC: paclitaxel; TMX: tamoxifen; VNB: vinorelbine

*Included in scenario analysis

Furthermore, the company did not justify the model assumption that the proportion of time spent on subsequent treatment during PPS would be 37% of PPS time. More importantly, clinical experts advised the ERG that the company's assumption was too low as patients would usually spend all but the last 3 months of their life on treatment. To reflect clinical expert opinion, the ERG ran a scenario using the time on post progression treatment reported in Table 47. Results of the ERG analysis are reported in Section 6.

When the ERG used its FP NMA to estimate treatment effectiveness in the model, the change in PFS and OS curves also impacted the time patients spent on the PPS state (as the latter is calculated as OS minus PFS). Overall, ABE-FUL remained the treatment for which patients spent [redacted] on PPS ([redacted] months). The ERG's approach needs to be caveated by the fact that patients would not remain on the same subsequent treatment until 3 months before death. Clinical experts advising the ERG explained that patients are likely to receive several rounds of chemotherapy before death, and so the ERG made some simplifying assumptions in order to estimate the costs of subsequent treatments. Given that the costs of chemotherapy regimens, TMX and EXE are considerably low and broadly similar, the ERG did not differentiate between these as further lines of treatment. However, FUL and EVE are expensive treatments, and so the assumption that patients would remain on these for the entire period of their subsequent therapy was likely to bias the costs of subsequent treatments upwards in the analysis. Therefore, the ERG assumed that patients receiving FUL or EXE-EVE as subsequent treatments in the model would do so for a limited amount of time, which was assumed to be the same as the time spent in the PFS state when given these treatments first. So, for example, if a patient received ABE-FUL in the model, the time spent on EXE-EVE as a subsequent therapy was set to be the same as the time spent in the PFS state by patients who receive EXE-EVE as their first treatment in the model. This is an optimistic assumption, given that as patients progress (and move to subsequent lines of therapy) they become less likely to tolerate treatments for long, and treatments are unlikely to be as effective as in previous lines of treatment, so the ERG assumption might result in an overestimation of EXE-EVE (and FUL) costs as a subsequent treatment. Decreasing the costs associated with subsequent treatments in the model increases the final ICERs for ABE-FUL vs all comparators. This is because ABE-FUL patients receive subsequent treatments for [redacted] than any other patients in the analysis. The ERG assumed that after subsequent treatment with FUL or EXE-EVE, patients would receive chemotherapy regimens (CAP) until 3 months before dead.

Time spent on subsequent treatments is one of the model's key drivers, therefore, the ERG advises that the Committee discusses the clinical plausibility of ABE-FUL patients receiving subsequent treatments for shorter periods than other patients in the model. To note, is that ABE-FUL patients spend less time on subsequent treatments due to their PFS period being longer. However, this has not been translated

into a proportional increase in OS with ABE-FUL, thus patients spend less time of subsequent treatments before they die.

Table 47. Time on treatment during PPS, ERG scenario

Treatment	Time on treatment (months)		Total time in PPS (months)
	Base case	ERG scenario	
ABE-FUL	[redacted]	[redacted]	[redacted]
FUL	[redacted]	[redacted]	[redacted]
EXE	[redacted]	[redacted]	[redacted]
EXE-EVE	[redacted]	[redacted]	[redacted]
TMX	[redacted]	[redacted]	[redacted]
CAP*	[redacted]	[redacted]	[redacted]

Abbreviations: ABE, abemaciclib; BEV, bevacizumab; CAP, capecitabine; EVE, everolimus; EXE, exemestane; FUL, fulvestrant; NA, not applicable; TMX, tamoxifen; ToT, time on treatment
*Included in scenario analysis

Finally, as described in Section 5.4.9.3, the company provided a scenario analysis with the corrected proportion of patients expected to receive post-progression therapy on disease progression ([redacted]). The ERG considers the company's revised estimate to be more reflective of clinical practice, given that clinical experts advising the ERG indicated that most patients chose to move on to the alternative treatment options available at the time disease progression. The impact of using the corrected estimates on the results is reported in Section 6.

Fulvestrant costs

The ERG has two concerns with the estimation of FUL costs in the model, relating with acquisition and administration costs.

Firstly, as described in Section 5.4.9.1, treatment with FUL requires an additional LD of 500mg on day 15 of the first treatment cycle at an acquisition cost of £522. However, the company did not include the correct LD acquisition cost in the model, and therefore underestimated the overall cost of FUL in the economic analysis. Furthermore, the company did not correct the additional implementation error in the FUL LD administration cost pointed out by the ERG (which consisted of the fact that the company applied the wrong administration cost to the FUL LD dose in the model).

Secondly, clinical experts advising the ERG disagreed with the company's assumption that FUL would be administered as part of a consultation with an oncologist, and that only the LD would have an associated administration cost. During the clarification stage, the ERG asked the company to reflect the assumptions accepted in TA503 and TA496, where 32.3% of subsequent fulvestrant administrations are delivered in the primary care setting and 67.7% are delivered in the outpatient setting, and to apply the respective administration cost to every treatment cycle of FUL.[19, 132] However, the company rejected

the ERG's request given it was considered that follow-up costs (Section 5.4.9.2) would capture any additional administration costs.

Therefore, the ERG corrected the implementation of the administration cost for the LD of FUL and ran a scenario analysis using the assumptions accepted in TA503 and TA496 (Table 48) and applying the FUL administration cost for every cycle of FUL received in the model. The impact of the ERG's analyses on the results are reported in Section 6.

Table 48. FUL administration costs estimated from TA496[19]

Setting	Weight	Unit cost
PSSRU 2017 Community nurse specialist 15 minutes - Cost per working hour (£43) Band 6[121]	32.3%	£10.75
NHS Reference Costs 2016-2017 Non-Consultant Led: Follow up Attendance Non-Admitted Face to Face, Medical oncology Code 370[120]	67.7%	£100.67
Total weighted administration cost	£71.63	

Health state (follow-up costs)

Clinical experts advised the ERG that the health state (follow-up) costs used by the company and taken from the MONARCH 2 and MONARCH 1 trials, are likely to overestimate the resource use in UK's clinical practice. Specifically, patients would not receive ECGs, and the frequency of CT scans, community nurse visits and oncologist consultations would be lower (i.e. every three months rather than every few weeks). Following this, the ERG considered the follow-up costs in TA496 for PFS and PPS to be more appropriate and therefore requested the company to provide a scenario analysis using those resources.[19] However, instead of employing the follow-up costs in TA496 for PFS and PPS, the company extracted the drug acquisition cost for third and subsequent lines of treatment (£1,200 per month).[19] Then, the company replaced the cost of PPS follow-up with a cost of £1,200 per month (£300 per weekly cycle) and removed third-line treatment costs (Table 43) from the economic model. As a result, the company replaced follow-up costs with drug acquisition costs. The ERG considers this to be an uninformative scenario given that drug acquisition costs are not equivalent to follow-up costs. To address this issue, the ERG explored a scenario using the follow-up costs (Table 49) accepted in TA496. The results of this analysis can be found in Section 6.

Table 49. Follow-up costs estimated from TA496[19]

Component	Frequency (per week*)	
	PFS	PPS
GP visits	Once a month (0.23)	Once a month (0.23)
Oncology consultant	Every 6 months (0.04)	Every 6 months (0.04)
Community nurse	Every 3 months (0.08)	Every 3 months (0.08)
Clinical nurse specialist	Once a month (0.23)	Once a month (0.23)

CT scan	Every 3 months (0.08)	Every 3 months (0.08)
Social worker	-	Every 2 months (0.11)

*4.348 weeks per month

Abbreviations: CT, computerised tomography; GP, General Practitioner; PFS, progression free survival; PPS, post-progression survival; PSSRU, Personal Social Services Research Unit

Dose of abemaciclib (ABE)

The cost of ABE in the economic analysis was based on the 150mg dose, although a proportion of patients in MONARCH 2 received a starting dose of 200 mg. As a result, the ERG ran a scenario where 27.5% (121 of 441) of patients received ABE at the 200-mg starting dose for 34 days, to reflect the patients enrolled in MONARCH-2 prior to the dose amendment. However, given that the proportion of time on the higher dose was relatively short, the impact on the ICER was negligible.

Dose of TMX

The company modelled the dose of TMX (40mg daily) based on the regimen reported in Stenbygaard *et al.* 1993.[119] This study was also included in the company's HR NMA to inform the effectiveness of TMX. However, clinical experts advising the ERG noted that the recommended daily dose for TMX in current clinical practice is normally 20mg given that no additional benefit, in terms of delayed recurrence or improved survival in patients has been demonstrated with higher doses (40mg daily).[61] Nonetheless, when the ERG amended the dose of TMX from 40 mg daily to 20 mg daily, the impact on the results was negligible, given the low acquisition cost of TMX.

Inconsistencies associated with CAP administrations

During the clarification stage, the company included CAP as a treatment option. However, the company only applied administration costs to CAP when it was received as a post-progression treatment. In addition, the company applied different regimens for CAP as a pre- and post-progression treatment: 14 administrations per 21- day cycle (i.e. one per day) and 28 administrations per cycle (i.e. two per day), respectively. Clinical experts advised the ERG that the same dose would be used during pre-progression and post-progression thus, the ERG amended the company's scenario analysis and included administration costs during pre- and post-progression treatment and 28 treatment administrations. Furthermore, the company had assumed that during PPS, treatment with CAP would incur a daily administration cost, for every day of treatment with CAP. Given that CAP is an oral treatment, this assumption is not clinically plausible and led to a considerable overestimation of CAP costs as a subsequent treatment. As mentioned above in this section, the higher the costs associated with subsequent treatments, the lower the ICERs for ABE-FUL vs all other treatments, thus, the company's

assumption resulted in an underestimation of the final ICERs. The ERG corrected this in the model, so that CAP administration costs were incurred once per treatment cycle (i.e. once every 21 days, as per TA296).

Hospitalisations

As described in Section 5.4.9.2, corrected hospitalisation data were provided by the company at clarification following a discrepancy identified by the ERG. However, hospitalisation data were obtained from a bespoke analysis by the company that the ERG was unable to validate. Therefore, to mitigate any uncertainty regarding the company's analysis of hospitalisations and given that the cost of treatment-emergent AEs would include hospitalisation costs, the ERG provided a scenario analysis excluding the cost of hospitalisations from the analysis. The impact of using the correct data is reported for all treatment arms in Section 6.

5.5 Results included in company's submission

5.5.1 Base case results

The company's base case results with the revised PAS are presented in Table 50, while Table 51 reports the fully incremental base case results. Based on the pairwise ICERs, ABE-FUL dominates EXE-EVE, with [redacted].

Table 50. Company's pairwise base case results (ABE-FUL versus comparator)

	ABE-FUL (1)	FUL (2)	EXE (3)	EXE-EVE (4)	TMX (5)	Incremental value (1-2)	Incremental value (1-3)	Incremental value (1-4)	Incremental value (1-5)
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LYs	3.64	3.50	3.33	3.45	3.72	0.14	0.31	0.19	-0.08
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	-	-	-	-	-	£41,702	£18,754	Dominant	£62,548

Abbreviations: ABE, abemaciclib; BEV, bevacizumab; EVE, everolimus; EXE, exemestane; FUL, fulvestrant; TMX, tamoxifen; ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years

Table 51. Company's fully incremental base case results

Treatment	Cost	QALYs	Incremental cost	Incremental QALY	ICER (cost per QALY gained)
TMX	[redacted]	[redacted]	-	-	-
FUL	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
EXE	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ABE-FUL	[redacted]	[redacted]	[redacted]	[redacted]	£62,548
EXE-EVE	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ABE, abemaciclib; BEV, bevacizumab; EVE, everolimus; EXE, exemestane; FUL, fulvestrant; TMX, tamoxifen; ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years

5.5.2 Sensitivity analysis

Deterministic sensitivity analysis

The company carried out a range of scenario analyses exploring the impact of changing assumptions surrounding various parameters. A list of the company's scenarios can be found in Section 3.8.2 of the CS. During the clarification stage the company added that eight parameters were varied in one-way sensitivity analysis (OWSA) and that those parameters (listed below) were chosen to represent the key drivers in the model specifically relating to ABE-FUL:

1. ABE-FUL PFS treatment effect (coefficient) (Lower/Upper 95% CI)
2. ABE-FUL OS treatment effect (coefficient) (Lower/Upper 95% CI)
3. ABE-FUL time-on-treatment treatment effect (coefficient) (Lower/Upper 95% CI)
4. Pre-progression state utility coefficient (Lower/Upper 95% CI)
5. Post-progression state utility coefficient (Lower/Upper 95% CI)
6. Drug price ABE-FUL (+/- 20%)
7. Discount rates for costs
8. Discount rates for benefits

However, the results of OWSA and scenario analyses for the updated model were not provided by the company during the clarification stage and due to time constraints, the ERG was unable to run these. Moreover, given the uncertainty in the company's base case analysis of treatment effectiveness, the results of OWSA for the company's base case would only provide small insight. The ERG's view is substantiated by the fact that the key drivers in the company's initial scenario analysis (excluding the revised PAS) related to survival estimates and included: interval censored adjustment; distribution for extrapolating duration of therapy; assessment of PFS; and distribution for extrapolating OS.

Additional scenario analyses which the ERG considers relevant are explained throughout Section 5 of this report and are reported Section 6.

Subgroup analysis

The company conducted an analysis exploring the subgroup of patients who were randomised to receive ABE at the 150 mg starting dose using data from the MONARCH 2 trial. Although the ERG has several issues regarding the company's base case analysis, the ERG considers the impact on the ICER in the

subgroup to be informative. The results of the subgroup analysis, generated by the ERG in the revised model are given in Table 52.

Compared with the base case analysis, the pairwise ICER for ABE-FUL compared to TMX increased from £62,548 to £72,661. ABE-FUL also remained dominant over EVE-EXE, as seen in the base case analysis.

Table 52 Results for subgroup analysis (150 mg starting dose)

[redacted]

Probabilistic sensitivity analysis

The company's original model included a PSA to assess the joint parameter uncertainty around the base case results using 10,000 PSA iterations. However, the company did not provide the PSA results for their updated HR-based NMA base case analysis. Furthermore, the company did not account for the correlation between the different HRs when they sampled clinical effectiveness data from the HRs (and 95% credible intervals) in their base case analysis. To address this issue, the ERG requested the company to use CODA output from OpenBUGs to ensure that the correlation between each sample was retained (i.e. the same iteration for each sample used for all treatments). Nonetheless, the company did not undertake the changes requested.

Furthermore, the company did not provide a PSA for their FP NMA scenario analysis, as to incorporate the CODA output into the model "…*would have required the model to store 6 million cells of data (10,000 PSA iterations with 1000 rows of data for the survival function and 6 treatments. The text file which stores this data is 700 megabytes*." As explained in Section 5.4.4. this referred computational complexity is likely related with the company's implementation of the FP NMA curves into the economic model and potentially could have been mitigated by implementing the beta parameters from the FP curves directly into the model, rather than estimating survival curves separately and including the latter in the model.

Overall, the ERG is concerned that the uncertainty in the company's analysis has not been appropriately accounted for, whether in the NMA HR base case analysis or in the FP NMA scenario. Due to time limitations, and the company's approach to implementing the FP NMA outputs in the economic model, the ERG could not run PSA for the company's results nor for the ERG's FP NMA results reported in Section 6.

6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

6.1 Model corrections

During the clarification stage, the ERG asked the company to correct the mistakes found by the ERG upon revision of the company's original model. The company provided a correction for some of these, however, as scenario analysis, instead of incorporating the corrections in the updated base case results. Therefore, the ERG has implemented these corrections in the company's base case analysis and reports the results in this section. The corrections made to the company's model have been discussed in detail in Section 5 of the report and consisted on:

1. Correctly implementing the administration cost of FUL in the model, using the company's estimate of administration costs;

2. Changing the daily administration costs of post-progression CAP to once per 21-day cycle of treatment;

3. Correctly implementing the acquisition cost of the FUL LD in the model;

4. Using the correct LOS data to estimate non-AE-related hospitalisation costs;

5. Removing the number of death events from the total PFS events, in order to estimate the percentage of patients who progressed and received subsequent treatments in MONARCH 2.

Overall, all the pairwise ICERs increased, when the ERG implemented the model corrections, compared to the company's base case results. EXE-EVE remained dominated by ABE-FUL.

Table 53. Company's pairwise base case results (ABE-FUL versus comparator)

	ABE-FUL (1)	FUL (2)	EXE (3)	EXE-EVE (4)	TMX (5)	(1-2)	(1-3)	(1-4)	(1-5)
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	-	-	-	-	-	£50,687	£57,247	Dominant	£82,621

Abbreviations: ABE, abemaciclib; BEV, bevacizumab; EVE, everolimus; EXE, exemestane; FUL, fulvestrant; TMX, tamoxifen; ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years

6.2 ERG scenario analysis

1. The scenario analyses undertaken by the ERG are explained throughout Section 5 of the report. Results of the exploratory analyses are reported in Table 54 and consist on the following:

2. The ERG replaced the company's OS and PFS FP NMA-derived curves by the ones estimated by the ERG using the FP NMA approach (PFS power of 0; OS power of -1.5). This also includes the TTD curves estimated by the ERG;

3. The ERG used both the PFS and PPS-related utility values from MONARCH 2 in the economic analysis ([redacted] vs [redacted]), respectively;

4. The ERG used the utility value for first-line therapy in Mitra *et al.* 2016 [0.77] and the second, third or later line utility in Mitra *et al*. 2016 [0.69]) to estimate a relative decrement to be applied to the PFS utility value from MONARCH 2 ([redacted]), in order to estimate the PPS utility ([redacted]);

5. The ERG removed AE-related disutilities from the model;

6. The ERG ran a scenario analysis including age-related utility decrements, using the published algorithm by Ara and Brazier 2010;[116]

7. The ERG used a set of alternative distributions for subsequent treatments received in the model, which have been validated by its clinical experts;

8. The ERG assumed that patients would receive subsequent treatments for the entire time spent on PPS, with the exception of the last 3 months;

9. The ERG caped the time patients could spend on FUL and EXE-EVE as subsequent treatments;

10. The ERG ran a scenario analysis including the resource use associated with follow-up care accepted in TA496;

11. The ERG ran a scenario analysis including the resource use associated with FUL administration costs accepted in TA496, and applied it for every cycle of FUL treatment in the model;

12. The ERG ran a scenario analysis excluding the cost of non-AE-related hospitalisations from the analysis;

13. The ERG removed the half-cycle correction from the model;

14. The ERG included the first-order FP OS curve with a power of -0.5. This scenario includes the ERG's FP NMA for PFS and the ERG's estimated TTD curves.

The ERG's exploratory analysis shows that ICERs for ABE-FUL compared with the other treatments are most sensitive to the method used to estimate treatment effectiveness in the model. When the ERG applied the ERG's FP NMA-based OS and PFS curves, together with the ERG's estimated TTD curves,

the ICERs decreased considerably for all treatments (and the ICER for ABE-FUL vs EXE-EVE remained dominant). The decrease in ICERs is mainly related with the ERG's estimation of TTD curves for all treatments. While the benefits associated with all treatments decreased, so did the total costs associated with each treatment, mainly ABE-FUL and EXE-EVE.

Another key driver of results is the choice of utility value for the PPS health state. As expected, the bigger the drop from the PFS to the PPS- related utility value, the lower the ICERs. Given that both ERG's exploratory analysis (2 and 3) increased the PPS value in the model, all ICERs increased substantially.

Assumptions related with subsequent treatments are reported as separate scenario analysis (6, 7 and 8). However, these are more meaningful when applied together, and thus are discussed in more detail in the next section.

Follow-up costs also have a considerable impact on the final ICER. When the resource use from TA496 is included in the model, ICERs increased for ABE-FUL vs all treatments.

Table 54. ERG's scenario analysis

	Results per patient	ABE-FUL (1)	FUL (2)	EXE (3)	EVE-EXE (4)	TMX (5)*	Incremental value			
							(1-2)	(1-3)	(1-4)	(1-5)
0	**Company's corrected base case (administration cost and acquisition cost associated with FUL LD, hospitalisation data and number of PFS events)**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-	-	-	-	-	£50,687	£57,247	Dominant	£82,621
1	**Using the ERG's FP NMA results for OS and PFS and adjusting TTD curves**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-	-	-	-	-	£41,719	£44,089	Dominant	Dominated
2	**PPS utility from MONARCH 2 ([redacted])**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-	-	-	-	-	£113,457	£102,278	Dominant	Dominated
3	**PPS utility using a -11% relative decrement (Mitra *et al.* 2016) on PFS utility**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-	-	-	-	-	£92,990	£89,733	Dominant	£611,615
4	**Remove AE-related disutilities**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-	-	-	-	-	£50,614	£57,183	Dominant	£82,451
5	**Age-related utility decrements included**									

	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-	-	-	-	-	£51,757	£58,360	Dominant	£84,299
6	**Change post-progression treatment distributions**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-	-	-	-	-	£51,234	£53,700	Dominant	£69,383
7	**Change time spent in PPS treatment from 37% of PPS to up 3 months before death**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-	-	-	-	-	£29,840	£57,133	Dominant	£42,945
8	**Capping the time patients could spend on FUL and EXE-EVE as subsequent treatments**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-	-	-	-	-	£49,375	£58,662	-£30,479	£80,247
9	**Using TA496 follow-up (health state) costs**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-	-	-	-	-	£62,737	£65,459	Dominant	£111,549
10	**Using TA496 FUL administration costs**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-	-	-	-	-	£52,348	£59,546	Dominant	£88,566
11	**Removing non-AE-related hospitalisation costs**									

	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-	-	-	-	-	£54,054	£59,797	Dominant	£89,595
12	**Removing half-cycle correction from the model**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-	-	-	-	-	£51,432	£57,790	Dominant	£84,139
13	**Using first-order FP OS curve with a power of -0.5 (compared to p = -1.5)**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-	-	-	-	-	£42,065	£44,258	Dominant	Dominated

Abbreviations: ABE, abemaciclib; AE, adverse event; BEV, bevacizumab; CAP, capecitabine; EVE, everolimus; EXE, exemestane; FUL, fulvestrant; FP, fractional polynomial; ICER, incremental cost-effectiveness ratio; LD, loading dose; LY, life years; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; PPS, post-progression survival; QALYs, quality-adjusted life years; TMX, tamoxifen; TTD, time to treatment discontinuation.
*This refers to CAP instead of TMX for the scenarios using the ERG's analysis of treatment effectiveness (1 and 13)

6.3 ERG base case ICER

In this section the ERG reports two ICERs reflecting two different scenarios for treatment effectiveness. One scenario assumes a bigger survival benefit for ABE-FUL compared with the other treatments, while the other portrays a more conservative scenario.

The ERG caveats the analysis presented with the very high degree of uncertainty embedded in the analysis of OS through the HR or FP NMA. This is mainly related with the lack of maturity of the MONARCH 2 OS data and thus on the survival benefit related with ABE-FUL when compared with FUL (and therefore, the other comparators included in the NMAs). The ERG's analysis is also caveated by the fact the TTD curve for ABE-FUL was estimated based on a HR derived from the comparison of PFS and TTD data in the ITT population of MONARCH 2. Nonetheless, as discussed throughout the report, using the ITT TTD data underestimates the costs of ABE-FUL in the model. Alternatively, the ERG recommends that the company provides the 150mg TTD data so that these can be used in the economic analysis.

The ERG's assumptions included in the analysis (and listed in the previous section) are the following:

2. The ERG replaced the company's OS and PFS FP NMA-derived curves by the ones estimated by the ERG using the FP NMA approach (PFS power of 0; OS power of -1.5). This also includes the TTD curves estimated by the ERG;

14. The ERG used the utility value for first-line therapy in Mitra *et al.* 2016 [0.77] and the second, third or later line utility in Mitra *et al*. 2016 [0.69]) to estimate a relative decrement to be applied to the PFS utility value from MONARCH 2 ([redacted]), in order to estimate the PPS utility ([redacted]);

15. The ERG removed AE-related disutilities from the model;

16. The ERG ran a scenario analysis including age-related utility decrements, using the published algorithm by Ara and Brazier 2010;[116]

17. The ERG used a set of alternative distributions for subsequent treatments received in the model, which have been validated by its clinical experts;

18. The ERG assumed that patients would receive subsequent treatments for the entire time spent on PPS, with the exception of the last 3 months;

19. The ERG caped the time patients could spend on FUL and EXE-EVE as subsequent treatments;

20. The ERG ran a scenario analysis including the resource use associated with follow-up care accepted in TA496;

21. The ERG ran a scenario analysis including the resource use associated with FUL administration costs accepted in TA496, and applied it for every cycle of FUL treatment in the model;

22. The ERG ran a scenario analysis excluding the cost of non-AE-related hospitalisations from the analysis;

23. The ERG removed the half-cycle correction from the model;

24. The ERG included the first-order FP OS curve with a power of -0.5. This scenario includes the ERG's FP NMA for PFS and the ERG's estimated TTD curves.

The ERG used Mitra *et al.* 2016 data to estimate the PPS-related utility in the base case analysis. However, the ERG provides all the relevant permutations of the ERG's base case ICERs using the alternative PPS utility value from MONARCH 2 in the economic analysis. Furthermore, given the uncertainty around the estimation of the PFS vs TTD HRs for ABE-FUL, the ERG ran a deterministic scenario analysis, with the aim of exploring the sensitivity of the final ICERs to variations in the parameter. The ERG also conducted deterministic sensitivity analysis on the assumption made for the time patients spend on FUL and EXE-EVE subsequent treatments. All these results are provided in a confidential appendix, including the everolimus PAS.

Results of the ERG analysis are reported in Table 55. The final ABE-FUL ICERs, compared with FUL and EXE are £70,634 and £63,436 per QALY gained, respectively, with the ICER against EXE-EVE being dominant and the ICER against CAP being dominated, for the more conservative OS analysis (i.e. using the OS FP with p=-0.5). The corresponding values using the FP OS curve with p=-1.5 are £52,351 and £52,002 for ABE-FUL compared with FUL and EXE. The ICER against EXE-EVE remained dominant (with ABE-FUL being associated [redacted] than EXE-EVE) and the ICER against CAP remained dominated, (with ABE-FUL being associated [redacted] than CAP). However, the FP NMA results for CAP are likely to be an overestimation of the drug's effectiveness, and so all ICERs against CAP should be interpreted with caution.

For completeness, the ERG ran the two alternative analyses with the PFS and PPS-related utility values from MONARCH 2 ([redacted] vs [redacted]), respectively, instead of using the Mitra *et al*. 2016 [0.69] value. The final ABE-FUL ICERs, compared with FUL and EXE are £80,604 and £68,116 per QALY gained, respectively, with the ICER against EXE-EVE being dominant, and the ICER against CAP remaining dominated, for the more conservative OS analysis (i.e. using the OS FP with p=-0.5). The corresponding

values using the FP OS curve with p=-1.5 are £55,448 and £54,038 for ABE-FUL compared with FUL and EXE. The ICERs against EXE-EVE and CAP remained dominant and dominated, respectively.

Table 56 and Table 57 present the results for the ERG's deterministic sensitivity analysis. Table 56 shows the impact on the final ICER when the HR used to estimate TTD curves (from the PFS curves) for ABE-FUL is varied. The ERG decreased the HR by 5%, 10% and finally assumed that the TTD and PFS curves for ABE-FUL would be the same (HR=1). The 5% and 10% reduction in the ERG's base case ICER ([redacted]) represents using HRs of [redacted] and, [redacted] respectively.

Varying the HR by 5% led to an increase in ICERs from £70,634 and £63,436 vs FUL and EXE, respectively to £78,996 and £67,391 per QALY gained. The ICER against EXE-EVE remained dominant and the ICER against CAP dominated, for the more conservative OS analysis (i.e. using the OS FP with p=-0.5), and using the Mitra et al, 2016 PPS utility. This shows that the model results are highly sensitive to small changes in the HR used to derive the ABE-FUL TTD curve in the model. When the HR was assumed to be 1, the ICERs for ABE-FUL vs FUL and EXE, rose to £120,775 and £87,152, respectively, per QALY gained.

The ABE-FUL ICER seem less sensitive to varying the time spent with FUL and EXE-EVE as subsequent treatments. When the ERG's decreased the time spent in FUL and EXE-EVE by 25% of the time used in the ERG's base case, the ICER for ABE-FUL vs FUL increased from £70,634 to £74,448, and it decreased from £63,436 vs EXE to £60,649 per QALY gained. The ICER against EXE-EVE remained dominant and the ICER against CAP dominated, for the more conservative OS analysis (i.e. using the OS FP with p=-0.5), and using the Mitra *et al*, 2016 PPS utility.

Table 55. ERG's exploratory analysis with all changes incorporated

	Results per patient	ABE-FUL (1)	FUL (2)	EXE (3)	EXE-EVE (4)	CAP* (5)	Incremental value			
							(1-2)	(1-3)	(1-4)	(1-5)
0	**Corrected base case**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	-					£50,687	£57,247	Dominant	£82,621**
1	**Using the ERG's FP NMA results for OS and PFS and adjusting TTD curves**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	-					£41,719	£44,089	Dominant	Dominated
3	**PPS utility using a -11% relative decrement (Mitra *et al*. 2016) on PFS utility**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	-					£92,990	£89,733	Dominant	£611,615**
	ICER with all changes incorporated	-					£52,288	£51,578	Dominant	Dominated
4	**Removed AE-related disutilities**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	-					£50,614	£57,183	Dominant	£82,451**
	ICER with all changes incorporated	-					£52,210	£51,525	Dominant	Dominated
5	**Age-related utility decrements included**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	**-**					£51,757	£58,360	Dominant	£84,299**
	ICER with all changes incorporated	-					£53,668	£52,778	Dominant	Dominated
6+7 +8	**Post-progression treatment in PPS from 37% to up to 3 months before death**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	[redacted]					£29,786	£53,150	Dominan	£8,384**
	ICER with all changes incorporated	**-**					£45,168	£46,116	Dominant	Dominated
9	**TA496 health state costs**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	-					£62,737	£65,459	Dominant	£111,549**
	ICER with all changes incorporated	-					£47,885	£45,994	Dominant	Dominated
10	**TA496 FUL administration costs**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	**-**					£52,348	£59,546	Dominant	£88,566**
	ICER with all changes incorporated	**-**					£49,254	£47,637	Dominant	Dominated
11	**Removing non-AE-related hospitalisation costs**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	**-**					£54,054	£59,797	Dominant	£89,595**

	ICER with all changes incorporated	**-**					£50,725	£48,406	Dominant	Dominated
12	**Remove half-cycle correction**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	-					£51,432	£57,790	Dominant	£84,139**
	ICER with all changes incorporated	-					£52,351	£52,002	Dominant	Dominated
13	**Using first-order FP OS curve with a power of -0.5 (compared to p = -1.5)**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	**-**					£42,065	£44,258	Dominant	Dominated
	ICER with all changes incorporated	**-**					£70,634	£63,436	Dominant	Dominated

Abbreviations: ABE, abemaciclib; AE, adverse event; BEV, bevacizumab; CAP, capecitabine; EVE, everolimus; EXE, exemestane; FUL, fulvestrant; FP, fractional polynomial; ICER, incremental cost-effectiveness ratio; LD, loading dose; LY, life years; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; PPS, post-progression survival; QALYs, quality-adjusted life years; TMX, tamoxifen; TTD, time to treatment discontinuation.
*This refers to TMX instead of CAP for the scenario using the company's corrected base case (0)
**ABE-FUL is compared to TMX instead of CAP when the ICER is compared with the base case

Table 56. Using alternative HRs to estimate TTD curve for ABE-FUL (with FP OS power of -0.5, and Mitra *et al* 2016 PPS utility)

	Results per patient	**ABE-FUL (1)**	**FUL (2)**	**EXE (3)**	**EVE-EXE (4)**	**CAP (5)**	**Incremental value**			
							(1-2)	**(1-3)**	**(1-4)**	**(1-5)**
0	**ERG base case**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-	-	-	-	-	£70,634	£63,436	Dominant	Dominated
a	**HR=1 for PFS vs TTD curve**									

	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-	-	-	-	-	£120,775	£87,152	Dominant	Dominated
b	**Reduce HR by 5% ([redacted])**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-	-	-	-	-	£78,996	£67,391	Dominant	Dominated
c	**Reduce HR by 10% ([redacted])**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-	-	-	-	-	£88,353	£71,817	Dominant	Dominated

Table 57. Varying the time patients spend on FUL and EXE-EVE as subsequent treatments (with FP OS power of -0.5, and Mitra *et al* 2016 PPS utility)

	Results per patient	**ABE-FUL (1)**	**FUL (2)**	**EXE (3)**	**EVE-EXE (4)**	**CAP (5)**	**Incremental value**			
							(1-2)	**(1-3)**	**(1-4)**	**(1-5)**
0	**ERG base case**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-	-	-	-	-	£70,634	£63,436	Dominant	Dominated
d	**Decreasing time spent in FUL and EXE-EVE as subsequent treatments by 5%**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-	-	-	-	-	£70,634	£63,477	Dominant	Dominated
e	**Decreasing time spent in FUL and EXE-EVE as subsequent treatments by 10%**									

	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-	-	-	-	-	£72,634	£63,518	Dominant	Dominated
f	**Decreasing time spent in FUL and EXE-EVE as subsequent treatments by 25%**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-	-	-	-	-	£74,448	£60,649	Dominant	Dominated
Abbreviations: ABE, abemaciclib CAP, capecitabine; EVE, everolimus; EXE, exemestane; FUL, fulvestrant; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; ToT, time on treatment										

7 END OF LIFE

The company did not consider ABE-FUL to be an end of life treatment.

8 OVERALL CONCLUSIONS

The ERG disagrees with the company's decision to use the HR NMA in their base case analysis, given that PHs are unlikely to hold across the network of studies included in the relative treatment analysis.

The ERG considers the company's method employed to run the FP NMA to have considerable limitations and notes that the results of the company's analysis are clinically implausible given that ~35% of ABE-FUL patients were considered cured at 30 months in the company's FP NMA-derived PFS curve and that ~15% of ABE-FUL, FUL and TMX patients live forever in the company's model. The plateau of the OS curves is clearly implausible, and given that it occurs at ~15%, compared to the plateau in PFS curves at ~35%, it also means that PFS and OS curves cross quite markedly. Therefore, the ERG ran its own analysis of relative treatment effectiveness, using the FP NMA approach.

The ERG is concerned with the high degree of uncertainty embedded in the OS analysis of relative treatment effectiveness of ABE-FUL compared with all other treatments. Given the immaturity of OS data in MONARCH 2, the ERG advises caution when interpreting all analysis undertaken involving these data. Furthermore, the costs of ABE-FUL are likely to be considerably underestimated in the economic analysis, given the discrepancy in the ITT TTD and the 150mg TTD data in MONARCH 2. This uncertainty is propagated through the economic analysis and thus, all the final ICERs. Unfortunately, the company's model does not capture this uncertainty, given that the PSA ran for the HR NMA base cases analysis is flawed, and that the FP NMA analyses did not include PSA.

The key drivers of the economic analysis are: the method used to estimate relative treatment effectiveness in the model (i.e. HR NMA vs FP NMA); the assumptions made around the estimation of TTD curves (and the consequent separation of TTD and PFS curves for ABE-FUL); the assumptions around subsequent treatments received and duration of the latter; the follow-up and CAP cost assumptions; and finally, the PPS-related utility value used in the analysis.

8.1 Implications for research

The ERG considers studies comparing abemaciclib plus fulvestrant versus other interventions used in clinical practice to treat HR+/HER2– aBC would add to the evidence base. Additionally, more mature data on the effect of abemaciclib plus fulvestrant on OS are required.

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10 APPENDICES

10.1 SLR eligibility criteria

Table 58. Eligibility (PICOS) criteria for SLR (reproduced from CS appendix D, Table 16)

Domain	Inclusion Criteria	Exclusion Criteria
Patient population	Adult females (≥ 18 years) Post-menopausal: via natural, surgical or ovarian suppression (GnRH) means. (Studies reporting on exclusively pre-menopausal patients were excluded. Studies where menopausal status was not reported were not excluded) HR+ (≥ 50% of study population reported as HR+) Locally advanced disease not amenable to curative treatment by surgery, or MBC Participants must fulfil at least one of the following: Relapsed with progression whilst receiving neo-adjuvant or adjuvant ET, with no subsequent ET received following progression Relapsed with progression within 12 months from completion of adjuvant ET, with no subsequent ET received following progression Relapse with 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 (AI) as first-line ET for metastatic disease. (Participants may not have received more than one line of chemotherapy for advanced disease) Presented de novo with metastatic disease and then relapsed with progression after receiving treatment with either an anti-oestrogen or an NSAI as first-line ET for metastatic disease	Studies with an exclusively pre-menopausal population were excluded Studies with populations of <50% with HR+ status Patients with >1 line of chemotherapy in the advanced setting
Intervention	Abemaciclib (single agent or combination therapy)	-
Comparator	For inclusion studies must have compared to at least one other listed treatment or placebo. Combinations of comparators that are not specified in the list below were not considered as comparators of interest. **ET – monotherapy** anastrozole exemestane fulvestrant letrozole megestrol acetate tamoxifen toremifene **Chemotherapy – monotherapy**	Combinations of comparators that are not specified in the inclusion criteria were not considered as comparators of interest.

	capecitabine docetaxel doxorubicin doxorubicin, liposomal eribulin gemcitabine paclitaxel paclitaxel, nanoparticle bound vinorelbine **Targeted therapy – monotherapy** Buparlisib Ribociclib **Combination chemotherapy** AC (doxorubicin and cyclophosphamide) CAF (cyclophosphamide and doxorubicin and fluorouracil) docetaxel and capecitabine gemcitabine and carboplatin gemcitabine and paclitaxel **Combination endocrine and targeted therapy** exemestane and everolimus palbociclib and fulvestrant palbociclib and letrozole palbociclib and anastrozole palbociclib and exemestane palbociclib, everolimus and exemestane palbociclib and tamoxifen ribociclib and fulvestrant ribociclib and letrozole ribociclib and anastrozole ribociclib and exemestane ribociclib and capecitabine ribociclib and tamoxifen buparlisib and tamoxifen buparlisib and paclitaxel buparlisib, ribociclib and letrozole **Combination chemotherapy and targeted agent** Paclitaxel and bevacizumab	
Outcomes	**Efficacy** Overall survival (OS) Progression-free survival (PFS) Progressive disease (PD) Partial response (PR) Complete response (CR) Stable disease (SD) Disease-free survival (DFS) Objective response rate (ORR) Disease control rate (DCR) Duration of response (DoR)	-

	Clinical benefit rate (CBR) **Safety** Grade 3 and 4 adverse events (AEs): Anaemia Bone pain Constipation Diarrhoea Fatigue/asthenia Febrile neutropenia Infections Leukopenia Nausea/ vomiting Neutropenia Pulmonary embolism Thrombocytoepenia Changes in blood creatinine levels Venous thromboembolism **Health-related quality of life (HRQoL)** EORTC QLQ-C30 FACT-B EQ-5D	
Study design	Randomised controlled trials (RCTs) Non-randomised studies (NRS) No language limit was applied to studies	Maximum tolerated dose studies / dose-escalation studies Dose limiting toxicity studies Pharmacokinetic / treatment mechanism studies Case studies and case series (not designed to compare clinical effectiveness) Commentaries Cytological studies
Other	No language limit applied to studies	-

Abbreviations: AE, adverse event; AI, aromatase inhibitor; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; EQ-5D, EuroQoL-5 Dimensions; FACT-B, Functional Assessment of Cancer Therapy – Breast; GnRH, gonadotrophin-releasing hormone; HR, hormone receptor; HRQoL, health-related quality of life; MBC, metastatic breast cancer; NRS, non-randomised studies; NSAI, non-steroidal aromatase inhibitor; RCT, randomised controlled trial.

10.2 Trial conduct MONARCH 2

Table 59. Summary of MONARCH 2 methodology (reproduced from CS, Table 5, pgs 33-38)

Location	Multicentre
Trial Design	Phase III, randomised, double-blinded, placebo-controlled study of ABE-FUL for advanced HR+/HER2− breast cancer that has progressed on or after prior endocrine therapy Patients were randomly assigned to receive ABE-FUL or PBO-FUL in a 2:1 ratio, using an interactive, web-based randomisation scheme (IWRS). Randomisation was stratified according to: metastatic site (visceral, bone only, or other) and ET resistance (primary or secondary): Primary ET resistance, as defined by ESMO guidelines, includes patients whose disease relapsed while receiving the first 2 years of neoadjuvant or adjuvant ET or progressed while receiving the first 6 months of ET for advanced breast cancer.[122] Patients who were not considered to have primary ET resistance were defined as having secondary resistance This was a double-blind study; patients, investigational sites, and the sponsor study team did not have immediate access to treatment assignments for any patients, except in emergency (see below). A minimum number of study personnel had access to treatment assignments prior to the primary PFS analysis. Access to unblinded data/documents was restricted. Efficacy information was not shared with sites until the study was completed. Upon overall study completion, investigators may have unblinded patients to study treatment assignment. In case of an emergency, the investigator had the sole responsibility for determining whether unblinding of a patient's treatment assignment was warranted. Patient safety must have always been the first consideration in making such a determination. Emergency unblinding for AEs was performed through the IWRS.
Eligibility criteria for participants	Women with HR+/HER2− locally advanced or metastatic BC who had progressed while receiving neoadjuvant or adjuvant endocrine therapy (ET), ≤12 months from the end of adjuvant ET, or while receiving first-line ET for metastatic disease.
Settings and locations where the data were collected	MONARCH 2 was an international, multicentre trial conducted in 142 centres across 19 countries, including Australia, Belgium, Canada, Denmark, Finland, France, Germany, Italy, Japan, Republic of Korea, Mexico, Poland, Puerto Rica, Romania, Russia, Spain, Switzerland, Taiwan and United States of America
Trial drugs	Patients received 500 mg fulvestrant by IM injection on Days 1 and 15 of the first cycle, and on Day 1 of subsequent cycles (every 28 days) Patients received abemaciclib or placebo twice daily during each 28-day cycle At study initiation, patients in the abemaciclib arm received 200 mg twice daily After a review of preliminary safety data and dose reduction rates from a Phase I study (I3Y-MC-JPBH [Phase 1b]), and subsequent blinded, early trial level safety review (TLSR) of MONARCH 2, the protocol was amended to reduce the starting dose to 150 mg for new patients. All patients randomised to receive the 200 mg underwent a mandatory dose reduction to 150 mg; if they had not already been dose reduced. In study JPBH, there were patients that discontinued treatment early due to diarrhoea, and most patients did not complete one cycle of treatment at the 200 mg Q12H dose level; or either had a dose reduction or omission. This finding prompted an early blinded TLSR in the MONARCH 2 population, in which it was found that one third of patients required a dose modification in the first 28-day cycle (based on the 2:1 randomisation ratio, this may have corresponded up to half of the patients treated with abemaciclib). Treatment continued until progressive disease (PD), death, or patient withdrawal Dose interruptions and reductions of abemaciclib or placebo were permitted according to pre-specified dose-adjustment procedures for patients who exhibited treatment-related toxicities. Fulvestrant dose reductions were permitted per US label as determined by the investigator Patients were not permitted to switch treatment groups If either abemaciclib or placebo was discontinued, patients were permitted to continue receiving fulvestrant. If fulvestrant required discontinuation, patients were permitted to continue receiving abemaciclib or placebo

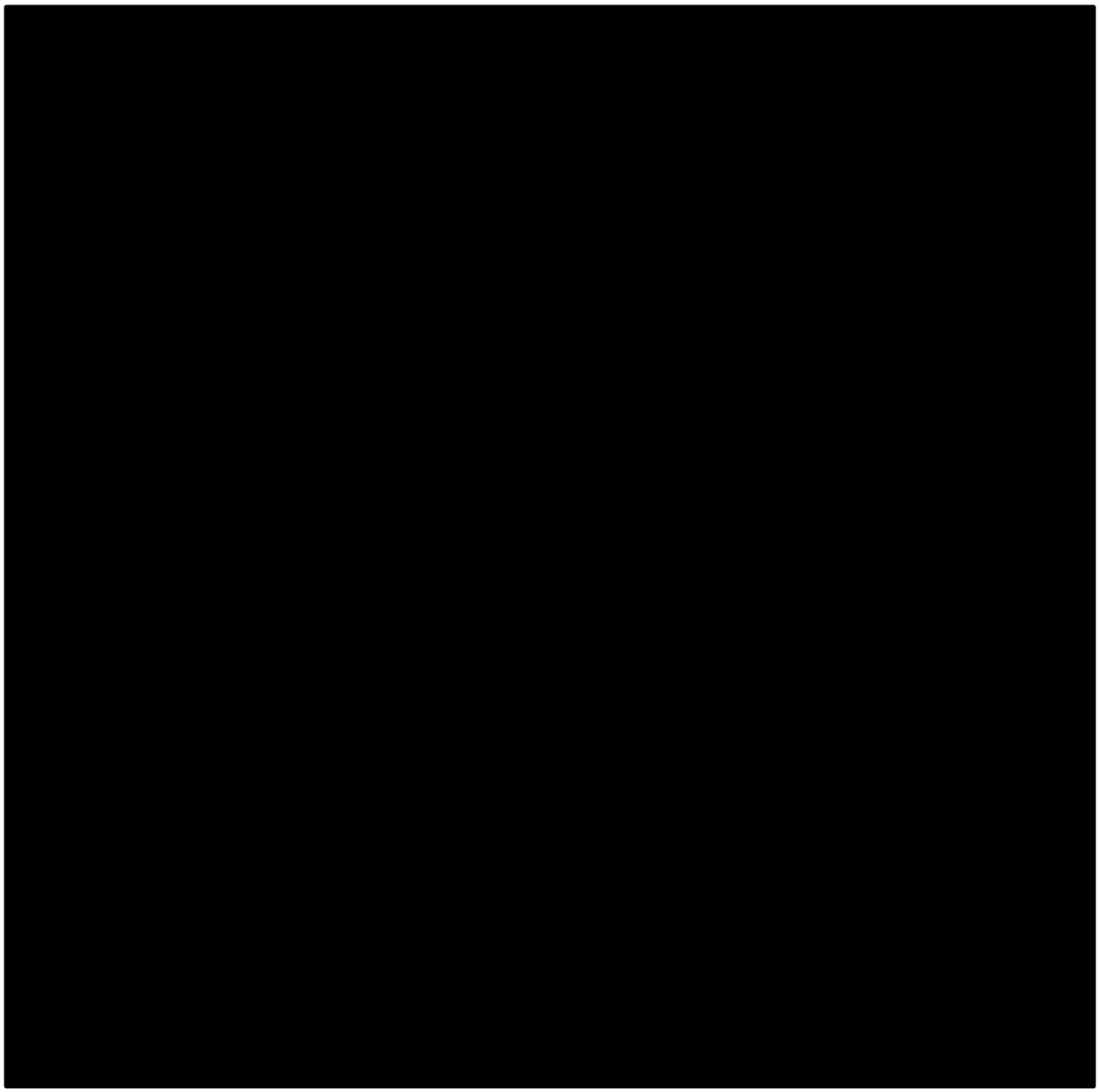
<table>
<tr><td rowspan="2">Permitted and disallowed concomitant medication[133]</td><td colspan="2">All forms of pre-medication, supportive care, and concomitant medications were recorded throughout each patient's participation in the study</td></tr>
<tr><td>Permitted therapies
Surgery and/or radiotherapy was permitted, but such patients did not receive study treatment in the period of 7 days prior and at least 14 days after surgery and/or radiotherapy
Full supportive care as judged by the treating physician
Growth factors (in accordance with ASCO guidelines)[134, 135]
Anti-diarrhoeal agents
Bisphosphonates or approved RANK-L targeted agents
Ovarian suppression with luteinising hormone-releasing hormone agonists for postmenopausal ovarian suppression</td><td>Prohibited therapies
Radiotherapy without concomitant surgery
Therapies for cancer not listed as permitted, including:
Aromatase inhibitors
Anti-oestrogens other than fulvestrant
Chemotherapy
Immunotherapy
Grapefruit juice, and inducers or strong inhibitors of CYP3A4
Bupropion
Efavirenz</td></tr>
<tr><td>Primary outcomes</td><td colspan="2">The primary efficacy measure was INV-assessed PFS as defined by the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1.[34] Tumour measurement images were collected and stored for all enrolled patients throughout the study. A blinded review of imaging scans was performed by an independent panel of radiologists.
PFS time was measured from the date of randomisation to the date of objective PD or death due to any cause, whichever was earlier. Baseline tumour measurements were performed on each patient within 28 days of randomisation by CT scans or MRI.
Tumour assessments were undertaken at baseline and approximately every 8 weeks for the first 12 months following randomisation and approximately every 12 weeks thereafter until the patient had objective disease progression, or until the primary analysis of PFS. Following objective PD, radiologic tests were no longer required, and the patient was followed up approximately every 12 weeks (±14 days) until death or overall study completion.
Bone-focussed imaging was performed in patients with bone lesions detected on baseline bone scintigraphy. Bone scintigraphy should have been repeated for all patients between Day 1 and Day 7 of every sixth cycle beginning with Cycle 7.
For those patients with non-measurable, bone-only disease, objective progression was established if at least one of the following criteria were met:
appearance of one or more new bone lesions (in bone or outside of bone), or
unequivocal progression of existing bone lesions
Pathological fracture, new compression fracture, or complications of bone metastases were not considered as evidence of disease progression, unless at least one of the above criteria were met.
For those patients with locally advanced disease for whom surgery was performed with no evidence of residual disease postoperatively, objective progression was established if at least one of the following criteria were met:
local recurrence
new development of metastatic disease
For patients with locally advanced disease for whom surgery was performed with evidence of residual disease postoperatively, new baseline measurements should have been taken and RECIST version 1.1 applied.[34]
If it was not known whether a patient had progressed or died at the time of analysis, PFS was censored at the last known progression-free assessment</td></tr>
<tr><td>Other outcomes used in the economic model/specified in the scope</td><td colspan="2">All efficacy and safety, and PROs, were pre-specified
Efficacy
OS: the time from the date of randomisation to the date of death from any cause
ORR: the proportion of patients with CR or PR according to RECIST version 1.1[34]
DCR: the proportion of patients with CR, PR, or SD according to RECIST version 1.17
DoR: the time from the date of first evidence of a confirmed CR or PR to the date of objective progression or death from any cause, whichever was earlier
CBR: the proportion of patients with CR, PR, or SD ≥6 months according to RECIST version 1.17
Safety</td></tr>
</table>

	During the study, all AEs were recorded and graded at every visit according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Any AEs resulting in dose reduction or discontinuation of treatment was reported and noted SAEs were defined as any adverse event that resulted in one of the following outcomes: Death A life-threatening experience (that is, immediate risk of dying) Persistent or significant disability/incapacity Initial or prolonged inpatient hospitalisation Congenital anomaly/birth defect Considered significant by the investigator for any other reason Patient-reported outcomes Pain intensity Responses for the modified Brief Pain Inventory-Short Form (mBPI-sf) items were captured through the use of 11-point numeric rating scales anchored at 0 (no pain or does not interfere) and 10 (pain as bad as you can imagine or completely interferes). Focused analysis was on “worst pain”. Use of pain medication was assessed, and data on each individual prescription and over-the-counter analgesic medication was recorded as per protocol. EORTC QLQ-C30 The EORTC QLQ-C30 questionnaire was administered as per protocol Response options for EORTC QLQ-C30 items 1 through 28 were "Not at all", "A little", "Quite a bit", and "Very much". Responses to EORTC QLQ-C30 Items 29 and 30 "Overall health" and "Quality of life" were defined on a 7-point scale ranged from 1 "Very poor" to 7 "Excellent" These responses were transformed resulting in a 0 through 100 continuums with higher score representing a higher ("better") level of functioning (physical, role, emotional, cognitive, social) or QoL; or a higher ("worse") level of symptoms or financial difficulty EQ-5D-5L The EQ-5D-5L is designed to be used in conjunction with other patient-reported measures and primarily of use in cost-effectiveness analyses Patients completed the 5-dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), 5-level (no problem, slight, moderate, severe, or extreme problem) assessment to provide data used for the development of patient-level utility measures. The EQ-5D-5L data were scored as described by van Hout et al (2012)[103] (EQ-5D-5L to EQ-5D-3L crosswalk) Patients also completed EQ-5D-5L visual analogue scale (VAS) "thermometer" measuring "Your health today" on a 100-point scale ranged from 0 "Worst health you can imagine" to 100 "Best health you can imagine”. Resource Utilisation Investigators were asked to report the use of concomitant medications (in particular, analgesics, bisphosphonates, and RANK-L targeted agents), blood product transfusions, radiation therapy, surgery and hospitalisation days
Pre-planned subgroups	Subgroup analyses of PFS were performed for each of following potential prognostic subgroup variables: All baseline stratification factors Starting dose (200 mg vs 150 mg) Measurable disease at baseline (yes vs no) Number of organs involved (1 vs 2 vs 3+) Age (<65 years vs ≥65 years) Region (North America, Europe, and Asia) Race (Caucasian, Asian, and Other) Progesterone receptor (PgR) status (positive vs negative) Where available, subgroup analyses of OS were to be performed as described for PFS

Abbreviations: AE, adverse event; AI, aromatase inhibitor; ASCO, American Society of Clinical Oncology; BOR, best overall response; CBR, clinical benefit rate; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; CYP3A4, Cytochrome P450 3A4; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; ET, endocrine therapy; EQ-5D-5L, EuroQol 5-Dimension; INV, investigator; NSAI, non-steroidal aromatase inhibitor; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PgR, progesterone receptor; PR, partial response; PS, performance status; RANK-L, receptor activator of nuclear factor kappa-B ligand; RECIST, Response Evaluation Criteria in Solid Tumours; SAE, serious adverse event; SD, stable disease; TEAE, treatment emergent adverse event; TLSR, trial level safety review.

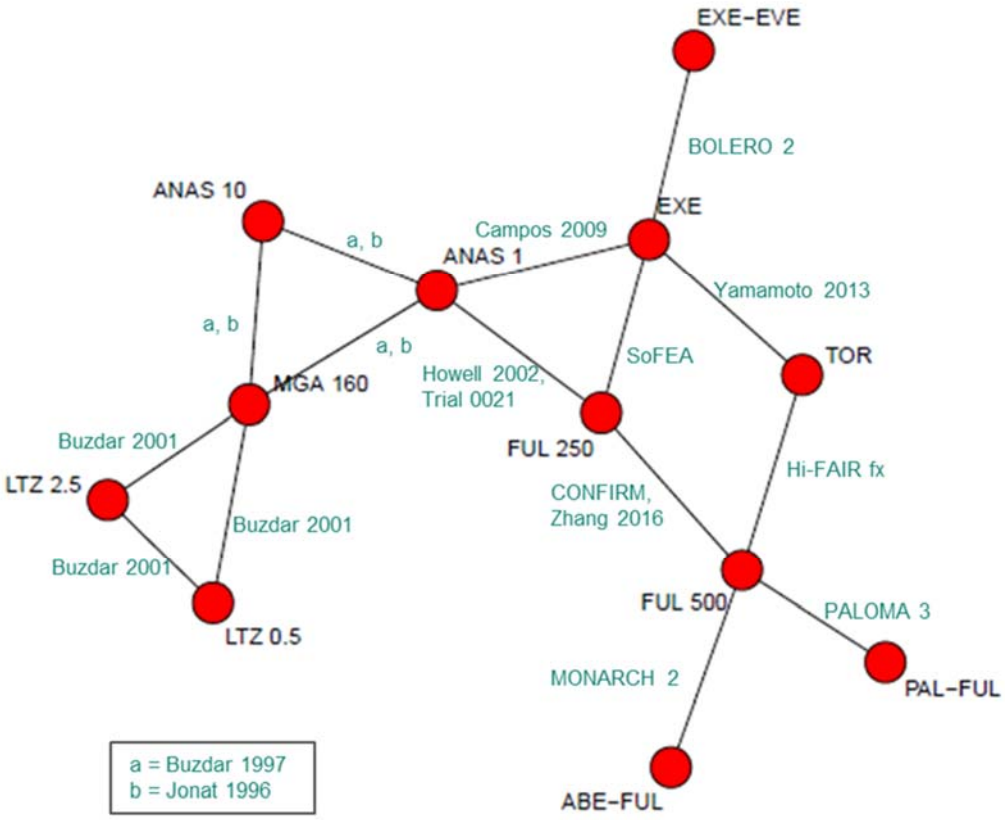
10.3 Patient flow diagram MONARCH 2

Figure 45. CONSORT diagram of participant flow in MONARCH 2 (reproduced from CS, Appendix K, Figure 12)



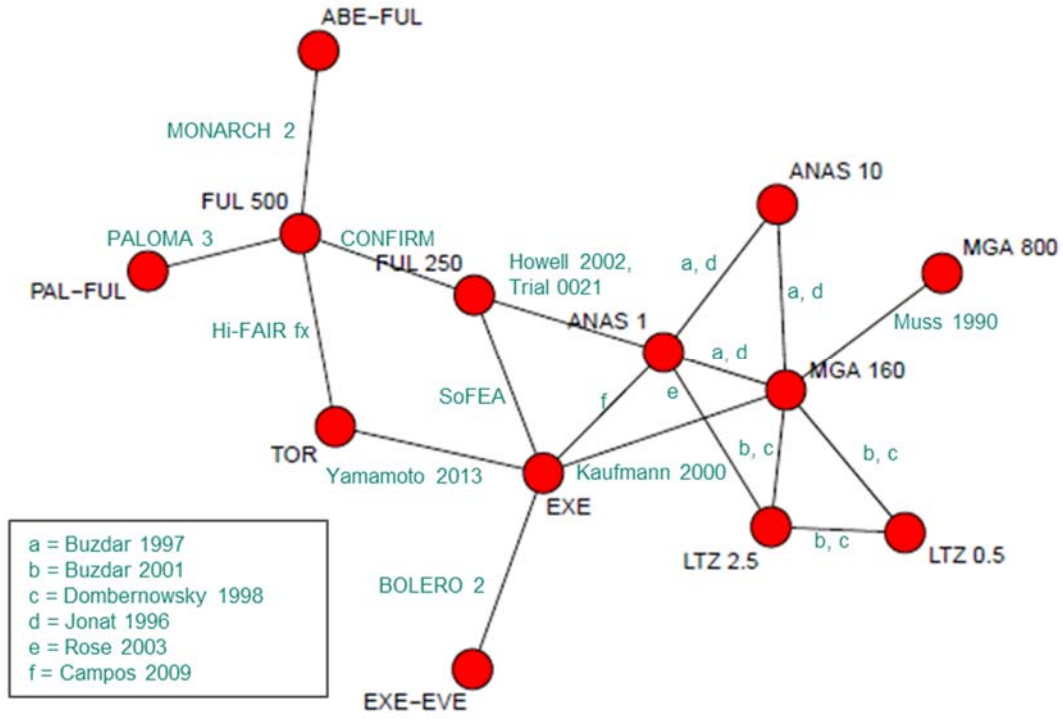
10.4 Networks for NMAs based on HRs and for binary outcomes

Figure 46. Network diagram for PFS (reproduced from CS Appendix D.1.3. Figure 4)



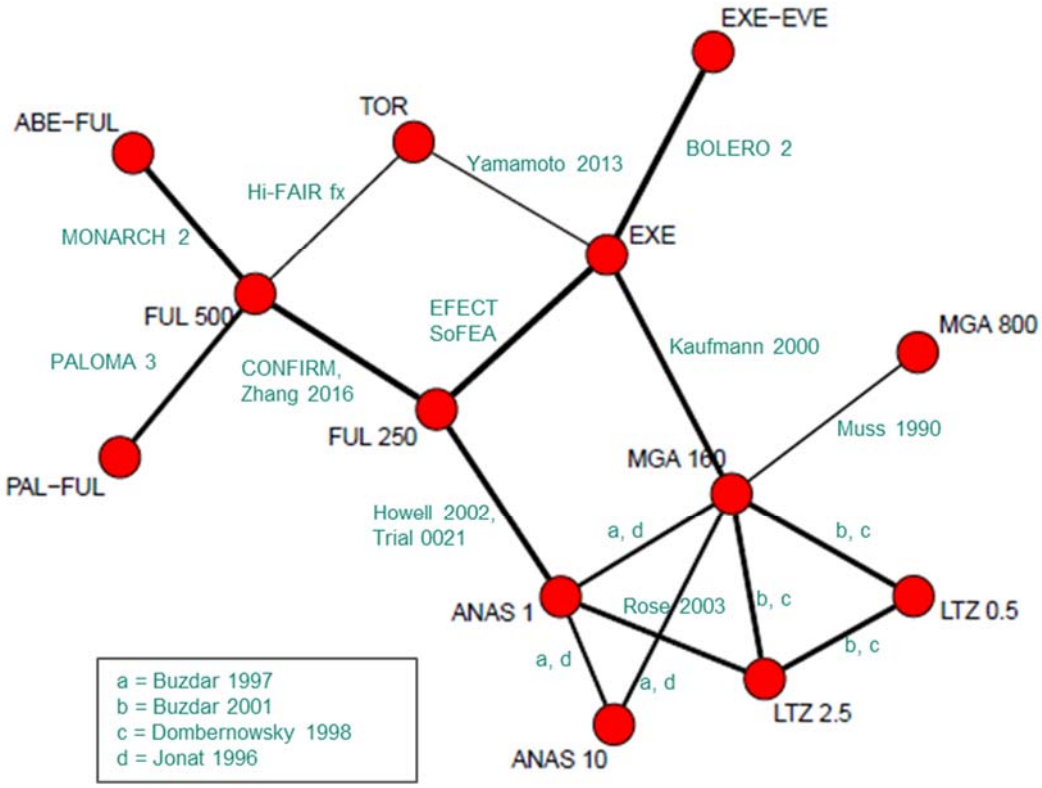
Abbreviations: ABE, abemaciclib; ANAS, anastrozole; EVE, everolimus; EXE, exemestane; FUL, fulvestrant; LTZ, letrozole; MGA, megestrol acetate; PAL, palbociclib; TOR, toremifene.

Figure 47. Network diagram for OS (reproduced from CS Appendix D.1.3. Figure 5)



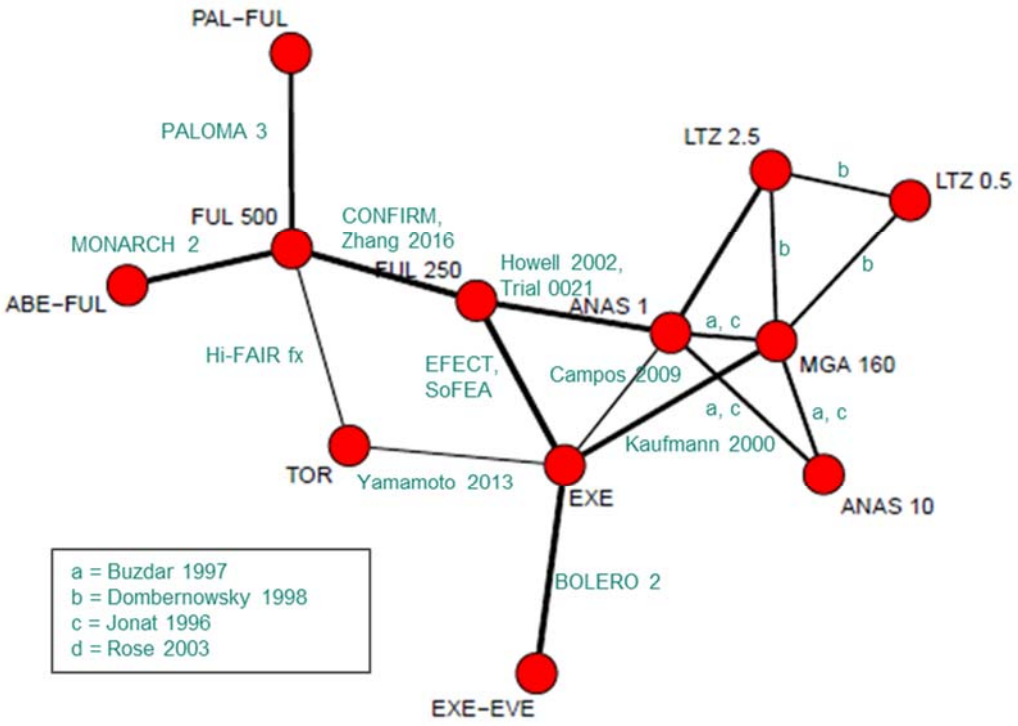
Eight studies included in the NMA had immature OS data: Buzdar 1997; Hi-FAIR fx; Howell 2002; Jonat 1996; PALOMA 3; Kaufmann 2000; Trial 0021; MONARCH 2.
Abbreviations: ABE, abemaciclib; ANAS, anastrozole; EVE, everolimus; EXE, exemestane; FUL, fulvestrant; LTZ, letrozole; MGA, megestrol acetate; PAL, palbociclib; TOR, toremifene.

Figure 48. Network diagram for ORR (reproduced from CS Appendix D.1.3. Figure 6)



Abbreviations: ABE, abemaciclib; ANAS, anastrozole; EVE, everolimus; EXE, exemestane; FUL, fulvestrant; LTZ, letrozole; MGA, megestrol acetate; PAL, palbociclib; TOR, toremifene.

Figure 49. Network diagram for CBR (reproduced from CS Appendix D.1.3. Figure 7)



Abbreviations: ABE, abemaciclib; ANAS, anastrozole; EVE, everolimus; EXE, exemestane; FUL, fulvestrant; LTZ, letrozole; MGA, megestrol acetate; PAL, palbociclib; TOR, toremifene..

10.5 Quality assessment

Table 60. Quality assessment of all included trials in the revised NMA (adapted from clarificatin response A4, Table 4)

		Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Blinding of care providers, participants and outcome assessors to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Other potential risks?
		Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.
BOLERO 2[53]	Company	Low	Low	Low	Low	Low	Low	Low	Yes
	ERG	Low	Low	Low	Low	Low	Low	Low	No
BOLERO 6[29]	Company	Low	High	Low	High	Low	Low	Low	No
	ERG	Low	Low	High	High	Low	Low	Low	No
CONFIRM[54]	Company	Low	Low	Low	Low	Low	Low	Unclear	No
	ERG	Low	Low	Low	Low	Low	Low	Low	No
Hi-FAIR fx[57]	Company	NR	NR	NR	NR	NR	NR	NR	NR
	ERG	Low	Unclear	Low	High	High	Low	High	Yes
Milla-Santos 2001[1]	Company	Low	Low	Low	Low	Unclear	Low	Unclear	No
	ERG	Low	Low	Low	Low	Unclear	Low	Low	No
MONARCH 2[27]	Company	Low	Low	Low	Low	Low	Unclear	Low	No
	ERG	Low	Low	Low	Low	Low	Low	Low	No
SoFEA[58]	Company	Low	High	Low	Unclear	Unclear	Unclear	Unclear	No
	ERG	Low	Low	Low	High	Low	Low	Low	No
Yamamoto 2013[59]	Company	Unclear	Unclear	Unclear	High	Unclear	Unclear	Unclear	No
	ERG	Low	Unclear	Low	High	Low	Low	Low	Yes
Zhang 2016[60]	Company	Unclear	Unclear	Low	Low	Low	Low	Unclear	No

	ERG	Low	Low	Low	Low	Low	Low	Low	No

10.6 Characteristics of included studies

Table 61. Summary of the methods of the included studies (adapted from CS Appendix D.1.2. Table 22)

Trial	Treatments	Study location	Primary endpoint	Phase	Blinded/ open-label
BOLERO-2[53]	EXE-EVE, EXE	Multicentre, International	PFS	III	Double-blind
BOLERO-6[29]	EXE-EVE, CAP	Multicentre, International	PFS	II	Open-label
CONFIRM[54]	FUL 500 mg, FUL 250 mg	Multicentre, international: 128 centres in 17 countries	PFS	III	Double-blind
Hi-FAIR fx[57]	TOR 120 mg, FUL 500 mg	NR	CBR	II	Open-label
Milla-Santos 2001[1]	TOR 60 mg, TMX	NR	CBR	III	Open-label
MONARCH 2[27]	ABE-FUL 500 mg, FUL 500 mg	Multicentre, International: in 19 countries	PFS	III	Double-blind
SoFEA[58]	FUL 250 mg, EXE	Multicentre: UK and South Korea	PFS	III	Open-label
Yamamoto 2013[59]	TOR 120 mg, EXE	Multicentre	CBR	II	Open-label
Zhang 2016[60]	FUL 500 mg, FUL 250 mg	China	PFS	III	Double-blind

Abbreviations: ABE, abemaciclib; ANAS, anastrozole; CBR, clinical benefit rate; EVE, everolimus; EXE, exemestane; FUL, fulvestrant; LTZ, letrozole; mg, milligrams; MGA, megestrol acetate; NMA, network meta-analysis; ORR, objective response rate; OS, overall survival; PAL, palbociclib; PFS, progression-free survival; SLR, systematic literature review; TOR, toremifene; TTP, time to progression.

Table 62. Eligibility criteria for the trials included in the revised NMA (adapted from clarification response A4, Table 1)

Study ID	Stage	CNS/ brain metastases permitted?	Visceral crisis permitted ?	HR/HER2 status	N prior ETs for aBC‡	N prior chemo-therapies for aBC‡
BOLERO-2 2012[53]	Advanced	No	-	HR+, HER2–	NS	≤1
BOLERO-6 2018[29]	Advanced	<2% of patients	-	HR+, HER2−	NS	NS
CONFIRM 2010[54]	Locally advanced or metastatic	No	-	HR+, HER2 NR	≤1	≤1
Hi-FAIR fx 2017[57]	Advanced or metastatic	-	-	HR+, HER2 NR	NS	NS
Milla-Santos 2001[1]	Advanced	-	-	HR+, HER2 NR	NS	NS

MONARCH 2[27]	Advanced	No	No	HR+, HER2–	≤1	None
SoFEA 2013[58]	Locally advanced or metastatic	-	No	HR+, HER2 NR	NS	≤1
Yamamoto 2013[59]	Metastatic	No	-	HR+, HER2 NR	NS	≤1
Zhang 2016[60]	Locally advanced or metastatic	-	No	HR+, HER2 NR	≤1	≤1
Abbreviations: BC, breast cancer; CNS, central nervous system; HER2, human epidermal growth receptor-2; HR, hormone receptor; NR, not reported; NS, not specified.						

Table 63. Blinding, PFS assessment and definition for the trials included in the revised NMA (adapted from clarification response A2, Table 1 and A4, Table 3)

Trial	Design	Data available	Definition of PFS/TTP
BOLERO-2[53]	Double blind	Local investigator Central review	PFS: date of randomisation to the date of first documented tumour progression or death from any cause, whichever occurs first
BOLERO-6[29]	Open label	Local Investigator	PFS: time from randomisation to first documented progression or death due to any cause
CONFIRM[54]	Double blind	NR	PFS: time elapsing between the date of random assignment and the date of the earliest evidence of objective disease progression or death from any cause before documented disease progression
Hi-FAIR fx[57]	Open label	NR	NR
Milla-Santos 2001[1]	Double blind	NR	TTP: NR
MONARCH 2[27]	Double blind	IA IRC	PFS: time from random assignment until objective PD or death for any reason
SoFEA[58]	Partially blinded - Participants and investigators were aware of assignment to FUL or EXE, but not of assignment to ANAS or placebo for patients in the groups assigned FUL	NR	PFS: time from randomisation to progression of existing disease, new sites of disease, secondary primary cancer or death from any cause
Yamamoto 2013[59]	Open label	NR	NR
Zhang 2016[60]	Double blind	NR	PFS: time from the first study visit (randomisation) to earliest objective disease progression, including death from any cause
Abbreviations: IA, investigator assessed; IRC, independent review centre; NR, not reported			

Table 64. Baseline characteristics for all trials included in the revised NMA (reproduced from clarification response A4, Table 6)

Study ID	Interventions	N	Age (years)					Menopausal status				ECOG/WHO performance status							
						Range		Pre-menopausal		Post-menopausal		0		1		2		≥3	
			Mean	Median	SD	Min	Max	n	%	n	%	n	%	n	%	n	%	n	%
BOLERO-2[53]	EXE-EVE	485	-	62	-	34	93	-	-	485	100	-	60	-	36	-	2	-	-
	EXE	239	-	61	-	28	90	-	-	239	100	-	59	-	35	-	3	-	-
BOLERO-6[29]	EXE-EVE	104	-	61	-	32	86	-	-	104	100	54	52	42	40	5	5	-	-
	EVE	103	-	61	-	38	88	-	-	103	100	48	47	50	49	3	3	-	-
	CAP	102	-	60	-	35	84	-	-	102	100	57	56	39	38	4	4	-	-
CONFIRM[54]	FUL 500 mg	362	-	61	-	-	-	-	-	362	100	-	-	-	-	-	-	-	-
	FUL 250 mg	374	-	61	-	-	-	-	-	374	100	-	-	-	-	-	-	-	-
Hi-FAIR fx[57]	TOR	53	-	64	-	44	83	-	-	53	100	46	86.8	-	-	-	-	-	-
	FUL 500 mg	52	-	65	-	44	91	-	-	52	100	44	84.6	-	-	-	-	-	-
Milla-Santos 2001[1]	TOR	106	61.3	-	-	56	75	-	-	106	100	74	70	19	20	7	10	-	-
	TMX	111	60.8	-	-	55	75	-	-	111	100	77	69	26	23	8	8	-	-
MONARCH 2[27]	ABE-FUL 500 mg	446	[redacted]	59	[redacted]	[redacted]	[redacted]	72	16.1	371	83.2	264	59.2	176	39.5	[redacted]	[redacted]	[redacted]	[redacted]
	FUL 500 mg	223	[redacted]	62	[redacted]	[redacted]	[redacted]	42	18.8	180	80.7	136	61	87	39	[redacted]	[redacted]	[redacted]	[redacted]
SoFEA[58]	FUL 250 mg	231	-	63.4	-	57	73.5	-	-	231	100	-	-	-	-	-	-	-	-
	EXE	249	-	66	-	59.2	75	-	-	249	100	-	-	-	-	-	-	-	-
Yamamoto 2013[59]	TOR	46	-	63	-	51	87	-	-	46	100	-	-	-	-	1	-	0	0
	EXE	45	-	62	-	49	87	-	-	45	100	-	-	-	-	1	-	0	0
Zhang 2016[60]	FUL 500 mg	111	53.6	55	10.1	26	80	0	0	111	100	-	-	-	-	-	-	0	0
	FUL 250 mg	110	53.1	55	10.2	31	76	0	0	110	100	-	-	-	-	-	-	0	0

Abbreviations: ABE, abemaciclib; ANAS, anastrozole; CAP, capecitabine; ER, oestrogen receptor; FUL, fulvestrant; EVE, everolimus; EXE, exemestane; TOR, toremifene; TMX, tamoxifen.

Table 65. Disease characteristics for the trials included in the revised NMA (reproduced from clarification response A4, Table 9)

Study	Intervention	N	ET resistance, %	Metastatic site, %			Measurable disease at baseline, %
				Bone	Visceral	Other	
BOLERO-2[53]	EXE-EVE	485	NR	76	56	Liver: 30	70
	EXE	239	NR	77	56	Liver: 33	68
BOLERO-6[29]	EXE-EVE	104	NR	13*	66	64	NR
	EVE	103	NR	16*	64	59	NR
	CAP	102	NR	24*	62	59	NR
CONFIRM[54]	FUL500	362	NR	NR	52.9	NR	NR
	FUL250	374	NR	NR	56.6	NR	NR
Hi-FAIR fx[57]	TOR	53	NR	NR	66	NR	NR
	FUL	52	NR	NR	55.6	NR	NR
Milla-Santos 2001[1]	TOR	106	NR	37.70	36.8	NR	NR
	TMX	111	NR	47	28	NR	NR
MONARCH 2[27]	ABE-FUL	446	Primary: 24.9 Secondary: 73.1	27.6*	54.9	16.8	71.3
	FUL	223	Primary: 26 Secondary: 73.1	25.6*	57.4	17	73.5
SoFEA[58]	FUL	231	NR	16	62	NR	NR
	EXE	249	NR	13	58	NR	NR
Yamamoto 2013[59]	TOR	46	NR	20	NR	Liver: 15.2	NR
	EXE	45	NR	31	NR	Liver: 13.3	NR
Zhang 2016[60]	FUL500	111	NR	NR	39	NR	51
	FUL250	110	NR	NR	47	NR	60

* Bone-only disease
Abbreviations: ABE, abemaciclib; AI, aromatase inhibitor; ANAS, anastrozole; CAP, capecitabine; ET, endocrine therapy; FUL, fulvestrant; EXE, exemestane: EVE, everolimus; NR, not reported.

Table 66. Prior therapy received by the patient populations of the trials included in the NMA (adapted from clarification response A4, Table 8)

Study	Intervention	N	Prior chemotherapy in the (neo)adjuvant setting, n (%)	Prior chemotherapy in the advanced setting, n (%)	Prior AI, n (%)	Most recent ET ([neo]adjuvant or metastatic), n (%)
BOLERO-2[53]	EXE-EVE	485	44	26	74[a]	Adjuvant therapy*: 21 therapy for metastatic disease*: 79
	EXE	239	40	26	75[a]	Adjuvant therapy*: 16 therapy for metastatic disease*: 84
BOLERO-6[29]	EXE-EVE	104	45	15	NR	NR
	EVE	103	42	19	NR	NR
	CAP	102	54	16	NR	NR
CONFIRM[54]	FUL500	362	51.1	22	NR	(Neo)adjuvant ET**: 48.3+4.4 ET for metastatic disease**: 35.9+9.9
	FUL250	374	53.5	18	NR	(Neo)adjuvant ET**: 45.2+7.2 ET for metastatic disease**: 33.4+13.9
Hi-FAIR fx[57]	TOR	53	42.8	13.2	100	(Neo)adjuvant ET: 22.6 ET for metastatic disease: 35.9+41.5
	FUL	52	34.2	11.5	100	(Neo)adjuvant ET: 15.4 ET for metastatic disease: 38.5+46.2
Milla-Santos 2001[1]	TOR	106	55.4	0	NR	NR
	TMX	111	61.3	0	NR	NR
MONARCH 2[27]	ABE-FUL	446	59.9	0.7	70.9	(Neo)adjuvant ET: 59 ET for metastatic disease: 38.3
	FUL	223	60.1	1.8	66.8	(Neo)adjuvant ET: 59.6 ET for metastatic disease: 38.1
SoFEA[58]	FUL250	231	NR	NR	NR	NR
	EXE	249	NR	NR	NR	NR
Yamamoto 2013[59]	TOR	46	NR	NR	100 (ANAS: 48 LTZ: 52)	TMX as prior therapy: 21

	EXE	45	NR	NR	100 (ANAS: 47 LTZ: 53	TMX as prior therapy: 24
Zhang 2016[60]	FUL500	111	88.3	22.5	47.7	Adjuvant ET: 45.0 ET for advanced disease: 25.2
	FUL250	110	85.5	18.2	42.7	Adjuvant ET: 38.2 ET for advanced disease: 20.9

[a] Most recent treatment was anastrozole or letrozole.
*Most recent therapy rather than specifically most recent ET therapy
** Progressed on rather than most recent ET
Abbreviations: ABE, abemaciclib; AI, aromatase inhibitor; ANAS, anastrozole; CAP, capecitabine; ET, endocrine therapy; FUL, fulvestrant; EXE, exemestane: EVE, everolimus; NR, not reported.

Table 67. Subsequent therapies received across the trials included in the revised NMA, where reported (reproduced from clarification response A4, Table 3)

Study	Intervention	N	Chemotherapy, n (%)	Endocrine Therapy, n (%)	Radiotherapy, n (%)	Targeted, n (%)	HER2 directed therapy, n (%)	Other, n (%)
BOLERO-6[29]	EXE-EVE	104	19	5	NR	NR	NR	NR
	EVE	103	19	10	NR	NR	NR	NR
	CAP	102	8	10	NR	NR	NR	NR
	TMX	111	NR	NR	NR	NR	NR	NR
CONFIRM[54]	FUL500	362	135 (37.3)	80 (22.1)	8 (2.2)	NR	0	4 (1.1)
	FUL250	374	142 (38.0)	74 (19.8)	8 (2.1)	NR	1 (0.3)	5 (1.3)
MONARCH 2[27]	ABE-FUL	446	Overall: [redacted] First subsequent line: [redacted]	Overall: [redacted] ([redacted]) First subsequent line: [redacted] ([redacted])	[redacted]	Overall: [redacted] ([redacted]) First subsequent line: [redacted] ([redacted])	NR	Overall: [redacted] ([redacted]) First subsequent line: [redacted] ([redacted])
	FUL	223	Overall: [redacted] First subsequent line: [redacted]	Overall: [redacted] First subsequent line: [redacted]	[redacted]	Overall: [redacted]First subsequent line: [redacted]	NR	Overall: [redacted] First subsequent line: [redacted]

Abbreviations: ABE, abemaciclib; CAP, capecitabine; FUL, fulvestrant; EVE, everolimus; EXE, exemestane; HER2, human epidermal growth factor receptor-2; TOR, toremifene; TMX: tamoxifen.

10.7 Proportional hazards assumption assessment

Table 68. Results of the weighted residual test for PFS and OS(adapted from CS, Appendix D.1.5. Table 27 and Table 28)

	Global test p-value	
Study	**PFS**	**OS**
BOLERO-2[53]	0.0049	0.1627
Buzdar 1997[43]	0.3009	0.2363
Buzdar 2001[42]	0.7978	0.7989
Campos 2009[52]	NR	NR
CONFIRM[54]	0.9286	0.8013
Dombernowsky 1998[48]	0.0073	0.8762
Howell 2002[50]	0.4206	NR
Jonat 1996[44]	0.1351	0
Kaufmann 2000[47]	NA	0.518
MONARCH 2[27]	[redacted]	[redacted]
Muss 1990[46]	NA	0.0084
Nishimura 2017 (Hi-FAIR fx)[57]	0.4073	0.6126
PALOMA 3[45]	0.0977	NR
Rose 2003[49]	NA	NR
SoFEA[58]	0.1157	0.5208
Trial 0021[51]	0.5833	NR
Yamamoto 2013[59]	0.2949	0.4571
Zhang 2016[60]	0.3167	NA

Abbreviations:CS, company submission; NA, not applicable; OS, overall survival; PFS, progression-free survival.

10.8 Fractional polynomial NMA statistics

10.8.1 Company's FP NMA statistics

Table 69. DIC statistics PFS – Fixed effects (reproduced from clarification response, separate document, Table 1)

Order	P1	P2	Dbar	pD	DIC	Rank
Second order	0	0	744.19	44.51	788.7	12
Second order	0	0.5	740.89	44.71	785.6	9
Second order	0	1	737.91	44.49	782.4	5
Second order	0	2	734.18	43.72	777.9	1
Second order	0	3	4.73E+12	-4.09E+12	6.49E+11	36
Second order	0.5	0.5	738.61	44.49	783.1	6
Second order	0.5	1	737.12	44.38	781.5	3
Second order	0.5	2	1.99E+11	5.95E+10	2.59E+11	34
Second order	0.5	3	3.25E+12	-2.41E+12	8.40E+11	38
Second order	-0.5	0	747.62	44.48	792.1	14
Second order	-0.5	0.5	743.22	44.58	787.8	10
Second order	-0.5	-0.5	752.19	44.71	796.9	19
Second order	-0.5	1	739.13	44.67	783.8	7

Second order	-0.5	2	3.63E+09	3.63E+09	7.26E+09	31
Second order	-0.5	3	4.75E+12	-3.75E+12	1E+12	40
Second order	1	1	737.38	44.52	781.9	4
Second order	1	2	2.68E+10	-1.32E+10	1.37E+10	32
Second order	1	3	3.52E+12	-2.00E+12	1.52E+12	43
Second order	-1	0	750.99	44.71	795.7	16
Second order	-1	0.5	745.71	44.79	790.5	13
Second order	-1	-0.5	756.08	44.72	800.8	23
Second order	-1	1	740.6	44.7	785.3	8
Second order	-1	-1	760.64	44.76	805.4	25
Second order	-1	2	1.77E+10	-2.28E+09	1.54E+10	33
Second order	-1	3	4.75E+12	-3.75E+12	1.00E+12	40
Second order	2	2	2.18E+12	-1.90E+12	2.82E+11	35
Second order	2	3	4.60E+12	-2.26E+12	2.34E+12	44
Second order	-2	0	755.63	44.57	800.2	21
Second order	-2	0.5	749.44	44.86	794.3	15
Second order	-2	-0.5	761.32	44.28	805.6	26
Second order	-2	1	743.16	44.74	787.9	11
Second order	-2	-1	766.32	44.08	810.4	28
Second order	-2	2	734.26	44.14	778.4	2
Second order	-2	-2	772.42	43.08	815.5	30
Second order	-2	3	2.78E+12	-2.12E+12	6.60E+11	37
Second order	3	3	7.71E+12	-6.55E+12	1.15E+12	42
First order	0	-	769.39	30.01	799.4	20
First order	0.5	-	766.76	30.04	796.8	18
First order	-0.5	-	773.03	29.97	803	24
First order	1	-	765.96	29.84	795.8	17
First order	-1	-	776.97	30.03	807	27
First order	2	-	770.83	29.37	800.2	21
First order	-2	-	783.01	29.79	812.8	29
First order	3	-	3.36E+12	-2.52E+12	8.40E+11	38

Table 70. DIC statistics OS – Fixed effects* (reproduced from clarification response, separate document, Table 3)

Order	P1	P2	Dbar	pD	DIC	Rank
Second order	0	0	1004.04	46.96	1051	7
Second order	0	0.5	1002.99	47.01	1050	3
Second order	0	1	1001.95	47.05	1049	1
Second order	0	2	4.85E+12	-4.03E+12	8.12E+11	39
Second order	0	3	7.26E+12	-6.76E+12	4.99E+11	29
Second order	0.5	0.5	1002.91	47.09	1050	3
Second order	0.5	1	1002.82	47.18	1050	3
Second order	0.5	2	4.08E+12	-3.16E+12	9.24E+11	41
Second order	0.5	3	7.558E+12	-7.002E+12	5.56E+11	30
Second order	-0.5	0	1005.3	46.7	1052	11
Second order	-0.5	0.5	1003.88	47.12	1051	7
Second order	-0.5	-0.5	1007.1	46.9	1054	17

Second order	-0.5	1	1001.85	47.15	1049	1
Second order	-0.5	2	2.48E+12	-1.76E+12	7.2E+11	36
Second order	-0.5	3	7.56E+12	-7E+12	5.56E+11	30
Second order	1	1	1004.82	47.18	1052	11
Second order	1	2	4.78E+12	-3.98E+12	7.99E+11	38
Second order	1	3	7.36E+12	-6.72E+12	6.4E+11	34
Second order	-1	0	1006.21	46.79	1053	14
Second order	-1	0.5	1005.08	46.92	1052	11
Second order	-1	-0.5	1008.4	46.6	1055	20
Second order	-1	1	1003.11	46.89	1050	3
Second order	-1	-1	1009.36	46.64	1056	23
Second order	-1	2	2.53E+12	-1.71E+12	8.2E+11	40
Second order	-1	3	7.56E+12	-7E+12	5.66E+11	32
Second order	2	2	5.62E+12	-4.86E+12	7.59E+11	37
Second order	2	3	7.4E+12	-6.7E+12	7E+11	35
Second order	-2	0	1007.76	46.24	1054	17
Second order	-2	0.5	1007.5	46.5	1054	17
Second order	-2	-0.5	1008.84	46.16	1055	20
Second order	-2	1	1006.51	46.49	1053	14
Second order	-2	-1	1009.5	45.5	1055	20
Second order	-2	2	4.936E+12	-3.784E+12	1.152E+12	43
Second order	-2	-2	1009.51	43.49	1053	14
Second order	-2	3	7.44E+12	-6.86E+12	5.8E+11	33
Second order	3	3	8.92E+12	-8.76E+12	1.6E+11	28
First order	0	-	1054.2	31.8	1086	25
First order	0.5	-	1068.25	31.75	1100	26
First order	-0.5	-	1029.33	31.67	1061	24
First order	1	-	1089.19	31.81	1121	27
First order	-1	-	1019.45	31.55	1051	7
First order	2	-	7.26E+12	-6.32E+12	9.4E+11	42
First order	-2	-	1019.97	31.03	1051	7
First order	3	-	Not possible to run			

* Table labelled as PFS random effects in the company's clarification response, which the ERG assumes is a miss-labelling based on the titles of the other tables in the document

10.8.2 ERG validation of company NMA statistics

Table 71. DIC statistics, ERG validation

Validation of company's FP NMA					
Second order FP					
P1	**P2**	**OS DIC**	**P1**	**P2**	**PFS DIC**
-1	-0.5	1053	-1	0	796
-0.5	-0.5	1054	-0.5	-0.5	797
-2	0	1055	-0.5	0	792
-1.5	0	1054	0	-1	796
-1	0	1053	0	-0.5	792
-0.5	0	1052	0	2	3.11E+11

0	-2	1055	0	1.5	781
0	-1.5	1054	0	1	783
0	-1	1054	0	0.5	786
0	-0.5	1052	0	0	789
2	0	2.20E+12	0.5	0	785
1	1	4.57E+11	0.5	0.5	783
1	0.5	1050	0.5	1	782
0.5	0.5	1051	1	0.5	782
1.5	0	1111	1	1	782
1	0	1049	1.5	1	784
0.5	0	1050	2	1	4.16E+11
0	0	1051			
0	0.5	1051			
0	1	1077			
0	1.5	1.28E+11			
First order FP					
0		1087			
0.5		1109			
1		9.20E+11			

10.8.3 ERG's FP NMA statistics

Table 72. DIC statistics for first and second order FPs for PFS and OS – Fixed effects

PFS simplified network		**OS simplified network**		**OS full network**	
Power	**DIC**	**Power**	**DIC**	**Power**	**DIC**
First order FPs					
-1	635	-2.5	776	-2.5	1065
-0.5	632	-2	774	-2	1059
0	631	-1.5	772	-1.5	1056
0.5	631	-1	773	-1	1059
1	7.27E+13	-0.5	781	-0.5	1068
		0	795	0	1087
		0.5	812	0.5	1109
		1	2.15E+14	1	9.20E+11
Second order FPs					
				P1	**P2**	
				-0.5	-1.5	1060
				-0.5	-1	1059
				-0.5	-0.5	1059
				-0.5	0	1057
				0	-0.5	1057
				0.5	-0.5	1056
				0.5	-1	1057
				0.5	-1.5	1058
				0.5	-2	1059

						0.5	-2.5	1061
Abbreviations: FP, fractional polynomial; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival.								

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Abemaciclib with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer after endocrine therapy [ID1339]

You are asked to check the ERG report from BMJ Group to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Monday 17 December 2018** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Factually Inaccurate Statements

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 29, "However, when compared with the TTD curves by starting dose of abemaciclib (i.e. 150mg vs 200mg populations) shown in Figure I, the ABE-FUL curve for the ITT population is considerably underestimating the time on treatment for patients receiving 150mg of abemaciclib … In fact, using the ITT TTD data leads to considerable underestimation of the ABE-FUL costs in the economic analysis." Page 143, "In fact, using the ITT TTD curve leads to a considerable underestimation of the ABE-FUL costs in the economic analysis."	Page 29, "However, when compared with the TTD curves by starting dose of abemaciclib (i.e. 150mg vs 200mg populations) shown in Figure I, the ABE-FUL curve for the ITT population ~~*is*~~ *appears to be* considerably underestimating the time on treatment for patients receiving 150mg of abemaciclib. *This would however need to be confirmed through survival analysis of the data* … ~~In fact,~~ Using the ITT TTD data ~~leads to considerable underestimation~~ *may underestimate* ~~of~~ the ABE-FUL costs in the economic analysis." Page 143, "~~In fact,~~ Using the ITT TTD curve may lead~~s~~ to a ~~considerable~~ *underestimation* of the ABE-FUL costs in the economic analysis."	In order to determine with certainty that the ABE-FUL curve for the ITT population is considerably underestimating the time on treatment for patients receiving 150 mg of abemaciclib, a survival analyses of the ITT and 150 mg groups would need to be conducted, and a comparison made between the curves. This would ensure any differences in sample size are taken into account and reflect the extrapolated TTD mean. A straightforward comparison of trial data between the populations is not sufficient to make this claim. In addition to this it should also be noted that the 150 mg data is immature relative to the ITT data and there is no statistically different between the two groups. Lilly would therefore kindly request that the ERG caveat this claim in the report – please see Lilly's proposed	The text has been amended in the report.

		amendment.	
Page 126, “Overall, using the company’s FP NMA leads to a considerable increase in all ICERs, compared with the company’s base case HR NMA.”	Page 126, “Overall, using the company’s FP NMA leads to a considerable increase in all ICERs, compared with the company’s base case HR NMA, when making the following assumptions regarding TTD: [ERG to insert assumptions].”	The increase in ICERs is also dependent upon the assumptions made regarding TTD.	Not a factual error. These analyses (the FP NMA and the HR NMA) use the company’s assumptions regarding the estimation of TTD.

Issue 2 Confidential marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 32, “during the trial period, [redacted] patients in the ABE-FUL arm and [redacted] patients in the FUL arm had a progression event (excluding death).”	The values of [redacted] and [redacted]) should be marked as AIC (the ERG has correctly marked these values as AIC on page 157).	These data are confidential.	The confidential marking will be updated as requested.
Unnecessary AIC marking in Table 14 on page 87, for the 150 mg ABE population (N=[redacted]).	AIC marking of N=320 should be removed.	NICE guidelines state that AIC marking should be kept to a minimum. This value is not confidential.	
Incorrect AIC marking on page 167: “the company estimated the proportion of patients expected to receive active therapy on disease progression as [redacted]/379 = [redacted].”	AIC highlighting should be added to ‘[redacted]’ and removed from ‘379’. AIC highlighting of ‘[redacted]’ should be retained.	The value of [redacted] is sourced from the MONARCH 2 CSR and is therefore confidential. The value of 379 is not confidential and should not be highlighted.	
Table 69, page 168: the number of PFS events for ABE-FUL and FUL should not be confidential.	AIC marking should be removed from the first row of Table 69.	NICE guidelines state that AIC marking should be minimised. This value is not confidential.	

Lack of AIC marking on Figures 19 to 23 (pages 110 to 116) and 39 to 42 (page 149 to 151).	Figures 19 to 23 and 39 to 42, which display NMA results for PFS and OS, should be highlighted in yellow to mark as AIC.	These figures display confidential PFS and OS data for ABE-FUL.	
Some confidential values in Table 35 on Page 165 are highlighted but not underlined.	All confidential values should be underlined as well as highlighted.	ACIC marking should be consistent to mark as confidential.	
Insufficient AIC marking in Table 68, page 231; the global test p-values for MONARCH 2 PFS ([redacted]) and OS ([redacted]) should both be highlighted and underlined.	Global test p-values for MONARCH 3 PFS and OS in Table 68 should be highlighted and underlined.	These data are confidential and should be highlighted and underlined to mark as confidential.	

Issue 3 General Errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
In Table A on Page 29, no precise source was given for median TTD data for ABE-FUL (ABE [redacted], FUL [redacted]), or FUL alone ([redacted]).	Please could the ERG clarify the precise source of median TTD from the MONARCH 2 trial, as Lilly were unable to verify these data.	This is necessary for transparency and accurate reporting of TTD data for ABE-FUL and FUL from the MONARCH 2 trial.	Not a factual error. The values in the ERG report are based on the company's reply to clarification question A7, Table 10 (with weeks converted to months).
There is inconsistency in reporting of data in Table B (page 29) and Table 26 (page 143): the HR is reported as [redacted] for ABE-FUL but PFS% at	This data should be consistent.	Inaccurate reporting of data.	The ERG thanks the company for pointing out the factual error. All the estimates should read 0.59, and these have been amended in the report.

median TTD reports [redacted].			
Inaccurate value in reporting on page 78, “Baseline scores for the five functional scales (physical, role, emotional, cognitive and social functioning) were all [redacted] and the baseline score for global health status was [redacted], in both treatment groups, indicating relatively high levels of functioning and QoL at baseline”	The value of ‘[redacted]’ should be replaced with ‘[redacted]’: “Baseline scores for the five functional scales (physical, role, emotional, cognitive and social functioning) were all [redacted] and the baseline score for global health status was [redacted], in both treatment groups, indicating relatively high levels of functioning and QoL at baseline”	Incorrect reporting of HRQoL data.	Not a factual error. The lowest baseline values were for [redacted], with a baseline score of [redacted] for ABE-FUL and [redacted] for PBO-FUL, both less than [redacted] but higher than [redacted].
In Table 15 (page 90), it appears that the ERG are suggesting Zhang 2016 data are used in the OS network, which is incorrect. Zhang 2016 does not present OS data.	In Table 15, there should be a red cross instead of a tick for Zhang 2016 in the OS limited network, to report that it was not used.	Inconsistent reporting of NMA methods. Zhang 2016 does not report OS data, and therefore this must be an error.	The ERG thanks the company for highlighting this factual error, which has been corrected in the report.
Incorrect referencing to data from the CS in the caption of Table 16 of the ERG report, page 100: “Adjusted indirect comparison results for TMX vs FUL 500 mg based on Milla-Santos 2001 and the HR NMA (adapted from CS Table 23)”	The caption should refer to Table 16 of the CS.	The caption refers the reader to the incorrect table.	The ERG thanks the company for highlighting this factual error, which has been corrected in the report.
The caption for Table 27 (Page	The caption should be changed to “Hazard	Misleading table caption; the	The ERG thanks the company

148) is incorrect; the HRs in the table are for OS, not PFS.	ratios (95% credible interval) for OS"	caption should reflect the presented data for clear and accurate reporting.	for highlighting this factual error. The caption has been changed to read OS.
The report is not clear on which analysis was the base case for the OS FP NMA and which should be considered the scenario analysis. On page 37 – "The curves for the FP model with p=–1 and p=–1.5 were very similar, however, the results of the PF model with p=–1.5, which had the best statistical fit of the two, was used as an alternative scenario for the ERG base case." On page 152 "As a scenario analysis, the ERG included the first-order FP OS curve with a power of -0.5"	Suggest to clarify language regarding which values were used as the base case and which were used as scenarios.	Unclear language is misleading as to which analysis the ERG consider to be the base case, and which should be considered as scenario analyses.	The ERG thanks the company for highlighting this factual error. The text has been amended in the report.
The model provided does not replicate some of the values in Table 54 and Table 55; specifically, the values presented for Scenario 8 in Table 54, and Scenario 6+7+8 in Table 55.	Please could the ERG verify that the values presented for these scenario analyses are correct.	As the model does not replicate all values in Table 54 and 55, Lilly are unable to cross-check the ICERs with the cumulative changes.	Not a factual error. The values in Table 54 and Table 55 are correct. The company might need to change the input on cells AI25 and AI29 in tab "DrugCosts" of the model to match the base case, by setting them to be equal to AI20 and AI32, respectively.

Abemaciclib with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer after endocrine therapy

ERRATUM

This report was commissioned by the NIHR HTA Programme as project number 17/141/03

BMJ Technology Assessment Group

This document contains errata in respect of the ERG report in response to the manufacturer's factual inaccuracy check.

The table below lists the page to be replaced in the original document and the nature of the change:

Page No.	Change
29	The 0.60 value in Table B was changed to 0.59
29	The text "However, when compared with the TTD curves by starting dose of abemaciclib (i.e. 150mg vs 200mg populations) shown in Figure I, the ABE-FUL curve for the ITT population is considerably underestimating the time on treatment for patients receiving 150mg of abemaciclib … In fact, using the ITT TTD data leads to considerable underestimation of the ABE-FUL costs in the economic analysis" was amended to "However, when compared with the TTD curves by starting dose of abemaciclib (i.e. 150mg vs 200mg populations) shown in Figure I, the ABE-FUL curve for the ITT population is underestimating the time on treatment for patients receiving 150mg of abemaciclib … It is the ERG's opinion that using the ITT TTD data leads to considerable underestimation of the ABE-FUL costs in the economic analysis"
90	The tick for Zhang 2016 in the limited network for OS has been changed to a cross.
100	The caption changed to refer to Table 16 of the CS
143	The text "In fact, using the ITT TTD curve leads to a considerable underestimation of the ABE-FUL costs in the economic analysis" was amended to "It is the ERG's opinion that using the ITT TTD curve leads to a considerable underestimation of the ABE-FUL costs in the economic analysis".
144	The 0.60 value in Table 26 was changed to 0.59
148	The word "PFS" was changed to "OS" in the caption of Table 27 and in the name of the second column of the table.
150	The text "As a scenario analysis, the ERG included the first-order FP OS curve with a power of -0.5. As explained in Section 4, the FP curve for p = -0.5 has a higher DIC statistic, indicating a worse fit when compared to the ERG's base case of p = -1.5. Nonetheless, given the uncertainty around the relative treatment effect for ABE-FUL compared with the other treatments in the OS NMA, the ERG considered the p = -1.5 curves to be relevant for a scenario analysis as these show a smaller, and thus more conservative, relative treatment effect for ABE-FUL compared with other treatments (Figure 42)." was amended to "The ERG's base case results included the first-order FP OS curve with a power of -0.5, while the power of -1.5 was used as a scenario analysis. As explained in Section 4, the FP curve for p = -0.5 has a higher DIC statistic, indicating a worse fit when compared to the curve for p = -1.5. Nonetheless, given the uncertainty around the relative treatment effect for ABE-FUL compared with the other treatments in the OS NMA, the ERG chose the p = -0.5 curves to as the base case OS curves as these show a smaller, and thus more conservative, relative treatment effect for ABE-FUL compared with other treatments (Figure 42)."

Table A. Median TTD and PFS across comparator treatments

	PFS	TTD	Source
ABE-FUL	16.4	[redacted]	MONARCH 2
FUL	9.3	[redacted]	MONARCH 2
EXE	3.2	3.2	BOLERO 2
EXE-EVE	7.8	EXE:6.8 EVE:5.5	BOLERO 2
EXE-EVE	8.4	Overall: 6.3	BOLERO 6
TMX	9.2	9.2	Milla-Santos, 2001[1]
Chemotherapy	9.6	9.6	BOLERO 6

Most importantly, the estimates shown in Table A indicate that the only treatments where there might be a difference (as far as medians are concerned) between PFS and TTD curves is ABE-FUL, FUL, and EXE-EVE. Therefore, the PFS curves for EXE, TMX and chemotherapy can be used as proxies to estimate TTD in the economic analysis. To estimate TTD for ABE-FUL, FUL, and EXE-EVE, the ERG used the company's proposed methodological approach, but used the MONARCH 2 and BOLERO 2 PFS curves instead of the HR NMA-derived ones. Table B reports the calculations undertaken by the ERG and the resulting HRs used to estimate TTD curves in the economic analysis.

Table B. ERG's HRs to estimate TTD curves

	PFS	TTD	PFS % at median TTD	HR
ABE-FUL	16.4	[redacted]	[redacted]	[log(0.5) / log([redacted])] = [redacted]
FUL	9.3	[redacted]	[redacted]	[log(0.5) / log([redacted])] = [redacted]
EXE-EVE (BOLERO 2)	7.8	EXE:6.8 EVE:5.5	PFS (6.8) = 0.55	[log(0.5) / log(0.55)] = 1.16
EXE-EVE (BOLERO 6)	8.4	6.3	PFS (6.3) = 0.59	[log(0.5) / log(0.59)] = 1.31

Figure F shows the TTD curves when the ERG's HRs were applied to the ERG's FP NMA PFS curves. The TTD curve for ABE-FUL has a considerable separation from the ABE-FUL PFS curve. This is a direct translation of the separation in TTD and PFS KM curves in the ITT analysis of MONARCH 2 data (Figure G and Figure H). However, when compared with the TTD curves by starting dose of abemaciclib (i.e. 150mg vs 200mg populations) shown in Figure I, the ABE-FUL curve for the ITT population is underestimating the time on treatment for patients receiving 150mg of abemaciclib. Given that abemaciclib will be given in 150mg regimens in clinical practice, and that the 150mg population sample size in MONARCH 2 was considerably bigger than the 200mg population, the ERG considers that the 150mg TTD data would have been a more appropriate choice to model TTD for ABE-FUL. It is the ERG's opinion that using the ITT TTD data leads to considerable underestimation of the ABE-FUL costs in the economic

Table 15. Summary of trials used to inform the network meta-analysis (adapted from CS Appendix D.1.3. Table 19)

Trial	Treatment A (ITT n)	Treatment B (ITT n)	Treatment C (ITT n)	Dichotomous		HR NMA		FP NMA			
								Full network*		Limited network**	
				ORR	CBR	OS	PFS	OS	PFS	OS	PFS
BOLERO-2[53]	EXE-EVE (485)	EXE (239)	NA	✓	✓	✓	✓	✓	✓	✓	✓
BOLERO-6[29]	EXE-EVE (104)	EVE (103)	CAP (102)	×	×	×	×	✓	✓	✓	✓
Buzdar 1997[43]	ANAS 1 mg (128)	ANAS 10 mg (130)	MGA 160 mg (128)	✓	✓	✓	✓	×	×	×	×
Buzdar 2001[42]	LTZ 0.5 mg (202)	LTZ 2.5 mg (199)	MGA 160 mg (201)	✓	×	✓	✓	×	×	×	×
Campos 2009[52]	EXE (65)	ANAS 1 mg (65)	NA	×	✓	✓	✓	×	×	×	×
CONFIRM[54, 55]	FUL 500 mg (362)	FUL 250 mg (374)	NA	✓	✓	✓	✓	✓	✓	✓	✓
Dombernowsky 1998[48]	LTZ 0.5 mg (188)	LTZ 2.5 mg (174)	MGA 160 mg (189)	✓	✓	✓	×	×	×	×	×
EFECT[56]	FUL 250 mg (351)	EXE (342)	NA	✓	✓	×	×	×	×	×	×
Hi-FAIR fx[57]	FUL 500 mg (52)	TOR 120 mg (53)	NA	✓	✓	✓	✓	✓	✓	×	×
Howell 2002[50]	FUL 250 mg (222)	ANAS 1 mg (229)	NA	✓	✓	✓	✓	×	×	×	×
Jonat 1996[44]	ANAS 1 mg (135)	ANAS 10 mg (118)	MGA 160 mg (125)	✓	✓	✓	✓	×	×	×	×
Kaufmann 2000[47]	EXE (366)	MGA 160 mg (403)	NA	✓	✓	✓	×	×	×	×	×
Milla-Santos 2001[1]	TMX 40 mg (111)	TOR 60 mg (106)	NA	×	×	×	×	✓	×	×	×
MONARCH 2[27]	ABE-FUL (446)	FUL 500 mg (223)	NA	✓	✓	✓	✓	✓	✓	✓	✓
Muss 1990[46]	MGA 160 mg (86)	MGA 800 mg (84)	NA	✓	×	✓	×	×	×	×	×
PALOMA 3[45]	PAL-FUL (347)	FUL 500 mg (174)	NA	✓	✓	✓	✓	×	×	×	×
Rose 2003[49]	LTZ 2.5 mg (356)	ANAS 1 mg (357)	NA	✓	✓	✓	×	×	×	×	×
SoFEA[58]	FUL 250 mg (231)	EXE 25 mg (249)	NA	✓	✓	✓	✓	✓	✓	✓	✓
Trial 0021[51]	FUL 250 mg (206)	ANAS 1 mg (194)	NA	✓	✓	✓	✓	×	×	×	×
Yamamoto 2013[59]	TOR 120 mg (46)	EXE 25 mg (45)	NA	✓	✓	✓	✓	✓	✓	×	×
Zhang 2016[60]	FUL 500 mg (111)	FUL 250 mg (110)	NA	✓	✓	×	✓	×	✓	×	✓

Figure 11. Forest plot of treatment effects relative to FUL 500 for OS using a fixed-effects HR NMA

Footnotes: The results presented give the median of the posterior distributions as these are less skewed by outlying observations compared to the mean. FUL 250 is not a licensed dose in the UK but was included in the NMA to help connect the full network of comparators.
Abbreviations: ABE: abemaciclib; CrI: credible interval; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; OS: overall survival; PFS: progression-free survival.

Table 16. Adjusted indirect comparison results for TMX vs FUL 500 mg based on Milla-Santos 2001 and the HR NMA (adapted from CS Table 16)

	OS, HR (95% CrI or CI)*	**PFS/TTP, HR (95% CrI or CI)***	**Source**
TOR vs TMX	[redacted]	[redacted]	Milla-Santos 2001[1]
TOR vs FUL 500 mg	[redacted]	[redacted]	NMA
Adjusted indirect comparison TMX vs FUL 500 mg	[redacted]	[redacted]	

*For TOR vs TMX the uncertainty is presented as 95% CI, for TOR vs FUL 500 mg the uncertainty is presented as 95% CrI, but for TMX vs FUL 500 mg the ERG is unsure of the unit of the interval quantifying the uncertainty as it is calculated based on a combination of CrI and CI
Abbreviations: CrI: credible interval; FUL: fulvestrant; HR: hazard ratio; NMA: network meta-analysis; OS: overall survival; PFS: progression-free survival; TOR: toremifene; TMX: tamoxifen.

BOLERO 6 shows a much higher separation in median TTD and median PFS estimates than BOLERO 2, however the company did not include BOLERO 6 in the discussion and therefore did not discuss the differences in median survival estimates. Nonetheless, BOLERO 2 trial's design is superior than that of BOLERO 6, thus the former is likely to be a more robust source of data.

Most importantly, the estimates shown in Table 25 indicate that the only treatments where there might be a difference (as far as medians are concerned) between PFS and TTD curves is ABE-FUL, FUL, and EXE-EVE. Therefore, the PFS curves for EXE, TMX and chemotherapy can be used as proxies to estimate TTD in the economic analysis. To estimate TTD for ABE-FUL, FUL, and EXE-EVE, the ERG used the company's second proposed methodological approach, but used the MONARCH 2 and BOLERO 2 PFS curves instead of the HR NMA-derived ones. Table 26 reports the calculations undertaken by the ERG and the resulting HRs used to estimate TTD curves in the economic analysis.

Figure 34 shows the TTD curves when the ERG's HRs were applied to the ERG's FP NMA PFS curves. The TTD curve for ABE-FUL has a considerable separation from the ABE-FUL PFS curve. This is a direct translation of the separation in TTD and PFS KM curves in the ITT analysis of MONARCH 2 data (Figure 35 and Figure 36). However, when compared with the TTD curves by starting dose of abemaciclib (i.e. 150mg vs 200mg populations) shown in Figure 37, the ABE-FUL curve for the ITT population is considerably lower than the 150mg ABE-FUL TTD curve. Given that abemaciclib will be given in 150mg regimens in clinical practice, and that the 150mg population size in MONARCH 2 was considerably bigger than the 200mg population, it is the ERG's opinion that the 150mg TTD curve would have been a more appropriate choice to model TTD for ABE-FUL. It is the ERG's opinion that using the ITT TTD curve leads to a considerable underestimation of the ABE-FUL costs in the economic analysis. During the clarification period, the ERG asked the company to provide the TTD data for the 150mg and the 200mg populations, however the company has not provided these.

Furthermore, the HRs for the TTD and PFS curves for ABE-FUL and EXE-EVE in BOLERO 2 ([redacted] vs 1.16) suggest that patients in ABE-FUL discontinue treatment before progression at higher rates that EXE-EVE patients.

Given that the HR used to estimate TTD curves in the economic analysis is one of the key model drivers, the ERG advises that the Committee considers the clinical plausibility of the assumptions underlying these clinical data. The ERG also recommends that the 150mg TTD data are used by the company to generate a more robust estimation of the costs of ABE-FUL in the economic analysis.

Finally, the ERG notes the caveat in the approach undertaken to estimate HRs in order to derive TTD curves. The starting point in this approach is to compare median TTD with median PFS values. However, comparison of medians is a reasonably weak approach, as equivalence (or difference) in

median survival estimates does not inform the difference in the curves' shape and doesn't necessarily translate an accurate picture of differences in mean survivals. Nonetheless, given that TTD data were not available for the comparator treatments, the use of median TTD estimates is necessary.

Table 26. ERG's HRs to estimate TTD curves (in months)

	PFS	TTD	PFS % at median TTD	HR
ABE-FUL	16.4	[redacted]	[redacted]	[log(0.5) / log([redacted])] = [redacted]
FUL	9.3	[redacted]	[redacted]	[log(0.5) / log([redacted])] = [redacted]
EXE-EVE (BOLERO 2)	7.8	EXE:6.8 EVE:5.5	PFS (6.8) = 0.55	[log(0.5) / log(0.55)] = 1.16
EXE-EVE (BOLERO 6)	8.4	6.3	PFS (6.3) = 0.59	[log(0.5) / log(0.59)] = 1.31

Figure 34. PFS and TTD in ERG's anaysis

[redacted]

Table 27. Hazard ratios (95% credible interval) for OS

Comparator	OS HR (CrI)
EXE (25 mg) (NMA)	[redacted]
EXE (25 mg)-EVE (10 mg) (NMA)	[redacted]
FUL (500 mg)	Reference
TMX (adjusted indirect comparison)	[redacted]
Abbreviations: ABE: abemaciclib; CrI: credible interval; EVE: everolimus; EXE: exemestane; FUL: fulvestrant.	

5.4.6.1 ERG critique

The CS reports that the CONFIRM population was more pre-treated and thus expected to be at a more advanced stage of the disease compared with the MONARCH 2 population. Clinical expert opinion sought by the ERG agreed that the CONFIRM population was more pre-treated and thus clinical outcomes could be expected to be worse relatively to outcomes in MONARCH 2. Nonetheless, the company used the CONFIRM data to adjust the extrapolated tails of the FUL and ABE-FUL curves in their base case analysis.

The CONFIRM data are considerably rich and complete, with a follow-up period close to seven years, whereas the MONARCH 2 OS data are very immature (with median OS not reached for either treatment arms at the end of the follow-up period of two years and four months). Interestingly, OS for the FUL arm of MONARCH 2 reached 54% at 28 months, while CONFIRM median survival was approximately 27 months (Figure 39). An earlier data cut-off analysis of the CONFIRM data showed a median survival of 25 months.[54, 55] Although the numbers at risk at 28 months in the FUL arm of MONARCH 2 (one patient) require caution when interpreting the OS curve, the 54% survival estimate is not dissimilar to the median OS for the shorter and longer follow-up analysis of the CONFIRM OS data.

Given the immaturity of OS data in MONARCH 2, the ERG advises caution when interpreting all analysis undertaken involving these data. Furthermore, the ABE-FUL and FUL OS curves in the trial show a very small – if any – benefit for ABE-FUL (with the OS HR not being statistically significant), potentially due to data immaturity. Therefore, the ERG sees the additional value in using CONFIRM data in the economic analysis. Furthermore, CONFIRM was included in the HR (and FP) NMA, therefore it should, to a reasonable degree, provide a comparable source of effectiveness for FUL.

Similar to the company's PFS analysis, the ERG disagrees with the company's decision to jointly fit the OS curves to the ABE-FUL and FUL arms of MONARCH 2 instead of using the HR obtained in their base case NMA to estimate the ABE-FUL OS curve. Moreover, given the immaturity of OS data in MONARCH 2, the company could have also considered using the CONFIRM FUL 500mg curve as the baseline FUL curve in the model (rather than the MONARCH 2 FUL curve) to then apply the NMA

forever. The plateau of the OS curves is clearly implausible, and given that it occurs at ~15%, compared to the plateau in PFS curves at ~35%, it also means that PFS and OS curves cross, which is equally implausible. Furthermore, the ABE-FUL and FUL curves cross, indicating that FUL patients might die at slower rates than ABE-FUL patients. This could be a result or the immature shape (and close tracking) of the ABE-FUL and FUL KM curves in MONARCH 2. The company did not provide a discussion of the clinical plausibility of their FP-NMA curves. Instead, it clarified that PFS curves were capped by OS curves, so the former would not cross the latter.

Figure 40. Company's FP-derived OS curves

Figure 41 reports the ERG's FP NMA-derived survival curves. The ERG used a first-order FP NMA, which produced more clinically plausible long-term extrapolations of OS, with virtually all patients being dead at approximately 13 years (160 months). As explained in Section 4, the ERG used the simplified FP NMA which excluded TMX from the network. The CAP curve crosses the ABE-FUL curve at approximately 30 months; however, CAP results should be interpreted with caution, as mentioned in Section 5.4.5.2.

The ERG's base case results included the first-order FP OS curve with a power of -0.5, while the power of -1.5 was used as a scenario analysis. As explained in Section 4, the FP curve for p = -0.5 has a higher DIC statistic, indicating a worse fit when compared to the curve for p = -1.5. Nonetheless, given the uncertainty around the relative treatment effect for ABE-FUL compared with the other treatments in the OS NMA, the ERG chose the p = -0.5 curves to as the base case OS curves as these show a smaller, and thus more conservative, relative treatment effect for ABE-FUL compared with other treatments (Figure 42). The curves also portray a more conservative scenario overall, as OS curves plateau close to zero much earlier than the