NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Abemaciclib with an aromatase inhibitor for untreated advanced hormone-receptor positive, HER2-negative breast cancer [ID1227]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Abemaciclib with an aromatase inhibitor for untreated advanced hormone-receptor positive, HER2-negative breast cancer [ID1227]

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5. **Patient group, professional group and NHS organisation submission** from:
   - Breast Cancer Now

6. **Expert statements** from:
   - Dr Andreas Makris – clinical expert, nominated by UK Breast Cancer Group
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7. **Evidence Review Group report** prepared by **Southampton Health Technology Assessments Centre (SHTAC)**

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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 an aromatase inhibitor for untreated advanced HR-positive, HER2-negative breast cancer [ID1227]

Pre-meeting briefing

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

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Advanced breast cancer (ABC) 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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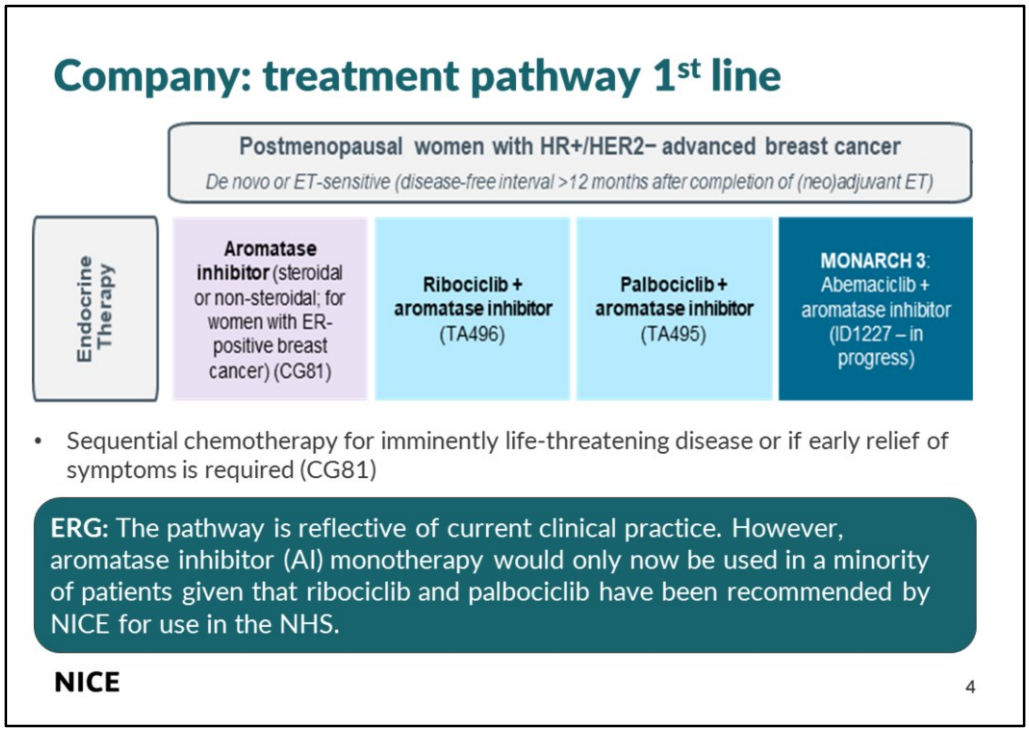
Key: HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive.



- Modified CS figure 2 page 19

Decision problem

	Final scope	Company
Population	People with advanced HR+/HER2− breast cancer that has not been previously treated with endocrine therapy	Postmenopausal women with advanced HR+/HER2− locoregionally recurrent or metastatic breast cancer who have had no prior systemic therapy for advanced disease
Intervention	Abemaciclib in combination with an aromatase inhibitor	Abemaciclib + non-steroidal aromatase inhibitor [i.e. anastrozole or letrozole]
Comparators	• Palbociclib with an aromatase inhibitor • Ribociclib with an aromatase inhibitor	• Palbociclib + aromatase inhibitor (letrozole) • Ribociclib + aromatase inhibitor (letrozole)
Outcomes	OS, PFS, RR, AE, HRQoL	OS, OS rate, PFS, RRs (ORR, DCR, CBR, DoR), AE, EORTC QLQ-C30, EQ-5D-5L

ERG: The company's decision problem reflects the final scope.

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Company: patients who have received treatment with endocrine therapy (ET) in the (neo)adjuvant setting with a disease-free interval >12 months from completion of ET are included (As defined in the MONARCH 3 trial)

Abbreviations: CBR: clinical benefit rate; CR: complete response; DCR: disease control rate; DoR: duration of response; EORTC QLQ-C/BR: European organisation for research and treatment of cancer quality of life questionnaires-core/breast cancer specific; ET: endocrine therapy; HRQoL: health-related quality of life; N/A: not applicable; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PR: partial response; PROs: patient-reported outcomes; PSS: personal social services; SD: stable disease

Preview: clinical effectiveness and treatment pathway issues

- How generalisable are MONARCH 3 results?
  - Is MONARCH 3 population representative of postmenopausal women with advanced or metastatic HR+/HER2- breast cancer previously untreated in advanced setting?
- Does the committee have a preference for the investigator assessed or the independent review of the outcome PFS?
- Network meta-analyses (NMA1) estimated the clinical effectiveness (PFS and OS) of abemaciclib+NSAI compared with ribociclib+NSAI, and palbociclib+NSAI
  - Is the level of clinical heterogeneity in the NMA1 acceptable?
  - Overall survival in MONARCH 3 (and other studies) is immature.
  - Networks for AEs, treatment discontinuation and HRQoL were not possible.
  - What is the committee's view of the NMA1 results?
- Does the committee consider that the effectiveness of the 3 CDK 4/6 inhibitors to be similar? Is a class effect for CDK 4/6 inhibitors likely?

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Abemaciclib (Verzenios, Eli Lilly)

Positive CHMP opinion	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 as initial endocrine-based therapy**
Mechanism of action	Selective dual inhibitor of cyclin-dependent kinase 4 and 6 (CDK4 and 6)
Administration	• 150 mg oral tablet twice daily for 28-days, in combination with aromatase inhibitor • Women must be in a postmenopausal state prior to therapy.
Acquisition cost	List price of abemaciclib: [redacted] per 28-day cycle
Cost of a course of treatment	Mean Time on Treatment: [redacted] months (modelled) Cost per mean Time on Treatment: [redacted] No PAS agreed with Department of Heath and Social Care.

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http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004302/smops/Positive/human_smop_001331.jsp&mid=WC0b01ac058001d127

"Verzenios is 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.

In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist."

- Combination with fulvestrant in women who have received prior endocrine therapy is subject to a forthcoming appraisal (ID1339)

Impact on Patients

Breast Cancer Now

- In the MONARCH-3 trial shows promise in improving progression-free survival compared to an aromatase inhibitor alone.
- As a first line treatment for metastatic disease, it has an important role in extending the time that hormone treatments work. This is an important delay before patients will eventually be offered chemotherapy, which is known to have severe side effects.
- The oral form makes it simple for patients to take. Apart from short-stay, regular blood tests, patients are not required to spend long lengths of time at the hospital, so it is unlikely that this will place a significant additional burden on patients and their families.
- There are some increased side effects from abemaciclib with an aromatase inhibitor, compared to an aromatase inhibitor alone, however not all patients will experience side effects. The benefits and risks of a treatment need to be clearly discussed with the patient to ensure they can make a decision that is right for them.

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Clinical evidence: MONARCH 3

Design	Phase III, multi-centre, placebo-controlled, randomised, double-blinded
Location	International: 158 sites & 22 countries; 4 sites in UK ([redacted])
Population	Postmenopausal women with HR+/HER2– locoregionally recurrent or metastatic breast cancer who had no prior systemic therapy in the advanced setting. Randomisation stratified by: • site of metastases: visceral (lung, liver, pleural, peritoneal, or adrenal gland involvement); bone only, or other; • prior (neo)adjuvant endocrine therapy: AI therapy (e.g. anastrozole, exemestane and letrozole), other, or no prior endocrine therapy.
Intervention and comparator	• Abemaciclib (N-328) 300mg/day for 28day cycle with a NSAI (either anastrozole or letrozole) • Placebo (N=165) with a NSAI (as above) • Dose interruptions and sequential dose permitted for treatment-related toxicities. If dose reduction beyond 50 mg twice daily needed, drug discontinued.
Outcomes	**Investigator-assessed PFS (primary),** OS, OS rate, RRs (ORR, DCR, CBR, DoR), TEAE, EORTC QLQ-C30, EQ-5D-5L, **also independent review PFS**

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- Crossover between the study arms was not permitted; patients were allowed to discontinue either abemaciclib/placebo or NSAI, and continue the other drug as a monotherapy

- PFS: Assessment of PFS for a randomly selected subset of patient scans was performed by an independent panel of radiologists at the interim analysis, with a full independent review of PFS for all randomised patients at the final analysis.

- Concomitant therapies also collected.

Abbreviations: AE: adverse event; 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; FSH: follicle-stimulating hormone; HRQoL: health-related quality of life; NSAI: non-steroidal aromatase inhibitor; ORR: objective response rate; OS: overall survival PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumours;[58] TEAE: treatment-emergent adverse event

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MONARCH 3: selected baseline characteristics

Baseline characteristic		Abemaciclib + NSAI, N=328	Placebo + NSAI, N=165
Mean age, years (SD)		[redacted]	[redacted]
Female, n (%)		328 (100.0)	165 (100.0)
Race, n (%)	White	186 (56.7)	102 (61.8)
	Asian	103 (31.4)	45 (27.3)
	Other	11 (3.4)	7 (4.2)
Region, n (%)	Europe	[redacted]	[redacted]
	Asia	[redacted]	[redacted]
	North America	[redacted]	[redacted]
ECOG performance status	ECOG 0	192 (58.5)	104 (63.0)
	ECOG 1	136 (41.5)	61 (37.0)
Disease setting, n (%)	De novo metastatic	135 (41.2)	61 (37.0)
	Metastatic recurrent	182 (55.5)	99 (60.0)
	Locoregionally recurrent	11 (3.4)	5 (3.0)
Median Duration of disease, months (IQR)		[redacted]	[redacted]
Initial diagnosis disease stage	Stage 0	[redacted]	[redacted]
	Stage 1	[redacted]	[redacted]
	Stage 2	[redacted]	[redacted]
	Stage 3	[redacted]	[redacted]
	Stage 4	[redacted]	[redacted]
Metastatic site, n (%)	Visceral	172 (52.4)	89 (53.9)
	Bone only	70 (21.3)	39 (23.6)
	Other	86 (26.2)	37 (22.4)
No. of organ sites, n (%)	1	96 (29.3)	47 (28.5)
	2	76 (23.2)	42 (25.5)
	≥3	154 (47.0)	75 (45.5)

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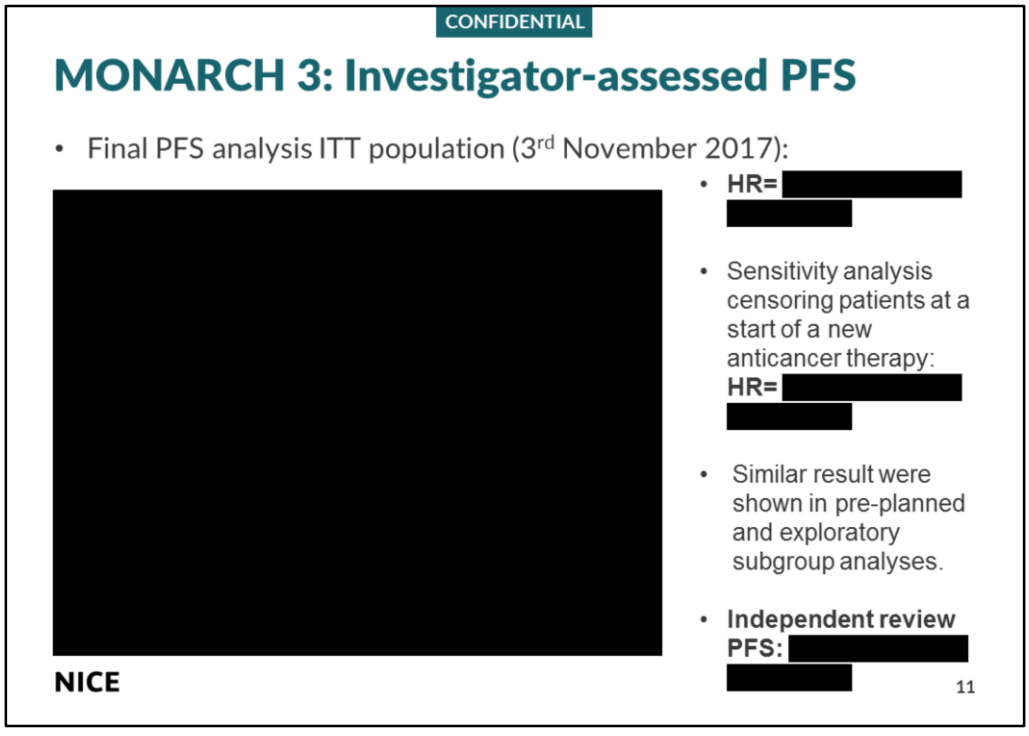
- Modified CS table 6 page 35

- **Abbreviations:** AI: aromatase inhibitor; ECOG; Eastern Cooperative Oncology Group; ER: oestrogen receptor; PgR: progesterone receptor; HER2: human epidermal growth factor receptor 2; IQR: Interquartile Range; NSAI: non-steroidal aromatase inhibitor.



CS Figure 4 page 43

PFS censoring for patients receiving anti-cancer treatment: clarification questions: A5 page 7

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MONARCH 3: Pre-planned PFS SG analyses

- Final investigator-assessed PFS SG analyses ITT population:

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Appendix E page 109 figure 9

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MONARCH 3: Overall Survival

- At the PFS final analysis ITT population (3rd November 2017):

OS data still immature, with [redacted] events ([redacted] deaths) in abemaciclib+ NSAI arm and [redacted] events ([redacted] deaths) in placebo +NSAI arm and with median OS [redacted]. OS Kaplan-Meier curves [redacted] over the 36 month observation period.

HR= [redacted]

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Final OS analysis to be done after 315 events.

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MONARCH 3: Survival at final analysis

	Abemaciclib + NSAI (n=328)	Placebo + NSAI (n=165)	Treatment Effect /p-value
Progression-free survival			
Median PFS, months Investigator assessed	[redacted]	[redacted]	[redacted]
24 month PFS rate, % Investigator assessed	[redacted]	[redacted]	[redacted]
Median PFS, months Independent Review	[redacted]	[redacted]	[redacted]
24 month PFS rate, % Independent Review	[redacted]	[redacted]	[redacted]
Overall survival			
Median OS, months	[redacted]	[redacted]	[redacted]
24 month OS rate, % (95% CI)	[redacted]	[redacted]	[redacted]
Number of deaths, n (%)	[redacted]	[redacted]	-

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ERG Table 7 page 54

And CS table 10 page 47

24 month PFS rate, % Independent Central Review taken from CSR addendum

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MONARCH 3: response rates

- At the PFS final analysis ITT population

Best overall response	Abemaciclib + NSAI N=328		Placebo plus NSAI N=165		Unstratified OR (95% CI)	p-value
	n (%)	95% CIb	n (%)	95% CIb		
CR	[redacted]					
PR	[redacted]					
SD	[redacted]					
≥6 months	[redacted]					
PD	[redacted]					
Not evaluabled	[redacted]					
Objective response rate (CR + PR)	[redacted]					
Disease control rate (CR + PR + SD)	[redacted]					
Clinical benefit rate (CR + PR + SD ≥6 months)	[redacted]					

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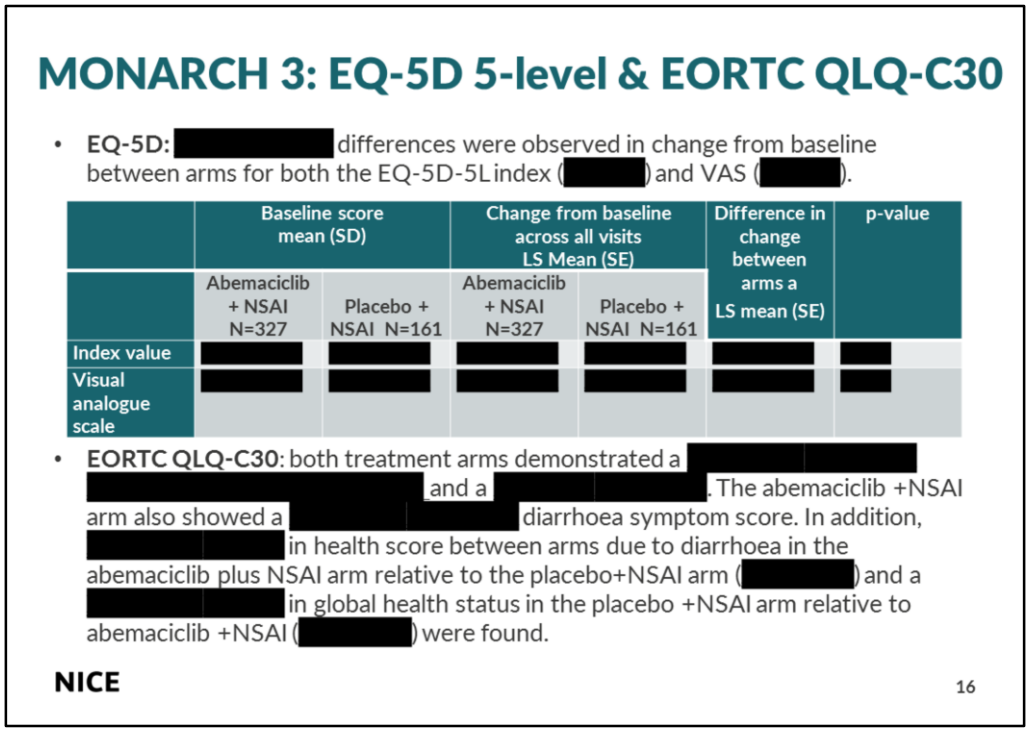
CS Table 11 page 50

Abbreviations: CI: confidence interval; IWRS: interactive web response system; N: number of patients in the intent-to-treat population; n: number of patients within category; NA: not applicable; NSAI: non-steroidal aromatase inhibitor; PD: progressive disease; RECIST: Response Evaluation Criteria in Solid Tumors.[58]



At the PFS final analysis safety population:

CS table 12 page 53

Abbreviations: EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; LS: least squares; NSAI: non-steroidal aromatase inhibitor; SE: standard error; SD: standard deviation.

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MONARCH 3: Treatment emergent adverse events (TEAE, safety population)

Percent of participants (patients may be counted in >1 category)	Abemaciclib + NSAI (n=327)	Placebo + NSAI (n=161)
Patients with ≥1 TEAE	[redacted]	[redacted]
TEAEs related to study treatment [b]		
Patients with ≥1 Grade 3 or higher TEAE		
Grade 3 or higher TEAE related to study treatment [b]		
Patients with ≥1 serious adverse event	[redacted]	[redacted]
Serious Adverse Events related to study treatment [b]		
Discontinuations of all study treatment due to an AE	[redacted]	[redacted]
Discontinuations of study treatment due to a SAE	[redacted]	[redacted]
Deaths due to adverse event	[redacted]	[redacted]

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Key: [b] Includes events that were considered related to study treatment as judged by the investigator.

ERG report page 61 Table 13

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Company: Treatment emergent adverse events (TEAE)

- **Overall, abemaciclib + NSAI was well-tolerated, with acceptable TEAE profile**
- The majority of patients in both treatment arms experienced at least one TEAE considered related to the study treatment
- For the abemaciclib + NSAI arm, diarrhoea, infection/infestations, neutropenia, fatigue and nausea were the most frequent TEAEs. Diarrhoea was predominantly of low grade and largely managed through medication.
- Serious AEs were reported by more patients in the abemaciclib + NSAI arm, due to a range of causes, with no prominent patterns observed.

ERG: Antidiarrhoeal medications were used in [redacted] of patients, [redacted] had dose reduction, [redacted] dose omission, and [redacted] discontinued treatment due to diarrhoea. Clinical experts confirmed that abemaciclib is associated with diarrhoea and that this is worse in the first few weeks and it then settles down.

- ERG agrees with company's conclusion, but notes that relatively high proportion of patients receiving abemaciclib reporting grade 3 diarrhoea ([redacted]) is clinically important.

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ERG: MONARCH 3

- Well conducted trial, but high frequency of AE such as diarrhoea could lead to unblinding and independent review PFS may be a better measure of PFS.
- Median duration of disease was [redacted] in ABE+NSAI vs. placebo ([redacted] months) and the proportion of patients with treatment-free interval of ≥36 months was higher (62.7 % vs 50.0%). This suggests that ABE+NSAI arm had some better prognostic factors at baseline, potentially favouring treatment effects.
- Withdrawals due to AE [redacted] in ABE+NSAI and withdrawals due to progressive disease [redacted] in ABE+NSAI (vs placebo).
- No cross-over was permitted, but ABE/placebo or NSAI could be discontinued. [redacted] in ABE+NSAI and [redacted] in placebo+NSAI received post-discontinuation therapy. Endocrine therapy ([redacted]) (e.g. fulvestrant) and chemotherapy ([redacted]; e.g. paclitaxel) were most common.
- The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Breast 23 (EORTC QLQ-BR23) was specified in CSR but results are not reported. There is a risk of selective reporting bias.
- OS results are immature.

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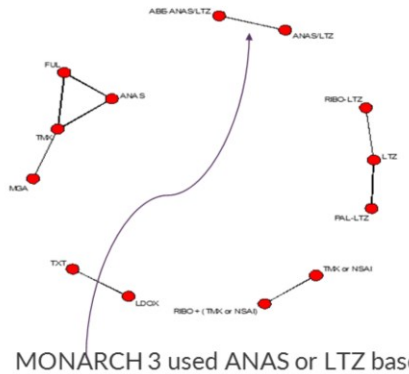
Network meta-analysis 1st line: NMA1



- MONARCH 3 used ANAS or LTZ based on investigator's choice: ANAS & LTZ pooled to connect MONARCH 3 to network
- Analyses included PFS, OS, ORR and CR.
- Networks for AEs, treatment discontinuation and HRQoL not possible due to limited data in primary studies.

- Company: heterogeneity in MONARCH 3, MONALEESA-2, PALOMA-1 & -2:
  1. Disease-free interval (DFI) following adjuvant therapy: in MONARCH 3 patients were >12 months since completion of (neo)adjuvant therapy with AI or anti-oestrogen therapy. In MONALEESA-2, PALOMA-1 & -2 patients were >12 months since adjuvant NSAI therapy, but DFI required for other hormonal therapies was unclear.
  2. Visceral involvement: Proportion of patients varied between arms and studies: 44% to 59%.
  3. Site of disease: only MONARCH 3 reported proportion of patients with liver metastases

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Text: CS page 65

Figure: appendix D page 62 figure 2

Abbreviations: ABE: abemaciclib; ANAS: anastrozole; EXE: exemestane; FUL: fulvestrant; LDOX: liposomal doxorubicin; LTZ: letrozole; MGA: megestrol acetate; OS: overall survival; PAL: palbociclib; PFS: progression-free survival; RIBO: ribociclib; TMX: tamoxifen; TOR: toremifene; TXT; docetaxel;

NMA1: 18 included studies

Included studies	Trial Name	Intervention A (ITT n)	Intervention B (ITT n)	Intervention C (ITT n)	Connected to network of evidence?				
					PFS	OS	ORR	CBR	CR
Bonneterre 2001	TARGET/ North American	ANAS (n=511)	TMX20 (n=510)	-	✓	✓	✓	✓	✓
Finn 2015	PALOMA-1/TRIO-18	PAL-LTZ (n=84)	LTZ (n=81)	-	✓	✓	✓	✓	✓
Goetz 2017	MONARCH 3	ABE-ANAS/LTZ (n=328)	ANAS/LTZ (n=165)	-	✓	✓	✓	✓	✓
Hortobagyi 2016	MONALEESA-2	RIBO-LTZ (n=334)	LTZ (n=334)	-	✓	✓	✓	✓	✓
Howell 2004	-	FUL250 (n=313)	TMX20 (n=274)	-	✓	✓	✓	✓	✓
Muss 1985	-	MGA (n=69)	TMX20 (n=67)	-	✓	✓	✓	✗	✓
Finn 2016	PALOMA-2	PAL-LTZ (n=444)	LTZ (n=222)	-	✓	✗	✓	✓	✗
Robertson 2016	FALCON	ANAS (n=232)	FUL500 (n=230)	-	✓	✗	✗	✗	✗
Gill 1993	-	MGA (n=60)	TMX40 (n=58)	-	✗	✓	✓	✗	✓
Hayes 1995	-	TMX20 (n=215)	TOR60 (n=221)	TOR200 (212)	✗	✓	✓	✗	✓
Iwata 2013	-	EXE (n=149)	ANAS (n=149)	-	✗	✓	✓	✓	✓
Milla-Sanos 2001	-	TOR60 (n=106)	TMX40 (n=111)	-	✗	✓	✓	✗	✓
Milla-Santos 2003	-	ANAS (n=121)	TMX40 (n=117)	-	✗	✓	✓	✓	✓
Mouridsen 2001	-	LTZ (n=453)	TMX20 (n=454)	-	✗	✓	✓	✓	✓
Paterson 1990	-	TMX20 (n=79)	MGA (n=77)	-	✗	✓	✓	✗	✓
Pyrhonen 1997	Nordic	TOR60 (n=214)	TMX40 (n=201)	-	✗	✓	✓	✗	✓
Robertson 2009	FIRST	ANAS (n=103)	FUL500 (n=102)	-	✗	✓	✓	✓	✗
Allegra 1985	-	MGA (n=65)	TMX20 (n=66)	-	✗	✗	✓	✗	✓

CS table 14 page 57

Abbreviations: ABE: Abemaciclib; ANAS: Anastrozole; CBR: Clinical benefit rate; CR: Complete response, EXE: Exemestane; FUL: Fulvestrant; LTZ: Letrozole; MGA: Megestrol acetate; ORR: Objective response rate; OS: Overall survival; PAL: Palbociclib; PFS: Progression-free survival; RIBO: Ribociclib; SLR: Systematic literature review; TMX: Tamoxifen; TOR: Toremifene.

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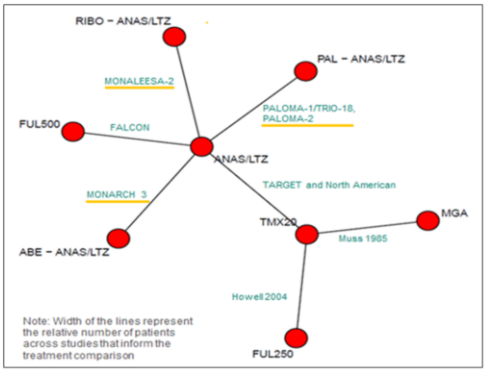
Company: NMA1 PFS results (8 studies)

[redacted]

Forest plot of treatment effects relative to NSAI for PFS using fixed effects model



- Similar estimates observed for ABE-ANAS/LTZ and comparators, [redacted] HR vs NSAI:

ABE-NSAI: HR [redacted] (95% CrI [redacted] to [redacted]),
RIBO-NSAI: HR [redacted] (95% CrI [redacted] to [redacted]),
PAL-NSAI: HR [redacted] (95% CrI [redacted] to [redacted]).

CS figure 10 page 60 (Forest plot of treatment effects relative to ANAS/LTZ for PFS, using FE model) and appendix D figure 3 page 68

Footnote: The results presented give the median of the posterior distributions as these are less skewed by outlying observations compared to the mean.

Abbreviations: ABE: abemaciclib; ANAS/LTZ: anastrozole/letrozole; CrI: credible interval; MGA; megestrol acetate; PAL: palbociclib; FUL500: fulvestrant 500 mg; RIBO; ribociclib; TMX20; tamoxifen 20 mg.

FUL250: fulvestrant 250 mg; FUL500: fulvestrant 500 mg; TMX20: tamoxifen 20 mg; MGA: megestrol acetate 160 mg; NSAI: non-steroidal aromatase inhibitor;

Similar HR estimates for PFS were observed between ABE-ANAS/LTZ and relevant comparators RIBO-ANAS/LTZ and PAL-ANAS/LTZ

The scoped treatment trials have been underlined in yellow.

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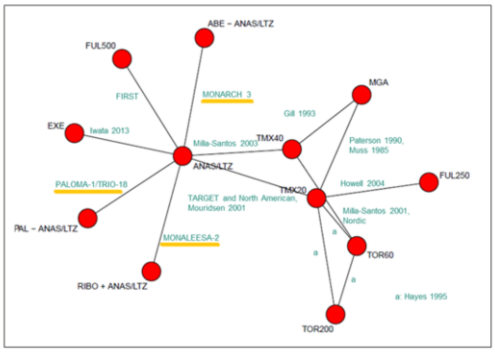
Company: NMA1 OS results (15 studies)

[redacted]

Forest plot of treatment effects relative to NSAI for OS using random effects model



- Final OS data only from PALOMA-1. MONARCH 3, MONALEESA-2, and PALOMA-2 immature OS .
- Treatment effects are highly uncertain:

RIBO-NSAI: HR [redacted] **(95% CrI** [redacted] **to** [redacted]**)**,
PAL-NSAI: HR [redacted] **(95% CrI** [redacted] **to** [redacted]**)**,
ABE-NSAI: HR [redacted] **(95% CrI** [redacted] **to** [redacted]**)**.

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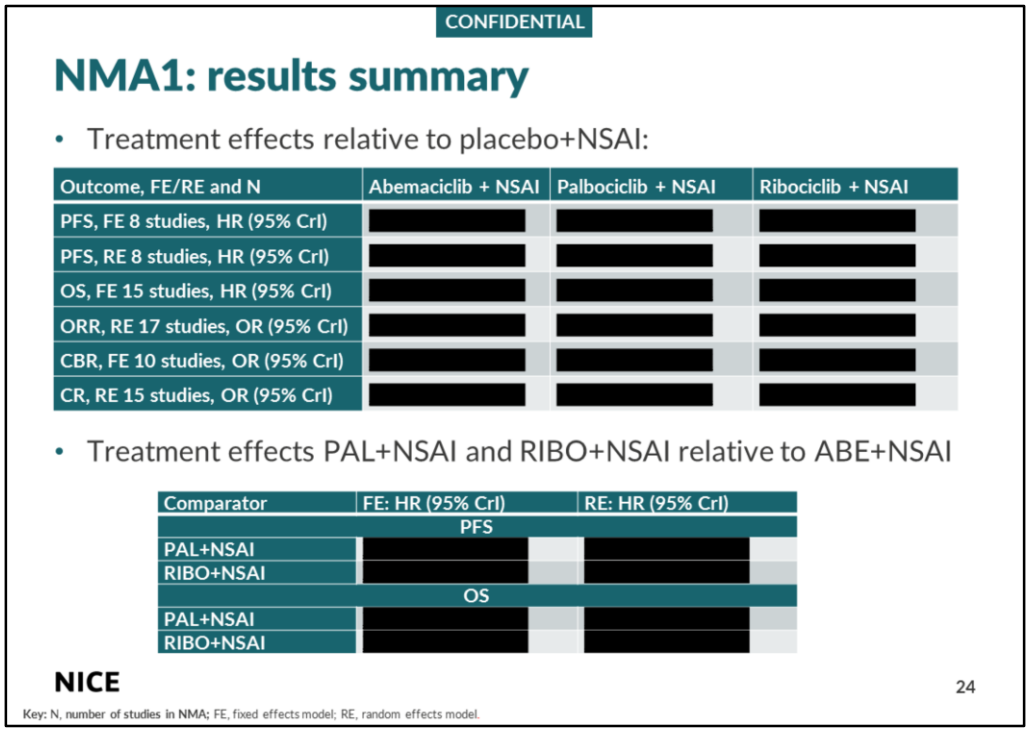
CS figure 11 page 61 (Forest plot of treatment effects relative to ANAS/LTZ for OS using RE model) and appendix D figure 4 page 69

The scoped treatment trials have been underlined in yellow.

Footnote: The results presented give the median of the posterior distributions as these are less skewed by outlying observations compared to the mean.

Abbreviations: ABE: abemaciclib; ANAS/LTZ: anastrozole/letrozole; CrI: credible interval; EXE: exemestane; MGA; megestrol acetate; PAL: palbociclib; FUL250: fulvestrant 250 mg FUL500: fulvestrant 500 mg; RIBO; ribociclib; TMX20; tamoxifen 20 mg; TMX40: tamoxifen 40 mg; TOR60: toremifene 60 mg; TOR200: toremifene 200 mg; MGA: megestrol acetate 160 mg; NSAI: non-steroidal aromatase inhibitor;



ERG report page 60 & 61 table 11 &12 and Clarification: table 2 & 3 page 9

Abbreviations: ABE-NSAI: abemaciclib plus NSAI; OS: overall survival; PAL-NSAI: palbociclib plus NSAI; RIBO-NSAI: ribociclib plus NSAI.

CBR, Clinical benefit rate

CR, Complete Response

ORR, Objective response rate

ERG: NMA1 critique

- NMA1 has been adequately conducted.
- However, there are some limitations and uncertainties
- For many trials it was not possible to ascertain similarity, or otherwise, of patient characteristics. Notably, there is variation between trials in the proportion of patients with visceral metastases, and the effect of this on the results is uncertain.
- The NMA1 method used assumes proportional hazards assumption. However, proportional hazards assumption did not hold for OS. Alternative approach assuming time-varying hazards should been used (albeit with immature OS data).
- Considers included trials similar in terms of age and previous treatment history for advanced cancer. However, due to reporting limitations a full assessment of clinical heterogeneity is not possible. The impact of this on the NMA1 is not clear and results of the NMA1 should be interpreted with caution. In addition, due to immaturity of OS data, OS NMA1 results are highly uncertain.
- Although there were limitations to the NMA1, the results were considered by clinical experts advising the ERG to be clinically plausible.

Clinical effectiveness and treatment pathway issues

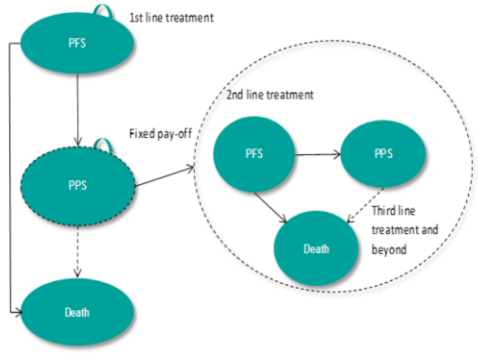
- How generalisable are MONARCH 3 results?
  - Is MONARCH 3 population representative of postmenopausal women with advanced or metastatic HR+/HER2- breast cancer previously untreated in advanced setting?
- Does the committee have a preference for the investigator assessed or the independent review of the outcome PFS?
- Network meta-analyses (NMA1) estimated the clinical effectiveness (PFS and OS) of abemaciclib+NSAI compared with ribociclib+NSAI, and palbociclib+NSAI
  - Is the level of clinical heterogeneity in the NMA1 acceptable?
  - Overall survival in MONARCH 3 (and other studies) is immature.
  - Networks for AEs, treatment discontinuation and HRQoL were not possible.
  - What is the committee's view of the NMA1 results?
- Does the committee consider that the effectiveness of the 3 CDK 4/6 inhibitors to be similar? Is a class effect for CDK 4/6 inhibitors likely?

Preview: cost-effectiveness issues

- What is the committee's view of the company's model?
  - Is the committee minded to consider that abemaciclib, ribociclib and palbociclib are similar?
    - If so is the use of this model appropriate for decision making, or would a cost comparison approach be reasonable?
    - If so what is the committee's view of the company's approach to modelling the cost of treatments?
- What is the committee's view of the company's data and assumptions?
  - Is the ERG's or the company's approach to time to treatment progression (TTP1) , progression free survival deaths (PFSD1), overall survival on 2nd line treatments (OS2) and utilities (PFS2) more appropriate?
  - Is the company's assumption of 27.5% PFS/OS gain appropriate?
  - OS data are immature, results from NMAs need to be interpreted with caution. What is the committee's view of the uncertainty of the cost-effectiveness estimates?

Company: model structure

- **Cohort state-transition model** with 2 health states (PFS1 & PPS1) and death, with **'fixed pay-off' sub-model**, a separate state-transition model with 2 health states (PFS2 & PPS2) and death, representing health outcomes and costs incurred on 2nd line and subsequent treatments applied post progression.



- Calibration is used to adjust the time spent in the pay-off sub-model to reflect an assumed relationship between PFS and OS:
  - in the base case, 'partial surrogacy' relationship is set at 27.5% PFS/OS gain
- monthly cycles with half-cycle correction
- Life time horizon (35 years)

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Key: PFS, progression-free survival; PPS, post-progression survival.

CS figure 15 page 85

Abbreviations: PFS1: first-line progression-free survival; PFS2: second-line progression-free survival; PPS: post-progression survival

1st -line model

- A cohort of patients enters the model in the PFS1 health state at the start of first-line treatments ABE+NSAI, PAL+NSAI, RIBO+NSAI or NSAI (NSAI alone included for context). Transition probabilities calculated from NMA1 and MONARCH 3. Patients may then:
  - Remain progression free.
  - Experience disease progression. Time to progression from first-line treatment (TTP1) is estimated as a survival curve, but unlike conventional progression-free survival, death is treated as a censoring event in the calculation of TTP1.
  - Die before disease progression. The progression-free death rate (PFD1) is conditional on the patient not having progressed. Unlike overall survival, progression is treated as a censoring event in the calculation of PFD1.
- The time to discontinuation of first-line treatment (TTD1) is estimated from trial data but constrained so that it ≤ TTP1.

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ERG: page 69

Time to progression **TTP**

progression-free death rate **PFD**

time to discontinuation **TTD**

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Company: time to progression (TTP1) ~ PFS1

- **Abemaciclib + NSAI and NSAI:** investigator-assessed PFS KM MONARCH 3 ITT were jointly modelled including a treatment indicator to provide joint estimates
  - exponential distribution selected (Weibull & Gompertz as scenario analyses)
  - Data were censored using the dates of tumour assessment (uncensored and baseline adjusted analyses used in a scenario)
  - PFS and OS curves modelled independently but PFS is restricted: PFS ≤ OS

MONARCH 3 survival rate, per month	
ABE-NSAI	[redacted]
NSAI	[redacted]

- **Comparators:** TTP for comparators was estimated by applying the relative treatment effects generated from NMA1 for PFS1 to NSAI TTP curve (not for ABE +NSAI), assuming equivalence of relative treatment effects for PFS and TTP:

TTP, median (months)	ABE+NSAI	NSAI*	PAL+NSAI	RIBO+NSAI
Modelled	[redacted]	[redacted]	[redacted]	[redacted]
Reported (trial)	(MONARCH 3)	(MONARCH 3)	20.2/27.6 (PALOMA-1/2)	25.3 (MONALEESA-2)

NMA1 results	HR (95% CrI)
ABE-NSAI*	[redacted]
PAL-NSAI	[redacted]
RIBO-NSAI	[redacted]
NSAI	Reference

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*Note: Not used in base case (included for reference).

Data on disease progression status were collected in the MONARCH 3 and MONARCH 2 trials at specific intervals, which does not necessarily reflect the underlying TTP for patients, as patients' disease may progress prior to their subsequent physician visit. Direct modelling of the Kaplan Meier (KM) data in this case can provide biased estimates of TTP or PFS without adjustment. Consequently, for analyses conducted to assess survival endpoints where the outcome of interest includes disease progression (i.e. TTP and PFS), two parametric analyses were conducted; one assuming dates of progression were exact and a second incorporating the potential for interval censoring (henceforth referred to as the 'interval-censored adjusted' analysis).

Abbreviations: ABE: abemaciclib; KM: Kaplan–Meier; NSAI: non-steroidal aromatase inhibitor; TTP: time to progression

ERG: TTP1 critique

- Agrees with the company's extrapolation of MONARCH 3 data
- Would prefer independent assessment of PFS due to the potential for loss of blinding caused by imbalances in AEs. However, agrees using investigator-assessed PFS as it was available in NMA2 studies. Notes that investigator-assessed PFS is less favourable than independent assessment of PFS.
- All 3 treatments have similar effects on PFS vs. NSAI, but there is a large difference in company's base case. This is due to different methods estimate TTP for abemaciclib (MONARCH 3) and for comparators (HRs relative to NSAI from NMA1).
  - Same methods should be used to provide a more reliable basis for comparisons. NMA1-based estimates for all treatments as used in company's scenario are ERG's preferred analysis (making abemaciclib relatively less cost-effective)
  - There is a small difference between NMA1 HRs used in the model and HRs reported in the submission. ERG tested the difference in scenario analyses.
- Uncertainty over the relative effects is not properly reflected in probabilistic sensitivity analysis, because HRs are sampled independently, not accounting for correlations in NMA1 results. ERG tests the uncertainty in sensitivity analyses.

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ERG: Corrected error in coding of Gompertz TTP1 interval-censored adjusted survival

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ERG: ABE + NSAI TTP NMA1 vs MONARCH 3

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ERG page 118 figure 9 **Time to first progression: company base case and NMA estimate for abemaciclib (interval-censored adjusted)**

Company model with log-normal, log-logistic and gamma curves digitised from CS Figures 19 and 20 and 21

Company: progression-free death rate (PFD1)

- **Abemaciclib + NSAI and NSAI**: Only 17 deaths for ABE-NSAI (N = 328) and 4 deaths for PBO-NSAI (N = 165) before progression in MONARCH 3. Thus non-parametric negative binomial regression models were used.
  - Data not baseline adjusted, with baseline-adjusted values as a scenario
- **Comparators**: The rate of deaths was estimated by applying the relative treatment effects generated from the NMA for OS to the rate estimated for NSAI, under the assumption of equivalence of relative treatment effects for OS and rate of deaths in pre-progression:

MONARCH 3 rate of pre-progression deaths	
Rate no adjustments (base case), per month	
ABE-NSAI	0.005
NSAI	0.002
Rate with adjustments (scenario), per month	
ABE-NSAI	0.002
NSAI	0.001

NMA1 results	OS HR (95% Credible interval)
ABE+NSAI *	[redacted]
PAL+NSAI	[redacted]
RIBO+NSAI	[redacted]
NSAI	reference

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*Note: Not used in company's base case.

Follow-up time in months was specified as an exposure variable to provide a rate estimate in the form of deaths per month of follow-up. An independent variable representing treatment group was incorporated into the regression model to generate rate estimates for ABE-NSAI and NSAI. Models were fitted with and without adjustment for baseline characteristics

For the model adjusted for baseline characteristics, no covariates were identified to be included in the final model using backwards stepwise selection. Forwards stepwise selection led to the following covariates being included in the model: ECOG status, prior endocrine therapy received in the (neo)adjuvant setting, and NSAI received in cycle 1. Given the limited number of events observed in the trial data, the model without adjustment for baseline characteristics was chosen as the base case. The model adjusted for baseline characteristics was included as a scenario analysis.

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ERG: PFD1 critique

- Given the rarity of pre-progression deaths, agrees with the company's estimation of PFD1 using MONARCH 3 data
- Corrected error: HRs relative to abemaciclib were used instead of HRs relative to NSAI
- But similarly to TTP1, rate of PFD1 for abemaciclib estimated from the MONARCH 3 is very different to that estimated using a HRs from NMA1 relative to NSAI: [redacted] and [redacted] respectively.
  - Same methods should be used to provide a more reliable basis for the comparison.
  - Despite the OS NMA1 limitations, NMA1-based estimates for all treatments are used in ERG preferred analysis.

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ERG: The assumption that relative treatment effects are the same for pre-progression deaths as for overall survival may also be wrong

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ABE + NSAI PFD NMA1 vs MONARCH 3

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ERG page 119 Figure 10 **Pre-progression death rates**

Source: Company model with ERG corrections to calculation of rates for palbociclib and ribociclib

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Company: TTD1 summary

- **Abemaciclib + NSAI and NSAI**: TTD KM data from MONARCH 3 modelled. Gamma distribution was chosen (lognormal, Gompertz & exponential in scenario analyses). Where TTD exceeded TTP, TTD was set equal to TTP.
- **Comparators:** TTD not reported in primary publications. TTD estimated from HR between median TTD provided in EMA publication for RIBO (20.30 months), SmPC for PALBO (19 months, relative to NSAI from MONARCH 3 ([redacted] moths).

TTD1 (months)	ABE+NSAI	NSAI	PAL+NSAI	RIBO+NSAI
Modelled mean	[redacted]	[redacted]	[redacted]	[redacted]
Modelled median				
Reported median (trial)	(MONARCH 3)	(MONARCH 3)	13.81/19.82 (PALOMA-1/2)	13.00 (MONALEESA-2)

ERG: agrees with the company's choice of curves.
- However, as the company notes, lower costs of ABE are driven by shorter time on treatment with ABE+NSAI. This difference is based on weak evidence.
- The company notes that including dose intensity of [redacted] for abemaciclib (ABE), 93% for palbociclib (PAL) and 88% for ribociclib (RIBO) increased ICERs by ≥15% in sensitivity analyses

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Appendix M table 50 page 212 and CS table 65 page 151

TTD1 for PALOMA1 & 2: calculated from days reported in TA495 committee papers by NICE technical team (table 10 in ERG report page 51).

"Fixed pay-off' sub-model

- It is a conventional three-state partitioned-survival model, with transition probabilities calculated from NMA2 of 2nd-line treatments:
  - Overall survival from the start of second-line treatment (OS2). This includes deaths that occur before and after progression.
  - Progression-free survival from the start of second-line treatment (PFS2). This includes deaths that occur before progression as events. For logical consistency, PFS2 is constrained in the model to be no more than OS2.
  - The proportion of PFS2 events that are deaths is used to separate probabilities of progression, pre-progression deaths and post-progression deaths. This proportion is estimated from two other survival curves: time to progression and progression-free death from the start of second-line treatment (TTP2 and PFD2), defined and estimated in the same way as TTP1 and PFD2.
- TTD2 cannot exceed PFS2. TTD3 is estimated as a fixed proportion of time spent in the PPS state in the fixed pay-off sub-model.

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ERG: page 70

Transition probabilities and costs in the fixed-pay-off model are weighted according to the proportions of patients assumed to start each of the included second-line treatments. The model includes costs for a third line of treatment (within the PPS state), but outcomes related to third-line treatment are not modelled explicitly.

Time to progression **TTP**

progression-free death rate **PFD**

time to discontinuation **TTD**

Network meta-analysis 2nd line: NMA2

- NMA2 conducted around MONARCH 2 (RCT comparing abemaciclib + fulvestrant with placebo + fulvestrant) to inform clinical effectiveness of 2nd line treatments:
- **NMA2** (19 studies): around MONARCH 2 with wide inclusion criteria to provide estimates (PFS, OS, ORR, CBR)
  - Fulvestrant 500 is reference treatment as comparator in MONARCH 2
  - SG analysis (2 studies) with patients with no prior chemotherapy in advanced setting to align with MONARCH 2 conducted for PFS (not used in model)

NMA2 Results summary:

- **PFS2** (14 studies): 2 treatments had statistically significantly higher PFS vs FUL 500: ABE-FUL: **HR** [redacted] **(95% CrI** [redacted]) and PAL-FUL: **HR** [redacted] **(95% CrI** [redacted])
  - SG analysis (PALOMA-3 SG & MONARCH 2) with no prior chemo had similar results: ABE-FUL: HR [redacted] **(95% CrI** [redacted]) and PAL-FUL: HR [redacted] **(95% CrI** [redacted])
  - FUL 250, ANAS 1 & EXE had statistically significantly lower PFS vs FUL 500
- **OS2** (17 studies): data from 8 studies (including PALOMA-3 & MONARCH 2) immature (median not reached in at least one arm). The OS2 results are therefore uncertain and showed no significant decreases in the HR compared to FUL 500.

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Abbreviations: ANAS: anastrozole; FUL: fulvestrant; LTZ; letrozole; NMA; network meta-analysis; NSAI: non-steroidal aromatase inhibitor; OS: overall survival;

MONARCH 2

- Phase III, multi-centre, placebo-controlled, randomised, double-blinded trial (N=669)
- Population: Postmenopausal women (≥18 years) with HR+/HER2– locally advanced disease not amenable to curative treatment by surgery or metastatic disease who:
  - relapsed on neo/adjuvant endocrine therapy, with no endocrine therapy received following progression, or
  - relapsed within 1 year after adjuvant endocrine therapy, with no endocrine therapy received following progression, or
  - relapsed >1 year after adjuvant endocrine therapy + relapsed after 1st-line endocrine therapy for metastatic disease, or
  - de novo with metastatic relapsed after 1st-line endocrine therapy for metastatic disease.

- With no prior chemotherapy for metastatic disease allowed

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Company: PFS2 summary

- **Fulvestrant:** IPD for MONARCH 2 SG (38% of the randomised population) that progressed on 1st line endocrine therapy were used to estimate the outcomes of patients receiving fulvestrant 2nd line in the model
- **Other treatments:** conducting separate subgroup NMA2s was not feasible. Instead HRs generated from NMA2 (ITT population) were used to estimate the outcomes of patients treated with other 2nd line treatments.
  - No chemotherapy studies in NMA2: chemotherapy data taken from Li et al. 2015
- Exponential distribution selected (Weibull & Gompertz as scenario analyses)
- data from the BOLERO-2 used in scenario analysis

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Abbreviations: ANAS: anastrozole; FUL: fulvestrant; LTZ; letrozole; NMA; network meta-analysis; NSAI: non-steroidal aromatase inhibitor; OS: overall survival;

ERG table 20 page 86

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Company: PFS2 modelling

- The RIBO+NSAI curve has obscured the other curves:

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CS figure 30 page 108

PFS2 for each of the comparators was estimated by applying the relative treatment effect generated from the second-line therapy NMA to the FUL PFS curve. PFS was weighted based on the proportions of each second-line treatment received by patients in the Kurosky (2015) study

Abbreviations: ABE: abemaciclib; EXE: exemestane; FUL: fulvestrant; INV: investigator; KM: Kaplan Meier; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; PFS: progression-free survival; RIBO: ribociclib

Footnotes: The 0 months' time point represents the start of PFS2 in the 'pay-off' state.

ERG: PFS2 critique

- MONARCH 2 subgroup (n=256) is broadly representative of patients progressing in MONARCH 3 and the PFS extrapolation is reasonable.
- But there is uncertainty over the relative effects of other 2nd line treatments due to concerns over the robustness of NMA2 due to clinical heterogeneity
- BOLERO-2 scenario: cannot verify whether the methods and results are consistent with those in TA496, due to lack of detail in submission and redactions in TA496
  - In both approaches, EVE+EXE has the best rates of PFS.
- NMA2: Small difference between HRs in model and HRs reported in submission.
  - No results for chemotherapy. Company used HRs from Li et al. (2015) as per TA496. But this was critiqued in TA496 as no rationale presented, and no rationale other the used in TA496 presented in this submission
  - Found and corrected error in confidence intervals for chemotherapy HR
  - No results for tamoxifen: unclear why. Instead HRs taken from Milla-Santos (2001; comparing tamoxifen with toremifene in 1st line setting). No rationale why this study was used included. The ERG was not able to replicate company's HRs

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Company: OS2 modelling

- OS2: estimated from MONARCH 2 fulvestrant OS data
- Extrapolations uncertain due to the immaturity of data

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CS figure 33 page 110

Appendix M2.5. Table 70 page 196

exponential distribution considered the most plausible based on clinical opinion

FUL: fulvestrant; KM: Kaplan Meier;

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Company: OS2 and PFD2 summary

- **Fulvestrant:** Exponential distribution used for MONARCH 2, but external data, CONFIRM trial, used to inform the long-term extrapolations: Weibull distribution was selected
  - HR from CONFIRM was applied to PBO-FUL MONARCH 2 data at 27.95 months (maximum follow-up) to extrapolate OS2
- **Other treatments**: HRs from NMA2, relative to the PBO-FUL OS curve **until** 27.95 months. After 27.95 months hazard rate assumed the same for all treatments (based on CONFIRM).
  - OS weighted based on 2nd-line treatment proportions from Kurosky et al. 2015
- **PFD2:** second-line pre-progression death rate estimated from external data:

treatment	PFS2 rate	source
EVE+EXE	0.005 (22/378)	BOLERO 2
EXE	0.003 (4/103)	Piccard et al. 2014
chemo	0.008	Li et al. 2001 (PFS HR)
Other	0.003	Assumed same as EXE

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Note: The RIBO+NSAI curve has obscured the other curves

CS figure 34 page 111

See model 3 state PP payoff for summary table

Abbreviations: ABE: abemaciclib; NSAI: non-steroidal aromatase inhibitor; OS: overall survival; PAL: palbociclib; RIBO: ribociclib

Footnotes: Note that the RI

BOLERO-2 trial, a study evaluating EVE-EXE and EXE plus placebo in HR+/HER2– ABC patients who had recurrence or progression whilst receiving previous therapy with a NSAI

BO+NSAI has obscured the other curves included in the plot

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ERG: OS2 and PFD2 critique

- **OS2:** Exponential curve is a poor fit to data for MONARCH 2 OS data. Gompertz distribution has the best fit, and clinical advice to the ERG is that the long-term survival prediction is more realistic (albeit pessimistic):

OS2	Year	FUL	ANAS	LTZ	EXE	TMX	EVE+EXE	Chemo
Exponential + CONFIRM	1	[redacted]						
	3							
	5							
	10							
Gompertz	1							
	3							
	5							
	10							

- No evidence is provided regarding the goodness-of-fit for CONFIRM data extrapolation.
- Given these concerns, we use the Gompertz curve fitted to MONARCH 2 data, without CONFIRM extrapolation, in ERG preferred analysis.
- **PFD2:** agrees with the use of BOLERO 2. Have some concerns, however given the rarity of PFSD2 and as the rates do not differ between the 1st line treatments, this unlikely to affect cost-effectiveness results.

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Table: OS from second-line treatment: ERG from survival curve estimates in the company model

ERG Table 21 page 89

Company: Overall survival calibration

- OS was modelled indirectly based on the time spent in each modelled state, with no adjustment, a gain in PFS would result in an equal gain on OS

  Time in PFS + OS in 2nd line treatment i.e. PPS pay off = OS

- Partial surrogacy assumption is applied by calibrating the time spent in the fixed-pay-off sub-model until a desired ratio between median PFS gain and median OS gain for the first-line comparators relative to NSAI is achieved
  - The same weight is applied to all 2nd line events (progressions, deaths before & after progression) for the comparator, so that proportion of time spent in 2nd line states (PFS2, PPS & death) is held constant as the calibration weights are changed
  - PALOMA-1, 27.5% OS/PFS partial surrogacy assumed:

Treatment	Calibration weights
ABE+NSAI	1.22
PAL+NSAI	1.16
RIBO+NSAI	1.25

ERG: calibration is correctly implemented. We also test the conservative assumption of no surrogacy and other intermediate values.

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Abbreviations: ABE: abemaciclib; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; PFS: progression-free survival; OS: overall survival; RIBO: ribociclib

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Company: Base case OS modelling

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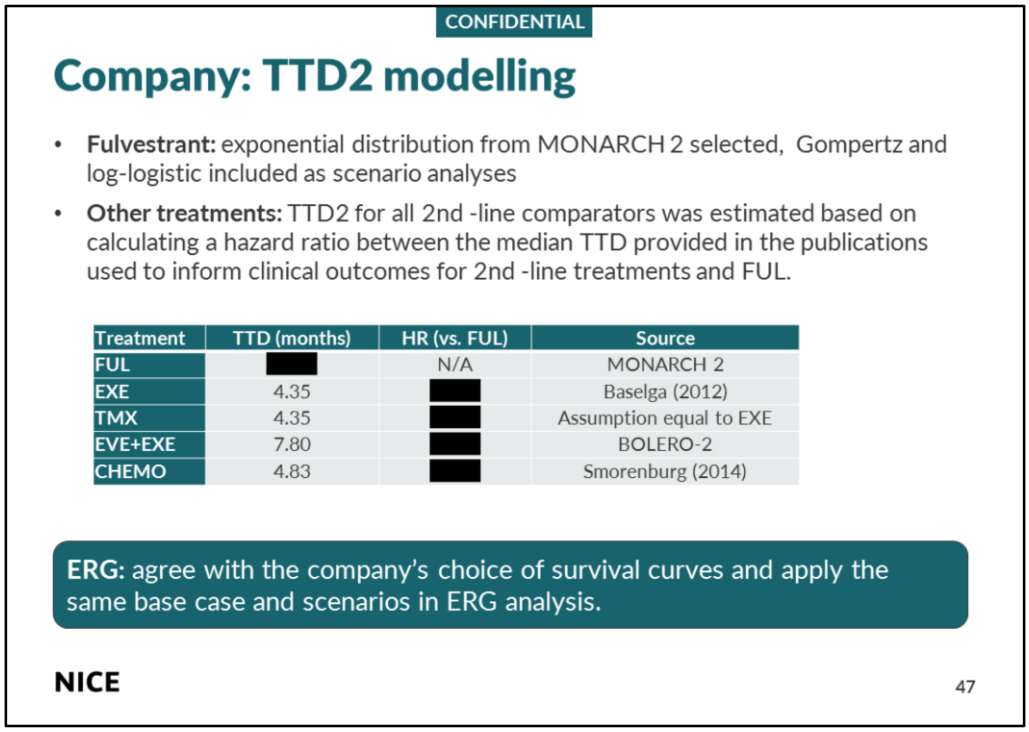
CS Figure 40 page 115

Abbreviations: ABE: abemaciclib; NSAI: non-steroidal aromatase inhibitor; OS: overall survival; PAL: palbociclib; RIBO: ribociclib



CS figure 38 page 114: Base case TTD extrapolations for second-line therapies

Abbreviations: ABE: abemaciclib; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; RIBO: ribociclib; TTD: time to treatment discontinuation

Footnotes: Note that the RIBO+N

Appendix M: table 78 page 212: TTD for second-line comparators

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Company: predicted and trial reported outcomes

Treatment	PFS (months)			ToT (months)			OS (months)		
	Modelled		Trial	Modelled		Trial/document	Modelled		Trial
	Mean	Median	Median	Mean	Median	Median	Mean	Median	Median
ABE-NSAI	[redacted]	[redacted]	[redacted] (MONARCH 3)	[redacted]	[redacted]	[redacted] (MONARCH 3)	[redacted]	[redacted]	NR (MONARCH 3)
PAL-NSAI	[redacted]	[redacted]	20.20 (PALOMA-1) 27.60 (PALOMA-2)	[redacted]	[redacted]	13.81 (PALOMA-1) 19.82 (PALOMA-2) 19.00 (SmPC)	[redacted]	[redacted]	37.5 (PALOMA-1)
RIBO-NSAI	[redacted]	[redacted]	25.30 (MONALEESA-2)	[redacted]	[redacted]	13.00 (MONALEESA-2) 15.10 (MONALEESA-7) 20.30 (EMA)	[redacted]	[redacted]	NR (MONALEESA-2)
NSAI	[redacted]	[redacted]	[redacted] (MONARCH 3) 8.50-18.00 (see CS table 65 for trials)	[redacted]	[redacted]	[redacted] (MONARCH 3) 6.10-13.90 (see CS table 65 for trials)	[redacted]	[redacted]	NR (MONARCH 3) 17.40-60.10 (see CS table 65 for trials)

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Appendix M table 50 page 212 and CS table 65 page 151 (NSAI info)

ToT for PALOMA1 & 2: calculated from days reported in TA495 committee papers by NICE technical team (table 10 in ERG report page 51).

Mean TOT for NSAI: model

Abbreviations: ABE: abemaciclib; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; PFS: progression-free survival; RIBO: ribociclib; ToT: time on treatment; OS: overall survival

In line with the final scope issued by NICE, NSAI alone is not a relevant comparator to abemaciclib plus NSAI. However, cost-effectiveness results are provided here to allow comparison to prior appraisals for palbociclib plus NSAI (TA495) and ribociclib plus NSAI (TA496)

Company: 3rd-line treatments

- Time on 3rd -line therapy was calculated based on an assumption that patients spent approximately 37% of their time in PPS (after progression from 2nd -line therapy) on treatment

	Average cost per month		
	PFS1	PFS2	PPS
Follow up care	£443	£635	£691
Adverse events	£106	-	-
Hospitalisation	£33	£46	£40
Best supportive care	£146	£146	£69
Total	£728	£828	£800
End of life	£4,379	£4,379	£4,379

ERG: clinical advice to the ERG is that it would be unusual for patients to spend as much as 63% of time after a second disease progression without treatment. Thus, the cost of treatment in the PPS health state is probably underestimated.

- In comparison in NICE TA496, the committee tested monthly costs in the PPS state in the region of £1140 to £1200 (ERG TA495 estimate) in decision making.

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ERG Table 29 page 102

ERG: 2nd and 3rd-line treatments

– concern that the estimated use of second and third-line treatments does not reflect current NHS practice. In particular, the company includes fulvestrant which is not recommended by NICE in this context:

	Company base case		ERG scenario	
	Second-line	Third-line	Second-line	Third-line
Chemotherapies	25.7%	30.4%	25%	50%
Capecitabine	12.3%	24.8%	12%	41%
Paclitaxel	6.2%	0.0%	6%	0%
Docetaxel	7.2%	0.0%	7%	0%
Eribulin	0.0%	5.6%	0%	9%
Endocrine therapies	66.3%	24.0%	35%	25%
Fulvestrant	**10.9%**	**10.1%**	**0%**	**0%**
Anastrozole	0.0%	0.0%	0%	5%
Letrozole	0.0%	0.0%	0%	5%
Exemestane	37.0%	6.2%	15%	5%
Tamoxifen	18.5%	7.7%	20%	10%
Everolimus + exemestane	8.0%	0.0%	40%	10%
No treatment	0.0%	45.6%	0%	15%

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ERG Table 25 page 99

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Company model: utilities

- Utilities for PFS1 were assumed to be the same for all treatments
- Pre-progression utilities: EQ-5D-3L data cross-walked from the EQ-5D-5L data collected in the MONARCH 3 for all patients combined
- Pay-off' utilities (PPS): utility of patients on 2nd -line treatment (PFS2) and PPS in the 'pay-off' was based on TA496 and Lloyd (2006)
- PFS2 (0.774) is >PFS1 ([redacted]). Therefore a scenario with PFS1 was set to 0.774 was included. Scenarios using MONARCH 2 conducted.

Health state		Utilities	Notes	Source
Company's base-case	PFS1	[redacted]	-	MONARCH 3
	PFS2	0.774/0.661/0.745	Endocrine/chemo/average	TA496-BOLERO 2
	PPS	0.505	-	Lloyd, 2006
MONARCH 3	PFS1	[redacted] (some patients may have experienced 2nd progression)		
	PFS2/PPS	[redacted]		
MONARCH 2	PFS2	[redacted]	Endocrine/chemo/average	MONARCH 2
	PPS	[redacted]	-	MONARCH 2
TA495	PFS1	0.72/0.71/0.74	Overall/NSAI/PAL+NSAI	PALOMA 2
	PFS2/PPS	0.505	-	Lloyd, 2006
TA496	PFS2	0.774 initial and 0.690 final		DSU
	PPS	0.505	-	Lloyd, 2006

CS table 27 page 117 and table 28 page 117

And ERG table 23 page 94

Abbreviations: PFS1: first-line progression-free survival; PFS2: second-line progression-free survival; PPS: post-progression survival

Average: As in previous NICE appraisals, including TA495 and TA496, an additional decrement of 0.113 (Peasgood et al. 2010)[53] is applied for the 25.66% of patients assumed to have chemotherapy at second-line

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ERG: utilities

- Although not statistically significant, ABE+NSAI utility was [redacted] than NSAI (difference of [redacted]. However, equivalent treatment-specific utilities are not available for all comparators. ERG therefore agrees with the company's decision to use the overall PFS1 [redacted]
- Notes that the company does not use MONARCH 3 post-progression estimate [redacted] and MONARCH 2 PFS2 estimate [redacted]
- PFS1 from MONARCH 3 [redacted] is lower than PFS2 from MONARCH 2 [redacted]. This might be a chance finding for two independent trial samples, or it might reflect a more structural incompatibility of patient selection or recruitment. Either way it is not realistic to assume a lower utility for PFS1 than for PFS2, as this implies that patients have a worse quality of life when progression-free at first-line than after disease progression at second-line.
- Due to inconsistency between PFS1 and PFS2 (PFS2 >PFS1) ERG follows TA496 approach that resulted in revision of the PFS2 value from 0.774 to 0.690.
- **ERG uses value of 0.690 for PFS2 in preferred analysis.**

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Company model: adverse reactions

- Impact of AEs on HRQoL incorporated by applying a QALY decrement. Grade 3–4 events occurring in > 5% of patients for at least 1 treatment included.
- **ABE-NSAI:** rates based on the TRAEs in MONARCH 3 ITT population
- **Comparators**: rates based on primary publications used in NMA1: PAL-NSAI, PALOMA2 Finn (2016) & Rugo SABCS (2018), and RIBO-NSAI, Hortobagyi (2016) and Hortobagyi ASCO (2017)

Event	ABE-NSAI	PAL-NSAI	RIBO-NSAI	NSAI	Decrement	Duration (days)
Alanine aminotransferase in.	[redacted]	0.2%	9.0%	[redacted]	-0.050	28.00
Anaemia	[redacted]	5.9%	2.4%	[redacted]	-0.119	16.07
Aspartate aminotransferase in.	[redacted]	0.0%	6.0%	[redacted]	0.000	0.00
Diarrhoea	[redacted]	1.4%	2.4%	[redacted]	-0.006	8.00
Hypertension	[redacted]	0.0%	10.0%	[redacted]	-0.153	8.00
Leukopenia	[redacted]	24.8%	21.0%	[redacted]	-0.003	13.96
Lymphopenia	[redacted]	0.0%	7.0%	[redacted]	0.000	34.00
Neutropenia	[redacted]	67.1%	59.0%	[redacted]	-0.007	15.09

ERG: Disutilities for adverse drug reactions are included in the model, but as the size and duration of the effects assumed are low, these have a negligible impact on cost-effectiveness results.

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CS table 29 page 168 and table 30 page 119, values taken from ERG table 22 page 92 as company's values are rounded.

Footnotes: *NSAI methodology is included here to contextualise the NSAI results presented in Section B.3.10

Abbreviations: ABE: abemaciclib; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; RIBO: ribociclib; in. increased.

For the **Adverse event QALY loss see ERG table 24 page 99**

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Summary: inputs for 1st line and utilities

	Treatment	Values	Company	ERG	Source
TTP1 (TTP≤OS)	NSAI rate	[redacted]	✓	✓	MONARCH 3: exponential
	ABE+NSAI rate		✓	×	
	ABE-NSAI vs NSAI		×	✓	NMA1
	PAL-NSAI vs NSAI		✓	✓	
	RIBO-NSAI vs NSAI		✓	✓	
PFD1	NSAI rate	0.002 per month	✓	✓	MONARCH 3: Negative binomial
	ABE-NSAI rate	0.005 per month	✓	×	
	ABE-NSAI vs NSAI	[redacted]	×	✓	NMA1
	PAL-NSAI vs NSAI		✓	✓	
	RIBO-NSAI vs NSAI		✓	✓	
TTD1 (TTD≤TTP)	NSAI		✓	✓	MONARCH 3: Generalised gamma
	ABE-NSAI		✓	✓	
	PAL-NSAI vs ABE	19.8 months: HR 0.81	✓	✓	PAL SmPC
	RIBO-NSAI vs ABE	20.3 months: HR 0.79	✓	✓	RIBO EMA assessment
Utilities	PFS1	[redacted]	✓	✓	MONARCH 3
	PFS2 ET/targeted	0.774	✓	×	TA496-BOLERO 2
	PFS2 chemo	0.661	✓	×	TA496-BOLERO 2
	PFS2 ET/targeted	0.690	×	✓	TA496 DSU
	PFS2 chemo	0.577	×	✓	TA496 DSU
	PPS	0.505	✓	✓	TA496 Lloyd, 2006

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CS table 57 page 136 and model sheet HR

CS Table 20 page 93

ERG table 16 page 73 and 26 page 98

NMAs of PFS and OS were conducted and the results were included in the model for TTP and pre-progression death, respectively, assuming the relative treatment differences were equivalent for these two endpoints.

ERG:

HRs for TTP1 in the model (as cited in CS Table 23) differ from those reported in CS Figure 10 B.2.9.2. These differences are small and we test the impact in ERG scenario analysis. The differences are tabulated in Table 18 page 78. also unclear if these values are AIC or not.

Abbreviations: ABE: abemaciclib; ANAS: anastrozole; EXE: exemestane; FUL: fulvestrant; LTZ: letrozole; NMA: network meta-

analysis; NSAI: non-steroidal aromatase inhibitor; OS: overall survival; PAL: palbociclib; PFS: progression-free survival; PPS: post-progression survival; RIBO: ribociclib; TMX: tamoxifen; TTP: time to progression;

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Summary: inputs for 2nd line

	Treatment	values	Company	ERG	Source
PFS2	FUL rate	[redacted]	✓	✓	MONARCH 2 SG: exponential
	ANAS vs FUL		✓	✓	NMA2
	LTZ vs FUL		✓	✓	
	EXE vs FUL		✓	✓	
	EVE+EXE vs FUL		✓	✓	
	TMX vs FUL		✓	✓	Mila-Santos 2001
	Chemo vs FUL	1.64 (0.85, 3.15)	✓	✓	Li et al 2015
OS2	FUL rate	[redacted]	✓	✗	MONARCH 2+ CONFIRM: exponential
	FUL rate		✗	✓	MONARCH: Gompertz
	ANAS vs FUL		✓	✓	NMA 2
	LTZ vs FUL		✓	✓	
	EXE vs FUL		✓	✓	
	EVE+EXE vs FUL		✓	✓	
	TMX vs FUL		✓	✓	Mila-Santos 2001
	Chemo vs FUL	HR 1.89 (0.72, 5.00)	✓	✓	Li et al 2015
PFD2	EVE+EXE	0.005 per month	✓	✓	BOLERO-2
	EXE	0.003 per month	✓	✓	
	Chemo vs FUL	1.64 (0.85 ,3.15)	✓	✓	Li et al 2015
TTD2	FUL	[redacted]	✓	✓	MONARCH 2: exponential
	ANAS	5.6 months: [redacted]	✓	✓	Rose 2003
	LTZ	5.9 months: [redacted]	✓	✓	Rose 2003
	EXE and TMX	4.4 months: [redacted]	✓	✓	Baselga 201, TMX assumed equal EXE.
	EVE+EXE	7.8 months: [redacted]	✓	✓	BOLERO 2
	Chemo	4.8 months: [redacted]	✓	✓	Smorenburg 2014

CS table 57 page 136 and model sheet HR

ERG table 19 page 81 and 26 page 98

Smorenburg 2014 (CAP, PAC & DOC assumed to be the same as CAP)

Time on 3rd -line therapy was calculated based on an assumption that patients spent approximately 37% of their time in PPS (after progression from 2nd -line therapy) on treatment. This assumption was based on clinical expert opinion

ERG: However, clinical advice to the ERG is that it would be unusual for patients to spend as much as 63% of time after a second disease progression without treatment. Thus, the cost of treatment in the PPS health state is probably underestimated. We vary the proportion of PPS spent on treatment (from 10 to 50%) to assess the impact of uncertainty around this parameter.

Results

- All results presented below were calculated using list prices.
- Results with confidential patient access scheme discounts and commercial access agreements for comparators and subsequent treatments are presented in a separate confidential appendix.
- The confidential appendix [cPAS] cannot be presented here.

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Company: base-case results using list prices

(before ERG error corrections)

- **Deterministic results**

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ABE+NSAI	£129,803	5.08	3.29	-	-	-	-	-
RIBO+NSAI	£148,170	5.02	3.22	£18,367.14	−0.06	−0.068	Dominated	Dominated
PAL+NSAI	£145,266	5.03	3.23	−£2,904.53	0.02	0.003	Dominated	Dominated

- **Probabilistic results**

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
PAL-NSAI	£139,631	4.92	3.15	-	-	-	-	-
RIBO-NSAI	£142,571	4.92	3.16	£2,940	0.00	0.01	£397,143.85	£397,143.85
ABE-NSAI	£125,581	4.96	3.21	-£16,990	0.04	0.05	Dominant	Dominant

ERG: probabilistic analysis did not reflect correlations between NMA parameters.

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CS table 59 page 141 and table 61 page 143

Abbreviations: ABE: abemaciclib; ICER: incremental cost-effectiveness ratio; LYG: life years gained; ABE: abemaciclib; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; QALYs: quality-adjusted life years; RIBO: ribociclib

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Company: summary of sensitivity analyses

- In scenario analyses, results were largely stable when varying model assumptions, with consistent ICER estimates, demonstrating the robustness of the model:

Decrease in base case ICER of ≥15%	Increase in base case ICER of ≥15%
1. Apply PFS–OS surrogacy (base case: partial [27.5%]; scenario: full [100%])	1. Source of ABE-NSAI treatment effect for PFS
2. Source of clinical outcomes in PPS (base case: from MONARCH 2; scenario: from BOLERO-2)	2. PPS utility source (base case: from Lloyd 2006 [0.505]; scenario: from MONARCH 2 [[redacted]])
3. Distribution for extrapolating 2nd -line OS, scenario 3 (base case: exponential with CONFIRM data extrapolation; scenario: Gompertz)	3. Distribution for extrapolating TTP, scenario 2 (base case: exponential; scenario: Gompertz)
4. Relative dose intensity (base case: off; scenario: on)	

ERG: Results were consistent across company's scenario analyses, and our results were similar.

- However, difference in QALYs between CDK 4/6 inhibitors was very small, and ranking of abemaciclib, ribociclib and palbociclib did change between scenarios.
- Company did not present one-way sensitivity analysis for model parameters, or tornado diagram so it is difficult to identify key drivers of the model.

CS table 64 page 148

Abbreviations: ABE-NSAI: abemaciclib plus NSAI; OS: overall survival; PFS1: progression-free survival on first-line treatment; PFS2: progression-free survival on second-line treatment; PPS: post-progression survival; TTP: time to progression

Results before ERG error corrections

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ERG: preferred assumptions and changes to model

- Corrected 4 minor errors in the coding of the model. These made very little difference to the company's results.
- ERG preferred analysis included the following changes to company's base case:
  - Estimation of time to progression (TTP1) and pre-progression deaths (PFD1) for ABE+NSAI estimated relative to fitted curves for NSAI using hazard ratios from NMA1 (as for the comparators).
  - A Gompertz OS curve from second-line treatment. This was more pessimistic than the company's assumption of exponential with CONFIRM trial extrapolation.
  - A utility of 0.69 for people free of progression at second line – as per the assumption suggested by the Decision Support unit in the NICE appraisal of ribociclib (TA496).

ERG: results with cumulative changes (ranked by QALY gains)

Analysis	Treatments	Total costs	Total QALYs	ICERs (£/QALY)	
				Incremental	ABE vs. comparator
ERG corrected company base case	NSAI	£56,152	2.997	Referent	£250,352
	PAL+NSAI	£152,268	3.273	Dominated	ABE+NSAI dom.
	RIBO+NSAI	£154,559	3.285	Dominated	ABE+NSAI dom.
	ABE+NSAI	£129,590	3.291	£250,352	-
+ ABE+NSAI TTP1 from NMA	NSAI	£56,152	2.997	Referent	£341,663
	ABE+NSAI	£130,514	3.215	£341,663	-
	PAL+NSAI	£152,268	3.273	Ext. dom.	£376,720 (SW)
	RIBO+NSAI	£154,559	3.285	£343,915	£343,915 (SW)
+ ABE+NSAI PFD1 from NMA	NSAI	£56,152	2.997	Referent	£289,982
	PAL+NSAI	£152,268	3.273	Dominated	ABE+NSAI dom.
	ABE+NSAI	£138,597	3.282	£289,982	-
	RIBO+NSAI	£154,559	3.285	£4,909,402	£4,909,402 (SW)
+ OS2 Gompertz	NSAI	£40,049	2.350	Referent	£208,333
	RIBO+NSAI	£142,614	2.750	Dominated	ABE+NSAI dom.
	PAL+NSAI	£140,748	2.761	Dominated	ABE+NSAI dom.
	ABE+NSAI	£127,062	2.768	£208,333	-
+ PFS2 utility 0.69 ~ERG preferred analysis	NSAI	£40,049	2.283	Referent	£192,356
	RIBO+NSAI	£142,614	2.719	Dominated	ABE+NSAI dom.
	PAL+NSAI	£140,748	2.727	Dominated	ABE+NSAI dom.
	ABE+NSAI	£127,062	2.735	£192,356	-

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SW = South West quadrant of the cost-effectiveness plane (ABE+NSAI less expensive and less effective than comparator).

ERG table 37 page 115

ERG summary page 124:

- The company's base case results (all drugs at list price) suggests that ABE+NSAI is marginally more effective and less expensive than the comparators PAL+NSAI and RIBO+NSAI. Compared with NSAI monotherapy, ABE+NSAI had an estimated ICER of around £250,000 per QALY gained. This result was quite consistent across the company's scenario analyses, and our results were similar, for our preferred set of assumptions and across a range of scenario analyses. The absolute difference in QALYs between the CDK 4/6 inhibitors was very small, and the ranking of abemaciclib, ribociclib and palbociclib did change between scenarios.
- However, as the company note, **the lower costs of abemaciclib are driven by a shorter time on treatment with ABE+NSAI**. We note that **this difference is based on weak evidence**, as hazard ratios between treatments were estimated from reported median time to discontinuation. Another aspect of the economic analysis that was

subject to uncertainty and may not be fully represented in the model is **adverse events**: **the assumed QALY loss with the included events was low, due to small disabilities and durations assumed**. Exploration of uncertainty around the model results was hampered by model run time.

End of life criteria

- A case has not been made for abemaciclib + NSAI meeting end of life criteria

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Innovation and equality consideration

Innovation:

- The company states that abemaciclib plus NSAI is a oral therapy with a tolerable safety profile that allows for continuous dosing which may be preferred by patients:
  - In the MONARCH 3 trial, the most frequently observed TEAE was diarrhoea ([redacted]); [redacted] and [redacted] experienced a grade 3 and 4 event, respectively. The majority of abemaciclib plus NSAI patients (76.3%) who experienced diarrhoea did not undergo any treatment modifications during the study, [redacted] had a dose reduction and [redacted] had a dose omission
  - It may be noted that the comparators palbociclib and ribociclib are associated with high levels of neutropenia: 55.3% grade 3 and 59.6% grade 3 or 4, respectively. As a result, treatment with palbociclib or ribociclib requires regular blood count monitoring and a seven-day treatment gap following every 21 days of treatment to allow for recovery

Equality consideration

- No equality issues were raised

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CS page 73

Cost-effectiveness issues

- What is the committee's view of the company's model?
  - Is the committee minded to consider that abemaciclib, ribociclib and palbociclib are similar?
    - If so is the use of this model appropriate for decision making, or would a cost comparison approach be reasonable?
    - If so what is the committee's view of the company's approach to modelling the cost of treatments?
- What is the committee's view of the company's data and assumptions?
  - Is the ERG's or the company's approach to time to treatment progression (TTP1) , progression free survival deaths (PFSD1), overall survival on 2nd line treatments (OS2) and utilities (PFS2) more appropriate?
  - Is the company's assumption of 27.5% PFS/OS gain appropriate?
  - OS data are immature, results from NMAs need to be interpreted with caution. What is the committee's view of the uncertainty of the cost-effectiveness estimates?

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Abemaciclib with an aromatase inhibitor for untreated advanced HR-positive, HER2-negative breast cancer ID1227

Document B

Company evidence submission

June 2018

File name	Version	Contains confidential information	Date
NICE Abemaciclib plus NSAI Document B	Final	Yes	29th June 2018

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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Abbreviations

Abbreviation	Definition
ABC	Advanced breast cancer
ABE	Abemaciclib
AC	Appraisal Committee
AESI	Adverse events of specific interest
AFT	Accelerated failure time
AIC	Academic in Confidence
ANAS	Anastrozole
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the curve
BEV	Bevacizumab
BIC	Bayesian inference criteria
BNF	British National Formulary
BOR	Best overall response
BSA	Body surface area
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CAP	Capecitabine
CBR	Clinical benefit rate
CDK	Cyclin-dependent kinase
CEAC	Cost effectiveness acceptability curves
CHMP	Committee for Medicinal Products for Human Use
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CSF	Colony stimulating factor
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A	Cytochrome P4503A
DCR	Disease control rate
DFI	Disease-rree interval
DNA	Deoxyribonucleic acid
DOC	Docetaxel
DoR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EMC	Electronic Medicines Consortium

EORTC-QLQ/BR	European Organization for Research and Treatment of Cancer Quality of Life Questionnaires-Core/Breast Cancer Specific
EPAR	European Public Assessment Reports
EQ-5D-5L	EuroQol 5-Dimension 5-Level
ERG	Evidence Review Group
ERI	Eribulin
ESMO	European Society of Medical Oncology
ESO	European School of Oncology
ET	Endocrine therapy
EVE	Everolimus
EXE	Examestane
F2F	Face to face
FACT-B	Functional Assessment of Cancer Therapy - Breast Cancer
FSH	Follicle stimulating hormone
FUL	Fulvestrant
G-CSF	Granulocyte-colony stimulating factor
GEM	Gemcitabine
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GP	General Practitioner
GR	Growth rate
HER2−	Human epidermal growth factor receptor 2
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IHC	Immunohistochemistry
INV	Investigator
IPD	Individual patient data
IQR	Interquartile range
IRC	Independent Review Committee
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IV	Intravenous
IWRS	Interactive Web Response System
IXA	Ixabepilone
KM	Kaplan-Meier
KOL	Key opinion leader
LDOX	Liposomal doxorubicin
LS	Least squares
LTZ	Letrozole
LYG	Life years gained
MAA	Marketing Authorisation Applications
MBC	Metastatic breast cancer
MGA	Megestrol acetate
MIMS	Monthly Index of Medical Specialties
eMIT	Electronic Market Information Tool
NFI	No further information
NHS	National Health Service
NMA	Network meta-analysis

NR	Not reported
NSAI	Non-steroidal aromatase inhibitor
ORR	Overall response rate
OS	Overall survival
PAC	Paclitaxel
PAL	Palbociclib
PAS	Patient access scheme
PBO	Placebo
PD	Progressive disease
PFS	Progression-free survival
PgR	Progesterone receptor
PH	Proportional hazards
PPS	Post-progression survival
PR	Progesterone receptor
PRO	Patient reported outcomes
PSA	Probabilistic sensitivity analyses
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life years
QAPFW	Quality-adjusted progression-free weeks
QAPFY	Quality-adjusted progression years
QQ	Quartile-quartile
RANK	Receptor activator of nuclear factor-kappaB ligand
RB	Retinoblastoma
RCT	Randomised controlled trial
RDI	Relative dose intensity
RIBO	Ribociclib
SAE	Serious adverse event
SD	Stable disease or standard deviation (in context of statistical analyses)
SE	Standard error
SERM	Selective oestrogen receptor modulators
SLR	Systematic literature review
SmPC	Summary of product characteristics
SOC	System organ class
STA	Single Technology Appraisal
TEAE	Treatment-emergent adverse event
TMX	Tamoxifen
TOR	Toremifene
ToT	Time on treatment
TPC	Treatment of physician's choice
TRAE	Treatment-related adverse event
TSD	Technical Support Document
TTD	Time to treatment discontinuation
TTP	Time to progression
UK	United Kingdom
VAS	Visual analogue score
VIN	Vinorelbine

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

B.1.1 *Decision problem*

The submission focuses on part of the technology's marketing authorisation. Abemaciclib is under review by the European Medicines Agency for the treatment of hormone receptor positive (HR+)/human epidermal growth factor receptor 2 negative (HER2−) locally advanced or metastatic breast cancer, within three distinct patient populations. The proposed patient population for this submission is the first listed below, and is narrower than the anticipated marketing authorisation, as NICE has chosen to appraise each patient population separately.[1-3]

- **In combination with an aromatase inhibitor as initial endocrine-based therapy (this submission)** or in women who have received prior endocrine therapy
- In combination with fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy (ID1339; Expected Appraisal Submission: August 2018)
- As monotherapy following disease progression after endocrine therapy and one or two chemotherapy regimens in the metastatic setting (ID1347; Expected Appraisal Submission: 2019)

The decision problem addressed by this submission is summarised in Table 1.

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 advanced HR+/HER2− breast cancer that has not been previously treated with endocrine therapy	Postmenopausal women with advanced HR+/HER2− locoregionally recurrent or metastatic breast cancer who have had no prior systemic therapy for advanced disease (patients who have received treatment with ET in the (neo)adjuvant setting with a disease-free interval[a] >12 months from completion of ET are included)	N/A
Intervention	Abemaciclib in combination with an aromatase inhibitor	Abemaciclib + non-steroidal aromatase inhibitor [i.e. anastrozole or letrozole]	N/A
Comparator(s)	Palbociclib with an aromatase inhibitor Ribociclib with an aromatase inhibitor	• Palbociclib + aromatase inhibitor (letrozole) • Ribociclib + aromatase inhibitor (letrozole)	N/A

Outcomes	Overall survival
	Progression-free survival
	Response rate
	Adverse effects of treatment
	Health-related quality of life
		• OS and OS rate at 1, 2, and 3 years[b]
		• PFS
		• Response rates
		  ○ ORR
		  ○ DCR
		  ○ CBR
		  ○ DoR
		• Safety and tolerability (adverse effects of treatment)
		• PROs (HRQoL):
		  ○ 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. If the technology is likely to provide similar or greater health benefits at	As per NICE reference case, cost-effectiveness is expressed in terms of incremental cost per QALY, and costs considered from the perspective of the NHS and PSS, with a sufficient time horizon.	Patient access schemes are available for palbociclib and ribociclib. However, these are confidential and 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
	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.		

[a] As defined in the MONARCH 3 trial.[4, 5] Also referred to as treatment-free interval. [b] At the time of cut-off for the MONARCH 3 trial, OS data were still immature and data are not expected within the appraisal timelines.
Abbreviations: CBR: clinical benefit rate; CR: complete response; DCR: disease control rate; DoR: duration of response; EORTC QLQ-C/BR: European organisation for research and treatment of cancer quality of life questionnaires-core/breast cancer specific; ET: endocrine therapy; HRQoL: health-related quality of life; N/A: not applicable; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PR: partial response; PROs: patient-reported outcomes; PSS: personal social services; SD: stable disease

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 is provided in the reference pack (more information is 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 & 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.[6]
Marketing authorisation/CE mark status	EMA marketing authorisation is expected in [redacted]. 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 as initial endocrine-based therapy (this submission)**, or in women who have received prior endocrine therapy* • *In combination with fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy* • *As monotherapy following disease progression after endocrine therapy and one or two chemotherapy regimens in the metastatic setting* Abemaciclib has the following contraindications: • Hypersensitivity to the active substance or to any of the excipients listed in the SmPC
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 a NSAI. Women must be in a postmenopausal state prior to therapy. • 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. 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: £[redacted]
Patient access scheme (if applicable)	N/A

Abbreviations: ALT: alanine aminotransferase**;** CDK**:** cyclin-dependent kinase; CYP3A: Cytochrome P4503A; EMA: European Medicines Agency; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; mg: milligram; N/A: not applicable; NHS: National Health Service; NSAI: non-steroidal aromatase inhibitor.
Source: Goetz et al. 2017, EPAR (European Public Assessment Reports) Verzenios[5, 7]

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.[8] The disease is responsible for 7% of all cancer deaths in the UK, with a mortality rate of 17.1 per 100,000.[8, 9]

With an annual breast cancer incidence of 0.08%, approximately 46,700 women in England and Wales are diagnosed with breast cancer each year.[10-12] Approximately 90%[10] of patients will have invasive breast cancer and the majority (95%)[10] of these women are estimated to have early and locally advanced disease.[10] Early breast cancer resides only in the breast and lymph nodes nearby, whereas locally advanced disease involves cancer in a large part of the breast and lymph nodes.[13] Both early and locally advanced breast cancers have not spread to other parts of the body, however, approximately 35%[10] of these women progress to advanced breast cancer. Advanced breast cancer refers to the spread of disease to other parts of the body such as the bones, liver, and lungs (metastatic cancer), or cancer that has grown directly into nearby tissues and cannot be completely removed by surgery.[14] In addition, a smaller proportion of women (13%) in the UK are estimated to have advanced disease at diagnosis.[10, 15]

Breast cancer incidence is strongly age-dependent with more than 80% of cases occurring in women over the age of 50,[16] and approximately 25% of cases occurring in women aged 75 and over.[17] As such, a large proportion of breast cancer patients are considered to be postmenopausal women.[18]

Breast cancers are classified according to the tissue type from which the tumour arises, and the HR and HER2 status, being denoted as either positive or negative. Approximately 64% of women with metastatic breast cancer in the UK have HR+/HER2− disease.[19] A number of HR+ breast cancer therapies regulate oestrogen signalling, collectively referred to as endocrine therapy (ET).[20] There are two broad types of ET: therapies that target oestrogen receptors, such as selective modulators (SERMs; e.g. tamoxifen) or selective down-regulators (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 and letrozole).[21]

Hormone receptors 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 (Rb) cellular pathway, which controls the progression of the cell cycle.[20, 24] CDK4 and CDK6 associate with D-type cyclins to promote progression through the cell cycle, promoting cell proliferation.[20] Oestrogen signalling is known to amplify cyclin D1 activity leading to enhanced CDK4 and 6 activity, thereby driving cancer cell proliferation.[20] Overexpression of cyclin D1 has been demonstrated to occur in more than 50% of breast cancers, the majority of which are HR+.[25] The relevant comparators to this submission; palbociclib and ribociclib are both inhibitors of the CDK pathway.

Effects of breast cancer on patients and carers

Advanced breast cancer is incurable, and patients with this stage of disease have the poorest prognosis, with a median overall survival (OS) of 2–3 years.[26] 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 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 questionnaire. 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.[27] 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, and acute distress.[28] Pain can also increase in intensity and frequency as the disease progresses. A study of patients with HER2− (HR+ or HR−) stage IV breast cancer, found that pain significantly increased with disease progression.[28] 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.[28] Prevention or slowing of disease

progression may therefore assist patients in avoiding the more severe pain associated with metastases.

Treatment to prevent the progression of disease and strategies to limit the side effects of subsequent therapies are crucial aspects of breast cancer care.[28] 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.[29]

Caregivers of breast cancer patients also experience a significant burden, including anxiety, stress and depression, as well as impairments to work productivity.[30] Providing further 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.[29]

There remains a need for alternative treatments with convenient administration regimens that are suitable for long-term, chronic use, to maintain quality of life whilst patients are progression free.[31] There is a strong preference for oral administration of ET options due to the avoidance of needles, sense of control and reduced time spent at medical appointments.[32, 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, work absenteeism, and caregiver time and their associated costs.[34] Although this is beyond the NICE perspective in terms of economic analysis, it remains a relevant consideration for the broader impact of managing breast cancer in the UK.

B.1.3.2 Abemaciclib

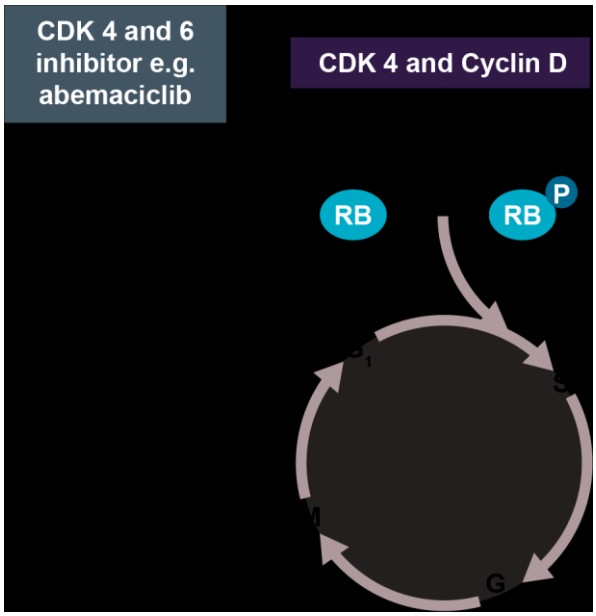
Description of abemaciclib

Abemaciclib ([LY2835219]; Verzenios, Eli Lilly) is an orally administered, potent, and selective small-molecular inhibitor of CDK4 and CDK6.[4]

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.[20] The cyclin D-CDK4 and 6 promote phosphorylation of the 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).[35]

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 subsequently suppressed.[6] Preclinical studies have shown that abemaciclib as a single agent or in combination with endocrine therapies can suppress tumour growth in ER+ xenograft models.[6]

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



Footnotes: Adapted from Dickson 2014[36]
Abbreviations: CDK: cyclin dependent kinase; P: phosphorylation; RB: retinoblastoma

CDK 4 and 6 inhibitors in combination with endocrine therapy demonstrate consistent therapeutic effect across the drug class, but differ in terms of their safety profiles and administration regimens. Compared with the CDK4 and 6 inhibitors ribociclib and palbociclib, abemaciclib provides a unique safety profile characterised by a lower incidence of haematological adverse events. Unlike ribociclib and palbociclib, the safety profile of abemaciclib allows for continuous dosing, which may help with patient compliance, while providing continuous tumour suppression.[7] Treatment holidays of seven days are necessary following 21 days of treatment, as part of each 28-day cycle with ribociclib and palbociclib, due to haematological toxicity, particularly neutropenia.[37-39] The most common adverse event of abemaciclib in clinical trials was diarrhoea,[5, 40, 41] which was of low severity (Grade 1 or 2) in the majority of cases or easily managed with anti-diarrhoeal medication.[5] Whilst some neutropenia was also evident with abemaciclib treatment, it was not considered a dose-limiting toxicity, nor severe enough to warrant an intermittent treatment schedule.[5, 40]

Abemaciclib also demonstrates unique pharmacological selectivity. In enzymatic assays, abemaciclib is 14-times more selective and potent for cyclin D1/CDK4 than for cyclin D3/CDK6.[6] 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.[4, 42] The selectivity of abemaciclib is evident in comparison to the other CDK inhibitors; compared with palbociclib, abemaciclib demonstrates greater selectivity for CDK4 versus CDK6, and compared with ribociclib, abemaciclib inhibits both CDK4 and 6 at lower concentrations. These differences in activity may translate into differential tissue responses, thus possibly providing abemaciclib with a unique clinical profile.

The MONARCH trials

Three clinical studies have investigated the use of abemaciclib in treating HR+/HER2− advanced or metastatic breast cancer. This submission focusses on the randomised phase III study (MONARCH 3), which evaluated abemaciclib or placebo in combination with a non-steroidal

aromatase inhibitor (NSAI; anastrozole or letrozole) first-line therapy. Participants were postmenopausal women with HR+/HER2− locoregionally recurrent or metastatic breast cancer, who were naïve to systemic treatment this setting.[5] PFS was significantly longer in patients treated with an NSAI plus abemaciclib, compared with patients treated with a NSAI plus placebo (hazard ratio = [redacted]). This improvement in PFS equates to a [redacted]% reduction in the risk of disease progression or death compared to those receiving NSAI monotherapy. The ORR was also significantly higher in the abemaciclib arm compared with the placebo arm.[5] Treatment with abemaciclib in combination with a NSAI exhibited a tolerable and manageable safety profile.[5]

The other two MONARCH trials are subject to separate NICE single technology appraisals (ID1339 for MONARCH 2, ID1347 for MONARCH 1). MONARCH 2, a randomised phase III trial, compared the efficacy and safety of abemaciclib plus fulvestrant with placebo plus fulvestrant in women with HR+/HER2− advanced or metastatic breast cancer who had progressed on or after prior ET.[40] PFS was significantly extended for abemaciclib plus fulvestrant patients versus placebo plus fulvestrant patients (median difference 7.1 months, hazard ratio = 0.553 [95% CI 0.449 to 0.681]). Patients treated with abemaciclib demonstrated a 44.7% reduction in the risk of disease progression or death.[40] 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 the higher dose of 200 mg, in women with refractory HR+/HER2− metastatic breast cancer.[41] These patients represent a poor-prognostic, heavily pre-treated population. At 12 months, the ORR was 19.7%, and overall continuous dosing of single-agent abemaciclib demonstrated positive clinical activity. Consistent with the results of MONARCH 3, MONARCH 2 and MONARCH 1 both demonstrated manageable safety profiles.

Clinical trial data demonstrates the efficacy of abemaciclib in combination with ET, as a first-line treatment option for HR+/HER2− locoregionally recurrent or metastatic breast cancer. Abemaciclib has been shown to significantly extend PFS when given in combination with a NSAI compared with a NSAI plus placebo.[5]

Marketing Authorisation and health technology assessment

- Marketing Authorisation Application (MAA) was submitted in July 2017.
- Committee for Medicinal Products for Human Use (CHMP) opinion is expected in 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 breast cancer has been provided. This is followed by a more detailed description of treatment for advanced breast cancer, which is the focus of the submission.

Summary of treatment pathway for early breast cancer (prior to the advanced stage)

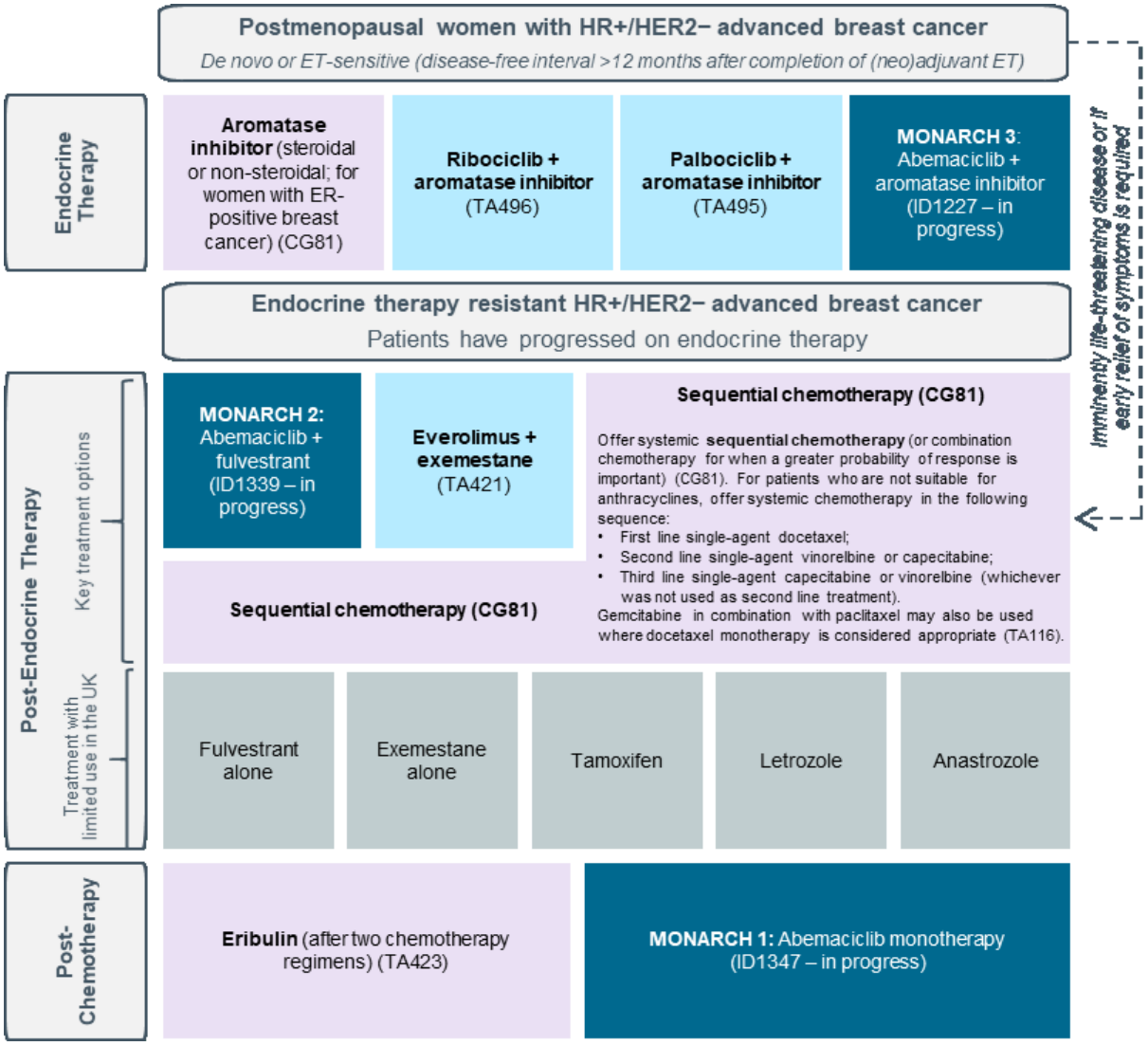
NICE Clinical Guideline 80 (CG80) recommend patients with early breast cancer undergo surgery and appropriate systemic therapy, unless significant comorbidity precludes surgery.[13] Adjuvant therapy is prescribed based on prognostic and predictive factors. Guidelines recommend adjuvant chemotherapy or radiotherapy to start as soon as clinically possible within 31 days of completion of surgery.

Adjuvant ovarian ablation or suppression in combination with tamoxifen, or adjuvant therapy with an aromatase inhibitor, tamoxifen or docetaxel, may also be recommended following surgery. This would depend on the patient's menopausal status, ER-receptor status, risk of relapse, previous tamoxifen treatment and lymph-node involvement.[13] Growing evidence supports the use of adjuvant ET with a NSAI for up to 10 years, extending disease-free survival and preventing recurrence of disease in postmenopausal women.[43, 44]

Advanced breast cancer: current treatment pathway

Recommendations for the management and treatment of advanced breast cancer are provided by the NICE clinical guideline CG81 and by NICE single technology appraisals.[1-3, 45-54] The clinical pathway for patients with advanced breast cancer, based on current NICE guidance is presented in Figure 2. The third 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.[26]

Figure 2. Clinical pathway for patients with HR+/HER2− advanced or metastatic breast cancer, based on current NICE guidance



Sources: ID1227,[1] ID1339,[2] ID1347,[3] NICE CG81,[49] TA116,[50] TA421,[51] TA423,[52] TA495,[53] TA496.[54]

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.[49] For patients who have received chemotherapy as initial treatment, ET is recommended following the completion of chemotherapy.[49]

Endocrine agents currently recommended by NICE include aromatase inhibitors and tamoxifen.[55] An aromatase inhibitor (either non-steroidal or steroidal) is recommended for postmenopausal women with HR-positive 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.[49] The third ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer also supports the use of ET as the preferred treatment option for HR+/HER2− breast cancer,[26] unless the patient has endocrine resistant disease. Patients with HR+ breast cancer may respond to endocrine therapy (endocrine sensitive), their disease may later become refractory to ET (acquired resistance), or patients may not respond to ET at the outset of treatment (*de novo* resistance).[21]

As of December 2017, NICE recommend initial treatment with CDK4 and 6 inhibitors palbociclib or ribociclib in combination with a NSAI at the same position in the treatment pathway as aromatase inhibitors alone i.e. for postmenopausal women with HR+/HER2− advanced breast cancer.[53-55] Notably, ESO-ESMO guidelines report the addition of a CDK4 and 6 inhibitor to ET to be a major advance in the management of advanced breast cancer, not seen since 2014. The guidelines support the use of palbociclib in combination with a NSAI as a preferred treatment option for HR+/HER2− breast cancer in postmenopausal women.[26]

Post-endocrine therapy (including chemotherapy)

NICE CG81 currently recommends sequential chemotherapy for patients who experience disease progression on ET.[49] Due to the significant toxicity burden associated with chemotherapy, treatment of advanced breast cancer patients aims to delay the initiation of chemotherapy as long as possible. According to NICE CG81, combination chemotherapy should only be considered for patients for whom treatment response is particularly important, providing the patient understands and accepts the additional toxicity.[49, 56] Everolimus in combination with exemestane (TA421),[51] or gemcitabine in combination with paclitaxel (TA116), [1] are also recommended as treatment options for postmenopausal women with HR+/HER2− advanced breast cancer as post-ET.[49, 50]

Post-chemotherapy

For patients with advanced breast cancer whose disease progresses on or after sequential chemotherapy (at least 2 regimens), eribulin is recommended as a treatment option.[52, 55]

Proposed position of abemaciclib in treatment pathway

This appraisal presents abemaciclib in combination with a NSAI in the same position in the treatment pathway as palbociclib and ribociclib (both in combination with a NSAI), as an initial treatment option for advanced HR+/HER2− breast cancer in postmenopausal women.[53, 54]

Other planned appraisals will evaluate the use of abemaciclib in different positions within the treatment pathway. This includes the use of abemaciclib in combination with fulvestrant

(MONARCH 2), and as monotherapy (MONARCH 1), for women of any menopausal status with HR+/HER2− advanced or metastatic breast cancer.

B.1.4 *Equality considerations*

The technology is unlikely to raise any equality concerns, considering that the technology will not exclude certain patient populations. Introduction of abemaciclib is not likely to lead to recommendations which differentially impact patients protected by the equality legislation or disabled persons.

B.2 Clinical effectiveness

Summary of clinical effectiveness systematic literature review (SLR)

- A SLR was conducted to identify relevant clinical evidence on the efficacy and safety of abemaciclib in combination with a non-steroidal aromatase inhibitor (NSAI) and potential comparators for the management of HR+/HER2− locoregionally recurrent or metastatic breast cancer with no prior systemic treatment for their advanced disease.
- The SLR identified one randomised controlled trial (RCT) for abemaciclib plus NSAI in the relevant patient population as defined by the NICE scope, for which published interim data were available (MONARCH 3).
- The results of the MONARCH 3 trial at the final analysis, including data for patient-reported HRQoL outcomes, are presented in the CSR addendum.[57]
- The primary outcome was investigator-assessed PFS as defined by RECIST version 1.1.[58]
- 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]).

Summary of clinical effectiveness of abemaciclib plus NSAI

- The MONARCH 3 study met its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in investigator-assessed PFS at the interim analysis. By delaying disease progression, the quality of life of patients is maintained for a longer period of time, and the need for treatment with chemotherapy regimens of high toxicity is delayed.
- At the final PFS analysis, [redacted] patients ([redacted]) in the abemaciclib plus NSAI arm and [redacted] patients ([redacted]) in the placebo plus NSAI arm had experienced PFS events of disease progression or death. PFS data were censored for [redacted] patients ([redacted]) in the abemaciclib plus NSAI arm and [redacted] patients ([redacted]) in the placebo plus NSAI arm.
- Median PFS was significantly prolonged in the abemaciclib plus NSAI arm ([redacted] months) relative to placebo plus NSAI ([redacted] months), with a HR of [redacted] (95% confidence interval [CI]: [redacted] to [redacted], 2-sided [redacted]).
- Treatment with abemaciclib plus NSAI provided patients with an additional [redacted] months of PFS in comparison to treatment with placebo plus NSAI, and a clinically meaningful reduction in the risk of disease progression or death of [redacted].
- [redacted] (HR [redacted] [95% CI, [redacted]]).
- At the time of the final analysis, [redacted], with a total of [redacted] events ([redacted] deaths) in the abemaciclib plus NSAI arm and [redacted] events ([redacted] deaths) in the placebo plus NSAI arm. [redacted], with a HR of [redacted] (95% CI [redacted]; 2-sided stratified log-rank [redacted]).
- At the final analysis, the ORR was [redacted] in the abemaciclib plus NSAI arm ([redacted] [95% CI: [redacted]] relative to placebo with NSAI ([redacted] [95% CI: [redacted]]), resulting in a statistically significant odds ratio of [redacted] ([redacted]) in favour of abemaciclib plus NSAI. This indicates that patients treated with abemaciclib plus NSAI had [redacted] odds of exhibiting a complete response (CR) or partial response (PR) than patients treated with placebo plus NSAI.
- The DCR for patients in the abemaciclib plus NSAI arm and the placebo plus NSAI arm were [redacted] (95% CI [redacted]) and [redacted] (95% CI [redacted]), respectively.
- The CBR for patients in the abemaciclib plus NSAI arm ([redacted] [95% CI [redacted]]) was significantly higher than for patients in the placebo plus NSAI arm ([redacted] [95% CI [redacted]]). This suggests that patients treated with abemaciclib plus NSAI were more

likely to exhibit a PR or CR and/or stable disease for at least six months than patients treated with placebo plus NSAI.

- The median DoR was longer in the abemaciclib plus NSAI arm (27.39 months [95% CI [redacted] to [redacted]] than in the placebo plus NSAI arm ([redacted] months [95% CI [redacted]])
- HRQoL as measured by the EORTC QLQ-C30 and EQ-5D-5L instruments, was generally stable and similar between treatment arms over the course of the study.
- A [redacted] ([redacted]. There were no large differences[59] in EORTC-QLQ-C30 scores, and therefore health status, between treatment arms.
- Overall, the [redacted], supporting that the overall health status of patients was maintained with the addition of abemaciclib to an NSAI throughout the study.

Summary of indirect treatment comparison

- A network meta-analysis (NMA) was conducted to compare the efficacy of relevant comparators for the MONARCH 3 indication using available data from RCTs.
- The reference treatment chosen for the analysis was the NSAIs (anastrozole [ANAS] / letrozole [LTZ]), with abemaciclib plus ANAS/LTZ (ABE-ANAS/LTZ), ribociclib plus ANAS/LTZ (RIBO-ANAS/LTZ) and palbociclib plus ANAS/LTZ (PAL-ANAS/LTZ) as relevant comparators.
- The endpoints chosen for analysis were PFS, OS, ORR, CBR and CR.
- ABE-ANAS/LTZ (HR [redacted]; 95% credible interval (CrI) [redacted]), RIBO-ANAS/LTZ (HR [redacted]; 95% CrI [redacted]) and PAL-ANAS/LTZ (HR [redacted]; 95% CrI [redacted]) each similarly showed a significantly lower hazard rate of progression or death compared to ANAS/LTZ.
- For OS, the data for ABE-ANAS/LTZ (MONARCH 3) and RIBO-ANAS/LTZ (MONALEESA-2) were immature at the time of analysis (i.e. median OS was not reached in at least one arm), and therefore the relative treatment effects from these trials are uncertain. RIBO-ANAS/LTZ and PAL-ANAS/LTZ both showed lower hazards of death compared to ANAS/LTZ, but these were not significant (HR [redacted]; CrI [redacted]; HR [redacted]; CrI [redacted] respectively). The treatment effect for ABE-ANAS/LTZ vs. ANAS/LTZ was statistically insignificant (HR [redacted] [CrI [redacted]]).
- No statistically significant OR estimates were observed for any treatment compared to ANAS/LTZ. PAL-ANAS/LTZ showed the highest odds of clinical benefit (OR [redacted]; 95% CrI [redacted]) compared to ANAS/LTZ. Comparable OR estimates were observed between ABE-ANAS/LTZ (OR [redacted]; 95% CrI: [redacted]) and RIBO-ANAS/LTZ (OR [redacted]; 95% CrI [redacted]).
- Overall, the treatment effects for each of the endpoints were similar between ABE-ANAS/LTZ, PAL-ANAS/LTZ and RIBO-ANAS/LTZ; supporting that the efficacy of abemaciclib plus ANAS/LTZ is at a minimum comparable to the other CDKs, ribociclib and palbociclib.
- In consideration of heterogeneity, the patient populations for the ABE-ANAS/LTZ (MONARCH 3), PAL-ANAS/LTZ (PALOMA1/TRIO-18, PALOMA-2) and RIBO-ANAS/LTZ (MONALEESA-2) trials were similar regarding HR+/HER2− status, age, postmenopausal status, stage of disease, performance status, proportion of patients with bone-only disease, and having no prior history of ET or chemotherapy in the advanced setting. However, there were differences between the trial populations in the required DFI following adjuvant therapy and the proportion of patients with visceral involvement. The proportion of patients with liver metastases was reported only in one trial (MONARCH 3). These factors should be considered when interpreting the results. The

trials for the comparators were closely connected in the network (one intermediate node [ANAS/LTZ]).

Summary of safety of abemaciclib plus NSAI

- The most frequent TEAEs reported by the investigator in the abemaciclib plus NSAI arm were diarrhoea ([redacted]), infections/infestations ([redacted]), neutropenia ([redacted]), fatigue ([redacted]), and nausea ([redacted]).
- Diarrhoea was predominantly of low grade in the abemaciclib plus NSAI arm, experienced by [redacted], [redacted], [redacted] and [redacted] at grades 1–4, respectively.
- In the abemaciclib plus NSAI arm, neutropenia was reported by [redacted] and [redacted] of patients at grade 3 and 4, respectively. The neutrophil count generally remained stable once decreased and was reversible following discontinuation. Febrile neutropenia was reported as a non-serious TEAE in [redacted] ([redacted]) in the abemaciclib plus NSAI arm.
- A higher proportion of patients ([redacted]) treated with abemaciclib plus NSAI experienced at least one treatment-emergent SAE, than those treated with placebo plus NSAI ([redacted]). The most common SAE reported was [redacted] ([redacted]) in the abemaciclib plus NSAI arm.
- Overall, abemaciclib plus NSAI was well-tolerated, with an acceptable AE profile.

Summary of innovation

- Abemaciclib plus NSAI delays disease progression, thus maintaining patient quality of life and delaying the need for cytotoxic chemotherapy regimens.
- Abemaciclib plus NSAI has a tolerable safety profile that allows for continuous dosing. A continuous treatment schedule may facilitate optimal inhibition of cell proliferation and tumour growth in patients; pre-clinical evidence has demonstrated that continuous inhibition of CDK4 and 6 is important for sustained cell growth arrest resulting in apoptosis or senescence.[5, 6, 60]

Conclusion

- Abemaciclib plus NSAI provided clinically meaningful improvements in PFS and ORR in patients with HR+/HER2- advanced breast cancer.
- Abemaciclib plus NSAI was well-tolerated, with an acceptable AE profile.
- The MONARCH 3 trial was methodologically robust and well reported, and considered to be at low risk of bias.
- The results of the MONARCH 3 study are well-aligned with the decision problem specified in the NICE scope and can be generalised to the UK population, with patients included from [redacted], and [redacted].

B.2.1 *Identification and selection of relevant studies*

A SLR was conducted to identify relevant clinical evidence on the efficacy and safety of abemaciclib in combination with a NSAI, and its potential comparators. The target patient population included women with HR+/HER2− locoregionally recurrent or metastatic breast cancer with no prior systemic treatment for their advanced disease. 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 RCT (MONARCH 3) for abemaciclib plus NSAI for which published literature of the interim analysis was available. The results of the MONARCH 3 trial at the final analysis, including data for the patient-reported HRQoL outcomes, are presented from the clinical

study report (CSR)[4] and CSR addendum.[57] A summary of clinical effectiveness evidence from MONARCH 3 is presented in Table 3.

Table 3. Clinical effectiveness evidence for abemaciclib plus NSAI

Study	**MONARCH 3 (NCT02246621)**		
Study design	Phase III, multi-centre, placebo-controlled, randomised, double-blinded trial		
Population	Postmenopausal women (≥18 years) with HR+/HER2− locoregionally recurrent or metastatic breast cancer who had no prior systemic therapy in the advanced setting		
Intervention(s)	Abemaciclib 150 mg twice daily (every 12 hours) on a continuous 28-day treatment cycle, in combination with a NSAI (either 1 mg/day anastrozole or 2.5 mg/day letrozole)		
Comparator(s)	Placebo taken twice daily (every 12 hours) plus a NSAI (1 mg/day anastrozole or 2.5 mg/day letrozole) taken daily on a continuous 28-day treatment cycle		
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 3 is the pivotal phase III study for abemaciclib plus NSAI in postmenopausal women with HR+/HER2− locoregionally recurrent or metastatic breast cancer who had no prior systemic therapy in the advanced setting. 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	Primary outcome
	Investigator-assessed PFS as defined by RECIST version 1.1.[58] Assessment of PFS for a randomly selected subset of patient scans was performed by an independent panel of radiologists at the interim analysis, with a full independent review of PFS for all randomised patients at the final analysis.
	Secondary outcomes
	• **OS** and OS rate at 1, 2, and 3 years[a]
	• Response rates
	  ○ ORR (CR + PR)
	  ○ DCR (CR + PR +SD)
	  ○ CBR (CR + PR + SD ≥6 months);
	  ○ DoR (measured from the date of first evidence of CR or PR to the date of objective progression or death due to any cause, whichever was earlier)
	• HRQoL and symptom burden
	  ○ EORTC QLQ-C30 (Core-30)
	  ○ **EQ-5D-5L**
	Safety measures
	• **TEAEs of treatment**		

All other reported outcomes	• Safety measures ○ Concomitant therapies		

[a] At the time of cut-off for the MONARCH 3 trial, OS data were still immature and data are not expected within the appraisal timelines. Outcomes in **bold** indicate those used in the economic model.

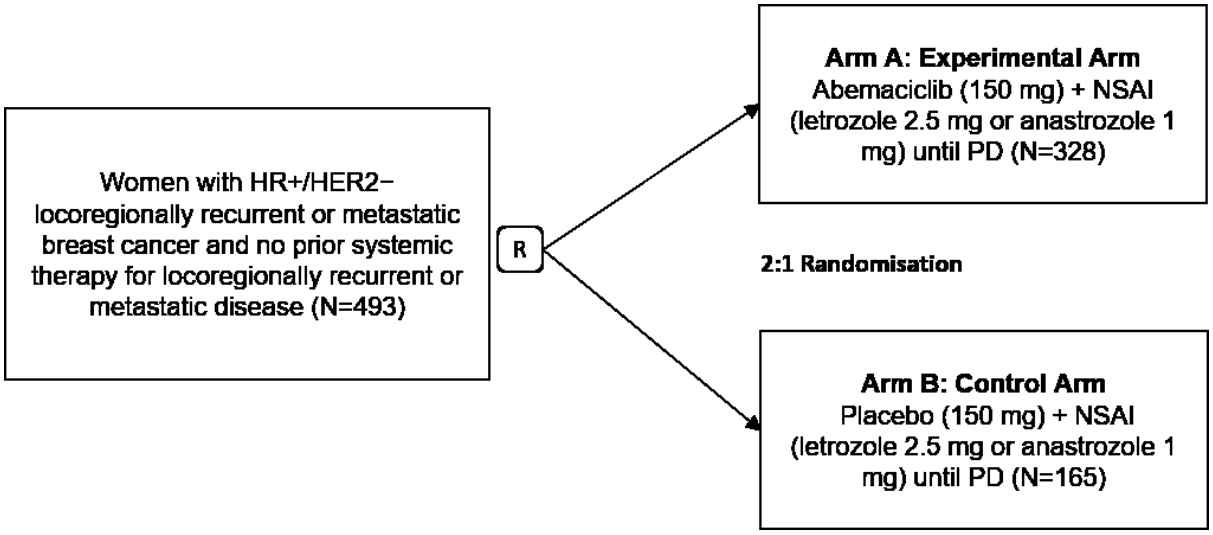
Abbreviations: AE: adverse event; CBR: clinical benefit rate; CR: complete response; DCR: disease-control rate; DoR: duration of response; EORTC QLQ: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FSH: follicle-stimulating hormone; HRQoL: health-related quality of life; NSAI: non-steroidal aromatase inhibitor; ORR: objective response rate; OS: overall survival PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumours;[58] TEAE: treatment-emergent adverse event.
Source: Goetz et al. 2017[5]; Eli Lilly Data on File (Clinical Study Report). 2017[4]

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

B.2.3.1 Trial design

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

Figure 3. Overview of study design for MONARCH 3



Abbreviations: HR: hormone receptor; HER2: human epidermal growth factor receptor 2; NSAI: non-steroidal aromatase inhibitor; PD: progressive disease.
Source: Goetz et al. 2017[5]

B.2.3.2 Eligibility criteria

The eligibility criteria for MONARCH 3 are presented in Table 4.

Table 4. Eligibility criteria for MONARCH 3

Inclusion criteria	Exclusion criteria

Patients were eligible for inclusion in the study if they met all of the following inclusion criteria:
• Had a diagnosis of HR+/HER2− breast cancer. Although not required as a protocol procedure, metastatic disease should have been considered for biopsy whenever possible to reassess HR and HER2 status if clinically indicated
  ○ HR+ breast cancer must have expressed, by immunohistochemistry (IHC), at least one hormone receptor (ER or PgR), as defined in the relevant ASCO/College of American Pathologists Guidelines[61]
  ○ HER2− breast cancer must not have demonstrated, at initial diagnosis or upon subsequent biopsy, overexpression of HER2 by either IHC or ISH as defined in the relevant ASCO/College of American Pathologists Guidelines[62]
• Had locoregionally recurrent disease not amenable to resection or radiation therapy with curative intent or metastatic disease
• Had postmenopausal status, defined as meeting one of the following:
  ○ Prior bilateral oophorectomy
  ○ Age ≥60 years
  ○ Age <60 years and amenorrheic (non-treatment-induced amenorrhea secondary to tamoxifen, toremifene, ovarian suppression or chemotherapy) for at least 12 months. FSH and oestradiol must have been in the postmenopausal range
• Had one of the following as defined by RECIST version 1.1[58]
  ○ Measurable disease
  ○ Non-measurable bone-only disease (blastic bone lesions, lytic bone lesions without a measurable soft tissue component, or mixed lytic-blastic bone lesions without a measurable soft tissue component
• Had a PS of ≤1 on the ECOG scale
	Patients were excluded from the study if they met any of the following exclusion criteria:
	• Had visceral crisis, lymphangitic spread, or leptomeningeal carcinomatosis. Visceral crisis was not the mere presence of visceral metastases but implied severe organ dysfunction as assessed by symptoms and signs, laboratory studies, and rapid progression of the disease
	• Had inflammatory breast cancer
	• Had clinical evidence or history of CNS metastasis
	• Were receiving or had previously received endocrine therapy for locoregionally recurrent or metastatic breast cancer (a patient may have been enrolled if she received prior [neo]adjuvant endocrine therapy [including, but not limited to antioestrogens or aromatase inhibitors] for localised disease. In addition, a patient may have been enrolled if she had received ≤2 weeks of NSAI in this disease setting immediately preceding screening and agreed to discontinue NSAI until study treatment initiation)
	• Had received prior (neo)adjuvant endocrine therapy with a DFI ≤12 months from completion of treatment
	• Were receiving or had previously received chemotherapy for locoregionally recurrent or metastatic breast cancer (patients may have been enrolled if they received prior (neo)adjuvant chemotherapy for localised disease.)
	• Had received prior treatment with:
	  ○ Everolimus
	  ○ Any CDK4/6 inhibitor (or participated in any CDK4/6 inhibitor clinical trial for which treatment assignment was still blinded)

Inclusion criteria	Exclusion criteria
• Had adequate organ function • Female and ≥18 years of age	• Had initiated bisphosphonates or approved receptor activator of nuclear factor kappa-B ligand (RANK-L) targeted agents (e.g. denosumab) <7 days prior to randomisation

Abbreviations: ASCO: American Society of Clinical Oncology; CDK; cyclin-dependent kinase; CNS: central nervous system; DFI: disease-free interval; ECOG: Eastern Cooperative Oncology Group; ER: oestrogen receptor; FSH: follicle-stimulating hormone; IHC: immunohistochemistry; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; ISH: in-situ hybridisation; NSAI; non-steroidal aromatase inhibitor; PgR: progesterone receptor; PS: performance status; RANK-L: receptor activator of nuclear factor-kappaB ligand; RECIST: Response Evaluation Criteria in Solid Tumours.[58]
Source: Eli Lilly Data on File (Clinical Study Report P40–42). 2017[4]

B.2.3.3 Summary of MONARCH 3 methodology

A summary of the methodology of MONARCH 3 is available in Table 5.

Table 5. Summary of MONARCH 3 methodology

Location	Multicentre
Trial Design	• Randomised, double-blinded, placebo-controlled, phase III study • Using an interactive web response system (IWRS), patients were randomised 2:1 to receive abemaciclib (150 mg twice daily) or matching placebo, in combination with an NSAI (1 mg/day anastrozole or 2.5 mg/day letrozole). Randomisation was stratified by: ○ nature of disease (visceral metastases [included lung, liver, pleural, peritoneal, or adrenal gland involvement at the time of randomisation], bone-only metastases or other) ○ prior (neo)adjuvant endocrine therapy (aromatase inhibitor therapy [e.g. anastrozole, exemestane, and letrozole), other, or no prior endocrine therapy) • Treatment was continued until disease progression, unacceptable toxicity, death, or patient withdrawal for any reason • Crossover between the study arms was not permitted; patients were allowed to discontinue either abemaciclib/placebo or NSAI, and continue the other drug as a monotherapy.[5] • Patients, investigational sites, and the sponsor study team did not have immediate access to investigational treatment assignments for any patients. A minimum number of Lilly personnel saw the randomisation table and treatment assignments prior to the interim analysis. Access to unblinded data/documents was controlled by restricting access to the data/documents in Lilly's data and statistical warehouse
Eligibility criteria for participants	Postmenopausal women with HR+, HER2- locoregionally recurrent or metastatic breast cancer who had not received prior systemic therapy in this disease setting The full inclusion and exclusion criteria are presented in Table 4.
Settings and locations where the data were collected	International (158 sites in 22 countries): Australia, Austria, Belgium, Canada, Germany, Spain, France, Greece, Israel, Italy, Japan, Korea, Mexico, Netherlands, New Zealand, Russia, Slovakia, Sweden, Turkey, Taiwan, United Kingdom (four sites) and United Sates of America
Trial drugs	• Abemaciclib arm (n=328): Abemaciclib 150 mg twice daily (every 12 [±2] hours) on a continuous 28-day treatment cycle, in combination with a NSAI (either 1 mg/day anastrozole or 2.5 mg/day letrozole) • Placebo arm (n=165): Placebo twice daily (every 12 [±2] hours) plus a NSAI (1 mg/day anastrozole or 2.5 mg/day letrozole) taken daily on a continuous 28-day treatment cycle

	• The starting dose at 150 mg twice daily was based on findings from the Phase 1 Studies JPBA[63] and JPBH[60], where there was evidence of clinical activity at doses of both 150 mg and 200 mg twice daily • Letrozole or anastrozole were taken orally every 24 hours (±2) on Days 1 through 28 of each 28 day-cycle. The majority (79.1%) of patients received letrozole, and patients should have remained on the same NSAI throughout the study. Notably, evidence has shown that letrozole and anastrozole are comparable in efficacy[64], therefore the choice of NSAI is unlikely to have differentially affected efficacy outcomes • All drugs were administered orally • Dose interruptions and sequential dose reductions (50 mg) of abemaciclib or placebo were permitted according to pre-specified dose-adjustment procedures for patients who exhibited treatment-related toxicities, but blinded study drug must have been discontinued if further dose reduction was required beyond 50 mg twice daily • In the event that blinded study drug was discontinued, a patient may have continued to receive letrozole or anastrozole. Dose adjustments for letrozole or anastrozole were not applicable, as only single-dose strength is approved for each medication
Permitted and disallowed concomitant medication	• Appropriate documentation of all forms of pre-medication, supportive care, and concomitant medication were recorded at each visit, and at the time of discontinuation and 30-day short-term follow-up visit • The use of concomitant therapies for cancer (including hormonal anticancer therapies, chemotherapy, and immunotherapy) or the use of megestrol acetate as an appetite stimulant, were not permitted while patients were on study treatment • A patient with locoregionally recurrent breast cancer may have received surgery with or without radiotherapy if study treatment rendered the tumour operable. Radiotherapy for other reasons (e.g. palliative) was not permitted without permanent discontinuation from study treatment. • Grapefruit juice as well as inducers (e.g. phenytoin or carbamazepine) and strong inhibitors of CYP3A should have been substituted or avoided if possible (inhibitors and/or inducers of CYP3A may alter the metabolism of abemaciclib) • Supportive management for diarrhoea included the use of anti-diarrhoeals (e.g. loperamide), IV rehydration, electrolyte replacement) • Use of analgesics, anti-emetics and anti-nauseants were permitted when indicated • All patients may have received supportive therapy with dexamethasone, preferably ≤7 days, if clinically indicated. Patients requiring >7 days of dexamethasone therapy did not incur a protocol deviation • Patients with bone metastases present on baseline imaging should have been appropriately treated with bisphosphonates or RANK-L targeted agents (e.g. denosumab) per respective approved labels. Initiation of treatment with bone-modifying agents must have begun at least 7 days prior to randomisation. Patients receiving bisphosphonates or RANK-L targeted agents should not have switched treatments (e.g. replaced a bisphosphonate with denosumab) while on study treatment.

Primary outcomes	• The pre-specified primary objective of this study was to compare treatment with abemaciclib plus NSAI therapy versus placebo plus NSAI therapy with respect to PFS in postmenopausal women with HR+, HER2- locoregionally recurrent or metastatic breast cancer who had not received prior systemic therapy in this disease setting. ○ The interim and final efficacy analyses were performed on the Intention to Treat (ITT) population, which included all randomised patients. ○ PFS was investigator-assessed at the interim and final analysis. Assessment of PFS for a randomly selected subset of patient scans was performed by an independent panel of radiologists at the interim analysis, with a full independent review of PFS for all randomised patients at the final analysis. ○ PFS time was measured from the date of randomisation to the date of objective progression or death due to any cause ○ Baseline tumour measurements were performed on each patient within 28 days of randomisation by computed tomography or magnetic resonance imaging scans. ○ Tumour assessments were performed locally according to RECIST version 1.1[58] on Day 21–28 of every second cycle beginning with Cycle 2 and continuing through Cycle 18, Day 21–28 of every third cycle after Cycle 18, and within 14 days of clinical progression ○ According to RECIST version 1.1[58], the finding of a new lesion should have been unequivocal and not attributable to findings thought to represent something other than tumour (e.g. some “new” bone lesions may have been simply healing or flare of pre-existing lesions). Pathologic fracture, new compression fracture, or complications of bone metastases were not considered to be evidence of disease progression, unless at least one of the above criteria were met. ○ For those patients with non-measurable, bone only disease, objective progression was established if the appearance of one or more new lesions (in bone or outside of bone), or unequivocal progression of existing bone lesions. For patients with locoregionally recurrent disease for whom surgery was performed while on study with evidence of residual disease postoperatively, new baseline measurements should have been taken and RECIST version 1.1[58] applied. ○ If a patient was not known to have progressed or died at the time of analysis, PFS time 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: defined as time from study randomisation to the date of death from any cause
	• OS rate at 1, 2, and 3 years
	• ORR: the proportion of patients with CR or PR according to RECIST version 1.1.[58]
	  ○ A CR refers to the disappearance of all target lesions.
	  ○ A PR refers to at least a 30% reduction in the sum of diameters of target lesions (taking as reference the baseline sum diameters)
	  ○ Local tumour assessments according to RECIST v1.1 were performed approximately every 8 weeks following randomisation for 18 months (to Cycle 18), then every 12 weeks and within 14 days of clinical progression
	• DCR: The proportion of patients with CR, PR, or SD according to RECIST version 1.1[58]
	• CBR: The proportion of patients with CR, PR, or SD ≥6 months according to RECIST version 1.1[58]
	• 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 is earlier
	• All efficacy analyses were performed on the ITT population, which included all randomised patients
	Safety
	• AEs were evaluated in the safety population (327 patients in the abemaciclib plus NSAI arm and 161 in the placebo plus NSAI arm), defined as all patients who received at least one dose of study drug
	• AEs (terms and severity grades were investigator-assigned using CTCAE version 4) were recorded at every visit, on Day 1 of every treatment cycle.
	• AEs were further classified as TEAE or SAE events
	• A TEAE was defined as any AE that began between the day of first dose and 30 days after treatment discontinuation (or up to any time if serious and related to study treatment), or any pre-existing condition that increased in CTCAE grade between the day of first dose and 30 days after treatment discontinuation (or up to any time if serious and related to study treatment).
	• SAEs were defined as any AE that resulted in one of the following outcomes:
	  ○ Death
	  ○ A life-threatening experience (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 PROs • The EORTC QLQ-C30 and EQ-5D-5L questionnaires were administered at baseline and then Day 1 of every second cycle beginning with Cycle 3-19, and Day 1 of every third cycle after Cycle 19 • PROs were evaluated in the safety population (327 patients in the abemaciclib plus NSAI arm and 161 in the placebo plus NSAI arm), defined as all patients who received at least one dose of study drug • EORTC QLQ-C30 ○ The questionnaire is comprised of five multi-item scales (physical, role, social, emotional and cognitive functioning) and 9 single items (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties). All scales and single-item measures of the EORTC QLQ-C30 range from 0–100, with a higher score representing a higher response or symptom level. Clinically relevant differences compared to baseline were reported as small, medium or large per EORTC QLQ-C30-specific evidence-based guidelines.[59, 65] • EQ-5D-5L ○ 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. Corroborating health status data were collected by patients completing the sixth and last EQ-5D-5L item: a VAS "thermometer" measuring "your health today" on a 100-point scale and ranging from 0 ("worst health you can imagine") to 100 ("best health you can imagine").
Pre-planned subgroups	Efficacy (PFS and OS) subgroups: • All baseline stratification factors ○ Nature of disease (visceral metastases vs. bone-only metastases vs. other) ○ Prior (neo)adjuvant ET (aromatase inhibitor therapy vs. other vs. no prior ET) • NSAI received at cycle 1 (letrozole vs anastrozole) • Disease setting (de novo metastatic vs recurrent metastatic vs locoregionally recurrent) • 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)

	• Baseline ECOG PS (0 vs 1)

Abbreviations: AE: adverse event**;** AI: aromatase inhibitor; BOR: best overall response; CBR: clinical benefit rate; CR: complete response; CTCAE: Common Terminology Criteria for Adverse Events; CYP3A: Cytochrome P4503A; DCR: disease control rate; DFI: disease-free interval; DoR: duration of response; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; ET: endocrine therapy; NSAI: non-steroidal aromatase inhibitor; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PgR: progesterone receptor; PS: performance status; RECIST: Response Evaluation Criteria in Solid Tumours; TEAE: treatment emergent adverse event; SAE; serious adverse event; SD: stable disease.
Source: Goetz et al. 2017[5]; Eli Lilly Data on File (JPBM Clinical Study Report. P77, 242-247). 2017[4]

B.2.3.4 Baseline characteristics

The baseline characteristics of patients included in the MONARCH 3 study are presented in Table 6. A total of 493 patients were randomised to abemaciclib plus NSAI (n=328) or placebo plus NSAI (n=165). Patient characteristics at baseline were well balanced between treatment groups. All patients were female, with an approximate mean age of 63 years ([redacted] vs [redacted] years in the abemaciclib and placebo arms, respectively). The [redacted] patients were [redacted] ([redacted]). [redacted] of included patients were enrolled at sites in Europe ([redacted]); including four sites in the UK, with [redacted] and [redacted] of patients enrolled at sites in Asia and North America, respectively.

Except for one patient for whom HR and HER2 receptor status was missing, all patients had HR+ breast cancer ([redacted]), and approximately [redacted] of patients had disease that was positive for both hormone receptors (ER and PgR). All patients had breast cancer that was HER2−. Overall, the median duration of disease (from initial diagnosis of disease to randomisation) was [redacted] months (range: [redacted] to [redacted] months). The majority of patients had de novo (39.8%) or recurrent ([redacted]%) metastatic disease, and a smaller proportion of patients had locoregionally recurrent disease ([redacted]%). All patients had an ECOG performance status of 0 or 1.

Prior systemic therapies were received by [redacted] patients ([redacted]), including [redacted] of patients in the neoadjuvant setting and [redacted] of patients in the adjuvant setting. Prior chemotherapy was received by [redacted] of patients. Approximately [redacted]% of patients had received prior ET including [redacted] patients ([redacted]) in the neo-adjuvant setting and [redacted] patients ([redacted]) in the adjuvant setting. Prior treatment with an aromatase inhibitor was recorded by 27.4% of patients and [redacted] of had received other prior endocrine therapy, most commonly tamoxifen ([redacted]).

Table 6. MONARCH 3 baseline characteristics

Baseline characteristic	Abemaciclib + NSAI N=328	Placebo + NSAI N=165
Age		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	63.0 (38.0, 87.0)	63.0 (32.0, 88.0)
Sex		
Female, n (%)	328 (100.0)	165 (100.0)
Race, n (%)[a,b]		
White	186 (56.7)	102 (61.8)
Asian	103 (31.4)	45 (27.3)
Other	11 (3.4)	7 (4.2)
Region, n (%)		
Europe	[redacted]	[redacted]
Asia	[redacted]	[redacted]
North America	[redacted]	[redacted]
ECOG performance status		
0	192 (58.5)	104 (63.0)

Baseline characteristic	Abemaciclib + NSAI N=328	Placebo + NSAI N=165
1	136 (41.5)	61 (37.0)
Disease setting, n (%)[c]		
De novo metastatic	135 (41.2)	61 (37.0)
Metastatic recurrent	182 (55.5)	99 (60.0)
Locoregionally recurrent	11 (3.4)	5 (3.0)
Receptor status, n (%)		
ER+/PgR+	[redacted]	[redacted]
ER+/PgR-	[redacted]	[redacted]
ER+/PgR unknown	[redacted]	[redacted]
ER-/PgR+	[redacted]	[redacted]
HER2 receptor status		
Negative	[redacted]	[redacted]
Missing[d]	[redacted]	[redacted]
Duration of disease (months)		
Median (IQR)	[redacted] ([redacted])	[redacted] ([redacted])
Initial diagnosis disease stage		
Stage 0	[redacted]	[redacted]
Stage 1	[redacted]	[redacted]
Stage 2	[redacted]	[redacted]
Stage 3	[redacted]	[redacted]
Stage 4	[redacted]	[redacted]
Metastatic site, n (%)[c]		
Visceral	172 (52.4)	89 (53.9)
Bone only	70 (21.3)	39 (23.6)
Other	86 (26.2)	37 (22.4)
No. of organ sites, n (%)[b]		
1	96 (29.3)	47 (28.5)
2	76 (23.2)	42 (25.5)
≥3	154 (47.0)	75 (45.5)
Prior (neo)adjuvant chemotherapy, n (%)		

Baseline characteristic	Abemaciclib + NSAI N=328	Placebo + NSAI N=165
Yes	125 (38.1)	66 (40.0)
No	203 (61.9)	99 (60.0)
Prior (neo)adjuvant endocrine therapy, n (%)		
None	178 (54.3)	85 (51.5)
AI	85 (25.9)	50 (30.3)
Other endocrine therapy	65 (19.8)	30 (18.2)
Treatment-free interval, n (%)[e]		
<36 months	42/150 (28.0)	32/80 (40.0)
≥36 months	94/150 (62.7)	40/80 (50.0)
Unknown	14/150 (9.3)	8/80 (10.0)
Measurable disease, n (%)		
Yes	267 (81.4)	130 (78.8)
No	61 (18.6)	35 (21.2)

Footnotes: [a] Race was self-reported; [b] Data was missing for remaining patients; [c] Percentage does not equal 100% as the result of rounding; [d] For one patient in the placebo plus NSAI arm, hormone receptor status and HER2 status were missing. The patient was not treated; [e] Treatment-free interval was calculated only for patients with prior endocrine therapy.
Abbreviations: AI: aromatase inhibitor; ECOG; Eastern Cooperative Oncology Group; ER: oestrogen receptor; PgR: progesterone receptor; HER2: human epidermal growth factor receptor 2; IQR: Interquartile Range; NSAI: non-steroidal aromatase inhibitor.
Source: Goetz et al. 2017;[5] Eli Lilly Data on File (JPBM Clinical Study Report P88, 91, 94). 2017[4]

B.2.3.5 Concomitant Medications

A total of [redacted] patients ([redacted]) in the abemaciclib plus NSAI arm and [redacted] patients ([redacted]) in the placebo plus NSAI arm received concomitant medications. Concomitant medications that were reported for [redacted] of patients in either arm included expected supportive therapies, such as loperamide and paracetamol [redacted] and [redacted] in the abemaciclib plus NSAI arm vs. [redacted] and [redacted] in the placebo plus NSAI arm, respectively). The use of bone-modifying agents was balanced between the two treatment arms; the most common bone-modifying agents were denosumab ([redacted] in the abemaciclib plus NSAI arm and [redacted] in the placebo plus NSAI arm) and zoledronic acid ([redacted] in the abemaciclib plus NSAI arm and [redacted] in the placebo plus NSAI arm). Selected concomitant medications are summarised by category in Table 7.

Table 7. Summary of categories of selected concomitant medications, safety population

Category	Abemaciclib + NSAI N=327 n (%)	Placebo + NSAI N=161 n (%)
Patients with ≥1 analgesic	[redacted]	[redacted]
Patients with ≥1 antidiarrheal	[redacted]	[redacted]
Patients with ≥1 antiemetics and anti-nauseants	[redacted]	[redacted]

Patients with ≥1 bone-modifying agents	[redacted]	[redacted]
Patients with ≥1 erythropoietic agents	[redacted]	[redacted]
Patients with ≥1 G-CSF/GM-CSF	[redacted]	[redacted]

Abbreviations: G-CSF: granulocyte-colony stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; NSAI: non-steroidal aromatase inhibitor;
Source: Eli Lilly Data on File (JPBM Clinical Study Report Addendum for the Final Progression-Free Survival Analysis. P16). 2018[57]

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

All efficacy analyses including the primary outcome of PFS were performed on the ITT population, and were performed by treatment arm. The ITT population included all randomised patients, including two patients in the abemaciclib arm and three patients in the placebo arm who did not receive treatment. No patients were excluded from the ITT analysis of PFS, and missing data were not imputed. Data were censored if there was death or progressive disease (PD) after ≥2 missed tumour assessments; no baseline tumour assessment; or no post-baseline tumour assessment. If it was not known if a patient had progressed or died at the time of analysis, PFS was censored at the last known progression-free assessment.

Safety measures (treatment-emergent adverse events [TEAEs]) and PROs (EORTC QLQ-C30 and EQ-5D-5L) were evaluated in the safety population (327 patients in the abemaciclib plus NSAI arm and 161 in the placebo plus NSAI arm), defined as all patients who received at least one dose of study drug. During the study, safety interim analyses were performed every 3 months.

At the time of the data cut-off for the pre-planned interim analysis of PFS (31st January 2017), 164 patients (50.0%) in the abemaciclib plus NSAI arm and 98 patients (59.4%) in the placebo plus NSAI arm had discontinued treatment. The most common reason for treatment discontinuation was PD ([redacted] patients in the abemaciclib plus NSAI arm and [redacted] patients in the placebo plus NSAI arm). At the final PFS analysis, [redacted] patients were still receiving treatment, including [redacted] patients ([redacted] in the abemaciclib plus NSAI arm and 35 patients ([redacted]) in the placebo plus NSAI arm. 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.2.

The statistical analyses used for the primary endpoint, alongside the sample size calculations and methods for handling missing data are presented in in Table 8.

Table 8. Summary of statistical analyses for MONARCH 3

Hypothesis objective	The study was designed to demonstrate superiority of abemaciclib plus NSAI to placebo plus NSAI with respect to PFS. The null and alternative hypotheses were defined as follows (letting $S_{LY}(t)$ and $S_P(t)$ denote the PFS functions of abemaciclib plus NSAI and placebo plus NSAI, respectively): • Null hypothesis (H0): SLY(t) = SP(t) i.e. no difference in PFS between treatment groups • Alternative hypothesis (H1): SLY(t) > SP(t) i.e. superior PFS in abemaciclib plus NSAI treatment group compared with placebo plus NSAI group
Statistical analysis	**Primary outcome**: • PFS was defined as the time from the date of randomisation to the date of objective progression or the date of death due to any cause • There was 1 planned interim analysis and 1 final analysis to test the above hypotheses • PFS was investigator-assessed at the interim and final analysis. Assessment of PFS for a randomly selected subset of patient scans was performed by an independent panel of radiologists at the interim analysis, with a full independent review of PFS for all randomised patients at the final analysis • The interim analysis was to be undertaken after approximately 189 investigator-assessed PFS events had been observed • The final PFS analysis was to be performed after [redacted] investigator-assessed PFS events had been observed • PFS was determined using a 1-sided stratified log-rank test with a type I error rate of 0.025 stratified by nature of disease (visceral metastases vs. bone-only metastases vs. other) and prior (neo)adjuvant ET (AI therapy vs. other vs. no prior ET) • Once statistical significance was declared at either the interim or final analysis, the study was to be declared positive based on the primary endpoint • PFS curves for each treatment arm were estimated using the Kaplan-Meier method. PFS rates were compared at 4-month intervals up to 24 months using a normal approximation for the difference between rates • A Cox proportional hazard model[66] stratified by nature of disease and prior (neo)adjuvant ET with treatment as a factor was used to estimate the HR between the 2 treatment arms and the corresponding CI and Wald p-value.[67]
Sample size, power calculation	• Assuming an HR of 0.67, this sample size yielded more than 80% statistical power to detect superiority of the abemaciclib plus NSAI arm over the placebo plus NSAI 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 plus NSAI arm was 10 months, then the HR of 0.67 amounted to an approximately 5-month (50%) improvement in median PFS for the abemaciclib plus NSAI arm under an additional assumption of exponential survival distribution.

Data management, patient withdrawals	• All patients were followed up for progression until the patient had objective disease progression or until the final analysis of PFS, 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: AI: aromatase inhibitor**;** BOR: best overall response; CI: confidence interval; DCR: disease control rate; DoR: duration of response; ET: endocrine therapy; HR: hazard ratio; ITT: intention-to-treat; NSAI: non-steroidal aromatase inhibitor; ORR: objective response rate; OS: overall survival**;** PD: progressive disease; PFS: progression-free survival.
Source: Eli Lilly Data on File (JPBM Clinical Study Report. P36, 65–70, 7). 2017[4]

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

Overall, the results of the MONARCH 3 study may 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 evidence to suggest that the authors measured more outcomes than were reported. There was no difference in the rates of treatment discontinuation between treatment arms. A summary of the quality assessment for MONARCH 3 is provided in Table 9. The full quality assessment can be found in Appendix D.3.

Table 9. Overview of quality assessment for MONARCH 3

	Risk of bias
Was randomisation carried out appropriately?	Low risk of bias
Was the concealment of treatment allocation adequate?	Low risk of bias
Were the groups similar at the outset of the study in terms of prognostic factors?	Low risk of bias
Were the care providers, participants and outcome assessors blind to treatment allocation?	Low risk of bias
Were there any unexpected imbalances in drop-outs between groups?	Low risk of bias
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Low risk of bias
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 risk of bias

Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)

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

Summary of clinical effectiveness results for abemaciclib plus NSAI

- At the time of the interim analysis of PFS, the MONARCH 3 study had met its primary endpoint, demonstrating statistically significant and clinically meaningful improvement in investigator-assessed PFS (HR 0.54; 95% CI 0.41 to 0.72; p=0.000021). By delaying disease progression, patients maintain their quality of life for a longer period of time, and the need for treatment with highly toxic chemotherapy regimens is delayed.
- At the final PFS analysis, [redacted] patients ([redacted]%) in the abemaciclib plus NSAI arm and [redacted] patients ([redacted]) in the placebo plus NSAI arm had experienced PFS events of disease progression or death. PFS data were censored for [redacted] patients ([redacted]) in the abemaciclib plus NSAI arm and [redacted] patients ([redacted]) in the placebo plus NSAI arm.
- Median PFS was significantly prolonged in the abemaciclib plus NSAI arm ([redacted] months) relative to placebo plus NSAI ([redacted] months), with a HR of [redacted] (95% confidence interval [CI]: [redacted], 2-sided [redacted]). Treatment with abemaciclib plus NSAI provided patients

with an additional [redacted] months of PFS, and corresponded to a clinically meaningful reduction in the risk of disease progression or death of [redacted].

- [redacted] ([redacted] [95% CI, [redacted]]).
- At the time of data cut-off, the OS data were still immature. [redacted] ([redacted], 95% CI: [redacted]; [redacted]).
- At the final analysis, the ORR was [redacted] in the abemaciclib plus NSAI arm ([redacted] [95% CI: [redacted] to [redacted]] relative to placebo with NSAI ([redacted] [95% CI: [redacted]]), resulting in a statistically significant odds ratio of [redacted] ([redacted]) in favour of abemaciclib plus NSAI. These results were similar to the results at the interim analysis.
- The DCR for patients in the abemaciclib plus NSAI arm and the placebo plus NSAI arm were [redacted] (95% CI [redacted]) and [redacted] (95% CI [redacted]), respectively.
- The CBR for patients in the abemaciclib plus NSAI arm ([redacted] [95% CI [redacted] was significantly higher than for patients in the placebo plus NSAI arm ([redacted] [95% CI [redacted] to [redacted]], suggesting that patients treated with abemaciclib plus NSAI were more likely to exhibit a PR or CR and/or stable disease for at least 6 months relative to placebo plus NSAI.
- The median DoR was longer in the abemaciclib plus NSAI arm ([redacted] months [95% CI [redacted]] than in the placebo plus NSAI arm ([redacted] months [95% CI [redacted]]).
- HRQoL as measured by the EORTC QLQ-C30 and EQ-5D-5L instruments, was generally stable and similar between treatment arms over the course of the study.
- A [redacted] ([redacted]. There were no large differences[59] in EORTC QLQ-C30 scores, and therefore health status, between treatment arms.
- Overall, the [redacted], supporting that the overall health status of patients was maintained throughout the study in both treatment arms.

B.2.6.1 Progression-Free Survival

The results of the interim and final analyses of PFS in MONARCH 3 are presented below. Supplementary data for PFS at the interim and final analyses are presented in Appendix L1.1.

Primary endpoint

The interim efficacy analysis of PFS (data cut-off 31st January 2017) was performed on the ITT population, including a total of 493 patients (328 patients in the abemaciclib plus NSAI arm and 165 patients in the placebo plus NSAI arm). The interim analysis occurred after 194 PFS events (108 [32.9%] in the abemaciclib plus NSAI arm and 86 [52.1%] in the placebo plus NSAI arm). The median follow-up was 17.8 months.[5]

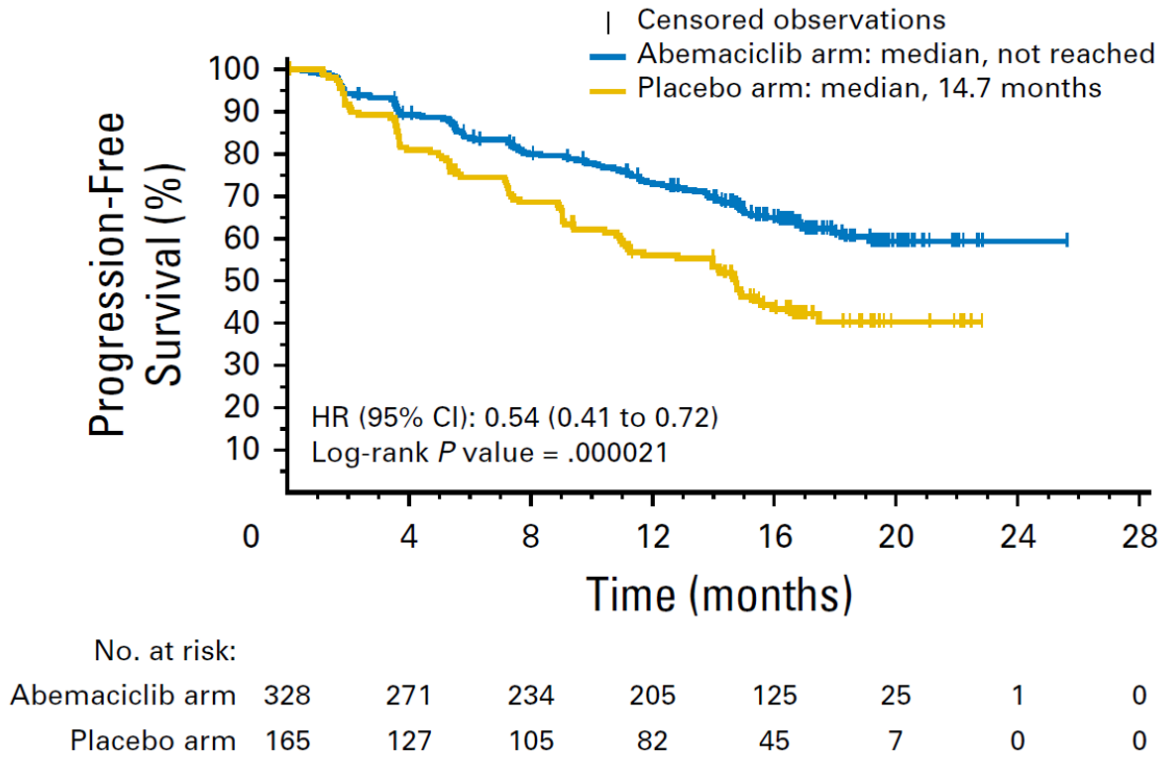
The MONARCH 3 study met its primary endpoint at the pre-planned interim analysis, demonstrating a statistically significant and clinically meaningful improvement in investigator-assessed PFS (HR 0.54; 95% CI 0.41 to 0.72; p=0.000021). This corresponded to a 45.7% reduction in the risk of disease progression or death for patients treated with abemaciclib plus NSAI. Median PFS was not reached in the abemaciclib plus NSAI arm, compared with 14.7

months in the placebo plus NSAI arm. PFS data were censored for 220 patients (67.1%) in the abemaciclib plus NSAI arm and 79 patients (47.9%) in the placebo plus NSAI arm.[5]

A Kaplan-Meier plot for investigator-assessed PFS is displayed in Figure 4. Early divergence of PFS by treatment group was evident and sustained from the time of first tumour assessment at eight weeks. PFS rates at 12 months were 73.0% and 56.1% for patients treated with abemaciclib plus NSAI and placebo plus NSAI, respectively (p=0.0004).

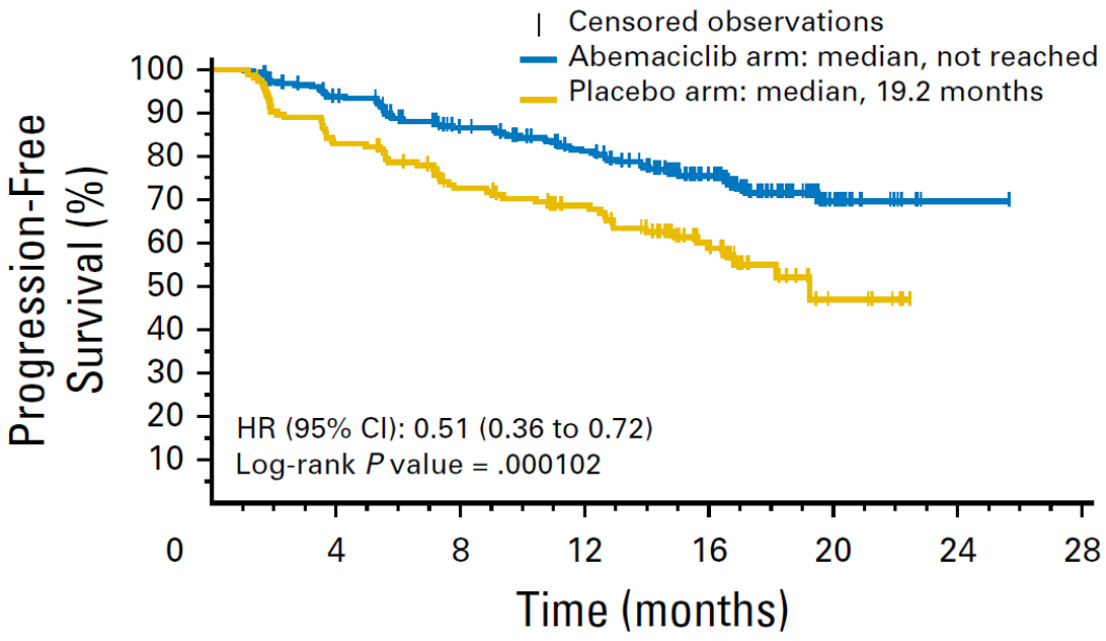
Interim analysis of PFS as evaluated by a blinded, independent review in the ITT population was consistent with investigator-assessed PFS (HR of 0.51 [95% CI 0.36 to 0.72]). A Kaplan-Meier plot for PFS by independent review at the interim analysis is displayed in Figure 5.

Figure 4. Kaplan-Meier plot of investigator-assessed progression-free survival in MONARCH 3 at the interim analysis, ITT population



Abbreviations: CI: confidence interval; HR: hazard ratio; NR: not reached; NSAI: non-steroidal aromatase inhibitor.
Source: Goetz et al. 2017[5]

Figure 5. Kaplan-Meier plot of progression-free survival by independent review in MONARCH 3 at the interim analysis, ITT population



No. at risk:								
Abemaciclib arm	328	271	230	203	124	26	1	0
Placebo arm	165	121	95	79	45	6	0	0

Abbreviations: CI: confidence interval; HR: hazard ratio; NR: not reached; NSAI: non-steroidal aromatase inhibitor.
Source: Goetz et al. 2017[5]

Final Analysis

The final efficacy analysis of investigator-assessed PFS (data cut-off 3rd November 2017) was performed on the ITT population, including a total of 493 patients (328 patients in the abemaciclib plus NSAI arm and 165 in the placebo plus NSAI arm). The median follow-up at the final analysis was [redacted] months. A total of [redacted] patients experienced PFS events: [redacted] patients ([redacted]) in the abemaciclib plus NSAI arm and [redacted] patients ([redacted]) in the placebo plus NSAI arm.[57]

Median PFS was significantly prolonged in the abemaciclib plus NSAI arm (median [redacted] months) relative to placebo plus NSAI (median [redacted] months); HR of [redacted] (95% CI: [redacted], 2-sided [redacted]). These results corresponded to a clinically meaningful reduction in the risk of disease progression or death of [redacted] for patients treated with abemaciclib plus NSAI. PFS data were censored for [redacted] patients ([redacted]) in the abemaciclib plus NSAI arm and [redacted] patients ([redacted]) in the placebo plus NSAI arm.[57]

A Kaplan-Meier plot of final investigator-assessed PFS is displayed in Figure 6. Early and sustained separation by treatment arm was apparent beginning at approximately [redacted] months. In the abemaciclib plus NSAI and placebo plus NSAI arms, the PFS rates were [redacted] and [redacted] at 12 months ([redacted]), and [redacted] and [redacted] at 24 months ([redacted]), respectively.[57]

The final PFS analysis as evaluated by a blinded, independent review in the ITT population was consistent with investigator-assessed PFS ([redacted] [95% CI, [redacted]]). A Kaplan-Meier plot for PFS by independent review is displayed in Figure 7.[57]

The PFS results presented here demonstrate the benefits that treatment with abemaciclib plus NSAI will provide for patients. A significantly prolonged PFS will provide patients with maintained quality of life for a longer period of time by preventing the worsening of symptoms that are associated with disease progression, and delay the onset of treatment with toxic chemotherapy regimens.

Figure 6. Kaplan-Meier plot of investigator-assessed progression-free survival in MONARCH 3 at the final PFS analysis, ITT population

Abbreviations: CI: confidence interval; HR: hazard ratio; NSAI: non-steroidal aromatase inhibitor
Source: Eli Lilly Data on File (JPBM Clinical Study Report Addendum for the Final Progression-Free Survival Analysis. P20). 2018[57]

Figure 7. Kaplan-Meier plot of progression-free survival by independent review in MONARCH 3 at the final PFS analysis, ITT population

Abbreviations: CI: confidence interval; HR: hazard ratio; NR: not reached; NSAI: non-steroidal aromatase inhibitor
Source: Eli Lilly Data on File (JPBM Clinical Study Report Addendum for the Final Progression-Free Survival Analysis. P36). 2018[57]

B.2.6.2 Overall Survival

At the time of the final PFS analysis (data cut-off 3rd November 2017), OS data were still immature, with a total of [redacted] events ([redacted] deaths) in the abemaciclib plus NSAI arm and [redacted] events ([redacted] deaths) in the placebo plus NSAI arm.

Median OS [redacted], with a HR of [redacted] (95% CI [redacted]; 2-sided stratified log-rank [redacted]). There was [redacted] between the two treatment arms for OS rates at one and two years. The OS rates at 3 years are immature at this time.

A Kaplan-Meier plot of OS in the ITT population is presented in Figure 8. A summary of OS results is presented in Table 10. OS data from the interim analysis (data cut-off 31st January 2017) are presented in Appendix L.

Figure 8. Kaplan-Meier plot of overall survival in MONARCH 3 at the time of final PFS analysis, ITT population

Abbreviations: HR: hazard ratio; ITT: intent-to-treat; NR: not reached; NSAI: non-steroidal aromatase inhibitor;
Source: Eli Lilly Data on File (JPBM Clinical Study Report Addendum for the Final Progression-Free Survival Analysis. P30). 2018[57]

Table 10. Summary of overall survival in MONARCH 3, ITT population, at the time of final PFS analysis

	Abemaciclib + NSAI N=328	Placebo + NSAI N=165	Treatment Effect /Difference/p-value[a]
Number of deaths, n (%)	[redacted]	[redacted]	[redacted]
Number of patients censored, n (%)	[redacted]	[redacted]	[redacted]

Alive	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]
Withdrawal by patients	[redacted]	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]	
p-value (2-sided) – log-rank stratified[b]	[redacted]	[redacted]	[redacted]
Hazard ratio (95% CI) – stratified[b]	[redacted]	[redacted]	[redacted]
Survival rate, % (95% CI)[c]	[redacted]	[redacted]	[redacted]
4 months	[redacted]	[redacted]	[redacted]
8 months	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]
16 months	[redacted]	[redacted]	[redacted]
20 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]

[a] Treatment effect/difference/p-values were computed based on comparator placebo. [b] Stratified by sensitivity to endocrine therapy and nature of disease per the IWRS. [c] 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation.
Abbreviations: CI: confidence interval; ITT: intent-to-treat; IWRS: interactive web response system; N: total number of patients in the ITT population; n: number of patients within category; NA: not applicable; NR: not reached; NSAI: non-steroidal aromatase inhibitor; OS: overall survival.
Source: Eli Lilly Data on File (JPBM Clinical Study Report P114). 2017[4]

B.2.6.3 Response Rate

The results reported for response rate are from the time of the final PFS analysis (Table 11). The results for best overall response (including ORR, DCR and CBR) at the interim analysis are presented in Appendix L.1.3.

ORR

Objective response rate, defined as the proportion of patients with best response of complete response (CR) or partial response (PR), was evaluated for patients in the ITT population (n=493) and for patients with measurable disease at baseline (n=397).

In the ITT population, the ORR was [redacted] for patients treated with abemaciclib plus NSAI compared with patients treated with placebo plus NSAI ([redacted] [95% CI [redacted]] versus [redacted] [95% CI [redacted] to [redacted]], respectively). This resulted in an OR of [redacted] ([redacted], indicating that patients treated with abemaciclib plus NSAI had [redacted] odds of exhibiting a CR or PR than patients treated with an NSAI alone (with placebo). [redacted] CRs ([redacted]) and [redacted] PRs ([redacted] were observed in the abemaciclib plus NSAI arm, compared with [redacted] CR ([redacted]) and [redacted] PRs ([redacted] in the placebo plus NSAI arm. The ORR was also [redacted] in the measurable disease population for patients treated with abemaciclib plus NSAI arm than for patients treated with placebo plus NSAI ([redacted] (95% CI [redacted] to [redacted]) for the abemaciclib plus NSAI arm and [redacted] (95% CI [redacted]) for the placebo plus NSAI arm (OR [redacted], [redacted]).

DCR

The DCR (CR + PR + stable disease [SD]) for patients in the abemaciclib plus NSAI arm (n=328) and the placebo plus NSAI arm (n=165) were [redacted] (95% CI [redacted] to [redacted]) and [redacted] (95% CI [redacted]), respectively. For patients with measurable disease (n=328), the DCR was [redacted] (95% CI [redacted]) in the abemaciclib plus NSAI arm and [redacted] (95% CI [redacted]) in the placebo plus NSAI arm.

CBR

The CBR (CR + PR + SD ≥ 6 months) for patients in the abemaciclib plus NSAI arm (n=328) and the placebo plus NSAI arm (n=165) were [redacted] (95% CI [redacted]) and [redacted] (95% CI [redacted]), respectively. For patients with measurable disease, the CBR was [redacted] (95% CI [redacted]) in the abemaciclib plus NSAI arm and [redacted] (95% CI [redacted]) in the placebo plus NSAI arm ([redacted]).

These results suggest that in the measurable disease population, patients treated with abemaciclib plus NSAI were more likely to exhibit a CR, PR and/or SD for at least six months than patients treated with placebo plus NSAI.

Table 11. Summary of best overall response by investigator assessment in MONARCH 3 at the time of final PFS analysis, ITT population

Best overall response[a]	Abemaciclib + NSAI N=328		Placebo plus NSAI N=165		Unstratified OR (95% CI)	p-value[c]
	n (%)	95% CI[b]	n (%)	95% CI[b]		
CR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not evaluable[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Objective response rate (CR + PR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease control rate (CR + PR + SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical benefit rate (CR + PR + SD ≥6 months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Response criteria used was RECIST version 1.1.[58] [b] CIs were based on the normal approximation. [c] p-value was calculated by Exact Cochran-Mantel-Haenszel test stratified by the randomisation strata IWRS Endocrine Therapy, IWRS Nature of Disease. Where a p-value was "NA," the computations were not done because there were fewer than 2 non-missing levels in the data. [d] Patients without adequate tumour assessment prior to treatment discontinuation +30 days or starting new anti-cancer therapy.
Abbreviations: CI: confidence interval; IWRS: interactive web response system; N: number of patients in the intent-to-treat population; n: number of patients within category; NA: not applicable; NSAI: non-steroidal aromatase inhibitor; PD: progressive disease; RECIST: Response Evaluation Criteria in Solid Tumors.[58]
Source: Eli Lilly Data on File (JPBM Clinical Study Report Addendum for the Final Progression-Free Survival Analysis. P36). 2018[57]

B.2.6.4 Duration of Response

The duration of response (DoR) time was measured from the date of first evidence of CR or PR to the date of objective progression or death due to any cause, whichever was earlier.

Median duration of response was longer for patients treated with abemaciclib plus NSAI ([redacted] months [95% CI [redacted]]) than for patients treated with placebo plus NSAI ([redacted] months [95% CI [redacted]]).

Of the [redacted] patients in the abemaciclib plus NSAI arm with a CR or PR as assessed by the investigator, [redacted] progression events and [redacted] deaths were observed, with [redacted] responders ([redacted]) continuing on treatment at the time of the analysis (data cut-off 3rd November 2017). Of the [redacted] patients in the placebo plus NSAI arm with a CR or PR as assessed by the investigator, [redacted] progression events and one death were observed, with [redacted] responders ([redacted] continuing on treatment at the time of the analysis.

Of the patients who responded in the abemaciclib plus NSAI arm, [redacted] were progression-free at 24 months with a median time to first response of [redacted] months (range [redacted] months), compared to [redacted] of patients and a median time to first response of [redacted] months (range [redacted] months) in the placebo plus NSAI arm.

Figure 9. Kaplan-Meier plot of duration of response by investigator assessment at the final PFS analysis

Abbreviations: NR: not reached; NSAI: non-steroidal aromatase inhibitor.
Source: Eli Lilly Data on File (JPBM Clinical Study Report Addendum for the Final Progression-Free Survival Analysis P27). 2018[57]

B.2.6.5 Health-Related Quality of Life

Measures of HRQoL were based on the safety population of 488 patients (327 patients in the abemaciclib plus NSAI arm and 161 patients in the placebo plus NSAI arm). Overall, across instruments and time points, patient completion rates were high and balanced between treatment arms: [redacted] (at baseline), [redacted] (on-therapy cycles; except Cycle 22, at [redacted]), and between [redacted] and [redacted] (follow-up visits).

EORTC QLQ-C30

At the final analysis, baseline values were similar between the abemaciclib plus NSAI and placebo plus NSAI arms across global health status, functional scales and symptom scale items. Of the individual function scale and symptom scale scores, most ([redacted]) did not reach the threshold to be considered either a small improvement or a small deterioration within each treatment arm.[65] Over the course of the study, both treatment arms demonstrated a [redacted] and a [redacted]. The abemaciclib plus NSAI arm also showed a [redacted].

Most of the differences between arms ([redacted]) did not reach the threshold to be considered a small improvement or deterioration, except a [redacted] in health score between arms due to [redacted] in the abemaciclib plus NSAI arm relative to the placebo plus NSAI arm ([redacted] and a [redacted] in [redacted] in the placebo plus NSAI arm relative to abemaciclib plus NSAI ([redacted]).[4] No differences between treatment arms that reached the threshold described by Cocks et al (2011)[59] were observed for any of the other function and symptom scales. These findings support that there were no large differences[59] in EORTC QLQ-C30 scores, and therefore health status, between treatment arms. Results from the final analysis (Table 12) were consistent with those from the interim analysis.

Table 12. Summary of between-arm EORTC QLQ-C30 in MONARCH 3 at the final PFS analysis, safety population

	Baseline score mean (SD)		Within-Group Change from Baseline[a] LS Mean (SE)		Between Group Change Difference[a] LS mean (SE)	Between group p-value[b]
	Abemaciclib + NSAI N=327	Placebo + NSAI N=161	Abemaciclib + NSAI N=327	Placebo + NSAI N=161		
Global health status[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Functional scales[c]						
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[c]						
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]

[a] Across all post-baseline visits (abemaciclib plus NSAI – placebo plus NSAI 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 higher score representing a higher ("better") level of functioning (C30: global health status; physical, role, emotional, cognitive, and social), or a higher ("worse") level of symptoms or financial difficulty.
Abbreviations: EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; LS: least squares; NSAI: non-steroidal aromatase inhibitor; SE: standard error; SD: standard deviation. **Source**: Eli Lilly Data on File (JPBM Clinical Study Report. P128). 2017[4]

EQ-5D-5L

EQ-5D-5L index and EQ-5D-5L "Your health today" visual analogue score (VAS) values were [redacted] (Table 13). [redacted] were observed in change from baseline between arms for both the EQ-5D-5L index ([redacted]) and VAS ([redacted]). A summary of the EQ-5D-5L result are presented in Table 13. These data support that the overall health status of patients was maintained throughout the study in both treatment arms.

Table 13. Summary of EQ-5D-5L and Visual Analogue Scale by visit in MONARCH 3 at the final PFS analysis, safety population

	Baseline score mean (SD)		Change from baseline[a] LS Mean (SE)		Difference in change between arms [a] LS mean (SE)	p-value [b]
	Abemaciclib + NSAI N=327	Placebo + NSAI N=161	Abemaciclib + NSAI N=327	Placebo + NSAI N=161		
Index value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visual analogue scale	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Across all post-baseline visits. [b] p-values are from Type 3 sums of squares mixed models repeated measures models: Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.
Abbreviations: EQ-5D-5L: EuroQol 5-Dimension 5-Level; LS: least squares; NSAI: non-steroidal aromatase inhibitor; SD: standard deviation; SE: Standard error;
Source: Eli Lilly Data on File (JPBM Clinical Study Report addendum P151). 2018

B.2.7 *Subgroup analysis*

A summary of pre-specified subgroup analyses are presented in Appendix E.

B.2.8 *Meta-analysis*

Due to the identification of only one study evaluating the efficacy and safety of abemaciclib plus NSAI in the relevant patient population as defined in the NICE scope for this appraisal, 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 relevant comparators for the MONARCH 3 indication using available data from randomised controlled trials (RCTs).
- The reference treatment chosen for the analysis was anastrozole or letrozole (ANAS/LTZ), with abemaciclib plus ANAS/LTZ (ABE-ANAS/LTZ), ribociclib plus ANAS/LTZ (RIBO-ANAS/LTZ) and palbociclib plus ANAS/LTZ (PAL-ANAS/LTZ) as relevant comparators.
- The endpoints chosen for analysis were PFS, OS, ORR, CBR and CR.
- ABE-ANAS/LTZ (HR [redacted]; 95% credible interval (CrI) [redacted]), RIBO-ANAS/LTZ (HR [redacted]; 95% CrI [redacted]) and PAL-ANAS/LTZ (HR [redacted]; 95% CrI [redacted]) each similarly showed a significantly lower hazard rate of progression or death compared to ANAS/LTZ.

- For the MONARCH 3 trial, median OS was not reached in both treatment arms and therefore the relative treatment effect from the trial is highly uncertain. RIBO-ANAS/LTZ and PAL-ANAS/LTZ both showed lower hazards of death compared to ANAS/LTZ, but these were not significant (HR [redacted]; CrI [redacted]; HR [redacted]; CrI [redacted] respectively). The treatment effect for ABE-ANAS/LTZ vs. ANAS/LTZ was statistically insignificant (HR [redacted] [CrI [redacted]]).
- No statistically significant OR estimates were observed for any treatment compared against ANAS/LTZ. PAL-ANAS/LTZ showed the highest odds of clinical benefit (OR [redacted]; 95% CrI [redacted]) compared against ANAS/LTZ, and similar OR estimates were observed between ABE-ANAS/LTZ (OR [redacted]; 95% CrI: [redacted]) and RIBO-ANAS/LTZ (OR [redacted]; 95% CrI [redacted]).
- Overall, the treatment effects for each of the endpoints were similar between ABE-ANAS/LTZ, PAL-ANAS/LTZ and RIBO-ANAS/LTZ, supporting that the efficacy of abemaciclib plus NSAI is at a minimum comparable to ribociclib or palbociclib plus NSAI (letrozole).
- In consideration of heterogeneity, the patient populations for the ABE-ANAS/LTZ (MONARCH 3), PAL-ANAS/LTZ (PALOMA1/TRIO-18, PALOMA-2) and RIBO-ANAS/LTZ (MONALEESA-2) trials were similar regarding HR+/HER2− status, age, postmenopausal status, stage of disease, performance status, proportion of patients with bone-only disease, and having no prior history of ET or chemotherapy in the advanced setting. However, there were differences between the trial populations in the required DFI following adjuvant therapy and the proportion of patients with visceral involvement. The proportion of patients with liver metastases was reported only in one trial (MONARCH 3). These factors should be considered when interpreting the results. The trials for the comparators were closely connected in the network (one intermediate node [ANAS/LTZ]).

B.2.9.1 Overview of the network meta-analysis

A network meta-analysis (NMA) was conducted to synthesise efficacy estimates for relevant treatments used in patients comparable to the MONARCH 3 population, and to provide a comparison between all relevant comparators for which data from RCTs were available. The reference treatment for the analysis was anastrozole or letrozole (ANAS/LTZ). Of the studies selected for inclusion in the NMA that included NSAI (plus placebo) as a treatment arm, MONARCH 3 was the only trial to have permitted patients to receive either ANAS or LTZ. To connect MONARCH 3 to the network, the NSAIs (ANAS and LTZ) were therefore pooled into one node, and were thus considered as one treatment arm in the analysis. This approach maintains randomisation in the MONARCH 3 trial. In pooling these therapies, it was assumed that the efficacies of ANAS and LTZ are the same across trials for the endpoints assessed. It is generally accepted, from a clinical perspective, that the NSAIs have comparable efficacy. Based on the recent NICE submissions for ribociclib and palbociclib in a similar indication to the MONARCH 3 trial, the clinical experts in both appraisals considered the NSAIs to be equivalent due to similar effectiveness and acquisition costs.[53, 54]

The comparators that were considered relevant to UK clinical practice as per the NICE submission scope and for inclusion in the NMA are as follows:

- Abemaciclib 300 mg plus anastrozole 1 mg or letrozole 2.5 mg (ABE-ANAS/LTZ)
- Palbociclib 125 mg plus anastrozole 1 mg or letrozole 2.5 mg (PAL-ANAS/LTZ)
- Ribociclib 600 mg plus anastrozole 1 mg or letrozole 2.5 mg (RIBO-ANAS/LTZ)

The following treatments are not considered to be relevant UK comparators but were included in the NMA in order to generate a fully connected network and to make optimal use of available data:

- Anastrozole 1 mg or letrozole 2.5 mg (ANAS/LTZ)
- Exemestane 2.5 mg (EXE)
- Fulvestrant 250 mg and 500 mg (FUL)
- Megestrol acetate 160 mg (MGA)
- Tamoxifen 20 mg or 40 mg (TMX)
- Toremifene 60 mg or 200 mg (TOR)

The NMA was conducted as described in the NICE DSU (Decision Support Unit) technical support documents (TSDs).[68-70] For the binary endpoints (ORR, CBR and CR), the methodology followed is as per the NICE DSU TSD for binary endpoints with a logit link function.[68] The parameters of interest modelled are the log odds ratios (which were converted to odds ratios [OR]), representing the relative difference in odds of achieving an objective response or clinical benefit for each treatment compared to the reference treatment chosen for the analysis (ANAS/LTZ).

For the survival endpoints (PFS and OS), the methodology followed is as per the Woods (2010) publication.[71] This publication provides methods for analysing multi-arm trials of time-to-event data that account for the correlation in relative treatment effect estimates (i.e. HRs) from such trials. As described in Woods (2010), additions can be made to the model to include studies reporting the number of events (i.e. count data and median survival for OS or PFS).[71] The parameters of interest modelled are the log hazard ratios (which were converted to HRs), representing the relative difference in the hazard rate for each treatment compared to the reference treatment chosen for the analysis. A summary of the trials used to perform the network meta-analysis can be found in Table 14. The MONALEESA-7[72] (RIBO in combination with TMX or NSAI vs. TMX or NSAI) and Yardley (2009;[73] liposomal doxorubicin [LDOX] vs. docetaxel [DOC]) studies did not connect via common comparators to the MONARCH 3 trial and were excluded.

The full methodology of the NMA, and the SLR that allowed for the identification of studies to be included in the NMA, are presented in Appendix D.

Table 14. Summary of trials used to perform network meta-analysis

References of trial	Trial Name	Intervention A (ITT n)	Intervention B (ITT n)	Intervention C (ITT n)	Connected to network of evidence?				
					PFS	OS	ORR	CBR	CR
Allegra 1985	-	MGA (n=65)	TMX20 (n=66)	-	N	N	Y	N	Y
Robertson 2016	FALCON	ANAS (n=232)	FUL500 (n=230)	-	Y	N	N	N	N
Robertson 2009	FIRST	ANAS (n=103)	FUL500 (n=102)	-	N	Y	Y	Y	N
Gill 1993	-	MGA (n=60)	TMX40 (n=58)	-	N	Y	Y	N	Y
Hayes 1995	-	TMX20 (n=215)	TOR60 (n=221)	TOR200 (212)	N	Y	Y	N	Y
Howell 2004	-	FUL250 (n=313)	TMX20 (n=274)	-	Y	Y	Y	Y	Y
Iwata 2013	-	EXE (n=149)	ANAS (n=149)	-	N	Y	Y	Y	Y
Milla-Sanos 2001	-	TOR60 (n=106)	TMX40 (n=111)	-	N	Y	Y	N	Y
Milla-Santos 2003	-	ANAS (n=121)	TMX40 (n=117)	-	N	Y	Y	Y	Y
Hortobagyi 2016	MONALEESA-2	RIBO-LTZ (n=334)	LTZ (n=334)	-	Y	Y	Y	Y	Y
Goetz 2017	MONARCH 3	ABE-ANAS/LTZ (n=328)	ANAS/LTZ (n=165)	-	Y	Y	Y	Y	Y
Mouridsen 2001	-	LTZ (n=453)	TMX20 (n=454)	-	N	Y	Y	Y	Y
Muss 1985	-	MGA (n=69)	TMX20 (n=67)	-	Y	Y	Y	N	Y
Pyrhonen 1997	Nordic	TOR60 (n=214)	TMX40 (n=201)	-	N	Y	Y	N	Y
Finn 2015	PALOMA-1/TRIO-18	PAL-LTZ (n=84)	LTZ (n=81)	-	Y	Y	Y	Y	Y
Finn 2016	PALOMA-2	PAL-LTZ (n=444)	LTZ (n=222)	-	Y	N	Y	Y	N
Paterson 1990	-	TMX20 (n=79)	MGA (n=77)	-	N	Y	Y	N	Y
Bonneterre 2001	TARGET and North American	ANAS (n=511)	TMX20 (n=510)	-	Y	Y	Y	Y	Y

Abbreviations: ABE: Abemaciclib; ANAS: Anastrozole; CBR: Clinical benefit rate; CR: Complete response, EXE: Exemestane; FUL: Fulvestrant; LTZ: Letrozole; MGA: Megestrol acetate; ORR: Objective response rate; OS: Overall survival; PAL: Palbociclib; PFS: Progression-free survival; RIBO: Ribociclib; SLR: Systematic literature review; TMX: Tamoxifen; TOR: Toremifene.

B.2.9.2 Results of the network meta-analysis

Eighteen studies met all of the criteria for inclusion in the NMA (i.e. population, endpoints and study design) and were connected to the MONARCH 3 trial. These studies are presented in Table 14. The base case results of the NMA are presented by endpoint: PFS, OS, ORR, CBR and CR.

For all outcomes, both FE and RE models converged and there was no evidence of one model fitting better than another. For ORR, CBR, OS and CR 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 effects. For PFS, FE model results are presented. Although the RE model converged for PFS, there was evidence of the prior distribution for the RE standard deviation dominating the posterior distributions for the treatment effects. 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, vague priors were used for the parameters and therefore in this case the results were less informed by the study data compared to the prior distributions used.

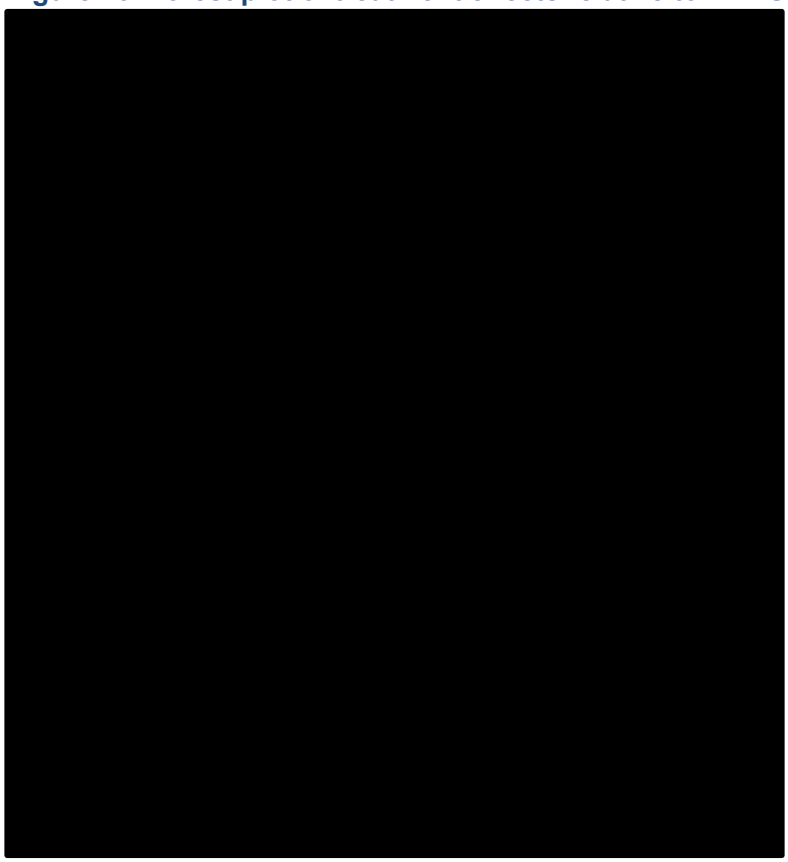
The binary and survival endpoint results have been presented as forest plots showing the relative treatment effects for each treatment in the network vs. the reference treatment. Results for the binary endpoints are presented as median odds ratios (ORs) and results for the survival endpoints are presented as HRs for each treatment comparison. In each case, the associated 95% credible interval (CrI) is presented alongside each relative treatment effect estimate. The CrI is similar to a CI for a Bayesian analysis but is interpreted as the probability that the relative treatment effect estimate lies within the interval. Network plots are presented in Appendix D.1.3 for each endpoint to illustrate how the studies and treatments are connected.

PFS

Eight studies formed a connected network of evidence for PFS. A forest plot summarising the relative treatment effects compared to ANAS/LTZ is presented in Figure 10.

Similar HR estimates for PFS were observed between ABE-ANAS/LTZ and relevant comparators RIBO-ANAS/LTZ and PAL-ANAS/LTZ. ABE-ANAS/LTZ (HR [redacted]; 95% CrI [redacted] to [redacted]), RIBO-ANAS/LTZ (HR [redacted]; 95% CrI [redacted] to [redacted]) and PAL-ANAS/LTZ (HR [redacted]; 95% CrI [redacted] to [redacted]) each showed a significantly lower hazard rate of progression or death compared against ANAS/LTZ.

Figure 10. Forest plot of treatment effects relative to ANAS/LTZ for PFS, using FE model

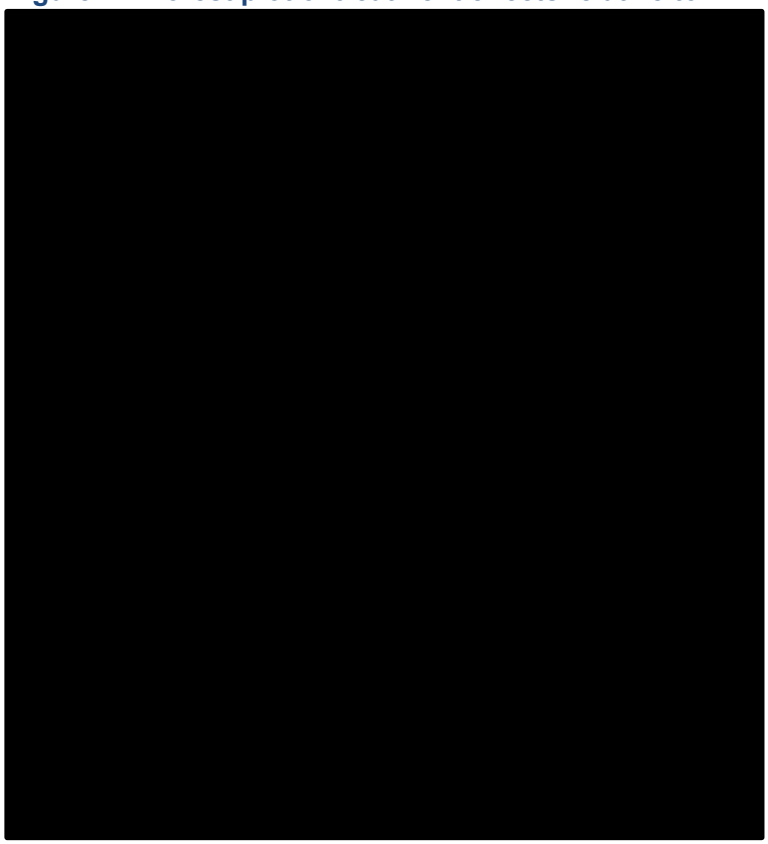


Footnote: The results presented give the median of the posterior distributions as these are less skewed by outlying observations compared to the mean.
Abbreviations: ABE: abemaciclib; ANAS/LTZ: anastrozole/letrozole; CrI: credible interval; MGA; megestrol acetate; PAL: palbociclib; FUL500: fulvestrant 500 mg; RIBO; ribociclib; TMX20; tamoxifen 20 mg.

OS

Fifteen studies formed a connected network of evidence for OS. A forest plot summarising the relative treatment effects compared to ANAS/LTZ is presented in Figure 11. Final OS data was only available in the PALOMA-1/TRIO-18 trial. It should be noted that the MONALEESA-2 (RIBO+ANAS/LTZ vs. ANAS/LTZ), MONARCH 3 (ABE-ANAS/LTZ vs. ANAS/LTZ) and PALOMA-2 (PAL-LTZ vs. LTZ) trials had immature survival data (i.e. median OS was not reached in at least one arm). Treatment effects from these trials are highly uncertain. RIBO-ANAS/LTZ and PAL-ANAS/LTZ both showed lower hazards of death compared to ANAS/LTZ, but these were not significant (HR [redacted]; CrI [redacted]; HR [redacted]; CrI [redacted] respectively. The treatment effect for ABE-ANAS/LTZ was statistically insignificant (HR [redacted] [CrI [redacted]]).

Figure 11. Forest plot of treatment effects relative to ANAS/LTZ for OS using RE model



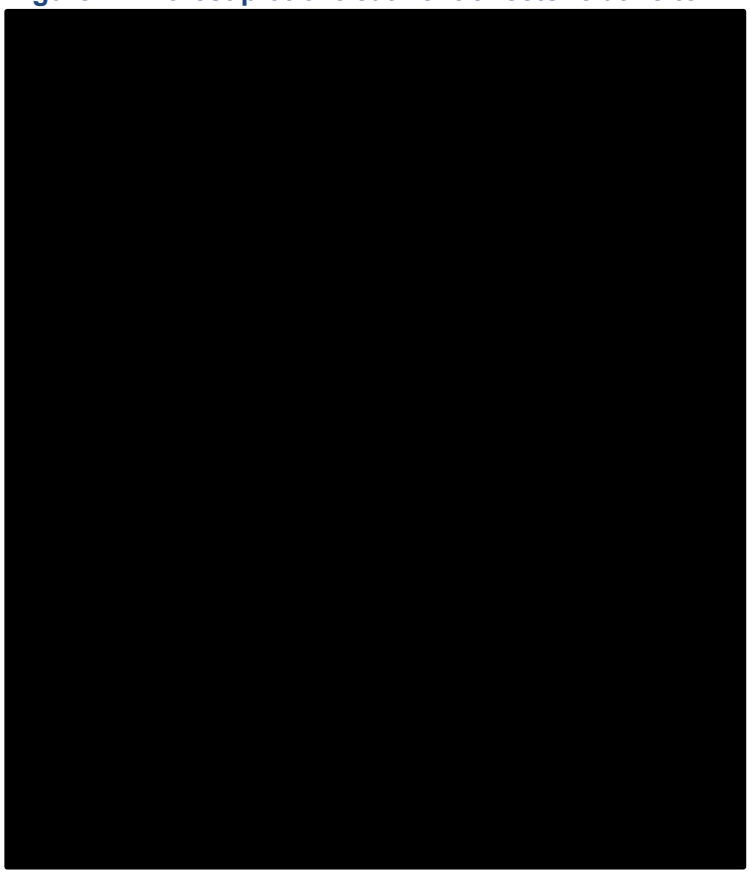
Footnote: The results presented give the median of the posterior distributions as these are less skewed by outlying observations compared to the mean.
Abbreviations: ABE: abemaciclib; ANAS/LTZ: anastrozole/letrozole; CrI: credible interval; EXE: exemestane; MGA; megestrol acetate; PAL: palbociclib; FUL250: fulvestrant 250 mg FUL500: fulvestrant 500 mg; RIBO; ribociclib; TMX20; tamoxifen 20 mg; TMX40: tamoxifen 40 mg; TOR60: toremifene 60 mg; TOR200: toremifene 200 mg.

ORR

Seventeen studies connected in a network of evidence for ORR. The results are presented as median odds ratios (with 95% credible intervals) in a forest plot (Figure 12).

Similar treatment effects were observed between combination therapies ABE-ANAS/LTZ, PAL-ANAS/LTZ and RIBO-ANAS/LTZ versus ANAS/LTZ, but none achieved statistical significance against ANAS/LTZ. RIBO-ANAS/LTZ showed the highest odds of achieving an objective response compared against the reference treatment ANAS/LTZ (OR [redacted]; 95% CrI [redacted]). ABE-ANAS/LTZ showed the second highest odds of achieving an objective response (OR [redacted]0; 95% CrI [redacted]), followed by PAL-ANAS/LTZ (HR [redacted]; [redacted]).

Figure 12. Forest plot of treatment effects relative to ANAS/LTZ for ORR using RE model



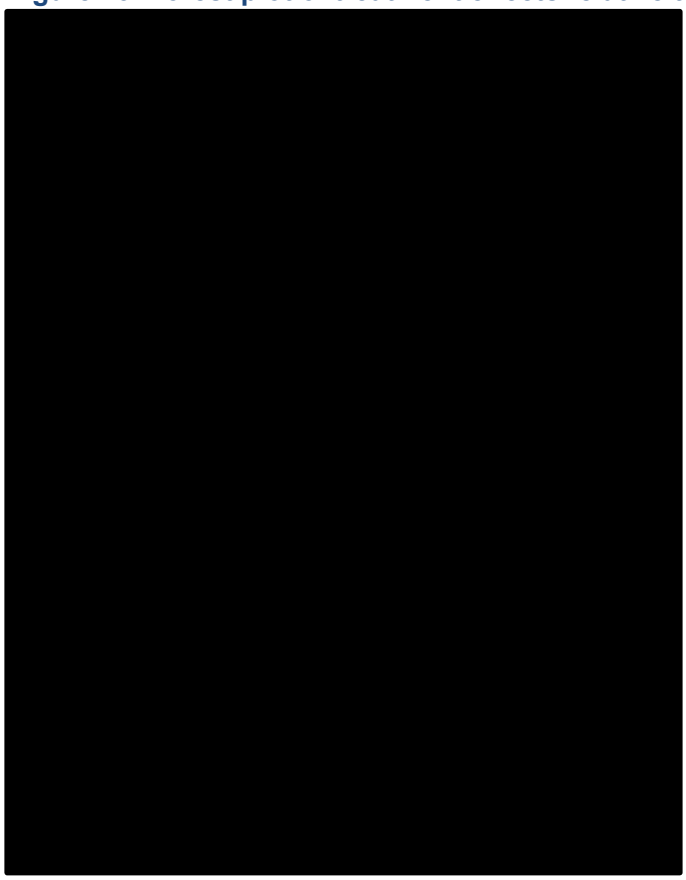
Footnote: The results presented give the median of the posterior distributions as these are less skewed by outlying observations compared to the mean.
Abbreviations: ABE: abemaciclib; ANAS/LTZ: anastrozole/letrozole; CrI: credible interval; EXE: exemestane; MGA; megestrol acetate; PAL: palbociclib; FUL250: fulvestrant 250 mg; FUL500: fulvestrant 500 mg; RIBO; ribociclib; TMX20; tamoxifen 20 mg; TMX40: tamoxifen 40 mg; TOR60: toremifene 60 mg; TOR200: toremifene 200 mg.

CBR

Ten studies formed a connected network of evidence for CBR. A forest plot summarising the relative treatment effects compared to ANAS/LTZ is presented in Figure 13.

No statistically significant OR estimates were observed for any treatment compared against ANAS/LTZ. PAL-ANAS/LTZ showed the highest odds of clinical benefit (OR [redacted]; 95% CrI [redacted]) compared against ANAS/LTZ but this was not significant. Similar OR estimates were observed between combination therapies ABE-ANAS/LTZ (OR [redacted]; 95% CrI: [redacted]) and RIBO-ANAS/LTZ (OR [redacted]; 95% CrI [redacted]).

Figure 13. Forest plot of treatment effects relative to ANAS/LTZ for CBR using RE model



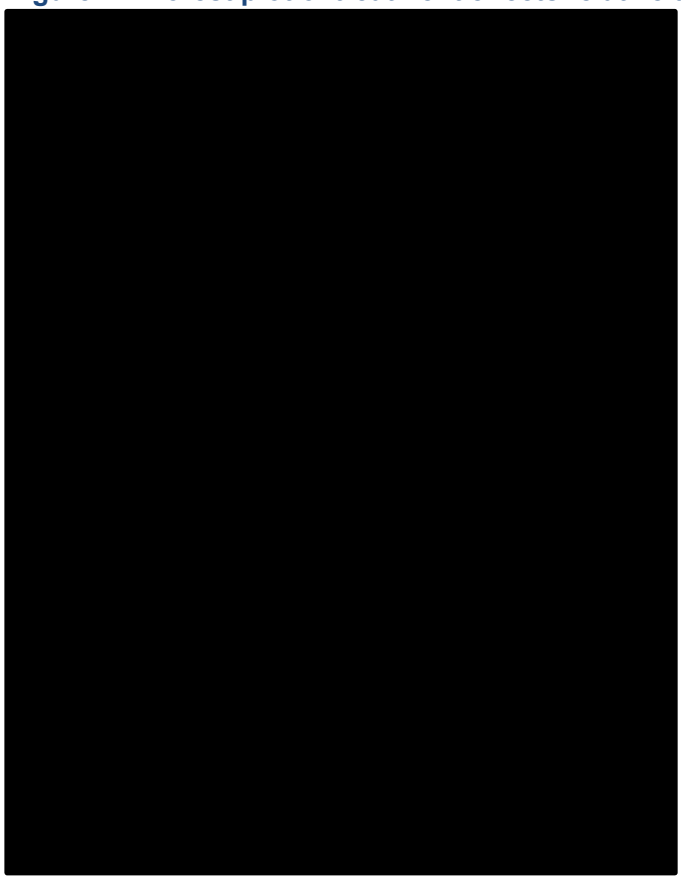
Footnote: The results presented give the median of the posterior distributions as these are less skewed by outlying observations compared to the mean.
Abbreviations: ABE: abemaciclib; ANAS/LTZ: anastrozole/letrozole; CrI: credible interval; EXE: exemestane; PAL: palbociclib; FUL250: fulvestrant 250 mg; FUL500: fulvestrant 500 mg; RIBO; ribociclib; TMX20; tamoxifen 20 mg; TMX40: tamoxifen 40 mg.

Complete response

Fifteen studies formed a connected network of evidence for CR. A forest plot summarising the relative treatment effects compared to ANAS/LTZ is presented in Figure 14.

No statistically significant OR estimates were observed for any treatment compared to ANAS/LTZ. ABE-ANAS/LTZ and RIBO-ANAS/LTZ combination treatments showed a higher odds of CR compared to ANAS/LTZ (OR [redacted]; 95% CrI [redacted]; OR [redacted]; 95% CrI [redacted], respectively). The ABE-ANAS/LTZ vs. ANAS/LTZ OR estimate was highly uncertain due to low event counts (9 and 1 CR events observed in ABE-ANAS/LTZ and ANAS/LTZ arms). These results need to be interpreted with caution due to the low event counts leading to uncertainty when modelling on the log-odds scale.

Figure 14. Forest plot of treatment effects relative to ANAS/LTZ for CR using RE model



Footnote: The results presented give the median of the posterior distributions as these are less skewed by outlying observations compared to the mean.
Abbreviations: ABE: abemaciclib; ANAS/LTZ: anastrozole/letrozole; CrI: credible interval; EXE: exemestane; PAL: palbociclib; FUL250: fulvestrant 250 mg; FUL500: fulvestrant 500 mg; MGA: megestrol acetate; RIBO; ribociclib; TMX20; tamoxifen 20 mg; TMX40: tamoxifen 40 mg; TOR60: toremifene 60 mg; TOR200: toremifene 200 mg.

B.2.9.3 Heterogeneity in the network meta-analysis

The following characteristics were considered to be similar across MONARCH 3 and the relevant comparator trials (MONALEESA-2, PALOMA 1/TRIO-18 and PALOMA-2):

- **HR+/HER2− status**: All trials enrolled patients with HR+/HER2− breast cancer.
- **Age**: Median age reported by arm ranged from 61 years to 64 years.
- **Postmenopausal status**: All comparator trials included only postmenopausal patients.
- **Stage of disease**: All comparator trials reported a high proportion of patients with stage IV disease.
- **Performance status**: All comparator trials enrolled patients with PS stage 0 or 1, excluding the PALOMA-2 trial, in which a small percentage of patients with PS stage 2 were included.
- **Number of prior chemotherapies and endocrine therapies received in the advanced setting**: The patient populations had no prior ET or chemotherapy in the advanced setting.
- **Site of disease**: The proportion of patients with bone only disease in each treatment arm was similar, ranging from 15% to 23.6%.

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

- **Required disease-free interval (DFI) following adjuvant therapy**: The MONARCH 3 trial enrolled patients if it had been over 12 months since the completion of (neo)adjuvant therapy with an aromatase inhibitor or anti-oestrogen therapy. The MONALEESA-2, PALOMA-1/TRIO-18 and PALOMA-2 trials enrolled patients in whom it had been over 12 months since adjuvant NSAI therapy, but the DFI required for other hormonal therapies was unclear.
- **Proportion of patients with visceral involvement**: The proportion of patients with visceral involvement varied between treatment arms and studies, ranging from 44% to 59%.
- **Site of disease**: The proportion of patients with liver metastases was reported only in the MONARCH 3 trial.

B.2.9.4 Sensitivity Analyses

There were no sensitivity analyses conducted as part of the NMA.

B.2.9.5 Uncertainties in the indirect and mixed treatment comparison

There were no treatment comparisons in the network with direct and indirect evidence between interventions of interest to the decision problem of this submission.

B.2.10 *Adverse reactions*

Summary of safety and tolerability of abemaciclib plus NSAI

- In the safety population, [redacted] of patients in the abemaciclib plus NSAI arm (N=327) had ≥1 treatment-emergent adverse event (TEAE) during the study, as well as [redacted] of patients in the placebo plus NSAI arm (N=161).
- While TEAEs in both arms were predominantly of low grade, the incidence of grade ≥3 TEAEs was greater in the abemaciclib plus NSAI arm ([redacted] grade 3, [redacted] grade 4) than in the placebo plus NSAI arm ([redacted] grade 3, [redacted] grade 4).
- The most frequent TEAEs of any grade reported by the investigator in the abemaciclib plus NSAI arm were diarrhoea ([redacted]), infections/infestations ([redacted]), neutropenia ([redacted]), fatigue ([redacted]), and nausea ([redacted]). The most frequent TEAEs in the placebo plus NSAI arm were infections/infestations ([redacted]), fatigue ([redacted]), diarrhoea ([redacted]) and nausea ([redacted]).
- The majority of diarrhoea events in the abemaciclib plus NSAI arm were grade 1 or 2 in severity ([redacted]), with [redacted] of patients reporting grade 3 diarrhoea. Diarrhoea was managed with the use of antidiarrhoeal medication and dose adjustments, although only [redacted] and [redacted] of patients had dose reductions or omissions due to diarrhoea. [redacted] patients discontinued treatment due to diarrhoea ([redacted]), indicating that this TEAE was manageable.
- A total of [redacted] of patients in the abemaciclib plus NSAI arm experienced neutropenia ([redacted] at grade 3 and [redacted] at grade 4) though once decreased, the neutrophil count typically remained stable during abemaciclib treatment and was reversible following discontinuation.[5]
- Serious adverse events were reported in [redacted] of patients in the abemaciclib plus NSAI arm and [redacted] in the placebo arm. Lung infection was the most frequent ([redacted] vs. [redacted], respectively). SAEs related to study treatment were reported for more patients in the abemaciclib plus NSAI arm than those in the placebo plus NSAI arm; [redacted] patients [redacted], and [redacted] patients ([redacted]), respectively.
- [redacted] and [redacted] of abemaciclib plus NSAI-treated patients discontinued study drug due to AEs and SAEs, respectively, compared to [redacted] and [redacted] of placebo plus NSAI patients.
- Deaths due to AEs while on the study or within 30 days of treatment discontinuation were reported for [redacted] patients [redacted]) in the abemaciclib plus NSAI arm, and [redacted] patients [redacted] in the placebo plus NSAI arm. The cause of death was generally considered to be confounded by multiple comorbid factors; no patterns were observed.
- Overall, abemaciclib plus NSAI was well-tolerated, with an acceptable TEAE profile.

B.2.10.1 Safety results informing the decision problem

The safety of abemaciclib plus NSAI in postmenopausal women with HR+/HER2− locoregionally recurrent or metastatic breast cancer was evaluated in the MONARCH 3 trial. The safety population comprised 327 patients in the abemaciclib plus NSAI arm and 161 in the placebo plus NSAI arm, defined as all patients who received at least one dose of study drug. One patient who was randomly assigned to placebo received abemaciclib during cycle one, and was subsequently counted in the abemaciclib safety population.

The median number of cycles received was comparable between the abemaciclib plus NSAI and placebo plus NSAI arms (16 versus 15 cycles, respectively). Median duration of therapy was 66.57 weeks for patients receiving abemaciclib plus NSAI and 60.29 weeks for patients receiving placebo plus NSAI.[57] Median abemaciclib relative dose intensity was 85.25%, and median placebo relative dose intensity was 98.25%.[57]

The safety of abemaciclib plus NSAI was evaluated through the assessment of TEAEs; treatment-emergent SAEs; TEAEs leading to dose adjustments, omissions, or discontinuation of abemaciclib; and TEAEs leading to deaths, adverse events of specific interest (AESIs), clinical laboratory results, vital signs, and electrocardiograms (ECGs).

As previously defined, TEAEs were graded for severity, and in cases where AEs existed without matching terminology within the CTCAE, the investigator was responsible for selecting the appropriate system organ class (SOC) and assessing severity grade based on the intensity of the event. During the study, TEAEs were collected at every visit and between visits, regardless of potential relationship to the study drug. Dose reductions and discontinuation of treatment were also recorded.[4]

B.2.10.2 Treatment-emergent adverse events

In the abemaciclib plus NSAI and placebo plus NSAI arms, TEAEs of any grade were experienced by [redacted] and [redacted] of participants, respectively (Table 15). While TEAEs in both arms were predominantly of low grade, the incidence of grade ≥3 TEAEs was greater in the abemaciclib plus NSAI arm ([redacted] grade 3, [redacted] grade 4) than in the placebo plus NSAI arm ([redacted] grade 3, [redacted] grade 4), with [redacted] and [redacted] considered related to study treatment as judged by the investigator, respectively.[4]

Table 15. Overall number of TEAEs in each arm of MONARCH 3, safety population

Number of patients[a]	Abemaciclib + NSAI N=327	Placebo + NSAI N=161
Patients with ≥1 TEAE, n (%)	[redacted]	[redacted]
Related to study treatment[b], (%)	[redacted]	[redacted]
Patients with ≥1 CTCAE ≥Grade 3 TEAE, n (%)	[redacted]	[redacted]
Related to study treatment[b], n (%)	[redacted]	[redacted]

[a] Patients may be counted in >1 category
[b] Includes events that were considered related to study treatment as judged by the investigator
Abbreviations: NSAI: non-steroidal aromatase inhibitor; TEAE: treatment-emergent adverse event.
Source: Eli Lilly Data on File (JPBM Clinical Study Report Addendum for the Final Progression-Free Survival Analysis P47). 2018[57]
Most frequent TEAEs

A summary of TEAEs by CTCAE grade in order of decreasing frequency can be found in Table 16. In the abemaciclib plus NSAI arm, the most frequently observed TEAEs of any grade were diarrhoea ([redacted]), infections/infestations ([redacted]), neutropenia ([redacted]), fatigue ([redacted]) and nausea ([redacted]) (Table 16).[5] In the placebo plus NSAI arm, the most frequently observed TEAEs of any grade were infections/infestations ([redacted]), fatigue ([redacted]), diarrhoea ([redacted]) and nausea ([redacted]) (Table 16).

Diarrhoea was predominantly of low grade in the abemaciclib plus NSAI arm, experienced by [redacted], [redacted], [redacted] and [redacted] at grades 1–4 respectively. The median onset was 8.0 days and the median duration was 10.5 days (grade 2) and 8.0 days (grade 3), indicating that diarrhoea was not a cause for concern when considering severity and duration.[5] Diarrhoea was often managed with antidiarrhoeal medications such as loperamide. Of the [redacted] patients who experienced diarrhoea as a TEAE, [redacted] patients ([redacted]%) reported the use of antidiarrhoeal medication.

Notably, the majority of abemaciclib plus NSAI patients (76.3%) who experienced diarrhoea did not undergo any treatment modifications; [redacted] had a dose reduction and [redacted] had a dose omission. Only [redacted] patients discontinued treatment due to diarrhoea ([redacted]), indicating that this TEAE was manageable. In the placebo plus NSAI arm, diarrhoea was mostly of grade 1 and rarely experienced at higher grades (1.2% at Grade 3).

In the abemaciclib plus NSAI arm, [redacted] and [redacted] of patients reported grade 3 and 4 neutropenia, respectively. Overall, once decreased, the neutrophil count typically remained stable during abemaciclib treatment and was reversible following treatment discontinuation. On the basis of central laboratory analysis, all grades of neutropenia were generally observed by cycle two. Febrile neutropenia was reported as a non-serious TEAE in [redacted] patient ([redacted]) in the abemaciclib plus NSAI arm.

Infections and infestations occurred in [redacted] of patients in the abemaciclib plus NSAI arm and [redacted] in the placebo plus NSAI arm, with most being of grade 2 severity ([redacted] vs. [redacted], respectively).

Fatigue experienced by patients in the abemaciclib plus NSAI arm was predominantly of mild severity, with only [redacted] of patients reporting fatigue at grade 3. A maximum of grade 2 fatigue was experienced by [redacted] of patients in the placebo plus NSAI arm.

Nausea in both arms was predominantly low grade, with only [redacted] of patients in both arms experiencing grade 3 nausea.

Table 16. TEAEs occurring in ≥15% of patients in either treatment arm of MONARCH 3, safety population

Preferred term	Abemaciclib plus NSAI (N=327)					Placebo plus NSAI (N=161)				
	CTCAE Grade 1	CTCAE Grade 2	CTCAE Grade 3	CTCAE Grade 4	All CTCAE Grades	CTCAE Grade 1	CTCAE Grade 2	CTCAE Grade 3	CTCAE Grade 4	All CTCAE Grades
Patients with ≥1 TEAE, n (%)	[redacted]									
Diarrhoea										
Infections and infestations										
Neutropenia										
Fatigue										
Nausea										
Anaemia										
Abdominal pain										
Vomiting										
Alopecia										
Decreased appetite										
Leukopenia										
Blood creatinine increased										
Headache										
Constipation										
ALT increased										
Arthralgia										
AST increased										
Back pain										
Rash										

[a] Includes any adverse event in the infections and infestations system organ class. NA: No Grade exists for this adverse event.
Abbreviations: ALT: alanine transaminase; AST: Aspartate Aminotransferase; CTCAE: Common Terminology Criteria for Adverse Events; NSAI: non-steroidal aromatase inhibitor
Source: Eli Lilly Data on File (JPBM Clinical Study Report Addendum for the Final Progression-Free Survival Analysis P49, 399). 2018[57]

Serious adverse events

At least one SAE was experienced by [redacted] patients ([redacted]) and [redacted] patients ([redacted]) in the abemaciclib plus NSAI and placebo plus NSAI arms, respectively. In the abemaciclib plus NSAI arm, [redacted] patients ([redacted]), experienced SAEs related to study treatment, as assessed by the investigator, compared with [redacted] patients ([redacted]) in the placebo plus NSAI arm. The most frequently reported SAEs in the abemaciclib plus NSAI arm were lung infection [redacted] and embolism ([redacted]), whilst dehydration ([redacted]), abdominal pain ([redacted]) and vomiting [redacted]) were most common in the placebo plus NSAI arm (Table 17).[4] In the abemaciclib plus NSAI arm, [redacted] of patients discontinued study treatment due to an SAE, compared with just [redacted] in the placebo plus NSAI arm. Only [redacted] of these discontinuations (all in the abemaciclib plus NSAI arm) were related to study treatment.

Table 17. Treatment-emergent SAEs occurring in ≥1% of patients in either arm of MONARCH 3, safety population

Preferred Term Reported Term	**Abemaciclib + NSAI** **N=327**	**Placebo + NSAI** **N=161**
Patients with ≥1 serious adverse event, n (%)	[redacted]	[redacted]
Lung infection, n (%)	[redacted]	[redacted]
Pneumonia, n (%)	[redacted]	[redacted]
Acute pneumonia, n (%)	[redacted]	[redacted]
Lung infection, n (%)	[redacted]	[redacted]
Bilateral pneumonia, n (%)	[redacted]	[redacted]
Interstitial pneumonia	[redacted]	[redacted]
Likely aspiration pneumonia, n (%)	[redacted]	[redacted]
Embolism, n (%)	[redacted]	[redacted]
Thromboembolic event[a], n (%)	[redacted]	[redacted]
Pulmonary embolism, n (%)	[redacted]	[redacted]
Pulmonary thromboembolia, n (%)	[redacted]	[redacted]
Pulmonary thromboembolism, n (%)	[redacted]	[redacted]
Chronic deep venous thrombosis, n (%)	[redacted]	[redacted]
Thromboembolism NFI, n (%)	[redacted]	[redacted]
Anaemia, n (%)	[redacted]	[redacted]
Anaemia, n (%)	[redacted]	[redacted]
Diarrhoea, n (%)	[redacted]	[redacted]
Diarrhoea, n (%)	[redacted]	[redacted]
Acute kidney injury, n (%)	[redacted]	[redacted]
Acute kidney injury, n (%)	[redacted]	[redacted]
Acute renal failure, n (%)	[redacted]	[redacted]

Preferred Term Reported Term	Abemaciclib + NSAI N=327	Placebo + NSAI N=161
Renal failure, n (%)	[redacted]	[redacted]
Dehydration, n (%)	[redacted]	[redacted]
Dehydration, n (%)	[redacted]	[redacted]
Vomiting, n (%)	[redacted]	[redacted]
Vomiting, n (%)	[redacted]	[redacted]
Pneumonitis, n (%)	[redacted]	[redacted]
Pneumonitis, n (%)	[redacted]	[redacted]
Urinary tract infection, n (%)	[redacted]	[redacted]
Urinary tract infection, n (%)	[redacted]	[redacted]
Abdominal pain, n (%)	[redacted]	[redacted]
Abdominal pain, n (%)	[redacted]	[redacted]

[a]For 1 patient with a thromboembolic event, the patient had events of pulmonary embolism and deep vein thrombosis. The other patient had aspiration thrombolysis conducted on right anterior tibial artery.
Abbreviations: NSAI: non-steroidal aromatase inhibitor; NFI: no further information
Source: Eli Lilly Data on File (Clinical Study Report addendum P55). 2017[57]

AEs leading to discontinuation of study treatment

In the abemaciclib plus NSAI arm, [redacted] of participants discontinued all study treatment due to an AE, compared with 3.1% in the control arm. The most frequent AEs leading to discontinuation of treatment in the abemaciclib plus NSAI arm were neutropenia ([redacted], alanine aminotransferase increase ([redacted]), lung infection ([redacted]), diarrhoea ([redacted]) and embolism ([redacted]). In the placebo plus NSAI arm, patients discontinued study drug due to urinary tract obstruction, spinal cord compression, general physical health deterioration, sudden death, and muscular weakness (1 patient each).[4] The most frequent cause of treatment discontinuation was progressive disease ([redacted] and [redacted] of patients in the abemaciclib plus NSAI and placebo plus NSAI groups, respectively).[57]

Number of deaths due to adverse events

Deaths due to AEs while on the study or within 30 days of treatment discontinuation were reported for [redacted] patients ([redacted]) in the abemaciclib plus NSAI arm, and [redacted] patients ([redacted]) in the placebo plus NSAI arm. An additional 4 deaths in the abemaciclib plus NSAI arm were deemed related to the study disease, as well as one in the placebo plus NSAI arm. The most common AEs resulting in death were lung infection ([redacted] patients), followed by embolism ([redacted] patients) and respiratory failure ([redacted]) in the abemaciclib plus NSAI arm. In this population of patients with locoregionally recurrent or metastatic breast cancer, the cause of death was generally confounded by multiple comorbid factors, and no patterns were observed.[4] For instance, venous thromboembolism is a known underlying risk for cancer patients and an expected outcome in the study population.[74]

B.2.10.3 Safety conclusions

The majority of patients in both treatment arms of MONARCH 3 experienced at least one TEAE considered related to the study treatment. For the abemaciclib plus NSAI arm, diarrhoea, infection/infestations, neutropenia, fatigue and nausea were the most frequent TEAEs. Diarrhoea was predominantly of low grade and largely managed through use anti-diarrhoeal medication,

and in patients who experienced neutropenia, the neutrophil count generally remained stable once decreased, and was reversible following treatment discontinuation.[5] Other frequently observed adverse events were manageable and commonly associated with breast cancer therapies. Serious adverse events were reported by a higher proportion of patients in the abemaciclib plus NSAI arm, due to a range of causes, with no prominent patterns observed.[5] No specific patterns were observed with regards to the deaths observed in the abemaciclib plus NSAI arm.[4] Overall, abemaciclib plus NSAI was well-tolerated, with an acceptable TEAE profile.

B.2.11 *Ongoing studies*

There are currently five ongoing studies in the UK investigating the efficacy and safety of abemaciclib in breast cancer patients, as detailed below.

- JPBM (MONARCH 3): Details of the MONARCH 3 trial are reported in Section B.2.3. 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.
- JPBL (MONARCH 2): A phase III randomised, double blind placebo-controlled study of fulvestrant with or without abemaciclib for women with HR+/HER2− locally advanced or metastatic breast cancer. 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.
- 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 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.[75]
- 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.[76]

B.2.12 *Innovation*

As HR+/HER2− advanced breast cancer remains incurable, there remains an unmet need to continue to improve survival and maintain HRQoL, which can be addressed by delaying disease progression and the onset of chemotherapy. Treatment of advanced HR+/HER2− breast cancer with abemaciclib has been explored in three separate populations; currently being assessed separately by NICE. Abemaciclib has demonstrated a tolerable safety profile in all populations, offers considerable improvements to PFS, and is provided as oral therapy with continuous dosing, which may be preferred by patients.[32,33]

Abemaciclib plus NSAI delays disease progression and thus the need for cytotoxic chemotherapy

Extending PFS is a key efficacy consideration for advanced breast cancer patients, as stated by the NICE technology appraisal guidance for both palbociclib (TA495) and ribociclib (TA496). MONARCH 3 demonstrated that abemaciclib plus NSAI results in significantly prolonged median PFS compared to placebo plus NSAI at the interim analysis (14.7 months vs. median PFS not met; HR 0.54)[5] and at the final analysis by [redacted] months ([redacted] months vs. [redacted] months). Delaying disease progression remains a treatment priority in terms of maintaining quality of life. A chart review and database analysis of 102 women with HER2−, stage IV (metastatic) breast cancer reported that disease progression is associated with worsening physical symptoms, treatment side effects and acute distress, as well as impaired performance[28].

Prolonging PFS and delaying disease progression, delays the need for chemotherapy. Postponing the initiation of chemotherapy is a priority for treatment strategies. Chemotherapy is commonly associated with a substantial negative impact on patients' quality of life. A cross-sectional study of breast cancer patients demonstrated a significant difference in depression, unmet sexual needs, disease-specific concerns, and physical and mental well-being between patients receiving chemotherapy and those receiving alternative treatment.[77] 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.[29]

Abemaciclib plus NSAI has a tolerable safety profile that allows for continuous dosing

Abemaciclib has a tolerable safety profile. In the MONARCH 3 trial, the most frequently observed TEAE was diarrhoea ([redacted]); [redacted] and [redacted] experienced a grade 3 and 4 event, respectively.[4] The majority of abemaciclib plus NSAI patients (76.3%) who experienced diarrhoea did not undergo any treatment modifications during the study, [redacted] had a dose reduction and [redacted] had a dose omission, indicating good management of this side effect.[5] Few patients experienced severe neutropenia ([redacted] grade 4) and [redacted] experienced grade 3,[5] with neutrophil counts remaining stable once decreased and reversing upon discontinuation.[5] Other frequently observed adverse events were manageable and commonly associated with breast cancer therapies.

It may be noted that the comparators palbociclib and ribociclib are associated with high levels of neutropenia: 55.3% grade 3[38] and 59.6% grade 3 or 4, respectively.[39] As a result, treatment with palbociclib or ribociclib requires regular blood count monitoring and a seven-day treatment gap following every 21 days of treatment to allow for recovery.[38, 39] While uncommon, the consequences of neutropenia in breast cancer patients can be severe in cases, including serious infections and increased mortality. For patients without fever, delays to therapy and dose modification may also be required, which may result in long term consequences of cancer outcomes.[78] The tolerable safety profile of abemaciclib allows for the therapy to be taken without treatment holidays, which may reduce the overall burden of treatment monitoring and may facilitate optimal inhibition of CDK4 and CDK6. Pre-clinical evidence has demonstrated that continuous inhibition of CDK4 and 6 is important for sustained cell growth arrest resulting in apoptosis or senescence.[5, 6, 60]

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

B.2.13.1 Principle findings from the clinical evidence base

Abemaciclib plus NSAI, provided clinically meaningful improvements in PFS and ORR in patients with HR+/HER− locoregionally recurrent or metastatic breast cancer.

The MONARCH 3 trial enrolled 493 patients across 22 countries, with a median follow-up period of 26.7 months in both arms. Results from the MONARCH 3 study demonstrated that treatment with abemaciclib plus NSAI was associated with a significantly extended PFS and an improved ORR, in comparison with a placebo plus NSAI.

The MONARCH 3 study achieved its primary endpoint by demonstrating a statistically significant improvement in PFS for abemaciclib plus NSAI, compared to placebo plus NSAI, at both the interim and final analyses. This improvement corresponds to a risk reduction for progression or death of [redacted] for patients treated with abemaciclib plus NSAI, and an additional [redacted] months of PFS at the final analysis. A significant benefit in PFS was also demonstrated across all pre-specified subgroups. PFS results were consistent between the investigator and independent assessments, indicating their reliability. An improvement in PFS is likely to translate to improved OS,[79] however the extent of this is currently uncertain.

A significantly greater proportion of patients treated with abemaciclib plus NSAI achieved a CR or PR, as defined by RECIST version 1.1[58] ([redacted] likelihood compared to the placebo plus NSAI arm).[58] Treatment with abemaciclib plus NSAI was associated with a significantly higher ORR relative to placebo plus NSAI.

Abemaciclib plus NSAI administration did not adversely affect HRQoL relative to the placebo plus NSAI arm, with no large difference[59] in EORTC QLQ-C30 score and no significant differences in EQ-5D-5L index or Visual Analogue Score, between treatment arms.

In conclusion, the results presented demonstrate the clinical efficacy of abemaciclib in combination with a NSAI in patients with incurable HR+/HER2− locoregionally recurrent or metastatic breast cancer, with a substantial and significant delay in disease progression. For patients with HR+/HER2− advanced breast cancer whose disease progresses on initial endocrine therapy, NICE currently recommends the use of sequential chemotherapy.[49] In patients with locoregionally recurrent or metastatic breast cancer who are treated with abemaciclib plus NSAI, disease progression and the need for treatment with toxic chemotherapy regimens is delayed for an additional [redacted] months, thereby providing patients with a maintained quality of life for a longer period of time.

The results of the indirect treatment comparison support that abemaciclib plus NSAI is of comparable efficacy to ribociclib plus letrozole and palbociclib plus letrozole in treating patients with HR+/HER2− locoregionally recurrent or metastatic breast cancer.

Overall, the treatment effects for each of the primary endpoints were similar between ABE-ANAS/LTZ, PAL-ANAS/LTZ and RIBO-ANAS/LTZ, supporting that the efficacy of abemaciclib plus ANAS/LTZ is at a minimum comparable across the CDK inhibitors. In consideration of heterogeneity among MONARCH 3 and the relevant comparator trials (MONALEESA-2, PALOMA 1/TRIO-18 and PALOMA-2), the patient populations were similar in multiple aspects (age, postmenopausal status, HR/HER2 receptor status, performance status, proportion of

patients with bone-only disease and prior chemotherapy/endocrine therapy). There were differences in patient disease characteristics including DFI and proportion of patients with visceral involvement. The proportion of patients with liver metastases was reported only in one trial (MONARCH 3). These factors should be considered when interpreting the results. The trials for the comparators were closely connected in the network (one intermediate node [ANAS/LTZ]).

Abemaciclib plus NSAI is associated with a manageable safety profile

The evidence base for abemaciclib in combination with an NSAI demonstrates a tolerable safety profile. The most common TEAEs were diarrhoea ([redacted]), infections and infestations ([redacted]), and neutropenia ([redacted]), though they were rarely of high severity ([redacted], [redacted], [redacted], respectively, at grade 4). Previous studies of abemaciclib support this conclusion, as reported in the MONARCH 2 study; where the most frequent AEs of any grade were also diarrhoea and neutropenia, of predominately grade 1 or 2 severity, which were both easily managed.[40]

The results demonstrate abemaciclib plus NSAI to be safe and tolerable, as an initial treatment regimen for postmenopausal women with advanced HR+/HER2− breast cancer.

B.2.13.2 Strengths and limitations of the clinical evidence base

Internal validity of MONARCH 3

As described in Section B.2.5, the MONARCH 3 trial was methodologically robust and well reported. The 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, with more than 80% statistical power.[4]
- 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 assessed independently in MONARCH 3 to minimise bias, as investigator-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.[80] However, independent review is also prone to bias given that information may be censored, for example the exclusion of unconfirmed local progressions.[81]

External validity of MONARCH 3

The results of the MONARCH 3 study can be generalised to the UK population, considering there was a high proportion of Caucasian patients, with [redacted] sites in the UK. The trial was well designed with a low risk of bias. The results are also well aligned with the decision problem specified in the NICE scope.[82] The external validity of the MONARCH 3 study is supported by the following:

- **Population** – All but one patient (due to missing data) had HR+/HER2− breast cancer,[4] and over half ([redacted]) of the MONARCH 3 study population had not previously been treated with endocrine therapy.[4] The study population of MONARCH 3 was defined as postmenopausal women with advanced HR+/HER2− breast cancer. More than 80% of breast cancer cases in the UK occur in women over the age of 50,[16] the majority of which are likely to be postmenopausal.[18] The MONARCH 3 study population is relevant to the epidemiology of breast cancer in the UK. The population included patients from four clinical trial sites across the UK.[4] Despite approximately 30% of patients in the MONARCH 3 study being of Asian ethnicity (from Japan, Taiwan and Korea), which constitutes a small proportion of the UK population (1.5%),[83] the majority ([redacted]) of the MONARCH 3 study population were [redacted] which is in line with the majority White population in the UK (86.0%).[83]
- **Intervention** – Abemaciclib was directly evaluated as a treatment option for postmenopausal women with HR+/HER2− advanced breast cancer, by comparing abemaciclib plus NSAI to placebo plus NSAI.
- **Comparator** – The efficacy and safety of abemaciclib was directly compared with that of placebo, each administered with either letrozole or anastrozole. The evidence presented in this submission (Section B.2.9) indirectly compares abemaciclib to two relevant comparators as specified in the NICE scope[14]; the CDK 4 and 6 inhibitors ribociclib and palbociclib, which have been recently recommended by NICE.[53, 54]
- **Outcomes** – 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, HRQoL and safety). PFS is considered to be a particularly valuable endpoint for comparing treatment regimens for patients with advanced breast cancer. Advanced breast cancer is a chronic disease, and measurement of PFS allows for a higher event frequency sooner in comparison to OS.[84] Furthermore, PFS is not influenced by subsequent therapies, with results therefore reflecting the efficacy of the study drug.[84, 85]
- Tumour assessment was performed according to RECIST v1.1[58] by both local and independent, blinded assessment, thereby minimising the potential subjectivity of tumour-based assessment.[86]

Limitations

- The impact of abemaciclib on OS of patients with HR+/HER2− advanced breast cancer has not yet been determined. The median follow-up times of [redacted] months in the abemaciclib plus NSAI arm and [redacted] months in the placebo plus NSAI arm were not long enough for OS data to become mature. Follow-up for overall survival is still ongoing, and the estimated data cut-off is May 2020.
- There has been no direct comparison of efficacy and safety between abemaciclib and ribociclib or palbociclib (all in combination with an NSAI) in a clinical trial setting, necessitating an indirect comparison to be performed between abemaciclib plus NSAI and these relevant UK comparators.
- The proportion of patients ([redacted]) with de novo metastatic breast cancer at baseline in the MONARCH 3 study population does not reflect the disease severity seen in UK clinical practice. Due to high quality diagnostic processes in the UK, breast cancer cases are commonly diagnosed before the occurrence of metastasis; just 13% of breast cancer patients present with metastatic breast cancer at diagnosis.[10, 15] This issue was also highlighted in

Technology Appraisals 495 and 496 for palbociclib and ribociclib,[53, 54] respectively, and was not considered to be a limitation.

B.2.13.3 Conclusion

Abemaciclib plus NSAI significantly improved PFS and ORR compared to NSAI in HR+/HER2− advanced breast, with a distinct and tolerable safety profile that allows for continuous dosing. Significant PFS improvement delays disease progression and the subsequent onset of chemotherapy regimens, providing patients with a maintained HRQoL for longer.

The quality of the evidence provided by the MONARCH 3 study is supported by robust and well-reported methodology, and the trial results are directly relevant to the management of HR+/HER2− breast cancer for postmenopausal women in NHS clinical practice.

B.3 Cost effectiveness

Summary of the cost-effectiveness evaluation

- A 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− locoregionally recurrent or metastatic breast cancer identified 31 relevant studies.
- A *de novo* cost-utility analysis was undertaken to assess the cost-effectiveness of abemaciclib plus NSAI for the treatment of women with advanced HR+/HER2− locoregionally recurrent or metastatic breast cancer who have had no prior systemic therapy in this setting.
- The analysis compared ABE-NSAI to PAL-NSAI and RIBO-NSAI, in line with the decision problem for this appraisal.
- A cohort state-transition model with three health states – PFS, post-progression survival (PPS), and death – was developed. The PPS state triggered a fixed 'pay-off' at the point of progression that attributed survival, costs and outcomes associated with progression. Patients entering the 'pay-off' received second- and third-line therapies informed by Kurosky et al. (2015), which reviewed medical records of advanced breast cancer patients in the UK.
- The analysis was consistent with the NICE reference case: a cost-utility analysis with an NHS and PSS perspective. Costs and benefits were discounted at a rate of 3.5% and a lifetime-equivalent time horizon of 35 years was used.
- Clinical outcomes for ABE-NSAI were based on the ITT population of the MONARCH 3 trial, using the final PFS data cut (3rd November 2017). Clinical outcomes for the first-line comparators and second-line treatments were estimated based on data from an SLR of RCTs conducted in MONARCH 3 and MONARCH 2[a]-aligned populations, respectively, and synthesised in an NMA for each indication.
- Health state utilities for first-line PFS were informed by EQ-5D-5L data collected directly from the MONARCH 3 trial. Utility estimates for the second-line PFS and PPS states were informed by data from TA496 and Lloyd et al. (2006).
- Costs and healthcare resource use were captured in the analysis for drug acquisition and administration for first-, second- and third-line treatments, best supportive care, follow-up and terminal care and AEs and hospitalisations.
- ABE-NSAI accrued a greater number of life years (LYs) and QALYs, and lower costs (due to shorter time on treatment) compared to both PAL-NSAI and RIBO-NSAI. Based on the list price only, ABE-NSAI dominated both PAL-NSAI and RIBO-NSAI in the base case.
- For the purposes of validation, cost-effectiveness results for ABE-NSAI versus NSAI were also presented; ABE-NSAI was associated with an incremental cost-effectiveness ratio (ICER) of £250,065 per QALY versus NSAI.
- In the scenario analyses, the economic results were largely stable when varying model assumptions, with consistent ICER estimates, demonstrating the robustness of the model. The PSA demonstrated that there was an 82% chance of ABE-NSAI being cost-effective at a threshold of £30,000 per QALY.
- In conclusion, the economic analysis found abemaciclib plus NSAI to be associated with a clinical benefit, as measured by LYs and QALYs, relative to the comparators defined by the scope of this submission, palbociclib and ribociclib plus NSAI.

[a]MONARCH 2 was a Phase III, randomised, placebo-controlled study that evaluated abemaciclib plus fulvestrant versus placebo plus fulvestrant for the treatment of women with HR+/HER2− ABC who experienced disease progression on or after prior endocrine therapy.

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− locoregionally recurrent 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 18; full details of the search strategy and the complete results are presented in Appendix G.

Table 18: 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[87]	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)[88]	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[89]	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[51]	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: EVE-EXE: 1.58 EXE: 1.37	Total costs: EVE-EXE: £49,748 EXE: £36,677	EXE-EVE vs EXE: £61,046 (without PAS)
Chemotherapy or combination chemotherapy and a targeted agent						
NICE TA214[90]	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[91]	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 VIN: 0.1136 vs CAP: 0.2683	Incremental costs: eribulin vs TPC: £5,586 vs GEM: £5,177 vs VIN: £4,041 vs CAP: £12,779	Eribulin vs TPC: £46,050 vs GEM: £27,183 vs VIN: £35,602 vs CAP: £47,631
NICE TA263[92]	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)[88]	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 VIN: 1.88 DOX: 1.88 CAP: 1.88 Total QALYs: EVE + EXE: 2.06 DOC: 0.95 VIN: 0.95 DOX: 0.95 CAP: 0.95	Total costs: EVE + EXE: £48,085 DOC: £31,835 VIN: £25,021 DOX: £23,743 CAP: £21,851	EXE-EVE vs DOC: £14,550 vs VIN: £20,653 vs DOX: £21,797 vs CAP: £23,491
NICE TA295[93]	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: nonsteroidal aromatase inhibitor; PAC: paclitaxel; PAL: palbociclib; 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; VIN: 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*

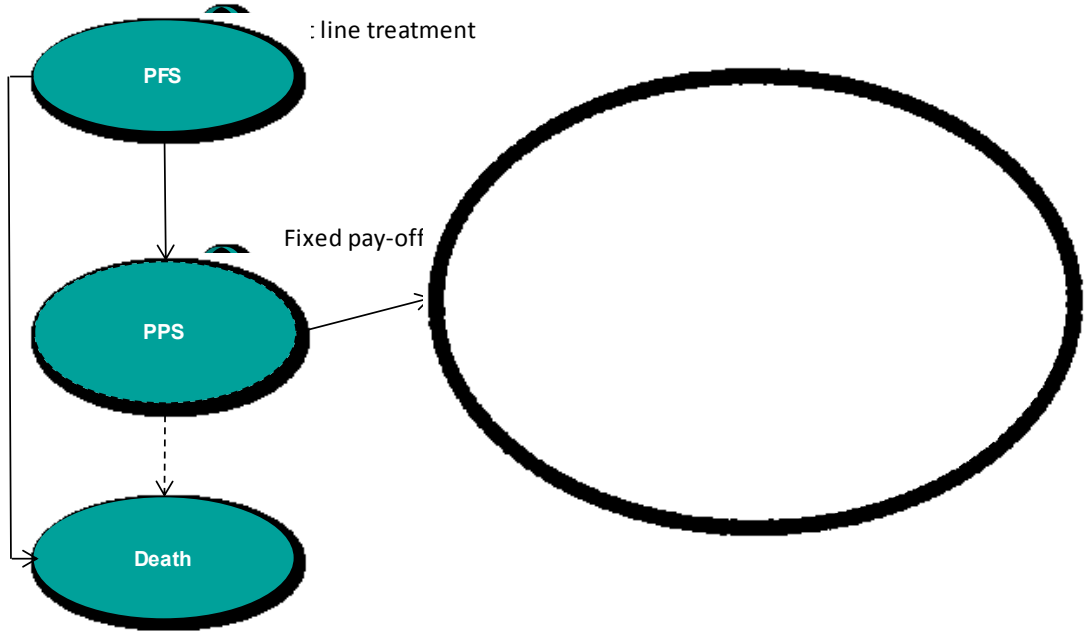
B.3.2.1 Patient population

In line with the final NICE scope for this appraisal, and in line with the MONARCH 3 trial, the *de novo* cost-effectiveness analysis presented here considers postmenopausal women with HR+/HER2− locoregionally recurrent or metastatic breast cancer who have had no prior systemic therapy for their advanced disease.

B.3.2.2 Model structure

A cohort state-transition model with three health states – PFS, post-progression survival (PPS), and death – was developed, and is illustrated in Figure 15. The PFS and death states were modelled as Markov states. However, once patients experienced disease progression, they did not explicitly transition into a PPS Markov state. Outcomes associated with progression were attributed at the point of progression based on the calculation of a fixed 'pay-off' that represented PPS, costs and outcomes. The PFS health state and post-progression 'pay-off' are described below.

Figure 15. Cohort state-transition model structure



Abbreviations: PFS1: first-line progression-free survival; PFS2: second-line progression-free survival; PPS: post-progression survival

PFS health state

Upon initiation, a cohort of 1,000 hypothetical individuals entered the model in the PFS health state (PFS1), where they received one of the following first-line treatments:

- ABE-NSAI
- PAL-NSAI
- RIBO-NSAI

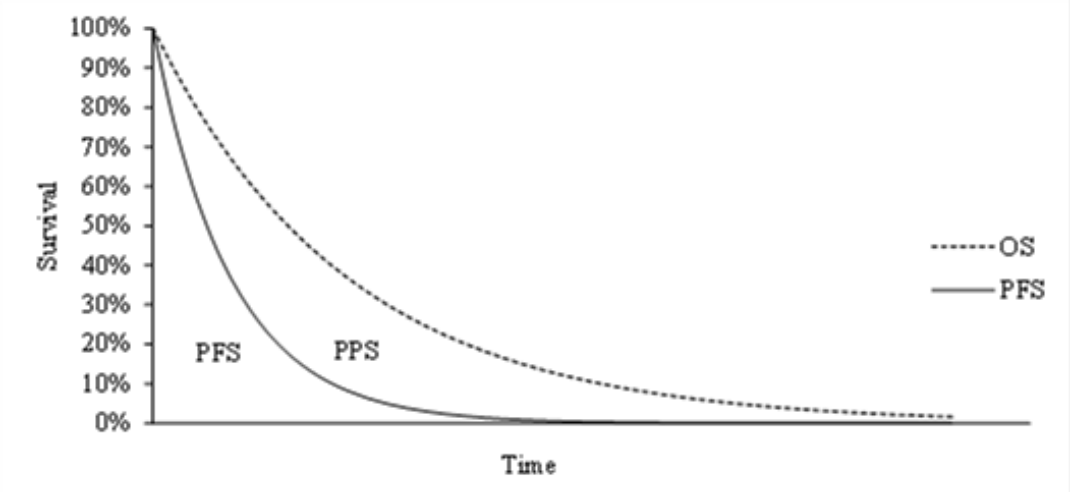
Patients remained in the PFS1 health state as long as they were alive and progression free (transition ‘a’). Patients experiencing disease progression from PFS received a fixed ‘pay-off’ (transition ‘b’). Patients who died without disease progression transitioned to the (absorbing) death state (transition ‘c’). The probability associated with each of these three transitions was estimated using multi-state modelling derived from individual survival analyses (where appropriate) for each possible transition. The difference between this approach and standard survival analysis is that any event that is not the event of interest was treated as a ‘censoring event’. For transition ‘b’, time-to-progression (TTP) data (where pre-progression deaths were censored) from the MONARCH 3 trial were modelled using survival analysis. For transition ‘c’, the rate of progression-free deaths from the MONARCH 3 trial was modelled using negative-binomial regression analysis.

To determine duration of treatment for ABE-NSAI, time-to-treatment discontinuation (TTD) was modelled independently using data from the MONARCH 3 trial. Outcomes for patients receiving therapies not evaluated by the MONARCH 3 trial (PAL-NSAI and RIBO-NSAI) were estimated by applying a HR estimated from the NMA of first-line treatments for locoregionally recurrent or metastatic breast cancer to the NSAI arm of the model.

Post-progression ‘pay-off’

Once patients transitioned out of the PFS state to PPS, the fixed ‘pay-off’ was applied to reflect the outcomes (costs and QALYs) associated with treatment of progressed patients with second- and later-line therapies. This was calculated using an ‘area under the curve’ (AUC) approach using data from the control arm of MONARCH 2, a Phase III, randomised, placebo-controlled study that evaluated abemaciclib plus fulvestrant (ABE-FUL) versus placebo plus fulvestrant (PBO-FUL) for the treatment of women with HR+/HER2− ABC who experienced disease progression on or after prior endocrine therapy and data from the CONFIRM trial, a Phase III RCT comparing fulvestrant 250 mg and 500 mg doses in postmenopausal women with ER-positive ABC.[40] The difference between the two outcomes represented PPS, illustrated in Figure 16, as per the approach taken in partitioned survival analysis.

Figure 16. Area under the curve approach used to calculate the fixed pay-off for post-progression



Abbreviations: OS: Overall Survival; PFS: progression-free survival; PPS: post-progression survival

While in PFS in the 'pay-off' (PFS2) patients received one of the following second-line therapies:

- Chemotherapy i.e. capecitabine (CAP), paclitaxel (PAC), docetaxel (DOC)
- Endocrine therapy (i.e. FUL, EXE, TMX)
- Targeted therapy (i.e. everolimus [EVE] + exemestane [EXE; EVE-EXE])

The choice of post-progression therapy and the proportion of patients receiving each therapy was informed by a study of patient characteristics and treatment patterns in the UK by Kurosky et al (2015)[94]. This study was utilised by the manufacturer of FUL in their submission for NICE TA503,[95] and reviews medical records of HR+/HER2− ABC patients in the UK. ANAS and LTZ were recorded in the Kurosky study as post-progression therapy options. However, the current model assumes that a treatment administered first-line would not be permissible as a second-line treatment following progression.

To determine costs and QALYs associated with the pay-off, PFS and OS were estimated directly from the survival curves from the PBO-FUL arm of the MONARCH 2 trial for patients receiving FUL as a second-line treatment.

The PFS and OS curves for other second-line treatments were estimated based on data from an NMA of trials comprising patient populations aligned with MONARCH 2, the methodology and results of which are presented in Appendix N. The Monarch 2 NMA provided relative efficacy estimates for each treatment versus FUL 500 mg (chosen as the reference treatment because it connected MONARCH 2 to all other trials). No study was identified from the SLR that compared an endocrine therapy to a chemotherapy or combination regimens of these treatments. Consequently, it was not possible to connect chemotherapy to the network. Therefore, the relative efficacy estimates for chemotherapy (relative to EVE-EXE) were sourced from a study by Li et al 2015.[96] The authors compared EVE-based treatment to chemotherapy. This study was used to estimate the efficacy outcomes of chemotherapy in the NICE TA for RIBO-NSAI.[54] The survival curve for each treatment was multiplied by the proportion of patients receiving each therapy to derive a weighted average survival by first-line therapy.

Patients progressing on their second-line regimen received further treatment, as per clinical practice, while in the PPS phase of the 'pay-off' calculation. These treatments included:

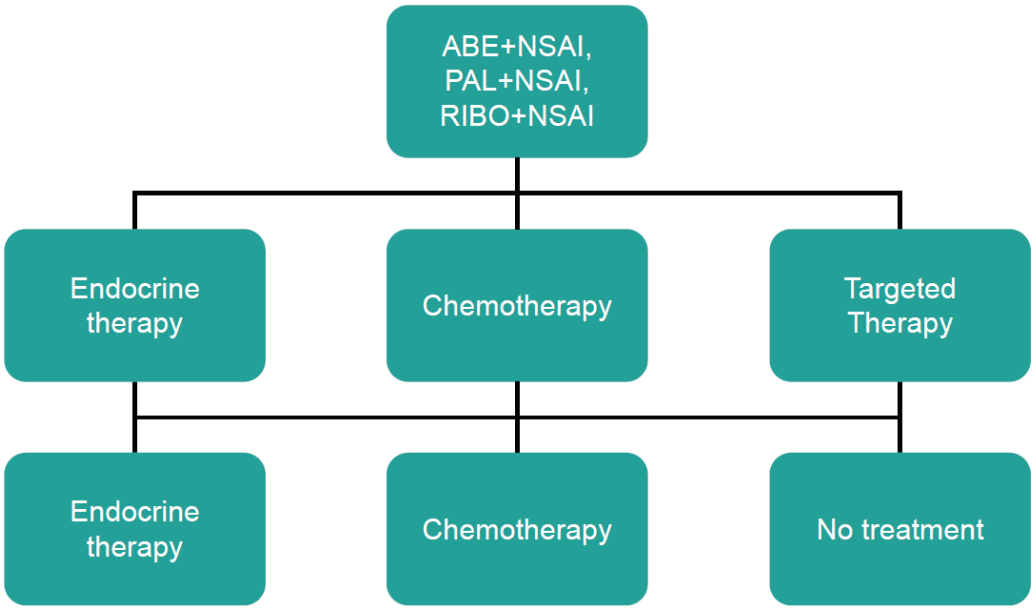
- Chemotherapy (i.e. CAP, eribulin [ERI])
- Endocrine therapy (i.e. FUL, TMX)

As per the choice of second-line therapy the choice of third-line therapy was informed by Kurosky et al (2015),[94] and NICE TA503.[95] The current model assumed that 54% of such patients received a third-line therapy while the remaining 46% receive no active treatment (best supportive care [BSC] alone). As noted above, ANAS and LTZ were not considered as third-line options as all patients would have received a NSAI at first-line. Time-on treatment for each third-line option was informed by the relevant studies included in a SLR performed internally of treatments for heavily pre-treated advanced breast cancer. Treatments received following progression on second-line therapy were included in the analysis as a weighted cost only. This was thought to be reasonable as differences in long-term outcomes associated with these therapies were unlikely to differ between comparators sufficiently to impact on cost-effectiveness estimates.

One of the key assumptions of the partitioned survival analysis approach is the independence of clinical endpoints. PFS and OS curves were modelled independently (i.e. using different parametric functions). It was possible for the PFS curve to lie above the OS curve, yielding negative occupancy of the 'post-progression' health state. For face validity, the model restricted PFS to be equal to OS in this instance.

The treatment pathway simulated by the model is illustrated in Figure 17.

Figure 17. Treatment pathway simulated by the model



Abbreviations: ABE: abemaciclib; EXE: exemestane; FUL: fulvestrant; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; RIBO: ribociclib; TMX: tamoxifen

Assumptions regarding the proportion of PFS gain translating to OS gain

In the model, OS was modelled indirectly based on time spent in each of the modelled states. As such, with no adjustment, a gain in PFS results in a gain of the same magnitude in overall time in the model (i.e. OS). As the OS data from the MONARCH 3 trial are immature, it is difficult to validate whether this level of OS gain is accurate. Based on ERG and Appraisal Committee (AC) feedback from the PAL and RIBO appraisals (TA495[53] and 496[97], respectively), a transfer of 100% of PFS gain to OS gain was determined to be unlikely. Therefore, the analysis applied a calibration factor which reduced time spent in the PPS 'pay-off' to adjust the gain in OS to approximately 27.5% of the gain in PFS, as per the PALOMA-1 trial,[98] and the approach preferred by the appraisal committee in TA495/496.[10, 97] The calibration factor was applied to all CDK 4 & 6 inhibitors as OS data from PALOMA-2 and MONALEESA 2, phase III trials of PAL-NSAI and RIBO-NSAI in HR+/HER2− ABC, respectively, are also immature.

Justification for model structure

A state transition approach with a fixed 'pay-off' for post-progression was deemed appropriate as it reflects the treatment pathway followed by patients with locoregionally recurrent or metastatic breast cancer. These patients may receive multiple lines of therapy, the outcomes of which are prognostic of long-term survival. Given the immaturity of OS data from the MONARCH 3 trial, and the availability of relatively mature data for patients having second-line treatment, the explicit modelling of second-line therapy to calculate the post-progression 'pay-off' provided a more

robust basis from which to extrapolate survival over a lifetime horizon and capture all relevant costs and outcomes. As recommended by the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 19,[99] the limitations of using partitioned survival analyses to extrapolate these second-line data were taken into consideration and the current model structure was preferred. Additionally, the criticism of the partitioned survival analysis methodology adopted by the manufacturer of palbociclib in NICE TA495[53] was taken into account. The extrapolation of immature OS would require strong assumptions regarding the relationship between PFS and OS, resulting in a high level of uncertainty.

Furthermore, one of the key structural assumptions of a Markov state-transition model is that the probability of transitioning out of any (non-initial) state is constant for all patients in the state at any given time, regardless of how long they have been in the state or any other disease history. This is commonly referred to as the Markovian or "memoryless" assumption. Where clinical trial data suggest that the probability of transitioning from a state is dependent on time in state or past history, tunnel states may be used to relax this assumption. However, this may become cumbersome and complex depending on the number of tunnel states required. The 'pay-off' approach permits the flexibility to reflect time dependencies in clinical outcomes in the post-progression state. The implementation of the 'pay-off' is somewhat simpler than implementing a large number of tunnel states, and makes it possible to test different distributions in extrapolating survival over the lifetime of a patients while capturing all costs and outcomes associated with post-progression survival.

Model characteristics

The model utilised monthly cycles over which transitions were modelled, and costs and outcomes accrued. A one-month cycle length is 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 to reduce the potential for bias in the cost-effectiveness estimates in all calculations, with the exception of treatment costs. It was deemed inappropriate to apply a half-cycle correction to treatment costs as the first-line treatments are oral therapies and assumed to be dispensed at the beginning of the cycle at full cost, regardless of whether or not patients complete the cycle.

Discount rates of 3.5% per annum were applied to both costs and benefits in the base case. Given the use of a 'pay-off' approach to calculate post-progression costs and outcomes, so called 'double discounting' was employed. Costs and outcomes that follow progression are discounted back to the initial point of progression; this discounted 'pay-off', when applied to patients at a given point in the model, is then further discounted back to model baseline. Scenario analyses in which the discount rate was set to 0% and 6% were also performed. A summary of model characteristics is provided in Table 19.

Table 19: Features of the economic analysis

	Previous appraisals		Current appraisal	
Factor	TA495[53]	TA496[97]	Chosen values	Justification
Modelling approach	Partitioned survival Markov model	Markov state-transition	Markov state-transition with a fixed 'pay-off' for post-progression	Refer to the 'Justification for model structure' in Section B.3.2.2
Perspective	NHS and PSS	NHS and PSS	NHS and PSS	In accordance with the NICE reference case[100]
Cycle length	28 days	Individual-based approach – time is sample directly	1 month	A monthly cycle is appropriate given the rate at which relevant clinical events may occur in this patient population
Time horizon	Lifetime (40 years)	Lifetime (40 years)	Lifetime (35 years)	A 35-year time horizon corresponds to the length of time in which survival in all arms reached <0.1% for the base case extrapolations. Hence this can be considered equivalent to lifetime.
Outcome measures	QALYs	QALYs	QALYs (base case); LYs (scenario)	In accordance with the NICE reference case[100]
Discount rate	3.5% per annum	3.5% per annum	3.5% per annum	In accordance with the NICE reference case[100]
Source of utilities	EQ-5D data were collected as part of the PALOMA-2[101] trial	EQ-5D data were derived directly from the underlying phase 3 trials, MONALEESA-2,[102] and BOLERO-2[103], and the NICE appraisal of	EQ-5D data were collected as part of the MONARCH 3[57] trial (PFS1) and TA496[54], (Lloyd, 2006)[104] (PFS2, PPS)	In accordance with the NICE reference case[100]

		palbociclib ID915[53]		
Source of costs	NHS Reference costs (2014–2015); PSSRU (2015)	NHS Reference costs (2015–2016); PSSRU (2016)	NHS Reference costs (2016–17); PSSRU (2017)	In accordance with the NICE reference case[100]

Abbreviations: EQ-5D: EuroQol 5-Dimension; NHS: national health service; PFS1: first-line progression-free survival; PFS2: second-line progression-free survival; QALYs: quality-adjusted life years; PSS: personal social services; PSSRU: personal social services research unit

B.3.2.3 Intervention technology and comparators

The following comparators were included in this cost-effectiveness analysis:

- Palbociclib + NSAI (PAL-NSAI)
- Ribociclib + NSAI (RIBO-NSAI)

Both comparators were implemented in the model as per their marketing authorisations, and are aligned with the decision problem for this appraisal (Section B.1.1). NSAI alone was also included in the analyses to facilitate comparison of economic results with prior appraisals.[53,54]

B.3.3 *Clinical parameters and variables*

B.3.3.1 Clinical outcomes

The model structure necessitated identification of time-to-event data for first- and second-line patients in the locoregionally recurrent or metastatic breast cancer setting. For first-line treatment, time to event was assessed for the PFS1 to PPS transition and the PFS1 to death transition. For the post-progression 'pay-off', PFS and OS were assessed. TTD for first- and second-line treatments was also determined. The following sections describe the data sources for each intervention (Section B.3.3.2), the patient characteristics (Section B.3.3.3) and interval censoring for progression-based endpoints (Section B.3.3.4). The process for estimating long-term clinical outcomes for each treatment line of the model is presented in Sections B.3.3.5–B.3.3.7.

B.3.3.2 Data sources

A summary of the sources used to assess clinical effectiveness of clinical data for ABE-NSAI, PAL-NSAI and RIBO-NSAI are presented in Table 20.

Table 20. Summary of clinical effectiveness data sources

Treatment	Endpoint data source			
	TTP*	Progression-free deaths*	PFS	OS
First-line (PFS1)				
ABE (150 mg) –NSAI (ANAS 1mg / LTZ 2.5 mg)	MONARCH 3; NMA (scenario)	MONARCH 3	N/A	N/A
PAL (125 mg)-NSAI (ANAS 1 mg / LTZ 2.5 mg)	NMA; PALOMA-1/TRIO-18,[105] PALOMA-2[106]	NMA; PALOMA-1/TRIO-18[105]	N/A	N/A
RIBO (600 mg)-NSAI (ANAS 1 mg / LTZ 2.5mg)	NMA; MONALEESA-2[107]	NMA; MONALEESA-2[107]	N/A	N/A
Second and subsequent lines (PFS2, PPS)				
FUL (500 mg)	MONARCH 2	MONARCH 2	MONARCH 2	MONARCH 2, CONFIRM[108]
ANAS (1 mg)	NMA; Howell et al. (2002),[109] Trial 0021,[110] CONFIRM,[111] Campos et al. (2009),[112] Buzdar et al. (1997),[113] Jonat et al. (1996)[114]	NMA; Howell et al. (2002),[109] Trial 0021,[110] CONFIRM,[108] Campos et al. (2009),[112] Rose et al. (2003),[115] Buzdar et al. (1997),[113] Jonat et al. (1996)[114]	NMA; Howell et al. (2002),[109] Trial 0021,[110] CONFIRM,[111] Campos et al. (2009),[112] Buzdar et al. (1997),[113] Jonat et al. (1996)[114]	NMA; Howell et al. (2002),[109] Trial 0021,[110] CONFIRM,[108] Campos et al. (2009),[112] Rose et al. (2003),[115] Buzdar et al. (1997),[113] Jonat et al. (1996)[114]
LTZ (2.5 mg)	NMA; Buzdar et al. (2001)[116]	NMA; Buzdar et al. (2001),[116] Dombernowsky et al. (1998),[117] Rose et al. (2003)[115]	NMA; Buzdar et al. (2001)[116]	NMA; Buzdar et al. (2001),[116] Dombernowsky et al. (1998),[117] Rose et al. (2003)[115]
EXE (25 mg)	NMA; BOLERO 2,[118] Campos et al. (2009),[112] SoFEA,[119] Yamamoto et al. (2013)[120]	NMA; BOLERO 2,[118] Campos et al. (2009),[112] Kaufman et al. (2000),[121] SoFEA,[119] Yamamoto et al. (2013)[120]	NMA; BOLERO 2,[118] Campos et al. (2009),[112] SoFEA,[119] Yamamoto et al. (2013)[120]	NMA; BOLERO 2,[118] Campos et al. (2009),[112] Kaufman et al. (2000),[121] SoFEA,[119] Yamamoto et al. (2013)[120]
TMX (40 mg)	Milla-Santos (2001)[122] and NMA	Milla-Santos (2001)[122] and NMA	Milla-Santos (2001)[122] and NMA	Milla-Santos (2001)[122] and NMA

Treatment	Endpoint data source			
	TTP*	Progression-free deaths*	PFS	OS
EVE (10 mg)-EXE (25mg)	NMA; BOLERO 2[118]	NMA; BOLERO 2[118]	NMA; BOLERO 2[118]	NMA; BOLERO 2[118]
Chemotherapy	Li (2015)[96]	Li (2015)[96]	Li (2015)[96]	Li (2015)[96]

Footnotes: *NMAs of PFS and OS were conducted and the results were included in the model for TTP and pre-progression death, respectively, assuming the relative treatment differences were equivalent for these two endpoints.
Abbreviations: ABE: abemaciclib; ANAS: anastrozole; EXE: exemestane; FUL: fulvestrant; LTZ: letrozole; NMA: network meta-analysis; NSAI: non-steroidal aromatase inhibitor; OS: overall survival; PAL: palbociclib; PFS: progression-free survival; PPS: post-progression survival; RIBO: ribociclib; TMX: tamoxifen; TTP: time to progression; xx

Sections B.3.3.2 to B.3.3.5 describe the sources used to assess clinical effectiveness for ABE-NSAI, PAL-NSAI, RIBO-NSAI, and second- and third-line treatments. Methods of parameterisation are described in Sections B.3.3.5 and B.3.3.6.

Abemaciclib in combination with an NSAI

Clinical outcomes for ABE-NSAI were based on the ITT population of the MONARCH 3 trial, using the final PFS data cut (database lock 3rd November 2017). A scenario analysis was performed using the NMA as the source of ABE-NSAI treatment effects.

First-line comparators and second-/third-line treatments

Clinical outcomes for the first-line comparators and second-line treatments in the model were estimated based on data from an SLR of RCTs conducted in MONARCH 3 and MONARCH 2 aligned populations, respectively (studies listed in Table 20), and synthesised in an NMA for each indication. The NMAs provided relative efficacy estimates for PFS and OS for each first-line treatment relative to an NSAI and versus FUL for those progressing on first-line endocrine therapy for ABC. The relative treatment effects were in the form of HRs representing the instantaneous risk of an event (i.e. death for OS, disease progression or death for PFS) for each comparator relative to the reference treatment (Table 23).

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

B.3.3.3 Patient characteristics

Body weight and body surface area (BSA) were required to calculate drug doses for intravenous therapies (IV). BSA data were not collected in the MONARCH 3 trial; as such, height and body weight data from MONARCH 3 were used to estimate BSA using the DuBois formula:[123]

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

These data are presented in Table 21.

Table 21. Model patient characteristics

Parameter	Mean	Source
Height (cm)	158.41	MONARCH 3 CSR[4]
Weight (kg)	67.99	MONARCH 3 CSR[4]
BSA (m^2)	1.70	Calculation (Du Bois, 1916)

Abbreviations: BSA: body surface area

Adjustment for baseline characteristics

When modelling the following clinical outcomes, additional models were adjusted for baseline characteristics and applied to TTP and deaths in pre-progression, as described in Section B.3.3.5.

Using the MONARCH 3 and MONARCH 2 data, additional models were fitted that adjusted for baseline characteristics through the inclusion of covariates. The baseline characteristics assessed were identified based on the following:

- Pre-planned subgroup analyses conducted for the MONARCH 3 and MONARCH 2 trials
- Prognostic factors as indicated by a literature review and input from key opinion leaders

This lead to the following baseline characteristics being assessed for inclusion in the covariate adjusted analyses:

- MONARCH 3:
    - Age
    - Race
    - Geographic location
    - Disease-free interval
    - Number of disease sites
    - Eastern Cooperative Oncology Group (ECOG) performance status
    - Visceral lesion
    - Site of metastases (liver, lung, bone only, chest wall, lymph nodes)
    - Disease setting (*de novo* metastatic, recurrent metastatic, loco-regionally recurrent)
    - Prior therapy received in neoadjuvant setting (treatment[s] received by each patient, e.g. tamoxifen)
    - Type of NSAI received at cycle 1
    - Measurable disease at baseline
    - Number of organs/disease sites at baseline (assumed to be defined the same)
    - Progesterone receptor (PR) status
    - Disease diagnosis (<10 years and ≥10 years)
    - Tumour grade (high-grade tumour vs. lower/intermediate grade)
- MONARCH 2:
    - Age
    - Race
    - Geographic location
    - Menopausal status - surgical/natural menopause, ovarian suppression (based on MONARCH 2 trial population)
    - Disease-free interval (time from initiation of [neo]adjuvant endocrine therapy to disease relapse)
    - Number of disease sites
    - ECOG performance status

- Prior treatments (based on MONARCH 2 trial population):
    - Prior endocrine therapy in metastatic setting
    - Prior endocrine therapy only in (neo)adjuvant setting
    - Prior (neo)adjuvant chemotherapy
- Number of chemotherapy lines in the (neo)adjuvant setting
- Number of prior hormone regimens in the (neo)adjuvant setting
- Nature of disease (visceral, bone only, or other)
- Sensitivity to endocrine therapy – primary resistance (relapsed while receiving first 2 years of [neo]adjuvant endocrine therapy), or secondary resistance (relapsed while receiving first 6 months of endocrine therapy for advanced disease)
- Measurable disease at baseline
- Number of organs involved at baseline
- Progesterone receptor status
- Starting dose
- Visceral lesion
- Site of metastases

To identify parsimonious models adjusting for baseline characteristics, backwards and forwards stepwise selection procedures were used. Backwards stepwise procedures were preferred as these tend to result in fewer characteristics being included in the final model. For the survival analyses, the stepwise procedures were first applied to fitted Cox models to identify the baseline covariates to adjust for, which were then included in the fitted parametric distributions. The covariate-adjusted analyses were included in a scenario.

B.3.3.4 Interval censoring for progression-based endpoints

Data on disease progression status were collected in the MONARCH 3 and MONARCH 2 trials at specific intervals, which does not necessarily reflect the underlying TTP for patients, as patients' disease may progress prior to their subsequent physician visit. Direct modelling of the Kaplan Meier (KM) data in this case can provide biased estimates of TTP or PFS without adjustment. Consequently, for analyses conducted to assess survival endpoints where the outcome of interest includes disease progression (i.e. TTP and PFS), two parametric analyses were conducted; one assuming dates of progression were exact and a second incorporating the potential for interval censoring (henceforth 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 results of this analysis are presented in Appendix M.2.2 and M2.7.

The interval-censored adjusted analysis was performed using the dates of tumour assessment to inform the intervals for patients that progressed. The time-to-event and event/censoring inputs for the survival analyses took the following approach:

- For patients that progressed:
    - Progression was considered as an event in both the TTP and PFS analyses

- Time-to-event was constructed as an interval between 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 the progression was recorded

- For patients that died before progression:
  - Death was censored in the TTP analysis, and considered an event in the PFS analysis
  - Time-to-event was time to death
- For patients that withdrew from the study prior to progression:
  - Withdrawal was censored in both the TTP and PFS analyses
  - Time-to-event was the time to withdrawal

B.3.3.5 Progression-free survival

TTP (PFS to PPS, required for transition probability b)

Time-to-progression for ABE-NSAI was estimated based on the ITT population of the MONARCH 3 trial. Two assessments of disease progression were conducted in the MONARCH 3 trial; per investigator (INV) and per independent review committee (IRC). The INV-assessed data for MONARCH 3 were used in the model to align with the primary endpoint in the MONARCH 3 trial. The majority of publications used to source data for the first-line comparators also reported INV-assessed data. For the comparators, the results of the NMA were applied to the fitted distributions to the MONARCH 3 data to attain relative TTP estimates.

ABE-NSAI and NSAI – general process for fitting distributions

Standard joint parametric models (including a covariate for treatment to estimate the effect of ABE-NSAI versus NSAI) were fitted to the INV-assessed TTP data from MONARCH 3. These included exponential, Weibull and Gompertz distributions (parameterised as proportional hazards models); and lognormal, log-logistic and gamma distributions (parameterised as accelerated failure time [AFT] models).

The process for selecting the most appropriate parametric model was based on an assessment of the within-trial and extrapolation predictions. It was 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 22 and are based on those described in the NICE DSU TSD14.[124]

Table 22. 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

Criteria	Method	Description
	Log-log plot (log cumulative hazards against log time)	As above
	AIC & 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 long-term observational KM data

Abbreviations: AIC: Akaike information criteria; BIC: Bayesian inference criteria; KM: Kaplan–Meier
Source: Latimer NR. NICE DSU Technical Support Document 14, 2013.[124]

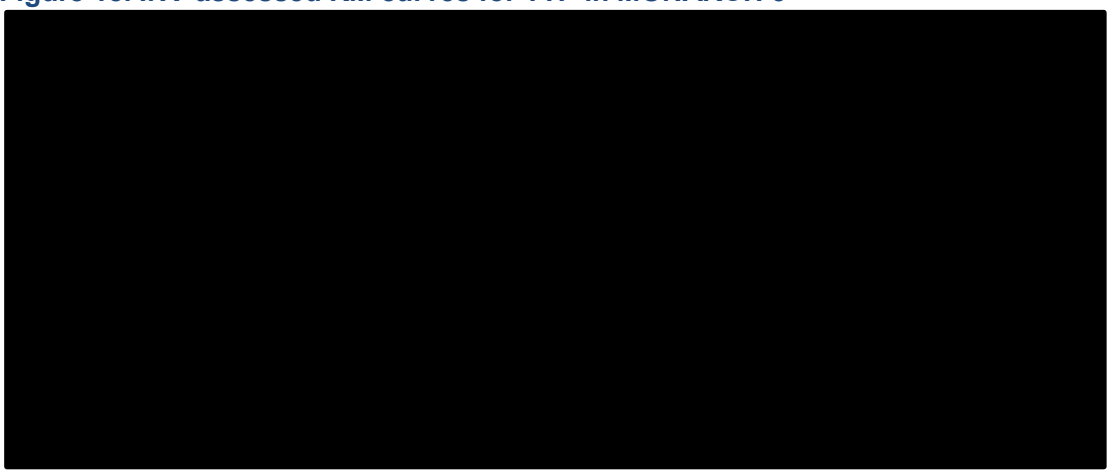
The AFT models differ from proportional hazards models in that they do not constrain the hazard to increase or decrease monotonically over time. The effect of treatment is captured via an acceleration factor (Φ-1) which acts on the baseline time scale, such that when Φ < 1, there is an acceleration in time to event on treatment, while Φ > 1 results in a deceleration in time to event on treatment.

Importantly, applying an HR to a baseline parametric curve on the hazard scale, which has an AFT functional form yields a different extrapolation to when the corresponding acceleration factor is incorporated in the baseline survivor function. Given that treatment effects for the comparators were obtained in the form of HRs, distributions that could provide treatment effect estimates as hazard ratios were preferred for the base case analyses.

Process applied to the MONARCH 3 trial data

The observed TTP KM data, based on the MONARCH 3 trial, are presented in Figure 18.

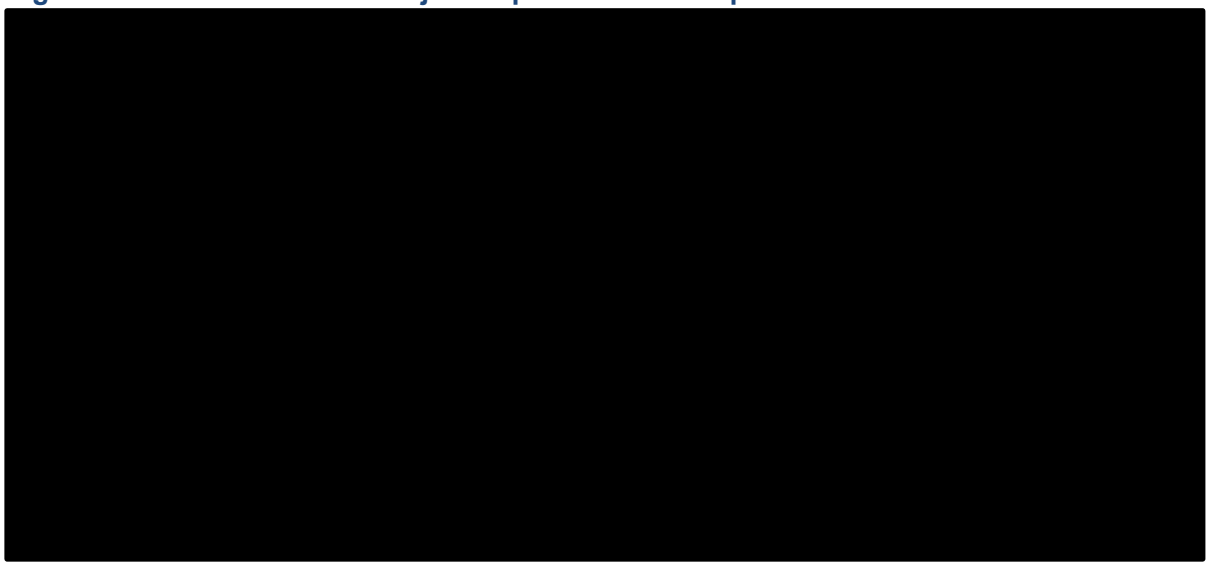
Figure 18. INV-assessed KM curves for TTP in MONARCH 3



Abbreviations: ABE: abemaciclib; INV: investigator; KM: Kaplan–Meier; NSAI: non-steroidal aromatase inhibitor; TTP: time to progression

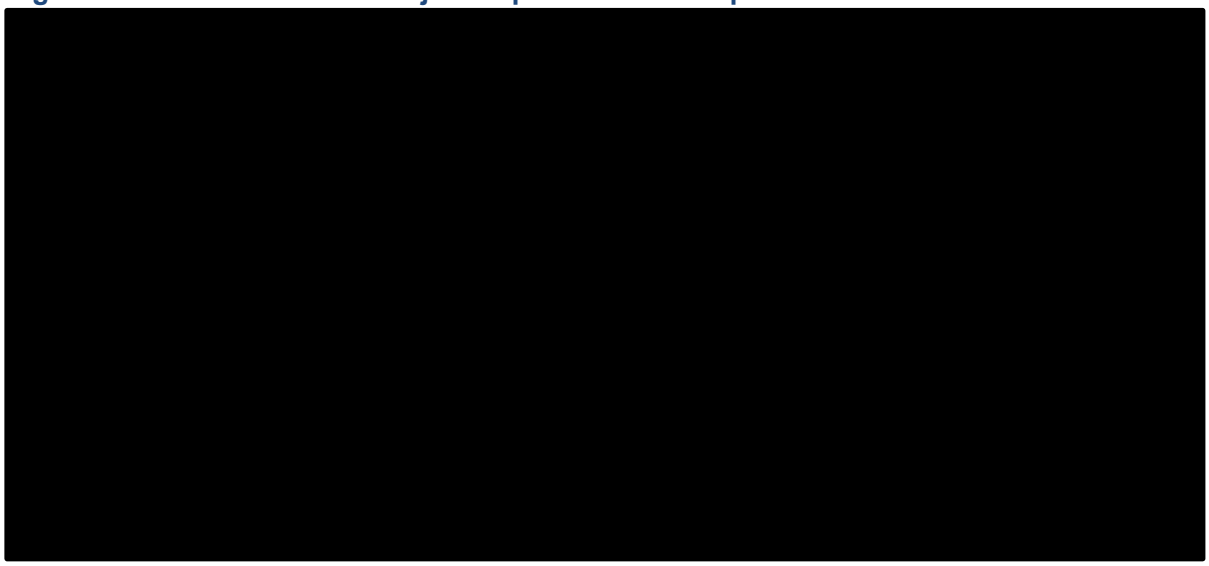
Cumulative hazard and log-log plots for assessing the proportional hazards assumption in MONARCH 3 are presented in Appendix M.1.2. Akaike information criteria (AIC) and Bayesian information criteria (BIC) statistics from modelling TTP for each fitted distribution are presented in Appendix M.2.1. Overlay plots of the KM curves and the parametric extrapolations based on the interval-censored adjusted analysis for ABE-NSAI and NSAI are presented in Figure 19 and Figure 20, respectively. Equivalent plots based on the unadjusted ITT analysis are presented in Appendix M.2.2.

Figure 19. Interval-censored adjusted parametric extrapolations of ABE-NSAI TTP



Abbreviations: ABE: abemaciclib; KM: Kaplan–Meier; NSAI: non-steroidal aromatase inhibitor; TTP: time to progression

Figure 20. Interval-censored adjusted parametric extrapolations of NSAI-TTP



Abbreviations: KM: Kaplan–Meier; NSAI: non-steroidal aromatase inhibitor; TTP: time to progression

The exponential and Weibull distributions provided the best fit based on AIC and BIC statistics (exponential provides the lowest AIC and BIC values), and the exponential, Weibull, Gompertz and gamma models all appeared to fit well to the observed data. The log-normal and log-logistic models appeared to overestimate survival after approximately 30 months.

In light of this, the exponential distribution was selected for the base case. Weibull and Gompertz distributions were each included as scenario analyses (Appendix M.2.1). A backwards stepwise selection procedure was used to identify covariates for inclusion in the parametric regression models to adjust for baseline characteristics: age, liver metastases, measurable disease at baseline, PR receptor status and tumour grade. Models with these covariates were included as a scenario analysis. The same distributions were included for the models adjusted for baseline characteristics (Appendix M.2.1).

Comparators

TTP for each of the comparators was estimated by applying the relative treatment effects generated from the NMA for PFS (Table 23) to the NSAI TTP curve, assuming equivalence of relative treatment effects for PFS and TTP.

Table 23. PFS hazard ratios estimated by the NMA

Comparator	HR (95% credible interval)
ABE-NSAI	[redacted]
PAL-NSAI	[redacted]
RIBO-NSAI	[redacted]
NSAI	Reference

Abbreviations: ABE: abemaciclib; HR: hazard ratio; NMA: network meta-analyses; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; PFS: progression-free survival; RIBO: ribociclib

Base case extrapolations

The base case TTP extrapolations for all treatments are displayed in Figure 21.

Figure 21. Base case TTP per INV extrapolations for all first-line comparators

Abbreviations: ABE: abemaciclib; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; PFS: progression-free survival; RIBO: ribociclib; TTP: time to progression
Footnotes: Note that the PAL+NSAI curve has been obscured by the RIBO-NSAI curve and as such is not visible

Deaths in pre-progression (PFS1 to death, required for transition probability c)

The rate of death in pre-progression for ABE-NSAI was estimated based on the MONARCH 3 trial data. However, only 17 deaths for ABE-NSAI (N = 328) and four deaths for PBO-NSAI (N = 165) were observed in the trial. Therefore, it was not deemed appropriate to model this endpoint using standard parametric survival modelling methods. Consequently, negative binomial regression models were used to estimate the constant rate of deaths for patients in pre-progression. Follow-up time in months was specified as an exposure variable to provide a rate estimate in the form of deaths per month of follow-up. An independent variable representing treatment group was incorporated into the regression model to generate rate estimates for ABE-NSAI and NSAI. Models were fitted with and without adjustment for baseline characteristics.

For the model adjusted for baseline characteristics, no covariates were identified to be included in the final model using backwards stepwise selection. Forwards stepwise selection led to the following covariates being included in the model: ECOG status, prior endocrine therapy received in the (neo)adjuvant setting, and NSAI received in cycle 1. Given the limited number of events observed in the trial data, the model without adjustment for baseline characteristics was chosen as the base case. The model adjusted for baseline characteristics was included as a scenario analysis.

The parameter estimates are provided in Appendix M.2.3 for the models with and without adjustment for baseline characteristics.

The rate of deaths in pre-progression for each of the comparators was estimated by applying the relative treatment effects generated from the NMA for OS (Table 24) to the rate estimated for NSAI, under the assumption of equivalence of relative treatment effects for OS and rate of deaths in pre-progression.

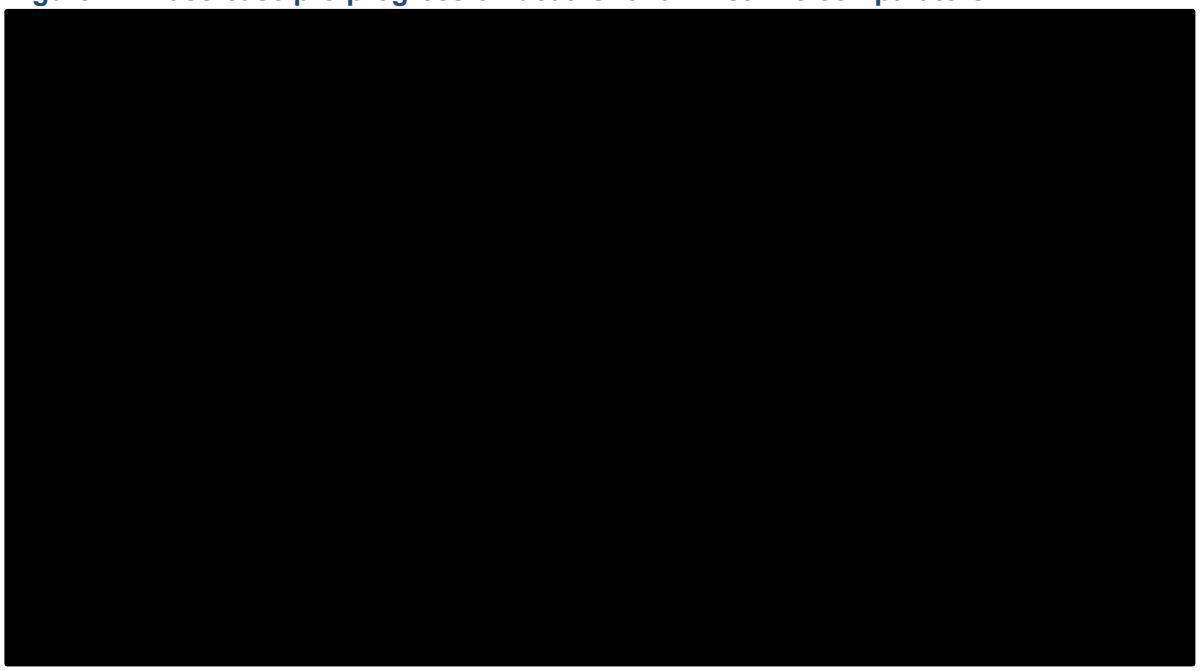
Table 24. Rate of pre-progression deaths – MONARCH 3

Model	Treatment	Rate
Without adjustment for baseline characteristics (base case)	ABE-NSAI	0.005
	NSAI	0.002
With adjustment for baseline characteristics (scenario)	ABE-NSAI	0.002
	NSAI	0.001

Abbreviations: ABE: abemaciclib; NSAI: non-steroidal aromatase inhibitor

The base case extrapolations for pre-progression deaths for all treatments are displayed in Figure 22.

Figure 22. Base-case pre-progression deaths for all first-line comparators



Abbreviations: ABE: abemaciclib; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; RIBO: ribociclib

TTD

An analysis of TTD was conducted to model the rate of treatment discontinuation and allow a more accurate estimation of drug acquisition costs for ABE-NSAI and the comparators.

TTD for ABE-NSAI and NSAI were estimated based on data from the MONARCH 3 trial. The observed KM TTD data are presented in Figure 23.

Figure 23. KM curves for MONARCH 3 TTD

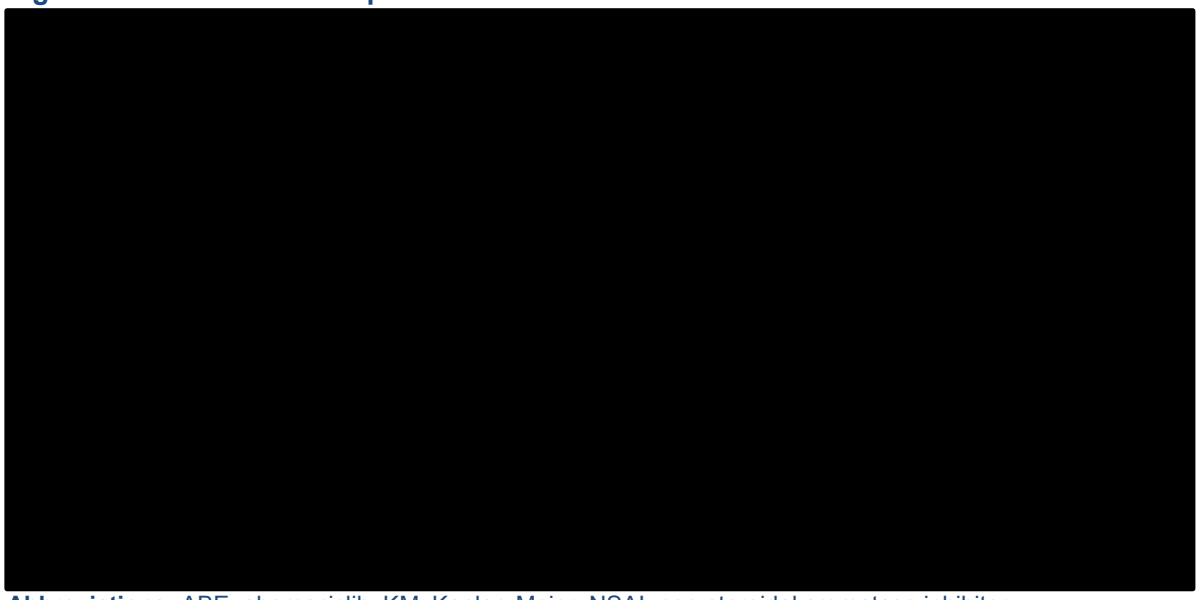
Abbreviations: ABE: abemaciclib; KM: Kaplan-Meier; NSAI: non-steroidal aromatase inhibitor; TTD: time to treatment discontinuation

The modelling approach and the process for selecting the most appropriate parametric model for TTD replicated that of TTP. Cumulative hazard and log-log plots are presented in Appendix

M.1.3. Overlay plots of the TTD KM curves for ABE-NSAI and NSAI with parametric extrapolations are presented in Figure 24 and Figure 25, respectively.

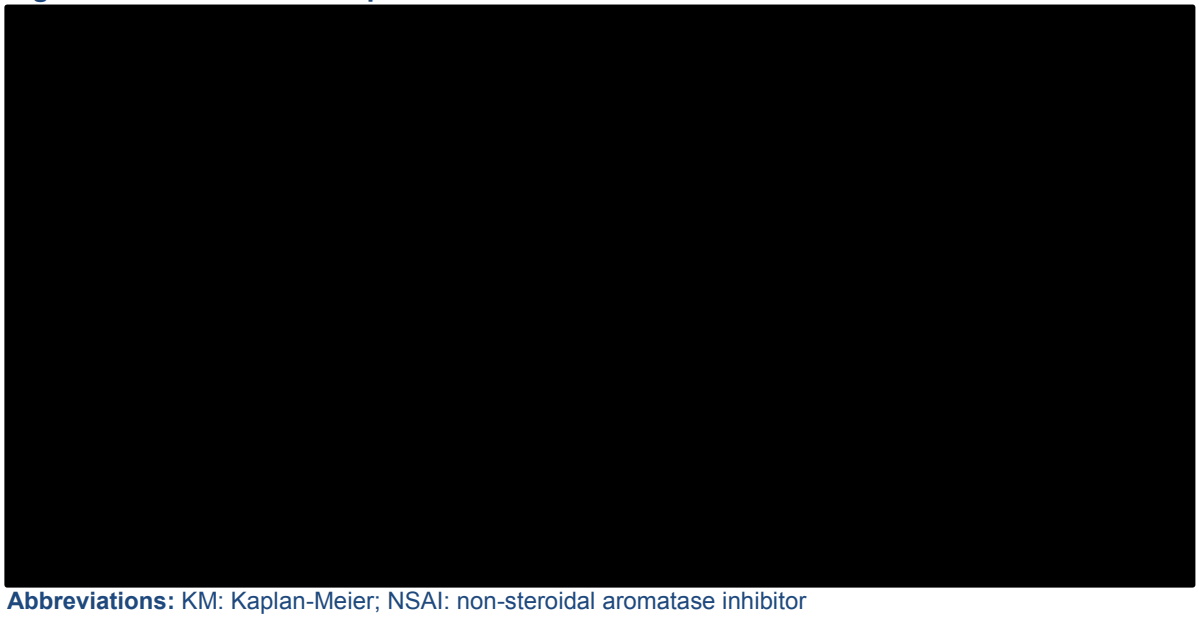
The cumulative hazard and log-log plots indicated a possible violation of the proportional hazards assumption, suggesting a proportional hazards model may not be appropriate for these data. On inspection of the quartile-quartile (QQ) plot (used to assess suitability of AFT models; Appendix M.2.4), the AFT model assumption appeared to have been met (i.e. treatment effect was multiplicative over time). Consequently, AFT models were considered more appropriate than proportional hazards models for joint modelling of TTD based on the MONARCH 3 data.

Figure 24. Parametric extrapolations of ABE-NSAI TTD



Abbreviations: ABE: abemaciclib; KM: Kaplan-Meier; NSAI: non-steroidal aromatase inhibitor

Figure 25. Parametric extrapolations of NSAI TTD



Abbreviations: KM: Kaplan-Meier; NSAI: non-steroidal aromatase inhibitor

Considering within-trial fit alone, the log-normal, gamma and Gompertz models all provided the closest fit to the MONARCH 3 data. The log-normal provided the best fit for the data based on the AIC and BIC statistics and the Cox-Snell residual plots. The gamma and Gompertz models

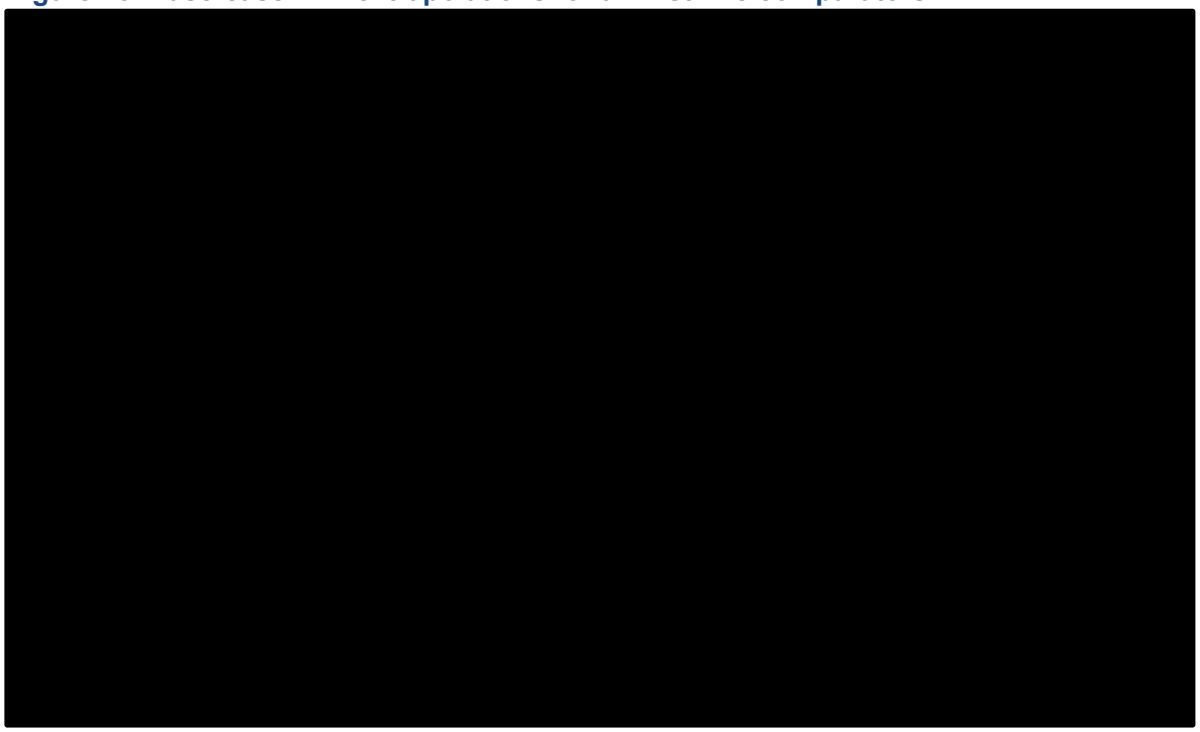
also fit well to the observed data based on these criteria, of which the Gompertz model provided the best fit based on the BIC; the gamma model appeared to overestimate TTD for NSAI after approximately 20 months.

Given the treatments modelled were treat-to-progression regimens, consideration was also given to the distribution chosen to model TTP in the base case, due to the expected correlation between these outcomes. An exponential distribution was chosen in the base case to model TTP. As a potential violation of the proportional hazards (PH) assumption was observed, an exponential model was not considered appropriate as the base-case distribution for TTD. Of the other distributions that fitted well to the MONARCH 3 data (log-normal, gamma and Gompertz), the gamma provided the closest extrapolation to the base-case extrapolations for TTP. The log-normal and Gompertz models showed higher estimates of TTD after approximately 140 months in both arms relative to the base-case TTP curves, indicating a potential overestimate of treatment duration. In light of this, a gamma distribution was chosen to model TTD in the base case with lognormal, Gompertz and exponential distributions included as scenario analyses.

KM estimates of TTD for the comparators not included in the MONARCH 3 trial were not reported in the primary publications of these therapies. TTD for all other comparators were estimated based on calculating a hazard ratio between the median TTD provided in the publications, SmPC and median TTD from MONARCH 3 for NSAI. This hazard ratio was then applied to the TTD distribution for NSAI in the model to attain relative estimates of TTD for the comparators (Appendix M.2.4).

The base-case TTD extrapolations for all treatments are displayed in Figure 26. The parameter estimates for the fitted parametric models are provided in (Appendix M.2.4).

Figure 26. Base-case TTD extrapolations for all first-line comparators



Abbreviations: ABE: abemaciclib; KM: Kaplan Meier; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; RIBO: ribociclib; TTD; time to treatment discontinuation
Footnotes: Note that the PAL+NSAI curve has been obscured by the RIBO-NSAI curve and as such is only partially visible

B.3.3.6 Post-progression survival

Data from the control arm of the MONARCH 2 trial and the results of the NMA evaluating FUL relative to other treatments for progression on ET were used to model clinical outcomes associated with second-line treatment in the base case model. As a scenario in the model, data from the BOLERO-2 trial, a study evaluating EVE-EXE and EXE plus placebo in HR+/HER2− ABC patients who had recurrence or progression whilst receiving previous therapy with a NSAI[125] (used in TA496[53]), were used to model clinical outcomes associated with second line treatment. In order to correspond to patients who would have progressed in the MONARCH 3 trial, the data relating to the population of the MONARCH 2 trial was restricted to include those who had progressed on prior endocrine therapy in the locally advanced or metastatic setting.

Second-line progression-free survival (PFS2)

PFS based on second-line patient data was analysed to inform the 'pay-off' for PPS (as described in B.3.2.2). The observed KM PFS data for the MONARCH 2 trial, based on the INV assessment, are presented in Figure 27.

Figure 27. KM curves for PFS in MONARCH 2

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

The modelling approach and process for selecting the most appropriate parametric model for this endpoint replicated that of TTP based on the MONARCH 3 data. The endpoint modelled was PFS, which included both time to progression and deaths as events. Models both adjusted and unadjusted for interval censoring were assessed. In the base case, the models adjusted for interval censoring were selected.

Cumulative hazard and log-log plots are presented in Appendix M.1.4. Overlay plots of the PFS KM curves for ABE-FUL and PBO-FUL with parametric extrapolations based on the fitted joint models, with adjustment for interval censoring, are presented in Figure 28 and Figure 29, respectively. The corresponding AIC and BIC statistics are presented in Appendix M.2.6. The corresponding estimates for the models unadjusted for interval censoring are presented in Appendix M.2, including the model parameter estimates, AIC and BIC statistics and Cox-Snell residual plots.

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. The exponential, Weibull and Gompertz distributions provided the best fit based on AIC and BIC statistics. The exponential distribution was selected to model TTP for FUL in the base case as it provided the best fit based on the BIC. Weibull and Gompertz distributions were included as scenario analyses. As described, only survival estimates for FUL were included in the model from these parametric distributions as ABE is not included in the model as a second-line treatment.

Figure 28. Parametric extrapolations of ABE-FUL PFS

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

Figure 29. Parametric extrapolations of FUL PFS

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

PFS2 for each of the comparators was estimated by applying the relative treatment effect generated from the second-line therapy NMA to the FUL PFS curve. PFS was weighted based

on the proportions of each second-line treatment received by patients in the Kurosky (2015) study.[94]

The base-case PFS2 extrapolations for all treatments are displayed in Figure 30. The parameter estimates for the fitted parametric models are provided in Appendix M.2.6.

Figure 30. Base-case PFS per INV extrapolations for second line

Abbreviations: ABE: abemaciclib; EXE: exemestane; FUL: fulvestrant; INV: investigator; KM: Kaplan Meier; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; PFS: progression-free survival; RIBO: ribociclib
Footnotes: The 0 months' time point represents the start of PFS2 in the 'pay-off' state. Note that the RIBO+NSAI curve has obscured the other curves

Overall survival

OS based on second-line patient data was analysed to inform the fixed 'pay-off' for PPS (as described in Section B.3.2.2). The observed, immature KM OS data for MONARCH 2 are presented in Figure 31.

Figure 31. KM curves for MONARCH 2 OS

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

The modelling approach and the process for selecting the most appropriate parametric models replicated that of TTP for first-line therapy.

Cumulative hazard and log-log plots are presented in Appendix M.1.3 for second-line OS. Overlay plots of the KM and parametric extrapolations based on the fitted joint models for ABE-FUL and FUL are presented in Figure 32 and Figure 33, respectively. The corresponding AIC and BIC statistics are presented in Appendix M.2.5.

The cumulative hazard and log-log plots indicated no evidence of a violation of the proportional hazards assumption, indicating a proportional hazards model may be appropriate for these data. The Gompertz distribution provided the best fit based on AIC and BIC statistics and Cox-Snell residual plots. Based on KOL input, the exponential, log-normal and log-logistic distributions provided plausible extrapolations of OS. Despite the poorer within-trial fit, the exponential distribution was included as the base case as it was considered to provide the most plausible extrapolation based on clinical opinion. The log-logistic and Gompertz distributions were included as scenario analyses.

Figure 32. Parametric extrapolations of ABE-FUL OS

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

Figure 33. Parametric extrapolations of FUL OS

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

Extrapolations beyond the trial period for the MONARCH 2 study were uncertain due to the immaturity of the trial data. To supplement this, external data was identified for FUL and included in the model. The CONFIRM trial,[108, 111] identified in the SLR in the MONARCH 2 indication, 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). Data from the CONFIRM trial were used to inform the long-term survival extrapolations in the base case.

The process for selecting distributions, described for TTP based on the MONARCH 3 data, 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 2011)[126] Based on this a Weibull distribution was selected. The hazard rate from this distribution was applied to the exponential distribution fitted to the PBO-FUL 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 PBO-FUL arms. 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 27.95 months in line with the maximum follow-up of the MONARCH 2 trial.

OS for each of the comparators was estimated by applying the relative treatment effect generated from the second-line therapy NMA, relative to the PBO-FUL OS curve until 27.95 months. It was assumed that the hazard rate for all comparators beyond this time point was the same as FUL based on the CONFIRM data. Overall survival was weighted based on the proportions of second-line treatment from Kurosky (2015).[94]

The base case OS extrapolations for all treatments are displayed in Figure 34.

Figure 34. Base case OS extrapolations for second-line treatments

Abbreviations: ABE: abemaciclib; NSAI: non-steroidal aromatase inhibitor; OS: overall survival; PAL: palbociclib; RIBO: ribociclib
Footnotes: Note that the RIBO+NSAI has obscured the other curves included in the plot

TTD

TTD for FUL was estimated based on data from the MONARCH 2 trial. The observed KM TTD data are presented in Figure 35.

Figure 35. KM curves for MONARCH 2 TTD

Abbreviations: ABE: abemaciclib; FUL: fulvestrant; KM: Kaplan Meier; TTD: time to treatment discontinuation

The modelling approach and process for selecting the most appropriate parametric model for this endpoint replicated that of TTP for first-line therapy. Cumulative hazard and log-log plots are presented in Appendix M.1.5. Overlay plots of the TTD KM and parametric extrapolations based on the fitted joint models for ABE-FUL and PBO-FUL are presented in Figure 36 and Figure 37, respectively. The corresponding AIC and BIC statistics and Cox-Snell residual plots are presented in Appendix M.2.8 for second-line TTD.

The cumulative hazard and log-log plots indicated no evidence of a violation of the proportional hazards assumption, indicating a proportional hazards model may be appropriate for these data.

The Gompertz distribution provided the best fit based on AIC and BIC statistics and Cox-Snell residual plots. The log-logistic and exponential distributions provided the second best fit based on the AIC and BIC criteria. Consideration was given to the distributions used to estimate PFS given the anticipated correlation between these endpoints and TTD, and in light of this, the exponential distribution was selected to model second-line TTD in the base case. The Gompertz and log-logistic models were also included as scenario analyses.

Figure 36. Parametric extrapolations of ABE-FUL TTD

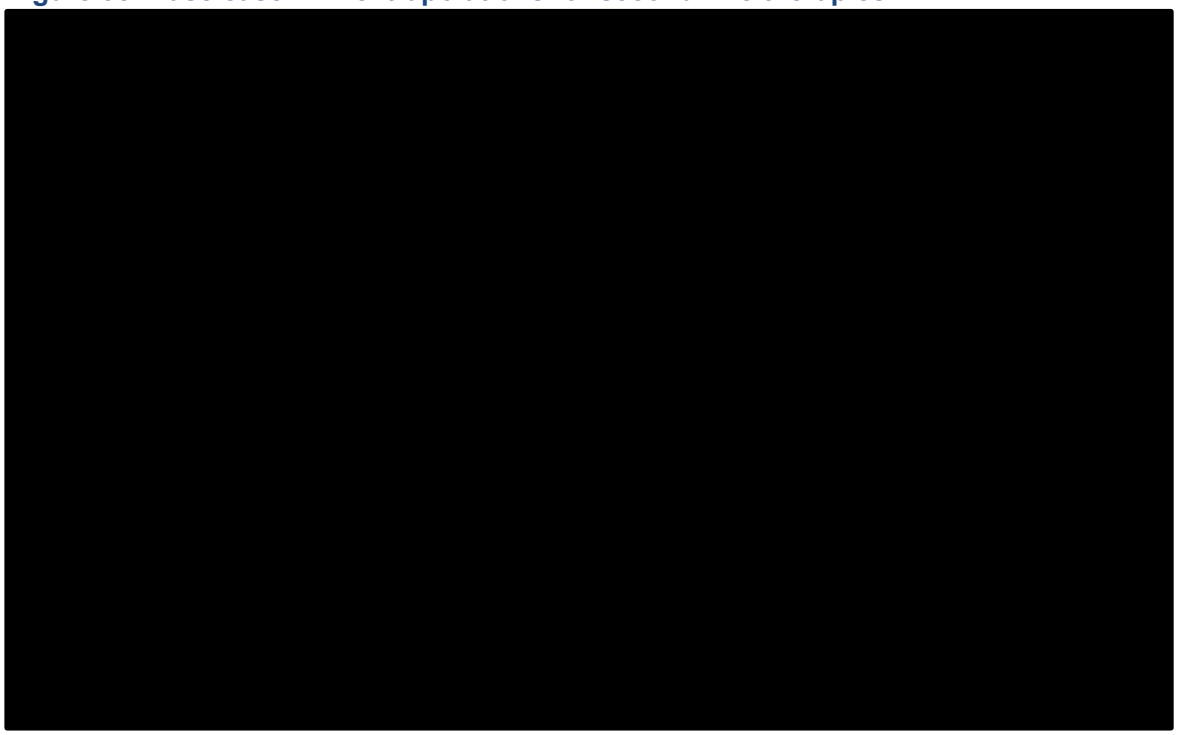
Abbreviations: ABE: abemaciclib; FUL: fulvestrant; KM: Kaplan Meier

Figure 37. Parametric extrapolations of FUL TTD

Abbreviations: FUL: fulvestrant; KM: Kaplan Meier

KM estimates of TTD for the second-line comparators not included in the MONARCH 2 trial were not reported in the primary publications used to support the NMA. TTD for all second-line comparators was estimated based on calculating a hazard ratio between the median TTD provided in the publications used to inform clinical outcomes for second-line treatments and FUL. This hazard ratio was then applied to the TTD distribution for FUL in the model to attain relative estimates of TTD for the other second-line interventions. Second-line data for this approach are included in Appendix M.2.8. TTD was weighted based on the proportions of second-line treatment from Kurosky (2015).[94] The base-case TTD extrapolations for all treatments are displayed in Figure 38. As a scenario analysis, second-line PFS was used to inform hazard ratios for second-line TTD.

Figure 38. Base case TTD extrapolations for second-line therapies



Abbreviations: ABE: abemaciclib; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; RIBO: ribociclib; TTD: time to treatment discontinuation
Footnotes: Note that the RIBO+NSAI has obscured the other curves included in the plot

B.3.3.7 Constructed OS based on PFS and PPS modelling

Calibration for partial PFS-OS surrogacy

As OS was modelled indirectly based on the time spent in each modelled state, with no adjustment, a gain in PFS would result in an equal gain on OS. Therefore, as described in Section B.3.2.2, the analysis applied a calibration factor based on the PALOMA-1 trial,[98] which reduced time spent in the post-progression survival 'pay-off' to adjust the gain in OS for CDK 4 & 6 inhibitors to approximately 27.5% of the gain in PFS. The calibration factor required to achieve this level of surrogacy for each CDK 4 & 6 inhibitor was calculated using the 'goalseek' function in Microsoft® Excel. The calibration factor was then applied to the scale parameters of the PFS and OS curves in the post-progression 'pay-off'. The calibration factors for the base case are presented in Table 25. A scenario was performed in which full PFS-OS surrogacy (100%) was assumed, as per the base case of the palbociclib manufacturer's submission (TA495).[53]

Table 25. PFS-OS surrogacy calibration factors

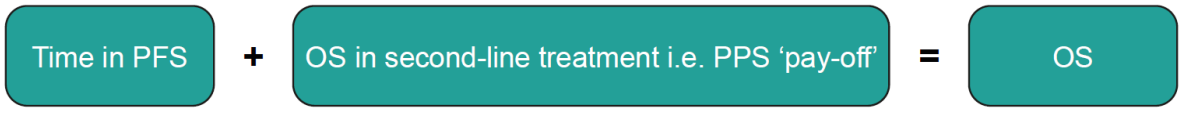
Treatment	Calibration factor
ABE+NSAI	1.22
PAL+NSAI	1.16
RIBO+NSAI	1.25

Abbreviations: ABE: abemaciclib; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; PFS: progression-free survival; OS: overall survival; RIBO: ribociclib

Calculation of OS

OS for each first-line treatment was modelled indirectly based on time spent in PFS1 and in the 'pay-off' states. In each cycle of the model, patients who progressed were assigned the mean time in PPS calculated in the 'pay-off', as illustrated in Figure 39.

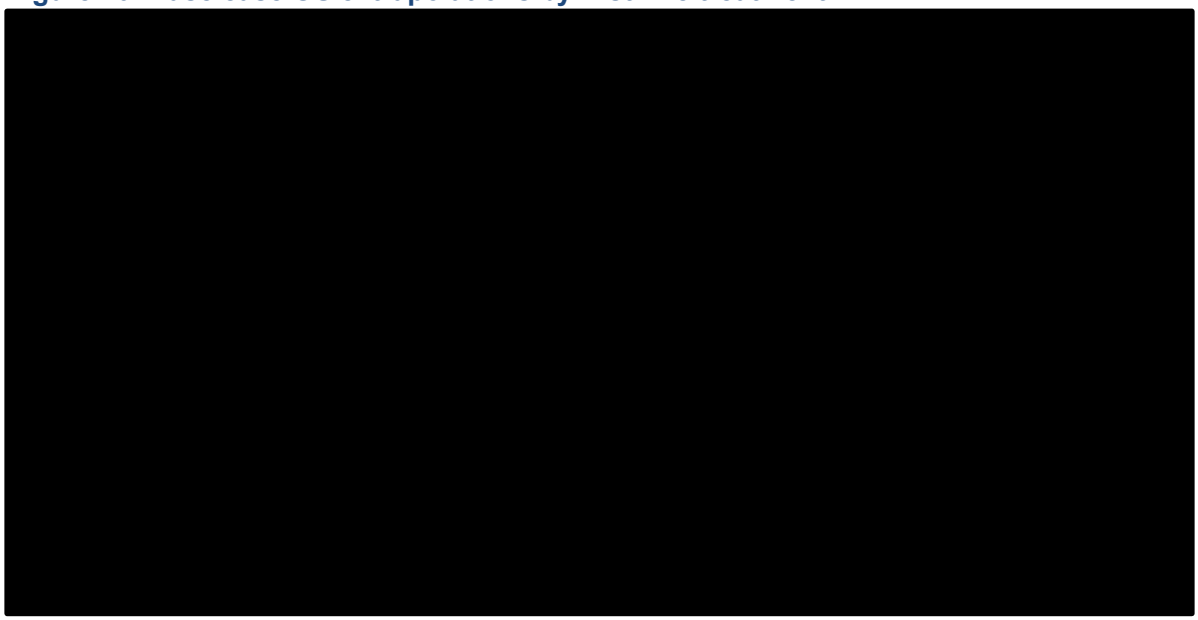
Figure 39. Calculation of OS



Abbreviations: PFS: progression-free survival; PPS: post-progression survival; OS: overall survival

The distribution of second-line treatments is assumed to be the same for each comparator arm of the model. Therefore, the shape of the OS curve for each first-line treatment is determined by the time that patients spend in PFS1. Estimated base case OS extrapolations are displayed in Figure 40.

Figure 40. Base case OS extrapolations by first-line treatment



Abbreviations: ABE: abemaciclib; NSAI: non-steroidal aromatase inhibitor; OS: overall survival; PAL: palbociclib; RIBO: ribociclib

B.3.4 *Measurement and valuation of health effects*

B.3.4.1 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− locoregionally recurrent 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− locoregionally recurrent 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− locoregionally recurrent or metastatic breast cancer. Due to the lack of studies identified evaluating patients representative of the patient population under consideration in this analysis, utility estimates collected in MONARCH 3 and adopted in previous NICE appraisals of the relevant patient population were preferred, as described below.

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

Estimates of HRQoL were applied to each health state in the model (i.e. PFS1, and PFS2 and PPS in the fixed 'pay-off').

Pre-progression utilities (PFS)

Using EQ-5D-3L data cross-walked from the EQ-5D-5L data collected in the MONARCH 3 trial, utilities were estimated for the first-line PFS health state (PFS1). A scenario analysis was performed in which EQ-5D-5L data were used to estimate PFS1 utility. Repeated measures regression models were fitted to these data to estimate utility, including the following covariates as main effects:

- Model 1: Baseline utility and post- versus pre-progression
- Model 2: Baseline utility, post- versus 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. Both models included a covariate for post- versus pre-progression periods. The predictions for pre-progression utilities from the regression models were included in the model to inform the first-line PFS health state. The regression models are provided in Appendix M.4. The health state utilities estimated by these regressions are presented in Table 26.

Table 26. Health state utilities (first-line PFS) predicted from the MONARCH 3 regression model

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

Abbreviations: ABE: abemaciclib; NSAI: non-steroidal aromatase inhibitor; PFS: progression-free survival

As a conservative approach, model 1 was applied in the base case to estimate PFS utility, given there was no significant difference identified when adjusting for treatment. This utility was applied to time spent in the PFS health state, irrespective of comparator received, under the assumption

that it was the health state, not treatment, that was driving HRQoL. The utilities from model 2 were applied as a sensitivity analysis. In this case, first-line PFS utility for ABE-NSAI was assumed to apply to all combination endocrine + targeted therapies (RIBO-NSAI, PAL-NSAI).

'Pay-off' utilities (PPS)

In the base-case analysis, the utility of patients on second-line treatment (PFS2) and PPS in the 'pay-off' was based on TA496[54] and Lloyd (2006),[104] which used values of 0.774 for PFS2 and 0.505 for PPS. As per the RIBO-NSAI NICE submission (TA496[97]), an additional utility decrement of 0.113 was applied to the second-line PFS utility for all chemotherapy regimens to reflect the expected decrease in HRQoL for these regimens compared to ET.[97]

Table 27 summarises the values and sources for both the pre- and post-progression utilities used in the base case.

Table 27. Health state utilities – base case

Health state	Utilities	Comparators	Source
PFS1	[redacted]	All	MONARCH 3[5]
PFS2	0.774	Endocrine +/- targeted therapies	TA496[53]
	0.661	Chemotherapies	TA496[53]
PPS	0.505	All	Lloyd, 2006[104]

Abbreviations: PFS1: first-line progression-free survival; PFS2: second-line progression-free survival; PPS: post-progression survival

Scenario analyses

PFS1 utility

It should be noted that the utility value used for patients in PFS receiving second-line treatment (PFS2) was higher than the [redacted] value used for PFS1. Therefore, based on the argument put forward by the manufacturer of PAL in TA496 that utility in first-line treatment would be expected to be at least as good as the utility for second-line treatment, if not better,[54] a scenario was included where the utility value for PFS1 was set to 0.774.

Post-progression utilities derived from MONARCH 2

As a scenario analysis, utilities were estimated for the PFS2 and PPS health states using EQ-5D-3L data cross-walked from EQ-5D-5L data from the MONARCH 2 trial. As with the approach used to model clinical outcomes using MONARCH 2 data, the cohort was restricted to those patients who had progressed on prior ET in the locally advanced or metastatic setting to replicate the MONARCH 3 patient population who progressed to second-line treatment. A repeated measures regression model was fitted to these data to estimate utility for the two health states (PFS2 and PPS) with the following covariates: baseline utility and post- versus pre-progression. This allowed for pre- and post-progression utility to be estimated across treatments representing utilities for second-line PFS and PPS states. The regression model is provided in Appendix M.4. The health state utilities estimated by these regressions are presented in Table 28.

Table 28. Health state utilities (second-line PFS and PPS) predicted from the MONARCH 2 regression model – scenario

Health state	Utilities
Pre-progression (PFS2)	[redacted]
Post-progression (PPS)	[redacted]

Abbreviations: PFS2: second-line progression-free survival; PPS: post-progression survival

B.3.4.3 Mapping

No mapping was performed in this analysis, as EQ-5D data were sourced directly from the MONARCH 3 and MONARCH 2 trials.

B.3.4.4 Adverse reactions

Rates of AEs for patients on ABE-NSAI were based on the TRAEs that occurred in the ITT population of the MONARCH 3 trial. TRAE rates for the comparators are based on the primary publications used in the NMA. AEs were selected for inclusion if they were grade 3–4 events occurring in more than 5% of patients for at least one comparator. Probabilities for AEs are shown in Table 29.

Table 29. Adverse event probabilities

Event	ABE-NSAI	PAL-NSAI	RIBO-NSAI	NSAI*
Alanine aminotransferase increased	[redacted]	0%	9%	[redacted]
Anaemia	[redacted]	6%	2%	[redacted]
Aspartate aminotransferase increased	[redacted]	0%	6%	[redacted]
Diarrhoea	[redacted]	1%	2%	[redacted]
Hypertension	[redacted]	0%	10%	[redacted]
Leukopenia	[redacted]	25%	21%	[redacted]
Lymphopenia	[redacted]	0%	7%	[redacted]
Neutropenia	[redacted]	67%	59%	[redacted]

Footnotes: *NSAI methodology is included here to contextualise the NSAI results presented in Section B.3.10
Abbreviations: ABE: abemaciclib; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; RIBO: ribociclib
Source: ABE-NSAI, MONARCH 3; PAL-NSAI, PALOMA2 (Finn (2016)[106] and Rugo SABCS (2018)[127]); RIBO-NSAI, Hortobagyi (2016)[107] and Hortobagyi ASCO (2017)[102]

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

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

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),[128] where available. This study mapped EORTC QLQ-C30 data collected in Kaufman (2015)[129] – a large RCT comparing ERI to CAP in patients

with ABC – onto the EQ-5D to estimate health state utilities and decrements associated with AEs. Utility decrements for AEs that were not reported in Hudgens (2016) were based on utility studies conducted in solid tumours. These data are presented in Table 30.

Table 30. Adverse event disutilities

Adverse event	Utility decrement	Source
Alanine aminotransferase increased	-0.050	TA503[95]
Anaemia	-0.119	TA503[95]/Swinburn 2010[130]
Aspartate aminotransferase increased	0.000	TA503[95]
Diarrhoea	-0.006	Hudgens 2016[128]
Hypertension	-0.153	Swinburn 2010[130]
Leukopenia	-0.003	Hudgens 2016[128]
Lymphopenia	0.000	Clinical opinion
Neutropenia	-0.007	Hudgens 2016[128]

Adverse event durations were not reported in Hudgens (2016). Considering this, durations were derived from NICE appraisals TA306[130] and TA503.[95] The AE durations included in the model are presented in Table 31.

Table 31. Adverse event durations

Adverse event	Duration (days)	Source
Alanine aminotransferase increased	28.00	Assumption as per TA503[95]
Anaemia	16.07	TA306 (Swinburn 2010)[130]
Aspartate aminotransferase increased	0.00	Assumption as per TA503[95]
Diarrhoea	8.00	TA306[131] (assumption: same as vomiting)
Hypertension	8.00	TA503[95]/Swinburn 2010[130]
Leukopenia	13.96	TA306 [131]
Lymphopenia	34.00	TA306 [131]
Neutropenia	15.09	TA306 (Nafees 2008)[131]

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 32.

Table 32. Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	Reference in submission (section and page number)	Justification
PFS1	[redacted] (Derived from regression analysis [Cholesky decomposition])	B.3.4.2, page 118	MONARCH 3
PFS2 (endocrine +/- targeted therapies)	0.774 (0.07)	B.3.4.2, page 118	Utilities are aligned with those in TA496[54]
PFS2 (chemotherapies)	0.661 (0.07)	B.3.4.2, page 118	
PPS	0.505 (0.07)	B.3.4.2, page 118	
Alanine aminotransferase increased	-0.050 (-0.0005)	B.3.4.4. page 120	Rates of AEs for patients on ABE-NSAI were based on TRAEs that occurred in the MONARCH 3 ITT population; AE rates for comparators are based on the primary publications used in the NMA
Anaemia	-0.119 (-0.0012)	B.3.4.4. page 120	
Aspartate aminotransferase increased	0.000 (0.000)	B.3.4.4., page 120	
Diarrhoea	-0.006 (-0.0001)	B.3.4.4. page 120	
Hypertension	-0.153 (-0.0015)	B.3.4.4. page 120	
Leukopenia	-0.003 (0.000)	B.3.4.4. page 120	
Lymphopenia	0.000 (0.000)	B.3.4.4. page 120	
Neutropenia	-0.007 (-0.0001)	B.3.4.4, page 120	

Abbreviations: ABE: abemaciclib; AE: adverse event; AR: adverse reaction; HS: health state; ITT: intention to treat; NMA: network meta-analysis; NSAI: non-steroidal aromatase inhibitor; PFS: progression-free survival; PPS: post-progression survival; 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 for first-, second-, and third-line treatments
- Section B.3.5.2: BSC, hospitalisations, terminal care, and follow-up care costs and resources
- Section B.3.5.3: AE management and costs

As per Section B.3.2.2, the perspective is that of the UK NHS and PSS. Drug costs for all pre-progression, post-progression and concomitant medications were primarily sourced from the electronic market information tool (eMIT)[132] national database and the Monthly Index of Medical Specialties (MIMS)[133] database of prescription and generic drugs, and clinical guidelines.

A SLR was conducted to identify relevant cost and healthcare resource use studies in HR+/HER2– locally advanced or metastatic BC. 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 BC patients.

B.3.5.1 Intervention and comparators' costs and resource use

Drug acquisition and administration costs for first-, second-, and third-line therapies are presented in the sections that follow.

First-line treatment costs

Drug acquisition

The doses required for each first-line treatment were calculated using dosing regimens, which were based on the ABE-NSAI and NSAI regimens received in the MONARCH 3 trial (ABE: 150 mg twice daily for 28 days) and the primary publications used in the NMA for the comparators. As a scenario, RDI (relative dose intensity), sourced from the MONARCH 3 trial and primary publications for comparators, was also included in calculating drug acquisition costs to show the exact cost of treatment without considering wastage.

All treatments were prescribed until discontinuation for reasons such as toxicity, withdrawal from the study and progression. Therefore, acquisition costs were assigned based on the TTD distributions (Section B.3.3.5). Treatment regimens and drug acquisition costs for each comparator are presented in Table 33 and Table 34, respectively. Drug acquisition costs per patient were calculated by determining the number of packs needed to provide the required dose and multiplying by the unit price per pack. This was then used alongside the monthly dose delivered to calculate the acquisition cost per month. The base case for the model assumes wastage; for oral therapies, once a patient begins a treatment cycle, the full cost of the cycle is applied regardless of whether they complete treatment of not, while for IV therapies the unused contents of a vial are discarded.

Table 33. Treatment regimens

Treatment	Dose (mg)	Admins per cycle	Cycle length (days)	Source
ABE-NSAI	ABE: 150 mg LTZ: 2.5 mg ANAS: 1 mg	ABE: 56 LTZ/ANAS: 28	28	MONARCH 3[5]
RIBO-NSAI	RIBO: 600 mg LTZ: 2.5 mg	RIBO: 21 LTZ: 28	28	MONALEESA-2[134]
PAL-NSAI	PAL: 125 mg LTZ: 2.5 mg	PAL: 21 LTZ: 28	28	PALOMA 3[135]
NSAI*	ANAS: 1 mg LTZ: 2.5 mg	28	28	MONARCH 3

Footnotes: *NSAI methodology is included here to contextualise the NSAI results presented in Section B.3.10
Abbreviations: ABE: abemaciclib; ANAS: anastrozole; LTZ: letrozole; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; RIBO: ribociclib

Table 34. Drug acquisition costs

Treatment	Drug	Units	Vial/ Pack size	Cost	Source
ABE-NSAI	ABE	150	56	£[redacted]	Eli Lilly Data on File
ABE-NSAI	LTZ	2.5	28	£2.71	eMIT, 12 month period to end June 2017[132]
ABE-NSAI	ANAS	1	28	£1.34	eMIT, 12 month period to end June 2017[132]
NSAI	LTZ	2.5	28	£2.71	eMIT, 12 month period to end June 2017[132]
NSAI	ANAS	1	28	£1.34	eMIT, 12 month period to end June 2017[132]
PAL-NSAI	PAL	75	21	£2,950.00	BNF Online, accessed 13th March 2018[136]
PAL-NSAI	PAL	100	21	£2,950.00	BNF Online, accessed 13th March 2018[136]
PAL-NSAI	PAL	125	21	£2,950.00	BNF Online, accessed 13th March 2018[136]
PAL-NSAI	LTZ	2.5	28	£2.71	eMIT, 12 month period to end June 2017[132]
PAL-NSAI	ANAS	1	28	£1.34	eMIT, 12 month period to end June 2017[132]
RIBO-NSAI	RIBO	200	21	£983.33	BNF Online, accessed 13th March 2018[136]
RIBO-NSAI	RIBO	200	42	£1,966.67	BNF Online, accessed 13th March 2018[136]
RIBO-NSAI	RIBO	200	63	£2,950.00	BNF Online, accessed 13th March 2018[136]

Treatment	Drug	Units	Vial/ Pack size	Cost	Source
RIBO-NSAI	LTZ	2.5	28	£2.71	eMIT, 12 month period to end June 2017[132]
RIBO-NSAI	ANAS	1	28	£1.34	eMIT, 12 month period to end June 2017[132]

Abbreviations: ABE: abemaciclib; ANAS: anastrozole; BNF: British national formulary; eMIT: electronic market information tool; LTZ: letrozole; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; RIBO: ribociclib

Drug administration

All pre-progression (first-line) drugs were administered orally, so no administration costs were applicable to this analysis. Pre-medications were not considered, as these were not considered relevant for administration of the first-line treatments in the model in the UK.

Second-line treatment costs

Drug acquisition

Therapies received in second line were modelled in the same way as treatments received in first line. Drug acquisition costs were calculated by combining dosing regimens, RDI adjustments and mean patient weight or BSA data (where applicable). RDI was included in the calculation of drug costs as a scenario in the model. Treatment regimens and RDI were based on the regimen received in the MONARCH 2 trial by patients in the PBO-FUL arm (500 mg every 28 days, plus a 500 mg loading dose in the first cycle) and the primary publications used in the NMA of clinical studies of second line treatments.

Acquisition costs were assigned based on the TTD distributions (Section B.3.3.6). Drug acquisition costs per patient were calculated by determining the number of vials/tablets needed to provide the required dose and multiplying by the unit price per vial/tablet. This was then used alongside the monthly dose delivered to calculate the acquisition cost per month.

The proportion of patients receiving each second-line therapy in the model are based on the study by Kurosky (2015).[94] These data are presented in Table 35. The distribution of second-line therapies received is equivalent for each of the first-line treatment arms.

Table 35. Second-line treatment proportions

	Proportion of patients
Chemotherapy	25.66%
CAP	48.00%
PAC	24.00%
DOC	28.00%
Endocrine therapy	66.34%
FUL	16.40%
EXE	55.74%
TMX	27.87%
EVE+EXE	8.00%

Abbreviations: ABE: abemaciclib; ANAS: anastrozole; CAP: capecitabine; DOC: docetaxel; ERI: eribulin; EVE+EXE: everolimus plus exemestane EXE: exemestane; FUL: fulvestrant; LTZ: letrozole; NSAI: non-steroidal aromatase inhibitor; PAC: paclitaxel; TMX: tamoxifen

Treatment regimens for second-line therapies were based on studies identified in the SLR, previous TAs and dosing guidance published by the BNF (Table 36). Treatment regimens and drug acquisition costs for each intervention are presented in Table 36 and Table 37, respectively. For FUL (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 per vial. This was applied to the monthly dose delivered to calculate the acquisition cost per month.

Table 36. Second-line treatment regimens

Treatment	Drug	Dose (mg)	Per unit	Admins per cycle	Cycle length	Source
CAP	CAP	1250	m^2	28	21	TA495 - company submission Table 44[53]
PAC	PAC	175	m^2	1	21	Perez 2001;[137] EMC Accessed 16th March 2018[138]
DOC	DOC	75	m^2	1	21	EMC Accessed 16th March 2018[138]
FUL	FUL (loading dose)	500	Fixed	2	28	BNF Online, Accessed 13th March 2018[136]
FUL	FUL	500	Fixed	1	28	
EXE	EXE	25	Fixed	28	28	TA495 - Table 46;[53] EMC Accessed 16th March 2018[53]
TMX	TMX	20	Fixed	30	30	BNF Online, Accessed 13th March 2018;[136] EMC Accessed 16th March 2018[53]
EVE+EXE	EVE	10	Fixed	28	28	TA495 - Table 46;[53] EMC Accessed 16th March 2017[53]
EVE+EXE	EXE	25	Fixed	28	28	TA495 - Table 46;[53] EMC Accessed 16th March 2018[53]

Abbreviations: ANAS: anastrozole; BNF: British national formulary; CAP: capecitabine; DOC: docetaxel; EMC: electronic medicines consortium; EVE+EXE: everolimus plus exemestane EXE: exemestane; FUL: fulvestrant; LTZ: letrozole; PAC: paclitaxel; TMX: tamoxifen

Table 37. Second-line therapy drug acquisition costs

Treatment	Drug	Units (mg/ml)	Vial size (ml)	Price	Source
CAP	CAP	150	60	£3.97	eMIT 2017, period ending June 2017[132]
CAP	CAP	500	120	£21.76	eMIT 2017, period ending June 2017[132]
PAC	PAC	100	17	£9.85	eMIT 2017, period ending June 2017[132]
PAC	PAC	150	25	£10.52	eMIT 2017, period ending June 2017[132]
PAC	PAC	300	50	£19.68	eMIT 2017, period ending June 2017[132]

Treatment	Drug	Units (mg/ml)	Vial size (ml)	Price	Source
PAC	PAC	30	5	£66.24	eMIT 2017, period ending June 2017[132]
DOC	DOC	160	8	£46.75	eMIT 2017, period ending June 2017[132]
DOC	DOC	20	1	£3.85	eMIT 2017, period ending June 2017[132]
DOC	DOC	80	4	£14.74	eMIT 2017, period ending June 2017[132]
FUL	FUL	250	2	£522.41	BNF Online, accessed 13th March 2018[136]
EXE	EXE	25	30	£3.69	eMIT 2017, period ending June 2017[132]
TMX	TMX	10	30	£7.02	eMIT, 12 month period to end June 2017[132]
TMX	TMX	10	30	£26.80	eMIT, 12 month period to end June 2017[132]
TMX	TMX	20	30	£1.59	eMIT, 12 month period to end June 2017[132]
EVE+EXE	EVE	2.5	30	£1,200.00	BNF Online, accessed 13th March 2018[136]
EVE+EXE	EVE	5	30	£2,250.00	BNF Online, accessed 13th March 2018[136]
EVE+EXE	EVE	10	30	£2,673.00	BNF Online, accessed 13th March 2018[136]
EVE+EXE	EXE	25	30	£3.69	eMIT 2017, period ending June 2017[132]

Abbreviations: ANAS: anastrozole; CAP: capecitabine; DOC: docetaxel; EVE+EXE: everolimus plus exemestane EXE: exemestane; FUL: fulvestrant; LTZ: letrozole; PAC: paclitaxel; TMX: tamoxifen

Drug administration

Costs associated with second-line treatment administration are presented in Table 38. All costs were sourced from the NHS reference costs.[139]

Table 38. Second-line drug administration costs

Treatment	Drug	Administration	Admins per cycle	Cost per administration	Source
CAP	CAP	Oral	1	£163.82	NHS reference costs 2016-17[140]
PAC	PAC	IV	1	£259.76	NHS reference costs 2016-17[140]
DOC	DOC	IV	1	£259.76	NHS reference costs 2016-18[140]
FUL	FUL (loading dose)	IM	1	£219.19	NHS reference costs, 2016-16[140]
FUL	FUL	IM	1	£0.00*	NHS reference costs, 2016-17[140]

Treatment	Drug	Administration	Admins per cycle	Cost per administration	Source
EXE	EXE	Oral	28	£0.00	N/A
TMX	TMX	Oral	30	£0.00	N/A
EVE+EXE	EVE	Oral	28	£0.00	N/A
EVE+EXE	EXE	Oral	28	£0.00	N/A

Footnotes: *FUL administration costs are assumed to be captured within follow-up appointments included in the FUL loading dose costs.
Abbreviations: ANAS: anastrozole; CAP: capecitabine; DOC: docetaxel; EVE+EXE: everolimus plus exemestane EXE: exemestane; FUL: fulvestrant; IM: intramuscular; LTZ: letrozole; PAC: paclitaxel; TMX: tamoxifen

Third-line treatment costs

Treatments received after progression from second-line therapy were included in the analysis as a weighted cost only. This was thought to be reasonable as differences in long-term outcomes associated with these therapies are unlikely to differ between comparators sufficiently to impact on cost-effectiveness estimates. A fixed cost of post-progression therapy was assigned to the proportion of patients who progress in each cycle (per month) for each first-line treatment. Costs were assigned based on the PFS adjusted by the proportion of PFS events that were disease progression, rather than death. The fixed cost of post-progression therapy was calculated by combining the following:

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

The proportion of patients who received each post-progression therapy was informed by the study by Kurosky (2015).[94] Fifty-four percent of patients were assumed to receive some type of systemic therapy following progression from second line, while 45.6% of patients were assumed to receive no treatment. These data are presented in Table 39.

Table 39. Third-line treatment proportions

Treatment	Treatment proportion
Chemotherapy	30.39%
CAP	81.58%
ERI	18.42%
Endocrine therapy	24.02%
FUL	41.93%
TMX	32.26%
No treatment	45.59%

Abbreviations: ABE: abemaciclib; ANAS: anastrozole; CAP: capecitabine; DOC: docetaxel; ERI: eribulin; EVE+EXE: everolimus plus exemestane EXE: exemestane; FUL: fulvestrant; LTZ: letrozole; NSAI: non-steroidal aromatase inhibitor; PAC: paclitaxel; TMX: tamoxifen

Treatment regimens were informed by previous TAs and dosing guidance published in the BNF, as presented in Table 40.

Table 40. Third-line treatment regimens

Treatment	Drug	Dose	Per unit	Administrations per cycle	Cycle length	Source
ERI	ERI	1.23	m^2	2	21	BNF Online, Accessed 13th March 2018; EMC Accessed 16th March 2018[136]
FUL	FUL	500	fixed	2	28	BNF Online, Accessed 13th March 2018[136]
FUL	FUL	500	fixed	1	28	
TMX	TMX	25	fixed	28	28	BNF Online, Accessed 13th March 2018; EMC Accessed 16th March 2018[136]

Abbreviations: ANAS: anastrozole; CAP: capecitabine; EMC: electronic medicines consortium; EXE: exemestane; FUL: fulvestrant; TMX: tamoxifen

Post-progression therapy costs comprised drug acquisition (Table 41) and drug administration (Table 42).

Table 41. Third-line drug acquisition costs

Treatment	Drug	Mg/tablet/vial	Tablets/vials per pack	Price per pack
ERI	ERI	0.44	2	£361.00
FUL	FUL	250	2	£522.41
FUL	FUL	250	2	£522.41
TMX	TMX	10	30	£7.02
TMX	TMX	10	30	£26.80
TMX	TMX	20	30	£1.59

Abbreviations: ANAS: anastrozole; CAP: capecitabine; ERI: eribulin; EXE: exemestane; FUL: fulvestrant; TMX: tamoxifen

Table 42. Third-line therapy administration costs

Treatment	Drug	Admins per cycle	Cost per admin	Source
ERI	ERI	2	£259.76	NHS reference costs 2016-17 SB12Z Deliver simple parenteral chemo at first attendance (day case only based on activity)[140]
FUL (loading dose)	FUL	1	£219.19	NHS Reference costs, 2016-16 WF01A Non-admitted F2F attendance, First, Service Code 370 (Medical Oncology)[140]
FUL	FUL	1	£0.00*	NHS Reference costs, 2016-17 WF01A Non-admitted F2F attendance, First, Service Code 370 (Medical Oncology)[140]

Footnotes: *FUL administration costs are assumed to be captured within follow-up appointments included in the FUL loading dose costs.

Abbreviations: ANAS: anastrozole; CAP: capecitabine; ERI: eribulin; EXE: exemestane; F2F: face to face; FUL: fulvestrant; TMX: tamoxifen

Time on third-line therapy was calculated based on an assumption that patients spent approximately 37% of their time in PPS (after progression from second-line therapy) on treatment. This assumption was based on clinical expert opinion. Estimated time on treatment based on this assumption is presented in Table 43.

Table 43. Time on third-line treatment

First-line treatment	Time in PPS (months)		
	On treatment	Off treatment	Total
ABE+NSAI	12.17	20.72	32.89
PAL+NSAI	12.26	20.88	33.15
RIBO+NSAI	12.26	20.88	33.15
NSAI	12.17	20.72	32.89

Footnotes: *NSAI methodology is included here to contextualise the NSAI results presented in Section B.3.10
Abbreviations: ABE: abemaciclib; EXE: exemestane; FUL: fulvestrant; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; RIBO: ribociclib; TMX: tamoxifen

A summary of the estimated total third-line treatment costs applied to each first-line treatment regimen is presented in Table 44.

Table 44. Total weighted third-line treatment costs

First-line treatment	Total
ABE+NSAI	£3,713.89
PAL+NSAI	£3,742.91
RIBO+NSAI	£3,742.91
NSAI*	£3,713.89

Footnotes: *NSAI methodology is included here to contextualise the NSAI results presented in Section B.3.10
Abbreviations: ABE: abemaciclib; EXE: exemestane; FUL: fulvestrant; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; RIBO: ribociclib; TMX: tamoxifen

B.3.5.2 Health-state unit costs and resource use

Best supportive care

BSC was defined as treatment that patients would receive based on their disease. BSC components comprised costs of pain management, anti-emetics, growth factors, bone modifying agents, treatments for anxiety/depression, erythropoietic agents, and treatments for venous thromboembolic disease. Components of BSC were identified from clinical guidelines, the MONARCH 3 trial (for the pre-progression health state) and the MONARCH 2 trial (for the post-progression health state).

It is possible that some BSC components may have been included in the treatment of AEs, which could result in the double-counting of costs. However, given that the BSC components are assigned equally across treatment arms at the same associated frequencies and to the same proportion of patients, the potential double-counting of costs is unlikely to have a material impact on incremental cost-effectiveness.

Specific treatments for each BSC component were identified from the MONARCH 3 trial for patients in PFS and the MONARCH 2 trial for the 'pay-off'. BSC components were selected based on the treatment with the highest utilisation in the trial. A summary of the BSC components and resource utilisation, and the corresponding costs of each BSC treatment, are provided in Table 45 and Table 46, respectively.

Table 45. BSC components and resource use

BSC component	Medication	Proportion of patients	SE	Units	Frequency	Source
PFS						
Pain management*	Oxycodone	8.6%	0.09%	200.00	Daily	MONARCH 3 CSR[4]; dose-BNF[136]
Antidiarrheals	Loperamide	49.6%	0.50%	16.00	Daily	MONARCH 3 CSR[4]; dose-BNF[136]
Anti-emesis or anti-nauseants	Ondansetron	8.6%	0.09%	16.00	Daily	MONARCH 3 CSR[4]; dose-BNF[136]
Bone-modifying agents	Denosumab	23.8%	0.24%	60.00	Bi-annually	MONARCH 3 CSR[4]; dose-BNF[136]
Erythropoietic agents	Erythropoietin	0.6%	0.01%	450.00	Weekly	MONARCH 3 CSR[4]; dose-BNF[136]
Growth factors	Filgrastim	3.3%	0.03%	5.00	Weekly	MONARCH 3 CSR[4]; dose-BNF[136]
PPS 'pay-off'						
Pain management*	Oxycodone	9.5%	0.09%	200.00	Daily	MONARCH 2 CSR[141]; dose-BNF[136]
Antiemesis or antinauseants	Ondansetron	9.8%	0.10%	16.00	Daily	MONARCH 2 CSR[141]; dose-BNF[136]
Depression or anxiety	Alprazolam	8.3%	0.08%	16.00	Daily	MONARCH 2 CSR[141]; dose-BNF[136]
Growth factors	Filgrastim	4.2%	0.04%	5.00	Weekly	MONARCH 2 CSR[141]; dose-BNF[136]

Abbreviations: BNF: British national formulary; BSC: best supportive care PFS: progression-free survival; PPS: post-progression survival
Footnotes: *Non-opioids have not been included as they were deemed inconsequential for the cost-effectiveness model

Table 46. BSC costs

BSC treatment	Unit cost	Source
Oxycodone	£0.120	BNF[136]
Loperamide	£0.100	BNF[136]
Ondansetron	£0.080	BNF[136]
Denosumab	£2.582	BNF[136]
Erythropoietin	£0.004	BNF[136]
Alprazolam	£0.050	BNF[136]

BSC treatment	Unit cost	Source
Filgrastim	£0.090	BNF[136]

Abbreviations: BNF: British national formulary; BSC: best supportive care

Hospitalisations

Hospitalisation data were included in the PFS state for first-line patients based on the MONARCH 3 trial data. Hospitalisation data were included in the post-progression state for second-line patients based on the pre- and post-progression data in the FUL arm of the MONARCH 2 trial. A scenario analysis for post-progression length of stay was performed using MONARCH 3 data.

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.

Pre-progression (PFS1)

In the MONARCH 3 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 all treatments. This was based on the lack of a difference in the rates between treatment arms of the MONARCH 3 trial. Hospitalisation data for PAL-NSAI and RIBO-NSAI were not reported in the primary publications used in the NMA.

The length of stay was estimated based on the MONARCH 3 data for pre- and post-progression periods, assuming this was the same between ABE-NSAI and NSAI. These data are presented in Table 47.

Table 47. Length of hospital stay for patients in MONARCH 3

Cohort	Treatment	Number of hospitalisations	Mean length of stay (days)	SD
Pre-progression (PFS1)	ABE-NSAI and NSAI	72	8.58	10.99

Abbreviations: PFS1: first-line progression-free survival; PFS2: second-line progression-free survival

The rate of hospitalisations was estimated by fitting Poisson regression models to the hospitalisation data and including covariates for progression status (post- vs. pre-progression) and treatment. Negative binomial models were fitted to the data However, these did not converge in a number of cases due to the low event counts. Therefore, only Poisson models were included in the model. Follow-up time in months was specified as an exposure variable to provide a rate estimate per month of follow-up. Both models with and without adjustment for baseline characteristics were assessed with models unadjusted for baseline characteristics included as the base case given the limited number of events occurred.

The parameter estimates for the models fitted in the base case (without baseline characteristic adjustment) and scenario analysis (with baseline characteristic adjustment) are presented in Appendix M.3.1. The unit cost per day was sourced from the 2016–17 NHS Reference costs[142] and converted to a cost per hospitalisation based on a mean length of stay (Table 48).

Table 48. Hospitalisation costs

Component	Mean cost	Source
Cost per day inpatient stay	£447.35	NHS Reference costs 16-17JD12D-L, Malignant breast disorders with/without interventions, non-elective long stay[140]

PFS2

The same approach was used to estimate the cost per hospitalisation as described for the first-line PFS state. In addition, only data for FUL were included in the model, stratified by pre- and post-progression. Unlike the analysis of clinical outcome data where the MONARCH 2 trial population assessed was restricted based on prior ET in the advanced setting, no restriction was placed on the population modelled for hospitalisations. This was due to the lack of event data observed from the MONARCH 2 trial. An assumption was made that the probability of hospitalisation and length of stay for all second-line treatments was the same as FUL. The length of stay data for FUL based on the MONARCH 2 trial is presented in Table 49.

Table 49. Length of hospital stay for patients in MONARCH 2 – PBO-FUL

Cohort	Treatment	Number of hospitalisations	Mean length of stay (days)	SD
Pre-progression (PFS2)	PBO-FUL	10	12.10	14.36
Post-progression (PPS)	PBO-FUL	7	10.29	4.96

Abbreviations: FUL: fulvestrant; PBO: placebo; PFS2: second-line progression-free survival; PPS: post-progression survival

As more events were observed in the pre-progression period of the MONARCH 2 trial for patients receiving PBO-FUL compared to the post-progression period of the MONARCH 3 trial, the corresponding MONARCH 2 length of stay data was used in the base case for second-line PFS.

The rates of hospitalisation by pre- and post-progression periods were estimated based on the observed number of hospitalisations and total follow-up time. The rate was then converted to a monthly probability to include in the model.

The rate per month was calculated as:

$$rate\ per\ month = \frac{total\ number\ of\ hospitalisations}{total\ follow\ up\ in\ months}$$

The resulting hospitalisation rates and probabilities are provided in Table 50.

Table 50. Hospitalisation rate and probability data from MONARCH 2 – PBO-FUL

Cohort	Treatment	Total hospitalisations	Total follow-up (days)	Rate of hospitalisations/ month	Probability of hospitalisations/ month
Pre-progression	FUL	18	63762	0.009	0.009
Post-progression	PBO-FUL	5	5273	0.029	0.029
Overall	PBO-FUL	23	69035	0.010	0.010

Abbreviations: FUL: fulvestrant; PBO: placebo

The same mean cost per inpatient hospitalisation used for the first-line PFS state was applied to the post-progression state (Table 48).

Summary of hospitalisation probabilities

Based on the analysis of rates of hospitalisation, a summary of the monthly probability of hospitalisation is provided in Table 51.

Table 51. Summary of base case hospitalisation probabilities by health state

Treatment	PFS1	PFS2	PPS
ABE+NSAI	0.0085	0.0086	0.0288
PAL+NSAI	0.0085	0.0086	0.0288
RIBO+NSAI	0.0085	0.0086	0.0288
NSAI*	0.0085	0.0086	0.0288

Footnotes: *NSAI methodology is included here to contextualise the NSAI results presented in Section B.3.10
Abbreviations: ABE: abemaciclib; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; PFS1: first-line progression-free survival; PFS2: second-line progression-free survival; RIBO: ribociclib
Source: PFS1 = Monarch 3 IPD, PFS2 and PPS = Monarch 2 IPD

Follow-up care

Follow-up care is defined as the routine monitoring of patients. Components of follow-up care were identified from the MONARCH 3 trial[141] (for the pre-progression health state), the MONARCH 2 trial[4] (for the post-progression health state) and NICE clinical guidelines.[143] Resource use was informed by the MONARCH 3 and MONARCH 2 trials for the PFS2 and PPS health states, respectively. The follow-up care components, proportions and frequencies are listed in Table 52.

Table 52. Follow-up care

Component	Proportion of patients	Frequency-PFS	Frequency-PPS	Frequency unit	Source
CT scan	100.00%	0.42	0.33	Cycle	MONARCH 3 CSR
Electrocardiogram	100.00%	0.33	0.17	Cycle	MONARCH 3 CSR
Complete blood count	100.00%	1.00	0.33	Cycle	MONARCH 3 CSR
Serum chemistry	100.00%	1.00	1.00	Cycle	MONARCH 3 CSR

Component	Proportion of patients	Frequency-PFS	Frequency-PPS	Frequency unit	Source
Oncologist consultation	100.00%	1.00	1.00	Cycle	MONARCH 3 CSR
GP visit (surgery)	100.00%	0.23	1.00	Cycle	NICE CG81[143] (package 1 PFS, package 2 PPS)
Community nurse (home visit)	100.00%	0.50	0.23	Week	NICE CG81[143] (package 1 PFS, package 2 PPS)
Clinical nurse specialist (home visit)	100.00%	0.23	0.50	Week	NICE CG81[143] (package 1 PFS, package 2 PPS)
X-ray	0.40% (PFS) 2.50% (PPS)	0.50	0.50	Week	MONARCH 3 CSR
Therapist	100.00%	-	0.50	Week	NICE CG81[143] clinical guidelines Package 2

Footnotes: Unit costs were sourced from the NHS Reference Costs 2016–17[142] and the Personal Social Services Research Unit (PSSRU) site[144] (Table 53).

Table 53. Follow-up care costs

Component	Cost	Source
CT scan	£112.07	NHS Reference costs,[140] RD24Z, CT of 2 areas with contrast, outpatient setting
Electrocardiogram	£256.35	NHS Reference costs,[140] 2016–17, EY51Z, Electrocardiogram monitoring or stress testing, Service Code 370 (Medical Oncology)
Complete blood count	£3.06	NHS Reference costs,[140] 2016–17, DAPS05, Haematology
Serum chemistry	£1.13	NHS Reference costs, [140] 2016-17, DAPS04, Clinical biochemistry
Oncologist consultation	£172.67	NHS Reference costs,[140] 2016–17, WF01A Non-admitted F2F attendance, First, Service Code 370 (Medical Oncology)
GP visit (home visit)	£38.00	PSSRU,[145] 2017, Per patient contact lasting 9.22 with qualifications minutes
Community nurse (home visit)	£12.00	PSSRU,[145] 2017, Community Nurse, Band 5, Cost per working hour, divided by 3 to calculate 20 minute-visit
Clinical nurse specialist (home visit)	£44.00	PSSRU,[145] 2017, Community Nurse, Band 6, Cost per working hour
X-ray	£0.00	NHS Reference costs, 2016–17,[140]
Therapist	£42.00	PSSRU,[145] 2017, Community Occupational Therapist, cost per working hour

Abbreviations: CT: computerised tomography; F2F: face to face; GP: general practitioner

Terminal care

Terminal care costs were assigned to all patients who died in the model; the costs were assumed to cover the care received by patients in the two weeks leading up to death. 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[49] (Table 54).

Table 54. Terminal care

Setting of care	Proportion of patients	Source
Hospital	40.00%	NICE CG81[143] clinical guidelines
Hospice	10.00%	NICE CG81[143] clinical guidelines
At home with community support	50.00%	NICE CG81[143] clinical guidelines

The unit costs of terminal care are presented in Table 55.

Table 55. Terminal care unit costs

Setting of care	Mean cost	Source
Hospital	£5,595.20	NICE CG81[143] package 3 inflated to 2015/2016 prices using the HCHS index,[146] as per TA496[54]
Hospice	£6,975.58	NICE CG81[143] package 3 inflated to 2015/2016 prices using the HCHS index,[146] as per TA496[54]
At home with community support	£2,886.78	NICE CG81[143] package 3 inflated to 2015/2016 prices using the HCHS index,[146] as per TA496[54]

B.3.5.3 Adverse reaction unit costs and resource use

The cost impact of AEs in first-line treatment was captured in the model analysis as a one-off fixed cost in the first cycle of the model. As described in Section B.3.4.4, the rates of AEs for patients on ABE-NSAI were based on TRAEs which occurred in the ITT population of the MONARCH 3 trial. AE rates for the comparators are based on the primary publications used in the NMA. AEs were selected for inclusion if they were grade 3–4 events occurring in more than 5% of patients for at least one intervention. For included AEs, the percentages of patients experiencing the event were entered into the model.

Unit costs associated with the AE were based on the 2016–17 NHS Reference Costs;[140] these are presented in Table 56.

Table 56. Adverse event costs

Event	Cost	Source
Alanine aminotransferase increased	£0.00	Managed by treatment discontinuation, therefore no cost assigned
Anaemia	£270.00	NHS reference costs 2016–17[140]
Aspartate aminotransferase increased	£0.00	Managed by treatment discontinuation therefore no cost assigned
Diarrhoea	£2.93	BNF[136]
Hypertension	£173.00	NHS reference costs 2016–17[140]
Leukopenia	£173.00	NHS reference costs 2016–17[140]
Lymphopenia	£173.00	NHS reference costs 2016–17[140]
Neutropenia	£173.00	NHS reference costs 2016–17[140]

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 base-case analysis inputs is presented in Table 57.

Table 57: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Model properties			
Cycle length	1 month	Fixed	B.3.2.2, page 90
Time horizon	35 years	Fixed	B.3.2.2, page 90
Discount rate (costs and outcomes)	3.5%	Fixed	B.3.2.2, page 90
Willingness to pay threshold	£30,000	Fixed	B.3.8.1, page 146
Patient height	158.41 cm	Fixed	B.3.3.3, page 95
Patient weight	67.99 kg	Fixed	B.3.3.3, page 95
Patient BSA	1.70 m^2	Fixed	B.3.3.3, page 95
Pre-progression: TTP			
TTP distribution (ABE-NSAI and NSAI)	Exponential	Multivariate normal	B.3.3.6, page 107
Treatment effect for PAL-NSAI (against NSAI)	[redacted]	Log-normal	B.3.3.5, page 101

Treatment effect for RIBO-NSAI (against NSAI)	[redacted]	Log-normal	B.3.3.5, page 101
Pre-progression: OS			
Pre-progression deaths	Negative binomial	Multivariate normal	B.3.5.2, page 131
Treatment effect for PAL-NSAI (against NSAI)	[redacted]	Log-Normal	B.2.9.2, page 61
Treatment effect for RIBO-NSAI (against NSAI)	[redacted]	Log-normal	B.2.9.2, page 61
Pre-progression: TTD			
TTD distribution (all comparators)	Generalised Gamma	Multivariate normal	B.3.3.5, page 103
Treatment effect for PAL-NSAI (against ABE-NSAI)	[redacted]	Fixed	B.3.3.5, page 103
Treatment effect for RIBO-NSAI (against ABE-NSAI)	[redacted]	Fixed	B.3.3.5, page 103
'Pay-off': proportion of patients receiving each second-line treatment			
Chemotherapies	25.66% (proportion of patients)	Gamma	B.3.5.1, page 124
Endocrine therapies	66.34% (proportion of patients)	Gamma	B.3.5.1, page 124
EVE-EXE	8% (proportion of patients)	Gamma	B.3.5.1, page 125
'Pay-off': PFS			
PFS distribution (FUL)	Exponential	Multivariate normal	B.3.3.6, page 107
Treatment effect for EXE	[redacted]	Log-normal	B.2.9.2, page 59
Treatment effect for TMX	[redacted]	Log-normal	B.2.9.2, page 59
Treatment effect for EVE-EXE	[redacted]	Log-normal	B.2.9.2, page 59
Treatment effect for chemotherapies	1.64	Log-normal	B.2.9.2, page 59
'Pay-off': OS			
OS distribution (FUL)	Exponential	Multivariate normal	B.3.3.6, page 109
Treatment effect for EXE	[redacted]	Log-normal	B.2.9.2, page 60
Treatment effect for TMX	[redacted]	Log-normal	B.2.9.2, page 60
Treatment effect for EVE-EXE	[redacted]	Log-normal	B.2.9.2, page 60
Treatment effect for chemotherapies	1.89	Log-normal	B.2.9.2, page 60
'Pay-off': TTD			

TTD distribution (FUL)	Exponential	Multivariate normal	B.3.3.6, page 112
Treatment effect for EXE	[redacted]	Fixed	Appendix N
Treatment effect for TMX	[redacted]	Fixed	Appendix N
Treatment effect for EVE-EXE	[redacted]	Fixed	Appendix N
Treatment effect for chemotherapies	1.66	Fixed	Appendix N
Utilities			
PFS1	[redacted]	Multivariate normal	B.3.4.2 page 116
PFS2 (endocrine +/- targeted therapies)	0.774	Multivariate normal	B.3.4.2, page 117
PFS2 (chemotherapies)	0.661	Multivariate normal	B.3.4.2, page 117
PPS	0.505	Multivariate normal	B.3.4.2, page 117
Alanine aminotransferase increased	-0.050	Multivariate normal	B.3.4.4, page 119
Anaemia	-0.119	Multivariate normal	B.3.4.4, page 119
Aspartate aminotransferase increased	0.000	Multivariate normal	B.3.4.4, page 119
Diarrhoea	-0.006	Multivariate normal	B.3.4.4, page 119
Hypertension	-0.153	Multivariate normal	B.3.4.4, page 119
Leukopenia	-0.003	Multivariate normal	B.3.4.4, page 119
Lymphopenia	0.000	Multivariate normal	B.3.4.4, page 119
Neutropenia	-0.007	Multivariate normal	B.3.4.4, page 119
Acquisition costs			
ABE (56 x 150 mg)	£[redacted] per pack	Fixed	B.3.5.1, page 122
LTZ (28 x 2.5 mg)	£2.71 per pack	Fixed	B.3.5.1, page 122
ANAS (28 x 1 mg)	£1.34 per pack	Fixed	B.3.5.1, page 122
PAL (21 x 75 mg)	£2,950 per pack	Fixed	B.3.5.1, page 122
PAL (21 x 100 mg)	£2,950 per pack	Fixed	B.3.5.1, page 122
PAL (21 x 125 mg)			
RIBO (21 x 200 mg)	£983.33 per pack	Fixed	B.3.5.1, page 122
RIBO (42 x 200 mg)	£1,966.67 per pack	Fixed	B.3.5.1, page 122
RIBO (63 x 200 mg)	£2,950 per pack	Fixed	B.3.5.1, page 123
CAP (60 x 150 mg)	£3.97 per pack	Fixed	B.3.5.1, page 124
CAP (120 x 500 mg)	£21.67 per pack	Fixed	B.3.5.1, page 124
PAC (17 x 100 mg)	£9.85 per pack	Fixed	B.3.5.1, page 125
PAC (25 x 150 mg)	£10.52 per pack	Fixed	B.3.5.1, page 125
PAC (50 x 300 mg)	£19.68 per pack	Fixed	B.3.5.1, page 125
PAC (30 x 5 mg)	£66.24 per pack	Fixed	B.3.5.1, page 125
DOC (8 x 160 mg)	£46.75 per pack	Fixed	B.3.5.1, page 125

DOC (1 x 20 mg)	£3.85 per pack	Fixed	B.3.5.1, page 125
DOC (4 x 80 mg)	£14.74 per pack	Fixed	B.3.5.1, page 125
FUL (2 x 250 mg)	£522.41 per pack	Fixed	B.3.5.1, page 125
EXE (30 x 25 mg)	£3.69 per pack	Fixed	B.3.5.1, page 125
TMX (10 x 30 mg)	£7.02 per pack	Fixed	B.3.5.1, page 125
TMX (10 x 30 mg)	£26.80 per pack	Fixed	B.3.5.1, page 125
TMX (20 x 30 mg)	£1.59 per pack	Fixed	B.3.5.1, page 125
EVE (30 x 2.5 mg)	£1,200 per pack	Fixed	B.3.5.1, page 125
EVE (30 x 5 mg)	£2,250 per pack	Fixed	B.3.5.1, page 125
EVE (30 x 25 mg)	£2,673 per pack	Fixed	B.3.5.1, page 125
ERI (2 x 0.44 mg)	£361 per pack	Fixed	B.3.5.1, page 128
Administration costs			
All oral endocrine therapies and regular doses of FUL	£0	Fixed	B.3.5.1, page 126
FUL loading dose	£219.19 per admin	Fixed	B.3.5.1, page 126
Oral chemotherapies (CAP)	£163.82 per admin	Fixed	B.3.5.1, page 125
IV chemotherapies (PAC, DOC ERI)	£259.76 per admin	Fixed	B.3.5.1, page 125 and 126
PFS	£869.96 per month	Gamma	B.3.6.1, page 139
Disease management costs			
PPS (2nd line treatment PFS)	£508.51 per month	Gamma	B.3.5.2
PPS (2nd line treatment PPS)	£799.72 per month	Gamma	B.3.5.2
Terminal care	£4,379	Gamma	B.3.5.2, page 135

Abbreviations: ABE: abemaciclib; ANAS: anastrozole; BSA: body surface area; CAP: capecitabine; CI: confidence interval; DOC: docetaxel; ERI: eribulin; EVE: everolimus; EVE-EXE: everolimus-exemestane; EXE: exemestane; FUL: fulvestrant; IV: intravenous; LTZ: letrozole; OS: overall survival; PAC: paclitaxel; PFS: progression-free survival; PPS: post-progression survival; TMX: tamoxifen; TTD: time to treatment discontinuation; TTP: time to progression; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; RIBO: ribociclib

B.3.6.2 Assumptions

Table 58 includes a summary of the key model assumptions.

Table 58. Summary of model assumptions

Component	Assumption	Justification
Comparators	• NSAI • PAL-NSAI • RIBO-NSAI	As per NICE scope[14]
Model structure and characteristics	State transition with fixed 'pay-off' for post progression	Reflects the treatment pathway for ABC and allows the use of external data to inform long term extrapolation of outcomes. This would not otherwise be possible in a state transition model with 3 health states.

Component	Assumption	Justification
	Calculation of post-progression 'pay-off' based on data from the FUL arm of the MONARCH 2 trial and the CONFIRM trial	Post-progression survival data from MONARCH 3 are immature, therefore clinical trial data were used from similar, progressed patient populations. Patients in the FUL arm of the MONARCH 2 trial are assumed to represent patients progressing from MONARCH 3, because the MONARCH 2 inclusion criteria require patients to have progressed on one prior endocrine therapy. Patients in the ABE-FUL arm of MONARCH 2 are excluded because patients in the MONARCH 3 trial are not expected to have ABE in second line. Given that OS data from the MONARCH 2 trial are immature, OS data from the CONFIRM trial are also used to inform longer term estimates; the CONFIRM trial has longer OS follow-up than MONARCH 2.
Modelling of OS	Modelled indirectly based on time spent in PFS and the post-progression 'pay-off'	OS data from MONARCH 3 are immature
	Assumes a surrogacy relationship between PFS and OS of approximately 27.5% (i.e., the modelled OS gain from CDK4/6 inhibitors with NSAI versus NSAI alone is reduced to 27.5% of the PFS gain).	Takes into account ERG feedback on the surrogacy relationship in previous TA's and, uses 27.5% as observed in PALOMA-2[10, 97, 147]
Second-line treatments	All patients who progress from first-line treatment assumed to receive a second-line treatment	Based on the real world study of treatment patients by Kurosky et al (2015)[94] as used in TA503.[148]
Third-line treatments	Included as a weighted cost only, clinical outcomes not taken into account	Outcome beyond second-line treatment assumed to be captured in the extrapolation of OS from MONARCH 2/CONFIRM trial data
First-line TTD	Where TTD exceeded TTP, TTD was set equal to TTP	For face validity; intuitively patients should not remain on first-line treatment after they have progressed
Second-line TTD	Where TTD exceeded second-line PFS, TTD was set equal to PFS	For face validity; intuitively patients should not remain on second-line treatment after they have progressed
Treatment effects	HRs for OS from the MONARCH 3 NMA use as a proxy for the relative risk of pre-progression deaths on first-line treatment	In the absence of relative risk data from other sources the HR for OS from the NMA was deemed to be a reasonable alternative
	HRs for OS and PFS for chemotherapy in second-line sourced from a study by Li et al which compared EVE-based treatment against chemotherapy.[96]	Chemotherapy was not part of the network identified for the MONARCH 2 NMA therefore we referred to TA496 for the source of HR[97]

Component	Assumption	Justification
Utilities	Utilities for PFS1 were assumed to be the same for all treatments	Quality of life is driven by the health state
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 endocrine therapies assigned zero cost for administration	These are taken in the patient's own home without need for clinician supervision
	Only the FUL loading dose incurs an administration cost. Zero cost is assigned to the administration of the monthly dose	The monthly dose is assumed to be administered during the monthly consultation with an oncologist
Disease management costs-PFS and PPS	Comprise of BSC, follow up care and hospitalisations based on proportion of patients requiring each component and unit cost	N/A

Abbreviations: BSC: best supportive care; EVE: everolimus; FUL: fulvestrant; HR: hazard ratio; NMA: network meta-analysis; OS: overall survival; ; PFS: progression-free survival; PPS: post-progression survival; TAs: technology appraisals; TTD: time to treatment discontinuation; TTP: time to progression; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; RIBO: ribociclib

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

Base-case results for the cost-effectiveness analysis are presented in Table 59.

In the incremental analysis, ABE-NSAI accrued a greater number of life years and QALYs compared to both PAL-NSAI and RIBO-NSAI, indicating that ABE-NSAI may potentially provide greater clinical benefit to patients compared to these two interventions. Based on the list price only, ABE-NSAI was further associated with lower costs versus PAL-NSAI and RIBO-NSAI, and therefore dominated both interventions. The lower costs were driven by shorter time on treatment for ABE-NSAI. Clinical outcomes presented in the model and disaggregated results of the base case ICER are presented in Appendix J.

Table 59: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ABE+NSAI	£129,803	5.08	3.29	-	-	-	-	-
RIBO+NSAI	£148,170	5.02	3.22	£18,367.14	−0.06	−0.068	Dominated	Dominated
PAL+NSAI	£145,266	5.03	3.23	−£2,904.53	0.02	0.003	Dominated	Dominated

Abbreviations: ABE: abemaciclib; ICER: incremental cost-effectiveness ratio; LYG: life years gained; ABE: abemaciclib; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; QALYs: quality-adjusted life years; RIBO: ribociclib

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 60.

Table 60. PSA distributions

Parameter	Distribution	Justification
Hazard ratios for treatment effect	Lognormal	Ratio, additive on log scale
Survival model coefficients (TTP, PFS, OS, TTD)	Multivariate normal	To capture correlation between normally distributed regression parameters
Progression-free deaths model coefficients	Multivariate	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-NSAI or NSAI)	Lognormal	Ratio, additive on log scale
Hospitalisations per month (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 month)	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
Unit costs	Gamma	Constrained on an interval from 0 to positive infinity

Abbreviations: ABE: abemaciclib; NSAI; non-steroidal aromatase inhibitor; OS: overall survival; PFS: progression-free survival; TTD: time to treatment discontinuation; TTP: time to progression

Results of the PSAs for the comparison of ABE-NSAI versus palbociclib and ribociclib, both in comparison with NSAI, are summarised in Table 61.

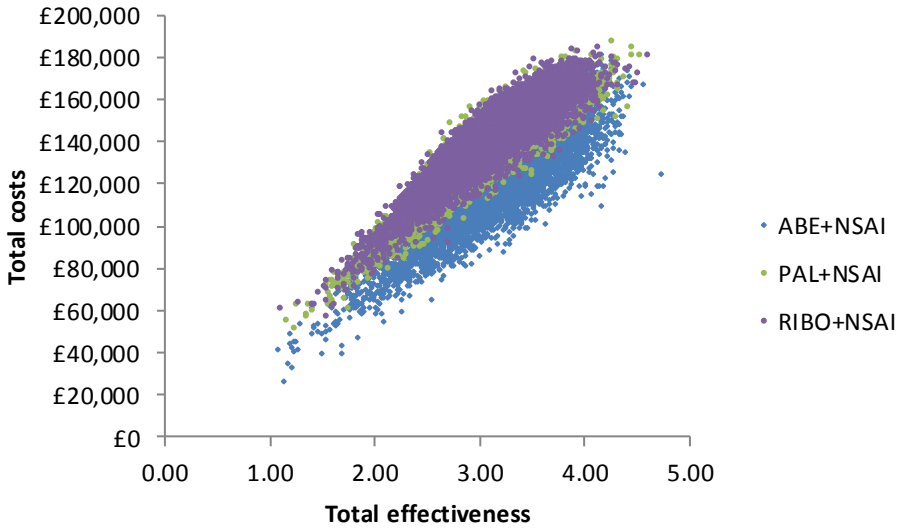
Table 61: Base-case results (probabilistic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
PAL-NSAI	£139,631	4.92	3.15	-	-	-	-	-
RIBO-NSAI	£142,571	4.92	3.16	£2,940	0.00	0.01	£397,143.85	£397,143.85
ABE-NSAI	£125,581	4.96	3.21	-£16,990	0.04	0.05	Dominant	Dominant

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

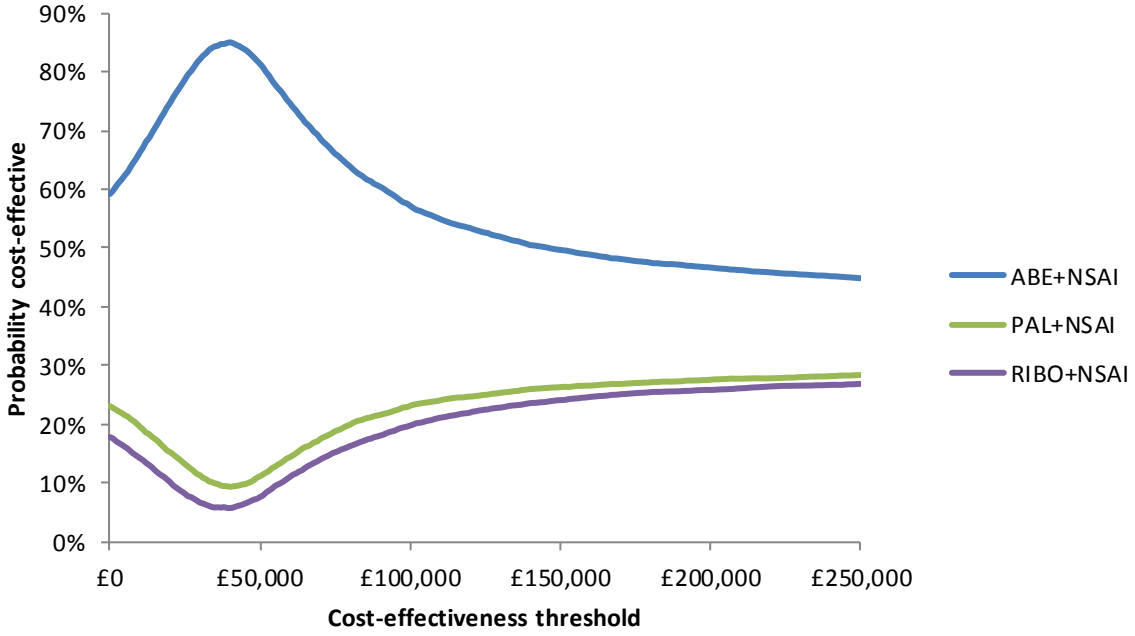
A scatter plot of the joint distribution of incremental costs and incremental QALYs from the PSA is shown in Figure 41, and the cost effectiveness acceptability curves (CEAC) and frontier corresponding with the above outputs is presented in Figure 42 and Figure 43, respectively.

Figure 41. Scatter plot of simulations on the cost-effectiveness plane



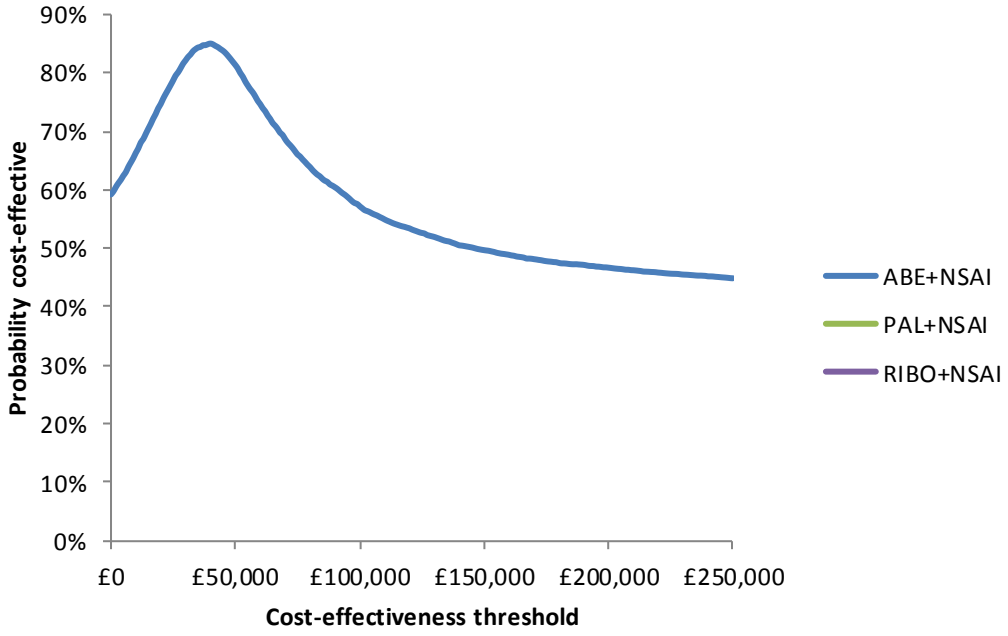
Abbreviations: ABE: abemaciclib; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; RIBO: ribociclib

Figure 42. Cost-effectiveness acceptability curve



Abbreviations: ABE: abemaciclib; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; RIBO: ribociclib

Figure 43. Cost-effectiveness acceptability frontier



Abbreviations: ABE: abemaciclib; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; RIBO: ribociclib

The probability of each comparator being cost effective at a willingness to pay threshold of £30,000 per QALY is presented in Table 62. At a willingness to pay threshold of £30,000 per QALY, ABE-NSAI had an 82% probability of being cost-effective.

Table 62. Probability of cost-effectiveness

Intervention	Probability of cost-effectiveness at £30,000 per QALY
ABE-NSAI	82%
PAL-NSAI	7%
RIBO-NSAI	11%

Abbreviations: QALY: quality-adjusted life year

B.3.8.2 Deterministic scenario analysis

Deterministic scenario analyses were conducted to explore the impact of assumptions that were included in the base case analysis. A description of each scenario analysis and the corresponding results are presented in Table 63.

Table 63. Scenario analysis results

Scenario	Base case value	Scenario	ABE+NSAI	NSAI	PAL+NSAI	RIBO+NSAI
Base-case	N/A	N/A	£250,065	Referent	Dominated	Dominated
Discount rate costs and benefits	3.50%	0.00%	£212,582	Referent	Dominated	Dominated
Discount rate costs and benefits	3.50%	6.00%	£279,248	Referent	Dominated	Dominated
Source of ABE-NSAI treatment effects for PFS	Joint model (MONARCH 3)	NMA	£341,342	Referent	£1,378,635	Dominated
Interval censoring adjustment	Interval censoring adjusted analysis	Unadjusted analysis	£250,065	Referent	Dominated	Dominated
Covariate adjustment	Interval censoring adjusted analysis	Covariate and interval censoring adjusted analysis	£222,795	Referent	Dominated	Dominated
Distribution for extrapolating TTP (scenario 1)	Exponential	Weibull	£240,007	Referent	Dominated	Dominated
Distribution for extrapolating TTP (scenario 2)	Exponential	Gompertz	£571,795	Referent	Dominated	Dominated
Distribution for extrapolating second-line PFS (scenario 1)	Exponential	Weibull	£256,368	Referent	Dominated	Dominated
Distribution for extrapolating second-line PFS (scenario 2)	Exponential	Gompertz	£278,660	Referent	Dominated	Dominated
Distribution for extrapolating second-line OS (scenario 1)	Exponential with CONFIRM data extrapolation	Exponential	£282,398	Referent	Dominated	Dominated
Distribution for extrapolating second-line OS (scenario 2)	Exponential with CONFIRM data extrapolation	Log-logistic	£245,869	Referent	Dominated	Dominated
Distribution for extrapolating second-line OS (scenario 3)	Exponential with CONFIRM data extrapolation	Gompertz	£197,053	Referent	Dominated	Dominated
Distribution for extrapolating first-line TTD	Gamma	Gompertz	£263,628	Referent	Dominated	Dominated
Distribution for extrapolating first-line TTD	Gamma	Lognormal	£254,708	Referent	Dominated	Dominated
Distribution for extrapolating first-line TTD	Gamma	Exponential	£223,727	Referent	Dominated	Dominated
Distribution for extrapolating second-line TTD	Exponential	Log-logistic	£250,065	Referent	Dominated	Dominated

Scenario	Base case value	Scenario	ABE+NSAI	NSAI	PAL+NSAI	RIBO+NSAI
Distribution for extrapolating second-line TTD	Exponential	Gompertz	£250,065	Referent	Dominated	Dominated
HRs for estimating second-line TTD	Versus FUL based on median ToT	Versus second-line PFS	£248,546	Referent	Dominated	Dominated
Utility model	Overall	Treatment-specific	£269,922	Referent	Dominated	Dominated
PPS utility source	Lloyd, 2006	MONARCH 2	£411,806	Referent	Dominated	Dominated
Second-line PFS utility source	TA496	MONARCH 2	£248,716	Referent	Dominated	Dominated
PPS hospital length of stay source	MONARCH 2	MONARCH 3	£248,499	Referent	Dominated	Dominated
Relative dose intensity	OFF	ON	£196,532	Referent	Dominated	Dominated
PFS1 utility value	MONARCH 3	Equal to PFS in second-line treatment	£209,593	Referent	Dominated	Dominated
Source of clinical outcomes in PPS	MONARCH 2	BOLERO-2	£182,754	Referent	Dominated	Dominated
Apply PFS–OS surrogacy	Yes (27.5%)	No (100%)	£159,286	Referent	Dominated	Dominated
PFS 1 utility source	EQ-5D-3L (crosswalk)	EQ-5D-5L	£250,065	Referent	Dominated	Dominated
Management of diarrhoea	Loperamide	Hospitalisation and loperamide	£251,084	Referent	Dominated	Dominated

Abbreviations: ABE: abemaciclib; FUL: fulvestrant; HR: hazard ratio; NMA: network meta-analysis; NSAI: non-steroidal aromatase inhibitor; OS: overall survival; PAL: palbociclib; PFS: progression-free survival; PPS: post-progression survival; RIBO: ribociclib; TTD: time to treatment discontinuation; TTP: time to progression; ToT: time on treatment

Footnotes: In line with the final scope issued by NICE, NSAI alone is not a relevant comparator to abemaciclib plus NSAI. However, cost-effectiveness results are provided here to allow comparison to prior appraisals for palbociclib plus NSAI (TA495) and ribociclib plus NSAI (TA496)

B.3.8.3 Summary of sensitivity analyses results

The probabilistic sensitivity analyses demonstrated that there is an 82% chance of ABE-NSAI being cost-effective at a threshold of £30,000 per QALY.

In the scenario analyses, the economic results were largely stable when varying model assumptions, with consistent ICER estimates, demonstrating the robustness of the model. Parameters with greatest influence on the ICER are presented in Table 64, and discussed further below.

Table 64. Scenario analysis parameters influencing the base ICER by ≥15%

Decrease in base case ICER of ≥15%	Increase in base case ICER of ≥15%
1. Apply PFS–OS surrogacy (base case: partial [27.5%]; scenario: full [100%])	5. Source of ABE-NSAI treatment effect for PFS
2. Source of clinical outcomes in PPS (base case: derived from MONARCH 2; scenario: derived from BOLERO-2)	6. PPS utility source (base case: derived from Lloyd 2006 [0.505]; scenario: derived from MONARCH 2 [redacted])
3. Distribution for extrapolating second-line OS, scenario 3 (base case: exponential with CONFIRM data extrapolation; scenario: Gompertz)	7. Distribution for extrapolating TTP, scenario 2 (base case: exponential; scenario: Gompertz)
4. Relative dose intensity (base case: off; scenario: on)	

Abbreviations: ABE-NSAI: abemaciclib plus NSAI; OS: overall survival; PFS1: progression-free survival on first-line treatment; PFS2: progression-free survival on second-line treatment; PPS: post-progression survival; TTP: time to progression

1. The extent that PFS may act as a surrogate for OS was subject to discussion in both TA495[53] and TA496,[54] with the committee concluding in both cases that it is likely that improved PFS translates into an OS gain, but that the relationship between progression-free and overall survival is complex and difficult to predict, a conclusion that was supported by expert clinicians. Partial surrogacy was adopted in the revised manufacturer models for both appraisals, with percentages of 27.5% PFS–OS surrogacy assumed in TA495 and 38.5% in TA496, the former statistic corresponding to a later data cut of PALOMA-1, an open-label trial of palbociclib plus letrozole versus letrozole plus placebo in HR+/HER2−, advanced breast cancer patients. A possible reason for this variability in PALOMA-1 was noted to be the randomness of patients' response to post-progression treatments. Based on TA495–6, the most conservative value for surrogacy was assumed in the model base case, however, it should be considered that the true value for PFS–OS surrogacy is likely to lie somewhere between 27.5% and 100%.
2. A scenario analysis was also performed where PPS clinical outcomes were derived from the BOLERO-2 trial, a study evaluating EVE-EXE and EXE plus placebo in HR+/HER2− advanced breast cancer patients who had recurrence or progression whilst receiving previous therapy with a NSAI.[125] Specifically, the control EXE arm was used as the referent from which to apply HRs from the NMA for PFS and OS, instead of the FUL arm from MONARCH 2. Adopting clinical outcomes from BOLERO-2 instead of the MONARCH 2 trial resulted in a significant decrease of the ICER. There are potential differences in the number

of prior endocrine therapies received between the populations included in each trial (with this eligibility criterion being unclear in the BOLERO-2 trial), which may explain this difference in progression and survival outcomes. Nevertheless, it was accepted by the committee in TA496,[54] following advice from DSU, that BOLERO-2 data are representative of disease progressing on first-line therapy; as such this is a credible scenario to consider in this economic analysis and closely aligns with the most recent NICE appraisal in this indication.

3. In the base case, second-line OS was based on an exponential distribution using long-term data from the CONFIRM trial to inform the extrapolations from 27.95 months onwards, in line with clinical opinion. However, the Gompertz distribution provided the best fit based on AIC and BIC statistics and Cox-Snell residual plots. As such, this model is also credible and was included as a scenario analysis, resulting in a substantial reduction in the ICER.
4. Adopting a RDI approach to dosing regimens for all treatments was included in a scenario in order to show the exact cost of treatment without considering wastage, which resulted in a substantial decrease in the ICER.
5. Changing the source of treatment effect of ABE-NSAI from the joint model of the MONARCH 3 trial arms to the NMA resulted in an increase to the ICER. However, given the heterogeneity between patient populations of trials included in the NMA (see Section B.2.9), the joint model based on the robustly-designed MONARCH 3 RCT may be considered a more reliable source of treatment effect for this parameter.
6. Adopting MONARCH 2 utilities for PPS resulted in an increase to the base case ICER. However, the post-progression utility of 0.505 derived from Lloyd 2006, a UK-based study examining the quality of life in metastatic breast cancer, was noted in both TA495 and -6 to be the preferred utility value for post-progression by the committee.
7. Adopting the Gompertz distribution in the scenario for TTP resulted in an increase to the base case ICER. However, as noted in Section B.3.3.5, model fit statistics indicated that this function was likely to have an inferior fit to the clinical trial data compared to the exponential function; clinical opinion was also that the exponential had the best fit to the trial data.

B.3.9 *Subgroup analysis*

No subgroup analyses were conducted.

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.[149] In addition, a technical validation of the cost-effectiveness 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 that might be raised by reimbursement authorities or model critics to be pre-empted and addressed in advance. The survival extrapolations were reviewed by an external 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 65 and discussed below.

The median PFS estimates for ABE-NSAI and NSAI were similar to those in the trial publications, although slightly lower in the ABE-NSAI arm due to the adjustment made in the analysis to account for interval censoring, as described in Section B.3.3.4. For PAL-NSAI and RIBO-NSAI, the estimates generated by the model were similar to those in trial publications.

The median ToT estimates across all comparators in the model were also similar to those in the trial publications.

Published median overall survival data were not available for ABE-NSAI or RIBO-NSAI; however, median OS for PAL-NSAI was available from the PALOMA-1 trial (37.5 months).[150] This was considerably lower than the OS estimates generated by the model for ABE-NSAI ([redacted]), RIBO-NSAI ([redacted]) and PAL-NSAI ([redacted]). This difference between estimates is expected to be due to the smaller population size in the PALOMA-1 trial compared to the MONARCH 3 trial and the potential differences in the disease-free interval between neo/adjuvant therapy and entry into the trial. Use of the NMA results account for these differences to an extent, as only relative treatment effects from the PALOMA-1 trial are included. For NSAI, OS from clinical trial publications ranged from 17.4 months (Milla-Santos, 2003)[151] to 60.1 months (Iwata, 2013),[152] compared to [redacted] generated by the model.

Table 65. Comparison of clinical outcomes generated by the model with clinical trial data

Comparator	PFS			ToT			OS		
	Median	Median from source	Source	Median	Median from source	Source	Median	Median from source	Source
ABE-NSAI	[redacted]	[redacted]	MONARCH 3 CSR	[redacted]	[redacted]	MONARCH 3 CSR	[redacted]	NR	MONARCH 3 CSR
NSAI	[redacted]	[redacted]	MONARCH 3 CSR	[redacted]	[redacted]	MONARCH 3 CSR	[redacted]	NR	MONARCH 3 CSR
	-	10.2	PALOMA 1/TRIO-18[98]	-	6.10ł	FIRST (Robertson 2009)[153]	-	48.40	FIRST[153]
	-	18.00	Milla-Santos(2003)[151]	-	10.9	TARGET and N American[154]	-	34.50	PALOMA 1/TRIO-18[150]
	-	8.50	TARGET & N American[154]	-	12.40	MONALEESA-2[134]	-	34.00	Mouridsen (2001)[137]
	-	16.00	MONALEESA-2[134]	-	13.90	FALCON[155]	-	17.40	Milla-Santos (2003)[151]
	-	14.50	PALOMA-2[106]	-	-	-	-	60.10	Iwata (2013)[152]
	-			-	-	-	-	39.20	TARGET and N American[154]
PAL-NSAI	[redacted]	20.20	PALOMA-1/TRIO-18[98]	[redacted]	19.00	PAL SmPC[38]	[redacted]	37.5	PALOMA-1/TRIO-18[150]
		27.60	PALOMA-22[106]						
RIBO-NSAI	[redacted]	25.30	MONALEESA-2[134]	[redacted]	13.00	MONALEESA-2[134]	[redacted]	NR	MONALEESA-2[134]
	-	-	-	-	15.10	MONALEESA-7[156]	-	-	-
	-	-	-	-	20.30	RIBO EMA assessment[157]	-	-	-

Abbreviations: ABE: abemaciclib; EXE: exemestane; FUL: fulvestrant; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; PFS: progression-free survival; RIBO: ribociclib; TMX: tamoxifen; ToT: time on treatment; OS: overall survival

Footnotes: In line with the final scope issued by NICE, NSAI alone is not a relevant comparator to abemaciclib plus NSAI. However, cost-effectiveness results are provided here to allow comparison to prior appraisals for palbociclib plus NSAI (TA495) and ribociclib plus NSAI (TA496)

Comparison to PAL and RIBO appraisals

To further validate the model, a comparison to the manufacturer base case cost-effectiveness results for the NICE appraisals of PAL-NSAI and RIBO-NSAI was planned.[53] Due to the manufacturer cost-effectiveness results from the RIBO-NSAI appraisal being redacted, it was only possible to perform a comparison of the ABE-NSAI analysis to that of PAL-NSAI. Furthermore, due to the absence of ribociclib from UK clinical practice at the time of the PAL-NSAI appraisal, only NSAI was included as a comparator. As such, to enable an informative comparison to be performed, cost-effectiveness results are presented in Table 66 for ABE-NSAI versus NSAI and base case manufacturer cost-effectiveness results for PAL-NSAI versus NSAI are presented in Table 67.

Compared to the PAL-NSAI manufacturer base case results, ABE-NSAI was associated with a significantly greater ICER versus NSAI. However, it should be considered that the PAL-NSAI base case results made a key assumption of full PFS–OS surrogacy, whereas the ABE-NSAI base case results assumed 27.5% surrogacy, as preferred by the committee in TA496–6.[53] As noted in Section B.3.8.3, assuming 100% PFS–OS surrogacy, the ICER for ABE-NSAI versus NSAI was £159,286, which may be deemed comparable to the PAL-NSAI base case ICER, with a difference of less than £10,000 per QALY.

It should be noted that the comparison may be limited by differences in structure, inputs and assumptions between the two models. In particular, revisions were made to the PAL-NSAI model throughout the appraisal following comment by the ERG and committee. As such, the results in Table 66 do not incorporate all committee-preferred inputs and assumptions, whereas the ABE-NSAI model has been developed to align as far as possible with the committee-preferred assumptions from both the PAL-NSAI and RIBO-NSAI appraisals. It was not possible to perform a comparison between the ABE-NSAI model and revised versions of the PAL-NSAI model, due to results presented later in the TA495 appraisal process being redacted.

Table 66. ABE-NSAI versus NSAI cost-effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
NSAI	56,449	4.86	3.00	-	-	-	-
ABE-NSAI	129,803	5.08	3.29	£73,353.52	0.21	0.29	250,065

Abbreviations: ABE: abemaciclib; ICER: incremental cost-effectiveness ratio; LYG: life years gained; NSAI: non-steroidal aromatase inhibitor; QALYs: quality-adjusted life years

Table 67. Manufacturer base case results from the palbociclib NICE appraisal (TA495)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Letrozole alone	21,843	3.02	1.77	-	-	-	-
Palbociclib + letrozole	116,696	3.79	2.40	94,853	0.78	0.63	150,869

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years
Source: Palbociclib manufacturer submission (TA495)[53]

B.3.11 *Interpretation and conclusions of economic evidence*

Summary of economic evidence for ABE-NSAI

In the incremental analysis, ABE-NSAI accrued a greater number of life years and QALYs compared to both PAL-NSAI and RIBO-NSAI, indicating that ABE-NSAI may potentially provide greater clinical benefit to patients compared to these two interventions. Based on the list price only, ABE-NSAI was further associated with lower costs versus PAL-NSAI and RIBO-NSAI, and therefore dominated both interventions. The lower costs were driven by lower time on treatment.

In the DSA (Deterministic Sensitivity Analysis), most scenarios did not change the ICER for ABE-NSAI significantly, reflecting the robustness of the model. Scenarios that resulted in a >20% reduction in the ICER included 100% PFS-OS surrogacy, use of alternative sources for PPS and second-line OS distribution, and the inclusion of RDI. Conversely, changing the source of ABE-NSAI PFS treatment effect, PPS utility source, and the distribution of TTP extrapolation resulted in >20% increase in the ICER; however, these scenarios were considered unlikely due to model fit, appraisal committee preference, and clinical opinion, respectively.

Model estimates of PFS were greater for ABE-NSAI relative to PAL-NSAI and RIBO-NSAI, resulting in a greater QALY gain. PAL-NSAI and RIBO-NSAI were both associated with higher total costs than ABE-NSAI, which was predominantly driven by the shorter time on treatment associated with ABE-NSAI.

Generalisability of the analysis

The economic evaluation is based on the patient population from the MONARCH 3 trial, which may be considered representative of advanced HR+/HER2− ABC patients receiving ET as an initial treatment in this setting in the UK, thus meeting the patient population specified in the final scope. The model included comparators deemed to be relevant to the UK as per the scope, and further included later lines of therapy that were selected based on a recent study[94] that reviewed the medical records of HR+/HER2− breast cancer patients in the UK. As per the NICE reference case, the analysis was conducted from an NHS and PSS perspective.

Strengths of the economic evaluation

The state transition approach with a ‘fixed pay-off’ for post-progression selected for this analysis reflects the treatment pathway followed by patients with HR+/HER2− ABC in the UK, which comprises multiple lines of therapy. Given the immaturity of OS data from the MONARCH 3 trial, and the availability of mature PFS data from the MONARCH 2 trial for patients receiving second-line treatment following disease progression, the explicit modelling of second-line therapy to calculate the post-progression ‘pay-off’ provided a more robust basis from which to extrapolate outcomes over a lifetime horizon.

Furthermore, learnings gained from the prior NICE appraisals of PAL-NSAI and RIBO-NSAI were explicitly taken into consideration in the design of the model, enabling incorporation of committee-preferred inputs and assumptions, such as the committee’s preferred value for PFS-OS surrogacy and post-progression utility values.

A large number of model inputs (clinical utility and resource use) were taken from the methodologically robust MONARCH 3 and MONARCH 2 trials, and parameter uncertainty was thoroughly explored through a PSA and a range of DSAs.

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.[158] The 5L data captured in both MONARCH 3 and 2 was mapped to the EQ-5D-3L value set in the base case analyses and DSAs.

Limitations of the economic evaluation

The immaturity of the MONARCH 3 OS data precluded its use to inform overall patient survival in the model. As described in Section B.3.3.7, it was necessary to indirectly estimate OS in the model by making assumptions on the proportion of PFS gain that translates into OS gain. A value of 27.5% PFS-OS surrogacy was assumed in the model base case, to align with committee preferences in TA495 and TA496.[54, 53] However, as described above, discussion during prior NICE appraisals has highlighted the relationship between PFS and OS as highly uncertain, with clinicians confirming that improved PFS is highly likely to confer improvements in OS, but that the precise extent of this translation is unclear. This is largely due to the lack of studies in this patient population in which OS data have reached maturity. Accordingly, in order to explore this uncertainty a scenario analysis was performed where by 100% PFS–OS surrogacy was assumed. It is anticipated that the true value of surrogacy is likely to lie somewhere between 27.5% and 100%.

Additional uncertainty is introduced into the model through incorporation of treatment effects from the NMA, which were associated with a number of limitations, as described below:

- OS data from a number of trials included in the NMA were immature at the time of the analysis. Median OS was not reached in at least one arm: MONARCH 3 (ABE-ANAS/LTZ vs. ANAS/LTZ), MONALEESA-2 (RIBO-ANAS/LTZ vs. ANAS/LTZ), and PALOMA 2 (PAL-NAS/LTZ), which is likely to have introduced substantial uncertainty into the treatment effects for OS.
- Heterogeneity between the patient populations included in the MONARCH 3 and the comparator trials (MONALEESA-2, PALOMA 1/TRIO-18 and PALOMA-2) was observed with regards to the required DFI following adjuvant therapy, the proportion of patients with visceral involvements and the site of disease.

Acquisition costs were a main driver of cost-effectiveness in the model and required estimation of the TTD for each of the comparators. TTD for the comparators outside the MONARCH 3 trial was informed by the relative difference in median values of TTD reported in trial publications. This was dependent on the trial data used and required an assumption to be made that the relative difference was constant over time.

Summary of the cost-effectiveness evaluation of abemaciclib plus NSAI

- A *de novo* cost-utility analysis was undertaken to assess the cost-effectiveness of abemaciclib plus NSAI for the treatment of women with advanced HR+/HER2− locoregionally recurrent or metastatic breast cancer who have had no prior systemic therapy, relative to palbociclib and ribociclib, both in combination with an NSAI.
- ABE-NSAI accrued a greater number of life years (LYs) and QALYs compared to both PAL-NSAI and RIBO-NSAI. ABE-NSAI was further associated with lower costs versus PAL-NSAI and RIBO-NSAI, and therefore dominated both interventions in the base case.
- For the purposes of validation, cost-effectiveness results for ABE-NSAI versus NSAI were also presented; ABE-NSAI was associated with an incremental cost-effectiveness ratio (ICER) of £250,065 per QALY versus NSAI.
- In the scenario analyses, the economic results were largely stable when varying model assumptions, with consistent ICER estimates, demonstrating the robustness of the model. The PSA demonstrated that there is an 82% chance of ABE-NSAI being cost-effective at a threshold of £30,000 per QALY.
- In conclusion, the economic analysis found abemaciclib plus NSAI to be associated with a clinical benefit, as measured by LYs and QALYs, relative to the comparators defined by the scope of this submission, palbociclib and ribociclib plus NSAI.

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Single technology appraisal

Abemaciclib with an aromatase inhibitor for untreated advanced HR-positive, HER2-negative breast cancer ID1227

Appendix of with-PAS Cost-Effectiveness Results

September 2018

File name	Version	Contains confidential information	Date
NICE Abemaciclib plus NSAI Appendix of with-PAS Cost-Effectiveness Results	Final	Yes	4th September 2018

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Abbreviations

Abbreviation	Definition
ABE	Abemaciclib
EQ-5D-3L	EuroQol-5 Dimensions-3 Level
EQ-5D-5L	EuroQol-5 Dimensions-5 Level
FUL	Fulvestrant
LYG	Life years gained
QALY	Quality adjusted life year
ICER	Incremental cost-effectiveness ratio
NMA	Network meta-analysis
NSAI	Non-steroidal aromatase inhibitor
OS	Overall survival
PAL	Palbociclib
PAS	Patient access scheme
PFS	Progression free survival
PSA	Probabilistic sensitivity analysis
RIBO	Ribociclib
TTD	Time to treatment discontinuation
TTP	Time to progression

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Abemaciclib list and with-PAS prices

The list and with-PAS prices for abemaciclib (ABE) are presented in Table 1.

Table 1: Abemaciclib list and with-PAS prices

UK approved name and brand name	Abemaciclib (Verzenios™)
List price	List price of abemaciclib: £[redacted] per 28-day cycle
Patient access scheme (PAS)	PAS price of abemaciclib: £[redacted] per 28-day cycle

Abbreviations: PAS: patient access scheme

Base-case results

Base-case results for the cost-effectiveness analysis incorporating the patient access scheme (PAS) for ABE are presented in Table 2.

[redacted].

Table 2: Base case cost-effectiveness results (with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ABE-NSAI	£[redacted]	5.08	3.29	[redacted]	-	-	[redacted]	[redacted]
PAL-NSAI	£145,266	5.03	3.23	[redacted]	–0.04	–0.065	[redacted]	[redacted]
RIBO-NSAI	£148,170	5.02	3.22	[redacted]	–0.02	–0.003	[redacted]	[redacted]

Abbreviations: ABE: abemaciclib; ICER: incremental cost-effectiveness ratio; LYG: life years gained; ABE: abemaciclib; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; QALYs: quality-adjusted life years; RIBO: ribociclib

Sensitivity analyses

Probabilistic sensitivity analysis

With-PAS results of the probabilistic sensitivity analysis (PSA) for the comparison of ABE-NSAI versus PAL-NSAI and RIBO-NSAI are summarised in Table 3.

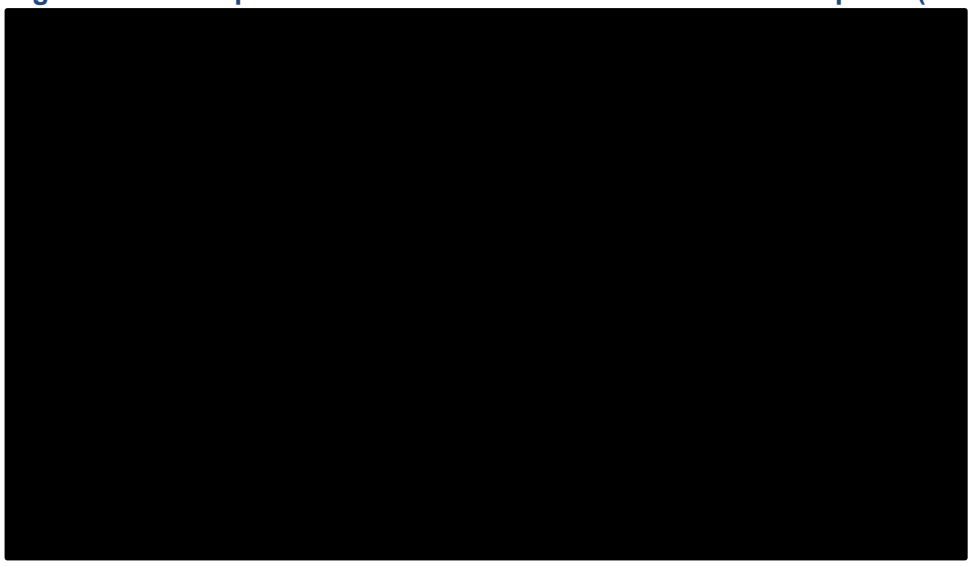
Table 3: Probabilistic cost-effectiveness results (with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
ABE-NSAI	[redacted]	5.28	3.40	[redacted]	-	-	[redacted]	[redacted]
PAL-NSAI	£142,505	5.17	3.30	[redacted]	–0.11	–0.097	[redacted]	[redacted]
RIBO-NSAI	£146,489	5.29	3.37	[redacted]	0.11	0.073	[redacted]	[redacted]

Abbreviations: ABE: abemaciclib; ICER: incremental cost-effectiveness ratio; LYG: life years gained; ABE: abemaciclib; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; QALYs: quality-adjusted life years; RIBO: ribociclib

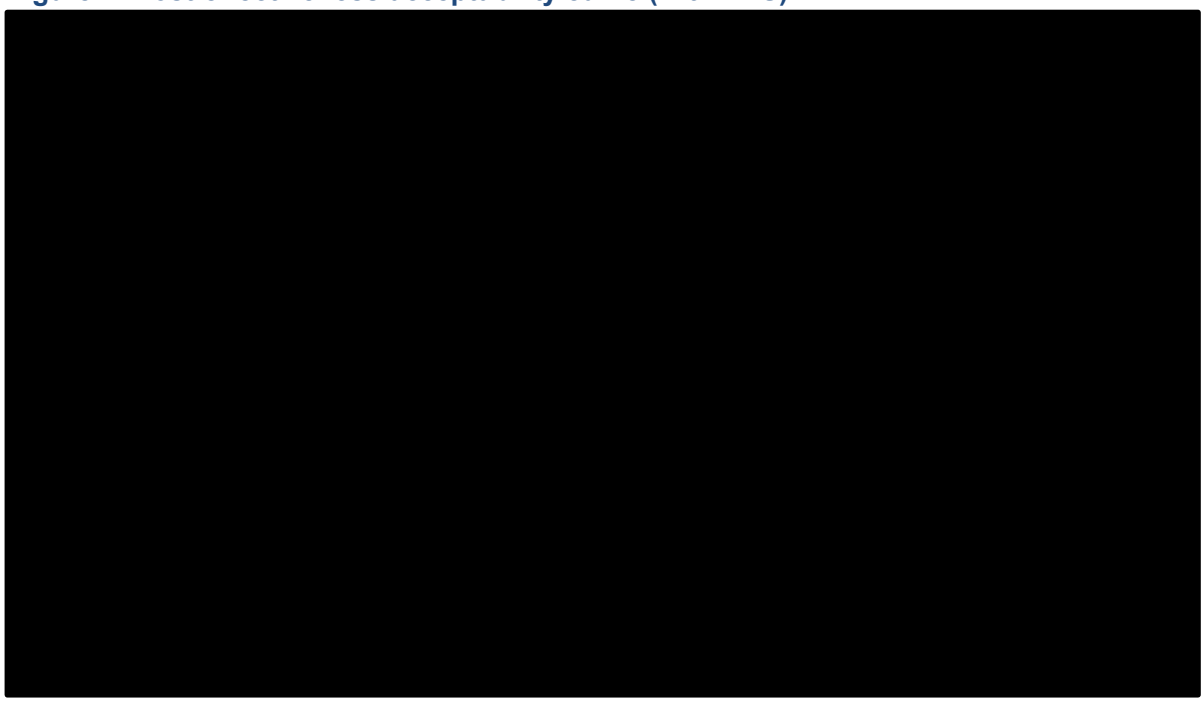
A scatter plot of the joint distribution of incremental costs and incremental QALYs from the PSA (with PAS) is shown in Figure 1, and the cost effectiveness acceptability curves and frontier corresponding with the above outputs (with PAS) are presented in Figure 2 and Figure 3, respectively.

Figure 1. Scatter plot of simulations on the cost-effectiveness plane (with PAS)



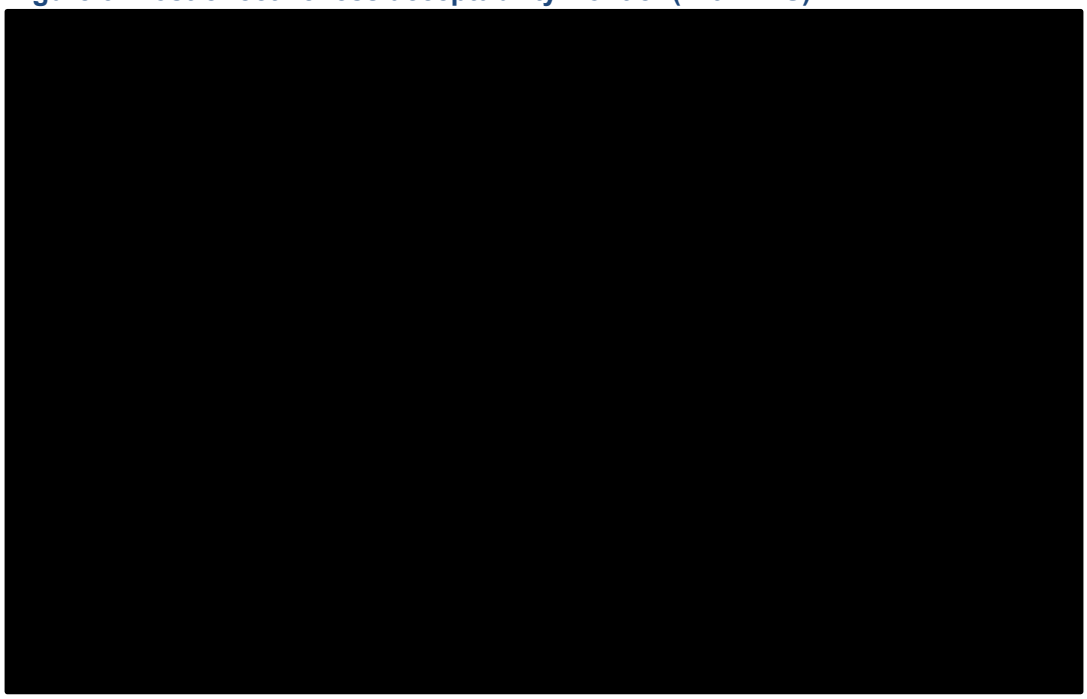
Abbreviations: ABE: abemaciclib; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; QALY: quality adjusted life year; RIBO: ribociclib

Figure 2. Cost-effectiveness acceptability curve (with PAS)



Abbreviations: ABE: abemaciclib; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; RIBO: ribociclib

Figure 3. Cost-effectiveness acceptability frontier (with PAS)



Abbreviations: ABE: abemaciclib; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; RIBO: ribociclib

The probability of each comparator being cost effective at a willingness to pay threshold of £30,000 per QALY is presented in Table 4. At a willingness to pay threshold of £30,000 per QALY, ABE-NSAI (with-PAS) had a [redacted] probability of being cost-effective.

Table 4. Probability of cost-effectiveness (with PAS)

Intervention	Probability of cost-effectiveness at £30,000 per QALY
ABE-NSAI	[redacted]
PAL-NSAI	[redacted]
RIBO-NSAI	[redacted]

Abbreviations: ABE: abemaciclib; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; QALY: quality adjusted life year; RIBO: ribociclib

Deterministic scenario analysis

Deterministic scenario analyses were conducted to explore the impact of assumptions that were included in the base case analysis. A description of each scenario analysis and the corresponding with-PAS results are presented in Table 5.

Table 5. Deterministic scenario analysis results (with PAS)

Scenario	Base case value	Scenario	ICER			
			ABE+NSAI	NSAI*	PAL+NSAI	RIBO+NSAI
Base-case	N/A	N/A	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate costs and benefits	3.50%	0.00%	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate costs and benefits	3.50%	6.00%	[redacted]	[redacted]	[redacted]	[redacted]
Source of ABE-NSAI treatment effects for PFS	Joint model (MONARCH 3)	NMA	[redacted]	[redacted]	[redacted]	[redacted]
Interval censoring adjustment	Interval censoring adjusted analysis	Unadjusted analysis	[redacted]	[redacted]	[redacted]	[redacted]
Covariate adjustment	Interval censoring adjusted analysis	Covariate and interval censoring adjusted analysis	[redacted]	[redacted]	[redacted]	[redacted]
Distribution for extrapolating TTP (scenario 1)	Exponential	Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Distribution for extrapolating TTP (scenario 2)	Exponential	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Distribution for extrapolating second-line PFS (scenario 1)	Exponential	Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Distribution for extrapolating second-line PFS (scenario 2)	Exponential	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Distribution for extrapolating second-line OS (scenario 1)	Exponential with CONFIRM data extrapolation	Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Distribution for extrapolating second-line OS (scenario 2)	Exponential with CONFIRM data extrapolation	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Distribution for extrapolating second-line OS (scenario 3)	Exponential with CONFIRM data extrapolation	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Distribution for extrapolating first-line TTD (scenario 1)	Gamma	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Distribution for extrapolating first-line TTD (scenario 2)	Gamma	Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Distribution for extrapolating first-line TTD (scenario 3)	Gamma	Exponential	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Base case value	Scenario	ICER			
			ABE+NSAI	NSAI*	PAL+NSAI	RIBO+NSAI
Distribution for extrapolating second-line TTD (scenario 1)	Exponential	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Distribution for extrapolating second-line TTD (scenario 2)	Exponential	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
HRs for estimating second-line TTD	Versus FUL based on median ToT	Versus second-line PFS	[redacted]	[redacted]	[redacted]	[redacted]
Utility model	Overall	Treatment-specific	[redacted]	[redacted]	[redacted]	[redacted]
PPS utility source	Lloyd, 2006	MONARCH 2	[redacted]	[redacted]	[redacted]	[redacted]
Second-line PFS utility source	TA496	MONARCH 2	[redacted]	[redacted]	[redacted]	[redacted]
PPS hospital length of stay source	MONARCH 2	MONARCH 3	[redacted]	[redacted]	[redacted]	[redacted]
Relative dose intensity	OFF	ON	[redacted]	[redacted]	[redacted]	[redacted]
PFS1 utility value	MONARCH 3	Equal to PFS in second-line treatment	[redacted]	[redacted]	[redacted]	[redacted]
Source of clinical outcomes in PPS	MONARCH 2	BOLERO-2	[redacted]	[redacted]	[redacted]	[redacted]
Apply PFS–OS surrogacy	Yes (27.5%)	No (100%)	[redacted]	[redacted]	[redacted]	[redacted]
PFS 1 utility source	EQ-5D-3L (crosswalk)	EQ-5D-5L	[redacted]	[redacted]	[redacted]	[redacted]
Management of diarrhoea	Loperamide	Hospitalisation and loperamide	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 3L: 3 level; 5L: 5 level; ABE: abemaciclib; EQ-5D: EuroQoL-5 Dimensions; FUL: fulvestrant; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; NMA: network meta-analysis; NSAI: non-steroidal aromatase inhibitor; OS: overall survival; PAL: palbociclib; PFS: progression-free survival; PPS: post-progression survival; RIBO: ribociclib; TTD: time to treatment discontinuation; TTP: time to progression

[redacted]

Validation

Comparison to PAL-NSAI and RIBO-NSAI NICE appraisals

Within their respective NICE appraisals, PAL-NSAI and RIBO-NSAI were each compared to NSAI in their cost-effectiveness analyses.[1, 2] RIBO and PAL each have a PAS in place, and with-PAS cost-effectiveness results are redacted from the respective NICE appraisals for each drug. A direct comparison versus the with-PAS ABE results therefore cannot be made here, however, the cost-effectiveness results including NSAI are nevertheless presented in Table 6.

Table 6. ABE-NSAI versus NSAI base case cost-effectiveness results (with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
NSAI	[redacted]	4.86	3.00	[redacted]	-	-	[redacted]
ABE-NSAI	[redacted]	5.08	3.29	[redacted]	0.21	0.29	[redacted]

Abbreviations: ABE: abemaciclib; ICER: incremental cost-effectiveness ratio; LYG: life years gained; NSAI: non-steroidal aromatase inhibitor; QALYs: quality-adjusted life years

References

1. NICE. Palbociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer [TA495]. Available at: https://www.nice.org.uk/guidance/ta495 (Accessed 27.02.18). 2017.
2. NICE. Ribociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer [TA496]. Available at: https://www.nice.org.uk/guidance/ta496 (Accessed 27.02.18). 2017.

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Single technology appraisal

Abemaciclib with an aromatase inhibitor for untreated advanced hormone-receptor positive, HER2-negative breast cancer [ID1227]

Dear James,

The Evidence Review Group, Southampton Health Technology Assessments Centre, and the technical team at NICE have looked at the submission received on 19 June 2018 from Eli Lilly. 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 Wednesday 25 July 2018. Your response and any supporting documents should be uploaded to 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 [redacted] in turquoise, and all information submitted as [redacted] 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 Thomas Feist, Project Manager (Thomas.Feist@nice.org.uk).

Yours sincerely

Joanna Richardson
Technical Adviser – Appraisals
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Encl. checklist for confidential information

Section A: Clarification on effectiveness data

General questions

A1. Please define what is meant by “locoregionally recurrent” breast cancer and confirm whether this potentially excludes any people with advanced breast cancer.

MONARCH 3 trial

A2. How many UK patients were randomised in the trial? (please provide numbers by trial arm).

A3. Please provide clarification on the reasons for discontinuation of treatment (n, %) per arm for MONARCH 3. It appears that the majority of discontinuations were due to progressed disease or adverse events, but the number of patients discontinuing for these reasons does not add up to the total number of discontinuations, suggesting there were other reasons for discontinuation or missing data on reasons for discontinuation (Appendix D p.106).

A4. Health related quality of life, company submission (CS) p.52, 1st paragraph: please clarify why completion rates were relatively low in cycle 22? [redacted]

A5. **Priority question.** It is stated that patient crossover was not allowed in the MONARCH 3 trial. Patients were allowed to discontinue either abemaciclib/placebo or NSAI and continue the other drug as monotherapy. How many patients in each arm discontinued each drug and received monotherapy? Did patients receive any other non-study treatments after discontinuation of study drugs (e.g. chemotherapy)? We note from the CSR (Table JPBM.14.21. that 29 patients were censored for PFS for receiving subsequent anticancer treatment). Please provide full details of the treatments given.

A6. Appendix E mentions some statistically significant interactions detected for certain patient sub-groups (race and geographic region). Please can you describe what interaction tests were performed. Was any adjustment made for multiple testing among the subgroup analyses? If so please provide details.

A7. The CS, page 38 describes the censoring criteria that were used for PFS. What was the rationale for the choice of these criteria? (e.g. study investigators’ choice, or FDA/EMA/regulator requirement?).

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A8. Please provide the rates of surgery in those with locoregionally recurrent disease by treatment arm and the respective rates with residual disease post surgery. Please also clarify if all of these patients had new baseline tumour assessments?

A9. **Priority question**. Please can you provide an unredacted copy of the MONARCH 3 study protocol (the version available as supplemental material in the Journal of Clinical Oncology is redacted).

A10. **Priority question**. Please can you supply the MONARCH 3 Statistical Analysis Plan. This is mentioned in the CSR as being available in a separate appendix.

Network meta-analysis (MONARCH 3 aligned)

A11. We note a discrepancy between CS table 14, and CS Appendix D.1.3 Table 16. CS table 14 lists a total of 18 studies used in the NMA, including 15 that provided OS data. CS Appendix D.1.3 Table 16 lists 17 studies of which 14 provided OS data. There are other discrepancies between these tables for the number of studies with data on ORR, CBR and CR. It appears that the study by Mila-Santos 2003 is included in CS table 14, but not in CS Appendix D.1.3 Table 16. Please provide an explanation for this discrepancy and confirm which of the two tables is correct.

A12. The NMA results presented are relative to aromatase inhibitor monotherapy. Please provide NMA results for the indirect comparison of ABE+NSAI versus the comparators in the scope of the appraisal (i.e. palbociclib and ribociclib).

A13. The CS lists potential sources of homogeneity and heterogeneity across the trials in the NMA (section B.2.9.3), what might the effects of these be on results? Please provide a fuller discussion.

a. Please clarify whether investigator or committee PFS was used for the trials included in NMA?

A14. **Priority question**. We note from Appendix D p.28, p.30-31, and p.100-101 that the study population eligibility criteria for the NMA are broader than the patient population enrolled in the MONARCH 3 trial. Appendix D Table 19 tabulates a limited number of baseline patient characteristics from the trials in the NMA. In order for us to fully judge the extent of clinical heterogeneity between the trials please provide the proportions of patients (n/%, by treatment arm) in each trial (where reported) by: HER2 status, HR status; visceral involvement; liver metastases; bone metastases; different disease free intervals (however defined by the studies); different disease settings (e.g. de novo metastatic, recurrent metastatic etc); measureable disease; prior therapy received in the neoadjuvant setting.

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A15. Please provide more information about the Bayesian methods used to conduct the NMA, including the number of iterations used for burn in and inferences, and the methods for assessing convergence.

A16. Was a consistency assessment performed for direct and indirect evidence included in the NMAs? If so, please describe which procedures were followed and what the results were.

A17. **Priority question**. Please can you report the Deviance Information Criterion (DIC) values that were generated to chose between fixed effect and random effects NMA models. Further, where the results of random / fixed effect model NMAs have been provided in the CS for an outcome please supply the corresponding random / fixed effect model results, to permit comparison between random and fixed effects for each outcome. As a minimum we would like to see the random effects NMA results for PFS (fixed effects are presented in the CS – Figure 10).

A18. Please could you supply the OpenBUGS code that was used to run the MONARCH 3 and MONARCH 2 aligned NMA.

A19. **Priority question**. Please can you provide the Kaplan-Meier data, the log cumulative hazard plots and the Schoenfeld residual plots that were visually inspected to ascertain whether the proportional hazards assumption holds in the NMA (CS Appendix D.1.5). Please also supply the results of the weighted residual test based on standardised Schoenfeld residuals.

A20. It is stated in CS Appendix D.1.5 that the HR, median and proportion event-free data, as estimated from individual patient data generated by digitised Kaplan-Meier graphs, were checked against the published estimates to ensure internal validity. Please can you comment on the results of this checking, and whether there was good internal validity. Please could you supply the estimated HR, median and proportion event-free data for PFS and OS so that we can independently check these against the published estimates.

Network meta-analysis (MONARCH 2 aligned)

A21. **Priority question.** The MONARCH 2 aligned NMA appears to play a pivotal role in the estimation of survival in the economic model. We therefore need to critically appraise it. However, only limited information is provided on it, in Appendix N. Please can you provide the same level of detail on this NMA as is currently provided in the submission on the MONARCH 3 aligned NMA, plus the additional information we have requested above for that NMA (e.g. full bibliographic details of the 18 studies included, plus tabulated baseline characteristics of patients, risk of bias

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assessments, network diagrams, programming code, discussion of clinical heterogeneity, etc).

Section B: Clarification on cost-effectiveness data

B1. We note that the economic model includes an alternative 4-state model structure, but that this has not been described in the CS and it is not used for scenario analysis or in validation of the main model results. Please can you explain the rationale for developing the 4-state model, and justify why you have not reported the methods or results.

B2. **Priority question.** Appendix M.2 presents estimates of parameter values for some selected survival distributions that are used in the model. However, others are omitted. We consider it likely that the committee will wish to consider alternative survival distributions and their impact on the sensitivity of the cost-effectiveness results. Please can you provide a revised version of the model including extrapolations of the survival curves for all six fitted distributions (exponential, Weibull, Gompertz, lognormal, log-logistic and generalised gamma) for each survival curve of interest: first-line TTP (adjusted and unadjusted for interval censoring); first-line TTD; second-line PFS (adjusted and unadjusted for interval censoring; second-line TTD; and second-line OS.

B3. Please could you add a one-way deterministic sensitivity analysis with results summarised using tornado diagrams. Committee members find this helpful in understanding the impact of uncertainty over individual model parameters and identifying key model drivers.

B4. **Priority question.** The ERG needs to fully understand and replicate the calibration method. It appears that the calibration factors for OS adjustment are only entered into the model as inputs and referenced within the model as “Calibration exercise”. Please provide formulas and steps showing how the calibration factors were derived or alternatively, provide the referenced calibration exercise.

B5. **Priority question.** The calibration factors are entered into the model as single point estimates with no estimates of uncertainty. The CS includes a scenario without the calibration process, but does not include any sensitivity analysis around these values. We think it is important to be able to reflect uncertainty using one-way sensitivity analysis. Please could you provide a measure of variation/variance or confidence interval around these calibration factors?

B6. In the model, calibration factors were applied to the OS as well as PFS curves in the three state PP payoff. As we understand it, the calibration factors are required to reflect the gain in OS. Please further explain why they are also applied to the PFS curves.

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Section C: Textual clarifications and additional points

C1. Reference 94 (Kurosky et al 2015) is a conference abstract. The submission appears to use a greater level of information than is provided in this abstract. We assume that a more detailed publication of this study was used by the company. If so, please provide a full citation and supply a copy of the report. We note that a 2017 publication of this study is now available: Kurosky, S. K., Mitra, D., Zanotti, G., & Kaye, J. A. (2017). Treatment Patterns and Outcomes of Patients With Metastatic ER(+)/HER-2(-) Breast Cancer: A Multicountry Retrospective Medical Record Review. Clin Breast Cancer. doi:10.1016/j.clbc.2017.10.008

C2. CS Appendix D.1.2, Table 9, page 28, under 'Exclusion criteria' ">10% of whole study population are currently receiving….". Should the symbol be "<" as on page 31?

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25th July 2018

Single technology appraisal

Abemaciclib with an aromatase inhibitor for untreated advanced hormone-receptor positive, HER2-negative breast cancer [ID1227]

Dear Joanna,

Thank you for the opportunity to respond to the clarification questions posed by the Evidence Review Group, Southampton Health Technology Assessments Centre, regarding the Eli Lilly and Company Limited (Lilly) submission for Verzenios (abemaciclib) [ID1227]. Please find below responses to the clarification questions. In summary Lilly has provided a response to all 29 questions posed, however Lilly would like to highlight the following:

- Lilly has agreed to provide the full SLR and NMA reports for the MONARCH 2 indication [AIC], as well as the Statistical Analysis Plan and study protocol documents for the MONARCH 3 study [CIC]. These materials should be treated as confidential as indicated.

- Furthermore, additional data have been provided within the responses to the clarification questions, some of which are also AIC. These data have been highlighted using underlining and yellow highlighting. Any figures that are AIC are indicated by a yellow outline. A confidentiality checklist is also enclosed, which describes the nature of these data.

If you require any further information, please let me know.

Yours sincerely,
James

James Parnham BPharm (Hons)
Head of HOHTA, Lilly UK

Abbreviations

Abbreviation	Definition
ABE	Abemaciclib
AIC	Academic in confidence/Akaike information criteria (in the context of modelling)
ANAS	Anastrozole
BIC	Bayesian information criterion
CBR	Clinical benefit rate
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response
CrI	Credible interval
CSR	Clinical study report
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
FDA	Food and Drug Administration
EMA	European Medicines Agency
EORTC-QLQ/BR	European Organization for Research and Treatment of Cancer Quality of Life Questionnaires-Core/Breast Cancer Specific
EPAR	European Public Assessment Reports
EQ-5D	EuroQol 5-Dimension
ET	Endocrine therapy
ER	Endocrine receptor
ERG	Evidence Review Group
FE	Fixed effects
FUL	Fulvestrant
HER2	Human epidermal growth factor receptor 2
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
INV	Investigator
IPD	Individual patient data
IRC	Independent Review Committee
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KM	Kaplan-Meier
LTZ	Letrozole
MGA	Megestrol acetate
NMA	Network meta-analysis
NR	Not reported
NSAI	Non-steroidal aromatase inhibitor
ORR	Overall response rate
OS	Overall survival
PAL	Palbociclib
PBO	Placebo
PFS	Progression-free survival
PgR	Progesterone receptor

PPS	Post-progression survival
PR	Progesterone receptor
PSA	Probabilistic sensitivity analyses
QALY	Quality-adjusted life years
RE	Random effects
RIBO	Ribociclib
SLR	Systematic literature review
STA	Single Technology Appraisal
TMX	Tamoxifen
TOR	Toremifene
TSD	Technical Support Document
TTD	Time to treatment discontinuation
TTP	Time to progression
UK	United Kingdom

Section A: Clarification on effectiveness data

General questions

A1. Please define what is meant by "locoregionally recurrent" breast cancer and confirm whether this potentially excludes any people with advanced breast cancer.

Locoregionally recurrent breast cancer is defined as the local or regional recurrence of breast cancer,[1] where cancer cells are identified in the same breast as the original tumour (local) or in nearby lymph nodes (regional).[2]

Patients included in the MONARCH 3 trial were required to have locoregionally recurrent breast cancer not amenable to resection or radiation therapy with curative intent, or metastatic disease.[3] This eligibility criterion thus aligns with the definition of 'advanced breast cancer' provided by NICE in the final scope for this appraisal,[4] which states that "cancer is '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."

MONARCH 3 trial

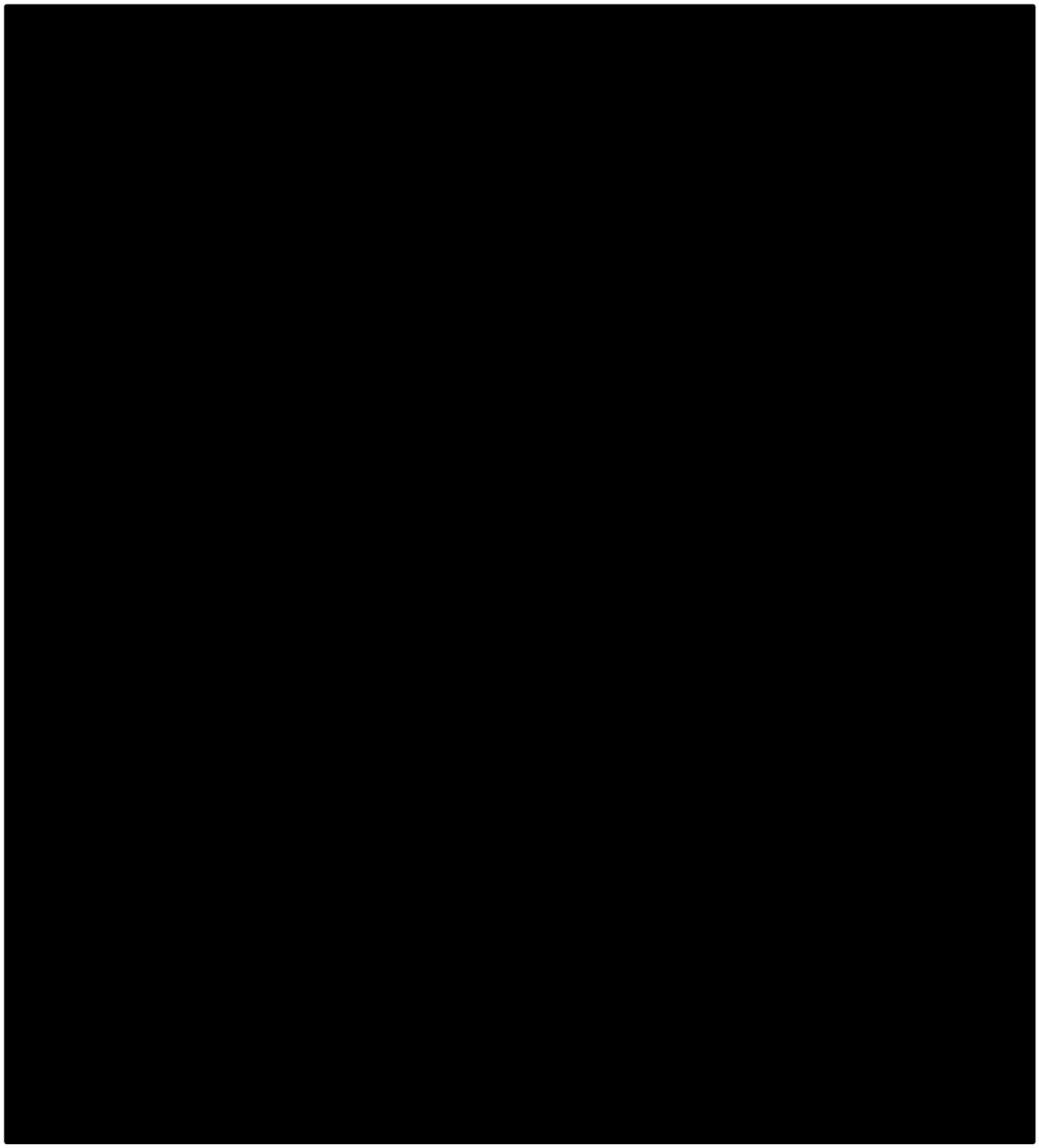
A2. How many UK patients were randomised in the trial? (please provide numbers by trial arm).

[redacted] patients from the UK were randomised in the MONARCH 3 trial; [redacted] were allocated to the abemaciclib plus NSAI arm and [redacted] to the placebo plus NSAI arm (Table JPBM.14.1, p242).[1]

A3. Please provide clarification on the reasons for discontinuation of treatment (n, %) per arm for MONARCH 3. It appears that the majority of discontinuations were due to progressed disease or adverse events, but the number of patients discontinuing for these reasons does not add up to the total number of discontinuations, suggesting there were other reasons for discontinuation or missing data on reasons for discontinuation (Appendix D p.106).

The full CONSORT diagram at the final PFS analysis, comprising all reasons for patient discontinuation in MONARCH 3, is presented in Figure 1.

Figure 1. CONSORT diagram of patient disposition at the time of the final analysis of PFS in MONARCH 3



Abbreviations: CONSORT: Consolidated Standards of Reporting Trials; ITT: intent-to-treat; NSAI: non-steroidal aromatase inhibitor; PFS: progression-free survival.
Source: MONARCH 3 CSR Addendum P14.[5]

A4. Health related quality of life, company submission (CS) p.52, 1st paragraph: please clarify why completion rates were relatively low in cycle 22? [redacted]

Lilly would like to highlight that the wording provided in the submission regarding questionnaire completion rates was unclear. Specifically, the cycle 22 completion rate of [redacted]% relates to the completion rate for the EQ-5D scale in the placebo plus NSAI treatment arm. A detailed description of the questionnaire completion rates at cycle 22 in both treatment arms of MONARCH 3 can be found below.

At cycle 22, the questionnaire completion rates for the abemaciclib plus NSAI treatment arm were [redacted], [redacted] and [redacted] for the EORTC QLQ-C30 (n=[redacted]), EORTC QLQ-BR23 (n=[redacted]) and EQ-5D scales (n=[redacted]), respectively. Between [redacted] and [redacted] patients did not complete each of the aforementioned scales at this visit. The reasons provided for not administering the scales were 'study site failed to administer' and 'other'. Reasons for non-administering the scales classified as 'other' are unavailable.[1]

The completion rates in the placebo plus NSAI treatment arm at cycle 22 were [redacted], [redacted] and [redacted] for the EORTC QLQ-C30 (n=[redacted]), BR23 (n=[redacted]) and EQ-5D scales (n=[redacted]), respectively. Between [redacted] and [redacted] patients in the placebo plus NSAI treatment arm did not complete each of the aforementioned scales at this visit. The reasons provided for not administering the scales were 'study site failed to administer' and 'other'.[1] Reasons for non-administering the scales classified as 'other' are unavailable.[1]

Overall, across questionnaires and time points, patient completion rate was high and balanced between treatment arms, and the lower completion rates observed at cycle 22 in the placebo plus NSAI arm were based on a small sample size.

A5. **Priority question.** It is stated that patient crossover was not allowed in the MONARCH 3 trial. Patients were allowed to discontinue either abemaciclib/placebo or NSAI and continue the other drug as monotherapy. How many patients in each arm discontinued each drug and received monotherapy? Did patients receive any other non-study treatments after discontinuation of study drugs (e.g. chemotherapy)? We note from the CSR (Table JPBM.14.21. that 29 patients were censored for PFS for receiving subsequent anticancer treatment). Please provide full details of the treatments given.

Discontinuation to monotherapy

A summary of treatment discontinuation in MONARCH 3 at the final PFS analysis, including details on the number of patients who received monotherapy abemaciclib/placebo or NSAI treatment, is presented in Table 1.

Table 1. Summary of treatment discontinuation in MONARCH 3, including discontinuation to monotherapy

	Abemaciclib + NSAI N=328	Placebo + NSAI N=165
Discontinued study treatment	[redacted]	[redacted]
Discontinued abemaciclib/placebo and NSAI at the same time	[redacted]	[redacted]
Discontinued abemaciclib/placebo prior to NSAI	[redacted]	[redacted]
Discontinued NSAI prior to Abemaciclib/Placebo	[redacted]	[redacted]

Abbreviations: NSAI: non-steroidal aromatase inhibitor.
Source: Lilly Data on File.[6]

Receipt of non-study treatments post-discontinuation

A summary and full listing of treatment post-discontinuation is provided in the CSR addendum (Section 5.4.3.4.1, page 30).[5] More patients remained on the abemaciclib plus NSAI arm than on the placebo plus NSAI arm at the time of the analysis ([redacted]% vs [redacted]%). The percentage of patients who received post-discontinuation therapies was higher in the placebo plus NSAI arm than in the abemaciclib plus NSAI arm ([redacted]% in the abemaciclib plus NSAI arm vs [redacted]% in the placebo plus NSAI arm). The most common post-discontinuation systemic therapies received were endocrine therapy ([redacted] patients [[redacted]%], predominantly fulvestrant [[redacted]%]) and chemotherapy ([redacted] patients [[redacted]%], predominantly paclitaxel [[redacted]%]). Of interest, [redacted] patients ([redacted]%) in the abemaciclib plus NSAI arm and [redacted] patients ([redacted]%) in the placebo plus NSAI arm received palbociclib as post-discontinuation systemic therapy, and [redacted] patients ([redacted]%) in the abemaciclib plus NSAI arm and [redacted] patients ([redacted]%) in the placebo plus NSAI arm received everolimus. No patients received ribociclib.[5]

PFS censoring for patients receiving anti-cancer treatment

Table JPBM.14.21. from the CSR was based on the interim data analysis.[1] At the final PFS data-cut, a total of [redacted] patients received anticancer therapy without documented progression. Treatments received by these [redacted] patients specifically are not available, however, Table JPBM.5.8 from the CSR addendum shows that of the patients who subsequently received chemotherapy as post-discontinuation therapy (n=[redacted], [redacted]% of all patients), [redacted]% received paclitaxel and [redacted]% received capecitabine.[5]

In order to assess the impact of those patients starting an anticancer therapy, a sensitivity analysis of PFS was performed where the date of new anticancer therapy was considered as an event. At the final PFS analysis, events were experienced by [redacted] patients ([redacted]%) in the abemaciclib plus NSAI arm and [redacted] patients ([redacted]%) in the placebo plus NSAI arm. Median time to progression, death, or starting new anticancer therapy was [redacted] months in the abemaciclib plus NSAI arm and [redacted] months in the placebo plus NSAI arm (HR = [redacted] [95% CI: [redacted]], p=[redacted]). These results were consistent with the primary PFS analysis of MONARCH 3.[6]

A6. Appendix E mentions some statistically significant interactions detected for certain patient sub-groups (race and geographic region). Please can you describe what interaction tests were performed. Was any adjustment made for multiple testing among the subgroup analyses? If so please provide details.

The p-value for the interaction term was derived from a Cox model with the treatment arm, the subgroup variable and treatment by subgroup interaction term as factors. No adjustment for multiplicity was performed.

A7. The CS, page 38 describes the censoring criteria that were used for PFS. What was the rationale for the choice of these criteria? (e.g. study investigators' choice, or FDA/EMA/regulator requirement?).

There was no specific request from regulatory agencies regarding the censoring criteria for PFS in MONARCH 3. However, censoring rules from the US FDA regulatory guidance were followed,[7] and there were no specific censoring criteria in the available EMA guidance.[8] There were no concerns from Lilly's steering committee or principal investigators regarding the censoring criteria used for PFS in MONARCH 3.

A8. Please provide the rates of surgery in those with locoregionally recurrent disease by treatment arm and the respective rates with residual disease post-surgery. Please also clarify if all of these patients had new baseline tumour assessments?

As per the inclusion criteria for MONARCH 3, patients with locoregionally recurrent disease who were not amenable to resection or radiation therapy with curative intent were enrolled in the study.[3] For the [redacted] patients with locoregionally recurrent disease, most patients had prior breast surgery in the distant past, long before study entry ([redacted] out of [redacted] patients in the abemaciclib plus NSAI arm and [redacted] out of [redacted] patients in the placebo plus NSAI arm). All [redacted] patients had new baseline tumour assessments.[6]

A9. **Priority question**. Please can you provide an unredacted copy of the MONARCH 3 study protocol (the version available as supplemental material in the Journal of Clinical Oncology is redacted).

The MONARCH 3 study protocol has been submitted alongside this document.

A10. **Priority question**. Please can you supply the MONARCH 3 Statistical Analysis Plan. This is mentioned in the CSR as being available in a separate appendix.

The MONARCH 3 statistical analysis plan has been submitted alongside this document.

Network meta-analysis (MONARCH 3 aligned)

A11. We note a discrepancy between CS table 14, and CS Appendix D.1.3 Table 16. CS table 14 lists a total of 18 studies used in the NMA, including 15 that provided OS data. CS Appendix D.1.3 Table 16 lists 17 studies of which 14 provided OS data. There are other discrepancies between these tables for the number of studies with

data on ORR, CBR and CR. It appears that the study by Mila-Santos 2003 is included in CS table 14, but not in CS Appendix D.1.3 Table 16. Please provide an explanation for this discrepancy and confirm which of the two tables is correct.

Table 14 in the CS provides the correct number of studies included in the NMA and the number of studies that informed each of the assessed outcomes. We additionally confirm that Mila-Santos 2003 was included in the final NMA. The reason for this discrepancy is that Table 16 in CS Appendix D.1.3 was based on an in-progress version of the NMA report and was erroneously not updated in the final appendices document.

A12. The NMA results presented are relative to aromatase inhibitor monotherapy. Please provide NMA results for the indirect comparison of ABE+NSAI versus the comparators in the scope of the appraisal (i.e. palbociclib and ribociclib).

Fixed and random effects results for ABE-NSAI versus PAL-NSAI and RIBO-NSAI for PFS and OS are presented in Table 2 and Table 3, respectively.

Table 2. Fixed and random effects results for ABE-NSAI versus PAL-NSAI and RIBO-NSAI for PFS

Treatment	HR (95% credible interval) (fixed effects model)	HR (95% credible interval) (random effects model)
ABE-NSAI	Referent	Referent
PAL-NSAI	[redacted]	[redacted]
RIBO-NSAI	[redacted]	[redacted]

Abbreviations: ABE-NSAI: abemaciclib plus NSAI; PAL-NSAI: palbociclib plus NSAI; PFS: progression-free survival; RIBO-NSAI: ribociclib plus NSAI.

Table 3. Fixed and random effects NMA results for ABE-NSAI versus PAL-NSAI and RIBO-NSAI OS

Treatment	HR (95% credible interval) (fixed effects model)	HR (95% credible interval) (random effects model)
ABE-NSAI	Referent	Referent
PAL-NSAI	[redacted]	[redacted]
RIBO-NSAI	[redacted]	[redacted]

Abbreviations: ABE-NSAI: abemaciclib plus NSAI; OS: overall survival; PAL-NSAI: palbociclib plus NSAI; RIBO-NSAI: ribociclib plus NSAI.

A13. The CS lists potential sources of homogeneity and heterogeneity across the trials in the NMA (section B.2.9.3), what might the effects of these be on results? Please provide a fuller discussion.

Section B.2.9.3 of the CS lists the sources of homogeneity and heterogeneity specifically across MONARCH 3 and the trials providing data for the comparators of interest (MONALEESA-2, PALOMA 1/TRIO-18 and PALOMA-2). Homogeneity between the trials was observed for a large

number of patient characteristics; any differences between any treatment effect modifiers and prognostic variables between trials is therefore anticipated to be minimal, thus lending reliability to the NMA results.

A small number of patient characteristics were found to either vary slightly between the trials of interest or were not reported and therefore could not be assessed for heterogeneity. One patient characteristic (for which data were collected in the SLR) fell into the latter category – the proportion of patients with visceral involvement – which may be an indicator of a difference in disease severity between trials.[9] However, as described above, the greater number of characteristics found to be homogeneous (e.g. stage of disease, performance status, number of prior therapies received in the advanced setting) indicate that patient disease severity was broadly similar across trials.

Overall, the heterogeneity of PFS assessments is not considered to have had a significant impact on the conclusions made.

a. Please clarify whether investigator or committee PFS was used for the trials included in NMA?

Investigator-assessed PFS was used for all interventions included in the NMA for PFS, as committee-assessed PFS was not provided in the publications for the comparator treatments to ABE-NSAI. A summary of investigator or committee assessment for PFS in the included trials is presented in Table 4.

Table 4. Intervention and PFS assessment in the trials included in the NMA

References of trial	Trial Name	Intervention A (ITT n)	Intervention B (ITT n)	Intervention C (ITT n)	Investigator or Committee assessed
Allegra 1985[10]	-	MGA (n=65)	TMX20 (n=66)	-	Not reported
Robertson 2016[11]	FALCON	ANAS (n=232)	FUL500 (n=230)	-	Investigator
Robertson 2009[12]	FIRST	ANAS (n=103)	FUL500 (n=102)	-	Investigator
Gill 1993[13]	-	MGA (n=60)	TMX40 (n=58)	-	Not reported
Hayes 1995[14]	-	TMX20 (n=215)	TOR60 (n=221)	TOR200 (n=212)	Not reported
Howell 2004[15]	-	FUL250 (n=313)	TMX20 (n=274)	-	Not reported
Iwata 2013[16]	-	EXE (n=149)	ANAS (n=149)	-	Not reported
Milla-Santos 2001[17]	-	TOR60 (n=106)	TMX40 (n=111)	-	Not reported
Milla-Santos 2003[18]	-	ANAS (n=121)	TMX40 (n=117)	-	Not reported

Hortobagyi 2016[19]	MONALEESA-2	RIBO-LTZ (n=334)	LTZ (n=334)	-	Investigator
Goetz 2017[3]	MONARCH 3	ABE-ANAS/LTZ (n=328)	ANAS/LTZ (n=165)	-	Investigator
Mouridsen 2001[20]	-	LTZ (n=453)	TMX20 (n=454)	-	Not reported
Muss 1985[21]	-	MGA (n=69)	TMX20 (n=67)	-	Investigator
Pyrhonen 1997[22]	Nordic	TOR60 (n=214)	TMX40 (n=201)	-	Investigator
Finn 2015[23]	PALOMA-1/TRIO-18	PAL-LTZ (n=84)	LTZ (n=81)	-	Investigator
Finn 2016[24]	PALOMA-2	PAL-LTZ (n=444)	LTZ (n=222)	-	Investigator
Paterson 1990[25]	-	TMX20 (n=79)	MGA (n=77)	-	Not reported
Bonneterre 2001[26]	TARGET and North American	ANAS (n=511)	TMX20 (n=510)	-	Not reported

Abbreviations: ABE: abemaciclib; ANAS: anastrozole; EXE: exemestane; FUL: fulvestrant; ITT: intent-to-treat; KM: Kaplan-Meier; LDOX: liposomal doxorubicin; LTZ: letrozole; MGA: megestrol acetate; OS: overall survival; PAL: palbociclib; PFS: progression-free survival; RIBO: ribociclib; TMX: tamoxifen; TMX20: tamoxifen 20 mg; TMX40: tamoxifen 40 mg; TOR: toremifene; TOR 60: toremifene 60 mg; TOR 200: toremifene 200 mg.

A14. **Priority question**. We note from Appendix D p.28, p.30-31, and p.100-101 that the study population eligibility criteria for the NMA are broader than the patient population enrolled in the MONARCH 3 trial. Appendix D Table 19 tabulates a limited number of baseline patient characteristics from the trials in the NMA. In order for us to fully judge the extent of clinical heterogeneity between the trials please provide the proportions of patients (n/%, by treatment arm) in each trial (where reported) by: HER2 status, HR status; visceral involvement; liver metastases; bone metastases; different disease free intervals (however defined by the studies); different disease settings (e.g. de novo metastatic, recurrent metastatic etc); measureable disease; prior therapy received in the neoadjuvant setting.

Further data on patient baseline and disease characteristics for MONARCH 3 and each of the relevant comparator trials (MONALEESA-2, PALOMA-1/TRIO-18 and PALOMA-2) are provided below; a summary of disease receptor status, disease characteristics at baseline, and prior therapy for the study populations are presented in Table 5, Table 6 and Table 7, respectively. The number of patients with measurable disease in each treatment arm of the relevant comparator trials are available in Table 20 on page 77 of the CS Appendices D1.4.

Raw patient numbers are not available for disease-free interval for all three trials of interest. In addition, data are not available for the PALOMA-1/TRIO-18 trial for the following requested characteristics: disease setting, and prior therapy received in the neoadjuvant setting. However, inclusion criteria regarding these characteristics are summarised for all relevant comparator trials in Table 8.

Table 5. Receptor status at baseline for the trials of interest to the submission

Study	Intervention	N	ER+, PgR+ n (%)	ER+, PgR− n (%)	ER−, PgR+ n (%)	ER+ n (%)	PgR+ n (%)	HER2+ n (%)
MONALEESA-2	RIBO-LTZ	334	-	-	-	332 (99.4)	271 (81.1)	0 (0)
MONALEESA-2	LTZ	334	-	-	-	333 (99.7)	278 (83.2)	0 (0)
PALOMA-1/TRIO-18	PAL-LTZ	84	-	-	-	84 (100)	-	0 (0)
PALOMA-1/TRIO-18	LTZ	81	-	-	-	81 (100)	-	0 (0)
PALOMA-2	PAL-LTZ	444	-	-	-	444 (100)	-	0 (0)
PALOMA-2	LTZ	222	-	-	-	222 (100)	-	0 (0)
MONARCH 3	ABE-ANAS/LTZ	328	[redacted]	[redacted]	-	[redacted]	-	0 (0)
MONARCH 3	PBO-ANAS/LTZ	165	[redacted]	[redacted]	-	-*	-	-*

*HR and HER2 status was missing for one patient in the placebo plus NSAI arm.

Abbreviations: ABE: abemaciclib; ANAS: anastrozole; ER: oestrogen receptor; HER2: human epidermal growth factor-receptor; HR: hormone receptor; LTZ: letrozole; NR: not reported; PAL: palbociclib; PBO: placebo; PgR: progesterone receptor; RIBO: ribociclib.

Table 6. Patient baseline disease characteristics in the trials of interest to the submission

Study	Intervention	N	Visceral involvement, n (%)	Proportion with bone only disease, n (%)	Proportion with liver metastases, n (%)	One organ involved, n (%)	Two organs involved, n (%)	≥Three organs involved, n (%)
MONALEESA-2	RIBO-LTZ	334	197 (59)	69 (20.7)	NR	100 (29.9)	118 (35.3)	114 (34.1)
MONALEESA-2	LTZ	334	196 (58.7)	78 (23.4)	NR	117 (35)	103 (30.8)	113 (33.8)
PALOMA-1/TRIO-18	PAL-LTZ	84	37 (44)	17 (20)	NR	NR	NR	NR
PALOMA-1/TRIO-18	LTZ	81	43 (53)	12 (15)	NR	NR	NR	NR
PALOMA-2	PAL-LTZ	444	214 (48.2)	103 (23.2)	NR	138 (31.1)	117 (26.4)	189 (42.6)
PALOMA-2	LTZ	222	110 (49.5)	48 (21.6)	NR	66 (29.7)	52 (23.4)	104 (46.9)
MONARCH 3	ABE-ANAS/LTZ	328	172 (52.4)	70 (21.3)	[redacted]	96 (29.3)	76 (23.2)	154 (47)
MONARCH 3	PBO-ANAS/LTZ	165	89 (53.9)	39 (23.6)	[redacted]	47 (28.5)	42 (25.5)	75 (45.5)

Abbreviations: ABE: abemaciclib; ANAS: anastrozole; HER2: human epidermal growth factor-receptor; LTZ: letrozole; NR: not reported; PAL: palbociclib; PBO: placebo; RIBO: ribociclib.

Table 7. Prior therapy received by the patient populations in the trials of interest to the submission

Study	Intervention	N	Prior chemotherapy in the (neo)adjuvant setting, n (%)	Prior chemotherapy in the metastatic setting, n (%)	Prior endocrine therapy in the (neo) adjuvant setting n (%)	Prior endocrine therapy in the metastatic setting n (%)	De novo disease (treatment naïve) n (%)
MONALEESA-2	RIBO-LTZ	334	146 (43.7)	0 (0)	175 (52.4)	0 (0)	114 (34.1)
MONALEESA-2	LTZ	334	145 (43.4)	0 (0)	171 (51.2)	0 (0)	113 (33.8)
PALOMA-1/TRIO-18	PAL-LTZ	84	NR	NR	NR	NR	NR
PALOMA-1/TRIO-18	LTZ	81	NR	NR	NR	NR	NR
PALOMA-2	PAL-LTZ	444	180 (40.5)	0 (0)	103 (23.2)	0 (0)	167 (37.6)
PALOMA-2	LTZ	222	126 (56.8)	0 (0)	48 (21.6)	0 (0)	81 (36.5)
MONARCH 3	ABE-ANAS/LTZ	328	125 (38.1)	[redacted]	[redacted]	[redacted]	135 (41.2)
MONARCH 3	PBO-ANAS/LTZ	165	66 (40.0)	[redacted]	[redacted]	[redacted]	61 (37.0)

Abbreviations: ABE: abemaciclib; ANAS: anastrozole; LTZ: letrozole; NR: not reported; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; PBO: placebo; RIBO: ribociclib.

Table 8. Inclusion criteria for disease stage and prior therapy permitted in the trials of interest to this submission

Study	Intervention	Stage of patients	Prior chemotherapy in metastatic setting permitted	Prior adjuvant ET permitted	Prior ET in metastatic setting permitted	Required DFI following adjuvant ET
MONALEESA-2	RIBO-LTZ	Locally confirmed recurrent or metastatic breast cancer	No	Yes	No	>12 months since adjuvant NSAI. Unclear for other hormonal therapy
	LTZ					
PALOMA-1/TRIO-18	PAL-LTZ	Advanced breast cancer, locally recurrent disease not amenable to surgery or evidence of metastatic disease	No	Yes	No	>12 months since adjuvant letrozole. Unclear for other therapies
	LTZ					
PALOMA-2	PAL-LTZ	Advanced breast cancer	No	Yes	No	>12 months since adjuvant NSAI. Unclear for other types of hormonal therapy
	LTZ					
MONARCH 3	ABE-ANAS/LTZ	Locoregionally recurrent disease, not amenable to resection or radiation therapy with curative intent, or metastatic disease	No	Yes	No	>12 months from completion of (neo)adjuvant endocrine therapy (aromatase inhibitors or anti-oestrogens)
	PBO-ANAS/LTZ					

Abbreviations: ABE: abemaciclib; ANAS: anastrozole; DFI: disease-free interval; ET: endocrine therapy; LTZ: letrozole; NSAI: non-steroidal aromatase inhibitor; PAL: palbociclib; PBO: placebo; RIBO: ribociclib.

A15. Please provide more information about the Bayesian methods used to conduct the NMA, including the number of iterations used for burn in and inferences, and the methods for assessing convergence.

NMA methodology

The underlying model for a NMA is a generalised linear model[27] where linear combinations of predictor variables are related to endpoints. The endpoints modelled are assumed to be derived from an underlying distribution that is chosen based on the type of endpoint. A link function is then specified to map the linear combination to the endpoint. The structure of NMAs therefore differs according to the type of endpoint being modelled.

Model fit

To assess the fit of the models to the observed data using the underlying likelihood function, the deviance (D) can be measured and compared between models. The FE and RE models were compared using the DIC which penalises the deviance by the effective number of parameters (p_D):

$$\bar{D} = -2 \times \log(likelihood)$$
$$DIC = \bar{D} + p_D$$

We compared fit of the FE and RE models using DIC criteria to decide which model results to use. Lower DIC indicates a relative improvement in fit.

Prior distributions

The NMA was conducted in a Bayesian framework that involves updating prior beliefs based on the data available to reflect the current state of knowledge.[28] This is achieved by placing prior distributions (commonly referred to as priors) on the parameters estimated. Study data included in the NMA are then used to update these priors jointly to provide the parameter estimates of interest. In our analyses, prior distributions will be placed on the relative treatment effects, study-specific effects and RE standard deviation (for RE models). As recommended in the UK NICE DSU TSD[27] flat priors were chosen for the treatment and study-specific terms. These were normally distributed with mean 0 and variance 10,000. For the RE standard deviation, a uniform distribution of parameters 0 and 5 was chosen. This distribution assumes that any value between 0 and 5 is equally likely to represent the between-study variance in the treatment effects. The parameters for the distributions were chosen to represent the likely extent of the variation from the mean between studies, given the endpoints assessed.

Initial values

Initial values were specified for the parameters being estimated with prior distributions, namely treatment effects, study-specific effects and RE standard deviations (for RE models). At each subsequent iteration new values for these parameters are sampled based on the previous value.[28]

As recommended in the NICE DSU document,[27] three chains of initial values were run to assess whether the choice of initial values affected the posterior estimate. The initial values for these parameters were chosen by selecting random samples from a normal distribution.

Simulations

The Markov Chain Monte Carlo estimator was run for a default number of 100,000 burn-in simulations and monitored for a further 150,000 simulations. Convergence and autocorrelation was assessed to ensure adequate convergence has been achieved. If required, the number of burn-in simulations and further update simulations were increased to achieve a level of convergence which is acceptable.

Convergence and autocorrelation

Convergence within and between chains were assessed using Brooks–Gelman–Rubin plots[29] and by examining trace plots. Convergence was assumed to be adequate if the parameter estimate range is consistent, and if there is little deviation in the estimates as the number of simulations is increased. The Rˆstatistic is the square root of the ratio of between-chain and within-chain variability, and is referred to as the potential scale reduction factor. A large value of Rˆfor a given parameter indicates that the between-chain variability is greater than the within-chain variability; a larger number of simulations may then be required to improve convergence. This statistic was investigated for all parameters estimated in the models.

Autocorrelation is a measure of the correlation between posterior simulations within a chain of a parameter. This was assessed for all parameters estimated in the models. Where autocorrelation is high, the number of simulations were increased or chains thinned in an attempt to reduce this.[28]

A16. Was a consistency assessment performed for direct and indirect evidence included in the NMAs? If so, please describe which procedures were followed and what the results were.

A consistency assessment was performed in line with NICE DSU guidance.[30] The results of this consistency assessment have not been presented below, as the only closed loops in the network involved comparisons that were not relevant to this appraisal. Consistency results from these loops therefore do not provide information on the validity of treatment effect estimates for comparators relevant to this appraisal.

A17. **Priority question**. Please can you report the Deviance Information Criterion (DIC) values that were generated to chose between fixed effect and random effects NMA models. Further, where the results of random / fixed effect model NMAs have been provided in the CS for an outcome please supply the corresponding random / fixed effect model results, to permit comparison between random and fixed effects for each outcome. As a minimum we would like to see the random effects NMA results for PFS (fixed effects are presented in the CS – Figure 10).

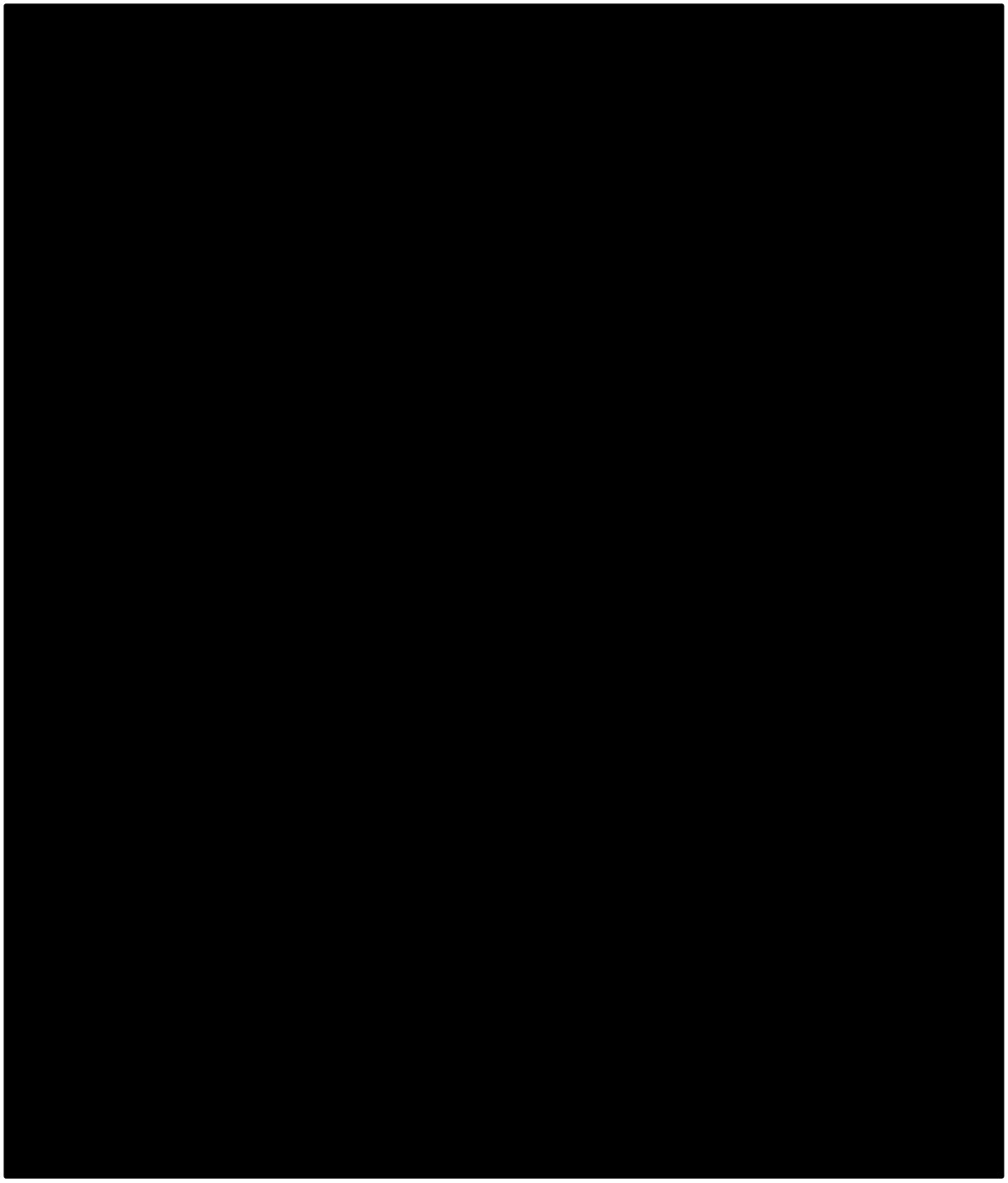
The total residual deviance and number of data points that were generated and used to choose between fixed effect and random effects NMA models are presented in Table 9. The random effects NMA results for PFS are presented in Figure 2.

Table 9. Goodness of fit statistics for the NMAs

Endpoint	DIC value		Total residual deviance		N data points
	FE	RE	FE	RE	
PFS	−4.654	−3.351	11.65	11.15	8
OS	−5.737	−4.085	17.73	17.8	17
ORR	315.1	314.6	37.44	33.65	35
CBR	303.6	304.3	20.63	19.8	20
CR	253.5	252.8	35.34	31.29	31

Abbreviations: CBR: clinical benefit rate; CR: complete response; DIC: Deviance Information Criterion; FE: fixed effect; PFS: progression-free survival; ORR: objective response rate; OS: overall survival; RE: random effects.

Figure 2. Forest plot of treatment effects relative to ANAS/LTZ for PFS using RE model



Abbreviations: ABE: abemaciclib; ANAS: anastrozole; CrI: credible interval; FUL250: fulvestrant 250 mg; FUL500: fulvestrant 500 mg; HER2: human epidermal growth factor-receptor; LTZ: letrozole; MGA: megestrol acetate; PAL: palbociclib; PBO: placebo; RIBO: ribociclib; TMX20: tamoxifen 20 mg.

A18. Please could you supply the OpenBUGS code that was used to run the MONARCH 3 and MONARCH 2 aligned NMA.

The Open BUGS code that was used to run the MONARCH 3 and MONARCH 2 aligned NMA is provided below:

Binary endpoint

Fixed effects model

```
# Binomial likelihood, logit link
# Fixed effects model
model{            # *** PROGRAM STARTS
for(i in 1:ns){        # LOOP THROUGH STUDIES
  mu[i] ~ dnorm(0,.0001)   # vague priors for all trial baselines
  for (k in 1:na[i]) {    # LOOP THROUGH ARMS
    r[i,k] ~ dbin(p[i,k],n[i,k])  # binomial likelihood
# model for linear predictor
    logit(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]
# expected value of the numerators
    rhat[i,k] <- p[i,k] * n[i,k]
#Deviance contribution
    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
       + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
   }
# summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
   }
totresdev <- sum(resdev[])   # Total Residual Deviance
d[1]<-0  # treatment effect is zero for reference treatment
rr[1]<-prob[1]/prob[refTx]
rd[1]<-prob[1]-prob[refTx]
logit(prob[1]) <- baseLod-d[baseTx]
# vague priors for treatment effects
for (k in 2:nt){ d[k] ~ dnorm(0,.0001)
          #or[k-1] <- exp(d[k])
    lor[k-1] <-d[k]
          logit(prob[k]) <- baseLod+d[k]-d[baseTx]
          rr[k] <- prob[k]/prob[refTx]
          rd[k] <- prob[k]-prob[refTx]
          }
baseLod ~ dnorm(0,0.002)
logit(baseProb) <- baseLod
for (bb in 1:nBase){
  baseR[bb] ~ dbin(baseProb,baseN[bb])
}
}                    # *** PROGRAM ENDS
```

Random effects model

```
# Binomial likelihood, logit link
# Random effects model for multi-arm trials
```

```
model{               # *** PROGRAM STARTS
for(i in 1:ns){          # LOOP THROUGH STUDIES
  w[i,1] <- 0  # adjustment for multi-arm trials is zero for control arm
  delta[i,1] <- 0       # treatment effect is zero for control arm
  mu[i] ~ dnorm(0,.0001)      # vague priors for all trial baselines
  for (k in 1:na[i]) {       # LOOP THROUGH ARMS
    r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
    logit(p[i,k]) <- mu[i] + delta[i,k] # model for linear predictor
    rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
#Deviance contribution
    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
      + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))     }
# summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {       # LOOP THROUGH ARMS
# trial-specific LOR distributions
    delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions (with multi-arm trial correction)
    md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
    taud[i,k] <- tau *2*(k-1)/k
# adjustment for multi-arm RCTs
    w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
    sw[i,k] <- sum(w[i,1:k-1])/(k-1)
   }
 }
totresdev <- sum(resdev[])      # Total Residual Deviance
d[1]<-0    # treatment effect is zero for reference treatment
rr[1]<-prob[1]/prob[refTx]
rd[1]<-prob[1]-prob[refTx]
logit(prob[1]) <- baseLod-d[baseTx]
# vague priors for treatment effects
for (k in 2:nt){ d[k] ~ dnorm(0,.0001)
                      lor[k-1] <- d[k]
                      #or[k-1] <- exp(d[k])
                      logit(prob[k]) <- baseLod+d[k]-d[baseTx]
                      rr[k] <- prob[k]/prob[refTx]
                      rd[k] <- prob[k]-prob[refTx]
                     }
sd ~ dunif(0,5)  # vague prior for between-trial SD
tau <- pow(sd,-2)  # between-trial precision = (1/between-trial variance)
baseLod ~ dnorm(0,0.002)
logit(baseProb) <- baseLod
for (bb in 1:nBase){
  baseR[bb] ~ dbin(baseProb,baseN[bb])
}
```

```
}               # *** PROGRAM ENDS
```

Survival endpoint

Fixed effects model

```
#Survival analysis - fixed effects analysis (A)
#intended for use on survival data to estimate hazard ratios but can be used for synthesising any
constant treatment effects
model{
#Define Prior Distributions
#On tx effect mean
 beta[1] < -0
 for (tt in 2:nTx){
  beta[tt]~dnorm(0,1.0E-6)
 }
#On individual study baseline effect
 for(ss in 1:nStudies){
  alpha[ss] ~ dnorm(0,1.0E-6)
 }
#Fit data
#For hazard ratio reporting studies
 for(ii in 1:LnObs ){
  Lmu[ii] < - alpha[Lstudy[ii]]*multi[ii] + beta[Ltx[ii]] - beta[Lbase[ii]]
  Lprec[ii] < - 1/pow(Lse[ii],2)
  Lmean[ii] ~ dnorm(Lmu[ii],Lprec[ii])
 }
#For binary data reporting studies
# for(ss in 1:BnObs){
#  logCumHaz[ss] < - alpha[Bstudy[ss]] + beta[Btx[ss]] - beta[Bbase[ss]]
#  cumFail[ss] < - 1-exp(-1*exp(logCumHaz[ss]))
#  Br[ss] ~ dbin(cumFail[ss], Bn[ss])
# }
# Calculate HRs
 for (hh in 1:nTx) {
  hr[hh] < -exp(beta[hh])
 }
# Ranking plot
 for (ll in 1:nTx) {
  for (mm in 1:nTx) {
   rk[ll,mm] < - equals(ranked(beta[],mm),beta[ll])
  }
 }
}
```

Random effects model

```
#Survival analysis - random effects analysis (B)
```

```
#intended for use on survival data to estimate hazard ratios but can be used for synthesising any
constant treatment effects
model{
#Define Prior Distributions
#on random tx effect variance
 sd~dunif(0,5)
 reTau < - 2/pow(sd,2)
#On tx effect mean
 beta[1] < -0
 for (tt in 2:nTx){
  beta[tt]~dnorm(0,1.0E-6)
 }
#On individual study baseline effect
 for(ss in 1:nStudies){
  alpha[ss] ~ dnorm(0,1.0E-6)
 }
#Define random effect
 for (ss in 1:nStudies){
  for(tt in 1:nTx){
   re[ss,tt]~dnorm(0,reTau)
  }
 }
#Fit data
#For hazard ratio reporting studies
 for(ii in 1:LnObs ){
  Lmu[ii] < - alpha[Lstudy[ii]]*multi[ii] + re[Lstudy[ii],Ltx[ii]] -
  re[Lstudy[ii],Lbase[ii]] + beta[Ltx[ii]] - beta[Lbase[ii]]
  Lprec[ii] < - 1/pow(Lse[ii],2)
  Lmean[ii] ~ dnorm(Lmu[ii],Lprec[ii])
 }
#For binary data reporting studies
# for(ss in 1:BnObs){
#  logCumHaz[ss] < - alpha[Bstudy[ss]] + re[Bstudy[ss],Btx[ss]] -
#  re[Bstudy[ss],Bbase[ss]] + beta[Btx[ss]] - beta[Bbase[ss]]
#  cumFail[ss] < - 1-exp(-1*exp(logCumHaz[ss]))
#  Br[ss] ~ dbin(cumFail[ss], Bn[ss])
# }
# Calculate HRs
 for (hh in 2:nTx) {
  hr[hh] < -exp(beta[hh])
 }
# Ranking plot
 for (ll in 1:nTx) {
  for (mm in 1:nTx) {
   rk[ll,mm] < - equals(ranked(beta[],mm),beta[ll])
  }
 }
```

}

A19. **Priority question**. Please can you provide the Kaplan-Meier data, the log cumulative hazard plots and the Schoenfeld residual plots that were visually inspected to ascertain whether the proportional hazards assumption holds in the NMA (CS Appendix D.1.5). Please also supply the results of the weighted residual test based on standardised Schoenfeld residuals.

An overview of the proportional hazards assessment for OS and PFS, including comments on the Kaplan-Meier data where applicable, is presented in Table 10. The available Kaplan-Meier plots for PFS are presented in Figure 3–Figure 12. The available Kaplan-Meier plots for OS are presented in Figure 13–Figure 28. The log cumulative hazard plots that were used to assess the proportional hazards assumption for PFS and OS are presented in Figure 29 and Figure 30, respectively. The Schoenfeld residual plots that were used to assess the proportional hazards assumption for PFS and OS are presented in Figure 31 and Figure 32, respectively. The results of the weighted residual tests for PFS and OS are presented in Table 11 and Table 12, respectively.

Table 10. Proportional hazards assessment of OS and PFS for each study

Study ID	Treatments included	PFS		OS	
		Acceptability of PH assumption based on KM data	Comments	Acceptability of PH assumption based on KM data	Comments
FALCON (Robertson 2016[11])	ANAS, FUL	✓	-	No KM available	-
FIRST (Robertson 2009[12])	ANAS, FUL	No KM available	-	✓	-
Gill 1993[13]	MGA, TMX	No KM available	-	×	Assumption holds up to approximately 30 months, where numbers at risk drop to about 20 for each treatment group
Hayes 1995[14]	TMX, TOR60, TOR200	No KM available	-	×	KM curves separate after approximately 30 months. No clear reason for violation
Howell 2004[15]	FUL, TMX	×	KM curves cross after approximately 12 months. No clear reason for violation	No KM available	-
Howell 2004 HR+[15]	FUL, TMX	✓	-	No KM available	-
Iwata 2013[16]	ANAS, EXE	No KM available	-	✓	-
Milla-Santos 2001[17]	TMX, TOR	No KM available	-	✓	-
Milla-Santos 2003[18]	ANAS, TMX	No KM available	-	×	KM curves cross after approximately 12 months. No clear reason for violation

MONALEESA-2 (Hortobagyi 2016[19])	LTZ, RIBO-LTZ	✓	-	×	KM curves separate out around 24 months. No clear reason for violation
MONARCH 3 (Goetz 2017[3])	ABE-LTZ/ANAS, LTZ/ANAS	✓	-	✓	KM curves cross after approximately 20 months. Immature survival and high level of censoring
Mouridsen 2001[20]	LTZ, TMX	No KM available	-	×	KM curves cross after approximately 36 months. No clear reason for violation
Muss 1985[21]	MGA, TMX	✓	KM curves separate after approximately 8 months, where numbers at risk drop to approximately 40 for each treatment group	✓	-
Nordic (Pyrhonen 1997[22])	TMX, TOR	No KM available	-	×	No clear reason for violation of assumption beyond 45 month time point
PALOMA-1/TRIO-18 (Finn 2015[23])	LTZ, PAL-LTZ	✓	-	×	KM curves cross after approximately 8 months, after which assumption appears to hold.
PALOMA-2 (Finn 2016[24])	LTZ, PAL-LTZ	✓	-	No KM available	-
Paterson 1990[25]	MGA, TMX	No KM available	-	×	KM curves cross at two different points after approximately 12 months. No clear reason for violation
TARGET and North American	ANAS, TMX	✓	-	✓	-

(Bonneterre 2001[26])					
TARGET and North American HR+ (Bonneterre 2001[26])	ANAS, TMX	No KM available	-	✓	-
Yardley 2009[31]	LDOX, TXT	×	KM curves separate after approximately 10 months, where numbers at risk drop to approximately 15 for each treatment group	✓	-

Abbreviations: ABE: abemaciclib; ANAS: anastrozole; EXE: exemestane; FUL: fulvestrant; KM: Kaplan-Meier; LDOX: liposomal doxorubicin; LTZ: letrozole; MGA: megestrol acetate; OS: overall survival; PAL: palbociclib; PFS: progression-free survival; PH: proportional hazards; RIBO: ribociclib; TMX: tamoxifen; TOR: toremifene; TOR 60: toremifene 60 mg; TOR 200: toremifene 200 mg.

Kaplan-Meier Data

Figure 3. FALCON PFS

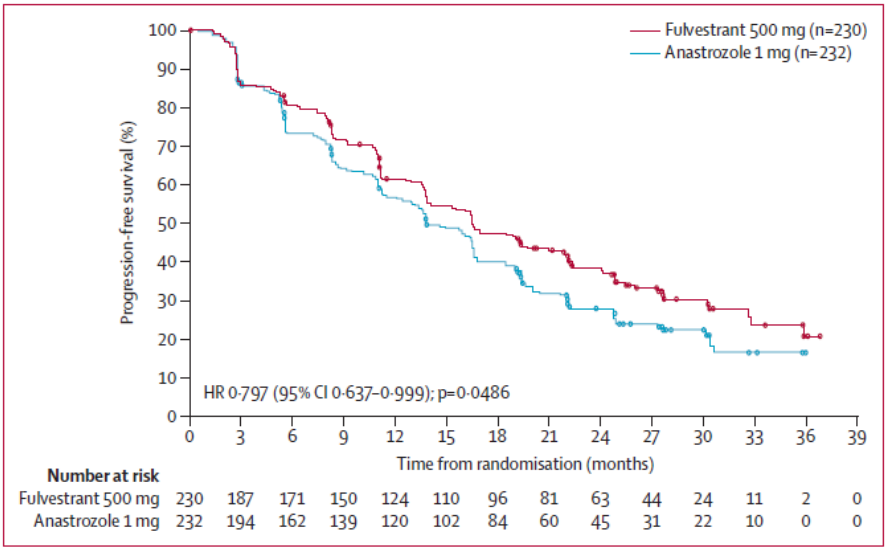


Figure 4. Howell 2004 (ITT) PFS

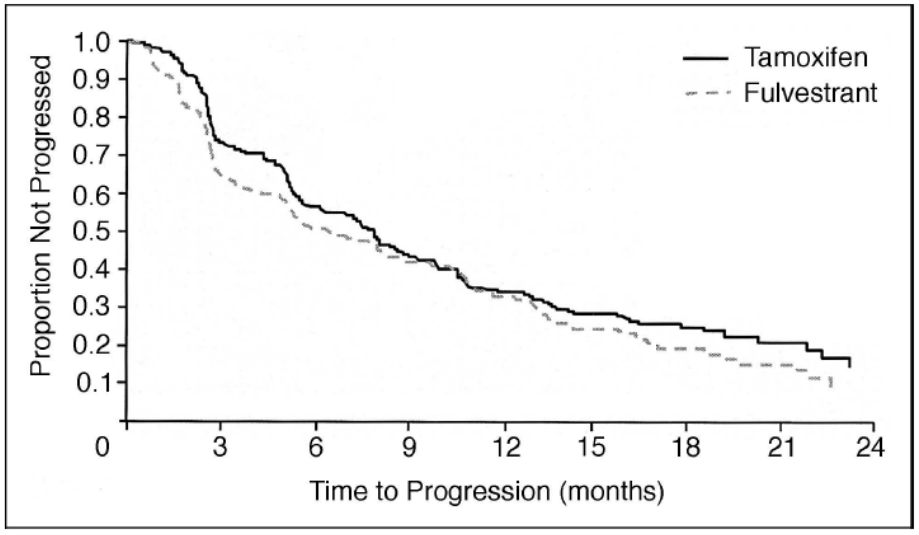


Fig 1. Kaplan-Meier plot for time to progression (all randomized patents).

Figure 5. Howell 2004 (HR+) PFS

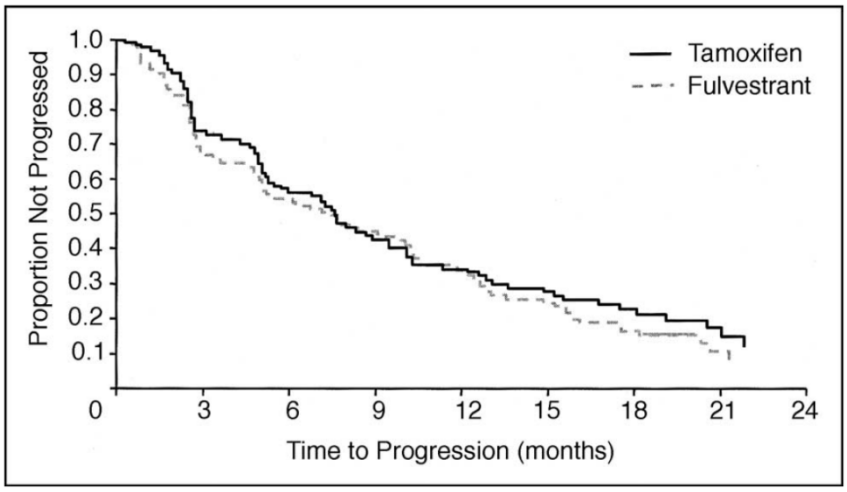
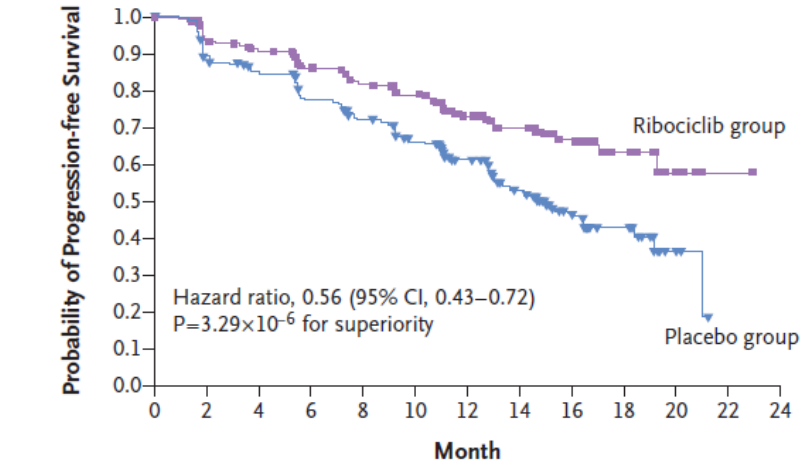


Figure 6. MONALEESA-2 PFS



No. at Risk

Ribociclib	334	294	277	257	240	226	164	119	68	20	6	1	0
Placebo	334	279	264	237	217	192	143	88	44	23	5	0	0

Figure 7. MONARCH 3 PFS

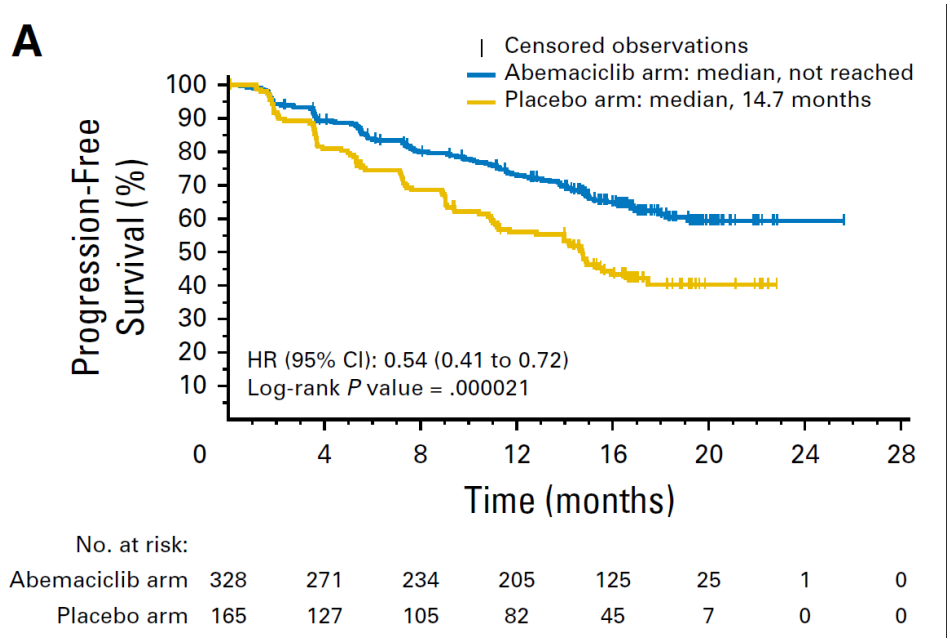


Figure 8. MUSS 1985 PFS

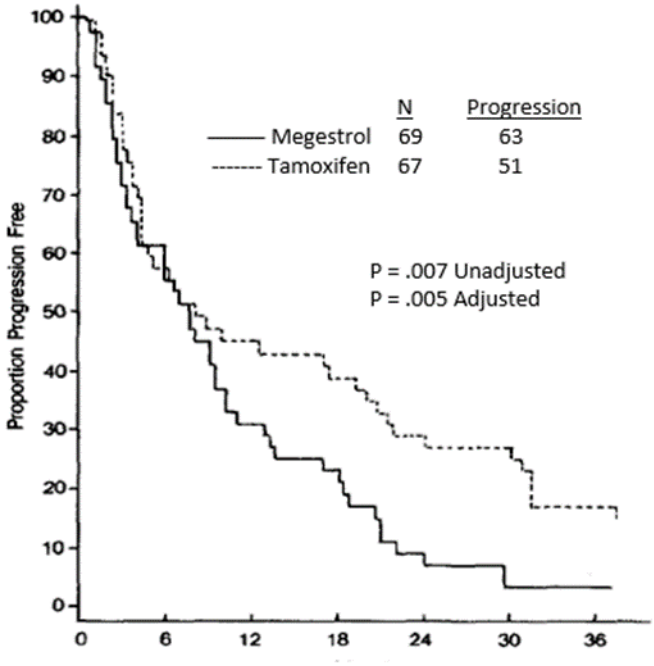


Fig 1. Time to progression (months) for all patients for initial treatment (Kaplan-Meier). Adjusted P-value determined using Cox proportional hazards model

Figure 9. PALOMA-1/TRIO-18 PFS

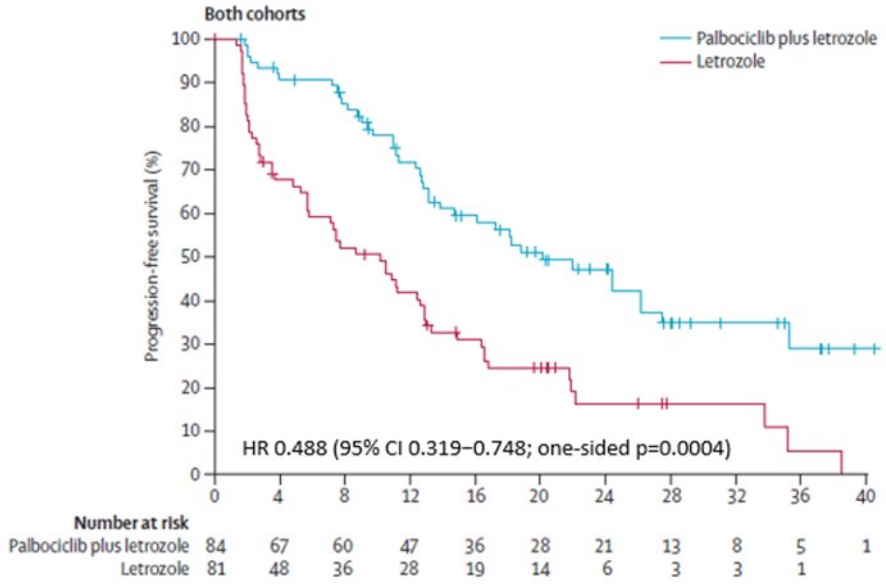


Figure 10. PALOMA-2 PFS

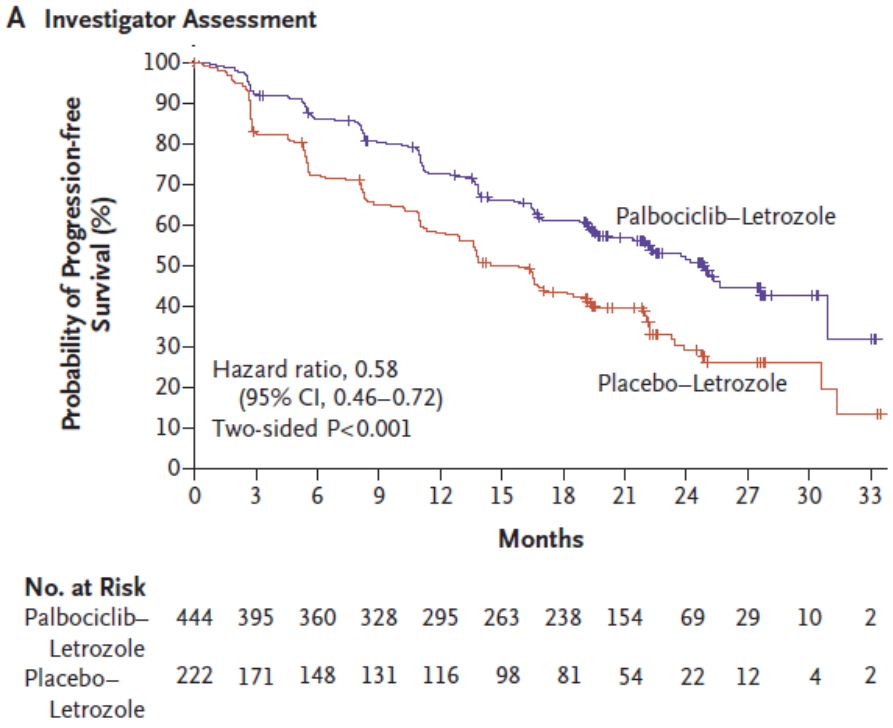


Figure 11. Target and North American PFS

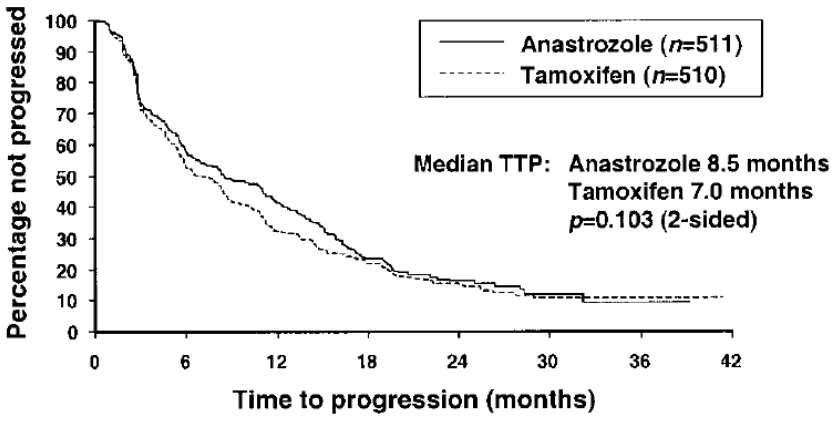


FIGURE 1. Kaplan–Meier plot of time to progression in patients receiving anastrozole 1 mg or tamoxifen 20 mg once daily.

Figure 12. Yardley 2009 PFS

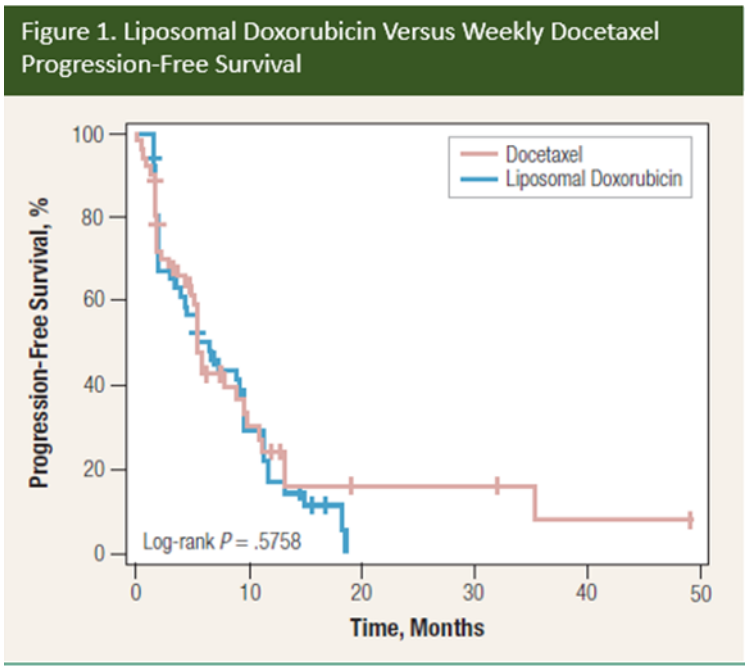
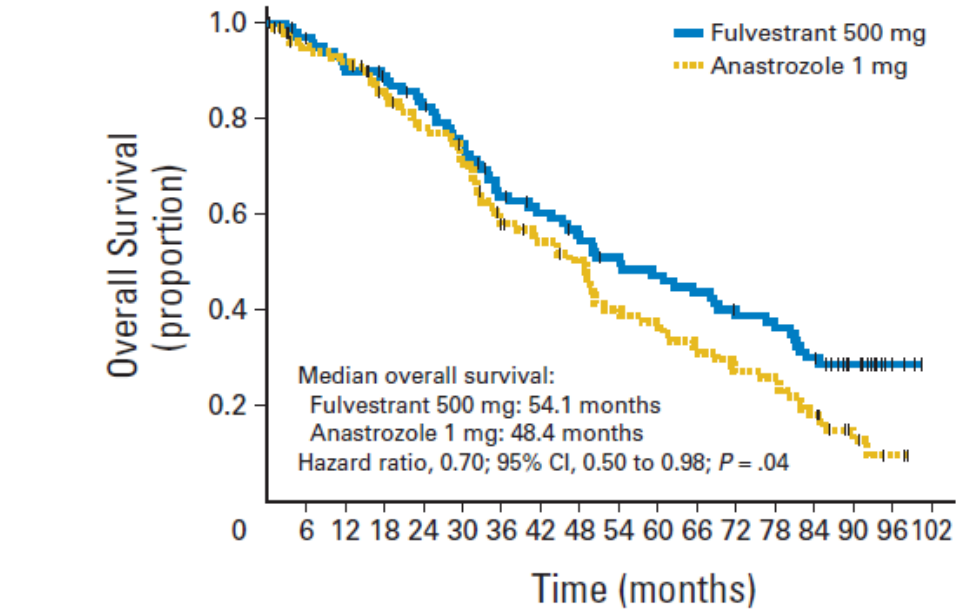


Figure 13. FIRST OS



No. at risk

Fulvestrant 500 mg	102	90	84	77	57	47	39	31	24	4
Anastrozole 1 mg	103	90	80	72	49	39	29	21	14	2

Figure 14. Gill 1993 OS

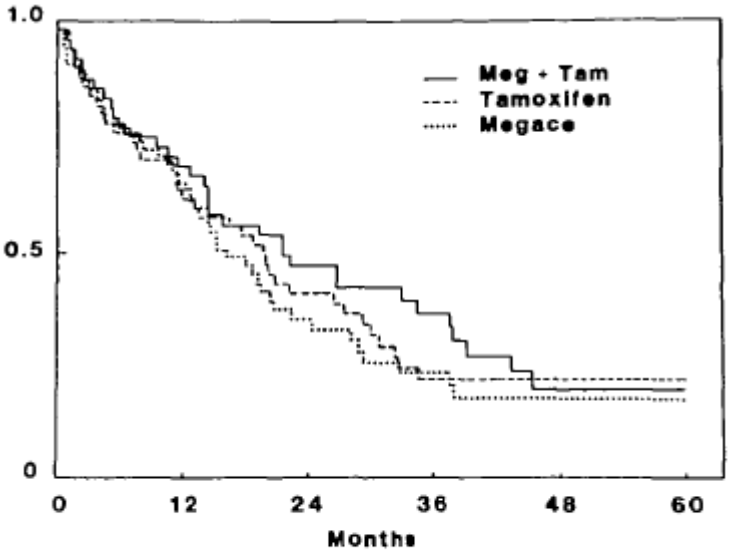


Fig. 2. Survival according to first randomized treatment (Megace ——; Megace and Tamoxifen ····· ; Tamoxifen – – – –).

Figure 15. Hayes 1995 OS

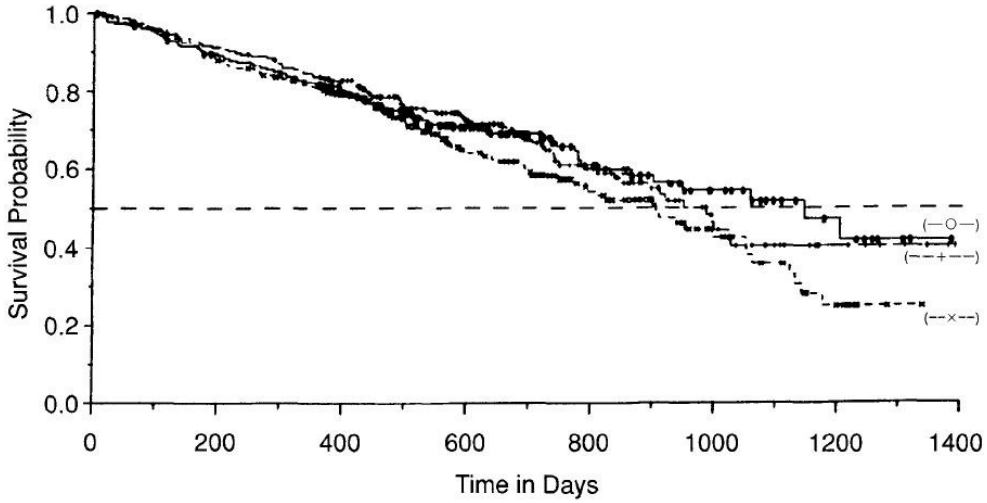
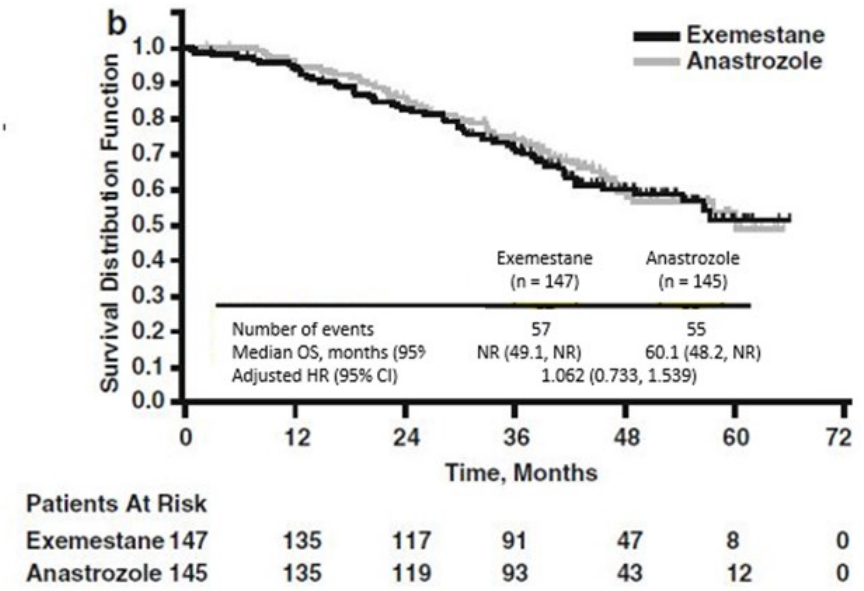


Fig 2. Overall survival for patients treated with TAM (+++, n = 215), TOR60 (OOO, n = 221), and TOR200 (×××, n = 212). Postmenopausal hormone receptor-positive or -unknown patients with metastatic breast cancer were randomly assigned to 1 of 3 arms as designated. Survival determined from time of study entry (*P* values: log-rank = .81; Wilcoxon = .74).

Figure 16. Iwata 2013 OS



images review committee, *TTP* time to progression. Reproduced with permission from Masuda et al. [24]

Figure 17. Milla-Santos 2001 OS

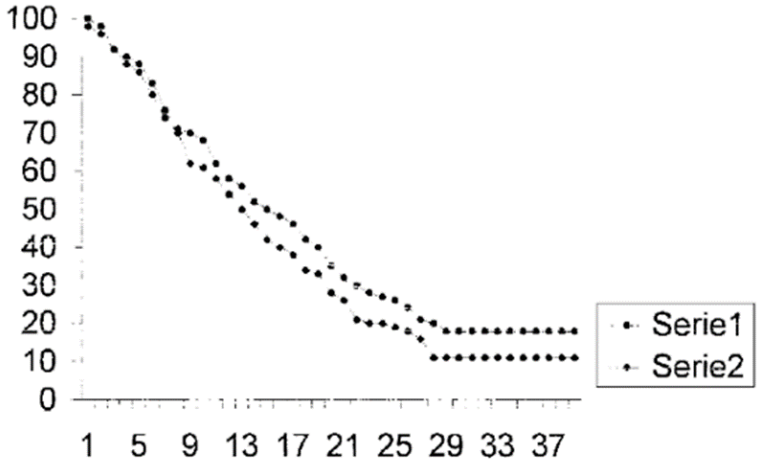
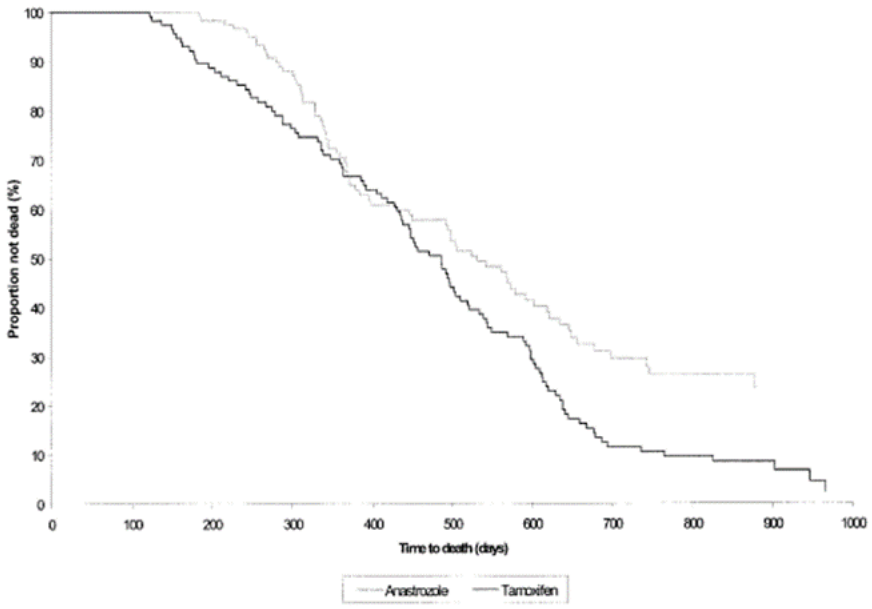


Figure 2. Overall survival (months). Serie 1=Toremifene, Serie 2 = Tamoxifen

Figure 18. Milla-Santos 2003 OS



Overall survival

Figure 19. MONALEESA 2 OS

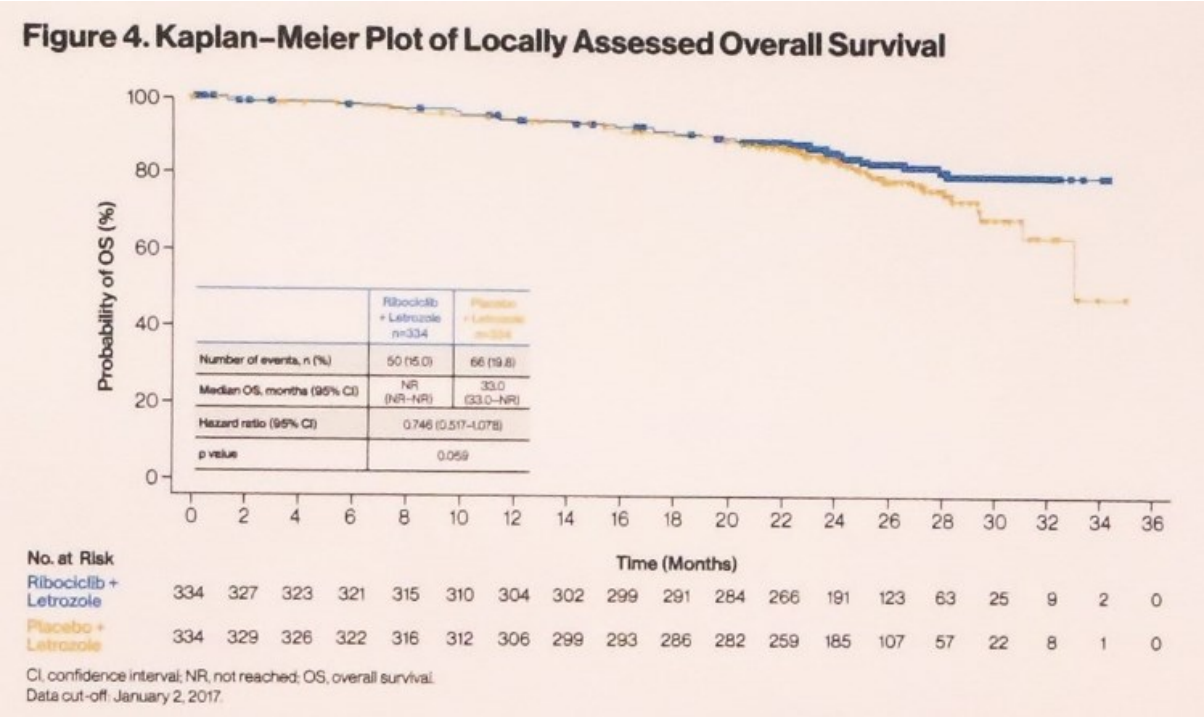


Figure 20. MONARCH 3 OS

Figure 21. Mouridsen 2003 OS

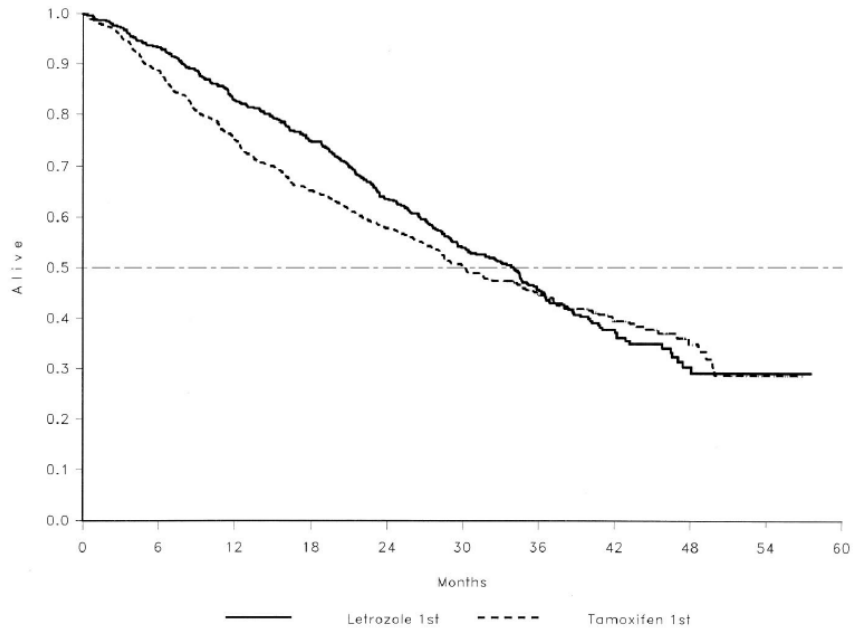


Figure 22. Muss 1985 OS

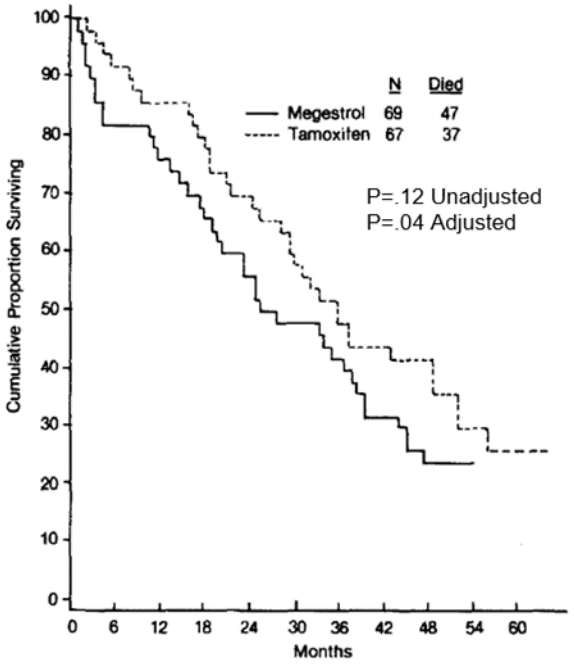


Fig 2. Survival for all patients by initial treatment (Kaplan-Meier). Adjusted *P*-value determined using Cox proportional hazards model.

Figure 23. Nordic OS

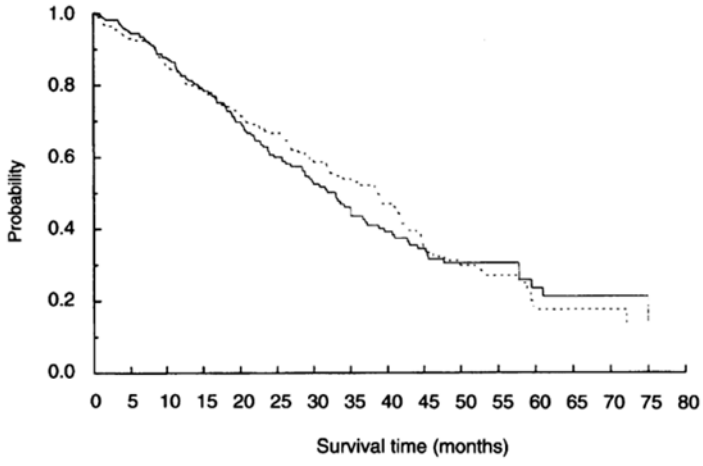


Figure 3 Overall survival among toremifene (——, $n = 214$) and tamoxifen (• • •, $n = 201$) treated patients ($P = 0.645$, log-rank test). Survival time was defined as the time between randomization and death. Patients who were alive were treated as censored observations from the time of randomization until the last date they were known to be alive (before 31 December 1993)

Figure 24. PALOMA-1/TRIO-18 OS

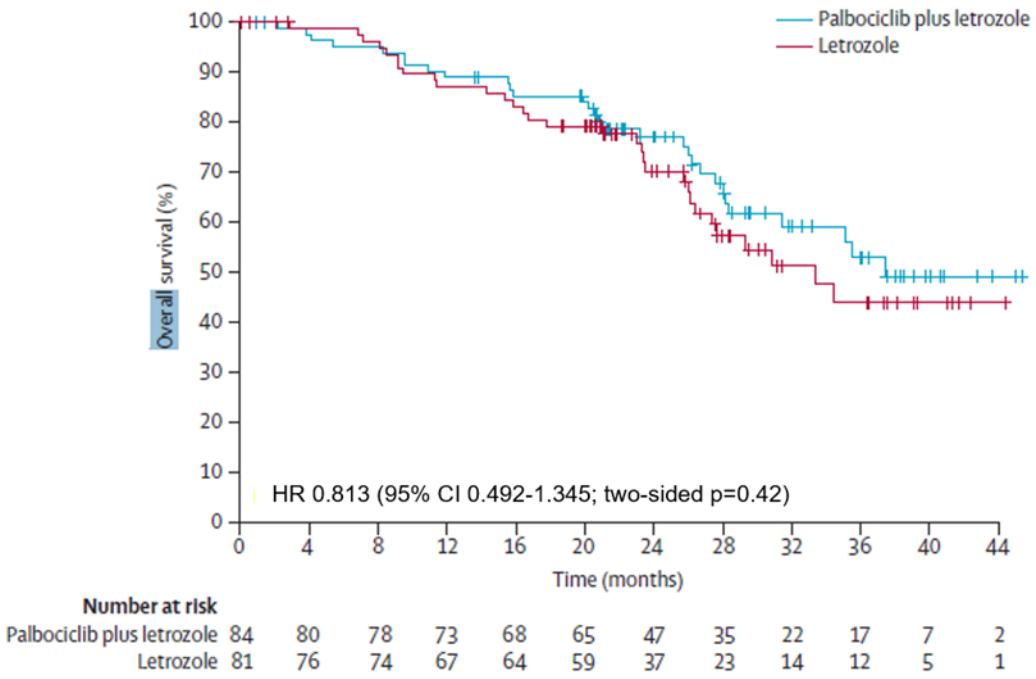


Figure 25. Patterson 1990 OS

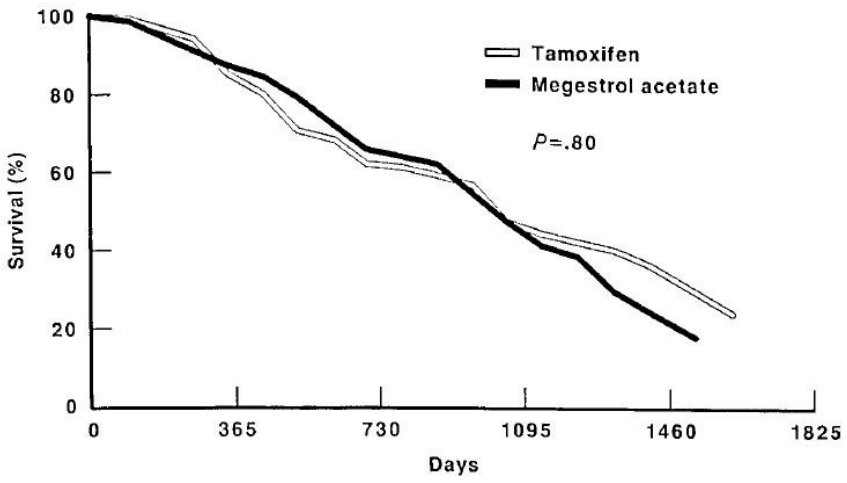


Fig 4. Megestrol acetate/tamoxifen breast cancer trial: actuarial survival from start of phase I, by study arm.

Figure 26. Target and North American (HR+) OS (ITT)

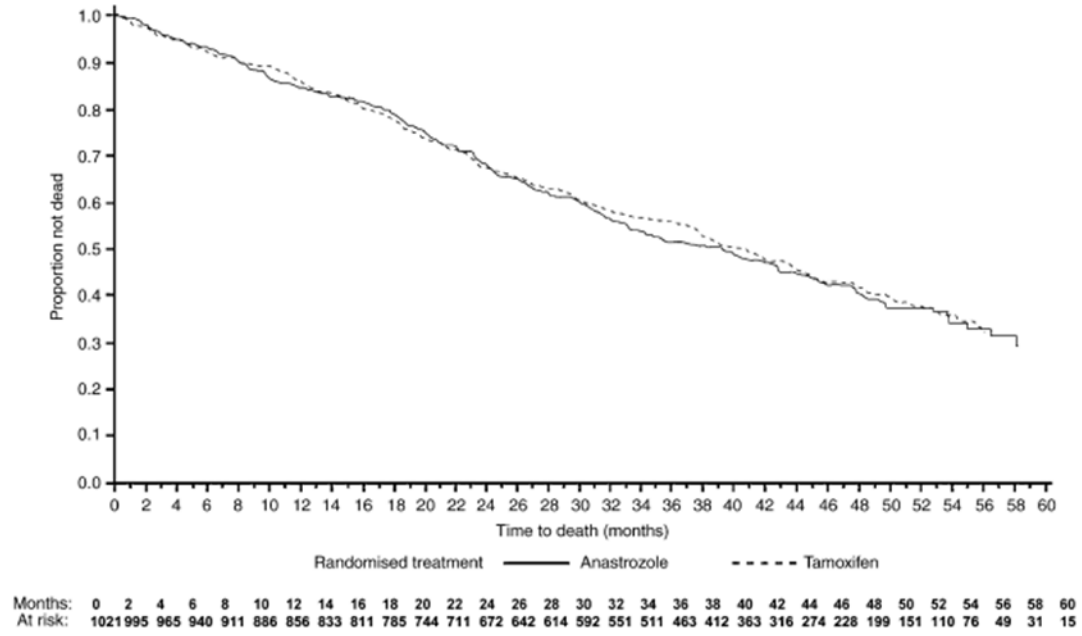


Fig. 2. Kaplan–Meier plot of time to death in the combined analysis of the overall population.

Figure 27. Target and North American (HR+) OS

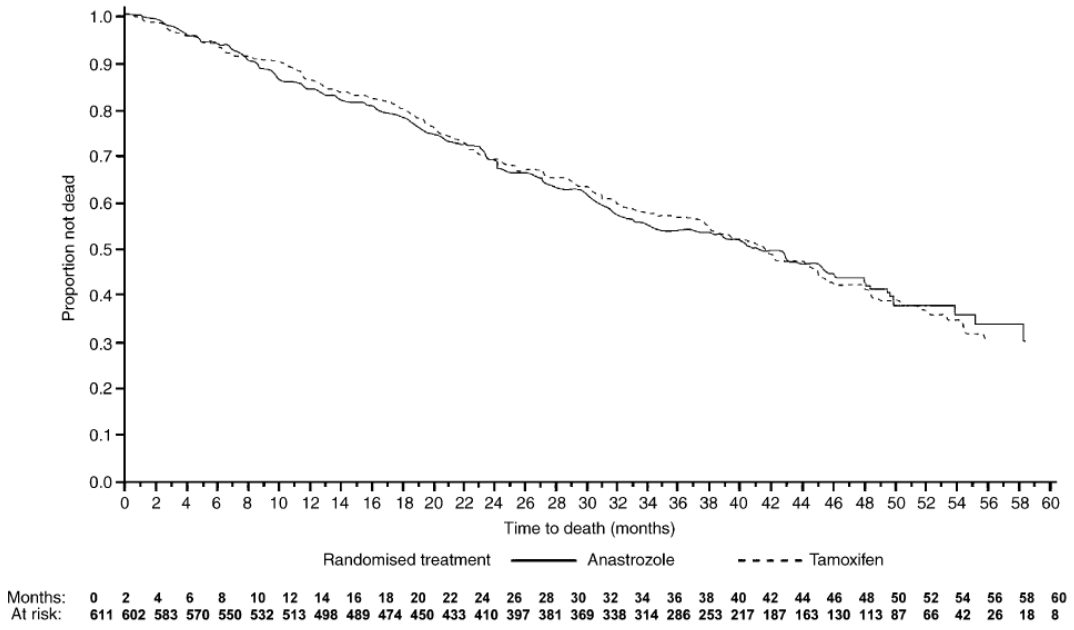


Fig. 3. Kaplan–Meier plot of time to death in the combined analysis of the ER + /PR + subgroup.

Figure 28. Yardley 2009 OS

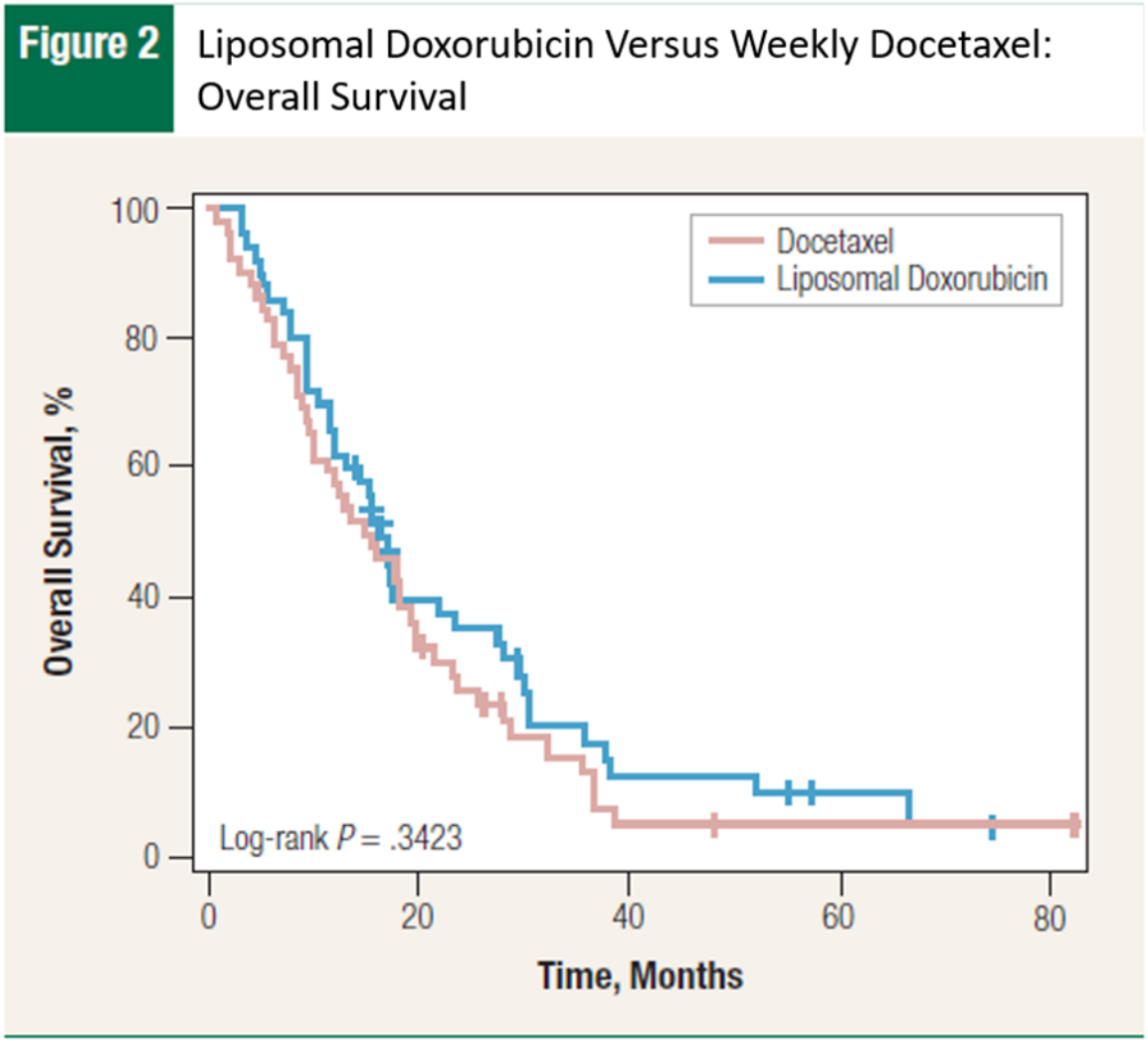


Figure 29. Log-log plots to assess proportional hazards assumptions for PFS

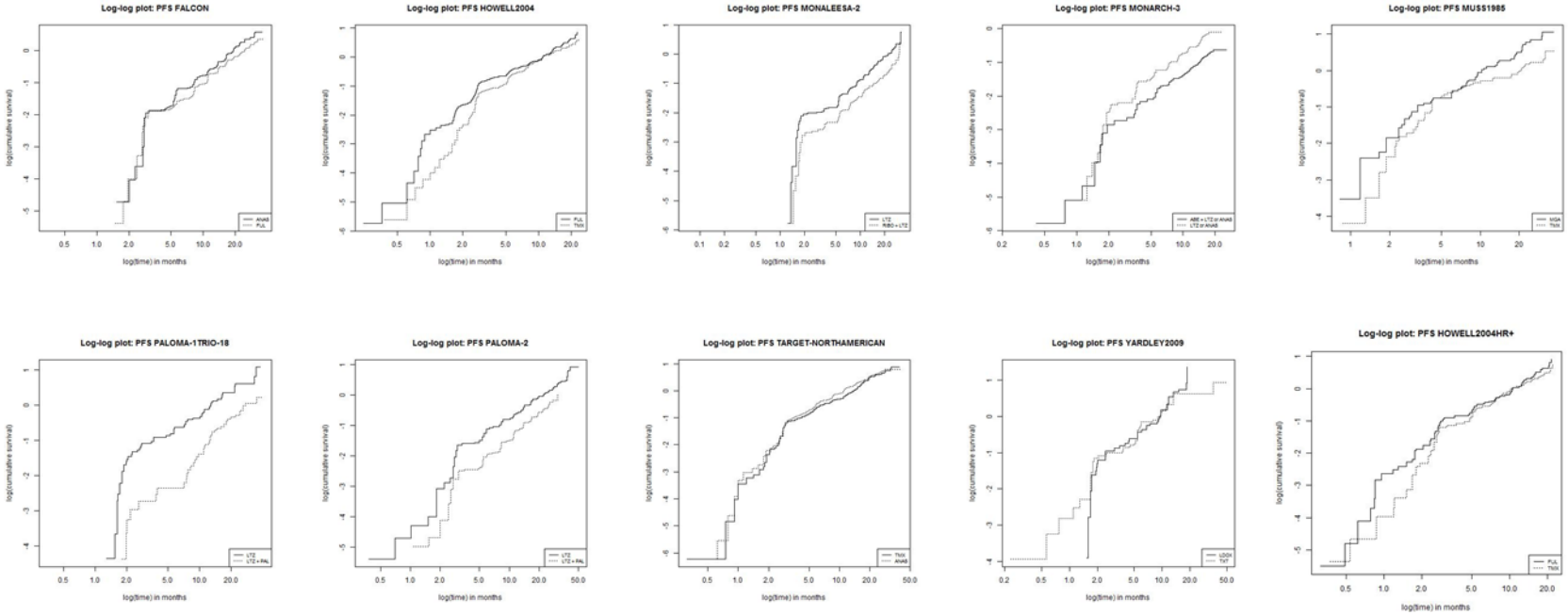


Figure 30. Log-log plots to assess proportional hazards assumptions for OS

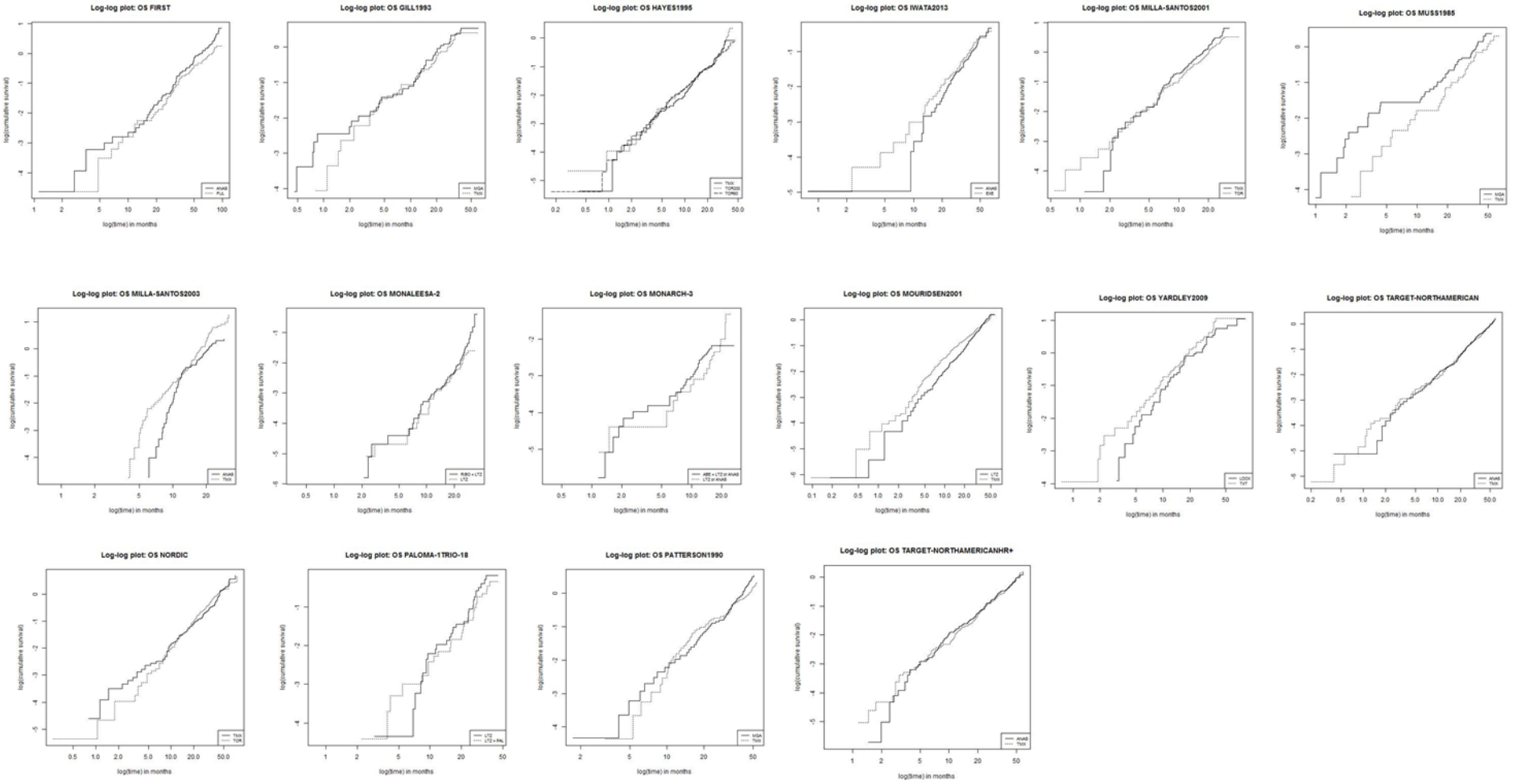


Figure 31. Schoenfeld residual plots to assess proportional hazards assumption for PFS

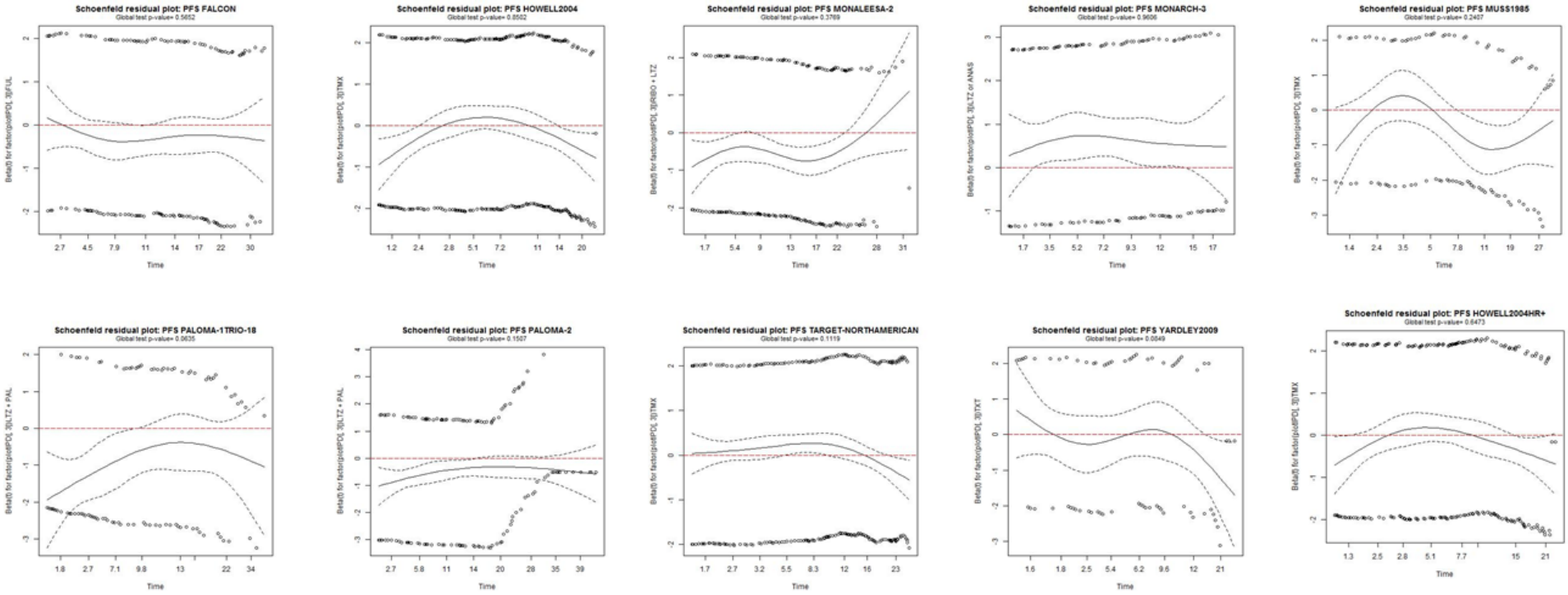


Figure 32. Schoenfeld residual plots to assess proportional hazards assumption for OS

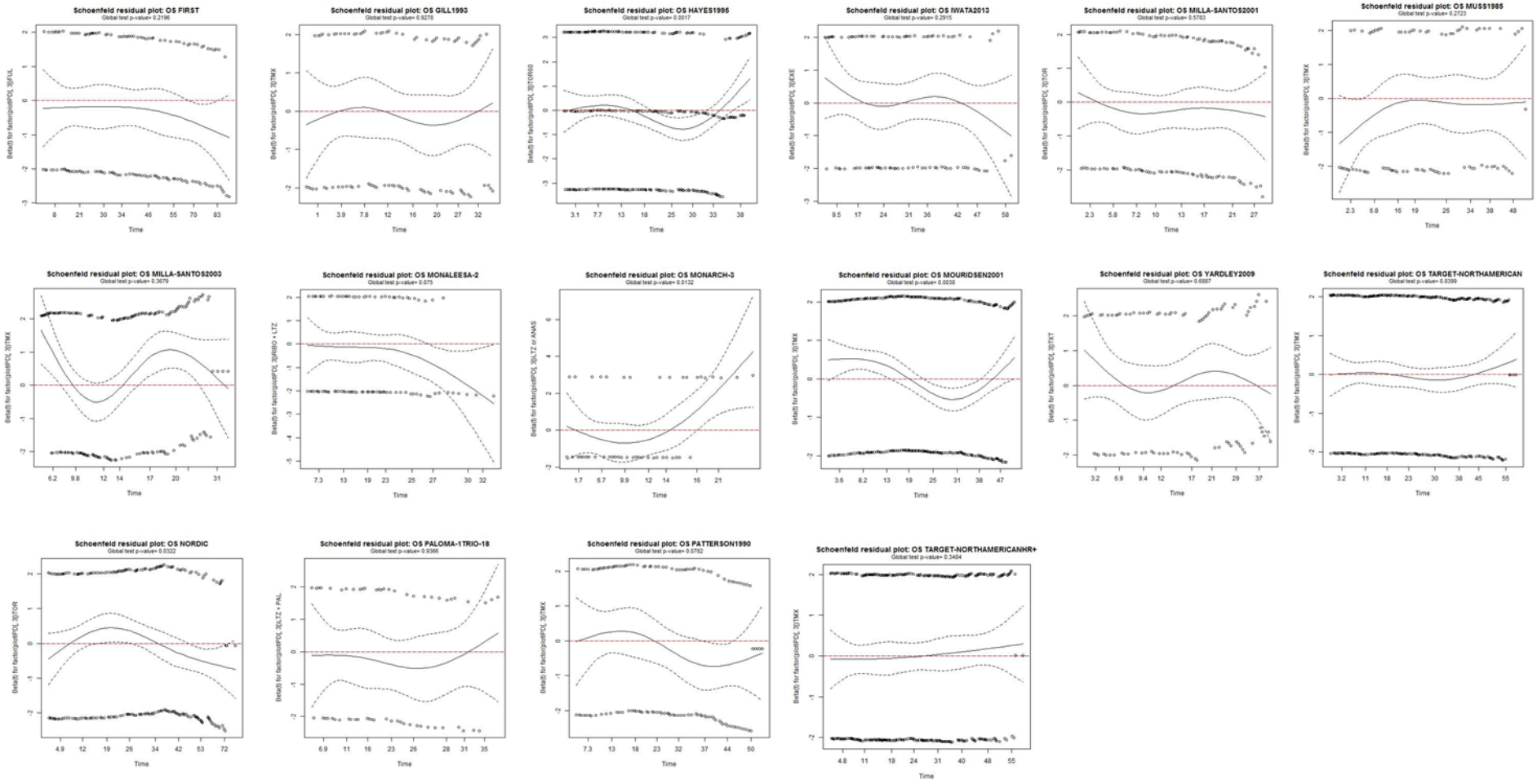


Table 11. Results of the weighted residual tests for PFS

Trial	Global test p-value
FALCON	0.5652
Howell 2004 (ITT)	0.8502
Howell 2004 (HR+ subgroup)	0.6473
MONALEESA-2	0.3769
MONARCH 3	0.9606
MUSS 1985	0.2407
PALOMA-1/TRIO-18	0.0635
PALOMA-2	0.1507
Target and North American (ITT)	0.1119
YARDLEY 2009	0.0849

Table 12. Results of the weighted residual tests for OS

Trial	Global test p-value
FIRST	0.2196
Gill 1993	0.9278
Hayes 1995	0.0017
Iwata 2013	0.2915
Milla-Santos 2001	0.5783
Milla-Santos 2003	0.3679
MONALEESA-2	0.075
MONARCH 3	0.0132
Mouridsen 2001	0.0038
Muss 1985	0.2723
Nordic	0.0322
PALOMA-1/TRIO-18	0.9366
Patterson 1990	0.0782
Target and North American (ITT)	0.8399
Target and North American (HR+ subgroup)	0.3484
Yardley 2009	0.6887

A20. It is stated in CS Appendix D.1.5 that the HR, median and proportion event-free data, as estimated from individual patient data generated by digitised Kaplan-Meier graphs, were checked against the published estimates to ensure internal validity. Please can you comment on the results of this checking, and whether there was good internal validity. Please could you supply the estimated HR, median and proportion event-free data for PFS and OS so that we can independently check these against the published estimates.

Where there was sufficient information in the publications to allow comparison, discrepancies between the data generated from IPD and the data from publications were small. In some studies, there was insufficient information in the publication to allow for comparison, and Kaplan-Meier curves from the digitised data and publication were visually inspected, see Table 13. Kaplan-Meier curves for PFS are supplied below the table. In cases where there were discrepancies, priority was given to the published data.

Table 13. Validation of digitised data against published estimates

Study ID	Treatment arm	Publication (latest OS and PFS data)		KM from publication		No of events from publication		HR (estimate, SE, CI, P-value) comments	Validation comments	HR (estimate, SE, CI, P-value) comments	Validation comments
		OS	PFS	OS	PFS	OS	PFS	OS	OS	PFS	PFS
Howell 2004[15]	FUL	-	Howell 2004	-	Howell 2004	-	NR	-	-	Small discrepancies between HRs and 95% confidence limits.	Small discrepancy between median survival times.
Howell 2004[15]	TMX	-	Howell 2004	-	Howell 2004	-	NR	-	-	Small discrepancies between HRs and 95% confidence limits.	Small discrepancy between median survival times.
Howell 2004 (HR+)[15]	FUL	-	Howell 2004	-	Howell 2004	-	NR	-	-	Small discrepancy between HR and 95%	Small discrepancy between median survival times: (7.5

										confidence limits	vs. 8.2 (reported))
Howell 2004 (HR+)[15]	TMX	-	Howell 2004	-	Howell 2004	-	NR	-	-	Small discrepancy between HR and 95% confidence limits	Small discrepancy between median survival times: (7.7 vs. 8.3 (reported))
Milla-Santos 2001[17]	TOR	Milla-Santos 2001	-	Milla-Santos 2001	-	73	-	Discrepancy between HRs (0.83 vs 0.97(reported))	Small discrepancies between median survival times and 95% confidence limits.		
Milla-Santos 2001[17]	TMX	Milla-Santos 2001	-	Milla-Santos 2001	-	81	-	Discrepancy between HRs (0.83 vs 0.97(reported))	Follow-up period looks slightly shorter than reported KM curve. Small		

									discrepancies between median survival times and 95% confidence limits.		
Muss 1985[21]	MGA	Muss 1988[32]	Muss 1988[32]	Muss 1988[32]	Muss 1988[32]	47	63	HR not reported	No summary statistics or HRs reported but KM plots look the same	-	Small discrepancy between median survival times.
Muss 1985[21]	TMX	Muss 1988[32]	Muss 1988[32]	Muss 1988[32]	Muss 1988[32]	37	51	HR not reported	No summary statistics or HRs reported but KM plots look the same	-	Discrepancy between median survival times (8.8 vs. 7.7 (reported)).
Nordic[22]	TOR	Pyrhonen 1997	-	Pyrhonen 1997	-	123	-	HR not reported	Small discrepancies between		

									median survival times and 95% confidence limits. Removed number of events to prevent data truncation (shorter follow-up period).		
Nordic[22]	TMX	Pyrhonen 1997	-	Pyrhonen 1997	-	115	-	HR not reported	Small discrepancies between median survival times and 95% confidence limits. Removed number of events to prevent		

									data truncation (shorter follow-up period).		
FIRST[12]	FUL	Ellis 2015[33]	Robertson 2009	Ellis 2015[33]	Robertson 2009	63	NR	Exact match to 2 d.p. (as reported) for all parameters	Small discrepancies in numbers at risk for 72, 90 and 96 months time point. 0.5 month discrepancy in median survival time.		
FIRST[12]	ANAS	Ellis 2015[33]	Robertson 2009	Ellis 2015[33]	Robertson 2009	74	NR	Exact match to 2 d.p. (as reported) for all parameters	0.4 month discrepancy in median survival time.		
PALOMA-1/TRIO-18[23]	LTZ + PAL	Finn 2015	Finn 2015	Finn 2015	Finn 2015	30	41	Small discrepancies between HRs and	Small discrepancies between	Discrepancy between HR and 95%	Small discrepancy between number of

								95% confidence limits	median survival times and 95% confidence limits.	confidence limits (HR: 0.4076 vs. 0.488 (reported))	events. Small discrepancy between median survival times. Discrepancies between 95% confidence limits for median survival time.
PALOMA-1/TRIO-18[23]	LTZ	Finn 2015	Finn 2015	Finn 2015	Finn 2015	31	59	Small discrepancies between HRs and 95% confidence limits	Small discrepancies between median survival times and 95% confidence limits.	Discrepancy between HR and 95% confidence limits (HR: 0.4076 vs. 0.488 (reported))	Small discrepancy between number of events. Small discrepancy between median survival times and 95% confidence limits.

Gill 1993[13]	MGA	Gill1993	Gill1993	Gill 1993	-	NR	NR	HR not reported	No summary statistics or HRs reported but KM plots look the same		
Gill 1993[13]	TMX	Gill1993	Gill1993	Gill 1993	-	NR	NR	HR not reported	No summary statistics or HRs reported but KM plots look the same		
Mourids en 2001[20]	LTZ	Mourids en 2003[34]	Mouri dsen 2001	Mourid sen 2003[34]	Mouri dsen 2001	NR	NR	HR not reported	Medians match to nearest integer (as reported)		
Mourids en 2001[20]	TMX	Mourids en 2003[34]	Mouri dsen 2001	Mourid sen 2003[34]	-	NR	NR	HR not reported	Medians match to nearest integer (as reported)		
Milla-Santos 2003[18]	ANAS	Milla-Santos 2003	Milla-Santo	Milla-Santos 2003	-	73	NR	Small discrepancies between	-		

			s 2003					HRs and 95% confidence limits			
Milla-Santos 2003[18]	TMX	Milla-Santos 2003	Milla-Santos 2003	Milla-Santos 2003	-	104	NR	Small discrepancies between HRs and 95% confidence limits	-		
Paterson 1990[25]	TMX	Paterson 1990	Paterson 1990	Paterson 1990	-	NR	59	HR not reported	No summary statistics or HRs reported but KM plots look the same		
Paterson 1990[25]	MGA	Paterson 1990	Paterson 1990	Paterson 1990	-	NR	52	HR not reported	No summary statistics or HRs reported but KM plots look the same		
Hayes 1995[14]	TMX	Hayes 1995	Hayes 1995	Hayes 1995	-	81	150	Small discrepancie	Small discrepanc		

								s between HRS and 95% CIs for HR	ies between median survival times.		
Hayes 1995[14]	TOR60	Hayes 1995	Hayes 1995	Hayes 1995	-	76	160	Small discrepancies between HRS and 95% CIs for HR	Small discrepancies between median survival times.		
Hayes 1995[14]	TOR200	Hayes 1995	Hayes 1995	Hayes 1995	-	95	155	Small discrepancies between HRS and 95% CIs for HR	2.3 month discrepancy between median survival times. Removed number of events to prevent data truncation (shorter follow-up period)		
Iwata 2013[16]	EXE	Iwata 2013	Iwata 2013	Iwata 2013	-	57	103	Wider confidence	Small discrepanc		

								limits reported, however HRs match to within 2 d.p.	y between lower 95% confidence limits for median survival times. Small discrepancy between numbers of events. Small discrepancy between numbers at risk at 60 month time point		
Iwata 2013[16]	ANAS	Iwata 2013	Iwata 2013	Iwata 2013	-	55	114	Wider confidence limits reported, however HRs match to within 2 d.p.	Small discrepancy between median survival times and lower 95% confidence limit. Small discrepanc		

									y between number of events.		
TARGET and North America n[26]	ANAS	Nabholtz 2003[35]	Bonneterre 2001	Nabholtz 2003[35]	Bonneterre 2001	286	NR	Small discrepancies s between HRs and 95% confidence limits	Small discrepancies between median survival times.	Small discrepancy between HRs	-
TARGET and North America n[26]	TMX	Nabholtz 2003[35]	Bonneterre 2001	Nabholtz 2003[35]	Bonneterre 2001	286	NR	Small discrepancies s between HRs and 95% confidence limits	Small discrepancies between median survival times.	Small discrepancy between HRs	-
TARGET and North America n[26]HR+	ANAS	Nabholtz 2003[35]	-	Nabholtz 2003[35]	-	168	-	HR not reported	No summary statistics or HRs reported but KM plots look the same		
TARGET and North	TMX	Nabholtz 2003[35]	-	Nabholtz 2003[35]	-	171	-	HR not reported	No summary statistics or HRs		

American[26]HR+									reported but KM plots look the same		
Yardley 2009[31]	LDOX	Yardley 2009	Yardley 2009	Yardley 2009	Yardley 2009	NR	NR	HR not reported	Small discrepancies between median survival times	-	Small discrepancies between median survival times and 95% confidence limits.
Yardley 2009[31]	TXT	Yardley 2009	Yardley 2009	Yardley 2009	Yardley 2009	NR	NR	HR not reported	Small discrepancies between median survival times	-	Small discrepancies between 95% confidence limits for median survival time.
MONALEESA-2	RIBO + LTZ	-	Hortobagyi 2016	-	Hortobagyi 2016	-	NR			Small discrepancy between HR and 95% confidence limits	Small discrepancies between numbers at risk for 2, 4 and 20

											month time points.
MONALEESA-2	LTZ	-	Hortobagyi 2016	-	Hortobagyi 2016	-	NR			Small discrepancy between HR and 95% confidence limits	Discrepancies between numbers at risk for all time points except for zero. Small discrepancies between median survival times and 95% confidence limits. Removed numbers at risk due to survival probability appearing high.
FALCON	FUL	-	Robertson 2016	-	Robertson 2016	-	143			Small discrepancies between HRs and	Small discrepancy between numbers of events.

										95% confidence limits.	Small discrepancies between numbers at risk at 21, 27 and 33 month time points. Small discrepancies between median survival times and 95% confidence limits.
FALCON	ANAS	-	Robertson 2016	-	Robertson 2016	-	166			Small discrepancies between HRs and 95% confidence limits.	Small discrepancy between numbers of events. Small discrepancies between numbers at risk at 18, 27 and 36 month time

											points. Small discrepancies between median survival times and 95% confidence limits.
PALOMA-2	PALBO + LTZ	-	Finn 2016	-	Finn 2016	-	194			Small discrepancies between HRs and 95% confidence limits.	Discrepancies between numbers at risk at 15, 21, 27 and 33 month time points. Small discrepancy between median survival times.
PALOMA-2	LTZ	-	Finn 2016	-	Finn 2016	-	137			Small discrepancies between HRs and 95%	Discrepancies between numbers at risk at 3, 21, 24 and 30 month time

										confidence limits.	points. Small discrepancies between median survival times and 95% confidence limits.
MONARCH 3[3]	ABE + (LTZ or ANAS)	CSR[1]	CSR[1]	CSR[1]	CSR[1]	32	108	Discrepancy between HR and 95% confidence limits (HRs: [redacted] vs 0.972 (reported))	Small discrepancy between numbers of events. Small discrepancy between number at risk at 24 month timepoint	Small discrepancy between HR and 95% confidence limits	Small discrepancies in numbers at risk for 4, 16 and 24 month time points.
MONARCH 3[3]	LTZ or ANAS	CSR[1]	CSR[1]	CSR[1]	CSR[1]	17	86	Discrepancy between HR and 95% confidence limits (HRs: [redacted] vs	Small discrepancy between number at risk at 20 month timepoint	Small discrepancy between HR and 95% confidence limits	Small discrepancy in number of events. Small discrepancy between

								0.972 (reported))			lower 95% confidence limits for median survival time. Discrepancy between upper 95% confidence limits for median survival time (not reached vs. 17.46 months (reported))

Abbreviations: ABE: abemaciclib; ANAS: anastrozole; CI: confidence interval; EXE: exemestane; FUL: fulvestrant; HR: hazard ratio; KM: Kaplan-Meier; LTZ: letrozole; MGA: megestrol acetate; NR: not reported; PFS: progression-free survival; OS: overall survival; TOR: toremifene; TOR 60: toremifene 60 mg; TOR 200: toremifene 200 mg; TXT: docetaxel; LDOX: liposomal doxorubicin; SE: standard error; TMX: tamoxifen.

Figure 33. Digitised KM curves for Falcon PFS

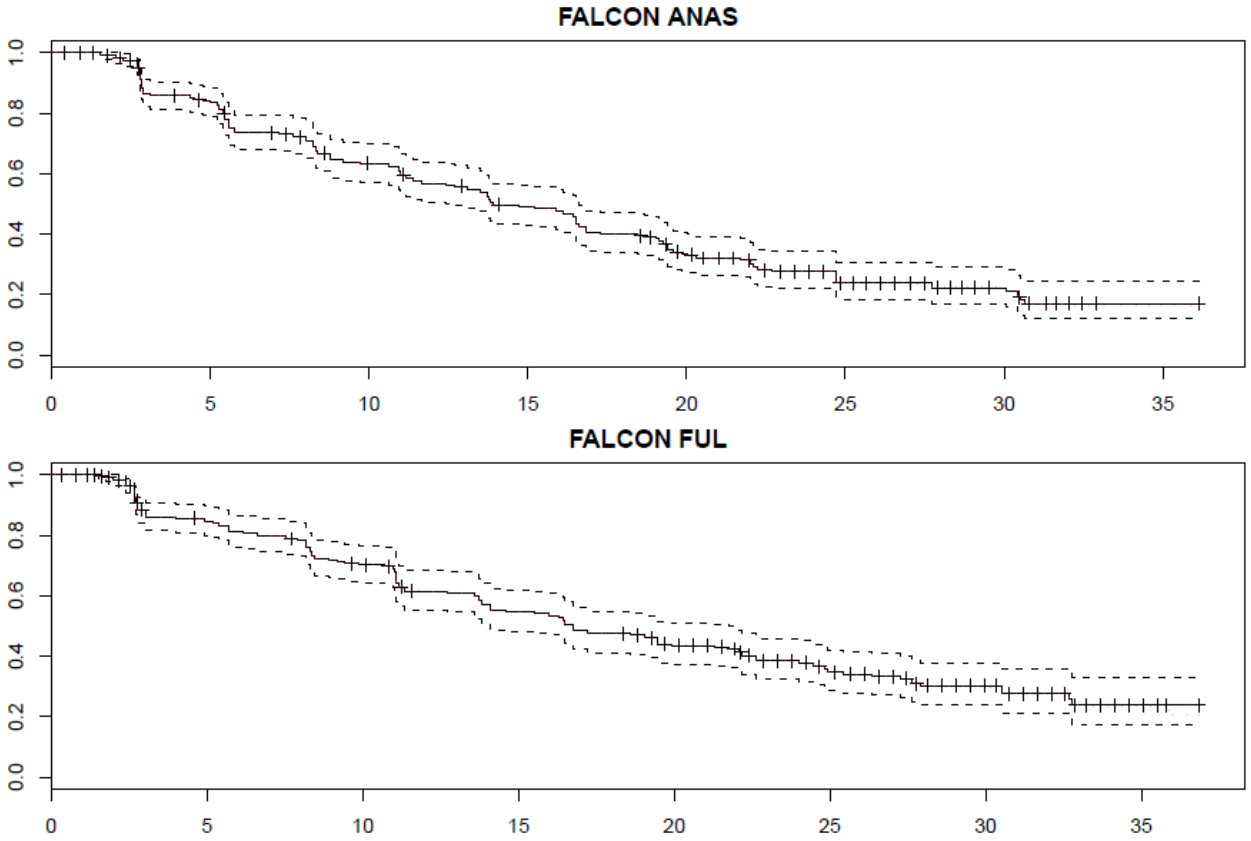


Figure 34. Digitised KM curves for Howell 2004 PFS (HR+)

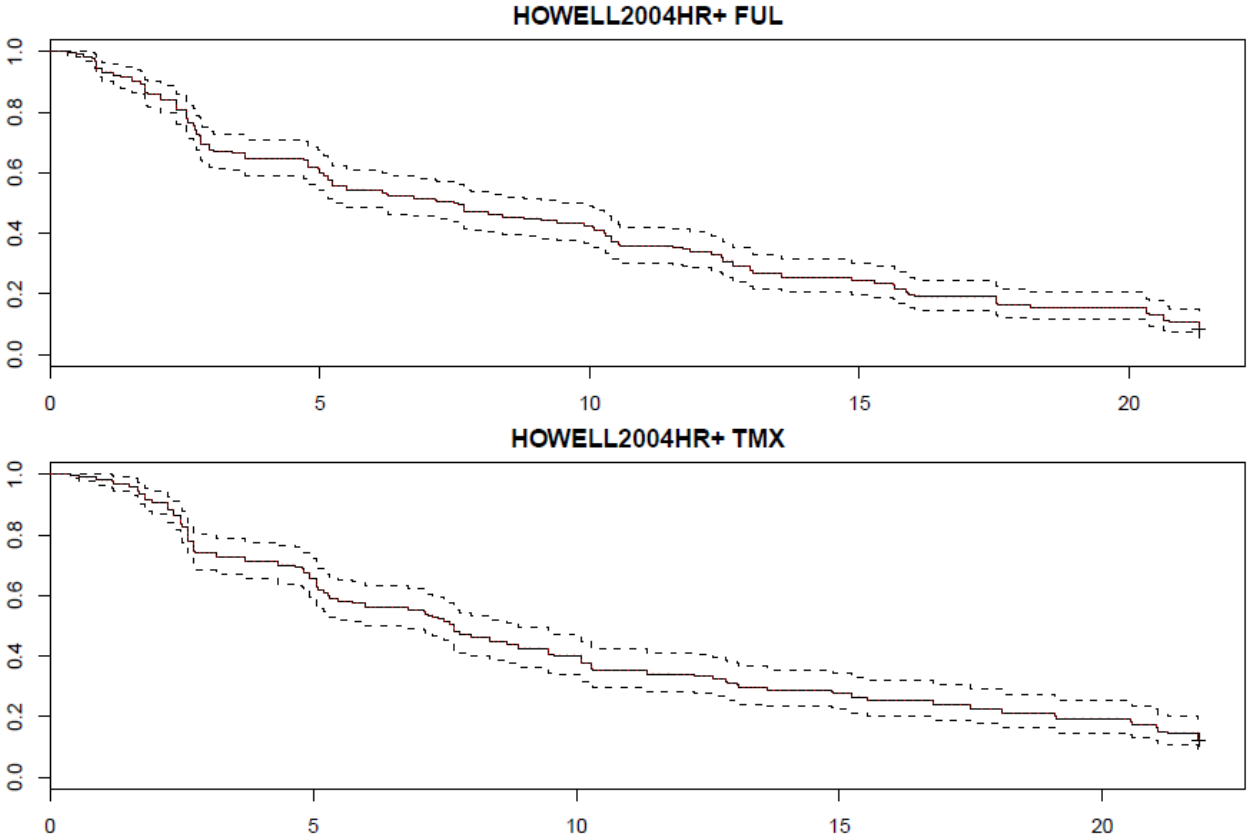


Figure 35. Digitised KM curves for Howell 2004 PFS

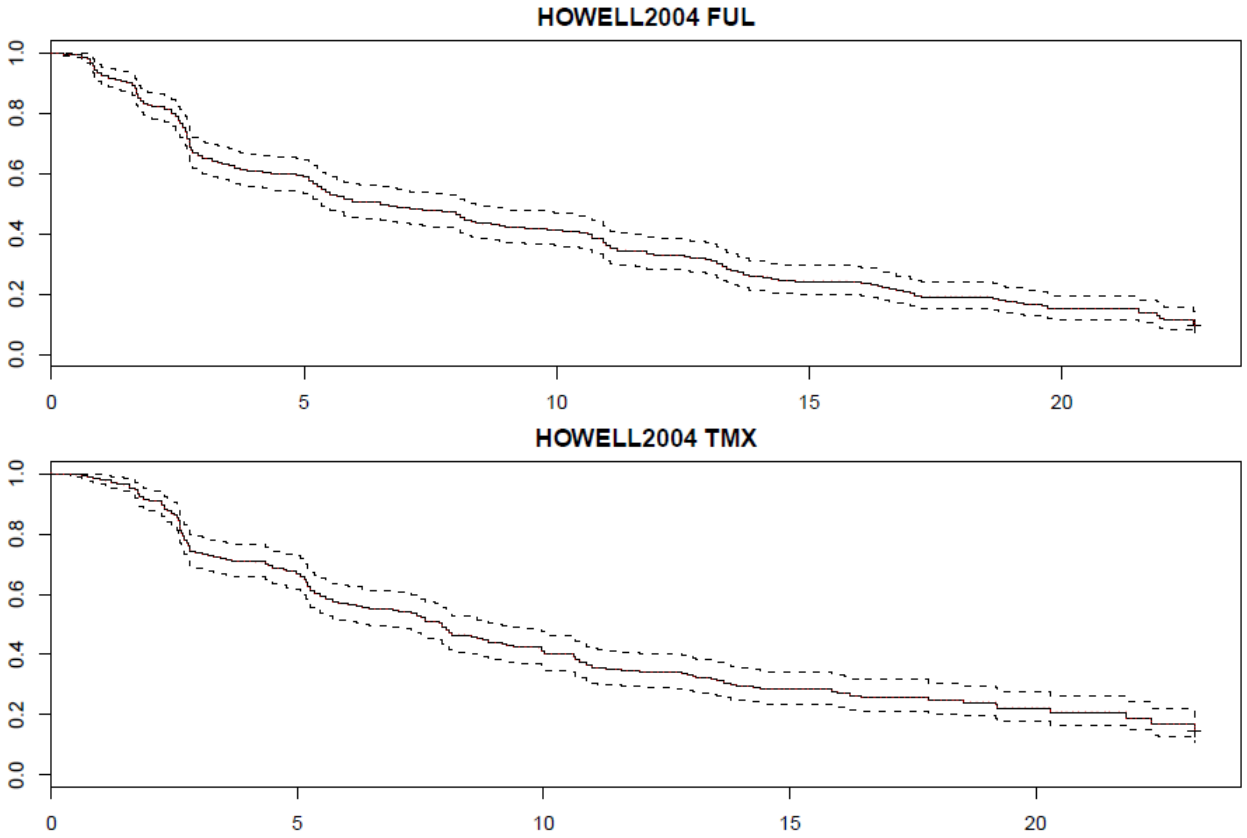


Figure 36. Digitised KM curves for MONALEESA-2 PFS

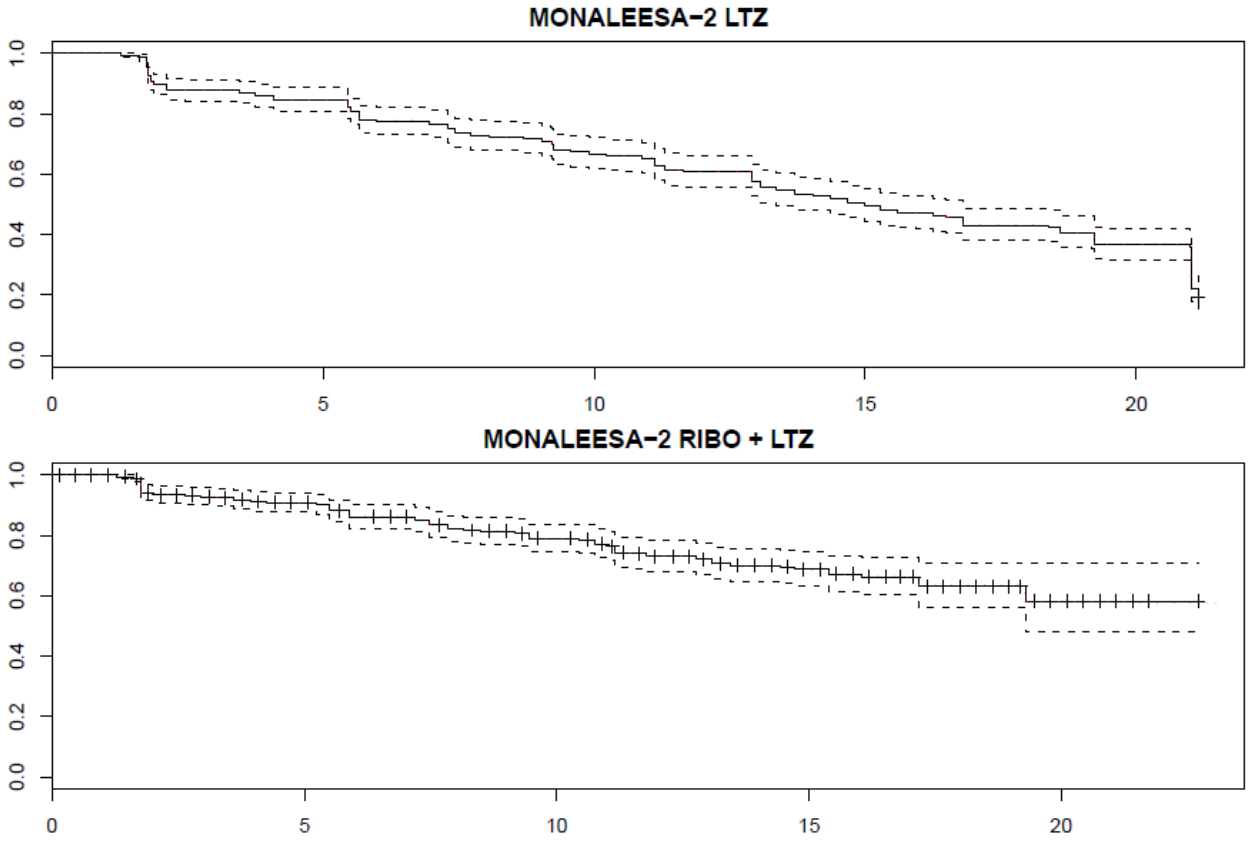


Figure 37. Digitised KM curves for MONARCH 3 PFS

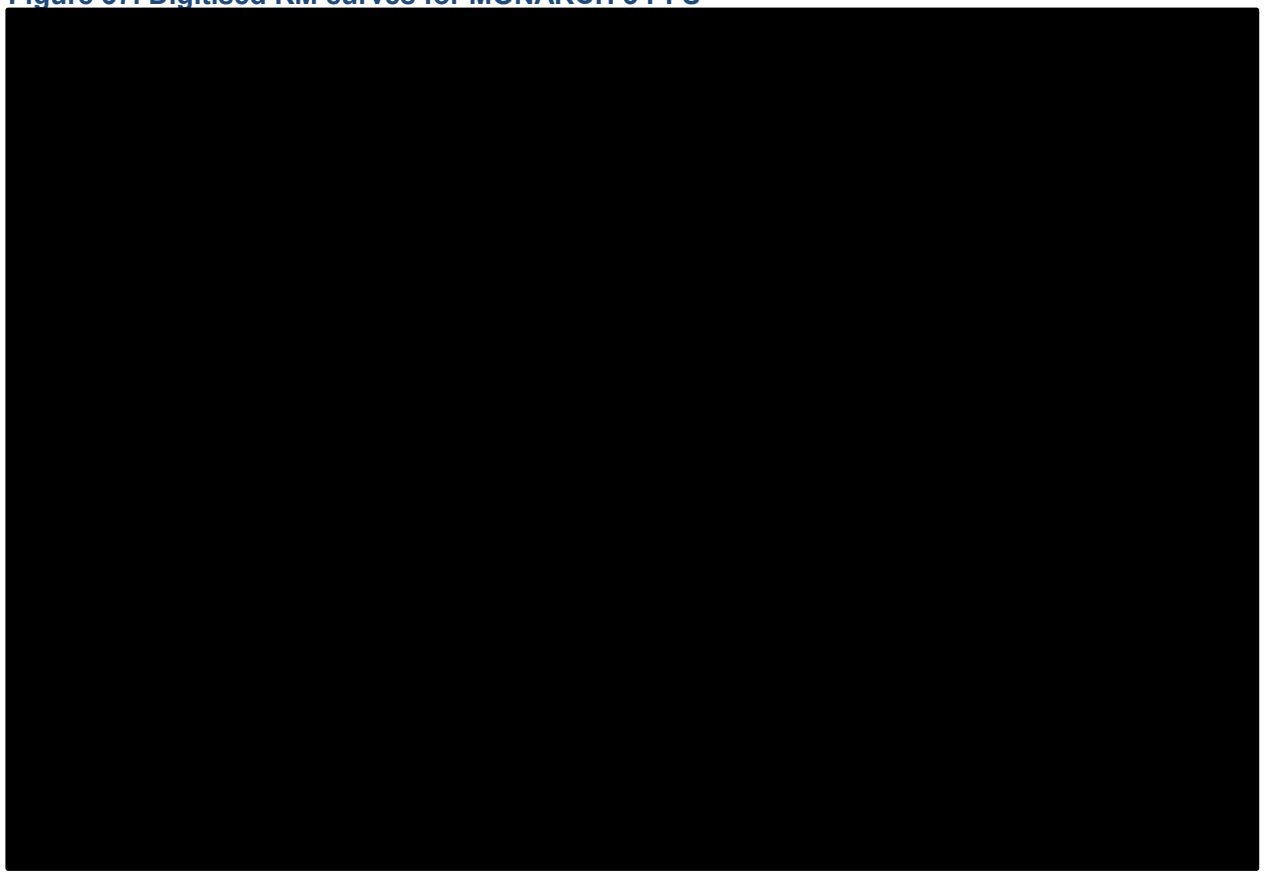


Figure 38. Digitised KM curves for PALOMA-1/TRIO-18 PFS

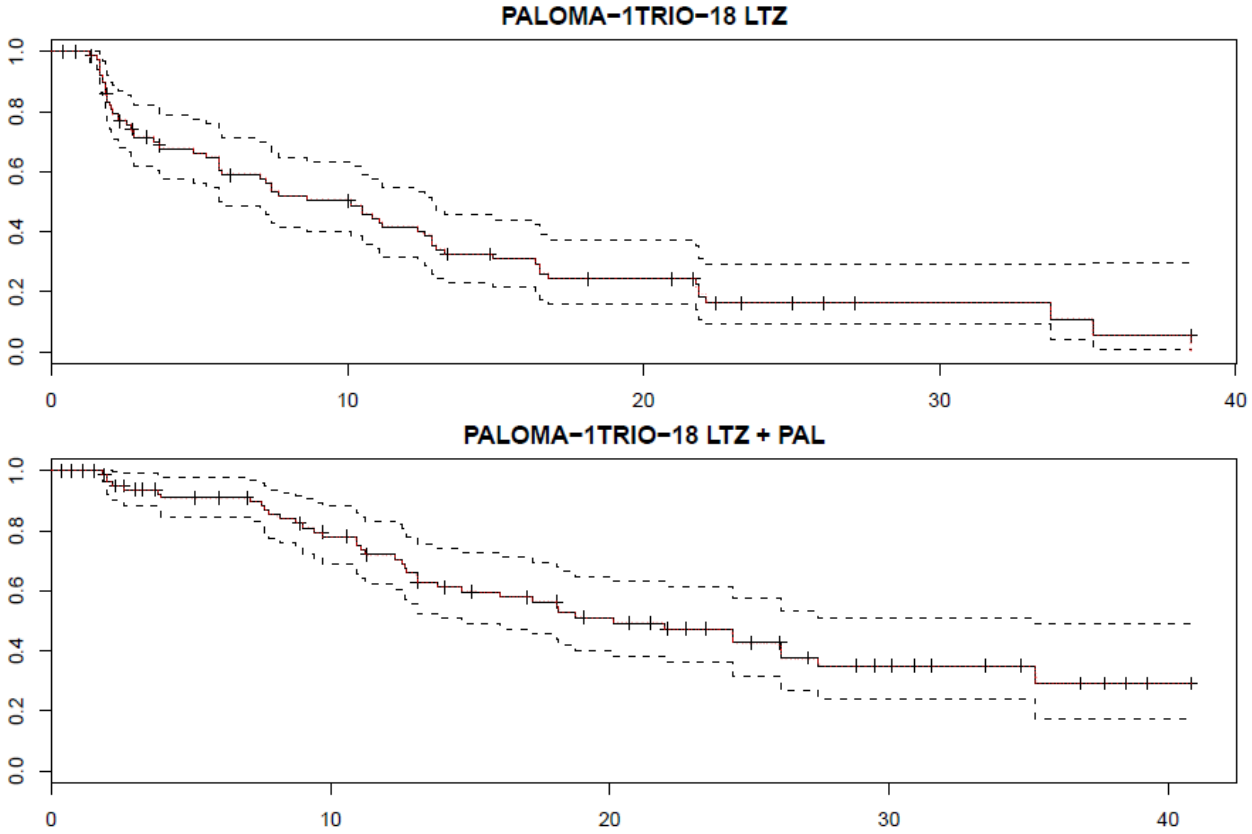


Figure 39. Digitised KM curves for PALOMA-2 PFS

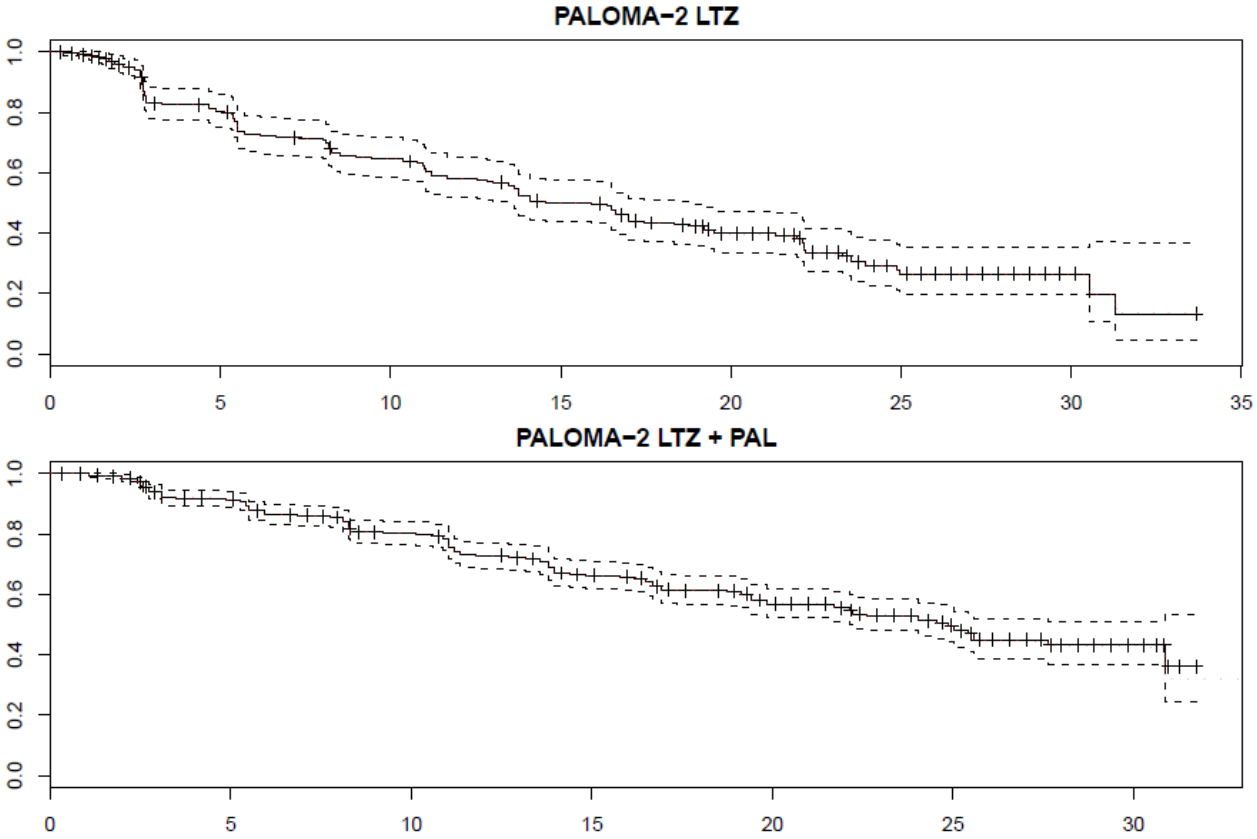


Figure 40. Digitised KM curves for Muss 1985 PFS

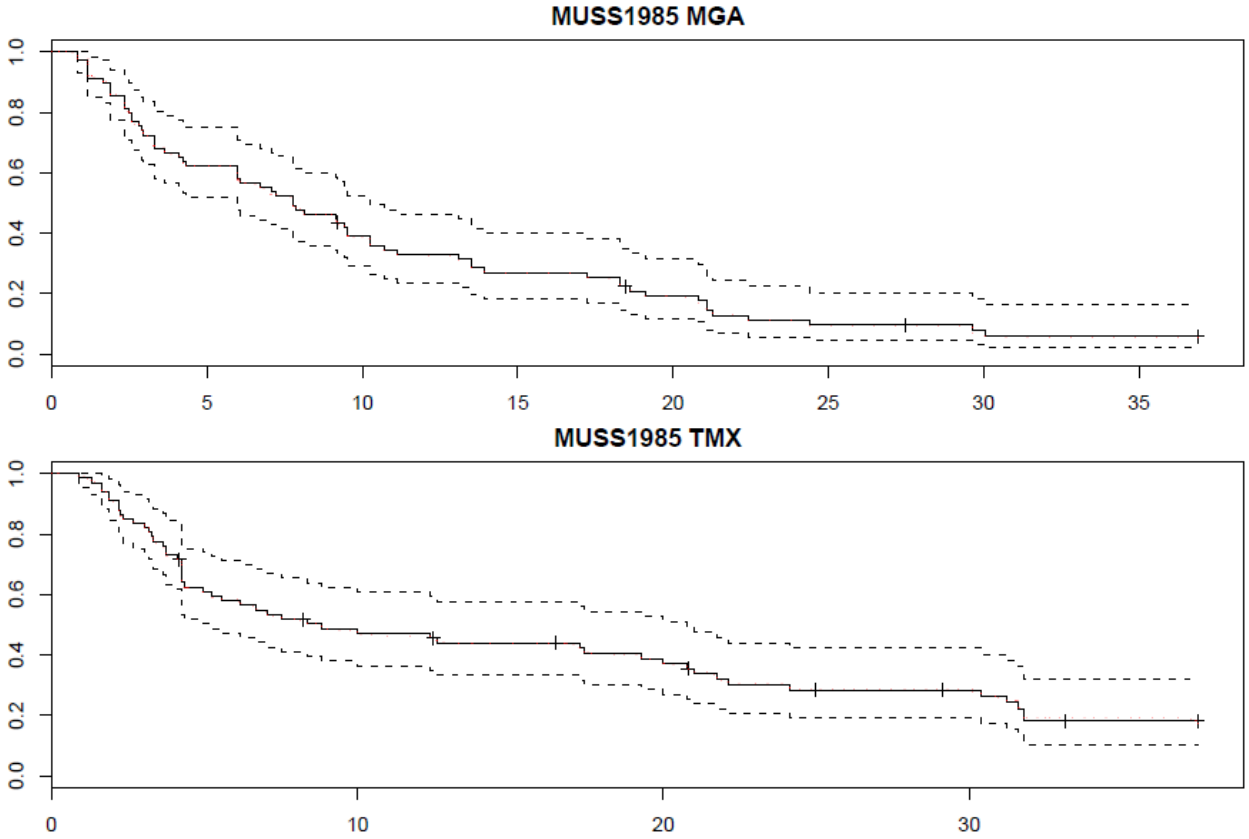


Figure 41. Digitised KM curves for Target and North American PFS

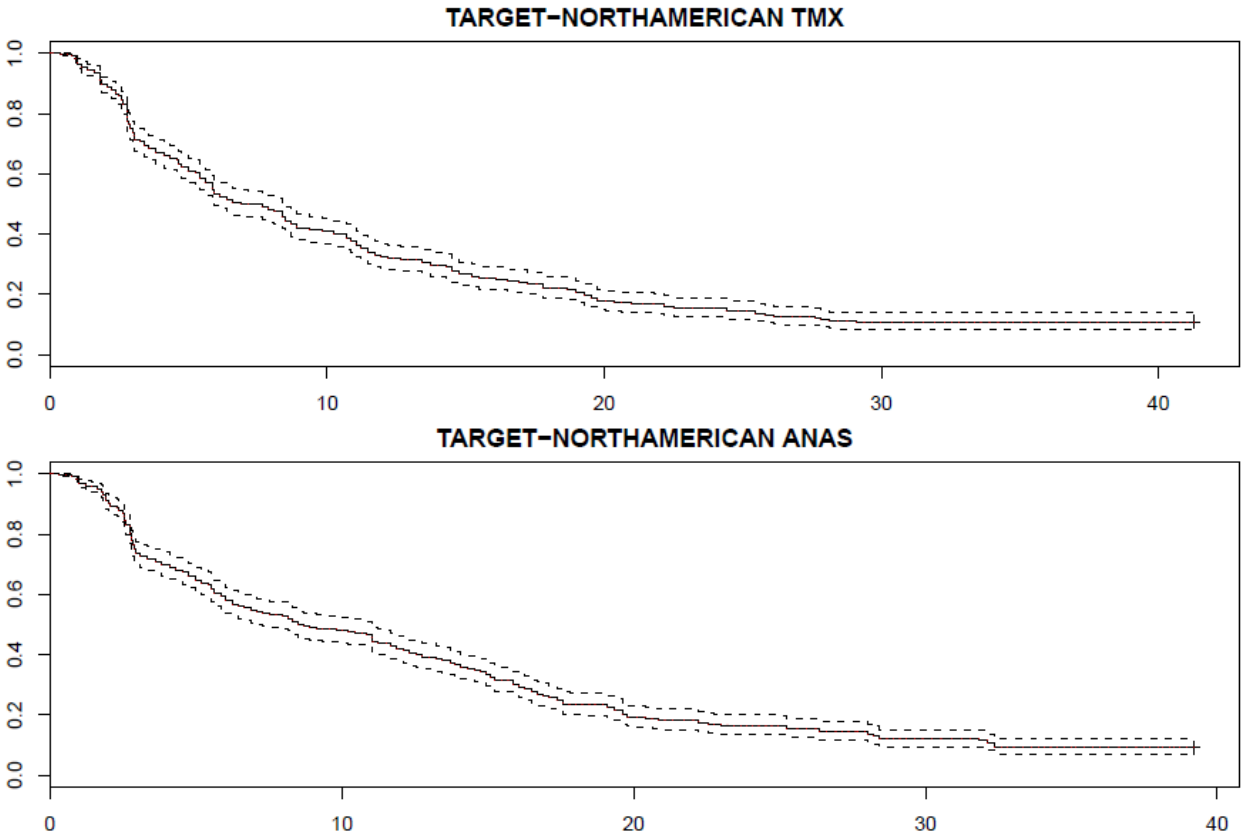
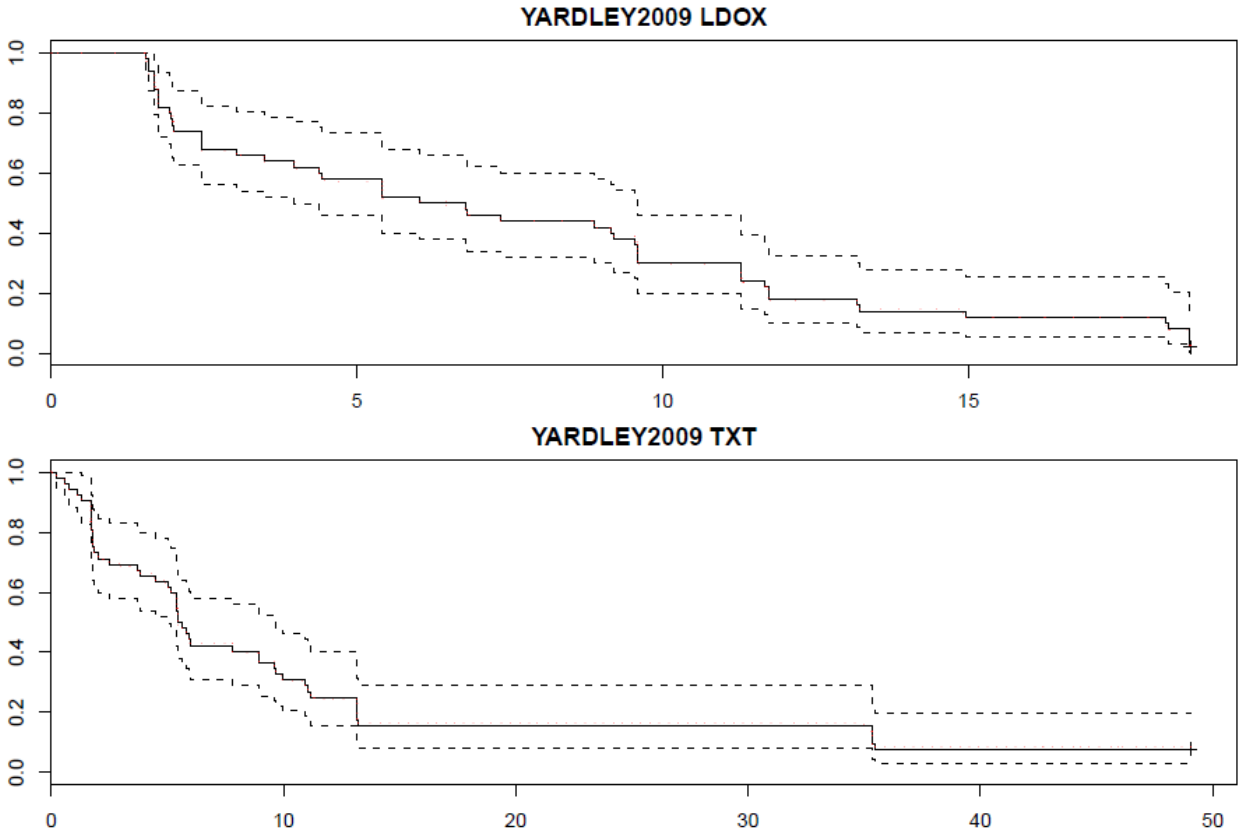


Figure 42. Digitised KM curves for Yardley 2009



Network meta-analysis (MONARCH 2 aligned)

A21. **Priority question.** The MONARCH 2 aligned NMA appears to play a pivotal role in the estimation of survival in the economic model. We therefore need to critically appraise it. However, only limited information is provided on it, in Appendix N. Please can you provide the same level of detail on this NMA as is currently provided in the submission on the MONARCH 3 aligned NMA, plus the additional information we have requested above for that NMA (e.g. full bibliographic details of the 18 studies included, plus tabulated baseline characteristics of patients, risk of bias assessments, network diagrams, programming code, discussion of clinical heterogeneity, etc).

The SLR and NMA reports for the MONARCH 2 indication are supplied alongside this document. Please note that the efficacy data for abemaciclib plus fulvestrant and fulvestrant included in the NMA analyses in the supplied report were sourced from the MONARCH 2 ITT population. In order to inform the second-line stage of the MONARCH 3 cost-effectiveness model, IPD for the subset of patients from the MONARCH 2 trial that had progressed on first-line endocrine therapy in the advanced breast cancer setting were used to estimate the outcomes of patients receiving fulvestrant as second-line therapy. Conducting a separate NMA for this subset of patients was not feasible, therefore the HRs generated from the NMA of the ITT population were used to estimate the outcomes of patients treated with other second-line treatments.

Section B: Clarification on cost-effectiveness data

B1. We note that the economic model includes an alternative 4-state model structure, but that this has not been described in the CS and it is not used for scenario analysis or in validation of the main model results. Please can you explain the rationale for developing the 4-state model, and justify why you have not reported the methods or results.

As noted by the ERG, an alternative 4-state model structure was investigated during development. This alternative was similar in structure to the model presented by the manufacturer of ribociclib in TA496 with the key difference being that it was implemented as a cohort model as opposed to an individual level simulation. During the NICE decision problem meeting the two alternative model structures were discussed, and we were advised to keep the alternative model in for use as a scenario. The PFS1 and PFS2 states were modelled as Markov transition states, however, patients experiencing disease progression in PFS2 did not explicitly transition into a PPS state. Outcomes following progression were attributed at the point of relapse based on the calculation of a fixed 'pay-off' for post-progression survival, costs, and outcomes.

The 4-state model was reported by the global technical report to give results that differed by ~6% from the base case model (using a wider set of comparators than relevant to NHS practice). Given that no important structural uncertainty had been revealed by the exercise, it was therefore decided that presenting methods and results for an entire additional model—representing a large volume of material, inputs and assumptions—would be of little or no value to UK submissions and the approach was not included or considered in the company submission to NICE and UK-specific results were not investigated.

B2. **Priority question.** Appendix M.2 presents estimates of parameter values for some selected survival distributions that are used in the model. However, others are omitted. We consider it likely that the committee will wish to consider alternative survival distributions and their impact on the sensitivity of the cost-effectiveness results. Please can you provide a revised version of the model including extrapolations of the survival curves for all six fitted distributions (exponential, Weibull, Gompertz, lognormal, log-logistic and generalised gamma) for each survival curve of interest: first-line TTP (adjusted and unadjusted for interval censoring); first-line TTD; second-line PFS (adjusted and unadjusted for interval censoring; second-line TTD; and second-line OS.

In selecting the distributions used to extrapolate all endpoints in the model, guidance from the NICE DSU technical support document 14 was followed.[36] For the within trial period, AIC and BIC statistics, Cox-Snell residuals, log-log and log cumulative plots (presented in Appendix M of the CS) were used to assess the fit of parametric models. Additionally, for the extrapolation period, the extrapolations resulting from each distribution are presented in the main body and Appendix M of the CS. For each endpoint, the three best fitting distributions are provided to explore uncertainty around the extrapolations. The only exception to this is for OS at the second-line stage, where due to the immaturity of trial data, clinical expert opinion was sought on the plausibility of different distributions in clinical practice. The best fitting distribution (Gompertz) based on AIC and BIC was deemed to be too pessimistic for this patient population and a different distribution (exponential) was therefore selected for the base case model, with the log-logistic and Gompertz included as scenarios.

The choice of three distributions provided in the model allows the committee to consider plausible alternative scenarios. We excluded the worst-fitting distributions, as we feel that these would not accurately reflect uncertainty, and may generate implausible ICERs that are unlikely to help the committee in the decision-making process.

B3. Please could you add a one-way deterministic sensitivity analysis with results summarised using tornado diagrams. Committee members find this helpful in understanding the impact of uncertainty over individual model parameters and identifying key model drivers.

The deterministic sensitivity analysis programmed into the model tests a number of scenarios in the model to help address uncertainty around different model parameters and assumptions. This includes testing the distributions selected to model clinical outcomes, the source of treatment effects, assumptions about time on treatment, utility values used in the model, etc. We believe these are key areas of uncertainty and the results of the scenarios show the magnitude of this uncertainty.

A one-way sensitivity analysis which varies the inputs by and arbitrary ±x% has not been included in the model as we do not believe it 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.[37]

B4. **Priority question.** The ERG needs to fully understand and replicate the calibration method. It appears that the calibration factors for OS adjustment are only entered into the model as inputs and referenced within the model as “Calibration exercise”. Please provide formulas and steps showing how the calibration factors were derived or alternatively, provide the referenced calibration exercise.

A key characteristic of state transition models such as this is the structural link between endpoints; as the model does not use an OS curve to inform survival (as in cohort partition modelling), increasing the amount of time spent in the “PFS” state results in an increase in the amount of time spent alive in the model. In effect, Markov models treat PFS as a surrogate for OS (i.e. a shift in time spent in any state in the model results in a shift of the same magnitude in OS).

In ERG and NICE appraisal committee feedback for PAL-NSAI (TA495) and RIBO-NSAI (TA496) for comparable indications,[38, 39] a transfer of 100% of PFS gain to OS gain was considered unlikely. Therefore, it was necessary to address the uncertainty surrounding the relationship between PFS and OS in HR+/HER2– advanced breast cancer.

Our model includes a calibration factor, which reduces time spent in the post-progression survival ‘pay-off’, ensuring that the gain in median OS for CDK 4 & 6 inhibitors versus NSAI alone is approximately 27.5% of the gain in median PFS. The calibration factor required to achieve this level of surrogacy for each CDK 4 & 6 inhibitor was estimated using the ‘goalseek’ function in Microsoft® Excel. Given that a different set of calibration factors is required every time settings that affect clinical outcomes in the model are changed, the ‘goalseek’ was written into the macro that generates the results of the model. This allows the calibration to happen automatically, regardless of which settings are selected by the user; in our testing, the goalseek function is the cause of the slow model speed (as Excel may test thousands of values).

When the user clicks “Run”, the model completes several steps (the VBA code is included at the end of the response to this question):

1. First, the model generates results using the current model inputs.
2. The model runs the goalseek to find the calibration factor required for each CDK to achieve the 27.5% surrogacy. In this model, the calibration factor applies to the scale parameters of the PFS and OS curves in the post progression pay-off.
3. Once the correct calibration factor has been estimated (ensuring the median OS gain is 27.5% of the median PFS gain), the model copies the calibration factor to the “HR” worksheet (cells E107:E110) and moves on to the next comparator.

It is important to note that because the model is programmed with monthly cycles, achieving exactly 27.5% is not always possible; monthly Markov cycles cannot be broken down into smaller components. Therefore, the number of months required for the calibration is rounded down to the nearest whole number.

In the revised model submitted on the 29th of June the macro is written as follows:

```
'Define variables
```

```
 Dim Index As Integer
    Index = 0
    Dim x As Integer
    x = Range("n.comp.analysis")
```

*** This section of the macro runs results for NSAI which is the referent for the calibration**

```
    Sheets("Trace").Range("comparator") = "NSAI"
    Sheets("Results").Range("BaseCase.Clinical1").Offset(1, 0) = Sheets("Results").Range("Results.BaseCase.Clinical").Value
     Sheets("Graphics").Range("PFS1.Survival").Offset(0, 1) = Sheets("Trace").Range("Trace.PFS").Value
    Sheets("Graphics").Range("OS.Survival").Offset(0, 1) = Sheets("Trace").Range("Trace.os").Value

i = 10

'Generate and store base case results for chosen comparator set without OS calibration

Do While Index < x

Application.Statusbar = "Running comparator " & Index + 1 & " of " & x & ", with calibration."

Worksheets("2nd line TTP").Range("Calibration.user").Value = 1

    Sheets("Trace").Range("comparator") = Sheets("Dashboard").Range("comparator1.user").Offset(Index, 0).Value
    Sheets("Results").Range("BaseCase.Outputs1").Offset(Index, 0) = Sheets("Results").Range("Results.BaseCase.Full").Value
    Sheets("Results").Range("BaseCase.Clinical1").Offset(Index, 0) =
Sheets("Results").Range("Results.BaseCase.Clinical").Value


    If Sheets("Dashboard").Range("comparator1.user").Offset(Index, 0).Value = "ABE+NSAI" Or
Sheets("Dashboard").Range("comparator1.user").Offset(Index, 0).Value = "PAL+NSAI" Or
Sheets("Dashboard").Range("comparator1.user").Offset(Index, 0).Value = "RIBO+NSAI" Or

    Dim set_cell_range As Range, to_value_range As Range, changing_cell_range As Range
    Dim to_value_val
    Dim temp_value
    Dim temp_range As Range
    Dim comp_loop As Range


    Set comp_loop = Worksheets("Dashboard").Cells(i - 3, 10)
    Worksheets("Trace").Range("comparator").Value = comp_loop.Value
    Set set_cell_range = Worksheets("Results").Cells(i, 16)
    On Error Resume Next
    to_value_val = Worksheets("Results").Cells(i, 18).Value
    Set changing_cell_range = Worksheets("2nd line TTP").Range("Calibration.user")

    'Run goalseek
    set_cell_range.GoalSeek _                    * This refers to the values in P10:P13 in the results tab of the model
                                        which calculate the gain in median OS against NSAI for each comparator
    Goal:=to_value_val, _                        * This refers to the values in R10:R13 in the Results tab of the model
                                        which calculate the gain in OS required to achieve the 27.5% surrogacy.
    ChangingCell:=changing_cell_range            * This refers to the calibration factor cell in the 2nd line TTP sheet

    'Paste calibration factor
    Worksheets("HR").Cells(97 + i, 5).Value = changing_cell_range.Value
    Worksheets("2nd line TTP").Range("Calibration.user").Value = "=vlookup(comparator,OS.Calibrationfactors,5,false)"

    Sheets("Trace").Range("comparator") = Sheets("Dashboard").Range("comparator1.user").Offset(Index,
0).Range("A1").Value
    Sheets("Results").Range("BaseCase.Outputs1").Offset(Index, 0) = Sheets("Results").Range("Results.BaseCase.Full").Value
    Sheets("Results").Range("BaseCase.Clinical1").Offset(Index, 0) =
Sheets("Results").Range("Results.BaseCase.Clinical").Value
```

```
    Sheets("Graphics").Range("PFS1.Survival").Offset(0, Index) = Sheets("Trace").Range("Trace.PFS").Value
    Sheets("Graphics").Range("OS.Survival").Offset(0, Index) = Sheets("Trace").Range("Trace.os").Value


    'Reset calibration factor to 1
    changing_cell_range.Value = "1"
   ' Worksheets("2nd line TTP").Range("Calibration.user").Value = "=vlookup(comparator,OS.Calibrationfactors,5,false)"
    End If

    i = i + 1
    Index = Index + 1
Loop
```

B5. **Priority question.** The calibration factors are entered into the model as single point estimates with no estimates of uncertainty. The CS includes a scenario without the calibration process, but does not include any sensitivity analysis around these values. We think it is important to be able to reflect uncertainty using one-way sensitivity analysis. Please could you provide a measure of variation/variance or confidence interval around these calibration factors?

The process of estimating the calibration factors does not provide confidence intervals or measures of variance; the model selects the factor value that achieves approximately 27.5% surrogacy between OS and PFS. Using any other value would result in a different surrogacy relationship. We would suggest that the calibration factor itself is not an area of uncertainty; what is uncertain is the surrogacy relationship between OS and PFS for CDK 4 and 6 inhibitors. Within the model, the dashboard contains an option for the user to enter a different proportion of the gain in median PFS that translates into a gain in median OS. This could be used to explore uncertainty around the surrogacy relationship. No additional information to inform uncertainty in the surrogacy relationship was identified in TA495 or TA496.[38, 39]

B6. In the model, calibration factors were applied to the OS as well as PFS curves in the three state PP payoff. As we understand it, the calibration factors are required to reflect the gain in OS. Please further explain why they are also applied to the PFS curves.

The calibration factors are designed to adjust OS for the patients (which is an output of the Markov model, rather than an input, as in cohort partition models). However, in the model the calibration factors only apply to PFS and OS in the second line. For simplicity, we decided to apply the same calibration factor for second-line PFS and second-line OS; we did not have any information to inform separate surrogacy relationships for second-line PFS and second-line OS. With the calibration factor applied, all the time spent in the PPS pay-off is reduced (including both time in second line PFS and second-line OS). If we were to calibrate only the second-line OS curve, and hold PFS2 constant, the second-line PFS and OS curves may cross in some situations, which would lack face validity.

Section C: Textual clarifications and additional points

C1. Reference 94 (Kurosky et al 2015) is a conference abstract. The submission appears to use a greater level of information than is provided in this abstract. We assume that a more detailed publication of this study was used by the company. If so, please provide a full citation and supply a copy of the report. We note that a 2017 publication of this study is now available: Kurosky, S. K., Mitra, D., Zanotti, G., & Kaye, J. A. (2017). Treatment Patterns and Outcomes of Patients With Metastatic ER(+)/HER-2(-) Breast Cancer: A Multicountry Retrospective Medical Record Review. Clin Breast Cancer. doi:10.1016/j.clbc.2017.10.008

NICE Technology Appraisal 503[40] should be considered the source for patient proportions allocated to second- and third-line treatments in the model, in place of Kurosky et al. 2015.[41] Treatments proportions for third-line treatment are taken from Table 66 of the manufacturer's submission. Patient proportions for second-line treatment published in Kurosky et al. 2015[41] were challenged by the ERG in this appraisal. Therefore, the ERG's preferred values for second-line therapy from Table 55 of the ERG report were used in this model.

C2. CS Appendix D.1.2, Table 9, page 28, under 'Exclusion criteria' ">10% of whole study population are currently receiving….". Should the symbol be "<" as on page 31?

The use of the '>' symbol on page 28 of the CS Appendix is correct. Studies in which >10% of the patient population were receiving or had previously received chemotherapy were excluded from the SLR, as they did not align sufficiently with the MONARCH 3 patient population. The use of '<' on page 31 is also correct; the statement is explaining that studies in which <10% of the patient population had previous exposure to chemotherapy were included in the SLR (but that no prior chemotherapy was permitted in the MONARCH 3 trial), therefore aligning with the aforementioned SLR exclusion criteria.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Abemaciclib with an aromatase inhibitor for untreated advanced hormone receptor-positive, HER2-negative breast cancer

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 Now
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 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 carers to include in your submission?	Information about the experiences of patients and carers is drawn from Breast Cancer Now's extensive networks. This includes formal studies about living with breast cancer such as the Big Breast Cancer Conversation, as well as informal insights collected from patients and carers.

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 treatments 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. A recent diagnosis of metastatic breast cancer will come as a shock to most patients and their families, as it is a terminal condition with a short life expectancy. Patients are keen to find treatments that will halt progression and extend life for as long as possible. It is important to most patients to start treatment quickly to get their disease under control. The type and severity of side effects experienced is also important for patients as these could impact negatively on their quality of life. Quality time with their loved ones will be a key objective in their treatment. Living with metastatic breast cancer is difficult to come to terms with for patients, their family, and friends. Patients' time is limited and treatments usually have some side effects. Patients therefore tell us that quality of life is just as important to consider as length of life, as they want to spend good quality time with their loved ones.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Post-menopausal patients with previously untreated metastatic hormone receptor-positive, HER2 negative breast cancer will now usually be offered a CDK4/6 inhibitor with an aromatase inhibitor to control their disease. The CDK4/6 inhibitors currently available to this group of patients are palbociclib and ribociclib. The aromatase inhibitor used in the trials of these drugs was letrozole, although anastrozole may also be used (it has been established in other appraisals for CDK4/6 inhibitors that there is a 'class effect' in this type of aromatase inhibitor). Once their disease progresses, patients may onto another aromatase inhibitor,

	or chemotherapy depending on issues including their specific cancer and on how well they tolerate the side effects of a drug. CDK4/6 inhibitors with an aromatase inhibitor significantly extend the time that patients are able to live without their condition progressing, giving them around an additional 10 months of good quality time with their loved ones compared to the alternative treatment option. We know how important this is to people living with incurable breast cancer. They are associated with some side effects. These include fatigue, nausea and neutrophenia - a condition where there are too few white blood cells, leading to increased susceptibility to infection. Full blood counts are required during treatment. However, neutropenia is manageable and reversible. We know that patients value access to these drugs because they are targeted treatments that cause fewer severe side effects than chemotherapy. This provides patients with a better quality of life compared to other treatments.
8. Is there an unmet need for patients with this condition?	CDK4/6 inhibitors with an aromatase inhibitor have recently been established as standard of care as a first line treatment for post-menopausal patients with previously untreated metastatic hormone receptor-positive, HER2 negative breast cancer. These drugs are innovative and represent a significant step forward in the treatment for this type of breast cancer.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The MONARCH-3 trial shows that patients taking abemaciclib plus an aromatase inhibitor enjoy prolonged progression-free survival compared to those taking an aromatase inhibitor alone. At the time of the interim analysis of the trial, the median duration of progression-free survival had not been reached among the group of patients receiving abemaciclib and an aromatase inhibitor, and was 14.7 months among the placebo group. Overall survival data was not mature at the time of interim analysis. Delaying progression means more quality time with family and loved ones as well as a delay to ultimately starting on systemic (non-targeted) chemotherapies, which are traditionally associated with more severe side effects and a poorer quality of life for patients. Delay to progression of disease can also have benefits for the mental health of patients, as lack of progression indicates that the medicine is working. A longer time to progression may mean that the patient is able to lead a more or less normal daily life throughout this time. Lack of progression of a metastatic cancer is also likely to bring some comfort to relatives and friends of the patient, as this is the best possible outcome for a terminal illness. Abemaciclib is administered orally, as are aromatase inhibitors that are given to patients alongside abemaciclib. This means patients are able to easily take this treatment in the comfort of their own home. However, some trips to the hospital will be necessary to monitor against serious side effects.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Abemaciclib with an aromatase inhibitor is associated with more side effects than an aromatase inhibitor as a monotherapy. The most common side effect is diarrhoea, but this is mostly of a low grade. The most common adverse (grade 3 or 4) side effects included neutropenia and leukopenia. These side effects will affect some patients more than others and the severity of side effects will determine whether patients will

	be able to continue taking this treatment. 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.
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 has been tested in post-menopausal women with metastatic hormone positive, HER2-negative breast cancer. This treatment could benefit a significant number of metastatic breast cancer patients. Exploratory subgroup analyses of the MONARCH-3 trial data suggest that abemaciclib with an aromatase inhibitor may provide a greater progression-free survival benefit in certain groups of patients. For example, the study authors highlight Asian patients (although an interaction between race and treatment effect was not noted in other trials on abemaciclib), those with an interval of less than 36 months between their primary and secondary breast cancer treatments, and those with liver metastases.
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?	No.

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- In the MONARCH-3 trial abemaciclib with an aromatase inhibitor shows promise in improving progression-free survival compared to an aromatase inhibitor alone.
- As a first line treatment for metastatic breast cancer, it has an important role in extending the time that hormone treatments work at controlling patients' disease progression. This is an important delay before patients will eventually be offered chemotherapy, which is known to have severe side effects.
- This drug is given in oral form, which makes it simple for patients to take. Apart from short-stay, regular blood tests, patients are not required to spend long lengths of time at the hospital, so it is unlikely that this will place a significant additional burden on patients and their families.
- There are some increased side effects from abemaciclib with an aromatase inhibitor, compared to an aromatase inhibitor alone, however not all patients will experience side effects. The benefits and risks of a treatment need to be clearly discussed with the patient to ensure they can make a decision that is right for them.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Abemaciclib with an aromatase inhibitor for untreated advanced hormone-receptor positive, HER2-negative breast cancer [ID1227]

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.

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 13 pages.

About you	
1. Your name	**Dr Andreas Makris**
2. Name of organisation	**UK Breast Cancer Group**

3. Job title or position	**Consultant Clinical Oncologist**
4. Are you (please tick all that apply):	**X** an employee or representative of a healthcare professional organisation that represents clinicians? **X** a specialist in the treatment of people with this condition? **X** 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 **X** 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.)	Relieve symptoms, improve quality of life, extend progression free survival and improve survival
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.)	Increase in progression –free survival by at least 3 months
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Despite initial response to treatment, most patients with metastatic breast cancer progress, require further treatment and eventually die from the cancer
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Non-steroidal aromatase inhibitor (letrozole or anastrozole) with palbociclib or ribociclib. Frail patients may receive an AI alone. Patients with symptomatic visceral metastases may receive chemotherapy as initial treatment
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE has recommended palbociclib or ribociclib as an option for treating hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer as initial endocrine therapy
• 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.)	Within the oncology community it is widely accepted that the majority of patients with locally advanced or metastatic breast cancer should receive an AI with a CDK4/6 inhibitor (palbociclib, ribociclib already NICE approved and abemaciclib is currently being considered). Patients with visceral metastases may be treated with chemotherapy and frail patients with an AI alone
• What impact would the technology have on the current pathway of care?	Patients with locally advanced or metastatic breast cancer who are hormone receptor-positive and HER2-negative who currently receive an AI + palbociclib or ribociclib may receive an AI + abemaciclib
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes

• How does healthcare resource use differ between the technology and current care?	Abemaciclib is another CDK4/6 inhibitor. It is given by daily administration continuously as opposed to palbociclib and ribociclib which are given daily for three weeks and then have a week's break before restarting the next cycle
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	In specialised oncology clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None as palbociclib and ribociclib are already being used for this indication in the NHS
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, I expect that abemaciclib will have similarly improved outcomes with palbociclib and ribociclib when added to an AI
• Do you expect the technology to increase length of life more than current care?	Trials of CDK4/6 inhibitors when added to AIs in patients with locally advanced or metastatic breast cancer are currently immature for overall survival. Such patients have a life expectancy that can extend to many years as there are other treatment options after progression on initial treatment with an AI +/- CDK 4/6 inhibitor, which is why differences in progression-free survival at initial treatment may not translate into differences in overall survival

• Do you expect the technology to increase health-related quality of life more than current care?	I expect a similar benefit of abemaciclib to palbociclib and ribociclib when added to an AI which would be greater than an AI alone. Although no quality of life data have been reported for Monarch 3 trial (AI +/- abemaciclib), an initial report from Monarch 2 (fulvestrant +/- abemaciclib) were presented at ASCO 2018. The combination of fulvestrant and abemaciclib, which resulted in longer progression-free survival, did not show statistically significant differences in patient-reported global health, functioning, or most symptoms compared to fulvestrant + placebo
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	In the trials of abemaciclib added to an AI all patient subgroups benefitted from abemaciclib
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	Abemaciclib is similar to current treatment of palbociclib and ribociclib. It is less myelosuppressive than palbociclib and may need less blood count monitoring after an initial treatment of 3-4 months. It is also given continuously rather than three weeks of every four as is the case with palbociclib and ribociclib. However, it causes more diarrhoea than the other CDK 4/6 inhibitors. In patients with visceral metastases who would have been treated with chemotherapy, the use of a CDK4/6 inhibitor with an AI would result in significantly less toxicity than chemotherapy

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	As with the other CDK 4/6 inhibitors in current use, toxicity may necessitate treatment delays and/or dose reductions. There would be no additional testing compared to the other CDK 4/6 inhibitors that are recommended by NICE
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	The introduction of the CDK 4/6 inhibitors in addition to AIs in the treatment of hormone-receptor positive HER2-negative locally advanced or metastatic breast cancer is a major advance in treatment of this disease. It has achieved a significant improvement in progression-free survival Hazard ratio 0.54 and median not yet reached, 14.7 months for placebo (Monarch 3), with low toxicity. Additionally objective

impact on health-related benefits and how might it improve the way that current need is met?	response rates are higher and can lead to a greater improvement in symptom control. CDK 4/6 inhibitors are currently being tested in the adjuvant setting after surgery in high-risk early breast cancer.
• Is the technology a 'step-change' in the management of the condition?	The introduction of CDK 4/6 inhibitors is an important improvement in the care pathway of patients with hormone-receptor positive HER2-negative locally advanced or metastatic breast cancer
• Does the use of the technology address any particular unmet need of the patient population?	Patients with hormone-receptor positive HER2-negative locally advanced or metastatic breast cancer can have a long survival but for most patients their disease progresses necessitating further treatment, including chemotherapy with more inconvenience to patients and more toxicity for patients
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?	CDK 4/6 inhibitors are generally well tolerated and allow many patients to live without symptoms or treatment toxicity when compared to AIs alone as they are more effective (improved progression-free survival and higher response rates)
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK	Yes, patients recruited in the Monarch 3 trial (Non-steroidal AI +/- abemaciclib) included patients with hormone-receptor positive HER2-negative locally advanced or metastatic breast cancer as would be seen

clinical practice?	in the current UK clinical practice
• 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?	Progressionfree survival, objective response rate, duration of response, toxicity, overall survival and quality of life. The trials are immature at present for overall survival and quality of life of Monarch 3 has not yet been presented
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I am aware
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 [TA496, TA495]?	No
22. How do data on real-world experience compare with the trial data?	I have not seen such 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.	N/A

Topic-specific questions	
24. Is a class effect for CDK 4/6 inhibitors likely?	Yes. However, some differences exist within this class of drugs with abemaciclib causing less myelosuppression and more diarrhoea than palbociclib

Key messages

25. In up to 5 bullet points, please summarise the key messages of your statement.

- Abemaciclib when added to an aromatase inhibitor is more effective than an aromatase inhibitor alone
- Abemaciclib when added to an aromatase inhibitor results in longer progression-free survival and higher objective response rates
- The combination of an abemaciclib and an aromatase inhibitor is well tolerated with manageable toxicity
- Abemaciclib has similar efficacy to palbociclib and ribociclib in cross-trial comparisons but no trials of direct comparisons of CDK4/6 inhibitors exist
- CDK 4/6 inhibitors are a major advance in the treatment of hormone-receptor positive and HER2-negative locally advanced and metastatic breast cancer

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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Single Technology Appraisal (STA)

Abemaciclib with an aromatase inhibitor for untreated advanced hormone receptor-positive, HER2-negative breast cancer [ID1227]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the statement submitted by Bread Cancer Now and consequently I will not be submitting a personal statement.

Name: .....Holly Heath.....

Signed: .....

Date: .....7 September 2018.....

.....

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Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Abemaciclib with an aromatase inhibitor for untreated advanced hormone receptor-positive, HER2-negative breast cancer

Produced by Southampton Health Technology Assessments Centre (SHTAC)

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None

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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

Jonathan Shepherd critically appraised the clinical effectiveness review, drafted the report, project managed the report and is the project guarantor. Olu Onyimadu critically appraised the economic evaluation, and drafted the report. Jill Colquitt critically appraised the clinical effectiveness review and drafted the report. Petra Harris critically appraised the clinical effectiveness review and drafted the report. Emma Loveman critically appraised the clinical

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[redacted]

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LIST OF ABBREVIATIONS

ABC	Advanced breast cancer
ABE	Abemaciclib
ABE+NSAI	Abemaciclib and non-steroidal aromatase inhibitor
ABE+FUL	Abemaciclib and fulvestrant
AE	Adverse event
AFT	Accelerated Failure Time
AI	Aromatase inhibitor
AIC	Akaike information criterion
ANAS	Anastrozole
BIC	Bayesian inference criteria
BNF	British National Formulary
BOR	Best overall response
BSA	Body surface area
BSC	Best supportive care
CBR	Clinical benefit rate
CDK	Cyclin-dependent kinase
CHMP	Committee for Medicinal Products for Human Use
CrI	Credible interval
CR	Complete Response
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DFI	Disease free interval
DIC	Deviance information criteria
DoR	Duration of response
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EPAR	European Public Assessment Report
ER(+)	oestrogen receptor (positive) (abbreviation for US spelling of estrogen)
ERG	Evidence Review Group
EQ-5D	EuroQol 5-Dimension
EXE	Exemestane
EVE+EXE	Everolimus + exemestane
FDA	Food and Drug Administration
FUL	Fulvestrant
HER2(+ or −)	Human epidermal growth factor receptor 2 (positive or negative)
HR	Hazard ratio
HR+	Hormone receptor-positive
HRQoL	Health related quality of life
IC	Interval censoring
ICER	Incremental cost effectiveness ratio
ITC	Indirect treatment comparison
ITT	Intention-to-treat

IV	Intravenous
KM	Kaplan-Meier
LTZ	Letrozole
N/A	Not applicable
NSAI	Non-steroidal aromatase inhibitor
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
NSAI	Non-steroidal aromatase inhibitor
OS	Overall survival
OS2	Overall survival from the start of second-line treatment
OR	Odds ratio
ORR	Objective response rate
PAL	Palbociclib
PAL+NSAI	Palbociclib and non-steroidal aromatase inhibitor
PAL+FUL	Palbociclib and fulvestrant
PAS	Patient access scheme
PD	Progressed disease
PF	Progression free
PFD1	Progression-free death from the start of first-line treatment
PFD2	Progression-free death from the start of second-line treatment
PFS	Progression free survival
PFS1	First-line progression-free survival
PFS2	Second-line progression-free survival
PgR	Progesterone receptor
PH	Proportional hazards
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient reported outcomes
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
RECIST	RECIST: Response Evaluation Criteria in Solid Tumours
RIBO	Ribociclib
RIBO+NSAI	Ribociclib and non-steroidal aromatase inhibitor
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
STA	Single Technology Appraisal
TEAE	Treatment emergent adverse events
TMX	Tamoxifen
TTD	Time to treatment discontinuation
TTD1	Time to discontinuation of first-line treatment

TTD2	Time to discontinuation of second-line treatment
TTP	Time to progression
TTP1	Time to progression from first-line treatment
TTP2	Time to progression from second-line treatment

SUMMARY

Scope of the company submission

The company submission (CS) assesses the clinical effectiveness and cost effectiveness of abemaciclib (ABE) in combination with a non-steroidal aromatase inhibitor (NSAI) in women with hormone-receptor positive (HR+), human epithelial growth factor receptor 2-negative (HER2-) advanced breast cancer. The comparators are palbociclib with an NSAI and ribociclib with an NSAI.

The decision problem generally meets the NICE scope, however, there are some differences in the population presented. The population in the decision problem is narrower by concentrating on locoregionally recurrent or metastatic breast cancer in post-menopausal women. The scope specified people with advanced breast cancer.

Summary of submitted clinical effectiveness evidence

A good quality systematic literature review of clinical effectiveness identified one randomised controlled trial (RCT) of abemaciclib relevant to the decision problem. The MONARCH 3 trial was a double blind, phase III RCT of abemaciclib (150 mg taken orally twice daily) and NSAI (ABE+NSAI) versus (vs) placebo+NSAI (n=493 patients randomised). The NSAIs used were either letrozole or anastrozole (investigator choice). A small number of patients from the UK ([redacted]) were enrolled in the trial. MONARCH 3 was judged by the ERG to be of reasonable methodological quality, though the possibility of unblinding, imbalance in drop-outs and selective reporting of outcomes increasing the risk of bias. The ERG believes that the company has identified all the relevant available RCTs of abemaciclib.

The CS presents interim results from MONARCH 3 (pre-specified and previously published) at a median follow-up of 17.8 months (data cut-off 31st January 2017), and results at the final progression free survival (PFS) assessment (from a confidential clinical study report) at a median follow-up of [redacted] months (data cut-off 3rd November 2017). Analyses were from an intention-to-treat (ITT) population for the majority of outcomes. The primary outcome of PFS (defined as the date of randomisation to objective progression or death) was investigator-assessed at the interim and final analysis. An independent review of PFS was also undertaken at both assessments.

There are no known trials of ABE+NSAI compared with the scoped comparators palbociclib (PAL) and ribociclib (RIBO). The CS present a Bayesian network meta-analysis (NMA) using published methods to perform indirect comparisons with these (and other) comparators (we refer to this as the 'first-line treatment NMA' in this report). A broad range of (non-scoped) comparator treatments were eligible from the SLR informing the NMA to allow a fully connected network. The NMA included a total of 18 RCTs, though only four of these were directly relevant to the decision problem: The MONARCH 3 trial of abemaciclib; the MONALEESA-2 trial of ribociclib; the PALOMA-1/TRIO-18 and PALOMA-2 trials of palbociclib (all with respective NSAIs). The ERG believes the SLR has identified all relevant RCTs. OS and PFS results from this NMA are used to inform the economic model: PFS results inform the time to first progression estimate and OS results inform the estimate of deaths before first progression (see below for a description of the economic model).

The company also briefly presents an additional NMA (in an appendix) to provide comparative evidence of abemaciclib as a second-line treatment in advanced breast cancer. The phase III MONARCH 2 RCT, which compares abemaciclib and fulvestrant to placebo and fulvestrant, is indirectly compared with trials of other endocrine therapies for patients who have progressed following first-line treatment for advanced breast cancer. This NMA (referred to in this report as the 'second-line treatment' NMA) was necessary as the OS data from the MONARCH 3 trial are immature and the economic model therefore includes a PFS2 health state to estimate OS from abemaciclib indirectly via the effects of second-line and subsequent treatment lines.

In the MONARCH 3 trial at the final PFS analysis:
Investigator assessed median PFS was [redacted] months in the ABE+NSAI group compared with [redacted] in the placebo+NSAI group; HR [redacted] (95% CI [redacted], 2-sided [redacted]), giving a reduction in the risk of progression of disease or death of 46%. Expert clinical advice to the ERG is that these results are clinically meaningful.

Median OS was [redacted], HR [redacted] (95% CI [redacted] 2-sided stratified log-rank [redacted]). [redacted] the OS rate at 24 months (ABE+NSAI [redacted] vs placebo+NSAI [redacted] OS data are currently immature ([redacted] events recorded, with final OS analysis to be done after 315 events).

The investigator assessed objective response rate (defined as the proportion of patients with best response of complete response (CR) or partial response (PR)), was [redacted] with ABE+NSAI compared with placebo+NSAI ([redacted]).

Among patients with an investigator assessed response (ABE+NSAI n=163, placebo+NSAI n=61), the median duration of response was [redacted] months (95% CI [redacted]) in the ABE+NSAI arm compared with [redacted] months (95% CI [redacted]) in the placebo+NSAI arm.

Health related quality of life (HRQoL), assessed on the global health status of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), showed a [redacted]. On the specific symptom scale of [redacted]) was observed, with [redacted] There was [redacted] in change from baseline in the EuroQol 5-Dimension 5-level (EQ-5D-5L) index score or visual analogue scale.

Proportions of participants with adverse events were higher in the ABE+NSAI arm for at least one adverse event judged as related to treatment ([redacted] ABE+NSAI vs [redacted] placebo+NSAI); grade ≥3 adverse events (ABE+NSAI arm [redacted] vs placebo+NSAI arm [redacted]; at least one serious adverse event (ABE+NSAI arm [redacted] vs placebo+NSAI arm [redacted]); serious adverse events judged to be related to study treatment (ABE+NSAI group [redacted]; placebo+NSAI group [redacted] and discontinuations of all study treatments (ABE+NSAI arm [redacted] vs placebo+NSAI arm [redacted]).

All treatment emergent adverse events, with the exception of arthralgia and back pain, occurred more frequently in the ABE+NSAI arm. Specific grade ≥3 adverse events of interest were diarrhoea (ABE+NSAI [redacted]; placebo+NSAI [redacted]); neutropenia (ABE+NSAI [redacted]; placebo+NSAI [redacted]) and leukopenia (ABE+NSAI [redacted]; placebo+NSAI [redacted]).

First-line treatment NMA results for abemaciclib, ribociclib and palbociclib:
For PFS (fixed effect model) all three treatments showed similar and statistically significant hazard ratios improving PFS relative to NSAI (ABE+NSAI [redacted]; PAL+NSAI [redacted]; RIBO+NSAI [redacted]). The random effects model resulted in similar hazard ratios but much wider credible intervals, and statistically nonsignificant differences relative to NSAI for each of the three treatments. There were no significant differences for the indirect comparisons between ABE+NSAI and PAL+NSAI or ABE+NSAI and RIBO+NSAI using either fixed or random effects models.

There were no statistically significant differences in OS for any of the three treatments relative to NSAI. Data for OS are immature and results are therefore uncertain. Similarly, there were no significant differences in OS for the indirect comparisons between ABE+NSAI and PAL+NSAI or ABE+NSAI and RIBO+NSAI using either fixed or random effects models. There were no statistically significant differences in measures of tumour response for any of the three treatments relative to NSAI.

Summary of submitted cost effectiveness evidence

Model structure and assumptions

The submission includes a three-state Markov model that estimates time spent progression-free on first-line treatment (PFS1) and time post-progression, for a cohort of people with HR+ HER2- advanced breast cancer. Costs and QALYs accumulated in the PFS1 health state are estimated in this model, but costs and QALYs after progression are estimated in a separate 'fixed pay-off' sub-model. The latter uses a 'partitioned survival' approach, using progression-free survival and overall survival outcomes for second-line treatments. Thus, PFS and OS evidence for second-line treatments contributes to estimating first line survival. Calibration enables exploration of uncertainty over the relationship between PFS and OS. The model adopts a 'partial surrogacy' approach, similar to that in the NICE appraisal of ribociclib TA496, with an assumption that the median gain in OS is a fixed proportion (27.5% in the base case) of the median gain in PFS for the first-line treatments.

Key model parameters are:

- *Clinical effectiveness*: Time to progression and deaths before progression for the first-line model, and PFS and OS for the second-line sub-model. These parameters are estimated individual data from the MONARCH 3 trial (first-line for ABE+NSAI and NSAI) and the MONARCH 2 trial (second-line fulvestrant), and from relative treatment effects from the first and second-line NMAs. This entails a series of assumptions that we critique in Chapter 4, and we highlight particular uncertainties below. In addition, as noted above, the company assumed a 'partial surrogacy' rate for calibration of the OS/PFS relationship of 27.5% (with 100% in scenario analysis).

- *Health Related Quality of Life*: Health state utility are derived from EQ-5D-5L data from patients in the MONARCH 3 and MONARCH 2 trials and from literature cited in other related NICE appraisals. MONARCH 3 was used in the company base case for the progression-free period at first-line ([redacted] for all comparators). For post-progression utilities, the company used the same estimates as the company in TA496, based on a formula reported by Lloyd et al. (2006): 0.774 for progression-free on second-line treatment, with an additional decrement of -0.113 for chemotherapy; and 0.505 for post second-line progression. Disutilities for adverse drug reactions are included in the model, but as the size and duration of the effects assumed are low, these have a negligible impact on cost-effectiveness results.

- *Use of second and third line treatments*

  The company assumes a mix of treatments at second and third line, based on the submission for the NICE appraisal of Fulvestrant at first line (TA503). This includes fulvestrant, exemestane, tamoxifen, everolimus with exemestane and chemotherapy.

- *Duration of treatment*

  Discontinuation rates for first and second-line treatments are modelled using survival curves, also estimated from MONARCH 3 (abemaciclib and NSAI) and MONARCH 2 (second-line fulvestrant). For other drugs, discontinuation is modelled relative to these curves, with hazard ratios estimated from median time to discontinuation reported in the key trials. Costs for third line treatments are included in the model, with an assumption that patients spend 37% of post-progression time on treatment.

- *Resource use and health care costs*

In addition to drug acquisition and administration costs (first, second and third line), the model includes costs for follow up care and monitoring, treatment of adverse drug reactions, hospital admissions, best supportive care and end of life care. Resource use was estimated using records from the MONARCH 3 and MONARCH 2 clinical trials, and recommendations in the NICE clinical guideline for advanced breast cancer (CG81). Average monthly non-drug costs were estimated at around £730 to £830 and end of life care at £4,400.

The company's base case results are shown in the table below – calculated at list price for abemaciclib and all comparators and subsequent treatments. Based on this analysis, the company concluded that ABE+NSAI is more effective, accruing more life years and QALYs, and less expensive than the comparators PAL+NSAI and RIBO+NSAI. They note that the lower costs are driven by a shorter time on treatment with ABE+NSAI.

Treatment	**Total**		**Incremental analysis ICER (£/QALY)**	**Pairwise ICERs ABE+NSAI vs. comparator (£/QALY)**
	Costs (£)	**QALYs**		
NSAI	£56,449	2.997	Referent	£250,065
PAL+NSAI	£145,266	3.225	Dominated	ABE+NSAI Dominant
RIBO+NSAI	£148,170	3.222	Dominated	ABE+NSAI Dominant
ABE+NSAI	£129,803	3.291	£250,065	-

The company presented similar results from a probabilistic sensitivity analysis (PSA), but we note that the probabilistic analysis did not reflect correlations between NMA parameters. The company present 29 deterministic scenario analyses, testing the impact of selected changes in model assumptions and parameters. These produced similar ICERs for ABE+NSAI compared with NSAI (in the range of £160,000 to £572,000 per QALY gained) and fewer QALYs at higher costs for the comparators PAL+NSAI and RIBO+NSAI compared with NSAI. The company did not present a one-way sensitivity analysis for model parameters, or tornado diagram.

Commentary on the robustness of submitted evidence

Strengths

- The company conducted a good quality systematic review to identify relevant clinical effectiveness trials. All relevant trials are believed to have been included.
- The clinical effectiveness evidence for abemaciclib comes from a relatively large (n=493 patients) phase III double-blind multinational RCT (MONARCH 3). The ERG judged this trial to be of reasonable methodological quality, though with some potential risks of bias (see below).
- The company's indirect comparison of abemaciclib with palbociclib and ribociclib (the first-line treatment NMA), used standard statistical methods, though there are some methodological limitations (see below).
- The economic model structure is appropriate, given the immaturity of overall survival data for abemaciclib and for the comparators ribociclib and palbociclib. There is considerable uncertainty over the assumptions and parameters of the second-line model and over the partial surrogacy assumption. However, a standard partitioned-survival approach would likely be even more uncertain.
- Methods used to estimate survival functions are generally appropriate, though parameters are not provided for some functions and the reporting is rather sparse.
- MONARCH 3 was used for the estimate of utility in the progression-free period at first-line ([redacted] for all comparators). This complies with the NICE reference case (assuming that crosswalk values are used as stated); uses EQ-5D-5L data collected directly from participants in the pivotal trial; and the methods of analysis are appropriate, although we do have some reservations related to lack of detail in reporting.
- We have a general preference for the treatment-specific utility estimates from MONARCH 3, because they reflect benefits and harms of treatments directly assessed by patients. But equivalent treatment-specific utilities are not available for all comparators. We therefore agree with the company's decision to use the overall PFS1 utility for all comparators in their base case.

Weaknesses and areas of uncertainty

- A high frequency of adverse events such as diarrhoea in the ABE+NSAI arm of the MONARCH 3 trial could have lead to unblinding, thus increasing the potential risk of detection and performance bias.
- The OS data from the MONARCH 3 trial are immature. The estimated study completion date is February 2020.
- There are some uncertainties associated with the first-line treatment NMA:
    - There is variation between the included trials in the proportion of patients with visceral metastases (affecting internal organs including the liver, lungs or brain), and the effect of this on the results is uncertain.
    - The NMA method used assumes the proportional hazards assumption holds for survival outcomes. However, this assumption could not be supported by available data for some trials.
    - Due to the immaturity of the OS data in the scoped treatment trials the ERG considers the results of the first-line OS NMA to be highly uncertain.
    - Despite the limitations listed above, the results were considered by clinical experts advising the ERG to be clinically plausible.
- There are likewise uncertainties associated with the second-line treatment NMA, namely:
    - Apparent clinical heterogeneity between the included trials in terms of percentage of patients with visceral metastases, the number of prior treatments for advanced breast cancer received and HER2 status. The comparability of the MONARCH 2 trial to the comparator trials is questionable.
    - Proportional hazards do not appear to hold for all the trials included, for both OS and PFS.
    - OS data are immature in some of the trials, including the MONARCH 2 trial. The results of the OS network should therefore be interpreted with caution.
- Exploration of uncertainty around the model results is limited. The PSA does not include correlations between NMA parameters and one-way deterministic sensitivity analysis is

not presented. The use of calibration within the model made it slow to run, so use of the PSA and other sensitivity analysis is difficult.

- On the basis of fit to observed data and clinical judgement on the plausibility of extrapolations, we agree with the choice of exponential survival curve for the time to progression on first-line treatment. We note, however, that the first line NMA indicated similar treatment effects for abemaciclib, ribociclib and palbociclib. This conflicts with the larger advantage predicted for abemaciclib when estimated directly from MONARCH 3 data. A similar issue arises when estimating the first-line pre-progression death rate, but in the opposite direction: direct estimation from MONARCH 3 for ABE+NSAI (jointly estimated with NSAI) gives a higher mortality rate than when this parameter is estimated from the NMA relative effects. Given that the decision problem is focussed on comparison between abemaciclib, ribociclib and palbociclib, it is important that comparators are modelled in a consistent way, and the NMAs are best source of evidence to judge relative treatment effects.
- At second-line, the company use data from the MONARCH 2 trial to estimate PFS and OS for second-line fulvestrant, with other drugs modelled relative to this curve using NMA results. As noted above, we have concerns over heterogeneity of the second-line trials and hence over the robustness of the NMA.
- The company choose to model second-line OS with an exponential curve fitted to the fulvestrant arm of MONARCH 2, and long-term extrapolation based on the CONFIRM trial. We disagree with this approach. Firstly, because the exponential curve had a poor fit to the MONARCH 2 data. Secondly, because very little information is provided to justify the fitting of the Weibull survival curve to the CONFIRM trial data. Based on evidence of goodness-of-fit and consideration of the plausibility of extrapolations, we consider the Gompertz or Log-logistic curves fitted to MONARCH 2 data are likely to be more reliable.
- Regarding the company's utility estimates in the base case, we suggest that the value used for second-line progression-free survival (0.69) in the final version of the TA496 appraisal looks more realistic than the original estimate, which is higher than the company's estimated for first-line utility.
- Our main concern over resource use assumptions: that the estimated use of second and third-line treatments does not reflect current NHS practice. In particular, the company includes fulvestrant which is not recommended by NICE in this context.

Summary of additional work undertaken by the ERG

We identified four minor errors in the coding of the model, which we correct. These made very little difference to the company's results. We also ran a range of scenario analyses to test uncertainties around model assumptions and parameters. Our preferred version of the model included the following changes to the company's base case:

- Estimation of time to progression and pre-progression deaths for ABE+NSAI estimated relative to fitted curves for NSAI using hazard ratios from the first-line NMA (as for other comparators.
- A Gompertz OS curve from second-line treatment. This was more pessimistic than the company's assumption of exponential with CONFIRM trial extrapolation.
- A utility of 0.69 for people free of progression at second line – as per the assumption suggested by the Decision Support unit in the NICE appraisal of ribociclib (TA496).
- And an alternative set of assumptions about use of second and third line treatments. This include the assumption that no patients would have fulvestrant, lower rates of exemestane monotherapy and higher rates of everolimus with exemestane at second line, higher rates of chemotherapy and fewer patients receiving no treatment at third line.

This version of the model (with list prices for all drugs) gave similar results to the company base case: an ICER of just under £200,000 per QALY gained for abemaciclib + NSAI compared with NSAI alone, compared with about £250,000 in the company's base case. For most scenarios tested, abemaciclib remained dominant or cost-effective compared with ribociclib and palbociclib. The absolute difference in QALYs between the CDK 4/6 inhibitors was very small, and the ranking of abemaciclib, ribociclib and palbociclib did change between scenarios. However, as the company note, the lower costs of abemaciclib are driven by a shorter time on treatment with ABE+NSAI. We note that this difference is based on weak evidence, as hazard ratios between treatments were estimated from reported median time to discontinuation.

1 Introduction to the ERG Report

This report is a critique of the company's submission (CS) to NICE from Eli Lilly and Company Limited on the clinical effectiveness and cost effectiveness of abemaciclib with an aromatase inhibitor for untreated advanced hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) breast cancer. It identifies the strengths and weaknesses of the CS. Clinical experts were consulted to advise the Evidence Review Group (ERG) and to help inform this report.

Clarification on some aspects of the CS was requested from the company by the ERG via NICE on (11th July 2018). A response from the company via NICE was received by the ERG on 26th July 2018 and this can be seen in the NICE committee papers for this appraisal.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The company presents an accurate overview of breast cancer and its pathogenesis in CS section B.1.3. Breast cancer is the most common cancer amongst women in the UK (age-standardised incidence rate of 95.0 per 100,000[1]) and is responsible for 7% of all cancer deaths in the UK (mortality rate of 17.1 per 100,000[1, 2]). The annual breast cancer incidence in England and Wales is 0.08% (~46,700 women),[3-5] of which approximately 90% of patients are diagnosed with invasive breast cancer.[3] The majority of these women (95%) are estimated to have early and locally advanced disease,[3] in which the cancer has not spread to other parts of the body. Approximately 35% of these women progress to advanced metastatic breast cancer,[3] where the disease has spread (metastasised) to other parts of the body (e.g. bones, liver, and lungs) or has grown into tissues and is unable to be removed completely by surgery.[6] An estimated 13% of women in the UK have advanced breast care at diagnosis.[3, 7] Advanced breast cancer is associated with poorer outcomes and is incurable, with a median overall survival (OS) of 2–3 years.[8]

The population of relevance to this appraisal is people with untreated advanced HR+ and HER2- breast cancer. Breast tumours are tested for oestrogen receptors (ER) and progesterone receptors (PgR), which stimulate tumour growth. ER+ or PgR+ tumours are commonly referred to as being HR+. The majority of HR+ tumours are both ER+ and PR+, while around 15% to 20% are ER+ only. Patients with HR+ breast cancer generally have an improved prognosis

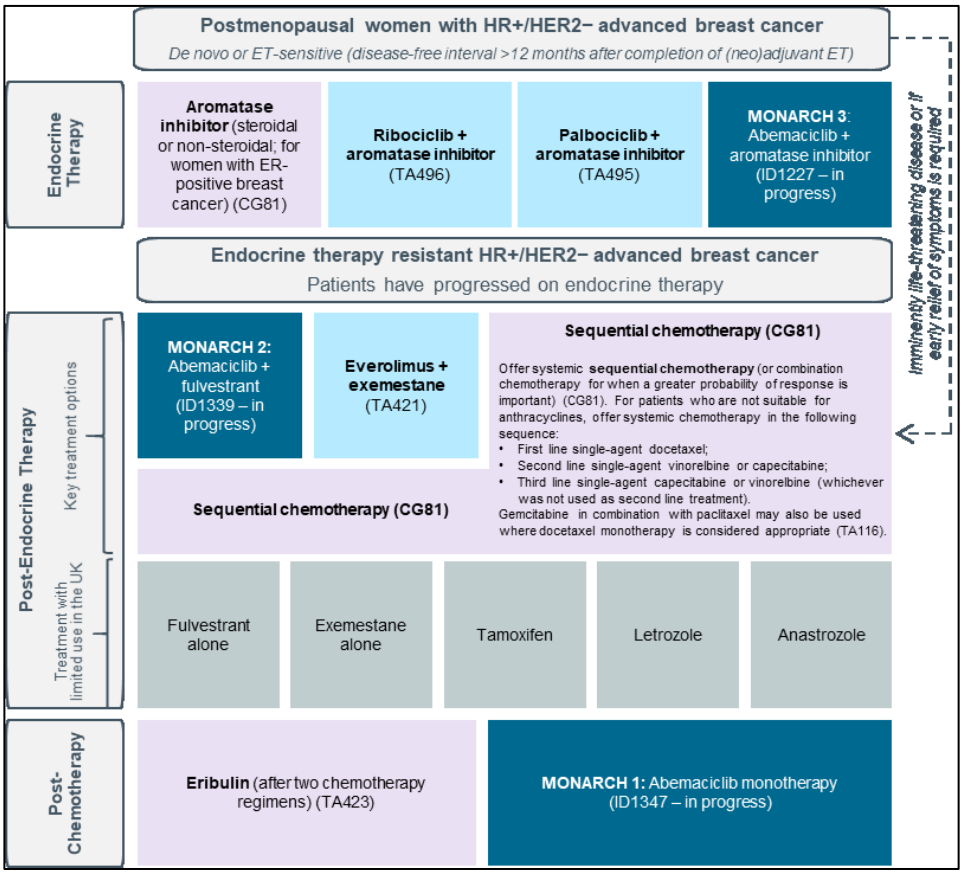
compared to those who are HR-negative (HR-), as tumours tend to grow more slowly and are more likely to respond to hormonal therapy (i.e. endocrine therapy). Endocrine therapy lowers the amount of available oestrogen or blocks existing oestrogen from binding to its receptor.

HER2 is a protein is found on the surface of breast cancer cells that can affect the growth of some cancer cells. Patients with HER2- breast cancer generally have an improved prognosis compared to those who are HER2+. The most common type of advanced breast cancer is ER+/HER2−, applying to approximately 64% of women with metastatic breast cancer in the UK.

The highest rates of breast cancer occur in older people, with ≥80% of cases in women over the age of 50 years (60 years or over for the majority of men) and 25% in women aged at least 75 years.[9] The CS describes the effects of breast cancer on patients and carers. Disease progression and side effects from treatment impact on the patient's ability to work, carry out of daily activities and on their emotional well-being. HER2- metastatic breast cancer is associated with worsening symptoms related to pain, fatigue, sleeplessness and acute distress.[10] This not only creates a burden for the patient, but also for their caregiver. Slowing disease progression and reducing treatment-related adverse events is therefore crucial for maintaining good health-related quality of life (HRQoL).[10]

2.2 Critique of company's overview of current service provision

The CS (Section B.1.3.3) describes the current treatment pathway for advanced breast cancer, based on current NICE guidance, and the intended position of abemaciclib in the pathway (Figure 1). Only abemaciclib in combination with an aromatase inhibitor (AI) as first-line treatment is relevant to this appraisal. Separate NICE appraisals will assess abemaciclib as a second-line and third-line treatment for advanced breast cancer (NICE ID1339 and ID1347, respectively). Expert clinical advisors to the ERG consider that the pathway is reflective of current clinical practice. However, they note that AI monotherapy would only now be used in a minority of patients given that ribociclib[11] and palbociclib[12] have been recommended by NICE for use in the NHS.



Source: CS Figure 2

Figure 1 Clinical pathway for patients with HR+/HER2− advanced or metastatic breast cancer being treated with abemaciclib + aromatase inhibitor

2.3 Critique of company's definition of decision problem

2.3.1 Population

The population described in the decision problem is post-menopausal women with advanced HR+/HER2− locoregionally recurrent or metastatic breast cancer, who have had no prior systemic therapy for advanced disease. (NB. in locoregional recurrent breast cancer the cells are identified in the same breast as the original tumour or in nearby lymph nodes, clarification question A1). Patients who have received treatment with endocrine therapy in the (neo)adjuvant setting with a disease-free interval >12 months from completion of endocrine therapy are included.

The ERG queried with clinical experts whether the inclusion of locoregionally recurrent breast cancer would potentially exclude patients with newly occurring (de novo) locally advanced breast cancer. The experts clarified that in routine practice the majority of these patients would be treated with chemotherapy in an attempt to downstage them and they would then receive surgery. The patients are unlikely to be entered into palliative treatment trials such as those relevant to this appraisal.

The company's decision problem reflects the patient population in the pivotal clinical trial of abemaciclib included in the CS (MONARCH 3[13] - see Table 2). While this approach appears reasonable, it does omit men with the disease potentially eligible under the NICE scope (the scope, which is aligned with the marketing authorisation, mentions "people with advanced hormone-receptor positive HER2-negative breast cancer"). The anticipated marketing authorisation does not exclude men (CS page10).

2.3.2 Intervention

The description of the intervention (abemaciclib + non-steroidal AI [ABE+NSAI]), is appropriate to the NHS and the NICE scope. Abemaciclib is a selective dual inhibitor of cyclin-dependent kinase 4 and 6 (CDK4 and 6). The starting dose of abemaciclib is 150 mg twice daily, reflecting the recommended dose of abemaciclib in the draft Summary of Product Characteristics (SmPC) when used in combination with endocrine therapy.[14] Abemaciclib should be taken continuously as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs. Dose interruption and/or dose reduction due to adverse events are recommended (see Table 1), such as for hematologic toxicities, diarrhoea and increased alanine aminotransferase levels.

Table 1 Dose adjustment recommendations for adverse reactions

Draft SmPC[14]	**Abemaciclib dose combination therapy[a]**
Recommended dose	150 mg twice daily
1st dose adjustment	100 mg twice daily
2nd dose adjustment	50 mg twice daily
3rd dose adjustment	-

[a] dose reductions for monotherapy not presented here

The decision problem states that either anastrozole or letrozole can be chosen as the NSAI to be used in combination with abemaciclib.

2.3.3 Comparators

The comparators are palbociclib + NSAI (PAL-NSAI) (letrozole) and ribociclib + NSAI (RIB+NSAI) (letrozole). These are appropriate for the NHS and reflect the NICE scope. Clinical experts advising the ERG consider palbociclib and ribociclib equivalent in effectiveness and safety, and the choice between them would be down to patient and clinician preference.

2.3.4 Outcomes

The outcomes stated in the CS scope are overall survival (OS), progression-free survival (PFS), tumour response rate, adverse effects of treatment and health-related quality of life (HRQoL). These are standard outcomes measured in cancer treatment trials and reflect those in the NICE scope.

2.3.5 Economic analysis

The economic analysis described in the decision problem is appropriate for the NHS. Cost-effectiveness is expressed in terms of the incremental cost per quality-adjusted life years (QALY) and costs are considered from the perspective of the NHS and personal social services (PSS), with a 35-year time horizon, using a Markov state-transition model with a fixed 'pay-off' for post-progression survival (see section 4 of this report for further description of the economic analysis).

2.3.6 Other relevant factors

The NICE scope does not contain any patient subgroups. The CS presents a summary of subgroup analyses of PFS and OS from the MONARCH 3 trial of abemaciclib (CS Appendix E). These are discussed in further detail in section 3.1.6 and section 3.3.6 of this report.

The company does not identify inequality issues that could be associated with the introduction or provision of abemaciclib (CS Section B.1.4). However, incidence is relatively uncommon the ERG consider that there is a potential issue of excluding men with advanced breast cancer. Expert clinical advice to the ERG is that in practice men with advanced breast cancer would be treated with goserelin acetate and palbociclib or ribociclib.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the company's approach to systematic review

3.1.1 Description of the company's search strategy

The CS reports four systematic literature searches:

- Clinical effectiveness evidence: searched from database inception to December 2015. Updated twice: March 2017 and January 2018 (CS Appendix D).
- Cost effectiveness: searched from 2010 to April 2016. Updated in November 2017 (CS Appendix G).
- Health related quality of life: searched from database inception to April 2016. Updated in November 2017 (CS Appendix H).
- Cost & healthcare resource identification measurement and valuation: searched from 2010 to 15th April 2016. Updated in November 2017 (CS Appendix I).

All four literature search strategies are of sound methodology, well documented and reproducible. An acceptable range of databases were searched with the application of appropriate syntax, good balance of descriptive terms and free text terms, with the use of suitable search filters. Key conferences were recorded as searched. The following ongoing trials databases were documented as searched: clinicaltrials.gov and the World Health Organisation International Clinical Trials Registry Platform (WHO ICTRP). No further published trials were identified by the ERG via an internet search and a Delphis database search (a University of Southampton cross-database search platform). The decision was therefore taken not to run full replicated update searches on the databases cited in the submission. An ongoing trials search, restricted to trials of abemaciclib that are currently recruiting patients, was undertaken by the ERG, to identify any other relevant trials not captured in the submission. Databases searched were clinicaltrials.gov, the UK Clinical Trials Gateway (UKCTG) and the WHO ICTRP (see section 3.3.9 for further details of ongoing studies). In summary, the ERG considers that the company's literature searches are all fit for purpose.

3.1.2 Statement of the inclusion/exclusion criteria used in the study selection

The CS clearly presents the eligibility criteria for the SLR (CS Appendix D.1.2, Table 9). The SLR was also used in the CS to identify studies of relevance to a network meta-analysis (NMA) which indirectly compares abemaciclib with relevant comparators. We describe this NMA in section 3.1.7 of this report.

3.1.2.1 Population

The company used wider population criteria for the SLR than the MONARCH 3 trial population criteria (see Table 2). The company justifies this because the specific characteristics of the patients in the MONARCH 3 trial meant that low returns of relevant literature were expected. The final included population was post-menopausal women with advanced HR+/HER2− locoregionally recurrent or metastatic breast cancer who have had no prior systemic therapy for advanced disease. Patients who had received treatment with endocrine therapy in the (neo)adjuvant setting with a disease-free interval of more than 12 months from completion of endocrine therapy were included). This reflects the patients in the MONARCH 3 trial, where the inclusion criteria were age ≥18 years, with patients required to be post-menopausal (either having had prior bilateral oophorectomy or aged ≥60 years).

3.1.2.2 Intervention

The inclusion criteria specify abemaciclib as single agent (not relevant to this appraisal) or combination therapy with NSAI. This is broader than the scope of this appraisal, but in line with the anticipated marketing authorisation which covers use of abemaciclib at first, second and third line treatment in locally advanced or metastatic breast cancer (see Figure 1).

3.1.2.3 Comparators

For inclusion studies had to compare to ≥1 listed treatments from below, or to placebo:

- Endocrine therapy (i.e. anastrozole; exemestane; fulvestrant; letrozole; megestrol acetate; tamoxifen; toremifene);
- Chemotherapy (i.e. capecitabine; docetaxel; doxorubicin; liposomal; gemcitabine; paclitaxel; nanoparticle bound; vinorelbine);
- Targeted therapy (i.e. buparlisib; ribociclib);
- Combination chemotherapy (i.e. AC (doxorubicin + cyclophosphamide); CAF (cyclophosphamide + doxorubicin + fluorouracil); docetaxel + capecitabine; gemcitabine + carboplatin; gemcitabine + paclitaxel);
- Combination endocrine and targeted therapy (i.e. buparlisib in combination with paclitaxel, or with ribociclib + letrozole, or with tamoxifen; exemestane + everolimus; palbociclib in combination with anastrozole, or with everolimus + exemestane, or with exemestane, or with fulvestrant, or with letrozole, or with tamoxifen; ribociclib in combination with anastrozole, or with capecitabine, or with exemestane, or with fulvestrant, or with letrozole, or with tamoxifen);
- Combination chemotherapy and targeted therapy (i.e. paclitaxel + bevacizumab).

Expert clinical advice to the ERG is that toremifene is no longer used, and that the chemotherapy drug eribulin is absent from the list. Also, buparlisib is not yet licensed; ribociclib is not licensed for use in combination with tamoxifen or capecitabine; and palbociclib is not licensed for use with exemestane + everolimus or tamoxifen.

Whilst the included comparators are broader than those listed in the NICE scope for this appraisal, the purpose was to identify relevant studies which could be included in the NMA (section 3.1.7.1). Additional comparators, even if not yet licensed or recommended by NICE, can link the NICE scoped treatments indirectly in networks.

3.1.2.4 Outcomes

The effectiveness and safety outcomes reflect those specified in the NICE scope and decision problem (OS, PFS, response rate; adverse effects of treatment; HRQoL).

3.1.2.5 Design

The eligibility criteria permits studies using randomised controlled trials (RCTs) and non-RCTs. Non-RCTs were identified in the first version of the SLR, but were not included in the updated SLR used to inform the CS as a sufficient number of RCTs were identified. The ERG considers this to be acceptable.

The CS presents a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram detailing the original literature search in 2015 and the two updated searches in 2017 and 2018. Details of excluded and included studies for all three searches are provided at each stage and a list of references for both are presented in the appendix of the CS (CS Appendix D.1.2, Table 10 and 11).

3.1.3 Identified studies

The company's SLR identified one phase III RCT, the MONARCH 3 trial, funded by Eli Lilly.[13] The CS presents sufficient summary details for the trial (CS section B.2.3: Table 4 trial inclusion and exclusion criteria; Table 5 trial design, intervention, population, outcomes, description of intention-to-treat (ITT) analysis, subgroups; Table 8 statistical analysis, power/sample size calculations, data management). A flow diagram details patient allocation and discontinuations (CS Appendix D.2, Figure 8). All relevant references were provided by the company electronically with the submission.

Patients in MONARCH 3 were randomised in a 2:1 ratio, with randomisation stratified by:

- site of metastases: visceral (lung, liver, pleural, peritoneal, or adrenal gland involvement); bone only, or other;
- prior (neo)adjuvant endocrine therapy: AI therapy (e.g. anastrozole, exemestane and letrozole), other, or no prior endocrine therapy.

A total of 328 patients were randomised to abemaciclib (150 mg taken orally twice daily) +NSAI and 165 to placebo+NSAI. The NSAIs were either letrozole (2.5 mg taken orally once daily) or anastrozole (1 mg taken orally once daily) in both treatment arms (investigator choice), with the majority of patients receiving letrozole (79.1%). The CS states that patients should have remained on the same NSAI throughout the study. Treatment was provided on a continuous 28-day treatment cycle.

Patients were not permitted to cross-over between trial arms; however, they were allowed to discontinue either abemaciclib/placebo or NSAI, and continue the other drug as a monotherapy. In response to a clarification question (A5) the company reported the percentage of patients receiving post-discontinuation therapies, ([redacted]% in the ABE+NSAI arm vs [redacted]% in the placebo+NSAI arm). The most common post-discontinuation therapies included endocrine therapy ([redacted]) (e.g. fulvestrant) and chemotherapy ([redacted]) (e.g. paclitaxel).

Patients' mean age was around 63 years, with the [redacted] of patients Caucasian ([redacted]) and [redacted] of included patients were enrolled at European sites ([redacted]), including four sites in the UK (Table 3). The company clarified that [redacted] patients from the UK were randomised in the MONARCH 3 trial; [redacted] were allocated to the ABE+NSAI arm and [redacted] to the placebo+NSAI arm (clarification question A2).

All patients with reported HR and HER2 receptors (missing data n=1, placebo arm) had breast cancer that was HER2- and around [redacted] had cancer that was positive for both ER and PgR hormone receptors. Baseline data for Eastern Cooperative Oncology Group (ECOG) performance status, disease setting, receptor status, initial diagnosis disease stage, metastatic site, number of organ sites, prior (neo)adjuvant chemotherapy/endocrine therapy and measurable disease were comparable between treatment arms. Median duration of disease was around [redacted] in the ABE+NSAI arm compared with placebo+NSAI arm ([redacted] months, respectively) and the proportion of patients with treatment-free interval

of ≥36 months higher (62.7 % vs 50.0% respectively). This suggests that the ABE+NSAI arm had some better prognostic factors at baseline, potentially favouring the treatment effects for this arm.

Around 40% of patients had de novo metastatic disease (slightly higher in the ABE+NSAI arm, Table 3) and approximately [redacted] had prior endocrine therapy in the neo(adjuvant) setting (slightly higher use of (neo)adjuvant NSAI in the placebo+NSAI arm).

The CS summarises selected categories of concomitant medication use (Table 3). Nearly all the patients received concomitant medication regardless of treatment allocation (ABE+NSAI [redacted], placebo+NSAI [redacted]), with details only reported for treatment received in [redacted] of patients. Differences between the treatment arms existed in the use of loperamide (an antidiarrhoeal) (ABE+NSAI [redacted] vs placebo+NSAI [redacted]) and therefore also in the antidiarrhoeal category (ABE+NSAI [redacted] vs placebo+NSAI [redacted], both [redacted] in patients receiving abemaciclib. Use of ≥1 antiemetics + anti-nauseants, erythropoietic agents, granulocyte-colony stimulating factor and granulocyte-macrophage colony stimulating factor [redacted] in patients receiving abemaciclib compared with placebo.

Table 2 Population as defined in the NICE scope, MONARCH 3, company decision problem and anticipated marketing authorisations

NICE final scope	Trial inclusion (MONARCH 3)	Company decision problem	Anticipated EMA marketing authorisation (CS p10)
People with advanced HR+/HER2− breast cancer that has not been previously treated with endocrine therapy	Postmenopausal women (≥18 years) with HR+/HER2− locoregionally recurrent or metastatic breast cancer who had no prior systemic therapy in the advanced setting Exclusion criteria: prior (neo) adjuvant ET with a disease free interval of ≤12 months from completion of treatment	Postmenopausal women with advanced HR+/HER2− locoregionally recurrent or metastatic breast cancer who have had no prior systemic therapy for advanced disease (patients who have received treatment with endocrine therapy in the (neo)adjuvant [a] setting with a disease-free interval >12 months from completion of ET are included).	Abemaciclib is expected to be indicated for the treatment of HR+/HER2− locally advanced or metastatic breast cancer: • **in combination with an aromatase inhibitor as initial endocrine-based therapy (current appraisal)** or in women who have received prior endocrine therapy • in combination with fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy • as monotherapy following disease progression after endocrine therapy and one or two chemotherapy regimens in the metastatic setting

[a] As defined in the MONARCH 3 trial

Table 3 Baseline characteristics - MONARCH 3 trial

Baseline characteristic	Abemaciclib + NSAI (n=328)	Placebo + NSAI (n=165)
Age		
Mean (SD)	[redacted]	[redacted]
Race, n (%) [a,b]		
White	186 (56.7)	102 (61.8)
Asian	103 (31.4)	45 (27.3)
Other	11 (3.4)	7 (4.2)
Region, n (%)		
Europe	[redacted]	[redacted]
ECOG performance status		
0	192 (58.5)	104 (63.0)
1	136 (41.5)	61 (37.0)
Disease setting, n (%)[c]		
De novo metastatic	135 (41.2)	61 (37.0)
Metastatic recurrent	182 (55.5)	99 (60.0)
Locoregionally recurrent	11 (3.4)	5 (3.0)
Receptor status, n (%)		
ER+/PgR+	[redacted]	[redacted]
ER+/PgR-	[redacted]	[redacted]
ER+/PgR unknown	[redacted]	[redacted]
ER-/PgR+	[redacted]	[redacted]
HER2 receptor status		
Negative	[redacted]	[redacted]
Missing[d]	[redacted]	[redacted]
Duration of disease (months)		
Median (IQR)	[redacted]	[redacted]
Prior (neo)adjuvant chemotherapy, n (%)		
Yes	125 (38.1)	66 (40.0)
No	203 (61.9)	99 (60.0)
Prior (neo)adjuvant endocrine therapy, n (%)		
None	178 (54.3)	85 (51.5)
Aromatase inhibitor	85 (25.9)	50 (30.3)
Other endocrine therapy	65 (19.8)	30 (18.2)
Treatment-free interval, n (%)[e]		
<36 months	42/150 (28.0)	32/80 (40.0)
≥36 months	94/150 (62.7)	40/80 (50.0)
Unknown	14/150 (9.3)	8/80 (10.0)
Measurable disease, n (%)		
Yes	267 (81.4)	130 (78.8)
No	61 (18.6)	35 (21.2)
Selected categories of concomitant medications during trial (safety population), n (%)		
	(n=327)	**(n=161)**
Patients with ≥1 analgesic	[redacted]	[redacted]
Patients with ≥1 antidiarrheal	[redacted]	[redacted]
Patients with ≥1 antiemetics and anti-nauseants	[redacted]	[redacted]
Patients with ≥1 bone-modifying agents	[redacted]	[redacted]
Patients with ≥1 erythropoietic agents	[redacted]	[redacted]
Patients with ≥1 G-CSF/GM-CSF	[redacted]	[redacted]

Source: CS Table 6 and 7 based on Goetz et al. 2017[13] and CSR. ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; G-CSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2; IQR, Interquartile Range; NSAI, non-steroidal aromatase inhibitor; SD, standard deviation.

[a] Race was self-reported; [b] Data was missing for remaining patients; [c] Percentage does not equal 100% as the result of rounding; [d] For one patient in the placebo+NSAI arm, HR status and HER2 status were missing. The patient was not treated; [e] Treatment-free interval was calculated only for patients with prior endocrine therapy.

3.1.4 Description and critique of the approach to validity assessment

Quality assessment of MONARCH 3 was undertaken by the company using NICE recommended criteria. A comparison of the company and ERG judgements for MONARCH 3 can be seen in Table 4.

Table 4 Company and ERG assessment of trial quality for MONARCH 3

NICE QA Criteria for RCT[a]	CS response	ERG response
1. Was the method used to generate random allocations adequate?	Low	Low
2. Was the allocation adequately concealed?	Low	Low
3. Were the groups similar at the outset of the study in terms of prognostic factors, e.g. severity of disease?	Low	Low (for most characteristics but not duration of disease or treatment-free interval, see section 3.1.1)
4. Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Low	Unclear: adequate blinding described but high frequency of adverse events such as diarrhoea in the ABE+NSAI arm could lead to unblinding.
5. Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Low	High: [redacted]
6. Is there any evidence to suggest that the authors measured more outcomes than they reported?	Low	High: The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Breast 23 (EORTC QLQ-BR23) was measured in MONARCH 3, but this is not mentioned in the CS or trial publication (mentioned in the CSR).
7. 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	Low

[a] Low = low risk of bias, high = high risk of bias, unclear = uncertain risk of bias.

The ERG agrees with most of the company's judgements for MONARCH 3, but notes that the higher frequency of adverse events such as diarrhoea in the ABE+NSAI arm could have led to unblinding of patients and care providers. This may potentially increase the risk of performance bias and detection bias (particularly affecting self-reported outcomes such as HRQoL). The reasons for discontinuation were not presented by trial arm in the CS; these were requested by the ERG and provided in clarification response A3. [redacted]

[redacted]. The ERG judged the MONARCH 3 trial to have a high risk of selective reporting bias, as the EORTC QLQ-BR23 trial was measured but not reported. The ERG obtained these results from the CSR.

3.1.5 Description and critique of company's outcome selection

The outcomes selected by the company are appropriate to the NICE scope and are commonly measured in a cancer trial. The details in the CS generally concur with those reported in the MONARCH 3 trial publication[13] and CSR except where stated below. The ERG consider that the outcomes appear to have been predefined.

The primary outcome of the MONARCH 3 trial was investigator-assessed PFS as defined by RECIST (RECIST: Response Evaluation Criteria in Solid Tumours) version 1.1.[15] PFS was measured from the date of randomisation to the date of objective progression or death due to any cause. A randomly selected subset of scans (number of scans not stated) was independently and blindly reviewed by a panel of radiologists at the interim analysis, and at the final analysis a full independent review of PFS was performed. The CS provides results for both investigator and independently reviewed PFS at both interim and final analysis, which the ERG considers appropriate.

Baseline tumour measurements (RECIST 1.1) were performed within 28 days of randomisation and then on Day 21–28 of every second cycle (approximately every eight weeks) between cycle 2 and cycle 18 and on day 21–28 of every third cycle (approximately every 12 weeks) after cycle 18, and then within 14 days of clinical progression. The finding of a new lesion was required to be unequivocal and not attributable to something other than a tumour. In the non-measurable, bone only disease cases, appearance of one or more new lesions (in bone or outside of bone), or unequivocal progression of existing bone lesions was required.

For those patients with locoregionally recurrent disease (around 3%) the CS states that in those in whom surgery was performed while on study with evidence of residual disease postoperatively, new baseline measurements should have been assessed. The CSR also describes that in [redacted]

- [redacted]

- [redacted]

The ERG asked for clarification (question A8) and the company response suggests that no participants had surgery while on study.

Response outcomes definitions as per RECIST 1.1 criteria were as follows:

- Complete response (CR), disappearance of all target lesions;
- Partial Response (PR), ≥30% reduction in the sum of diameters of target lesions (taking baseline sum diameters as the reference);
- Clinical benefit rate (CBR), the proportion of patients with CR, PR, or stable disease (SD) ≥6 months;
- Duration of Response (DoR), date of first evidence of CR or PR ([redacted]) to the date of objective progression or death due to any cause, whichever was earlier.

Expert clinical advice to the ERG confirms that clinical benefit rate (CR + PR + SD ≥6 months) is a clinically relevant outcome and used in practice.

The CS also reports the best overall response (BOR) which was categorised as CR, PR, SD, PD, or not evaluable except for those with bone-only, non-measurable disease, where it was limited to CR, SD, PD and not evaluable (partial response is not a criterion in non-measurable disease). SD was further classified as ≥ 6 months (best response of SD and PFS ≥ 6 months) or < 6 months.

Safety and patient reported outcomes (PROs) were evaluated on a safety population (defined as all patients who received at least one dose of study drug, 327 abemaciclib + NSAI vs 161 placebo + NSAI). The ERG considers that the ITT population should have been used for the analysis of PROs although number of patients in the two analysis sets were similar, see section 3.3.5 of this report.

The CS says that PROs of HRQoL were measured with European Organisation for Research and Treatment of Cancer Quality of Life Core 30 questionnaire (EORTC QLQ-C30) and EuroQol 5-Dimensions 5-Levels (EQ-5D-5L) administered at baseline, day 1 of every second cycle between cycle 3-19 and day 1 of every third cycle thereafter. Both measures are validated tools, they are briefly described in the CS (p 33) although the details of scoring and transformation of the data are only reported in the CSR. The CSR says that [redacted] This is a validated module of the EORTC QLQ-C30 for breast cancer.

Adverse events were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4 and further classified as treatment emergent or serious. Treatment emergent adverse events (TEAE) were defined as any adverse event that began between the first dose and 30 days after treatment discontinuation, or any pre-existing condition that increased CTCAE grade between the first dose and 30 days after treatment discontinuation (except there was no time limit on treatment emergent serious events). Serious Adverse Events (SAE) were defined as any adverse event that resulted in death; a life-threatening experience; persistent or significant disability/incapacity; initial or prolonged inpatient hospitalisation; congenital anomaly/birth defect; or were considered significant by the investigator for any other reason.

PFS, OS and some adverse events inform the economic analysis, see Section 4.3.4.1.

3.1.6 Description and critique of the company's approach to trial statistics

3.1.6.1 Sample size and power calculation

The MONARCH 3 RCT was a superiority trial which was powered for an interim analysis of the primary outcome, PFS, to be undertaken after approximately [redacted] investigator-assessed PFS events had been observed. The final PFS analysis was to be performed after [redacted] investigator-assessed PFS events had been observed. The statistical power calculation assumed a hazard ratio (HR) of 0.67 for ABE+NSAI vs placebo+NSAI, median PFS for placebo-NSAI of 10 months to yield > 80% power of the 1-sided log-rank test at a type 1 error of 0.025 (the HR of 0.67 amounted to approximately five months [50%] improvement in median PFS for the ABE+NSAI under an additional assumption of exponential survival distribution). The ERG considers that the power calculation was defined apriori, though the source of the assumptions was not stated.

The interim analysis of PFS (31st January 2017) was undertaken on the ITT population (ABE+NSAI n=328; placebo+NSAI n=165). At this time 164 patients (50.0%) in the ABE+NSAI arm and 98 patients (59.4%) in the placebo+NSAI arm had discontinued treatment. The final PFS analysis (3rd November 2017) was undertaken on the ITT population by which time [redacted] in the ABE+NSAI arm and [redacted] in the placebo+NSAI arm had discontinued treatment.

3.1.6.2 Analysis populations

Interim and final efficacy analyses were performed on the ITT population (n=493), which included all randomised patients, including two patients in the abemaciclib arm and three patients in the placebo arm who did not receive treatment. There were no exclusions from

the ITT analysis and missing data were not imputed [redacted] As stated earlier, the safety population was defined as all patients who received at least one dose of study drug, ABE+NSAI n=327 vs placebo+NSAI n= 161).

3.1.6.3 Statistical test methods

PFS was analysed with a one-sided stratified log-rank test with a type I error rate of 0.025, stratified by nature of disease (visceral metastases vs. bone-only metastases vs. other) and prior (neo)adjuvant endocrine therapy. Kaplan-Meier curves were used to estimate median PFS for each treatment arm; rates were compared at 4-month intervals using a normal approximation for the difference between rates. A stratified Cox proportional hazard model was used to calculate the hazard ratio between groups. In CS Appendix D.1.5 the assessment of proportional hazards (for all trials in the first-line treatment NMA) suggested that the assumption was reasonable for MONARCH 3 PFS data, although data were immature for OS (see section 3.1.7 for discussion of proportional hazards in the NMA).

Censoring occurred where it was not known if there had been progression or death at the time of analysis, with participants being censored at the last known progression-free assessment. Data were also censored if there was death or progressive disease after two or more missed tumour assessments; no baseline tumour assessment; or no post-baseline tumour assessment. The ERG asked the company to clarify the choice of censoring criteria used (clarification question A7). The company reported that there was no specific request from regulatory agencies regarding the censoring criteria for PFS in MONARCH 3. Censoring rules from the US FDA regulatory guidance were followed, there were no specific censoring criteria in the available European Medicines Agency (EMA) guidance. The ERG considers the use of the FDA guidance is reasonable.

The methods of statistical analyses for the other outcomes were not reported in the CS. [redacted] (provided in response to clarification question 10).

[redacted]

The MONARCH 3 trial publication[13] states that stratified tests using the Cochran-Mantel-Haenszel test were performed to compare response outcomes between treatment arms and that tests were performed at the two-sided 0.05 level and used 95% confidence intervals (CI)

unless stated. [redacted]

3.1.6.4 Subgroup analyses

The CS presents clinical effectiveness results for pre-planned subgroup analyses of PFS (for baseline stratification factors and other factors such as disease setting, see section 3.3.6), and post hoc exploratory subgroups on other factors associated with prognosis or endocrine therapy sensitivity. Subgroup analyses for OS were performed, but not presented in the CS, as the data are immature.

[redacted] In response to clarification question A6 the company states that the p-value for the interaction term was derived from a Cox model with the treatment arm, the subgroup variable and treatment by subgroup interaction term as factors. No adjustment for multiplicity in the subgroup analyses was performed (i.e. no correction was made to avoid erroneous inferences being made from multiple simultaneous statistical tests). Many of the pre-planned and exploratory subgroups had small sample sizes, particularly in the placebo group, and confidence intervals around the HRs are wide which need to be considered when interpreting their results. The NICE scope did not include any subgroups.

> **ERG conclusions:** the statistical approach of the MONARCH 3 trial reasonable. The power calculation for the primary outcome is appropriate; an ITT population was used for efficacy analyses; standard survival analysis methods were used, and both investigator and central independent assessment of PFS was undertaken. Caution is required in the interpretation of subgroup analyses as these are not statistically powered to show effects.

3.1.7 Description and critique of the company's approach to the evidence synthesis

As only one trial of abemaciclib in this indication was included in the submission, MONARCH 3, a direct meta-analysis of abemaciclib trials was not possible. The CS provides a narrative review of the trial, with data presented in tables and text.

The CS reports two NMAs indirectly comparing abemaciclib with other treatments:

- The MONARCH 3 trial-aligned NMA is the main focus in the CS (hereafter referred to in this report as the '**first-line treatment NMA'**), as it presents comparative evidence of abemaciclib as a first-line treatment for advanced breast cancer (i.e. within the scope of this NICE appraisal). The results of this NMA inform the economic model: PFS informs the time to first progression estimate and OS informs the deaths before first progression estimate (described in further detail in section 4.3.4.2 of this report).
- A separate NMA is reported, the MONARCH 2 trial-aligned NMA (hereafter referred to in this report as the '**second-line treatment NMA'**), to provide comparative evidence of abemaciclib as a second-line treatment in advanced breast cancer. This NMA is aligned with the patient population of the MONARCH 2 RCT,[16] which compares abemaciclib plus fulvestrant vs placebo plus fulvestrant in HR+ HER2- advanced breast cancer patients who had progressed following (neo)adjuvant or first lie advanced breast cancer endocrine treatment. The second-line treatment NMA was necessary as the OS data from the MONARCH 3 trial are immature and the economic model therefore includes a PFS2 health state to estimate OS from abemaciclib indirectly via the effects of second-line and subsequent treatment lines (we explain this in more detail in section 4.3.3 of this report). This NMA is briefly reported in CS Appendix N. The company provided the ERG with a separate confidential report[17] describing it (and an accompanying SLR report[18]) as part of their response to clarification questions.

In the following sub-sections we provide a description and critique of the first-line treatment NMA (see also Appendix 9.1 for a quality assessment checklist of this NMA). We provide a separate description and critique of the second-line treatment NMA in Appendix 9.2 of this report.

3.1.7.1 First-line treatment NMA evidence networks

The CS reports the results of five separate NMA networks, for the outcomes PFS, OS, ORR, CBR and CR, respectively. Following a feasibility assessment (details not reported in the CS) the CS concluded that networks for grade 3-4 adverse events, treatment discontinuation and HRQoL were not possible due to limited available data in primary studies (CS Appendix D.1.3). Only PFS and OS outcomes are used to inform the economic model, therefore the ERG's critique focuses mostly on these two networks.

The inclusion criteria for the NMA are reported in CS Appendix D.1.2. These criteria are broader than the NICE scope, and permit inclusion of a range of comparator treatments

including endocrine therapies, chemotherapies, targeted therapies, and combinations of these. The CS states that these additional comparators were included in the NMA "to generate a fully connected network and to make optimal use of available data" (CS page 56). The ERG considers this is a reasonable decision as it enables more data to be included for the anastrozole/letrozole reference comparator (see below for more information on this). The inclusion criteria also differed from the NICE scope in relation to patient characteristics (HER2 and HR status, and previous treatment status). We discuss these below in section 3.1.7.4 in relation to clinical heterogeneity.

The company's SLR search identified potentially relevant studies for inclusion in the NMA (CS Appendix D.1.1. and D.1.2). A total of 20 trials met the inclusion criteria for the SLR, of which 18 were included in the NMA (2 of the 20 were excluded as they could not be connected to the network). The number of trials contributing data for the respective outcome measures (individual networks) varied according to trial data availability:

- PFS n=8
- OS n=15
- (PFS or OS n=17)
- ORR n=17
- CBR n=10
- CR n=15

The network diagrams for PFS and OS are reproduced from the CS in Figure 2 and Figure 3 respectively below. As can be seen, the NMA networks include the three scoped treatments (abemaciclib, palbociclib and ribociclib) plus additional treatments outside of the scope of this appraisal: anastrozole/letrozole monotherapy; exemestane 2.5mg, fulvestrant 250mg/ 500 mg; megestrol acetate 160 mg; tamoxifen 20mg/40mg and toremifene 60 mg or 200 mg. Hereafter we refer to these as the non-scoped treatments.

Data for the scoped treatments are provided by their respective pivotal RCTs:

- Abemaciclib + anastrozole/letrozole vs placebo + anastrozole/letrozole - MONARCH 3[13]
- Ribociclib + letrozole vs placebo + letrozole - MONALEESA-2[19]
- Palbociclib + letrozole vs letrozole - PALOMA-1/TRIO-18[20] (NB. This is a single trial)
- Palbociclib + letrozole vs placebo + letrozole - PALOMA-2[21]

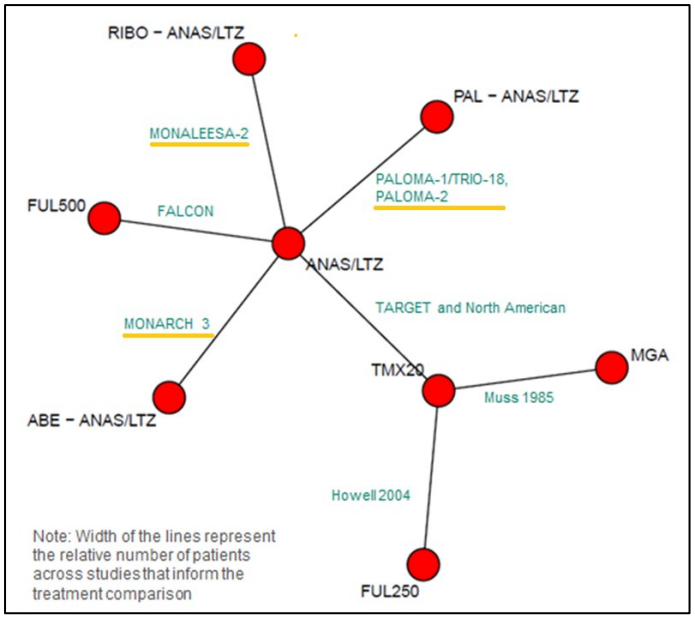
3.1.7.2 PFS network

The PFS network is a star-shaped network in which abemaciclib is connected to comparator treatments via a reference treatment, anastrozole/letrozole. There are no comparisons informed by both direct and indirect evidence in this network. The single abemaciclib trial included in the NMA, MONARCH 3, compared abemaciclib and anastrozole/letrozole with placebo and anastrozole/letrozole. This is the only trial in the network to have included both anastrozole and letrozole in a single trial arm. The other trials evaluated either anastrozole or letrozole as separate trial arms. To connect MONARCH 3 to the network anastrozole and letrozole were therefore pooled into one node and considered as one treatment arm. This is based on the assumption that the effectiveness of these two treatments is similar, and the CS notes that this assumption has been accepted in previous NICE appraisals in this indication (e.g. TA495[12] and TA496[11]). Clinical experts to the ERG in this current appraisal likewise agreed that they are equivalent in effectiveness.

The ERG notes that the reference treatment node in all the networks is anastrozole/letrozole monotherapy, however, in the MONARCH 3, MONALEESA-2 and PALOMA-2 trials the connecting comparator arm is placebo + NSAI (anastrozole/letrozole). This makes the assumption that the combination of placebo with NSAI is equivalent to NSAI alone. The CS does not discuss this assumption. The comparator arm in the PALOMA1/TRIO-18 trial was letrozole monotherapy (i.e. no placebo). The ERG considers the company's assumption to be acceptable for the purposes of connecting treatments in the networks.

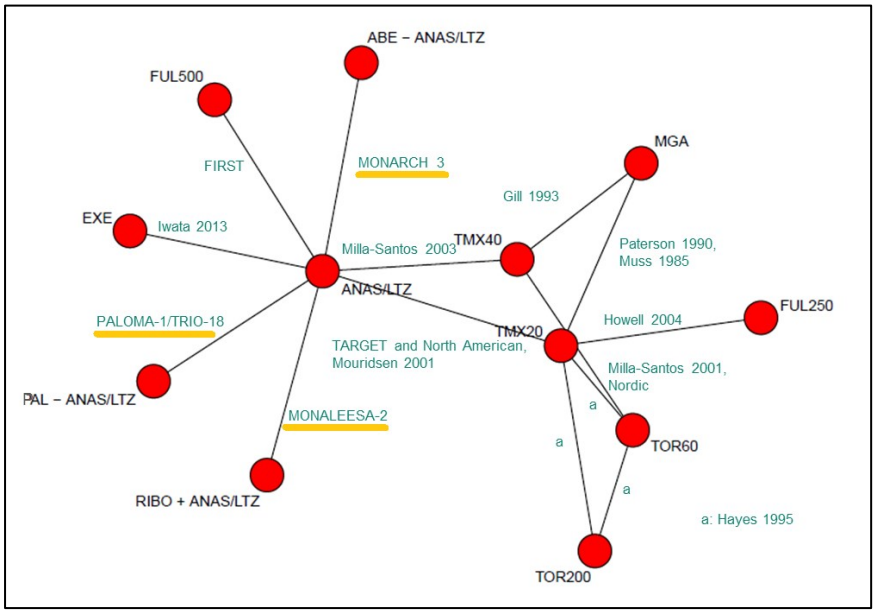
3.1.7.3 OS network

The OS network includes a larger number of treatments than the PFS network. Abemaciclib is connected to comparator treatments via an anastrozole/letrozole node (again, assuming equivalence in effectiveness of these two aromatase inhibitors). Comparisons between abemaciclib and palbociclib / ribociclib are only made indirectly, though other comparisons between non-scoped treatments are informed by both direct and indirect evidence, as illustrated by closed evidence loops. The ERG is not aware of any other studies of the scoped comparators that are eligible for inclusion.



Source: CS Appendix D.1.3 (Figure 3). The scoped treatment trials have been underlined by the ERG in yellow. ABE-ANAS/LTZ: abemaciclib plus anastrozole/letrozole; ANAS/LTZ: anastrozole/letrozole; FUL250: fulvestrant 250 mg; FUL500: fulvestrant 500 mg; TMX20: tamoxifen 20 mg; MGA: megestrol acetate 160 mg; PAL-ANAS/LTZ; palbociclib plus anastrozole/letrozole; RIBO-ANAS/LTZ: ribociclib plus anastrozole/letrozole

Figure 2 Network diagram for PFS, first-line treatment NMA network



Source: CS Appendix D.1.3 (Figure 4) The scoped treatment trials have been underlined by the ERG in yellow. ABE-ANAS/LTZ: abemaciclib plus anastrozole/letrozole; ANAS/LTZ: anastrozole/letrozole; EXE: exemestane; FUL250: fulvestrant 250 mg; FUL500: fulvestrant 500 mg; TMX20: tamoxifen 20 mg; TMX40: tamoxifen 40 mg; MGA: megestrol acetate 160 mg; PAL-ANAS/LTZ; palbociclib plus anastrozole/letrozole; RIBO-ANAS/LTZ: ribociclib plus anastrozole/letrozole; TOR60: toremifene 60 mg; TOR200: toremifene 200 mg.

Figure 3 Network diagram for OS, first-line treatment NMA network

3.1.7.4 Clinical heterogeneity assessment

The CS provides an assessment of clinical heterogeneity amongst the studies included in the NMA (CS Section B.2.9.3). This assessment is in relation to the MONARCH 3 trial and

the pivotal trials of the scoped comparators (MONALEESA-2; PALOMA-1/TRIO-18; PALOMA-2). In CS Appendix D.1.5 a heterogeneity assessment is provided for all the trials included in the NMA (i.e. the trials of the scoped and non-scoped treatments). Below we discuss clinical heterogeneity among the scoped treatment trials (n=4), then we discuss clinical heterogeneity among all 18 scoped and non-scoped treatment trials. We distinguish between the scoped and non-scoped treatments because the former are directly relevant to the decision problem and their results inform the economic evaluation. The latter are used to connect networks but are not directly relevant to the decision problem.

3.1.7.4.1 Heterogeneity assessment among scoped treatment trials

The scoped treatment trials are large, multi-centre, international, drug company-sponsored, double-blind, phase III trials, each containing several hundred patients. The exception is the PALOMA-1/TRIO-18 trial which was a smaller (n=165 patients) open-label phase II trial. [20]. The PALOMA and MONALEESA-2 trials were assessed in recent NICE appraisals of palbociclib (TA495)[12] and ribociclib (TA496),[11] respectively.

The CS considers that the trials of the scoped treatments are similar in terms of characteristics such as age, disease characteristics (e.g. cancer performance status; cancer stage; bone-only disease, menopausal status, HR+/HER2− status), and absence of previous endocrine therapy or chemotherapy in the advanced disease setting. The ERG has independently assessed these characteristics and agree that they are similar.

The CS highlights three areas where clinical heterogeneity was identified:

- **Required disease-free interval (DFI)** following adjuvant therapy. All trials enrolled patients with a DFI of over 12 months since adjuvant NSAI therapy. The MONARCH 3 trial also included patients with a DFI of over 12 months for (neo)adjuvant anti-oestrogen therapy. However, in the other trials the DFI for other hormonal therapies was not clear. The ERG assessed the proportion of patients at baseline in the trials within stated DFI categories. However, the trials report DFI according to different interval classes (e.g. < or ≥ 36 months;[13] ≤ or > 12 months [21]) making it difficult to compare trials.
- **Proportion of patients with visceral metastases**. This varied from 44% to 59% across treatment arms. The MONARCH 3 trial was towards the middle of this range (52%-54% of patients).
- **Site of disease**. Only the MONARCH 3 trial reported the proportion of patients with liver metastases (16%), although not by treatment arms and only reported as a post hoc subgroup analysis.

Expert clinical advice to the ERG is that these are key prognostic factors in this patient group. Visceral metastases confers a worse prognosis than bone metastases alone. The ERG considers that the difference between trials in visceral metastases in particular could potentially bias the results of the NMA, though it is not clear whether this would over or under-estimate the relative effectiveness of abemaciclib. The CS does not come to a firm conclusion about whether or not the above factors contribute to heterogeneity amongst the trials in the NMA, and what impact that might have on outcomes. The ERG asked the company to provide a discussion of the likely impact of any heterogeneity on the results of the NMA (clarification question A13). The company responded that the trials were homogenous for a large number of patient characteristics, with any differences 'anticipated to be minimal, thus lending reliability to the NMA results'. The company did not speculate what the impact of differences between the trials in visceral metastases might be.

Expert clinical advisors to the ERG are not aware of any additional key prognostic factors that should be noted in assessment of clinical heterogeneity.

The ERG also observes that the percentage of patients with newly diagnosed advanced/metastatic breast cancer varies between 34%[19] and 52%[20] across treatment arms in the trials. As noted earlier (section 2.1), this is a higher percentage than is commonly experienced in the UK (where rates of newly identified advanced/metastatic breast cancer are commonly in the range 10%-15%). This issue was discussed by the appraisal committee in NICE TA495[12] and clinical experts involved commented that they would not expect to see a difference in treatment effect for patients with newly diagnosed advanced/metastatic breast cancer. However, one clinical expert advising the ERG commented that patients who are newly diagnosed could be considered to have biologically different disease since this has never been exposed to hormonal therapy, whereas the remainder of the patients have remained disease free for at least 12 months after completing adjuvant hormonal therapy (most patients will have received two to five years of treatment).

3.1.7.4.2 Heterogeneity assessment among all trials including in the NMA (scoped and non-scoped treatments)

The reporting dates of the 18 trials vary from 1985 to 2017, reflecting the evolution of new treatments for advanced breast cancer over the decades (e.g. tamoxifen, anastrozole, letrozole, fulvestrant). Pivotal phase III and some phase II trials of these treatments have been included (CS Appendix Table 18). Given the long period of time over which the trials were conducted and published it is likely that delivery of clinical care and evaluation of

treatment effectiveness in the trials may have changed (e.g. introduction of testing for hormone receptors, broader use of a number of hormonal therapies, the use of bisphosphonates/denosumab and improvements in imaging/monitoring of patients to more clearly identify treatment benefit). This may be a source of heterogeneity in the network, though one of the expert clinical advisors to the ERG commented that changes to the supportive care environment would not significantly affect treatment effects.

CS Appendix Table 19 provides a very limited summary of patients' baseline characteristics across the 18 trials included in the NMA (age, performance status and menopausal status only). The CS states that the trials can be considered to be similar in terms of these characteristics. The ERG agrees with this assertion (however, see below).

The trials were also similar in other patient characteristics:

- The CS reports that none of the trials in the NMA included patients who had received prior endocrine therapy for advanced breast cancer.
- The CS also reports that all but two of the trials in the NMA omitted patients receiving prior chemotherapy for advanced breast cancer.

The ERG notes uncertainty about trial similarity for some patient characteristics:

- **Cancer performance status.** Whilst most of the patients in the trials had a favourable ECOG performance status (i.e. a PS <2) there was variability across the trials in the percentage of patients with PS 1, ranging between 15.4% to 57%. Seven trials did not report the performance status of patients. However, expert clinical advice to the ERG is that the difference between performance status of 0 and 1 is minimal and they can be grouped together for practical purposes.
- **HER2 status**. The inclusion criteria for the NMA specified that ≥80% of the trial study population should have HER2- breast cancer, but studies in which HER2 status was unknown were also eligible (HER2 testing was not routinely performed in older studies). The HER2 status of patients was unknown in 12 of the 18 trials in the NMA, and one trial permitted inclusion of HER2 +/- patients[22] (CS Appendix Table 24).
- **HR status.** All of the trials included in the NMA included women with HR+ breast cancer, though the CS does not report the percentage of women in each trial with HR+ breast cancer (the inclusion criteria for the NMA specified that trials in which ≥50% of women had HR+ breast cancer were eligible for inclusion). The company provided the percentage of women with HR+ breast cancer on request (clarification question A14) but only for the scoped treatment trials, not for all trials in the NMA as

was requested. For the scoped treatment trials the percentage of women with HR+ breast cancer (ER +) was [redacted]-100%, thus a high degree of similarity between trials.

The CS identifies areas of heterogeneity from consideration of the baseline characteristics of the trials (CS Appendix D.1.5). These include the same characteristics (prognostic factors) as identified for the scoped comparator studies discussed above: DFI; proportion of patients with visceral involvement and site of disease (e.g. liver metastases, bone only disease). The CS notes that there was incomplete reporting of these details in the studies, prohibiting a full assessment of clinical heterogeneity. Where details were reported there was variability between trials, such as DFI (reported in 6 of the 18 trials) where mean or median values ranged from 16 months (median) to 6.4 years (mean). The CS reports that meta-regression was not considered feasible due to the limited number of trials available. The ERG agrees with this as generally a minimum of 10 studies are required to perform meta-regression.[23]

The ERG asked the company to provide additional tabulated patient characteristics, including the proportion of patients with visceral involvement; liver metastases; DFI and prior therapy in the adjuvant setting (clarification question A14). The company provided these for the scoped treatment trials only, therefore the ERG is unable to make further comment on these characteristics in the non-scoped treatments in the NMA.

ERG conclusion

The ERG considers that the trials included in the NMA are similar in terms of patient characteristics such as age and previous treatment history for advanced breast cancer. However, due to reporting limitations in the trial publications a full assessment of clinical heterogeneity across the trials is not possible. The scoped treatment trials appear similar, though there was variation between them in the proportion of patients with visceral metastases. The impact of this on the results of the NMA are not clear. For this reason the results of the NMA should be interpreted with caution.

3.1.7.5 Critical appraisal of trials included in the first-line treatment NMA

CS Appendix Table 25 provides tabulated risk of bias assessments of all 18 included trials, using the NICE recommended criteria. The CS states that all trials were judged to be good quality with acceptable risk of bias (low or unclear risk of bias across the criteria). The CS reports that high risk of bias was mainly encountered with regard to blinding (of care providers, participants and outcome assessors) to treatment allocation “as several trials were open-label” (CS Appendix D.1.7). However, the ERG notes that only two of the trials were open-label (CS Appendix Table 18), 10 were double-blind, and in the remaining 6 trials

blinding was not reported. Thus, in half of the trials the risk of bias from lack of blinding was low and in the remaining half the risk of bias was mainly unclear; this is apparent in CS Appendix Table 25. It should be noted that outcomes such as OS are less prone to detection bias associated with lack of blinding than other outcomes such as PFS or tumour response, but performance bias (systematic differences in care) can occur.

The ERG did an independent critical appraisal of the scoped-comparator trials (Table 5). For the MONALEESA-2 trial,[19] the ERG largely agreed with the company's assessment, but, as with the MONARCH 3 trial, noted that adverse events may lead to unblinding. The ERG also considered there was evidence of selective outcome reporting.

For PALOMA-1/TRIO-18[20] and PALOMA-2,[21] the ERG gave more favourable assessments for randomisation and concealment of allocation, indicating a low risk of selection bias, but note a slightly higher proportion of patients with ECOG performance status 0 in the palbociclib + letrozole arm of PALOMA-2. In the PALOMA-1/TRIO18 trial,[20] an unplanned interim analysis was undertaken as almost twice as many patients in the control group of cohort 1 discontinued because of disease progression, therefore this trial is considered by the ERG to have a high risk of bias. The ERG considered that selective reporting bias was evident in PALOMA-1/TRIO-18[20] but not PALOMA-2,[21] and that ITT analysis was appropriate in PALOMA-2.

The ERG has not performed an independent critical appraisal of the non-scoped comparator trials included in the NMA. However, we note that the risk of bias as judged by the company was unclear in many trials for adequate randomisation, concealment of allocation, attrition, and use of ITT analysis. Thus, our conclusion is that the risk of bias in these trials is mostly uncertain.

3.1.7.6 Statistical NMA methods used

CS section B.2.9.1 and CS Appendix D.1.5 report details of the statistical methods used to conduct the NMA, citing methods described in NICE Decision Support Unit (DSU) Technical Support Documents 2, 3 and 4.[24-26] Binary outcomes (ORR, CBR, CR) were estimated using a logistic regression model using a binomial likelihood and a logit link function. For survival endpoints (i.e. PFS and OS) the CS cites a publication (itself cited in Technical Support Document 2) by Woods et al[27] which describes methods for NMA on the log-hazard scale combining count data (e.g. number of patients with an event at a point in time) and hazard ratio statistics (based on time to event data).

Table 5 Company and ERG assessment of trial quality for the NICE scoped comparator trials

NICE QA Criteria for RCT[a]		MONALEESA-2 [19] Ribociclib + letrozole vs letrozole	PALOMA-1/TRIO-18 Palbociclib + letrozole vs letrozole[20]	PALOMA-2 Palbociclib + letrozole vs letrozole[21]
1. Was randomisation carried out appropriately?	CS:	Low	Unclear	Unclear
	ERG:	Low	Low	Low
Comment: PALOMA-1/TRIO18: Interactive web-based randomisation system; PALOMA-2: Centralized internet/telephone registration system.				
2. Was concealment of treatment allocation adequate?	CS:	Low	Low	Unclear
	ERG:	Low	Low	Low
Comment: PALOMA-2: Centralized internet/telephone registration system.				
3. Were groups similar at outset in terms of prognostic factors?	CS:	Low	Unclear	Low
	ERG:	Low	Unclear	Unclear
Comment: PALOMA-1/TRIO18: slight imbalances in some characteristics; PALOMA-2: Slightly higher proportion with ECOG performance status 0 in palbociclib + letrozole group.				
4. Were care providers, participants and outcome assessors blind to treatment allocation?	CS:	Low	High	Low
	ERG:	Unclear	High	Low
Comment: MONALEESA-2: Adverse events may have led to unblinding.				
5. Were there any unexpected imbalances in drop-outs between groups?	CS:	Unclear	Unclear	Unclear
	ERG:	Unclear	High	Unclear
Comment: MONALEESA-2: Discontinuations due to progression were higher in the comparator group (therefore not unexpected); and discontinuations due to adverse events were higher in the ribociclib group. PALOMA-1/TRIO18: Publication states that an unplanned interim analysis was done as almost twice as many patients in the control group of cohort 1 discontinued because of disease progression. PALOMA-2: Discontinuations due to progression were higher in the comparator group (therefore not unexpected); and discontinuations due to adverse events were higher in the palbociclib group.				
6. Is there any evidence that authors measured more outcomes than reported?	CS:	Unclear	Low	Unclear
	ERG:	High	High	Low
Comment: MONALEESA-2: Most outcomes reported, but time to definitive deterioration of ECOG performance status in one category of the score not reported. PALOMA-1/TRIO18: Change from baseline in Modified Brief Pain Inventory in Pain Interference Scale (mBPI-sf) not reported.				
7. Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	CS:	Low	Low	Unclear
	ERG:	Low	Low	Low

[a] Low = low risk of bias, high = high risk of bias, unclear = uncertain risk of bias.

This method was designed to allow NMAs to include data from trials where the survival data is expressed in varying forms, thus potentially allowing a greater number of trials to be included in the same analysis. The CS doesn't explicitly state this as a rationale for using the Woods et al method.[27] The ERG considers that the use of Woods et al[27] method to be appropriate for the NMA of OS and PFS in this appraisal.

3.1.7.6.1 Proportional hazards assessment

An assessment of proportional hazards of survival data was conducted by the company. The company digitised Kaplan-Meier graphs for PFS and OS from the trials to estimate underlying individual patient data using a published algorithm.[28] The HR, median and proportion of patients event-free at a specific timepoint were checked against the published estimates to ensure internal validity. The CS did not report the results of this checking and the ERG requested this from the company (clarification question A20). The company provided a table describing discrepancies between the published and the digitised data. They report (unquantified) "small" discrepancies in HRs and CIs and median survival times in many of the trials. They also report quantified discrepancies (not described as "small") for some trials, including the scoped treatment trials. The company state that where there were discrepancies priority was given to the published data. The ERG considers this acceptable.

The CS reports that the proportional hazards assumption was tested by visual inspection of the Kaplan-Meier curves, log-cumulative hazard plots, Schoenfeld residual plots and the results of a weighted residual test based on standardised Schoenfeld residuals. The CS did not provide these curves, plots and the rest results, so the ERG requested these (clarification question A19). The company provided the requested information but did not provide any interpretation of them. The ERG's interpretation is as follows:

- The PFS log-log plots generally show initially overlapping lines which separate and become parallel over time (parallel lines indicates that the proportional hazard assumption is considered to hold). The OS log-log plots for mainly trials show overlapping lines over time.
- The Schoenfeld residual plots for both PFS and OS show variations over time in the residuals, illustrated by increasing and decreasing slopes in the curves between residual points. Horizontal shaped curves would indicate that hazards are proportional over time. The PFS curves are appear less variable over time than the OS curves suggesting that proportional hazards are more likely to hold.
- The results of the weighted residual tests for PFS showed no statistically significant trend between the residuals and time for any trials ($p>0.05$), indicating that the

proportional hazard assumption holds. For OS there were statistically significant trends ($p<0.05$) for four trials, including MONARCH 3.

The company's judgements on proportional hazards for PFS and OS in the 17 trials with OS or PFS data are presented in CS Appendix Table 23. Their judgements only appear to have been based on inspection of the Kaplan-Meier curves, rather than the other plots and statistical tests they provided (as discussed above).

- **PFS**: Kaplan-Meier data were unavailable for the whole trial population in nine trials and also for the HR+ subgroup of one trial. The proportional hazards assumption was accepted for the whole trial population in seven trials (including all of the pivotal scoped-comparator trials) and in the HR+ subgroup of one trial, and rejected in one trial (a non-scoped comparator). The ERG has visually inspected the Kaplan-Meier curves for the scoped-comparator trials and agree that proportional hazards appear to be supported.
- **OS**: Kaplan-Meier data were not available for three trials, and in a further eight trials the proportional hazards assumption was judged not to be supported. In the remaining six trials the assumption was supported.

The CS and the ERG have the following observations for the scoped-comparator trials:

- The ERG notes that in the MONARCH 3 trial the two [redacted] with final OS analysis to be done after 315 events). The CS states that due to immature survival data, conclusions regarding the proportional hazards assumption in this trial are uncertain. (NB. However, in CS Appendix Table 23 the proportional hazard assumption was accepted for the MONARCH 3 trial, despite noting that Kaplan-Meier curves cross after 20 months, immature survival and high level of censoring.)
- The CS notes that MONALEESA-2[19] trial OS data were immature at the time of analysis and that the Kaplan-Meier curves for the two treatments lie on top of each other until around month 24 when they begin to separate. The ERG also notes that updated results from the MONALEESA-2 trial were published in April 2018[29] (data cutoff 2nd January 2017) and that these show that the OS data are still immature (NB. these data are used in the NMA).

- For the PALOMA-2 trial[21] the CS states that no Kaplan-Meier OS data were available to inform assessment of proportional hazards. The trial publication states that data on OS were immature at the time of this analysis of the primary end point, and the final OS analysis will be performed when a total of 390 deaths occur. The ERG has not identified any updated OS results for this trial since this trial publication. This is a particular limitation for the indirect comparison between abemaciclib and palbociclib as the only OS data available for this comparison comes from a relatively small phase II open-label study (PALOMA-1/TRIO-18).[20]

The CS states that due to the immaturity of the data and the lack of a clinical rationale for explaining non-constant treatment effects over time between treatments they chose to conduct the NMA for OS based on an assumption of proportional hazards. They urge caution in the consideration of the results of the NMA due to the data immaturity. The CS states that there is no clinical rationale to justify a more complex NMA methodology assuming non-constant treatment effects over time between treatments. The ERG notes that company submissions for other NICE appraisals have used NMA methods such as fractional polynomials[30] for comparing treatments when proportional hazards are not supported or uncertain (e.g. TA463[31] and TA512[32]).

ERG conclusion:

It would have been appropriate for the company to have considered methods that incorporate time-varying hazards in the current appraisal as an alternative to the adopted methods. Nonetheless, the OS data from the MONARCH 3 and MONALEESA-2 trials would still be immature for this outcome and the NMA results – whichever approach was taken - would consequently be uncertain.

3.1.7.6.2 Outcome data used in NMA

CS Appendix tables 20 and 21 report the PFS and OS results (respectively) from the 18 trials (CS Table 22 reports the response rate results used in the NMA of response outcomes). Results for the ITT population and selected subgroups (e.g. patients with measurable disease) are tabulated. The ERG presumes that the results for the ITT population were used in the NMA, however, this is not explicitly stated in the CS. The ERG notes that the aforementioned assessment of proportional hazards (CS Appendix table 23) included both ITT populations and HR+ subgroup populations for two (non-scoped treatment) trials.

The ERG has checked the PFS and OS data in CS Appendix tables 20 and 21 for the scoped-comparator trials and note the company has used the most up to date data available where available.

The company also provided a summary of whether investigator or independent committee PFS assessments were available in the included trials (clarification response A13 Table 4). This was not reported by 10 trials and was reported as investigator-assessed by eight trials. The company state 'the heterogeneity of PFS assessments is not considered to have had a significant impact on the conclusions made'. The ERG notes that in the NICE appraisal of palbociclib (TA495[12]) the appraisal committee expressed a preference for blinded independent assessments of PFS, given that the higher rate of specific adverse events associated with palbociclib which may have unblinded some patients and investigators in the PALOMA trials. As discussed earlier in this report (section 3.1.4), there was a higher rate of diarrhoea in the abemaciclib arm of the MONARCH 3 trial potentially leading to unblinding. Although blinded independent committee PFS assessments are available in this trial these were not used in the NMA.

3.1.7.6.3 Bayesian modelling methods

Observed data were included in the model using a normal likelihood. The treatment effect model had a linear regression structure with the predicted log HR equal to the sum of the difference between the two treatment coefficients (CS Appendix D.1.5). The CS reports that a vague prior $\beta \sim N(0, 10^4)$ was to be used for the treatment effect coefficients. The CS does not provide a justification for the prior chosen and it is not stated whether choice of prior was explored by in sensitivity analysis. However, the ERG notes that vague priors are recommended by NICE DSU guidelines for treatment effect measures in NMAs.[24]

The ERG requested the company to provide more information about the Bayesian methods used to conduct the NMA (clarification question A15). The company provided the information requested. The ERG notes that the procedures reported for choosing initial parameter values and assessing convergence within and between chains as described are recommended by NICE DSU guidelines.[24]

The company reported that an assessment of the consistency of the direct and indirect evidence was performed in accordance with NICE DSU guidelines,[26] but did not provide further information on it in response to a clarification question (clarification question A16). The company's justification was that closed evidence loops containing both direct and

indirect evidence were only present for comparisons between non-scoped treatments in the networks. The ERG considers this justification reasonable.

As stated above, all treatments included in the NMA were compared to a reference treatment, anastrozole/letrozole monotherapy. The results are presented as pairwise comparisons between each treatment and the reference treatment (CS Figures 10-14). The ERG requested the company to provide NMA results for the indirect comparison of ABE+NSAI vs the comparators in the scope of the appraisal (i.e. palbociclib and ribociclib). The company provided these and they have been summarised later in this report (section 3.3.7).

OpenBUGS software (software package version 3.2.3) was used to conduct the analysis and the company provided the programming code on request from the ERG (clarification question A18).

3.1.7.6.4 Model fitting

The choice between a random effects and a fixed effect model was informed by the Deviance Information Criterion (DIC). The DIC is commonly used to compare the fit of Bayesian statistical models, whereby the model with the smallest DIC is estimated to be the model that would best predict a replicate dataset which has the same structure as that currently observed.[33] The company provided the DIC values upon request (clarification question A17).

The CS presents random effects NMA for all but one outcome measure. For the PFS outcome a fixed effect model was presented. Random effects models are appropriate when it is suspected that included trials may be heterogeneous. The ERG therefore regards use of random effects models to be more appropriate for this set of trials. The ERG requested the results for both random and fixed effect models for all outcomes, to permit comparison of their results (clarification question A17). The company supplied the random effects PFS results only. The ERG notes that these results provide similar point estimates to the fixed effect results, though wider credible intervals are generated by the random effects model (as would be expected) and they now cross the null line showing no statistically significant effects for ABE+NSAI and each of the scoped comparator treatments (see section 3.3.7 of this report for the results). The ERG also notes that the random effects PFS credible intervals are very wide, but in comparison, the width of the random effects OS credible

intervals are of a much smaller magnitude (they are more in-keeping with the PFS fixed effects credible intervals). There is no explanation given for this inconsistency.

3.1.7.7 Summary of the ERG's appraisal of the first-line treatment NMA

The ERG considers that, overall, the NMA has been adequately conducted. Standard Bayesian methods have been used, as recommended by the NICE Decision Support Unit. The pivotal trials of the scoped treatments have been included, and the ERG regards these to be generally at low risk of selection bias but may be at risk of other biases. The ERG is not aware of any relevant trials that have been omitted from the NMA.

However, there are some limitations and uncertainties:

- For many trials it was not possible to ascertain similarity, or otherwise, of patient characteristics. Notably, there is variation between trials in the proportion of patients with visceral metastases, and the effect of this on the results is uncertain.
- The NMA method used assumes the proportional hazards assumption holds for survival outcomes. However, this assumption could not be supported by available data for some trials. Amongst the scoped-treatment trials proportional hazards appeared to hold for PFS, but not for OS, where OS data are currently immature. The CS concludes that there is no clinical rationale to justify using an NMA approach that assumes non-constant treatment effects. However, the ERG considers that an alternative approach assuming time-varying hazards would have been informative (albeit with immature OS data).
- Due to the immaturity of the OS data in the scoped treatment trials the ERG considers the results of the OS NMA to be highly uncertain.

Although there were limitations to the NMA, the results were considered by clinical experts advising the ERG to be clinically plausible (we summarise these results later in section 3.3.7 of this report).

Finally, the ERG notes that recent NICE appraisals of treatments in this indication (palbociclib TA495 and ribociclib TA496) did not include an NMA. Therefore, no comparison of the methods and results of the NMAs in the current appraisal with previous NMAs has been possible.

3.2 Summary statement of company's approach to systematic review

Table 6 provides a critical appraisal of the company's SLR of clinical effectiveness.

Table 6 Quality assessment (CRD criteria) of CS review

CRD Quality Item; score Yes/No/Uncertain with comments	ERG comments
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	**Yes** The eligibility criteria were set apriori. The eligibility criteria were used to identify trials of relevance to the decision problem, including trials for the NMA. Eligibility of potential trials for the NMA was wider than the NICE scope, including a number of other potential treatment options. The eligibility criteria suggest that all studies were required to have abemaciclib as the intervention and the other potential treatment options were listed only as comparators. However, the SLR included studies of the other potential treatments as interventions.
2. Is there evidence of a substantial effort to search for all relevant research?	**Yes** The searches were of sound methodology, well documented and reproducible with an acceptable range of databases searched. As such the ERG did not consider it necessary to replicate the main searches. An update for the searches of ongoing studies was completed.
3. Is the validity of included studies adequately assessed?	**Yes** The studies were adequately assessed although the ERG differs in assessment on more than one risk of bias criterion (selective reporting bias, blinding and drop outs for the pivotal RCT). Risk of bias was assessed for all of the studies included in the NMA.
4. Is sufficient detail of the individual studies presented?	**Yes**
5. Are the primary studies summarised appropriately?	**Partly** The CS omits some of the pre-specified outcomes but these were available in the CSR.

CRD = Centre for Reviews and Dissemination

The company's evidence synthesis is clearly reported and presents the key information that the ERG would expect to see. It is unlikely there is any error in the inclusion of studies from the SLR and the ERG does not consider that any key trials are likely to have been missed. The NMA included all studies of possible relevance in this population group, which were broader than those specified in the NICE scope. The ERG considers this to be appropriate.

The review processes reported in CS Appendix D.1.2 appear appropriate. Two reviewers independently assessed studies for inclusion through a two-stage process. One reviewer extracted data into a piloted data extraction worksheet and a second reviewer checked extractions. Excluded studies with reasons were reported and a PRISMA style flow chart. It is unclear whether one or two reviewers assessed each study for risk of bias, however, the ERG considers that it is unlikely that the CS have introduced biases from the processes used for the SLR.

3.3 Summary of submitted evidence

In the following sub-sections we summarise the results of the MONARCH 3 trial.

3.3.1 Progression-free survival

The CS provides interim and final efficacy analyses for both investigator assessed (primary outcome) and Independent Central Review assessed PFS; the final analyses only are summarised in Table 7. At a median follow-up of [redacted] months, investigator assessed median PFS was [redacted] months in the abemaciclib + NSAI group compared with [redacted] in the placebo + NSAI group; HR [redacted] (95% CI [redacted], 2-sided [redacted]), giving a reduction in the risk of progression of disease or death of 46%. PFS survival rate at 24 months was [redacted] vs [redacted] respectively. Outcomes by Independent Central Review were slightly more favourable than investigator assessment in both treatment arms (Table 7).

3.3.2 Overall survival

Overall survival data were immature at the final data cut, with median survival [redacted], HR [redacted] (95% CI [redacted] 2-sided stratified log-rank [redacted]), Table 7. [redacted] overall survival rate at 24 months (abemaciclib + NSAI [redacted] vs placebo + NSAI [redacted]

Table 7 Survival at final analysis

	Abemaciclib + NSAI (n=328)	Placebo + NSAI (n=165)	Treatment Effect / Difference /p-value
Progression-free survival			
Median PFS, months Investigator assessed	[redacted]	[redacted]	[redacted]
Median PFS, months Independent Central Review	[redacted]	[redacted]	[redacted]
24 month PFS rate, % Investigator assessed	[redacted]	[redacted]	[redacted]
24 month PFS rate, % Independent Central Review[a]	[redacted]	[redacted]	[redacted]
Overall survival			
Median OS, months	[redacted]	[redacted]	[redacted]
24 month OS rate, % (95% CI)	[redacted]	[redacted]	[redacted]

[a] Source: CSR addendum
CI, confidence interval; NSAI, non-steroidal aromatase inhibitor; OS, overall survival; PFS, progression free survival.

3.3.3 Response rates

The objective response rate (RECIST 1.1 complete response or partial response) by investigator assessment was [redacted] with abemaciclib +

NSAI compared with placebo + NSAI ([redacted]) (Table 8). [redacted]

8[redacted]

3.3.4 Duration of response

Among patients with an investigator assessed response (abemaciclib + NSAI n=163, placebo + NSAI n=61), the median duration of response was [redacted] months (95% CI [redacted]) in the abemaciclib + NSAI arm compared with [redacted] months (95% CI [redacted]) in the placebo + NSAI arm (Table 8).

Table 8 Best overall response and duration of response (investigator assessment)

	Abemaciclib + NSAI N=328		Placebo plus NSAI N=165		OR	p-value
	n (%)	95% CI	n (%)	95% CI		
Objective response rate, CR + PR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease control rate, CR + PR + SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical benefit rate, CR + PR + SD ≥6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD ≥6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not evaluable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Months	**95% CI**	**Months**	**95% CI**		
Duration of response	[redacted]	[redacted]	[redacted]	[redacted]	-	-

CI, confidence interval; CR, complete response; NA, CS states 'the computations were not done because there were fewer than 2 non-missing levels in the data'; NSAI: non-steroidal aromatase inhibitor; PD, progressive disease; PR, partial response; SD, stable disease.

3.3.5 Health related quality of life

The CS states that patient completion rates for HRQoL instruments were high, apart from in cycle 22. In response to clarification question A4, the company provided further details on

the completion rates for each arm during this cycle, including reasons for non-completion, and noted that the low rate reported in the CS was for one arm (placebo + NSAI) for one of the three instruments (EQ-5D scale). The ERG notes that the completion rates for each instrument were lower in the placebo group, but the reasons for this are not clear. HRQoL measures were analysed on the safety population set (without imputation of missing data), rather than the ITT analysis set.

3.3.5.1 EORTC QLQ-C30

Global health status

[redacted]

9[redacted]

[redacted] in the CS. The ERG notes that there is no category for a 'large' difference (unequivocal clinical relevance) for this symptom.[34]

[redacted]

9[redacted]

3.3.5.2 EQ-5D-5L

There was [redacted] in change from baseline in the EQ-5D-5L index score or visual analogue scale (Table 9).

3.3.5.3 EORTC QLQ-BR23

Compared with placebo + NSAI,

[redacted] with

abemaciclib + NSAI. There were no significant differences in between group changes on the other function and symptom scales (Table 9).

Table 9 HRQoL outcomes change from baseline[a] (safety population)

LS Mean (SE)	Abemaciclib + NSAI (n=327)	Placebo + NSAI (n=161)	Between group change difference[a]	p-value
EORTC QLQ-C30				
Global health status	[redacted]	[redacted]	[redacted]	[redacted]
Functional scales (higher score = better)				
Physical functioning	[redacted]	[redacted]	[redacted]	[redacted]
Role functioning	[redacted]	[redacted]	[redacted]	[redacted]
Emotional functioning	[redacted]	[redacted]	[redacted]	[redacted]
Cognitive functioning	[redacted]	[redacted]	[redacted]	[redacted]
Social functioning	[redacted]	[redacted]	[redacted]	[redacted]
Symptom scale items (higher score = worse)				
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Nausea and vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]
Appetite loss	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Financial difficulties	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-5L				
Index value	[redacted]	[redacted]	[redacted]	[redacted]
Visual analogue scale	[redacted]	[redacted]	[redacted]	[redacted]
EORTC QLQ-BR23[b]				
Functional scales (higher score = better)				
Body image	[redacted]	[redacted]	[redacted]	[redacted]
Sexual functioning	[redacted]	[redacted]	[redacted]	[redacted]
Future perspective	[redacted]	[redacted]	[redacted]	[redacted]
Symptom scale items (higher score = worse)				
Systemic therapy side effects	[redacted]	[redacted]	[redacted]	[redacted]
Breast symptoms	[redacted]	[redacted]	[redacted]	[redacted]
Arm symptoms	[redacted]	[redacted]	[redacted]	[redacted]

See CS Table 12 p.53 and CS Table 13 p.54 for baseline values.

EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer Quality of Life Breast cancer; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Core 30 questionnaire; EQ5D-5L: EuroQol 5-Dimensions 5-Levels; LS: least squares. [a] Across all post-baseline visits. [b] From CSR addendum.

3.3.6 Sub-group analyses results

3.3.6.1 Progression-free survival

Pre-planned subgroup analyses for PFS were undertaken for the following subgroups (see CS Appendix E Figure 9):

- Baseline stratification factors
    - Site of metastases (visceral metastases, bone-only metastases, other)
    - Prior (neo)adjuvant endocrine therapy (aromatase inhibitor, other, no prior endocrine therapy)
- Other subgroups:
    - NSAI received at Cycle 1 (letrozole, anastrozole) *(note this is missing from CS Appendix E Figure 9)*
    - Disease setting (de novo metastatic, recurrent metastatic, locoregionally recurrent) *(note that locoregionally recurrent was not a category in CS Appendix E Figure 9)*
    - Measurable disease at baseline (yes, no)
    - Number of organs involved (1, 2, 3+) *(note this is missing from CS Appendix E Figure 9)*
    - Age (<65 years, ≥65 years)
    - Region (North America, Europe, Asia)
    - Race (Caucasian, Asian, and other) *(note this is missing from CS Appendix E Figure 9)*
    - Progesterone receptor status (positive, negative)
    - Baseline ECOG PS (0, 1)

In addition, the CS describes additional exploratory subgroup analyses on factors associated with prognosis and/or sensitivity to endocrine therapy; these are not described as pre-planned (see CS Appendix E Figure 10):

- Disease diagnosis (<10 years, ≥10 years, de novo metastatic)
- Tumour grade (high-grade tumour, low/intermediate grade, unknown)
- Disease free interval (de novo metastatic, <3 years, ≥3 years, recurrent with no adjuvant chemotherapy)

- Presence of liver metastasis at baseline (yes, no)

The direction of the treatment effect was consistent across all of the above subgroups (favouring ABE+NSAI). However, there were two statistically significant interactions (the following data are from the CSR, and reflect the final PFS assessment in the ITT population): race ([redacted]) and geographic region ([redacted]). A greater treatment effect was found in Asian patients ([redacted]) compared with Caucasian patients ([redacted]), and in Asia ([redacted]) compared with Europe ([redacted]) and North America ([redacted]).

The CS explains this difference as being driven by the reduced performance of the control arm in Asian patients (particularly in Taiwan and Korea), in which there were a larger proportion of patients with a poorer prognosis at baseline.

No further details are provided in the CS, however the CSR states that [redacted] The ERG notes that the interaction p-values were not adjusted for multiplicity testing (clarification question A6).

3.3.6.2 Overall survival

Subgroup analyses were not presented for OS due to immature data; the ERG consider this to be reasonable.

3.3.6.3 Response rate

The CS provided response rates for the subgroup with measurable disease at baseline (n=397, 81%), these are summarised in Table 10.

Table 10 Response rates in subgroup with measurable disease at baseline

	Abemaciclib + NSAI N=267		Placebo plus NSAI N=130		OR	p-value
	n (%)	95% CI	n (%)	95% CI		
Objective response rate, CR + PR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease control rate, CR + PR + SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical benefit rate, CR + PR + SD ≥6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Source CSR addendum.
CR, complete response; PR, partial response; SD, stable disease; OR= Odds ratio

The ORR and CBR, but not the DCR, were significantly higher in the abemaciclib + NSAI arm compared with placebo + NSAI in this subgroup. As non-measurable disease cannot have a best response of partial response, these outcomes cannot be assessed for the subgroup with non-measurable bone-only disease.

3.3.7 Network meta-analysis results

The treatment effects of ABE+NSAI and each of the scoped comparators relative to placebo+NSAI are summarised in Table 11. Effects for the other (non-scoped) treatments included in the NMA can be seen in CS Figures 10 to 14. The CS did not present indirect comparisons between the scoped treatments; these were requested by the ERG and were provided in clarification question response (A12) for PFS and OS only (Table 12).

For PFS using the fixed effects model, all three treatments showed similar and statistically significant HRs improving PFS relative to placebo+NSAI (Table 11). Using the random effects model (provided in response to clarification question A17) resulted in similar point estimates but much wider credible intervals, and statistically nonsignificant differences relative to placebo+NSAI for each of the three treatments. There were no significant differences for the indirect comparisons between ABE+NSAI and PAL+NSAI or ABE+NSAI and RIBO+NSAI using either fixed or random effects models (Table 11).

There were no statistically significant differences in OS for any of the three treatments relative to NSAI (Table 11). However, OS data are currently immature in the trials therefore these results are uncertain. Similarly, there were no significant differences in OS for the indirect comparisons between ABE+NSAI and PAL+NSAI or ABE+NSAI and RIBO+NSAI using either fixed or random effects models (Table 12).

There were also no statistically significant differences in ORR, CBR or complete response for any of the three treatments relative to NSAI (Table 11). The estimate for abemaciclib + NSAI complete response was highly uncertain due to low event counts.

Table 11 Summary of treatment effects relative to placebo+NSAI for the scoped treatments

Outcome, number of studies in NMA	Abemaciclib + NSAI	Palbociclib + NSAI	Ribociclib + NSAI
PFS, FE 8 studies, HR (95% CrI)	[redacted]	[redacted]	[redacted]
PFS, RE 8 studies, HR (95% CrI)[a]	[redacted]	[redacted]	[redacted]
OS, RE 15 studies, HR (95% CrI)	[redacted]	[redacted]	[redacted]
ORR, RE 17 studies, OR (95% CrI)	[redacted]	[redacted]	[redacted]
CBR, RE 10 studies, OR (95% CrI)	[redacted]	[redacted]	[redacted]
CR, RE 15 studies, OR (95% CrI)	[redacted]	[redacted]	[redacted]

FE = Fixed effects model; RE = Random effects model; HR = Hazard ratio; OR = Odds ratio
[a] clarification response A17.

Table 12 Treatment effects for ABE+NSAI vs PAL+NSAI and RIBO+NSAI for PFS and OS

Comparator	HR (95% CrI) (*fixed* effects model)	HR (95% CrI) (*random* effects model)
PFS		
PAL+NSAI	[redacted]	[redacted]
RIBO+NSAI	[redacted]	[redacted]
OS		
PAL+NSAI	[redacted]	[redacted]
RIBO+NSAI	[redacted]	[redacted]

Source: clarification question response A12

3.3.8 Summary of adverse events

Adverse events were reported for the safety population, which was all patients who received at least one dose of study drug (327 abemaciclib + NSAI; 161 placebo + NSAI), at the final analysis. Summary treatment emergent adverse events (TEAEs) are described in Table 13.

Table 13 Summary rates of key treatment emergent adverse events (safety population)

Percent of participants[a]	Abemaciclib + NSAI (n=327)	Placebo + NSAI (n=161)
Patients with ≥1 TEAE	[redacted]	[redacted]
TEAEs related to study treatment [b]	[redacted]	[redacted]
Patients with ≥1 Grade 3 or higher TEAE	[redacted]	[redacted]
Grade 3 or higher TEAE related to study treatment [b]	[redacted]	[redacted]
Patients with ≥1 serious adverse event	[redacted]	[redacted]
Serious adverse events related to study treatment [b]	[redacted]	[redacted]
Discontinuations of all study treatment due to an AE	[redacted]	3.1

Discontinuations of study treatment due to a SAE	[redacted]	[redacted]
Deaths due to adverse event	[redacted]	[redacted]

[a] Patients may be counted in >1 category. [b] Includes events that were considered related to study treatment as judged by the investigator.

Rates appeared to differ between groups for:

- Proportions with at least one TEAE related to treatment as judged by the investigator ([redacted] abemaciclib + NSAI vs [redacted] placebo + NSAI);
- Proportions with grade ≥3 TEAEs (abemaciclib + NSAI arm [redacted] vs placebo + NSAI arm [redacted], with [redacted] and [redacted] considered related to study treatment as judged by the investigator, respectively);
- Proportions with at least one serious adverse event (SAE) (abemaciclib + NSAI arm [redacted] vs placebo + NSAI arm [redacted]);
- Serious adverse events considered related to study treatment as judged by the investigator (abemaciclib + NSAI group [redacted] placebo + NSAI group [redacted];
- Discontinuations of all study treatments (abemaciclib plus NSAI arm [redacted] vs placebo plus NSAI arm 3.1%).

The CS provides details of TEAEs (grades 1-4 and all grades) occurring in at least 15% of participants in CS Table 16 (CS p69), not reproduced here. All TEAS, with the exception of arthralgia and back pain, occurred more frequently in the abemaciclib + NSAI arm. At any grade, diarrhoea ([redacted]), infections/infestations ([redacted]), neutropenia ([redacted]), fatigue ([redacted]) and nausea ([redacted]) were the most frequently experienced TEAEs in the abemaciclib plus NSAI arm. Infections/infestations ([redacted]), fatigue ([redacted]), diarrhoea ([redacted]), nausea ([redacted]) and arthralgia ([redacted]) were the most frequently experienced TEAEs of any grade in the placebo plus NSAI arm. At grade 3 or higher, the most commonly experienced TEAEs in the abemaciclib + NSAI arm were neutropenia ([redacted] grade 3 / [redacted] grade 4); diarrhoea ([redacted] grade 3 / [redacted] grade 4, see below for more details of diarrhoea); leukopenia ([redacted] grade 3 / [redacted] grade 4); infections and infestations ([redacted] grade 3 / [redacted] grade 4) and anaemia ([redacted] grade 3 / [redacted] grade 4), Table Y. Rates of grade 3 or 4 TEAEs in the placebo + NSAI arm were low; there were no events that were reported more commonly than others, see Table 14 for those most commonly reported in the abemaciclib + NSAI arm.

Specific TEAEs related to study treatment were not reported in the CS but were identified in the CSR addendum from the final analysis. Any grade diarrhoea made up the majority of these events in both the abemaciclib + NSAI arm ([redacted]) and the placebo + NSAI arm

([redacted]); the majority of which were grade 1 or 2. Rates of other TEAEs related to study treatment that were commonly experienced included any grade neutropenia ([redacted] and [redacted] in the abemaciclib + NSAI arm and placebo + NSAI groups respectively, with [redacted] of ≥grade 3 in the former group) fatigue ([redacted] and [redacted] in the abemaciclib + NSAI arm and placebo + NSAI groups respectively, mostly < grade 3) and nausea ([redacted] and [redacted] in the abemaciclib + NSAI arm and placebo + NSAI groups respectively, mostly < grade 3).

Grade 3 or higher rates of anaemia, ALT and AST increase, diarrhoea, hypertension, leukopenia, neutropenia and lymphopenia are used in the economic model.

3.3.8.1 Diarrhoea

Diarrhoea was more common in the abemaciclib plus NSAI group than the placebo group (CS Table 16). The majority of diarrhoea was grade 1 and 2 ([redacted] and [redacted] respectively), see above for rates at grade 3 and 4. The CS says that the median onset of diarrhoea was 8.0 days and the median duration was 10.5 days for grade 2 and 8.0 days for grade 3. In the abemaciclib plus NSAI arm 76.3% did not undergo any treatment modifications due to diarrhoea; [redacted] had a dose reduction and [redacted] had a dose omission. [redacted] discontinued treatment due to diarrhoea. The ERG clinical experts confirmed that abemaciclib is associated with diarrhoea and that this is worse in the first few weeks and it then settles down. Antidiarrhoeal medications were used in [redacted].

3.3.8.2 Serious adverse events

Rates of participants experiencing at least one SAE were higher in the abemaciclib + NSAI group ([redacted]) than the placebo + NSAI group ([redacted]) (Table 13). Specific SAEs by treatment group are presented for those occurring in at least 1% of participants in CS Table 17 (p 70); rates of all events were higher in the abemaciclib + NSAI arm. Lung infection [redacted], embolism ([redacted]), anaemia ([redacted]), diarrhoea ([redacted]) and acute kidney injury ([redacted]) were the most commonly reported SAEs in the abemaciclib + NSAI group, and dehydration ([redacted]), abdominal pain ([redacted]) and vomiting [redacted]) were most common in the placebo + NSAI group.

The CS concludes that abemaciclib + NSAI was well tolerated with an acceptable TEAE profile. Expert clinical advice to the ERG agrees with this conclusion, though it was noted that the relatively high proportion of patients receiving abemaciclib reporting diarrhoea ([redacted]) is clinically important.

3.3.8.3 Comparator treatment summary adverse events

The CS did not present adverse events for the scoped comparators. The ERG has summarised the key events here from their pivotal phase III RCTs, for information (Table 14).

Table 14 Grade 3 or higher adverse events reported in the four included trials (most commonly experienced in the MONARCH 3 RCT abemaciclib arm)

AE, %	MONARCH 3		MONALEESA-2		PALOMA 1 and 2	
	Abemaciclib + NSAI	Placebo + NSAI	Ribociclib + letrozole	Placebo + letrozole	Palbociclib + letrozole	Placebo + letrozole
Neutropenia	[redacted]	[redacted]	59.3[a]	0.9[a]	1: 54.2[a] 2: 66.4[a]	1: 1 2: 1.4[a]
Diarrhoea	[redacted]	[redacted]	1.2[a]	0.9[a]	1: 4.0[a] 2: 1.4[a]	1: 0 2: 1.4[a]
Leukopenia	[redacted]	[redacted]	21.0[a]	0.6[a]	1: 19[a] 2: 24.8[a]	1: 0 2: 0
Infections + infestations	[redacted]	[redacted]	4.2[ab]	2.4[ab]	1: NR 2: NR	1: NR 2: NR
Anaemia	[redacted]	[redacted]	1.2[a]	1.2[a]	1: 6.0[a] 2: 5.4[a]	1: 1.0[a] 2: 1.8[a]

[a] Calculated by ERG; [b] Reported as 'infections'.

3.3.8.3.1 Ribociclib

In the MONALEESA-2 trial 98.5% of patients in the ribociclib + letrozole arm and 97.0% of patients in the placebo + letrozole group experienced an adverse event.[19] The proportions experiencing any grade 3 or higher event was higher in the ribociclib + letrozole group than the placebo group (81.1% vs 32.7%). The most commonly reported adverse event was neutropenia, with ≥ grade 3 neutropenia experienced in 59.3% and 0.9% in the two groups respectively. Other commonly reported adverse events at grade 3 or higher included leukopenia (21.0% and 0.6%, respectively) and hypertension (9.9% and 10.9%). As an adverse event of interest in the current appraisal diarrhoea at any grade was experienced in 35% in the ribociclib + letrozole group and 22.1% in the placebo group. SAEs were experienced in 21.3% in the ribociclib group and 11.8% in the placebo group. Rates of discontinuation of treatment due to adverse events was 7.5% in the ribociclib + letrozole group and 2.1% in the placebo + letrozole group.

3.3.8.3.2 Palbociclib

In the two RCTs of palbociclib + letrozole the proportions experiencing any adverse events were similar; in PALOMA-1/TRIO-18[20] 100% in the palbociclib + letrozole arm and 84.4% in the placebo + letrozole arm; in PALOMA-2[21] 98.9% in the palbociclib + letrozole arm and 95.5% in the placebo + letrozole arm. The most common adverse events in the palbociclib + letrozole groups of each trial were neutropenia, leukopenia, and fatigue. Diarrhoea was

experienced in 20.5% of participants in the palbociclib + letrozole group and 10% in the placebo + letrozole group in the PALOMA-1/TRIO-18.[20] In the PALOMA 2 trial[21] rates were 26.1% and 19.4% in the two groups respectively. SAEs were experienced in 19.6% of participants in the palbociclib + letrozole group and in 12.6% of participants in the placebo + letrozole group of PALOMA-2. Rates of discontinuation owing to TEAEs were 13% in the palbociclib + letrozole group and 2% in the placebo + letrozole group in PALOMA-1/TRIO-18. In PALOMA-2, discontinuation of any study treatment due to adverse events occurred in 9.7% in and 5.9%, respectively.

3.3.9 Ongoing studies

The company states that there are currently five ongoing studies in the UK investigating the efficacy and safety of abemaciclib in breast cancer patients (CS Section B.2.11). One of these is the MONARCH 3 trial, as follow-up for overall survival is still ongoing. The other four studies are not relevant to this appraisal. An update search for ongoing trials was undertaken by the ERG (restricted to trials of abemaciclib currently), which did not identify any additional ongoing studies with relevant comparators.

4 COST EFFECTIVENESS

4.1 Overview of company's economic evaluation

The company's submission to NICE includes:

i) a review of published economic evaluations of treatment options for the management of HR+/HER2- advanced breast cancer (CS section B.3.1).

ii) a report of an economic evaluation undertaken for the NICE STA process. The cost effectiveness of ABE+NSAI is compared with RIBO+NSAI and PAL+NSAI for untreated HR+/HER2- advanced breast cancer (CS section B.3.2).

4.2 Company's review of published economic evaluations

The company report a systematic literature review conducted to identify cost-effectiveness evidence relevant to treatment options for the management of HR+/ HER2- locally advanced or metastatic breast cancer. The methods of systematic review and results are reported in CS Appendix G and summary information about included cost-effectiveness studies relevant to the UK setting is presented in CS Table 18 (B.3.1). This included seven NICE technology appraisals (TA214; TA239; TA250; TA263; TA295; TA421; TA423), one paper (Das et al. 2013)[35] and an abstract (Polyani et al. 2014)[36], none of which related to comparators in the current appraisal. Three of the non-UK publications related to scoped-comparators: Bhattacharya (2016); Mamiya (2017) and CADTH (2016), all of which on palbociclib. However, none of these papers reported useful information about model input parameters that would add to the existing information in NICE TA495.

4.3 Critical appraisal of the company's submitted economic evaluation

4.3.1 NICE reference case

The ERG considers that the company's economic evaluation meets NICE's reference case requirements (Table 15).

Table 15 NICE reference case requirements

NICE reference case requirements:	Included in submission	ERG comment
Decision problem: As per the scope developed by NICE	Yes	However, population is restricted to postmenopausal women
Comparator: As listed in the scope developed by NICE	Yes	Palbociclib or ribociclib with an aromatase inhibitor (letrozole)
Perspective on costs: NHS and PSS	Yes	
Evidence on resource use and costs: Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes	
Perspective on outcomes: All direct health effects, whether for patients or, when relevant, carers	Yes	
Type of economic evaluation: Cost utility analysis with fully incremental analysis	Yes	
Synthesis of evidence on outcomes: Based on a systematic review	Yes	
Time horizon: Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes	
Measuring and valuing health effects: Health effect should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL.	Yes	
Source of data for measurement of HRQoL: Reported directly by patients and/or carers.	Yes	Yes for PFS1, but PFS2 and PPD use general public valuations [37]
Source of preference data: Representative sample of the UK population	Yes	
Equity considerations: An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	Yes	
Discount rate: 3.5% pa for costs and health effects	Yes	

4.3.2 Decision problem

4.3.2.1 Population

While the NICE scope considers a broad population of people with advanced HR+/HER2- breast cancer, the decision problem addressed by the company is narrowed to address postmenopausal women with advanced HR+/HER2− locoregionally recurrent or metastatic breast cancer who have had no prior systemic therapy for advanced disease. No patient subgroups are included in the NICE scope of the CS.

The modelled cohort is women of 65 years and above. To estimate drug doses for intravenous treatments, a body surface area (BSA) of 1.70 m^2 were assumed. Given that BSA data were not collected directly from the MONARCH 3 trial, height and body weight were used to estimate BSA. An average weight of 67.99kg and a height of 158.41cm were used for this estimation.

4.3.2.2 Interventions and comparators

The comparators in the model are palbociclib or ribociclib with an aromatase inhibitor, which are currently licensed for use in the UK NHS and correspond to the NICE scope.

The first-line NMA and economic model treat the NSAIs letrozole and anastrozole as a single class (i.e. similar in efficacy and safety). This reflects conclusions in previous NICE appraisals that in clinical practice AIs are considered to be equivalent, with similar effectiveness and acquisition costs (NICE TA495 and TA496).

In the previous NICE appraisals TA495 and TA496, the committees also considered NSAI monotherapy as a comparator for ribociclib + NSAI and palbociclib + NSAI. However, NSAI monotherapy is not specified as a comparator in the scope for this current appraisal. The company includes NSAI as a reference treatment in the first-line NMA and in the economic model. We therefore report input parameters and results for NSAI to provide context for the included comparators.

4.3.3 Model structure and assumptions

The company describes the model structure and key characteristics in CS section B.3.2.2. Monthly cycles are used to reflect state-transitions and the accrual of costs and outcomes. With the exception of treatment costs, which are incurred at the beginning of each month, a half-cycle correction is incorporated. Costs and QALYs are discounted at an annual rate of 3.5%. The model uses a 35-year time horizon, so could be said to reflect a lifetime since survival approaches 0.1% for all arms in base case by the end of this time period.

The company's illustration of the model is reproduced in Figure 4 below.

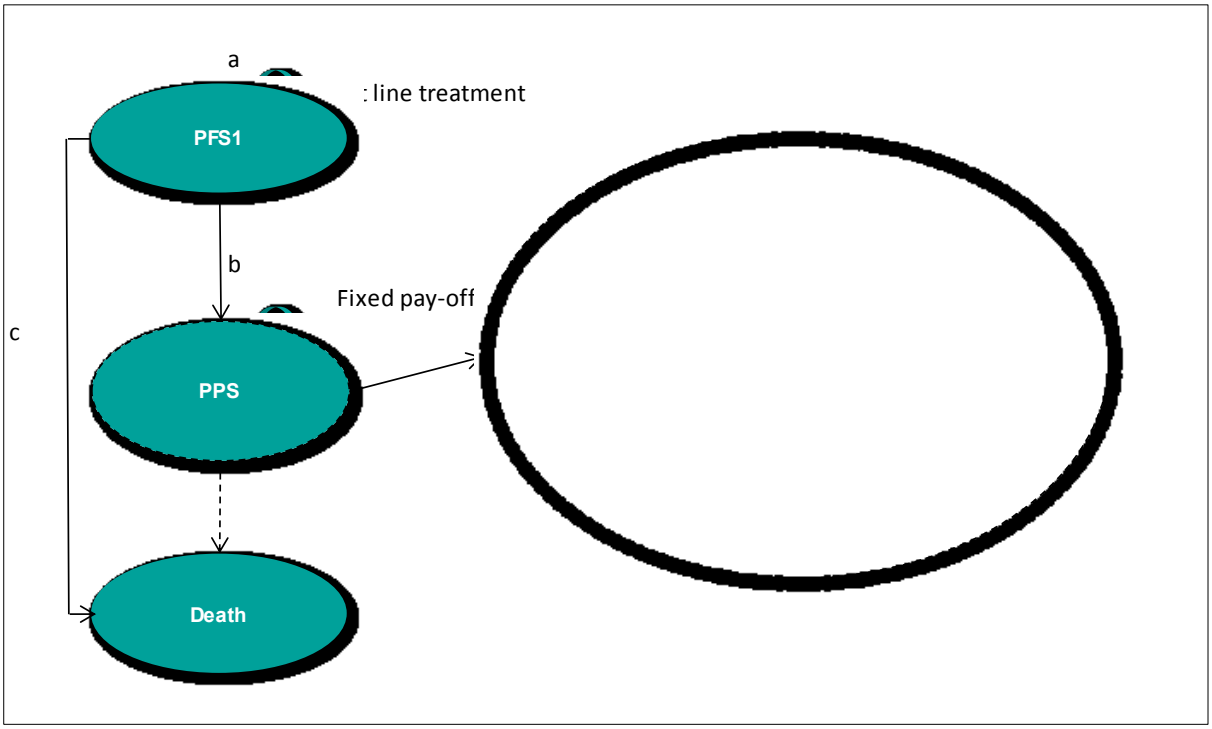


Figure 4 Illustration of model structure (CS Figure 15)

Abbreviations: PFS1: first-line progression-free survival; PFS2: second-line progression-free survival; PPS: post-progression survival

The model can be thought of as encapsulating a main model starting from first-line treatment and a 'fixed pay-off' sub-model starting from second-line treatment.

First-line model: This comprises three states; progression free survival (PFS1), post-progression survival (PPS) and death. A cohort of patients enters the model in the PFS1 health state at the start of first-line treatment with one of the included comparators (ABE+NSAI, PAL+NSAI or RIBO+NSAI) or NSAI. Patients may then:

a. Remain progression free.
b. Experience disease progression. Time to progression from first-line treatment (TTP1) is estimated as a survival curve, but unlike conventional progression-free survival, death is treated as a censoring event in the calculation of TTP1.
c. Die before disease progression. The progression-free death rate (PFD1) is conditional on the patient not having progressed. Unlike OS, progression is treated as a censoring event in the calculation of PFD1.

Methods used to estimate TTP1 and PFD1 are discussed in section 4.3.4.2 below.

When patients experience a first disease progression a 'fixed pay-off' is applied, representing health outcomes and costs that are incurred while patients receive second-line treatment and subsequent treatment and care. This pay-off is calculated in a separate sub-model (the dashed circle in Figure 4).

Fixed pay-off sub-model: This accounts for treatment and outcomes after the first disease progression. It is a conventional three-state partitioned-survival model, with transition probabilities calculated from:

- Overall survival from the start of second-line treatment (OS2). This includes deaths that occur before and after progression.
- Progression-free survival from the start of second-line treatment (PFS2). This includes deaths that occur before progression as events. For logical consistency, PFS2 is constrained in the model to be no more than OS2.
- The proportion of PFS2 events that are deaths is used to separate probabilities of progression, pre-progression deaths and post-progression deaths. This proportion is estimated from two other survival curves: time to progression and progression-free death from the start of second-line treatment (TTP2 and PFD2), defined and estimated in the same way as TTP1 and PFD2.

Methods used to estimate the post-progression transition probabilities using OS2, PFS2, TTP1 and PFD2 are discussed in section 4.3.4.3.

Transition probabilities and costs in the fixed-pay-off model are weighted according to the proportions of patients assumed to start each of the included second-line treatments. The

model includes costs for a third line of treatment (within the PPS state), but outcomes related to third-line treatment are not modelled explicitly.

The treatment pathway illustrated below shows the classes of treatment offered at first, second and third-line.

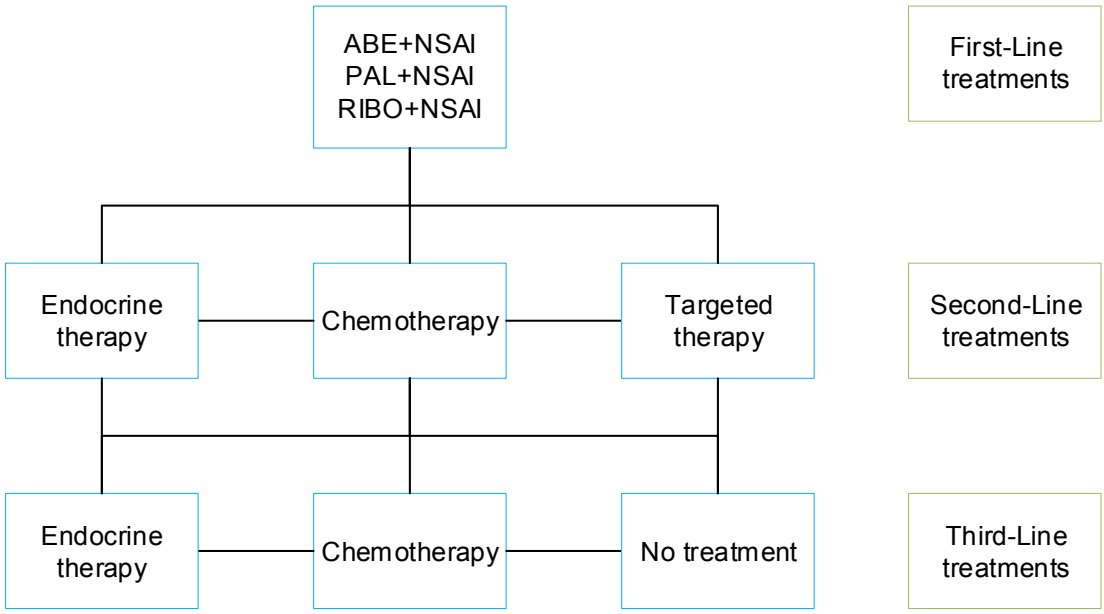


Figure 5 Treatment pathway (adapted from CS Figure 17)

Patients are assumed to stop first-line treatment when their disease progresses, or earlier if, for example, they experience intolerable adverse effects. The time to discontinuation of first-line treatment (TTD1) is estimated from trial data but constrained so that it cannot exceed TTP1. Similarly, time to discontinuation of second-line treatment (TTD2) cannot exceed PFS2. Time on third line treatment is estimated as a fixed proportion of time spent in the PPS state in the fixed pay-off sub-model.

The company's assumptions about initiation, utilisation and discontinuation of drugs are discussed in section 4.3.6.2 below.

4.3.3.1 Appropriateness of model structure and assumptions

Earlier models for NICE technology appraisals in breast cancer, including the palbociclib appraisal (NICE TA495), have taken the conventional three-state (PFS, OS and death) partitioned survival approach.[38] The ribociclib appraisal (NICE TA496) and this current company submission explicitly model a second-line of treatment and time to second progression (PFS2) using multi-state modelling. This approach is motivated as a way of

reducing uncertainty over immature first-line overall survival data. The CS cites immaturity of the MONARCH 3 OS data as the main reason for adopting this approach. The ribociclib model was an individual-level simulation. In this current appraisal, the company applies similar principles but implemented in a cohort model. They note that building a strictly Markov state-transition model would require a 'memoryless' assumption, where the probability of death would be the same for every individual after a first progression, regardless of how long they had spent in the PFS1 state. To overcome this problem, a 'compartmental' approach is used to keep track of successive cohorts of patients entering the fixed pay-off sub-model.

Calibration is used to adjust the time spent in the pay-off sub-model to reflect an assumed relationship between PFS and OS. In the base case, the company assumes a 'partial surrogacy' relationship, with the gain in OS being a fixed proportion of the gain in PFS (27.5%). This follows the approach in the ribociclib appraisal (TA496) and the DSU report for that appraisal.[39, 40] Without calibration, the model would automatically assume a direct gain in OS equal to the gain in PFS (100% surrogacy), which is not justified due to the uncertain and immature OS data from MONARCH 3. See section 4.3.4.3.4 below for a description of the source of the 27.5% surrogacy assumption and of how partial surrogacy is implemented.

ERG conclusions: The model structure and assumptions are appropriate. Given the immaturity of overall survival data for abemaciclib and for the comparators ribociclib and palbociclib, a conventional partitioned-survival approach would be subject to high uncertainty. The 'PFS2' fixed pay-off sub-model incorporates additional information about the effectiveness of second-line treatments. It also has the advantage that different patterns of second-line treatment use can be explored, modifying both the costs and outcomes. This is important as current UK practice differs from that in the RCTs on which the model is based. In addition, the calibration enables manipulation and exploration of uncertainty over the relationship between PFS and OS.

4.3.4 Clinical effectiveness

4.3.4.1 Overview of clinical parameters

The company summarise sources for transition probability estimates in CS Table 20 (CS section B.3.3.2) and base case values in CS Table 57 (B.3.6.1). Further detail is provided in CS sections 3.3.2 through to 3.3.7.

4.3.4.2 First-line transition probabilities

Table 16 Base case transition probabilities: first-line treatment

		Treatment	Base case	Source
TTP1	Time to first progression	NSAI	[redacted]	Exponential survival estimated from MONARCH 3 data adjusted for interval-censoring but not for patient baseline characteristics (CS Figure 21 B.3.3.5)
		ABE+NSAI	[redacted]	
		ABE+NSAI[c]	[redacted]	PFS hazard ratios compared with NSAI from first-line NMA, fixed effects (CS Table 23 B.3.3.5)[a]
		PAL+NSAI	[redacted]	
		RIBO+NSAI	[redacted]	
PFD1	Death rate before first progression	NSAI	0.002 per month	Negative-binomial regression of MONARCH 3 data not adjusted for patient baseline characteristics (CS Table 24 B.3.3.5)
		ABE+NSAI	0.005 per month	
		ABE+NSAI[c]	[redacted][b]	OS hazard ratios compared with NSAI from first-line NMA (CS Figure 11 B.2.9.2)
		PAL+NSAI	[redacted]	
		RIBO+NSAI	[redacted]	

[a] HRs for TTP1 in the model (as cited in CS Table 23) differ from those reported in CS Figure 10 B.2.9.2. These differences are small and we test the impact in ERG scenario analysis.

[b] The HR for ABE+NSAI ([redacted]) implies a pre-progression death rate only slightly higher than that for NSAI. The reason for this discrepancy is unclear.

c Not used in company base case (included here for reference).

4.3.4.2.1 Time to first progression (TTP1)

The company used individual patient data from the MONARCH 3 trial to estimate time to first progression for abemaciclib + NSAI and for NSAI. This analysis was conducted on the final PFS dataset (3rd November 2017) for the ITT population, with investigator assessment of progression.

MONARCH 3 analysis: investigator vs independent assessment

The company state that they use investigator-assessed progression as this is the primary endpoint in MONARCH 3 and is consistent with most trials included in the first-line NMA,

whereas independently-assessed progression was reported for fewer trials. However, there are arguments in favour of independent assessment of progression. Concerns were raised about the robustness of investigator assessment in NICE TA495 and TA496 due to the potential for un-blinding caused by the higher incidence of haematological adverse events with palbociclib and ribociclib than with NSAI (TA495 paragraph 4.3 and TA496 3.4). There are similar issues for MONARCH 3 trial because of the higher incidence of diarrhoea in the abemaciclib arm.

> **ERG conclusion**: We prefer independent assessment of progression outcomes due to the potential for loss of blinding caused by imbalances in adverse events. However, we acknowledge the importance of aligning outcomes in the NMA and the absence of independently-assessed outcomes for some trials. We therefore use investigator-assessed outcomes in the ERG preferred analysis. This is conservative because PFS is less favourable with investigator assessment than with independent assessment (CS B.2.6.1 Figures 6 and 7).

MONARCH 3 analysis: Adjustment for interval censoring

Tumour assessment in MONARCH 3 was conducted periodically (every other cycle up to cycle 18, then every third cycle and within 14 days of clinical progression) (CS Table 5). This explains the 'stepped' appearance of the Kaplan-Meier curves for PFS (CS Figures 6 and 7). In reality, progression will have occurred between assessments, thus recorded time to progression will tend to overestimate true time to progression. The company adjust for this using interval-censoring (CS B.3.3.4): the timing of progression events is coded as an interval between the preceding tumour assessment and the assessment at which the progression was recorded. The company use interval censored (IC) TTP1 estimates in their base case analysis and present a scenario without interval-censoring.

> **ERG conclusion**: We agree with the company's use of IC adjustment to estimate time to progression and use this in our preferred analysis. Like the company, we run a scenario without IC adjustment to test its impact on cost-effectiveness results.

MONARCH 3 analysis: Adjustment for baseline characteristics

The company do not adjust for baseline patient characteristics in their base case estimate of TTP1 from MONARCH 3, but they include baseline covariates in a scenario analysis. The covariates that were considered for inclusion are listed in CS section B.3.3.3. They include

variables for pre-planned subgroup analyses and additional prognostic factors identified by a literature review and discussion with experts. The company state that they performed backward and forward stepwise procedures to covariate selection but favoured the backward approach as this tends to include fewer variables. The variables included in the final covariate-adjusted equation were: age, liver metastases, measurable disease at baseline, PgR receptor status and tumour grade. In addition, a treatment group indicator was included as an explanatory variable.

> **ERG conclusion**: We agree with the company's approach to adjustment for baseline characteristics. The methods used to select covariates are reasonable and important prognostic variables are included. However, we support the use of unadjusted estimates in the base case, as this is more conservative.

MONARCH 3 analysis: Parametric survival functions

The company fitted parametric models for TTP1 in MONARCH 3, including a treatment indicator to provide joint estimates for abemaciclib + NSAI and NSAI. They tested three proportional hazards (PH) models (exponential, Weibull and Gompertz) and three accelerated failure time models (log-normal, log-logistic and gamma). Interval-censored adjusted curves are shown in CS Figures 19 and 20 and unadjusted curves are in CS Figures 25 and 26, M.2.2. CS Appendix M also includes supporting evidence for their choice of curves, sections M.1.1, M.2.1 and M.2.2.

The company concludes:

- Exponential and Weibull provide the best fit based on AIC (Akaike information criterion) and BIC (Bayesian inference criteria) statistics;
- In addition, Gompertz and gamma appear to fit the observed data well;
- Log-normal and log-logistic appear to overestimate survival after about 30 months;
- Proportional hazards models are compatible with the use of hazard ratios to estimate treatment effects for the comparators, whereas the accelerated failure time models are not.

For their base case, the company use an exponential function for time to first progression, with Weibull and Gompertz scenarios. Parameter values for these distributions are given in CS Tables 61, 62 and 62 for interval-censored, interval-censored and covariate adjusted and unadjusted models respectively (CS M.2.1). The CS and model do not include parameters

for the fitted log-normal, log-logistic or gamma distributions, and the company did not provide these parameters in response to a clarification question.

ERG considerations on the choice of parametric functions for TTP1:

- Cumulative hazards and log-log plots support the assumption of proportional hazards (CS Appendix M.1.1 Figures 15 and 16). We accept the company's argument that PH functions should be preferred because they are compatible with the use of hazard ratios to estimate results for the comparator treatments.
- For the interval-censored model, AIC and BIC statistics suggest that the exponential curve has the best fit to the trial data, followed by Weibull and Gompertz models (Table 60 M.2.1).
- Visual inspection of the curves (see Figure 8 in Appendix 9.3 of this report) indicates that all functions except log-normal have a good fit to the abemaciclib + NSAI arm. The fit is less good for the NSAI arm, particularly for the log-normal and log-logistic.
- Table 17 below shows estimated proportions of patients whose disease has not progressed within 1, 2, 3, 5 and 10 years of initiation of first-line treatments. Results are broadly consistent across the parametric functions, with the exception of the log-normal and log-logistic, which predict fewer late progressions. Clinical advisors to the ERG have suggested that 1% to 4% survival without progression at 10 years is more realistic than 9%: indicating that the exponential extrapolation may be appropriate.

We note an error in the coding of Gompertz TTP1 interval-censored adjusted survival in the company's submitted model. The formulae incorrectly reference the shape parameter for the baseline covariate model. There is also an error in reporting of the shape parameter for the Weibull curve in Table 61 in Appendix M (CS M.2.1). However, the value in the model (0.951) seems correct as the resulting curve fits the Kaplan-Meier curve and matches that in CS Figures 19 and 20.

ERG conclusion: The exponential, Weibull and Gompertz estimates of time to first progression provide a good fit to MONARCH 3 trial results. On the basis of statistical fit and clinical judgement on long-term extrapolations, we agree with the use of exponential as a base case, with Weibull and Gompertz as scenarios.

Due to a coding error, the company scenario with Gompertz TTP1 is not reliable. We present corrected results Section 4.4.1 below.

Table 17 Proportion of cohort without progression: (interval-censored adjusted)

	Year	Kaplan-Meier	Exp.	Weibull	Gompertz	Gamma	Log-normal	Log-logistic
NSAI (MONARCH 3)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	10		[redacted]	[redacted]	[redacted]			
ABE+NSAI (MONARCH 3)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	10		[redacted]	[redacted]	[redacted]			
ABE+NSAI (HR vs. NSAI)	0		[redacted]	[redacted]	[redacted]			
	1		[redacted]	[redacted]	[redacted]			
	2		[redacted]	[redacted]	[redacted]			
	3		[redacted]	[redacted]	[redacted]			
	5		[redacted]	[redacted]	[redacted]			
	10		[redacted]	[redacted]	[redacted]			
PAL+NSAI HR vs. NSAI)	0		[redacted]	[redacted]	[redacted]			
	1		[redacted]	[redacted]	[redacted]			
	2		[redacted]	[redacted]	[redacted]			
	3		[redacted]	[redacted]	[redacted]			
	5		[redacted]	[redacted]	[redacted]			
	10		[redacted]	[redacted]	[redacted]			
RIBO+NSAI HR vs. NSAI)	0		[redacted]	[redacted]	[redacted]			
	1		[redacted]	[redacted]	[redacted]			
	2		[redacted]	[redacted]	[redacted]			
	3		[redacted]	[redacted]	[redacted]			
	5		[redacted]	[redacted]	[redacted]			
	10		[redacted]	[redacted]	[redacted]			

Source: Company model with log-normal, log-logistic and gamma distributions digitised from CS Figures 19 and 20

PFS hazard ratios from first-line NMA

TTP1 for ribociclib + NSAI and palbociclib + NSAI are estimated using PFS hazard ratios relative to NSAI estimated from the first-line NMA. This entails the assumption of equal relative treatment effects for PFS and TTP. We consider this a reasonable approximation given the rarity of pre-progression death (21 out of 493 patients in MONARCH 3): the difference between PFS and TTP lies in how deaths before progression are analysed (an event in PFS but censored in TTP).

There are small differences between the PFS hazard ratios used in the model (CS Table 23 section B.3.3.5) and the fixed effect results reported in CS section B.2.9.2 Figure 10 – see Table 18 below. We also show results from the random effects model, as reported in response to a clarification question (A17). Although the random effects model converged, the credible intervals were implausibly wide. We therefore focus on the fixed effects model.

Table 18 PFS hazard ratios reported in CS: first-line NMA

Comparator	**Median hazard ratio (95% credible interval)**		
	CS Table 23 B.3.3.5 (as in model)	Fixed effects CS Figure 10 (B.2.9.2)	Random effects (clarification question A17 response Figure 2)
Abemaciclib + NSAI	[redacted]	[redacted]	[redacted]
Palbociclib + NSAI	[redacted]	[redacted]	[redacted]
Ribociclib + NSAI	[redacted]	[redacted]	[redacted]
NSAI	Reference	Reference	Reference

Source: CS Table 23 and CS Figure 3

Base case estimates of first-line TTP for the comparators are shown in CS Figure 21. We reproduce this graph adding a curve for abemaciclib estimated relative to NSAI using the PFS HR (see Figure 9 in Appendix 9.3 of this report). This shows that the base case estimate of TTP1 for abemaciclib from MONARCH 3 data is more favourable than the NMA estimate relative to NSAI, calculated in the same way as the other comparators. The reasons for this difference are unclear given that the only data for abemaciclib in the first-line NMA comes from MONARCH 3. Possible explanations include: the use of median HRs from the NMA but means for regression coefficients from MONARCH 3; and differences in relative treatment effects for TTP and PFS. The company conducted a scenario analysis with the NMA-based estimate of PFS1 for abemaciclib as well as for the other comparators. This made abemaciclib relatively less cost-effective.

ERG conclusion: The first-line NMA indicated that the three treatments have very similar effects on extending PFS compared with NSAI. Therefore, the large difference in time to first progression for comparators in the company's base case is questionable. This occurs because different estimation methods are used for ABE+NSAI (regression analysis of MONARCH 3 data) and for the PAL+NSAI and RIBO+NSAI (hazard ratios relative to NSAI from NMA). For a more reliable comparison, we use NMA-based estimates of TTP1 for all comparators relative to NSAI in ERG preferred analysis.

Uncertainty over the relative effects of the three comparators on PFS is not properly reflected in the company's probabilistic sensitivity analysis, because the HRs are sampled independently, not accounting for correlations between NMA results. We conduct additional deterministic sensitivity analysis to investigate the impact of uncertainty over the PFS HRs.

4.3.4.2.2 Deaths before first progression (PFD1)

Estimation of PFD1 from MONARCH 3

Pre-progression death rates for abemaciclib+NSAI and for NSAI were estimated from MONARCH 3 data. As few deaths before progression were observed - 17 deaths out of 328 patients in the intervention arm and 4 out of 165 patients in the control arm - the company used a negative binomial regression rather than a parametric survival model. They included follow-up time as an exposure variable and a treatment indicator. Forward stepwise regression identified ECOG status, prior adjuvant endocrine therapy and the type of NSAI received as co-variates. However, the company chose to use the simpler model without covariates for their base case. Parameters for the models with and without covariates are shown in CS Tables 65 and 66, M.2.3.

OS hazard ratios from first-line NMA

Hazard ratios for OS were used to estimate PFD1 rates for ribociclib and palbociclib: OS random effects model, see Table 16 above and CS Figure 11 B.2.9.2. This entails the assumption of equal treatment effects for OS and the rate of deaths before progression. However, the OS HRs were incorrectly applied relative to the progression-free death rate for abemaciclib, rather than for NSAI. This can be seen in CS Figure 22, as the survival rate is

shown to be highest for NSAI despite hazard ratios below 1 for ribociclib and palbociclib. We show a corrected version of this graph in Figure 9 (Appendix 9.3 of this report).

We also note that the rate of pre-progression deaths for abemaciclib estimated from the MONARCH 3 negative binomial regression is very different to that estimated using a HR relative to NSAI: [redacted] and [redacted] respectively. The reason for this difference is unclear, though we note that the regression approach uses mean coefficient values whereas the NMA approach uses median HRs. The assumption that relative treatment effects are the same for pre-progression deaths as for overall survival may also be wrong. Whatever the correct value for abemaciclib, we are concerned that the use of a different estimation method for the other comparators may bias relative estimates of cost-effectiveness.

ERG conclusion: We agree with the company's approach to estimating pre-progression death rates from MONARCH 3 data: the constant hazard estimated by negative binomial regression and omission of covariates in the base case is appropriate given the rarity of this event. However, the estimated death rates for palbociclib and ribociclib are higher than they should be because the model applies hazard ratios to the wrong comparator. We correct this in ERG analysis.

As was the case for TTP1, different methods are used to estimate PFD1 for abemaciclib for the comparators. The pre-progression death rate for abemaciclib and is considerably higher in the base case (estimated directly from MONARCH 3 data) than when it is estimated in the same way as the other comparators (with HRs relative to NSAI). We highlighted uncertainty and limitations in the first-line OS NMA (section 3.1.7 above). Nevertheless, we believe that the first-line NMA still provides the best available foundation for comparisons between abemaciclib, ribociclib and palbociclib. We therefore use first-line NMA-based estimates relative to NSAI for all three comparators in ERG preferred analysis.

4.3.4.3 Post-progression transition probabilities

Table 19 reports the transition probabilities used to estimate the effects of second-line treatment.

Table 19 Post-progression transition probabilities (before calibration)

		Treatment	Base case [a]		Source
Distribution of second-line treatments (used to weight costs and transitions)		FUL	10.9%		ERG scenario in NICE fulvestrant appraisal (TA503). With additional assumption that NSAI is not repeated at second-line. (CS Table 35 B.3.5.1)
		ANAS	-		
		LTZ	-		
		EXE	37.0%		
		TMX	18.5%		
		EVE+EXE	8%		
		Chemo	25.7%		
PFS2	Progression free survival from start of second-line treatment	FUL	[redacted] per month		MONARCH 2 subgroup parametric survival regression, exponential (CS Figure 29 B.3.3.6)
		ANAS	[redacted]	[redacted]	PFS HRs relative to fulvestrant (from model)[b] estimated from second-line NMA (see Appendix 9.2 below)
		LTZ	[redacted]	[redacted]	
		EXE	[redacted]	[redacted]	
		EVE+EXE	[redacted]	[redacted]	
		TMX	[redacted]	[redacted]	Estimated from Milla-Santos 2001[41]
		Chemo	1.64	(0.85, 3.15)	HR vs. EVE+EXE, Li et al. 2015 [42]
OS2	Overall survival from start of second-line treatment	FUL	[redacted] per month		MONARCH 2 parametric survival regression, exponential
			[redacted] per month		CONFIRM hazard after maximum MONARCH 2 follow-up (27.95 months)
		ANAS	[redacted]	[redacted]	OS hazard ratios relative to fulvestrant (from model) [b], estimated in second-line NMA (see Appendix 9.2 below)
		LTZ	[redacted]	[redacted]	
		EXE	[redacted]	[redacted]	
		EVE+EXE	[redacted]	[redacted]	
		TMX	[redacted]	[redacted]	Milla-Santos 2001[41] and second-line NMA
		Chemo	1.89	(0.72, 5.00)	HR vs. EVE+EXE, Li et al. 2015[42]
PFD2	Progression free death rate at second-line	EVE+EXE	0.005 per month		Rate of on-treatment progression in BOLERO-2[43]
		EXE	0.003 per month		
		Chemo	1.64	(0.85, 3.15)	PFS2 HR for chemo (Li et al. 2015).[42] Other treatments assumed equal to EXE.

a Base case probabilities before calibration adjustment for partial surrogacy

b Values and credible intervals from model. Note these differ from the values in the forest plots in CS Appendix N Figures 33 and 35 (N.1.2)

4.3.4.3.1 Progression-free survival on second-line (PFS2)

Methods used to estimate PFS2 are described in CS section B.3.3.6.

Estimation of PFS2 from MONARCH 2

MONARCH 2 was a randomised, placebo-controlled trial comparing abemaciclib + fulvestrant with placebo + fulvestrant (see Appendix 9.2.4 of this report for a comparison of the MONARCH 3 and MONARCH 2 populations).[16]

For the economic model, the company fitted parametric survival curves to MONARCH 2 data for a subgroup of patients (38% of the randomised population) in this trial who had progressed on prior endocrine therapy for advanced disease to reflect the population at second-line in the current decision problem. Models were fitted with and without IC adjustment, although the unadjusted results are not used. The regression included a treatment indicator, but only estimates for the control arm (fulvestrant 500mg) are used in the model. The resulting PFS2 curves for fulvestrant are shown in CS Figure 29 (CS section B.2.2.6).

The company used similar methods to select the parametric function for PFS2 as for the first-line survival functions, concluding:

- Cumulative and log-log hazard plots show no evidence of violation of proportional hazards, so a proportional hazards model may be appropriate (CS Figures 21 and 22, M.1.4);
- Exponential, Weibull and Gompertz provide the best fit based on AIC and BIC statistics (CS Table 72, CS Appendix M.2.6);
- Exponential was chosen for the company base case, as it has the most favourable BIC. Weibull and Gompertz were used in scenario analyses. CS Table 73 (CS Appendix M.2.6) for parameters for these three survival functions.

PFS2 hazard ratios from second-line NMA

The CS states that the HRs for second-line treatments were obtained from the company's second-line NMA (CS Appendix N). See Appendix 9.2 for the ERG critical appraisal of the second-line NMA. We note concerns over clinical heterogeneity between the included trials, also highlighted by the company. The network included MONARCH 2, which had narrower inclusion criteria than other included trials. It also appears that data for the ITT population from this trial were used in the NMA, rather than the subgroup of patients who progressed

on endocrine therapy for advanced disease which was used to fit the fulvestrant curves for the economic model.

We note that the PFS HRs in the model for treatments in the second-line NMA (anastrozole, letrozole, everolimus and exemestane + everolimus) are similar but not exactly the same as values in the forest plot for the second-line NMA (CS Figure 33, CS Appendix N.1.2).

Tamoxifen and chemotherapy are included in the economic model but not in the company's second-line NMA. Chemotherapy was eligible for inclusion in the network and some chemotherapy trials (n=9) were identified, but they could not be connected to the network as no study compared an endocrine therapy to chemotherapy monotherapy or combination treatment. The model uses hazard ratios from a paper by Li et al. (2015) [42] for chemotherapy: 0.61 (95% CI: 0.32-1.17) for PFS and 0.53 (95% CI: 0.20-1.39) for OS for "everolimus based therapy' vs chemotherapy (the inverse of these hazard ratios were used in the model and applied relative to everolimus + exemestane (EVE+EXE)). The Li at al. paper was also used in the submission for the previous NICE appraisal of ribociclib (TA496). The ERG for that appraisal criticised the lack of rationale for the selection of this study as the source of evidence for second-line treatment effects of chemotherapy. They also commented on the lack of clarity in the Li et al. paper about whether 'everolimus based therapy' refers only to everolimus monotherapy or if it also includes everolimus combination therapy. We share these concerns.

We note that the confidence intervals for the chemotherapy HRs are incorrectly entered in the economic model, with the lower and upper limits the wrong way round. This has the effect of excluding uncertainty over this parameter from the probabilistic sensitivity analysis. We correct this error in ERG analysis.

The CS does not state why NMA results are not reported for tamoxifen, as this is listed as one of the treatments for inclusion and some of the included trials had tamoxifen arms. The source of relative treatment effects for tamoxifen is not discussed in the CS. The model specifies that HRs were obtained from a paper by Milla-Santos (2001), which is a report of an RCT comparing tamoxifen with toremifene in a first-line setting for advanced breast cancer.[41] The company does not justify choice of this source. The model indicates that PFS and OS hazard ratios for tamoxifen relative to fulvestrant were calculated by multiplying HRs relative to toremifene from the Milla-Santos paper by HRs for toremifene relative to

fulvestrant from the second-line NMA.[17] We could not replicate the values in the model (as in Table 19 above), although our results were similar.

BOLERO-2 scenario analysis

The company present a scenario for second-line PFS and OS based on the BOLERO-2 trial: a phase III RCT comparing everolimus + exemestane with exemestane in postmenopausal women with HR+/HER2- advanced breast cancer with recurrence or progression during or after treatment with an NSAI.[43, 44] See Appendix 9.4 of this report for a comparison of the MONARCH 2 and BOLERO-2 patient populations.

It is difficult to judge whether MONARCH 2 or BOLERO-2 provide a better source for extrapolation of post-progression outcomes. Having considered the available evidence, we consider that patients in the MONARCH 2 subgroup are broadly representative of patients progressing in the MONARCH 3 trial, with the caveat that this only applies to a relatively small sub-group of patients of the MONARCH 2 trial who had progressed on endocrine therapy for advanced disease (38%) (see Appendix 9.4 of this report). In NICE TA496, the committee accepted the assumption that patients in BOLERO-2 are representative of patients in MONALEESA-2 (the pivotal first-line trial that compared RIBO+NSAI with placebo+NSAI). We cannot verify whether the analysis of BOLERO-2 data for TA496 is consistent with that in the current appraisal, due to lack of detail in the current CS and redactions in the TA496 committee papers.

The company fitted parametric PFS curves to reconstructed BOLERO-2 data (from digitised Kaplan-Meier curves) for everolimus and exemestane + everolimus. They use a log-normal survival function for the scenario and parameters for log-logistic and gamma survival functions are also provided in the model. The company does not justify the choice of the log-normal distribution or provide any statistics or graphs to assess model fit. Values for fulvestrant, anastrozole and letrozole are estimated using hazard ratios relative to exemestane from the company's second-line NMA: cited in the model as [redacted], [redacted] and [redacted] for PFS and [redacted], [redacted] and [redacted] for OS. The company assumes equal treatment effects for exemestane, tamoxifen and letrozole.

We compare long-term PFS estimates from the company base case (MONARCH 2 exponential) and scenario (BOLERO-2 log-normal) in Table 20 below. The results are broadly similar, although the BOLERO-2 scenario gives slightly less favourable projections

than the MONARCH 2 base case. A clinical advisor to the ERG has indicated that the EVE+EXE estimates seem unrealistically high.

Table 20 PFS from second-line treatment: (interval-censored adjusted)

	Year	FUL	ANAS	LTZ	EXE	TMX	EVE+EXE	Chemo
MONARCH 2	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BOLER- 2	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: produced by the ERG from survival curve estimates in the company model

ERG conclusions:

The company extrapolation of PFS for second-line fulvestrant is reasonable. We consider that the MONARCH 2 subgroup is broadly representative of patients progressing in the MONARCH 3 trial. And we agree with the use of IC adjustment and selection of the exponential survival curve for the base case, with Weibull and Gompertz scenarios.

There is uncertainty over the relative effects of other second-line treatments. We have concerns over the robustness of the second-line NMA, due to clinical heterogeneity (see Appendix 9.2). There are also small discrepancies between the PFS hazard ratios used in the model and values reported in the CS (CS Appendix N). The company has not provided justification for the choice of sources for chemotherapy and tamoxifen.

The BOLERO-2 trial analysis provides a useful cross-check for the MONARCH 2 results, particularly as BOLERO-2 was used for the assessment of post-progression outcomes in the NICE appraisal of ribociclib (TA492). However, the company has not provided any supporting evidence for the use of a log-normal curve for extrapolation of PFS.

4.3.4.3.2 Overall survival on second-line treatment (OS2)

Estimation of OS2 from MONARCH 2

The company estimates second-line OS curves for second-line treatments using a similar approach as for PFS. Fitted parametric curves for OS in the fulvestrant arm of MONARCH 2 are shown in CS Figure 33. Evidence for the fit of these curves is provided in CS Appendix M. The company concludes that there is no evidence of a violation of the proportional hazards assumption in MONARCH 2 OS data (though note that in their separate second-line treatment NMA report[17] they state that, based on Schoenfeld residual plots, the proportional hazards assumption for OS could not be supported for this trial). They note that the Gompertz curve has the best fit based on AIC and BIC statistics and Cox-Snell residual plots (CS Appendix M.2.5), but that the exponential, log-normal and log-logistic extrapolations are plausible, based on key opinion leader input. The company chose to use the exponential in their base case, with log-logistic and Gompertz in scenario analyses.

It is difficult to draw any meaningful conclusions about the validity of the proportional hazards assumption for OS from the MONARCH 2 trial, as the treatments are intertwined in the cumulative hazard and the log-log hazard plots (CS Figure 19 and 20 CS Appendix M), but this is not important, as the model only uses estimates for the fulvestrant arm. We question the decision to use an exponential curve for the company's base case, as this had a poor fit to MONARCH 2 survival data.

Long-term OS2 extrapolation from CONFIRM

Due to immaturity of the MONARCH 2 survival data (CS Figure 31 B.3.3.6), the company make use of data from the CONFIRM trial for extrapolation of OS2.[45, 46] CONFIRM was a randomised trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with HR+ advanced breast cancer. The company state that they chose this source as it is the only study from the second-line NMA that provided long-term OS data for fulvestrant (500 mg): reporting data up to 80 months, by which time around 20% of patients remained in the trial. We present information about the CONFIRM population in Appendix 9.4.

The company state that they fitted parametric distributions to reconstructed Kaplan-Meier data from the CONFIRM fulvestrant 500 mg arm. The CS states that they chose the Weibull

distribution for the CONFIRM extrapolation, but no information is provided to justify this choice. The company base case uses the MONARCH 2 exponential survival curve for fulvestrant up to the maximum follow-up (27.95 months). Extrapolation after this time is based on applying the hazard rate from the CONFIRM extrapolation. The resulting survival curve for fulvestrant is shown in CS Figure 34 (B.3.3.6).

OS2 hazard ratios from second-line NMA

The company estimates OS curves for other second-line treatments by applying hazard ratios relative to the survival curve for fulvestrant. The hazard ratios are estimated from the same sources as for PFS and we have the same concerns about differences between hazard ratios in the model and those cited in the CS and the sources of estimates for chemotherapy and tamoxifen (see Table 19).

Table 21 below shows second-line survival estimates from the company's base case model (MONARCH 2 exponential with Weibull extrapolation from CONFIRM) and also log-logistic and Gompertz extrapolations (MONARCH 2 without CONFIRM extrapolation). Clinical advice to the ERG suggests that the exponential and log-logistic estimates seem to overestimate long-term survival. One clinical advisor suggested to us that the Gompertz extrapolations are more reflective of current clinical experience, although another clinical expert has noted that they appear overly pessimistic.

Table 21 OS from second-line treatment

	Year	FUL	ANAS	LTZ	EXE	TMX	EVE+EXE	Chemo
Exponential with CONFIRM	0	[redacted]						
	1							
	2							
	3							
	5							
	10							
Log-logistic	0	[redacted]						
	1							
	2							
	3							
	5							
	10							
Gompertz	0	[redacted]						
	1							
	2							
	3							
	5							
	10							

Source: produced by the ERG from survival curve estimates in the company model

ERG conclusions:

We disagree with the company's choice of an exponential survival function to model second-line OS for fulvestrant, as this has a poor fit to the MONARCH 2 data.

We are also concerned about the lack of evidence regarding the choice of Weibull distribution for the CONFIRM trial extrapolation. No evidence is provided regarding the goodness-of-fit of this or alternative parametric functions.

The Gompertz distribution has the best fit to MONARCH 2 data and clinical advice to the ERG is that the long-term survival predictions from the Gompertz are maybe more realistic than the alternatives presented by the company, although they may be rather too pessimistic. We therefore use Gompertz OS extrapolations in the ERG preferred analysis and include the log-logistic and exponential with CONFIRM extrapolations in scenario analysis.

4.3.4.3.3 Progression-free death rate on second-line (PFD2)

Additional information is required for the fixed pay-off model to estimate the three sets of transition probabilities (PFS2 to death, PFS2 to PPS and PPS to death) from PFS and OS curves – an issue that always arises with partitioned survival models. The approach taken is not discussed in the CS, but inspection of the model shows that PFS2 events are split into progressions and deaths using estimates of second-line time to progression (TTP2) and progression-free death rates (PFD2). The company use similar methods to estimate TTP2 as for PFS2: understandably as these outcomes only differ in that pre-progression deaths are included in the latter but not the former. In the base case, an exponential survival model fitted to data from the fulvestrant control arm in the MONARCH 2 trial is used for TTP2, but this yields the same results as for PFS2. Weibull and Gompertz parameters do differ between TTP2 and PFS2, but these are not used in the model.

The second-line pre-progression death rate is therefore estimated from external data. A simple monthly mortality rate estimated from on-treatment death rates in the BOLERO-2 trial: 0.005 per month (22 per 378 patient years) for everolimus + exemestane and 0.003 per month (4 per 103 patient years) for exemestane (Piccart et al. 2014).[43] The company assumes a higher mortality rate with chemotherapy (0.008 per month), based on the PFS hazard ratio from Li et al. (2001).[47] Rates for other second-line treatments are assumed to be the same as for exemestane. The overall probability of pre-progression deaths on second-line treatment is 0.005 per month, weighting by the company's assumed distribution of second-line treatments. A clinical advisor to the ERG has noted that this is a bit higher than expected.

> **ERG conclusions**: We agree with the use of BOLERO-2 trial data to estimate pre-progression death rates on second-line treatment, as this trial is larger with more mature survival data than MONARCH 2. We have some concerns over the source of relative effects between second-line treatments. We also note that uncertainty over the second-line pre-progression death rate is not factored into the company's deterministic or probabilistic sensitivity analysis. However, given the rarity of pre-progression deaths and the fact that rates do not differ between the first-line comparators, this parameter is very unlikely to affect cost-effectiveness results.

4.3.4.3.4 Overall survival calibration

A 'partial surrogacy' assumption is applied by calibrating the time spent in the fixed-pay-off sub-model until a desired ratio between median PFS gain and median OS gain for the first-line comparators relative to NSAI is achieved. The target for the calibration is 27.5% in the company base case. To achieve this target, the calibration weights are: 1.22 for ABE+NSAI; 1.41 for PAL+NSAI; 1.45 for RIBO+NSAI; and 1 for the reference treatment NSAI (CS Table 25, CS section B.3.3.7). For each comparator, the same weight is applied to all second-line event rates (progressions, deaths before progression and deaths after progression), thus holding the proportion of time spent in the three second-line health states (PFS2, PPS and death) constant. The calibration is implemented using the Excel 'goal seek' function. This is also applied within each PSA iteration; so, a different set of calibration factors is estimated for each iteration. Uncertainty over the calibration target itself is not reflected in the PSA. The company conducts a scenario analysis with 'full surrogacy' (i.e. calibration weights of 1 for all comparators).

The base case target of 27.5% surrogacy reflects the 'lower bound' specified by the committee for the NICE appraisal of palbociclib (TA495), based on fitting an exponential curve to final OS and PFS data from the PALOMA-1 trial. The TA495 committee concluded that the extension of PFS1 is likely to result in some improvement in OS, although the choice between the lower bound (27.5%) and upper bound (100%) is a source of uncertainty. The NICE DSU reviewed evidence on the relationship between PFS and OS, concluding that evidence on full surrogacy is 'inconclusive'.[39] Similarly, the NICE committee for appraisal TA496 concluded that ribociclib + NSAI improves PFS, that this is likely to result in some improvement in OS, that a degree of partial surrogacy is 'probably more likely' than full surrogacy, but that the magnitude of the relationship is highly uncertain.

> **ERG conclusion**: We consider that the company have correctly implemented the calibration and that they test an appropriate the range of assumptions about the magnitude of the surrogacy relationship between OS and PFS, as requested by previous NICE appraisal committees TA495 and TA496 (from 27.5% to 100% surrogacy). We also test the conservative assumption of no surrogacy and other intermediate values in our analyses.

4.3.4.4 Adverse event rates

The model applies adverse event (AE) related QALY decrements and costs as one-off penalties at the start of first-line treatment. Grade 3-4 treatment-related AEs that occurred for at least 5% of patients for at least one comparator are included, based on the main publication for each comparator in the NMA: see Table 22 below (CS Table 29, B.3.4.4). Adverse events were not modelled explicitly for second or third line treatments.

Table 22 Adverse event probabilities in the model (adapted from CS Table 29)

Event	ABE+NSAI	NSAI	PAL+NSAI	RIBO+NSAI
Alanine aminotransferase increased	[redacted]	[redacted]	0.2%	9.0%
Anaemia	[redacted]	[redacted]	5.9%	2.4%
Aspartate aminotransferase increased	[redacted]	[redacted]	0.0%	6.0%
Diarrhoea	[redacted]	[redacted]	1.4%	2.4%
Hypertension	[redacted]	[redacted]	0.0%	10.0%
Leukopenia	[redacted]	[redacted]	24.8%	21.0%
Lymphopenia	[redacted]	[redacted]	0.0%	7.0%
Neutropenia	[redacted]	[redacted]	67.1%	59.0%

Sources: ABE+NSAI and NSAI, ITT population from MONARCH 3 CSR; PAL+NSAI from PALOMA 2;[48, 49] RIBO+NSAI from MONALEESA-2.[19, 50]

Incidence of neutropenia and leukopenia were high for all three of the CDK4/6 inhibitors, but particularly so for palbociclib and ribociclib. Abemaciclib is associated with a high incidence of diarrhoea The committee for the palbociclib appraisal (TA495) concluded that although incidence of neutropenia is high, adverse events are manageable and treatment discontinuation in practice will tend to be lower than in the trials. Clinical experts advising in TA496 stated that AEs are more common at treatment initiation and are usually resolved with dose reductions and interruptions (TA496). This view was supported by the clinical advisers to the ERG.

Other adverse effects that are important to patients are omitted from the model: in particular, fatigue, nausea, vomiting and infection. Almost all of the events included are measurements

that often do not impact on how the patient feels, whereas nausea/vomiting and fatigue are symptoms that patients have to live with/adapt to and infection often causes symptoms that make patients feel less well. Raised serum creatinine was another toxicity reported in a significant proportion of patients treated with abemaciclib that was not seen with palbociclib or ribociclib but is important to note as this treatment will potentially be used in older patients with HR+ metastatic breast cancer who may have existing renal impairment. This suggests that the effects of adverse treatment effects may have been underestimated in the model.

4.3.5 Health related quality of life

4.3.5.1 Health state utilities

The company report a systematic literature review of utility studies (CS B.3.4.1 and Appendix H) but conclude that studies found were not representative of the population of interest. Instead, utilities for the model are estimated from analysis of EQ-5D-5L data from MONARCH 3 and MONARCH 2 and from previous NICE appraisals – reported in CS Tables 26, 27 and 28 (B.3.4.2). We summarise sources in Table 23 and discuss further below.

Table 23 Health state utility estimates

Source	PFS1	PFS2[a]	PPS	Comments
Company analysis				
Base case	[redacted] Overall	0.745[a]	0.505	MONARCH 3 Model 1 for PFS1. Others from TA496
Scenario 1	[redacted] NSAI	0.745[a]	0.505	Treatment specific PFS1 from MONARCH 3 (Model 2)
	[redacted] Other			
Scenario 2	0.774	0.745[a]	0.505	PFS1 assumed equal to PFS2 (without chemotherapy)
Scenario 3	[redacted]	[redacted][a]	0.505	PFS2 from MONARCH 2 pre-progression utility
Scenario 4	[redacted]	0.745[a]	[redacted]	PPS estimated from MONARCH 3 progression disutility applied to PFS1[c]
Company estimates form trial data [b]				
MONARCH 3	[redacted] Overall	[redacted]		EQ-5D-5L adjusted for repeated measures, baseline utility and progression, with / without treatment arm
	[redacted] NSAI			
	[redacted] ABE+NSAI			
MONARCH 2		[redacted]	[redacted]	As above, without treatment
Previous NICE appraisals				
TA495 (palbociclib)	0.72 Overall	0.505	0.505	PALOMA 2 EQ-5D-3L, mean baseline values for PFS1. Estimated from Lloyd et al.[37] by ERG.[51]
	0.71 NSAI			
	0.74 PAL+NSAI			
TA496 (ribociclib)	Redacted in committee papers	0.774 initial 0.690 final, suggested by DSU	0.505	PFS1 from MONALEESA-2 EQ-5D-5L mixed model for repeated measures. PFS2 based on Lloyd et al. model [37] adjusted for BOLERO-2 age and response. DSU proposed reduction.[39]

[a] Weighted mean with disutility of 0.113 (Peasgood et al. 2010 [39]) applied for patients on chemotherapy at secondline (25.66%). Utility assumed equal for other second-line treatments.

[b] Values from CS Tables 26 to 28 and model.

[c] CS states scenario is based on MONARCH 2, but model applies MONARCH 3 disutility

4.3.5.1.1 Analysis of EQ-5D-5L data from MONARCH 3

EQ-5D-5L was administered in MONARCH 3 at baseline, at the start of alternate 28-day cycles up to cycle 19 and then at every third cycle. There were no significant differences between arms in change from baseline to final PFS EQ-5D-5L index or visual analogue scores - see section 3.3.5 above.

To inform the economic model, the company further analysed these data using a mixed model for repeated measures, with adjustment for baseline utility and progression (Model 1) and with an additional treatment variable to provide separate estimates for NSAI and ABE+NSAI (Model 2): see CS B.3.4.2 for methods and CS Appendix M.4.2 for results. We note that the CS omits important information about the methods of analysis: the population (safety or ITT); and the extent of missing data or whether attempts were made to impute missing values. The company states that utilities were calculated for the base case using the 'cross-walk' procedure, as recommended by NICE for consistency with UK EQ-5D-3L index values (CS B.3.4.2).[52] However, the CS reports the same results for the 'crosswalk' (CS M.4.2) as 'EQ-5D-5L' (CS M.4.1), and similarly in the model.

The company use the pre-progression utility from Model 1 ([redacted]) for PFS1 in their base case for all first-line interventions. They state that this is conservative, as there was no significant difference between treatments in Model 2. [redacted] The company use Model 2 results in a scenario, applying the ABE+NSAI PFS1 utility to all first-line treatments, which increased the ICER for ABE+NSAI vs NSAI.

The company do not use MONARCH 3 post-progression estimates for the economic analysis. Estimates were consistent between the utility models: mean [redacted] and [redacted] from Model 1 and Model 2 respectively. This results in an overall post-progression utility of [redacted], without treatment adjustment. We note that it is not obvious whether this estimate applies to the PFS2 or PPS health state, since some patients may have experienced a second progression during trial follow up.

ERG conclusions: The general approach to utility estimation from MONARCH 3 EQ-5D-5L data is appropriate, with use of a mixed model for repeated measures and

adjustment for baseline utility, progression and treatment group. We do have some reservations however about the reliability of the results because the CS omits information about the analysis population and handling of missing data.

Analysis of EQ-5D-5L data from MONARCH 2

The company reports a similar analysis of EQ-5D-5L data from the MONARCH 2 trial to inform second-line utility estimates (CS B.3.4.2 and M.4.2). This was conducted on the subgroup of patients who had progressed on prior endocrine therapy in the locally advanced or metastatic setting. A mixed regression model for repeated measurements was used, with adjustment for baseline utility and an indicator variable for progression, but no treatment indicator.

The company does not use MONARCH 2 utility estimates for their base case, although the pre-progression utility ([redacted]) is used for in a scenario for PFS2. This is assumed to apply for patients on endocrine or targeted therapies. As in previous NICE appraisals, including TA495 and TA496, an additional decrement of 0.113 (Peasgood et al. 2010)[53] is applied for the 25.66% of patients assumed to have chemotherapy at second-line. This results in an overall mean PFS2 utility estimate of [redacted]. The company also state that they use MONARCH 2 to estimate PPS utility in another scenario (see CS Table 28, B.3.4.2). However, examination of the model shows that this scenario actually uses the progression disutility from the MONARCH 3 analysis applied to the PFS1 utility: [redacted]. The post-progression utility estimated from the MONARCH 2 analysis is higher: [redacted].

ERG conclusions: The MONARCH 2 utility analysis shares the same strengths and weaknesses as the MONARCH 3 analysis described above. However, there is additional uncertainty about the compatibility of the MONARCH 2 subgroup with the MONARCH 3 population. The fact that pre-progression utilities from MONARCH 3 ([redacted]) are lower than pre-progression utilities from MONARCH 2 ([redacted]) is problematic. This might be a chance finding for two independent trial samples, or it might reflect a more structural incompatibility of patient selection or recruitment. Either way it is not realistic to assume a lower utility for PFS1 than for PFS2, as this implies that patients have a worse quality of life when progression-free at first-line than after disease progression at second-line.

4.3.5.1.2 Utility estimates from previous NICE appraisals

Utilities for the PFS1 health state in the appraisals for palbociclib and ribociclib (TA495 and TA496) were estimated using EQ-5D data from the PALOMA-2 and MONALEESA-2 trials respectively. The results are not available for ribociclib, because they are redacted in the NICE committee papers. For TA495, the company submission reports PFS utilities for palbociclib plus letrozole (0.74) and letrozole (0.71). The ERG for TA495 argued that this difference was not statistically significant and used a mean averaged across both arms (0.72). We also note that utility estimates from PALOMA-2 were just the treatment baseline values, assumed to apply for the duration of the pre-progression state.

For the post-progression health states, the company in the present appraisal relies on precedent for their base case: 0.774 for PFS2 (endocrine or targeted therapy) and 0.505 for PPS. These values are the same as in the Novartis submission for the NICE appraisal of ribociclib (TA496), derived in previous appraisals from a standard gamble study by Lloyd et al. (2006).[37] In this study, members of the UK general public were asked to value hypothetical health states for patients with metastatic breast cancer, described in vignettes. Results were analysed in a mixed model with a logistic transformation to estimate changes in utility related to the age of the respondent, stage of disease and treatment toxicities. The utility of 0.505 for progressed disease was calculated from the Lloyd et al. formula by the ERG in TA495 (by adjusting for the mean age of participants in the EQ-5D-3L UK value set survey).[51]

The estimate of 0.774 for PFS2 originated in TA421, calculated from the Lloyd et al. formula for stable disease, allowing for the treatment response rate in the BOLERO-2 trial. However, we note that the PFS2 value of 0.774 was not used in the final analysis for TA496. This was because the PFS1 utility estimated from the MONALEESA-2 trial exceeded 0.774, which was considered unrealistic. The DSU[39] suggested a revised value of 0.69 for PFS2, which was accepted by Novartis. The TA496 committee concluded that this assumption was appropriate for decision making but that the resulting utilities may undervalue the quality of life for patients in the progression-free state.

In the current appraisal, the company acknowledge the inconsistency in their base case of using a PFS2 utility that is higher than the PFS1 utility. They address this in a scenario in which they increase the PFS1 utility to 0.774. However, an alternative approach, as in TA496, would be to reduce the PFS2 utility.

ERG conclusions:

We consider that MONARCH 3 is the best source for the PFS1 utility ([redacted]): it complies with the NICE reference case (assuming crosswalk values are used); uses EQ-5D-5L data collected directly from participants in the pivotal trial; and the methods of analysis are appropriate, although we do have some reservations about lack of detail in reporting. We have a general preference for the treatment-specific utility estimates from MONARCH 3, because they reflect benefits and harms of treatments directly assessed by patients. However, equivalent treatment-specific utilities are not available for all comparators. We therefore agree with the company's decision to use the overall PFS1 utility for all comparators in their base case.

For post-progression utilities, the company's decision to use estimates from previous NICE appraisals derived from the Lloyd et al. formula has the merit of consistency between appraisals, although it does not comply with the NICE reference case, as health state measures are not obtained from patients. We consider that the company fails to address the inconsistency between the pre and post-progression utilities in their base case, as they use a PFS2 value that is higher than the PFS1 value. This same problem arose in TA496 and resulted in revision of the PFS2 value from 0.774 to 0.690. We suggest that this value should also be used in the current appraisal. We conduct one-way sensitivity analysis for PFS1 and PFS2, changing them from upper to lower bounds while respecting the assumption that the utility for PFS1>PFS2>PPS.

4.3.5.2 Adverse events

Assumptions underlying the estimation of QALY loss associated with treatment-related adverse events for first-line treatment options are described in CS B.3.4.4. In addition to the probability of modelled adverse events (see section 4.3.4.4 above), this includes a disutility and duration for each AE (CS Table 30 and 31 respectively). The company report that a systematic literature review was consulted to identify sources for these parameters, but that no relevant studies were identified. No further details of this search are provided. Cited sources for AE parameters are Hudgens et al. (2016)[54], Swinburn et al. (2010)[55] and NICE appraisals TA306 (pixantrone for non-Hodgkins lymphoma[56]) and TA503 (fulvestrant for untreated HR+ advanced breast cancer[57]).

We summarise the modelled AE QALY loss per person starting first-line treatment in Table 24 below. These values are very low due to the short duration (from 0 to 34 days) and small

disutility (0 to 0.153) attached to the events. Clinical advice to the ERG suggests that differences in the adverse event profiles of comparators can affect HRQoL. For abemaciclib, diarrhoea is more frequent, but this is easily controllable and usually short-lived. Patients on palbociclib and ribociclib may have low white cell count but not episodes of sepsis that could affect HRQoL.

Table 24 Adverse event QALY loss

First-line treatment	QALY loss per person starting treatment	Source
NSAI	-0.00062	Weighted means based on AE probabilities, utility decrements and durations (CS Tables 29-31)
ABE-NSAI	-0.00008	
PAL-NSAI	-0.00054	
RIBO-NSAI	-0.00100	

4.3.6 Resource use and costs

4.3.6.1 Use of second and third line treatment options

The company's base case assumptions about the proportions of patients receiving second and third-line treatment options are summarised in CS Tables 35 and 39 respectively – summarised in Table 25 below.

Table 25 Use of second and third-line therapies (adapted from CS Table 35 and 39)

	Company base case		ERG scenario	
	Second-line	Third-line	Second-line	Third-line
Chemotherapies	**25.7%**	**30.4%**	**25%**	**50%**
Capecitabine	12.3%	24.8%	12%	41%
Paclitaxel	6.2%	0.0%	6%	0%
Docetaxel	7.2%	0.0%	7%	0%
Eribulin	0.0%	5.6%	0%	9%
Endocrine therapies	**66.3%**	**24.0%**	**35%**	**25%**
Fulvestrant	10.9%	10.1%	0%	0%
Anastrozole	0.0%	0.0%	0%	5%
Letrozole	0.0%	0.0%	0%	5%
Exemestane	37.0%	6.2%	15%	5%
Tamoxifen	18.5%	7.7%	20%	10%
Everolimus + exemestane	**8.0%**	**0.0%**	**40%**	**10%**
No treatment	**0.0%**	**45.6%**	**0%**	**15%**

These are based on assumptions in the NICE appraisal of fulvestrant for untreated HR+ advanced breast cancer (TA503)[57] and the company's assumption that NSAIs would not be used following use at first line.

> **ERG conclusion**: Clinical advice to ERG suggests that these distributions do not reflect current NHS practice and policy. Fulvestrant is not used at second or third line, because it is not recommended by NICE (TA239) and fewer patients have exemestane monotherapy now that everolimus + exemestane are recommended by NICE (TA421). At third-line, a greater proportion of patients have chemotherapy (around 50%), with few patients receiving no treatment (10-15%). NSAIs may also be used sometimes at third-line. We test the impact of a scenario based on this clinical advice in ERG analyses.

4.3.6.2 Duration of treatment

We summarise methods used to model treatment duration in Table 26. For first- and second -line treatments, similar methods are used as for TTP and PFS: with parametric survival curves fitted to MONARCH 3 (NSAI and ABE+NSAI) and MONARCH 2 (FUL), adjusted for other comparators with hazard ratios. However, as time to discontinuation is not reported in trial publications, hazard ratios were estimated based on reported median treatment durations. Third line treatment is only included in the model as a cost, applied for a fixed proportion of time spent in the PPS health state.

Table 26 Time to treatment discontinuation

		Treatment	**Base case**		**Source**
TTD1	Time to discontinuation of first-line treatment	NSAI ABE+NSAI	Gamma survival curves (joint fit)		MONARCH 3, IC-adjusted (CS Figures 24 & 25)
		[redacted]	[redacted]		Hazard ratios relative to NSAI estimated from median times on treatment (CS Appendix M Table 68 M.2.4)
		[redacted]	[redacted]	[redacted]	
		PAL+NSAI	19.8 months	HR 0.81	
		RIBO+NSAI	20.3 months	HR 0.79	
TTD2	Time to discontinuation of second-line treatment	FUL			
		[redacted]	[redacted]		Hazard ratios relative to fulvestrant, estimated from median times on treatment (CS Appendix M Table 78 M.2.4)
		ANAS	5.6 months	[redacted]	
		LTZ	5.9 months	[redacted]	
		EXE	4.4 months	[redacted]	
		TMX	4.4 months	[redacted]	
		EVE+EXE	7.8 months	[redacted]	
		CAP	4.8 months	[redacted]	
		PAC	4.8 months	[redacted]	
		DOC	4.8 months	[redacted]	

Third line: proportion of time in PPS spent on treatment	37%	

[a] Not used in company base case (included here for reference).

Time to discontinuation of first-line treatment (TTD1) with ABE+NSAI and NSAI is estimated using parametric survival models fitted to MONARCH 3. Estimation methods are similar to those for TTP1 (see CS section B.3.3.5 and CS Appendix M.1.2 and M.2.4). The company concludes that treatment effects are multiplicative over time, rather than proportional, and that the log-normal, gamma and Gompertz models provide a good fit to the observed data. However, as treatment continuation is constrained by progression (modelled as an exponential), the company ruled out the log-normal and Gompertz curves for the base case (they 'overshoot' progression). They therefore chose the gamma distribution for TTD1, with log-normal, Gompertz and exponential curves used as scenarios. Note the model does also constrain time to discontinuation to not exceed time to progression. Time to discontinuation of the other first-line comparators (PAL+NSAI and RIBO+NSAI) was estimated relative to NSAI using hazard ratios estimated from median times to discontinuation. The resulting TTD1 extrapolation curves are shown in CS Figure 26.

The process for fitting time to discontinuation of second-line treatment (TTD2) was similar to that for PFS2 (CS section B.3.3.6 and CS Appendix M.1.5 and M.2.8). Joint parametric survival curves were fitted to MONARCH 2 data, although only the curve for the fulvestrant curve was used in the model. The company concluded that there was no evidence of violation of the proportional hazards assumption and that the Gompertz curve has the best fit to trial data. However, this overshoots progression, modelled with an exponential curve. The company decided to use an exponential curve for TTD2 in the base case and Gompertz and log-logistic curves for scenario analysis. Consideration of CS Figure 37, which shows the fitted parametric curves in relation to the Kaplan-Meier curve for the fulvestrant arm of MONARCH 2, indicates that exponential does provide a reasonable fit for TTD2.

4.3.6.2.1 Duration of third-line treatment

The company estimates time on third-line therapy, calculated based on an assumption that patients spend approximately 37% of their time on treatment after progression from second-line treatment. This assumption was based on clinical expert opinion. Estimated time on treatment based on this assumption is presented in Table 27.

ERG conclusion:

We agree with the company's choice of survival curves for time to discontinuation of first and second-line treatments and apply the same base case and scenarios in ERG analysis. However, clinical advice to the ERG is that it would be unusual for patients to spend as much as 63% of time after a second disease progression without treatment. Thus, the cost of treatment in the PPS health state is probably underestimated. We vary the proportion of PPS spent on treatment (from 10 to 50%) to assess the impact of uncertainty around this parameter.

Table 27 Time on third-line treatment (CS Table 43)

First-line treatment	Time in PPS (months)		
	On treatment	Off treatment	Total
ABE+NSAI	12.17	20.72	32.89
PAL+NSAI	12.26	20.88	33.15
RIBO+NSAI	12.26	20.88	33.15
NSAI	12.17	20.72	32.89

4.3.6.3 Drug costs

Table 28 Drug acquisition and administration costs

Drug	Dose Per cycle	Cycle	Dose intensity[b]	Drug cost		Admin. Per month
				Per cycle	Per month	
ABE	8,400 mg	28 days	[redacted]	[redacted]	[redacted]	
PAL	2,625 mg	28 days	93%	£2,950	£3,205	
RIBO	12,600 mg	28 days	88%	£2,950	£3,205	
LTZ	70 mg	28 days	[redacted]	£2.71	£2.94	
ANAS	28 mg	28 days	[redacted]	£1.34	£1.46	
CAP	59,437 mg	21 days	100%	£21.56	£31.22	£237
PAC	297 mg	21 days	78%	£0.39	£0.56	£376
DOC	127 mg	21 days	78%	£4.65	£6.74	£376
ERI	4 mg	21 days	87%	£1,714	£2,482	£752
FUL	500 mg	28 days	[redacted]	£522	£568	£238[a]
EXE	700 mg	28 days	100%	£3.44	£3.74	
TMX	608 mg	30 days	100%	£1.61	£1.61	
EVE	280 mg	28 days	100%	£2,495	£2,710	

[a] Loading dose only
[b] Not applied in base case (includes wastage)

Table 28 above, summarises drug acquisition and administration costs, including:

- Treatment regimens and acquisition costs: CS section B.3.5.1; Tables 33 and 34 for first-line; and Tables 36 and 37 for second-line.

- The base case assumes wastage (100% of dose for oral therapies and disposal of unused vial contents for IV therapies). The company conducts a scenario analysis with reduced costs according to the relative dose intensities shown in Table 28, derived from the primary trial publications for first-line therapies, MONARCH 2 for fulvestrant, Beuselinck et al. (2009)[58] for paclitaxel, Kaufmann et al. (2015)[59] for eribulin and assumptions for other second and third line treatments.
- No administration costs were applied for oral treatments, except for capecitabine, for which the NHS Reference cost for oral chemotherapy was incurred. Paclitaxel, docetaxel and eribulin incurred a cost per cycle for delivery of simple chemotherapy. A cost for face-to-face, first medical oncology visit was assumed for the first, loading dose of fulvestrant.

4.3.6.4 Health care costs

The model includes additional costs for follow up and care. These include:

- **Follow up care and monitoring**. See CS Tables 52 and 53. This includes diagnostic tests, outpatient oncology consultation, GP surgery visits, community and clinical nurse specialist care at home and therapy. These costs are related to health state, with resource used informed by MONARCH 3 and MONARCH 2 data and packages of care defined in the NICE Advanced Breast Cancer guideline (CG81).
- **Treatment for adverse reactions**. See CS Table 56, B.3.5.3. The cost of treatment adverse events was modelled as a one-off fixed cost at the start of treatment. The company assumed one outpatient visit for grade 3/4 hypertension, leukopenia, lymphopenia and neutropenia and a blood transfusion for anaemia. In their base case, the company assumed that grade 3/4 diarrhoea would be treated with loperamide, but they conducted a sensitivity analysis assuming a non-elective short-stay hospital admission.
- **Hospitalisation**. CS B.3.5.2 and Tables 47 to 51. Admission rates and lengths of stay were estimated by health state (PFS1, PFS2 and PPS) based on observations in the MONARCH 3 and 2 studies.
- **Best supportive care**. CS B.3.5.2 and Tables 45 and 46. This included palliative medications, with rates of use taken from the MONARCH 3 and 2 data.
- **End of life care.** Place of death and and packages of care were based on the NICE Advanced breast cancer clinical guidelines, CG81.

With the exception of first-line drug costs and treatment for adverse events, costs were the same for the first-line comparators. We summarise the monthly non-drug costs by health state in Table 29.

Table 29 Average monthly health care costs

	Average cost per month		
	PFS1	**PFS2**	**PPS**
Follow up care	£443	£635	£691
Adverse events	£106	-	-
Hospitalisation	£33	£46	£40
Best supportive care	£146	£146	£69
Total	**£728**	**£828**	**£800**
End of life	£4,379	£4,379	£4,379

For comparison, in NICE TA495 (palbociclib) the ERG estimated a mean cost per cycle of £1200 per cycle for active treatment states and £975 for best supportive care. The committee noted that these estimates were similar to confidential estimates by the Cancer Drugs Fund clinical lead in consultation with experts from the Chemotherapy Clinical Reference Group of NHS England. The committee agreed that the ERG estimates for post-progression costs are plausible. In NICE TA496 (ribociclib), the committee tested monthly costs in the PPS state in the region of £1140 to £1200 (ERG TA495 estimate) in decision making.

4.3.7 Model validation

The company report an external validation of their model was conducted by an analyst who was not initially involved in the model design or programming. The CS describes a series of iterations between analysts to identify and address areas of disagreement. The company also sought the opinion of their clinical experts to review the outputs from survival extrapolations.

The ERG checked the company's economic model for transparency and validity. The model was developed in Microsoft Excel and the visual basic codes were accessible.

We conducted a range of 'white box' tests to verify model inputs, calculations and outputs which consisted of:

- Cross-checking of all parameter inputs against values in the CS and cited sources;

- Checking that model outputs such as base case deterministic results and results of scenario analysis reported in the CS were reproducible by manually running the model;
- Checking individual equations and formulas within the model;
- Testing the logic of formulas in the model by substituting model inputs with a range of extreme values;
- Checking that visual basic codes did what they were designed to do.

Generally, we found the economic model to be of a good quality, with very few errors in input parameters, logic or coding. We identified a few small errors that we report and correct in section 4.4.1 below. However, these errors did not make any substantive difference to the results of cost-effectiveness analysis.

4.3.8 Company cost effectiveness results

Results from the economic model are presented in Section B.3.7, page 140 of the CS.

The base case results, presented in terms of incremental cost per QALY gained (Table 30) show that PAL+NSAI and RIBO+NSAI are both dominated by ABE+NSAI (that is, it has lower costs and higher QALYs). Model outputs from ERG corrections are reported in section 4.4.1 of this report and show minor variations from the company's results, however these differences do not alter the company's conclusions.

Table 30 Company base case results – deterministic (CS Table 59)

Treatment	Total		Incremental analysis ICER (£/QALY)	Pairwise ICERs ABE+NSAI vs. comparator (£/QALY)
	Costs (£)	QALYs		
NSAI	£56,449	2.997	Referent	£250,065
PAL+NSAI	£145,266	3.225	Dominated	ABE+NSAI Dominant
RIBO+NSAI	£148,170	3.222	Dominated	ABE+NSAI Dominant
ABE+NSAI	£129,803	3.291	£250,065	-

The CS summarises the results of the PSA stating that there is a 82% probability of ABE+NSAI being cost-effective, relative to PAL+NSAI and RIBO+NSAI, at a threshold willingness to pay of £30,000 per QALY gained.

Table 31 Company base case results – probabilistic (CS Table 61)

Treatment	Total		Incremental analysis ICER (£/QALY)	Pairwise ICERs ABE+NSAI vs. comparator (£/QALY)
	Costs (£)	QALYs		
NSAI				
PAL+NSAI	£139,631	3.15	-	-
RIBO+NSAI	£142,571	3.16	£397,144	£397,144
ABE+NSAI	£125,581	3.21	Dominant	Dominant

One-way sensitivity analyses

The company does not present one-way sensitivity analyses in the CS. In response to the ERG's clarification question B3, the company states that it does not believe one-way sensitivity analysis are crucial to decision making.

Scenario analysis

The CS reports a deterministic scenario analysis to explore the impact of base case assumptions in 29 scenarios. Results of these analyses are presented below (Table 32).

Table 32 Company scenario results (Adapted from CS Table 63)

Scenario	Base case value	Scenario	ICER (£ per QALY gained)		
			ABE+NSAI	PAL+NSAI	RIBO+NSAI
Base-case	N/A	N/A	£250,065	Dominated	Dominated
Discount rates	3.50%	0.00%	£212,582	Dominated	Dominated
Discount rates	3.50%	6.00%	£279,248	Dominated	Dominated
ABE+NSAI PFS1 treatment effect	Joint model MONARCH 3	NMA	£341,342	£1,378,635	Dominated
IC adjustment	IC-adjusted analysis	Unadjusted analysis	£250,065	Dominated	Dominated
Covariate adjustment	IC-adjusted analysis	Covariate and IC-adjusted analysis	£222,795	Dominated	Dominated
TTP1 (scenario 1)	Exponential	Weibull	£240,007	Dominated	Dominated
TTP1 (scenario 2)	Exponential	Gompertz	£571,795	Dominated	Dominated
PFS2 (scenario 1)	Exponential	Weibull	£256,368	Dominated	Dominated
PFS2 (scenario 2)	Exponential	Gompertz	£278,660	Dominated	Dominated
OS2 (scenario 1)	Exponential + CONFIRM	Exponential	£282,398	Dominated	Dominated
OS2 (scenario 2)	Exponential + CONFIRM	Log-logistic	£245,869	Dominated	Dominated
Second-line OS (scenario 3)	Exponential + CONFIRM	Gompertz	£197,053	Dominated	Dominated
TTD1	Gamma	Gompertz	£263,628	Dominated	Dominated
TTD1	Gamma	Log-normal	£254,708	Dominated	Dominated
TTD1	Gamma	Exponential	£223,727	Dominated	Dominated
TTD2	Exponential	Log-logistic	£250,065	Dominated	Dominated
TTD2	Exponential	Gompertz	£250,065	Dominated	Dominated
HRs for TTD2	Vs FUL based on median ToT	Vs second-line PFS	£248,546	Dominated	Dominated
Utility model	Overall	Treatment-specific	£269,922	Dominated	Dominated
PPS utility source	Lloyd, 2006	MONARCH 2	£411,806	Dominated	Dominated

Second-line PFS utility	TA496	MONARCH 2	£248,716	Dominated	Dominated
PPS hospital length of stay	MONARCH 2	MONARCH 3	£248,499	Dominated	Dominated
Relative dose intensity	OFF	ON	£196,532	Dominated	Dominated
PFS1 utility value	MONARCH 3	Equal to PFS in second-line treatment	£209,593	Dominated	Dominated
Source of clinical outcomes in PPS	MONARCH 2	BOLERO-2	£182,754	Dominated	Dominated
Apply PFS–OS surrogacy	Yes (27.5%)	No (100%)	£159,286	Dominated	Dominated
PFS 1 utility source	EQ-5D-3L (crosswalk)	EQ-5D-5L	£250,065	Dominated	Dominated
Management of diarrhoea	Loperamide	Hospitalisation and loperamide	£251,084	Dominated	Dominated

The scenarios are clearly stated and justified. PAL+NSAI and RIBO+NSAI are dominated by ABE+NSAI in all scenarios. We reran the company's scenarios after effecting our corrections and they are reported in section 4.4.2 of this report.

Probabilistic sensitivity analysis

The company's model computes PSA results based on 10,000 iterations. The ERG finds that running the PSA is computationally challenging (running the 28 scenarios takes over 2 hours) due to the calibration calculations required to adjust OS.

The ERG is of the opinion that 1000 iterations are sufficient to produce reasonably stable results. Our rerun of the PSA at 1000 iterations takes about 30 minutes.

4.4 Additional work undertaken by the ERG

4.4.1 ERG corrections to company model

We identified some minor errors in the company's model, as shown in Table 33 below.

Table 33 ERG corrections to company model

Aspect of model	Problem	ERG Correction
1.Hazard ratios and relative risks	Upper and lower confidence interval values for second-line chemotherapy are entered the wrong way round for all clinical outcomes in the model. This wrong entry only affects the results of the probabilistic analysis.	Reordered chemotherapy hazard ratio and relative risk confidence interval values for second-line time to progression, second-line progression-free deaths, second-line progression-free survival and second-line overall survival.
2.Pre-progression deaths	PAL and RIBO estimated relative to ABE.	Corrected so that the extrapolated hazards of pre-progression deaths for patients on PAL and RIBO are estimated relative to NSAI.
3. TTP1	Extrapolations from Gompertz distributions for ABE+NSAI (unadjusted) and NSAI (unadjusted) use shapes from IC and covariate adjusted calculations.	We corrected the formulas to so that the appropriate shapes are used.
4. The percentage of PFS events that are deaths	The company model estimates this from an incorrect denominator – PFS2 events instead of the sum of patients experiencing progression and pre-progression deaths in the payoff sub model).	We corrected the appropriate formulas in the model. This gives a fixed proportion of 4.4% of the people leaving PFS each month which matches the input assumptions.

4.4.2 Results from ERG corrected company base case

The results of the company's base case with ERG corrections are presented in Table 34.

Table 34 Company base case results (ERG corrected) - deterministic

Treatment	Total		Incremental analysis ICER (£/QALY)	Pairwise ICERs ABE+NSAI vs. comparator (£/QALY)
	Costs (£)	QALYs		
NSAI	£56,152	2.997	Referent	£250,352
PAL+NSAI	£152,268	3.273	Dominated	ABE+NSAI Dominant
RIBO+NSAI	£154,559	3.285	Dominated	ABE+NSAI Dominant
ABE+NSAI	£129,590	3.291	£250,352	-

Table 35 shows the ERG corrected version of the company's scenario analyses.

Table 35 Company scenario results (ERG corrected)

Scenarios	Treatments	Total costs (£)	Total QALYs	Incremental ICER (£/QALY)	Pairwise ICER ABE+NSAI vs. comparator
Discount rates: 0.00%	NSAI	63,783	3.381	Referent	£212,804
	PAL+NSAI	170,307	3.721	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	172,946	3.735	Dominated	ABE+NSAI Dominant
	ABE+NSAI	144,531	3.760	£212,804	-
Discount rates: 6.00%	NSAI	51,717	2.774	Referent	£367,282
	PAL+NSAI	141,688	3.014	Dominated	£187,961
	RIBO+NSAI	143,775	3.025	£6,988,613	-
	ABE+NSAI	120,879	3.021	£279,586	£6,988,613
ABE+NSAI treatment effects for PFS: NMA	NSAI	56,152	2.997	Referent	£342,211
	PAL+NSAI	152,268	3.273	Ex Dominated	£188,241
	RIBO+NSAI	154,559	3.285	£343,915	-
	ABE+NSAI	130,514	3.215	£341,663	£343,915
Interval censoring unadjusted	NSAI	56,152	2.997	Referent	£250,352
	PAL+NSAI	152,268	3.273	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	154,559	3.285	Dominated	ABE+NSAI Dominant
	ABE+NSAI	129,590	3.291	£250,352	-
Covariate and interval censoring adjusted	NSAI	58,122	3.127	Referent	£223,086
	PAL+NSAI	159,934	3.400	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	161,058	3.400	Dominated	ABE+NSAI Dominant
	ABE+NSAI	142,262	3.504	£223,086	-
TTP1 Weibull	NSAI	56,305	3.018	Referent	£330,052
	PAL+NSAI	155,494	3.311	Dominated	£170,309
	RIBO+NSAI	158,148	3.327	£5,606,781	-
	ABE+NSAI	129,213	3.322	£240,299	£5,606,781
TTP1 Gompertz	NSAI	56,506	3.051	Referent	£311,553
	PAL+NSAI	162,059	3.396	£2,469,570	£935,832
	RIBO+NSAI	165,016	3.399	£935,832	-
	ABE+NSAI	127,893	3.382	£215,479	£2,184,412
PFS2 Weibull	NSAI	55,987	3.007	Referent	£256,648
	PAL+NSAI	152,229	3.273	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	154,529	3.285	Dominated	ABE+NSAI Dominant
	ABE+NSAI	129,528	3.294	£256,648	-
PFS2 Gompertz	NSAI	55,226	3.045	Referent	£278,905
	PAL+NSAI	152,010	3.284	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	154,329	3.295	Dominated	ABE+NSAI Dominant
	ABE+NSAI	129,214	3.310	£278,905	-

OS2 Exp.	NSAI	71,084	3.584	Referent	£282,820
	PAL+NSAI	165,287	3.804	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	167,238	3.801	Dominated	ABE+NSAI Dominant
	ABE+NSAI	142,943	3.838	£282,820	-
OS2 Log-logistic	NSAI	57,047	3.031	Referent	£246,160
	PAL+NSAI	153,251	3.322	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	155,397	3.327	Dominated	ABE+NSAI Dominant
	ABE+NSAI	130,419	3.329	£246,160	-
OS2 Gompertz	NSAI	40,049	2.350	Referent	£244,796
	PAL+NSAI	140,748	2.761	£1,250,081	-
	RIBO+NSAI	142,614	2.750	Dominated	ABE+NSAI Dominant
	ABE+NSAI	117,466	2.743	£197,123	£1,250,081
TTD1 Gompertz	NSAI	56,150	2.997	Referent	£263,915
	PAL+NSAI	151,324	3.273	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	153,716	3.285	Dominated	ABE+NSAI Dominant
	ABE+NSAI	133,567	3.291	£263,915	-
TTD1 Log-normal	NSAI	56,152	2.997	Referent	£254,995
	PAL+NSAI	152,038	3.273	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	154,263	3.285	Dominated	ABE+NSAI Dominant
	ABE+NSAI	130,952	3.291	£254,995	-
TTD1 Exp	NSAI	56,148	2.997	Referent	£224,015
	PAL+NSAI	136,447	3.273	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	139,204	3.285	Dominated	ABE+NSAI Dominant
	ABE+NSAI	121,861	3.291	£224,015	-

TTD2: Log-logistic	NSAI	56,152	2.997	Referent	£250,352
	PAL+NSAI	152,268	3.273	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	154,559	3.285	Dominated	ABE+NSAI Dominant
	ABE+NSAI	129,590	3.291	£250,352	-
TTD2 Gompertz	NSAI	56,152	2.997	Referent	£250,352
	PAL+NSAI	152,268	3.273	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	154,559	3.285	Dominated	ABE+NSAI Dominant
	ABE+NSAI	129,590	3.291	£250,352	-
TTD2 vs 2nd line PFS	NSAI	56,728	2.997	Referent	£248,834
	PAL+NSAI	152,179	3.273	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	154,444	3.285	Dominated	ABE+NSAI Dominant
	ABE+NSAI	129,720	3.291	£248,834	-
Treatment specific utility	NSAI	56,152	3.009	Referent	£270,232
	PAL+NSAI	152,268	3.263	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	154,559	3.275	Dominated	ABE+NSAI Dominant
	ABE+NSAI	129,590	3.281	£270,232	-
PPS MONARCH 2	NSAI	56,152	3.425	Referent	£539,015
	PAL+NSAI	152,268	3.597	Dominated	£218,068
	RIBO+NSAI	154,559	3.608	£5,621,400	-
	ABE+NSAI	129,590	3.603	£412,280	£5,621,400
PFS utility MONARCH 2	NSAI	56,152	2.992	Referent	£249,002
	PAL+NSAI	152,268	3.269	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	154,559	3.281	Dominated	ABE+NSAI Dominant
	ABE+NSAI	129,590	3.287	£249,002	-
PPS LOS MONARCH 3	NSAI	57,858	2.997	Referent	£248,787
	PAL+NSAI	153,562	3.273	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	155,846	3.285	Dominated	ABE+NSAI Dominant
	ABE+NSAI	130,836	3.291	£248,787	-
Relative dose intensity	NSAI	55,697	2.997	Referent	£196,802
	PAL+NSAI	145,059	3.273	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	141,672	3.285	Dominated	ABE+NSAI Dominant
	ABE+NSAI	113,427	3.291	£196,802	-
PFS1 utility = PFS2 utility	NSAI	56,152	3.077	Referent	£209,834
	PAL+NSAI	152,268	3.406	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	154,559	3.419	Dominated	ABE+NSAI Dominant
	ABE+NSAI	129,590	3.427	£209,834	-
PPS BOLERO-2	NSAI	49,909	2.660	Referent	£199,854
	PAL+NSAI	144,078	3.113	Ex Dominated	£55,929
	RIBO+NSAI	145,475	3.138	£278,607	-
	ABE+NSAI	122,096	3.055	£183,093	£278,607

Full surrogacy	NSAI	56,152	2.997	Referent	£156,794
	PAL+NSAI	159,387	3.633	Ex Dominated	£70,232
	RIBO+NSAI	162,269	3.674	£156,794	-
	ABE+NSAI	133,339	3.481	Ex Dominated	£150,253
Utility source EQ5D-5L	NSAI	56,152	2.997	Referent	£250,352
	PAL+NSAI	152,268	3.273	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	154,559	3.285	Dominated	ABE+NSAI Dominant
	ABE+NSAI	129,590	3.291	£250,352	-
Diarrhoea Hosp. and loperamide	NSAI	56,196	2.997	Referent	£251,371
	PAL+NSAI	152,320	3.273	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	154,648	3.285	Dominated	ABE+NSAI Dominant
	ABE+NSAI	129,933	3.291	£251,371	-

4.4.3 ERG preferred assumptions and scenario analyses

Table 36 below summarises ERG preferred assumptions and scenario analyses, as discussed earlier in this report.

Table 36 ERG preferred assumptions and scenarios (NB. changes to base case in bold)

	Company base case	ERG preferred and scenarios	ERG comments
Decision problem			
Population	HR+/HER2- untreated advanced breast cancer (median age 63 at baseline)	No change	As per scope
Comparators	PAL+NSAI and RIBO+NSAI	No change	As per scope. We also report NSAI, as this is used in the model for reference
Model structure			
Health states & transitions	PFS1, PFS2, PPS, Death	No change	The model structure is appropriate for the decision problem and NICE reference case. It is also consistent with the ribociclib model (TA496)
Time horizon	35 years (lifetime)	No change	
Cycle length	Monthly, half cycle correction	No change	
Discount rates	3.5% per year costs & effects	No change	
Time to first progression			
Interval-censoring	IC-adjustment applied	Scenario: no IC adjustment	IC-adjustment for potential bias due to delayed identification of progression
Baseline adjustment	No baseline covariates	Scenario: baseline covariates included	Adjusts for imbalance in important prognostic factors (see 4.3.4.2.1)
TTP1 extrapolation	NSAI and ABE+NSAI exponential survival curves, joint fit to MONARCH 3 data	**ABE+NSAI estimated relative to NSAI with NMA1 PFS HR**	Exponential has best fit with a plausible extrapolation. But more reliable to use same method for ABE+NSAI curve as for comparators
		Scenario: ABE+NSAI direct fit	Company base case for comparison
		Scenario: Weibull	Alternative curves with good fit
		Scenario: Gompertz	

	Company base case	ERG preferred and scenarios	ERG comments
PFS1 HRs	RIBO+NSAI & PAL+NSAI vs. NSAI from NMA1 PFS HRs (as reported in CS Table 23)	Scenario: Use NMA1 results for all treatments in CS Fig 10	To test impact of inconsistency
		Range: Vary PFS HR for ABE+NSAI between 0.5 and 0.6	To test sensitivity to relative effects for key driver of clinical effectiveness
Death rate before first progression			
PFD1	0.2% per month NSAI 0.5% per month ABE+NSAI	**ABE+NSAI estimated relative to NSAI with NMA1 OS HR**	Fixed rate from negative binomial regression on MONARCH 3 data is appropriate. But more reliable to use same method for ABE+NSAI and comparators
		Scenario: ABE+NSAI direct fit	
Second-line survival			
PFS2 extrapolation	FUL fitted to control arm of MONARCH 2 - exponential	Scenario: Weibull	Agree with exponential as base case. Test other well-fitting distributions
		Scenario: Gompertz	
OS2 extrapolation	FUL exponential fitted to MONARCH 2 to 27.95 months CONFIRM after	**Gompertz**	Alternative assumption with better fit to observed data and clinical judgment on plausibility of extrapolation
		Scenario: log-logistic	
		Scenario: exponential +CONFIRM	
Source for PFS2 and OS2	MONARCH 2	BOLERO-2	Alternative source for second-line outcomes, as in company scenario
PFS-OS surrogacy			
Median gain in OS as % of median gain in PFS	27.5%	Range: 10%, 50%, 100%	High uncertainty over surrogacy assumption (TA496)
Treatment duration			
TTD1 survival	Gamma	Scenario: Lognormal	Same as company
		Scenario: Gompertz	
		Scenario: exponential	
TTD2 survival	Exponential	Scenario: log-logistic,	Same as company
		Scenario: Gompertz	

	Company base case	ERG preferred and scenarios	ERG comments
TTD3 survival	Assumes 37% of PPS on third-line treatment	Range: 10%, 50%	Clinical advice to the ERG indicates that patients would spend less time without treatment.
Adverse events			
AE rates	CS Table 29	Range: upper and lower 95% confidence interval limits for ABE+NSAI AE rates	Given uncertainty over relative AE rates test sensitivity of results to upper and lower limits for ABE+NSAI
Utilities			
Health state utilities	PFS1: [redacted] PFS2: 0.774 (ET/targeted) PFS2: 0.661 (chemotherapy) PPS: 0.505	PFS1: [redacted] **PFS2: 0.690** (ET/targeted) PFS2: 0.577 (chemotherapy) PPS: 0.505	Apply DSU assumption about PFS2 utility from TA496 to ensure that PFS1>PFS2>PPS
		Range: PFS1 0.690, 0.774	One-way extreme value sensitivity analysis to explore uncertainty
		Range: PFS2 0.505, [redacted]	
Resource use & costs			
Drug use	Second and third line as per TA503, with additional assumption of no NSAI	Scenario: ERG clinical scenario (see Table 25 above)	Test sensitivity of results to increased use of targeted therapy at second line and chemotherapy at third-line
AE costs	Assumes cost of loperamide only for grade 3/4 diarrhoea	Scenario: Add cost of admission for grade 3/4 diarrhoea	Test sensitivity to higher AE costs for ABE+NSAI

4.4.4 Results from ERG analysis

4.4.4.1 ERG preferred assumptions

Table 37 reports the company's original base case results, the ERG's corrected company base case results and, cumulatively, a series of ERG preferred assumptions. The final part of the table (labelled 'ERG 2L drug use') represents the ERG's base case results. As can be seen, abemaciclib + NSAI remains dominant.

Table 37 Cumulative ERG assumptions – deterministic at list prices

Analysis	Treatments	Total costs	Total QALYs	Incremental ICERs (£/QALY)	Pairwise ICERs ABE vs. comparator
Company original base case	NSAI	£56,449	2.997	Referent	£250,065
	PAL+NSAI	£145,266	3.225	Dominated	ABE+NSAI dom.
	RIBO+NSAI	£148,170	3.222	Dominated	ABE+NSAI dom.
	ABE+NSAI	£129,803	3.291	£250,065	-
ERG corrected company base case	NSAI	£56,152	2.997	Referent	£250,352
	PAL+NSAI	£152,268	3.273	Dominated	ABE+NSAI dom.
	RIBO+NSAI	£154,559	3.285	Dominated	ABE+NSAI dom.
	ABE+NSAI	£129,590	3.291	£250,352	-
+ ABE+NSAI TTP1 from NMA	NSAI	£56,152	2.997	Referent	£341,663
	ABE+NSAI	£130,514	3.215	£341,663	-
	PAL+NSAI	£152,268	3.273	Ext. dom.	£376,720 (SW)
	RIBO+NSAI	£154,559	3.285	£343,915	£343,915 (SW)
+ ABE+NSAI PFD1 from NMA	NSAI	£56,152	2.997	Referent	£289,982
	PAL+NSAI	£152,268	3.273	Dominated	ABE+NSAI dom.
	ABE+NSAI	£138,597	3.282	£289,982	-
	RIBO+NSAI	£154,559	3.285	£4,909,402	£4,909,402 (SW)
+ OS2 Gompertz	NSAI	£40,049	2.350	Referent	£208,333
	RIBO+NSAI	£142,614	2.750	Dominated	ABE+NSAI dom.
	PAL+NSAI	£140,748	2.761	Dominated	ABE+NSAI dom.
	ABE+NSAI	£127,062	2.768	£208,333	-
+ PFS2 utility 0.69 (TA496 final value)	NSAI	£40,049	2.283	Referent	£192,356
	RIBO+NSAI	£142,614	2.719	Dominated	ABE+NSAI dom.
	PAL+NSAI	£140,748	2.727	Dominated	ABE+NSAI dom.
	ABE+NSAI	£127,062	2.735	£192,356	-
+ ERG 2L drug use	NSAI	£47,230	2.318	Referent	£195,730
	PAL+NSAI	£146,607	2.738	Dominated	ABE+NSAI dom.
	RIBO+NSAI	£148,784	2.752	Dominated	ABE+NSAI dom.
	ABE+NSAI	£133,041	2.757	£195,730	-

SW = South West quadrant of the cost-effectiveness plane (ABE+NSAI less expensive and less effective than comparator).

Table 38 reports the results of the ERG's scenario analyses.

Table 38 ERG preferred assumptions - deterministic

ERG scenario		Treatment	Total Costs (£)	Total QALYs	Incremental ICER (£/QALY)	Pairwise ICERs ABE+NSAI vs. comparator
ERG preferred		NSAI	£45,359	2.283	Referent	£190,838
		RIBO+NSAI	£147,369	2.720	Dominated	ABE+NSAI dom.
		PAL+NSAI	£145,556	2.728	Dominated	ABE+NSAI dom.
		ABE+NSAI	£131,753	2.736	£190,838	-
1	**Not IC adjusted**	NSAI	£47,230	2.318	Referent	£195,730
		PAL+NSAI	£146,607	2.738	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£148,784	2.752	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£133,041	2.757	£195,730	-
2	**IC and baseline adjusted**	NSAI	£48,905	2.426	Referent	£210,805
		ABE+NSAI	£134,855	2.833	£210,805	-
		RIBO+NSAI	£155,116	2.868	Dominated	£585,195
		PAL+NSAI	£153,993	2.868	£552,743	£552,743
3	**TTP1 - Joint model (M3)**	NSAI	£47,230	2.318	Referent	£156,923
		PAL+NSAI	£146,607	2.738	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£148,784	2.752	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£132,721	2.863	£156,923	-
4	**TTP1 - Weibull**	NSAI	£47,409	2.341	Referent	£189,086
		PAL+NSAI	£149,458	2.778	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£151,926	2.793	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£133,533	2.797	£189,086	-
5	**TTP1 - Gompertz**	NSAI	£47,663	2.378	Referent	£162,135
		PAL+NSAI	£156,569	2.897	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£134,402	2.913	£162,135	-
		RIBO+NSAI	£159,783	2.920	£3,801,382	£3,801,382
6	**PFS1 HRs - CS Figure 10**	NSAI	£47,230	2.318	Referent	£195,730
		PAL+NSAI	£146,572	2.734	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£148,283	2.743	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£133,041	2.757	£195,730	-
7	**PFS1 HRs - ABE+NSAI 0.5**	NSAI	£47,230	2.318	Referent	£180,970
		PAL+NSAI	£146,607	2.738	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£148,784	2.752	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£131,626	2.785	£180,970	-
8	**PFS1 HRs - ABE+NSAI 0.55**	NSAI	£47,230	2.318	Referent	£202,367
		PAL+NSAI	£146,607	2.738	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£133,047	2.742	£202,367	-
		RIBO+NSAI	£148,784	2.752	£1,613,579	£1,613,579
9		NSAI	£47,230	2.318	Referent	£266,681
		ABE+NSAI	£131,233	2.633	Ex dom.	-

ERG scenario		Treatment	Total Costs (£)	Total QALYs	Incremental ICER (£/QALY)	Pairwise ICERs ABE+NSAI vs. comparator
	PFS1 HRs - ABE+NSAI: 0.60	PAL+NSAI RIBO+NSAI	£146,607 £148,784	2.738 2.752	Ex dom. £234,092	£146,930 £147,704
10	**PF Deaths**	NSAI ABE+NSAI PAL+NSAI RIBO+NSAI	£47,230 £124,090 £146,607 £148,784	2.318 2.631 2.738 2.752	Referent Ex dom. Ex dom. £234,092	£245,883 - £210,358 £203,691
11	**PFS2 Weibull**	NSAI PAL+NSAI RIBO+NSAI ABE+NSAI	£46,834 £146,528 £148,682 £132,964	2.323 2.736 2.750 2.755	Referent Dominated Dominated £199,503	£199,503 ABE+NSAI Dominant ABE+NSAI Dominant -
12	**PFS2 Gompertz**	NSAI PAL+NSAI RIBO+NSAI ABE+NSAI	£45,399 £146,495 £148,695 £132,931	2.326 2.737 2.751 2.756	Referent Dominated Dominated £203,688	£203,688 ABE+NSAI Dominant ABE+NSAI Dominant -
13	**OS2 Log-logistic**	NSAI PAL+NSAI ABE+NSAI RIBO+NSAI	£67,348 £161,459 £147,619 £163,906	3.031 3.294 3.302 3.311	Referent Dominated £295,768 £1,917,513	£295,768 ABE+NSAI Dominant - £1,917,513
14	**OS2 Exponential + CONFIRM**	NSAI PAL+NSAI ABE+NSAI RIBO+NSAI	£66,219 £161,692 £147,847 £164,009	2.994 3.304 3.312 3.315	Referent Dominated £256,312 £7,229,037	£256,312 ABE+NSAI Dominant - £7,229,037
15	**BOLERO 2 PFS2 & OS2**	NSAI PAL+NSAI ABE+NSAI RIBO+NSAI	£59,501 £148,733 £135,128 £149,577	2.652 3.091 3.103 3.118	Referent Dominated £167,526 £992,631	£167,526 ABE+NSAI Dominant - £992,631
16	**OS/PFS surrogacy - 10%**	NSAI PAL+NSAI ABE+NSAI RIBO+NSAI	£47,230 £143,544 £129,380 £146,100	2.318 2.645 2.645 2.670	Referent Dominated £251,315 £665,323	£251,315 ABE+NSAI Dominant - £665,323
17	**OS/PFS surrogacy - 50%**	NSAI ABE+NSAI PAL+NSAI RIBO+NSAI	£47,230 £135,026 £149,108 £151,613	2.318 2.821 2.826 2.842	Referent £174,758 Ex dom. £761,947	£174,758 - £2,475,919 £761,947
18	**OS/PFS surrogacy - 100%**	NSAI PAL+NSAI ABE+NSAI RIBO+NSAI	£47,230 £151,244 £137,531 £153,909	2.318 3.016 3.022 3.035	Referent Dominated £128,251 £1,299,209	£128,251 ABE+NSAI Dominant - £1,299,209

ERG scenario		Treatment	Total Costs (£)	Total QALYs	Incremental ICER (£/QALY)	Pairwise ICERs ABE+NSAI vs. comparator
19	**TTD1 lognormal**	NSAI	£47,230	2.318	Referent	£129,571
		PAL+NSAI	£151,014	3.016	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£138,461	3.022	£129,571	-
		RIBO+NSAI	£153,613	3.035	£1,202,036	£1,202,036
20	**TTD1 Gompertz**	NSAI	£47,229	2.318	Referent	£132,731
		PAL+NSAI	£150,300	3.016	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£140,684	3.022	£132,731	-
		RIBO+NSAI	£153,066	3.035	£982,245	£982,245
21	**TTD1 exponential**	NSAI	£47,227	2.318	Referent	£113,977
		PAL+NSAI	£135,423	3.016	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£127,478	3.022	£113,977	-
		RIBO+NSAI	£138,554	3.035	£878,702	£878,702
22	**TTD2 log-logistic**	NSAI	£47,230	2.318	Referent	£128,251
		PAL+NSAI	£151,244	3.016	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£137,531	3.022	£128,251	-
		RIBO+NSAI	£153,909	3.035	£1,299,209	£1,299,209
23	**TTD2 Gompertz**	NSAI	£47,230	2.318	Referent	£128,251
		PAL+NSAI	£151,244	3.016	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£137,531	3.022	£128,251	-
		RIBO+NSAI	£153,909	3.035	£1,299,209	£1,299,209
24	**TTD3 - 10%**	NSAI	£44,723	2.318	Referent	£195,815
		PAL+NSAI	£144,090	2.738	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£146,254	2.752	Dominated	ABE+NSAI dom.
		ABE+NSAI	£130,571	2.757	£195,815	-
25	**TTD3 - 50%**	NSAI	£48,437	2.318	Referent	£195,689
		PAL+NSAI	£147,818	2.738	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£150,002	2.752	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£134,231	2.757	£195,689	-
26	**AE rates diarrhoea**	NSAI	£48,437	2.318	Referent	£195,689
		PAL+NSAI	£147,818	2.738	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£150,002	2.752	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£134,231	2.757	£195,689	-
27	**AE rates leukopenia**	NSAI	£48,437	2.318	Referent	£195,696
		PAL+NSAI	£147,818	2.738	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£150,002	2.752	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£134,234	2.757	£195,696	-
28		NSAI	£48,437	2.318	Referent	£195,707

ERG scenario		Treatment	Total Costs (£)	Total QALYs	Incremental ICER (£/QALY)	Pairwise ICERs ABE+NSAI vs. comparator
	AE rates neutropenia	PAL+NSAI	£147,818	2.738	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£150,002	2.752	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£134,238	2.757	£195,707	-
29	**Utility PFS1 0.69**	NSAI	£48,437	2.264	Referent	£213,952
		PAL+NSAI	£147,818	2.648	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£150,002	2.661	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£134,231	2.665	£213,952	-
30	**Utility PFS1 0.774**	NSAI	£48,437	2.398	Referent	£173,864
		PAL+NSAI	£147,818	2.870	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£150,002	2.886	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£134,231	2.891	£173,864	-
31	**Utility PFS2 (ET/targeted) 0.505**	NSAI	£48,437	2.185	Referent	£169,191
		PAL+NSAI	£147,818	2.672	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£150,002	2.688	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£134,231	2.692	£169,191	-
32	**Utility PFS2 (ET/targeted) 0.724**	NSAI	£48,437	2.343	Referent	£201,489
		PAL+NSAI	£147,818	2.750	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£150,002	2.764	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£134,231	2.769	£201,489	-
33	**Utility PFS2 (chemotherapy) 0.505**	NSAI	£48,437	2.301	Referent	£191,792
		PAL+NSAI	£147,818	2.729	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£150,002	2.744	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£134,231	2.748	£191,792	-
34	**Utility PFS2 (chemo) 0.724**	NSAI	£48,437	2.354	Referent	£204,158
		PAL+NSAI	£147,818	2.755	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£150,002	2.769	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£134,231	2.774	£204,158	-
35	**Second and third line therapies**	NSAI	£41,154	2.283	Referent	£191,941
		RIBO+NSAI	£143,612	2.720	Dominated	ABE+NSAI Dominant
		PAL+NSAI	£141,758	2.728	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£128,047	2.736	£191,941	-
36	**Hospitalisation for diarrhoea**	NSAI	£48,482	2.318	Referent	£196,371
		PAL+NSAI	£147,871	2.738	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£150,092	2.752	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£134,574	2.757	£196,371	-

5 END OF LIFE

The CS does not present a justification for NICE's end of life criteria to be applied.

6 INNOVATION

The company provides a justification for abemaciclib to be considered a treatment innovation on the following basis:

- Abemaciclib delays disease progression and thus the need for cytotoxic chemotherapy to be given. Expert clinical opinion to the ERG is that the increase in PFS is clinically meaningful.
- Abemaciclib has a favourable safety profile which permits continuous dosing. The CS notes that palbociclib and ribociclib are associated with higher levels of neutropenia which requires regular blood count monitoring and treatment gaps at the end of each 21 day cycle. Expert clinical advice to the ERG is that reduced neutropenia-associated myelosupression would be a minor advantage when choosing a between abemaciclib and palbociclib / ribociclib.

7 DISCUSSION

7.1 Summary of clinical effectiveness issues

The MONARCH 3 trial showed a gain of [redacted] months in median PFS for the combination of abemaciclib and NSAI compared to NSAI alone. This is regarded to be a clinically meaningful benefit and is in-keeping with PFS gains for the other CDK 4/6 inhibitors ribociclib (and NSAI) (median difference 9.3 months[19, 29]) and palbociclib (and NSAI) (median difference 13.1 months[21, 49]). The indirect comparison of these treatments showed no statistically significant differences between them.

Abemaciclib can therefore be considered similar in effects to existing NICE recommended treatments in delaying cancer progression, one of the key treatment goals for patients with advanced breast cancer. The effect of abemaciclib on overall survival is currently unclear, as the duration of follow-up is not yet long enough to have measured the required number of events (deaths) needed for the analysis (the estimated study completion date is April 2020). A similar lack of follow-up of survival also applies to the palbociclib and ribociclib pivotal phase III trials. Thus, the clinical effectiveness of these CDK 4/6 inhibitors in terms of overall

survival is uncertain, hence the need for the alternative approach to economic modelling used by the company (which used a fixed-pay model to include subsequent treatment lines).

Abemaciclib can be considered to have a reasonable safety profile. Notably, grade 3/4 diarrhoea was higher for patients taking abemaciclib than it was in the trials of palbociclib and ribociclib. Incidence of neutropenia and leukopenia was high for all three of the CDK4/6 inhibitors, but particularly so for palbociclib and ribociclib. Diarrhoea can impair quality of life, though is commonly short-lived and can be managed.

MONARCH 3 was a multi-national trial with only a small number of patients from the UK participating. Whilst the patient population in the trial may be generalisable to the UK, it should be noted that around 40% of patients in the trial presented with de novo advanced breast cancer. This is a higher percentage than is commonly experienced in the UK (incidence in the range 10%-15%). This was also the case in the comparator trials of palbociclib and ribociclib. In NICE TA495 it was noted that a difference in treatment effect between patients with recurrent advanced breast cancer and patients with newly diagnosed advanced breast cancer would be unlikely. One of the expert clinical advisors to the ERG noted that patients with de novo advanced breast cancer could be considered to have biologically different disease (due to absence of prior hormonal therapy). Whether this would modify treatment effects is unclear. [redacted]

7.2 Summary of cost effectiveness issues

The company's base case results (all drugs at list price) suggests that ABE+NSAI is marginally more effective and less expensive than the comparators PAL+NSAI and RIBO+NSAI. Compared with NSAI monotherapy, ABE+NSAI had an estimated ICER of around £250,000 per QALY gained. This result was quite consistent across the company's scenario analyses, and our results were similar, for our preferred set of assumptions and across a range of scenario analyses. The absolute difference in QALYs between the CDK 4/6 inhibitors was very small, and the ranking of abemaciclib, ribociclib and palbociclib did change between scenarios. However, as the company note, the lower costs of abemaciclib are driven by a shorter time on treatment with ABE+NSAI. We note that this difference is based on weak evidence, as hazard ratios between treatments were estimated from

reported median time to discontinuation. Another aspect of the economic analysis that was subject to uncertainty and may not be fully represented in the model is adverse events: the assumed QALY loss with the included events was low, due to small disabilities and durations assumed. Exploration of uncertainty around the model results was hampered by model run time.

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9 APPENDICES

9.1 ERG critical appraisal of the first-line treatment NMA

For a description and detailed critique of this NMA see section 3.1.7 of this report.

Checklist	**Response yes/no**
Does the CS present an NMA?	Yes
Are the NMA results used to support the evidence for the clinical effectiveness of the intervention	Yes
Are the NMA results used to support the evidence for the cost-effectiveness of the intervention	Yes
Homogeneity	
1. Is homogeneity considered?	Yes (CS section B.2.9.3 and Appendix D.1.5).
2. Are the studies homogenous in terms of patient characteristics and study design?	Unclear. The CS identifies some areas of heterogeneity (CS section B.2.9.3) but the effect of these on results is unclear.
3. Is the method used to determine the presence of statistical heterogeneity adequate? (e.g. Chi-squared test, I-squared statistic)	Not reported
4. If the homogeneity assumption is not satisfied, is clinical or methodological homogeneity across trials in each set involved in the indirect comparison investigated by an adequate method? (e.g. sub group analysis, sensitivity analysis, meta-regression)	No. The CS states methods such as meta-regression were not considered feasible due to limited study availability.
Similarity	
1. Is the assumption of similarity stated?	No
2. Have they justified their assumption?	N/A
Consistency	
1. Does the analysis explicitly assess consistency?	No The CS notes that none of the comparisons in which direct and indirect evidence is available involved scoped comparators (section B.2.9.5). The ERG notes indirect and direct evidence is available for some of the non-scoped comparators included in the OS, ORR and CR (but not PFS) networks. Clarification response A16 states that a consistency assessment was undertaken but results were not presented as the only closed loops involved

		comparisons not relevant to this appraisal.
	2. Does the method described include a description of the analyses/ models/ handling of potential bias/ inconsistency/ analysis framework?	No
	3. Are patient or trial characteristics compared between direct and indirect evidence trials?	No
	4. If Q3 is yes, and inconsistency is reported, is this accounted for by not combining the direct and indirect evidence?	N/A

Criterion	**ERG assessment**
ITC purpose	
1. Are the NMA results used to support the evidence for the clinical effectiveness of the intervention?	Yes, for the indirect comparison of abemaciclib vs ribociclib and vs palbociclib via a common comparator (NSAI), although the results for the indirect comparisons of abemaciclib vs ribociclib and palbociclib were not presented (provided in clarification question response A12).
2. Are the NMA results used to support the evidence for the cost-effectiveness of the intervention?	Yes. The NMA results for the outcomes of PFS and OS are used to inform the economic model.
Evidence selection	
3. Are inclusion/exclusion criteria adequately reported?	Yes, CS Appendix D.1.2. These are broader than the NICE scope, to permit inclusion of non-scoped comparators, with the aim of including more data in the network.
4. Is quality of the included studies assessed?	Yes, CS Appendix Table 25 provides tabulated risk of bias assessments of all 18 included trials, using the NICE recommended criteria. The CS states that all studies were judged to be good quality with acceptable risk of bias. High risk of bias was judged for blinding as several trials were open-label. The ERG notes that the risk of bias was judged unclear in many studies for some items, including adequate randomisation, concealment of allocation, attrition, and use of ITT analysis / appropriate methods for handling missing data.
Methods – statistical model	
5. Is the statistical model described?	Yes, CS Appendix D.1.5. Further clarification on some procedures was requested by the ERG.
6. Has the choice of outcome measure used in the analysis been justified?	Yes, see 'Feasibility assessment' heading in CS Appendix D.1.3. The outcomes considered were chosen due to their relevance to the MONARCH 3 therapy setting and for the cost-effectiveness model. Outcomes included PFS, OS, ORR, CBR, and CR. PFS and OS are used in the economic model.
7. Has a structure of the network been provided?	Yes, network diagrams are provided for all outcomes, in CS Appendix D.1.3 (Figure 2 to 7).

8. Is homogeneity considered?	Yes. The CS provides a discussion of characteristics where studies were similar, and where there were some differences between studies (CS section B.2.9.3 and Appendix D.1.5).
9. Are the studies homogenous in terms of patient characteristics and study design?	Unclear. The CS identifies some areas of heterogeneity (CS section B.2.9.3) but the effect of these on results is unclear.
10. If the homogeneity assumption is not satisfied, is clinical or methodological homogeneity across trials in each set involved in the indirect comparison investigated by an adequate method? (e.g. sub group analysis, sensitivity analysis, meta-regression)	No. The CS reports that meta-regression was not considered feasible due to limited study availability. The ERG agrees with this as generally a minimum of 10 studies are required to perform meta-regression.
11. Is the assumption of similarity stated?	No.
12. Is any of the programming code used in the statistical programme provided (for potential verification)?	No. Requested by the ERG and provided in clarification question response A18.
Sensitivity analysis	
13. Does the study report sensitivity analyses?	No (stated in CS B.2.9.4).
Results	
14. Are the results of the ITC presented?	Yes, in CS section B.2.9.2. The ERG notes that results are presented for each treatment relative to the reference treatment (letrozole/anastrozole), rather than relative to the scoped comparators (ribociclib and palbociclib). These were requested from the company by the ERG and provided in clarification question response A12.
15. Does the study describe an assessment of the model fit?	Yes. CS Appendix D.1.5 describes use of the Deviance Information Criterion to assess fit of random effects and fixed effect models. The ERG requested the DIC values from the company and these were provided in clarification question response A17.
16. Has there been any discussion around the model uncertainty?	Yes in various sections. The CS notes the immaturity of the OS data and the lack of evidence to support the proportional hazards assumption (CS p.94) as potential limitations in the analysis, also the low event counts for CR (CS p. 63) and, heterogeneity in DFI and the proportion of patients with visceral metastases and the site of disease (CS p.156).
17. Are the point estimates of the relative treatment effects accompanied by some measure of variance such as confidence intervals?	Yes, credible intervals are given to accompany the point estimates.
Discussion - overall results	
18. Does the study discuss both conceptual and statistical heterogeneity?	Yes – conceptual (clinical) heterogeneity is discussed. Statistical heterogeneity is not discussed (NB. this only applies to pairwise

	comparisons in network loops where comparisons include both direct and indirect evidence).
Discussion - validity	
19. Are the results from the indirect/NMA compared, where possible, to those just using direct evidence?	No. None of the comparisons in which direct and indirect evidence is available involved scoped comparators. Indirect and direct evidence is available for some of the non-scoped comparators included in the network.

9.2 ERG critical appraisal of the second-line treatment NMA

Information used to complete this checklist is taken from a confidential separate report of the second-line treatment NMA,[17] and a separate confidential report of the associated SLR of second-line treatments in advanced or metastatic breast cancer of relevance to the MONARCH 2 trial,[18] provided to the ERG by the company in response to a clarification question (A21).

Checklist		**Response yes/no**
Does the MS present an NMA?		Yes
Are the NMA results used to support the evidence for the clinical effectiveness of the intervention		No
Are the NMA results used to support the evidence for the cost-effectiveness of the intervention		Yes (not directly for abemaciclib, but used to provide comparative evidence of second-line endocrine treatments for the economic model)
Homogeneity		
	1. Is homogeneity considered?	Yes (NMA report sections 3.9 and 4.2)
	2. Are the studies homogenous in terms of patient characteristics and study design?	No. Although there were similarities for a number of characteristics, the company states 'Ultimately, the comparability of MONARCH 2 to the identified studies is questionable' (p. 31)
	3. Is the method used to determine the presence of statistical heterogeneity adequate? (e.g. Chi-squared test, I-squared statistic)	Not reported
	4. If the homogeneity assumption is not satisfied, is clinical or methodological homogeneity across trials in each set involved in the indirect comparison investigated by an adequate method? (e.g. sub group analysis, sensitivity analysis, meta-regression)	No. The NMA report states methods such as meta-regression were not considered feasible due to limited study data availability. Only one sensitivity analysis was considered feasible.
Similarity		
	1. Is the assumption of similarity stated?	No
	2. Have they justified their assumption?	N/A
Consistency		
	1. Does the analysis explicitly assess consistency?	Yes (NMA report section 3.8 and section 5)
	2. Does the method described include a description of the analyses/ models/ handling of potential bias/ inconsistency/ analysis framework?	Yes

	3. Are patient or trial characteristics compared between direct and indirect evidence trials?	No
	4. If Q3 is yes, and inconsistency is reported, is this accounted for by not combining the direct and indirect evidence?	N/A

Criterion	ERG assessment
NMA purpose	
1. Are the NMA results used to support the evidence for the clinical effectiveness of the intervention?	No
2. Are the NMA results used to support the evidence for the cost-effectiveness of the intervention?	Yes, NMA results are used to provide comparative evidence of second-line treatments for the economic model.
Evidence selection	
3. Are inclusion/exclusion criteria adequately reported?	Yes, NMA report section 2.1. These are broader than the inclusion criteria for the MONARCH 2 trial[16] as a low volume of matching studies was anticipated.
4. Is quality of the included studies assessed?	Yes, SLR report section 4.7, using NICE recommended criteria. The SLR report states that all studies were assessed as being of good quality with an acceptable risk of bias, but notes in many studies an unclear risk of bias was assigned across multiple domains due to lack of reporting.
Methods – statistical model	
5. Is the statistical model described?	Yes, NMA report section 3 and Appendix A.
6. Has the choice of outcome measure used in the analysis been justified?	Yes, NMA report section 3.2, based on a feasibility assessment (NMA report section 3.1) and economic model requirements. Of the four outcomes included the ERG notes that only PFS and OS are used in the economic model.
7. Has a structure of the network been provided?	Yes for all outcomes, NMA report Figures 4.1, 4.3, 4.4, 4.6, 4.8
8. Is homogeneity considered?	Yes, NMA report sections 3.9 and 4.2.
9. Are the studies homogenous in terms of patient characteristics and study design?	No. Although there were similarities for a number of characteristics (age, post-menopausal status and cancer performance status), the report states 'ultimately, the comparability of MONARCH 2 to the identified studies is questionable' (NMA report page 30). The MONARCH 2 trial assessed a very specific population (HR+/HER2-, ≤ 1 prior endocrine therapy and no prior chemotherapy permitted in the advanced setting), whereas the other studies allowed prior chemotherapy in the advanced setting and some trials allowed for more than one prior endocrine therapy in the advanced setting. The proportion of patients with visceral metastases ranged from 13.5% to 100% where reported, although definitions varied (and was

	often not reported). HR+/HER2- status differed or was unknown across a number of trials.
10. If the homogeneity assumption is not satisfied, is clinical or methodological homogeneity across trials in each set involved in the indirect comparison investigated by an adequate method? (e.g. sub group analysis, sensitivity analysis, meta-regression)	No. The NMA report states methods such as meta-regression were not considered feasible due to limited study data availability. Only one sensitivity analysis was considered feasible.
11. Is the assumption of similarity stated?	No.
12. Is any of the programming code used in the statistical programme provided (for potential verification)?	Yes, NMA report Appendix E.
Sensitivity analysis	
13. Does the study report sensitivity analyses?	Yes, NMA report section 3.10. Only one sensitivity analysis was considered feasible.
Results	
14. Are the results of the NMA presented?	Yes, NMA report section 4.
15. Does the study describe an assessment of the model fit?	Yes, NMA report section 3.6.3 and Appendix A. Deviance Information Criterion (DIC) is used to assess fit of random effects and fixed effect models and for consistency / inconsistency models.
16. Has there been any discussion around the model uncertainty?	Yes, NMA report section 6. The immaturity of OS data was noted.
17. Are the point estimates of the relative treatment effects accompanied by some measure of variance such as confidence intervals?	Yes, credible intervals are given to accompany the point estimates.
Discussion - overall results	
18. Does the study discuss both conceptual and statistical heterogeneity?	Conceptual (clinical) heterogeneity is discussed. Statistical heterogeneity is not discussed
Discussion - validity	
19. Are the results from the indirect/NMA compared, where possible, to those just using direct evidence?	No. However, an inconsistency assessment was conducted.

The second-line treatment NMA was conducted to inform cost-effectiveness modelling of second-line treatments for advanced breast cancer in the “fixed pay-off” sub-model (see section 4.3.4.3 of this report for a description of how the NMA informs modelling of second-line treatment).

An SLR was conducted to identify relevant trials.[18] The search was run in December 2015, and updated in March 2017 and January 2018. This appears to be the same search that was

run for the assessment of clinical effectiveness of abemaciclib as a first-line treatment for advanced breast cancer, reported in the CS (see section 3.1.1 of this report).

9.2.1 Eligibility criteria

The aim was to set criteria to include studies similar to the MONARCH 2 trial.[16] However, the criteria were set to be broader than the population in MONARCH 2 as it was anticipated there would be a low volume of relevant evidence given that MONARCH 2 included patients with specific characteristics (women with advanced HR+, HER2-, breast cancer which had progressed on endocrine therapy, who had not received chemotherapy for advanced breast cancer).

- Intervention: abemaciclib as monotherapy or combination therapy
- Population: women with advanced breast cancer including
    - Trials where ≥50% of the trial population were HR+
    - Trials in which HER2 status of patients was not stated
    - Trials with patients who had received prior chemotherapy or >1 prior endocrine therapy in the advanced setting
- Comparators: endocrine monotherapy, chemotherapy monotherapy, targeted therapy monotherapy, combination chemotherapy, combination endocrine and targeted therapy and combination chemotherapy and targeted therapy.
- Outcomes: survival (OS and PFS), disease free-survival, response (CR, PR, SD), ORR, duration of response, CBR, disease control rate, grade 3 and 4 adverse events, and HRQoL.

A total of 29 trials met the inclusion criteria for the SLR. Of these, nine were unable to be included in the NMA because they did not include an endocrine therapy comparison and therefore could not be connected to the networks. All of these nine trials included chemotherapy treatments (e.g. paclitaxel, gemcitabine, capecitabine), thus the NMA does not compare endocrine therapy with chemotherapy treatments (as noted in CS Figure 2). In addition, one eligible trial of endocrine therapy was excluded as it could not be connected to the outcome networks.[60]

A total of 19 trials were included in the NMA as a whole, with the number of trials included in each outcome network varying (see section 9.2.2 below). The CS reports that the following treatments were not considered clinically relevant to the MONARCH 2 trial-aligned population because they are considered older therapies not commonly used, or not licensed doses:

- Letrozole 0.5mg
- Megestrol 160mg
- Megestrol 800mg
- Toremifene

The CS therefore only reports results for what it considers to be relevant treatments:

- Abemaciclib and fulvestrant (ABE+FUL)
- Anastrozole 1mg (ANAS 1)
- Anastrozole 10mg (ANAS 10)
- Letrozole 2.5mg (LTZ 2.5)
- Exemestane (EXE)
- Everolimus + exemestane (EVE+EXE)
- Fulvestrant 250mg (FUL 250)
- Fulvestrant 500mg
- Palbociclib + fulvestrant 500mg (PAL+FUL)
- Tamoxifen (TMX)

The ERG notes that some, but not all, of these treatments are included in the company's economic model (see 4.3.4.3 of this report), and that not all are recommended or have been appraised by NICE:

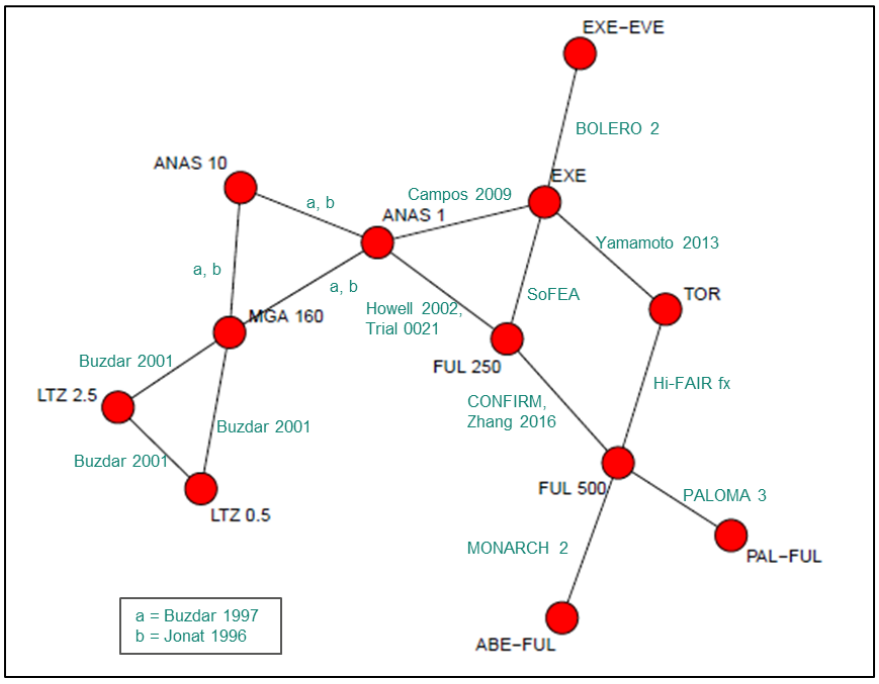
- Abemaciclib + fulvestrant has not yet been appraised by NICE; guidance is expected to be issued in summer 2019 (NICE ID1339). It is not included in the company's economic model as a second-line treatment.
- Anastrozole and letrozole are not included in the company's economic model as second-line treatments.
- Exemestane monotherapy does not appear to have been appraised by NICE in this indication. It is included in the company's economic model as a second-line treatment.
- Exemestane + everolimus is recommended by NICE (TA421[61]). It is included in the company's economic model as a second-line treatment.
- Fulvestrant 500 mg is not recommended by NICE as a second-line treatment for advanced breast cancer (NICE TA239[62]). It is used as a reference treatment in the NMA (chosen because it was the comparator arm in the MONARCH 2 trial). Fulvestrant 500mg (but not 250mg) is included in the company's economic model as a second-line treatment.

- Palbociclib + fulvestrant has not yet been appraised by NICE in this indication (appraisal currently suspended – NICE ID916). It is not included in the company's economic model as a second-line treatment.
- Although tamoxifen was eligible to be included in the NMA, no PFS or OS data were available from the single trial identified that included this treatment (NMA report Table D.1).[60] Tamoxifen is included in the company's economic model as a second-line treatment. We discussed earlier in this report (section 4.3.4.3) how the clinical effectiveness of tamoxifen as a second-line treatment has been estimated for the model.
- Although trials of chemotherapy could not be connected in the NMA, the company's economic model does include chemotherapy as a second-line treatment [specifically, capecitabine, paclitaxel and docetaxel (CS Table 35)]. The clinical effectiveness data for chemotherapy is from a retrospective chart review of 137 postmenopausal HR+/HER2- metastatic breast cancer women in community-based oncology practices in the US (CS Table 20).[42] The specific chemotherapies administered to patients in this study is not reported in the study publication. The CS did not provide a rationale for using this study in preference to any others, though did state that the study had been used to estimate the efficacy outcomes of chemotherapy in the NICE TA496 (ribociclib) (CS section B.3.2.2). We noted concerns about this study earlier in this report (section 4.3.4.3.1).

In summary, the treatments included in this NMA comprise a range of endocrine therapies, though not all of them have been recommended/appraised by NICE. The NMA does not include comparisons between endocrine therapy and chemotherapy. The treatments that are included in the economic model are exemestane + everolimus, exemestane monotherapy, fulvestrant 500 mg, tamoxifen, and chemotherapy (capecitabine, paclitaxel and docetaxel). The only results from the second-line treatment NMA that are used in the economic model are for the comparison of exemestane monotherapy with fulvestrant and the comparison of exemestane + everolimus with fulvestrant.

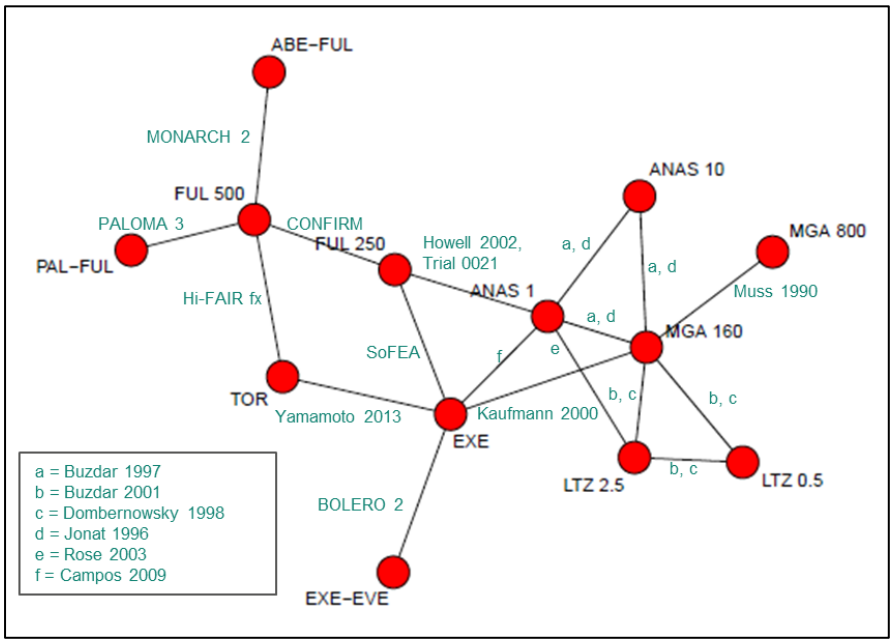
9.2.2 Evidence networks

A feasibility assessment was conducted to assess whether it was possible to construct networks for outcome measures. The following outcomes were considered relevant and feasible: PFS, OS, ORR, and CBR. Only PFS and OS are used in the economic model and therefore we focus on these outcomes in this ERG report. Network diagrams for PFS (n=14 trials) and OS (n=17 trials) are shown in Figure 6 and Figure 7 respectively.



(reproduced from Figure 4.1)[17]

Figure 6 Network diagram for PFS, second-line treatment NMA network



(reproduced from Figure 4.4)[17]

Figure 7 Network diagram for OS, second-line treatment NMA network

Fulvestrant 500mg is the reference treatment and connects abemaciclib + fulvestrant to the network. All treatments are compared pairwise to fulvestrant 500mg; there are no other treatment comparisons presented in the NMA report (though a probabilistic ranking of

treatments based on the odds of an event is given for the response outcomes of ORR and CBR in Appendix G).[17] The networks comprise comparisons that are informed by both direct and indirect evidence (closed loops) as well as comparisons only informed by indirect evidence.

9.2.3 Statistical methods

The statistical approach used is similar to that used to conduct the first-line treatment NMA (as described in more detail in section 3.1.7 of this report). In brief:

- A Bayesian generalised linear model is used, based on NICE DSU guidelines.[24]
- Fixed and random effects modelling is undertaken with selection of model according to best fit (based on DIC values). Both random effects and fixed effects model are presented for PFS, but only fixed effects results are presented for OS as there was evidence of the prior around the random effects standard deviation dominating the posterior estimates (it is not stated why). Given the observed clinical heterogeneity in the networks (see section 9.2.4 below) the ERG considers the random effects model would have been more appropriate in principle.
- Vague prior distributions were chosen for treatment and study-specific term, in accordance with DSU methodological guidance.[24]
- OpenBUGS software was used to run the analysis (the code is provided in Appendix E the NMA report). A Markov chain Monte Carlo simulator was run for 50,000 burn-in simulations with a further 100,000 simulations for convergence to the posterior distribution (Brooks-Gelman-Rubin plots).

The ERG notes that OS data are immature (median OS not reached in at least one arm) in eight of the trials, including the MONARCH 2 trial. (The final OS analysis of this trial will be conducted at 441 OS events. The estimated study completion date is February 2020.[16] However, none of the remaining seven trials included comparisons that were used in the economic model.

An inconsistency assessment was performed to determine the level of consistency between direct and indirect evidence in the NMA networks, based on the approach recommended by the NICE DSU.[26] For PFS and OS both the total residual deviance and DIC values remained similar (<5 point difference) between consistency and inconsistency models, indicating no inconsistency.

The validity of the assumption of proportional hazards of survival data was tested using the same methods as used in the first-line treatment NMA (i.e. log cumulative hazard plots, Schoenfeld residual plots, weighted residual test based on standardised Schoenfeld residuals). The NMA report states that the assumption held across the majority of trials. Where there was evidence of non-proportional hazards the potential reasons were suggested to be high levels of censoring in the tails, interval censoring for PFS and immature survival data. The ERG's interpretation is that proportional hazards do not hold for all of the trials in the NMA, with the assumption less likely to hold for OS than PFS. An NMA approach that allows for time-varying hazards should have been considered as an alternative to the approach used. The immaturity of the survival data is a particular limitation and creates significant uncertainty in the results of the OS network.

9.2.4 Heterogeneity assessment

The NMA report provides a discussion of clinical heterogeneity amongst the set of trials included in the NMA. This was based on a comparison of baseline trial characteristics, and expert clinical opinion on potential treatment effect modifiers. Tabulated study characteristics are presented in the accompanying SLR report.[18]

The NMA report identifies three areas of potential clinical heterogeneity:

- Proportion of patients with visceral involvement, ranging from 13.5% to 100%, where reported.
- Number of prior treatments for advanced breast cancer. The MONARCH 2 trial only permitted patients to have received one (or fewer) endocrine therapies, and no chemotherapy for advanced breast cancer. All of the other trials (where stated) permitted prior use of chemotherapy for advanced breast cancer and some permitted more than one endocrine therapy.
- HR/HER2 status. The majority of trials reported that HR+ patients were eligible for inclusion, however, the majority (n=14/19) of the trials did not specify HER2 status in the eligibility criteria (Table 3.1 of the NMA report[17]).

The second-line treatment NMA report states that it was not possible to conduct meta-regression to address heterogeneity due to limited study data available. The ERG concurs that this would not have been feasible. A sensitivity analysis was performed for PFS using a sub-group of patients who had not received prior chemotherapy corresponding to the ITT

population of MONARCH 2. There was only one trial reported to have provided data for this subgroup, the PALOMA 3 trial which compared palbociclib + fulvestrant vs fulvestrant. The comparison of these two trials (i.e. ABE-FUL vs PAL-FUL) was not included in the economic model.

The NMA report judges that the comparability of MONARCH 2 to the identified trials is questionable, due to the specific eligibility characteristics of MONARCH 2. However, if the inclusion criteria for the NMA had been restricted to fully match the MONARCH 2 trial there would have been very few eligible trials included. The ERG agrees with these observations. We also consider that there is a higher degree of clinical heterogeneity in the second-line treatment NMA than in the first-line NMA (section 3.1.7 of this report).

The NMA report does not state whether any statistical heterogeneity tests were performed for head-to-head pairwise comparisons.

9.2.5 Risk of bias

The NMA report does not comment on the risk of bias in the included trials.[17] The accompanying SLR report[18] provides an assessment of bias using NICE's recommended criteria. The report states that all studies were assessed as being of good quality with an acceptable risk of bias (bias that would not have a large impact on study outcomes). Across trials, the risk of bias was largely assessed as being of either low risk or unclear risk over each of criteria. The ERG notes that one of the included trials (Hi-FAIR) is missing from the risk of bias assessment.

The ERG has not performed an independent risk of bias assessment of these trials, but notes that there were very few trials (n=4) judged at high risk of bias on any one criterion. In terms of risk of selection bias, over half the trials were judged unclear for randomisation and concealment of allocation procedures (n=12 and n=11 respectively). In contrast, the majority of trials (n=17/19) were judged to have equivalent trial arms at baseline suggesting that the risk of selection bias may be low (for measured trial characteristics at least). The risk of bias associated with lack of blinding was judged low in over half the trials (n=11). The risk of bias from unexpected imbalances in drop-outs between groups was unclear in the majority of trials (n=13), as was the case for bias from missing data (n=16). The risk of bias from selective reporting of outcomes was generally low (n=12). Overall, the risk of bias was largely assessed as either low or unclear over each of the criteria.

9.2.6 Results

Brief results are presented here, for PFS and OS outcomes only.

[redacted]

[redacted]

9.2.7 Summary of the ERG's appraisal of the second-line treatment NMA

The ERG's main comments on the second-line treatment NMA are:

- The search strategy used in the SLR of second-line treatments appears to be similar to that used to identify studies for the SLR of abemaciclib as a first-line treatment for advanced breast cancer. As stated earlier in this report (section 3.1.2) the ERG considers the search strategies are fit for purpose. The ERG has not formally critically appraised the second-line treatment SLR but it is unlikely that there is a risk of bias in the identification, selection and critical appraisal of the included trials.[18]
- A range of endocrine therapies are included in the NMA. The only results from the NMA that are used in the economic model are for the comparison of exemestane monotherapy with fulvestrant and exemestane + everolimus vs fulvestrant.
- The included trials appear to be clinically heterogeneous, as acknowledged by the company. The comparability of the MONARCH 2 trial to the comparator trials is questionable due to its specific patient inclusion criteria.
- Reporting limitations means that in many studies an unclear risk of bias was assigned across multiple domains due to lack of reporting.

- The NMA methods are similar to those used for the first-line treatment NMA (i.e. based on NICE DSU technical support document 2). These are appropriate.
- However, proportional hazards do not appear to hold for all the trials included for both OS and PFS, indicating that a NMA approach that allows for time-varying hazards should have been considered as an alternative.
- OS data are immature in eight trials, including the MONARCH 2 trial. The results of the OS network should therefore be interpreted with caution.

9.3 Graphs of survival extrapolations used in model

Figure 8 Time to first progression: parametric survival estimated from MONARCH 3 (interval-censored adjusted)
Source: Company model with log-normal, log-logistic and gamma curves digitised from CS Figures 19 and 20

Figure 9 Time to first progression: company base case and NMA estimate for abemaciclib (interval-censored adjusted)
Source: Company model with log-normal, log-logistic and gamma curves digitised from CS Figures 19 and 20

Figure 10 Pre-progression death rates
Source: Company model with ERG corrections to calculation of rates for palbociclib and ribocicl

9.4 Comparison of baseline characteristics of trials used in the company's economic analysis for post-progression survival: MONARCH, BOLERO-2 and CONFIRM

As discussed earlier in this report, the post-progression survival data from the MONARCH 3 trial are immature, therefore clinical-effectiveness data were used from similar, progressed patient populations from alternative trials. Patients in the placebo + fulvestrant arm of the MONARCH 2 trial are assumed to represent patients progressing after treatment from the MONARCH 3 trial. The MONARCH 2 trial[16] inclusion criteria require patients to have progressed on one prior endocrine therapy. The OS data from the MONARCH 2 trial are also immature, so OS data from the CONFIRM trial[45, 63] are also used to inform longer-term estimates.

The ERG has explored the plausibility of the assumption that patients in the MONARCH 2 and CONFIRM trials are representative of patients progressing from MONARCH 3. We also explored this assumption in relation to the BOLERO-2 trial since this is also used in the CS to estimate post-progression survival in a scenario analysis.

The MONARCH 3 trial considered patients eligible for inclusion if they had received no systematic therapy for advanced disease, their cancer had progressed after at least 12 months following the completion of (neo)adjuvant endocrine therapy, or if they presented with de novo advanced breast cancer. This is a key difference from the other three trials, which permitted inclusion of patients who had progressed during (neo)adjuvant therapy, or less than 12 months after adjuvant treatment. These trials also permitted patients for inclusion if they progressed whilst receiving endocrine therapy for advanced breast cancer. Thus, they comprised mixed populations of patients who had progressed from the (neo)adjuvant setting (thus they were now receiving their first treatment for advanced breast cancer) or who had progressed from the advanced breast cancer setting (thus were now receiving their second treatment for advanced breast cancer). Only the patients in the latter sub-group can be considered comparable to the patients in the MONARCH 3 trial. This sub-group varied in size considerably between the trials:

- MONARCH 2 - patients receiving most recent endocrine therapy for metastatic cancer: n=256 (38%)
- BOLERO-2 - purpose of most recent treatment: treatment of advanced or metastatic cancer: n=586 (81%)

- CONFIRM - progression after first-line treatment for advanced breast cancer (>12 months after adjuvant endocrine treatment) / progression after first-line treatment for advanced breast cancer (de novo advanced breast cancer): n=343 (47%)

Thus, the MONARCH 2 trial has the lowest proportion of patients who had progressed from the advanced breast cancer setting (i.e. comparable to the patients in MONARCH 3 who progressed on treatment). The CS restricts the analysis of post-progression survival to this sub-group.

Table 39 provides a comparison of baseline characteristics of the four trials, in terms of demographic details, disease characteristics and prior treatments received. Note that these characteristics apply to the ITT populations and not for the relevant subgroups noted above. Also note that many details for the CONFIRM trial were not reported, including HER2 status, limiting our interpretation of its comparability to MONARCH 3. The trials appear generally comparable (where reported) in terms of median age, ECOG performance status, HER2 receptor status, PgR receptor status, and percentage of patients with visceral metastases (except CONFIRM where this slightly higher). There was some variation in race (with a higher percentage of white patients in BOLERO-2 compared to the MONARCH trials) and in region (a higher percentage of patients from North America and lower percentage of patients in Europe and Asia in BOLERO-2). None of the trials had quite as high a percentage of patients with measurable disease as MONARCH 3.

A recent publication of the CONFIRM trial[46] reports a post-hoc comparison of results for the sub-group of patients treated with fulvestrant first-line for advanced breast cancer (n=387) and the sub-group being treated second-line for advanced breast cancer (i.e. the sub-group of relevance to this appraisal as discussed above, n=343). A comparison of baseline characteristics between these two sub-groups showed that they were generally similar, with some exceptions relating to previous treatment with aromatase inhibitors, adjuvant antioestrogen therapy, prior chemotherapy, and bone only disease (higher in the first-line treatment sub-group). The ERG notes that the median age in the second-line treatment sub-group was 63 years (vs 58-59 years in the first-line treatment group) which is closer to the median age of patients in MONARCH 3 (63 years) that the other trials.

Table 39 Comparison of baseline characteristics of trials used in the company's economic analysis for post-progression survival: MONARCH, BOLERO-2 and CONFIRM

Baseline characteristic	First-line ABC treatment trial	Second-line ABC treatment trials		
	MONARCH 3 (n=493)[13] ABE+NSAI vs placebo+NSAI	MONARCH 2 (n=669)[16] ABE+FUL vs placebo+FUL	BOLERO-2 (n=724)[64] EVE+EXE vs placebo+EXE	CONFIRM (N=736)[45, 63] FUL 500 vs FUL 250
Age, years				
Median (range)	63 (32-88)	59 - 62 (32-91)	61 - 62 (28-93)	61
Race, n (%)				
White	288 (58%)	373 (56%)	74% - 78%	NR
Asian	148 (30%)	214 (32%)	19% - 20%	NR
Other	18 (4%)	42 (6%)	2%-3%	NR
Region, n (%)				
Europe	[redacted]	279 (42%)	275 (38%)	NR
Asia	[redacted]	212 (32%)	137 (19%)	NR
North America	[redacted]	178 (27%)	274 (38%)	NR
Other	[redacted]	0	38 (5%)	NR
ECOG performance status				
0	296 (60%)	400 (60%)	59%-60%	NR
1	197 (40%)	263 (39%)	35%-36%	NR
Receptor status, n (%)				
PgR+	382 (77%)	510 (76%)	523 (72%)	507 (69%)
PgR-	106 (22%)	140 (21%)	184 (25%)	188 (26%)
Missing / unknown	5 (1%)	19 (3%)	17 (3%)	41 (5%)
HER2 receptor status				
Negative	[redacted]	100%[a]	100%[a]	NR
Metastatic site, n (%)				
Visceral	261 (53%)	373 (56%)	406 (56%)	471 (64%)
Bone only	109 (22%)	180 (27%)	NR	162 (22%)
Other	123 (25%)	113 (17%)	NR	NR
No. of organ sites, n (%)				
1	143 (29%)	264 (40%)	60%[b]	NR
2	118 (24%)	202 (30%)	36%[b]	NR
≥3	229 (46%)	200 (30%)	2%[b]	NR
Prior (neo)adjuvant chemotherapy, n (%)				
Yes	191 (39%)	401 (60%)	306 (42%)	NR
Prior (neo)adjuvant endocrine therapy, n (%)				
Yes	230 (47%)	NR	NR	475 (65%)
Prior endocrine therapy for advanced breast cancer, n (%)				

Baseline characteristic	First-line ABC treatment trial	Second-line ABC treatment trials		
	MONARCH 3 (n=493)[13] ABE+NSAI vs placebo+NSAI	MONARCH 2 (n=669)[16] ABE+FUL vs placebo+FUL	BOLERO-2 (n=724)[64] EVE+EXE vs placebo+EXE	CONFIRM (N=736)[45, 63] FUL 500 vs FUL 250
Yes	0	256 (38%)	NR	353 (48%)
Prior chemotherapy for advanced breast cancer, n (%)				
Yes	0	0	186 (26%)	NR
Measurable disease, n (%)				
Yes	397 (81%)	482 (72%)	500 (69%)	501 (68%)

NR= Not reported; N/A = Not applicable; AI = Aromatase inhibitor; ABC = advanced breast cancer
NB. Where numbers do not sum to the total number randomised / percentages do not sum to 100 this is due to missing data, or rounding. Some numbers / percentages have been calculated by the ERG (rather than as originally reported in trial publications).
[a] Number not explicitly stated but study publication says the eligible women were HER2;
[b] Defined as number of metastatic sites in the trial publication
[c] includes no previous chemotherapy (n=232) and chemotherapy only in the (neo)adjuvant therapy setting (n=306).

Overall, the MONARCH 2 trial appears to be the most comparable to MONARCH 3 in terms of patient demographic and disease characteristics. However, only 38% of patients in MONARCH 2 are representative of the patients in MONARCH 3 (i.e. patients who had progressed from the advanced breast cancer setting). The baseline characteristics of this sub-group are not presented.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Abemaciclib with an aromatase inhibitor for untreated advanced hormone-receptor positive, HER2-negative breast cancer [ID1227]

You are asked to check the ERG report from SHTAC to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Tuesday 28 August 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 response
On page 10: "The decision problem generally meets the NICE scope, however, there are some differences in the population presented. The population in the decision problem	Pages 10, 23 and 24: It is suggested that this wording be removed.	Following receipt of a positive opinion for abemaciclib from the Committee for Medicinal Products for Human Use (CHMP) on 26th July 2018, the licence wording has been confirmed as follows:	We have removed the wording as requested in the light of the CHMP opinion which wasn't available to us when we wrote the report.

is narrower by concentrating on locoregionally recurrent or metastatic breast cancer in post-menopausal women. The scope specified people with advanced breast cancer." Similarly, on page 23: "While this approach appears reasonable, it does omit men with the disease potentially eligible under the NICE scope (the scope, which is aligned with the marketing authorisation, mentions "people with advanced hormone-receptor positive HER2-negative breast cancer"). The anticipated marketing authorisation does not exclude men (CS page 10)." Similarly, on page 24: "However, incidence is relatively uncommon the ERG consider that there is a potential issue of excluding men with advanced breast cancer. Expert clinical advice to the ERG is that in practice men with advanced breast cancer would be treated with goserelin acetate and palbociclib or ribociclib." The suggested narrowing of the patient population in the CS is not		"Verzenios is 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. In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist." The specific patient population included in the MONARCH 3 trial was formally stated in the decision problem table (CS, Section B.1.1, Table 1). However, evidence from the MONARCH 3 trial was used to support the licence wording for abemaciclib, which includes locally advanced and metastatic patients, and is not restricted to locoregionally recurrent and metastatic patients. In addition, abemaciclib will not be licensed for the treatment of men, and therefore cannot be considered by NICE within this appraisal. This appraisal therefore considers	

factually accurate.		the full licence anticipated to be granted for abemaciclib, and does not restrict this patient population in any way.	
The rationale for presenting an additional NMA in the manufacturer submission is not accurate. On page 11: "The company also briefly presents an additional NMA (in an appendix) to provide comparative evidence of abemaciclib as a second-line treatment in advanced breast cancer."	It is suggested that the statement be updated to the following: "The company also briefly presents an additional NMA (in an appendix, and also in a subsequently supplied report as requested by the ERG) to provide relative OS and PFS estimates for second-line treatments included in the cost-effectiveness model. In order to estimate the outcomes of patients receiving fulvestrant as second-line therapy, individual patient data (IPD) for the subset of patients from the MONARCH 2 trial that had progressed on first-line endocrine therapy in the advanced breast cancer setting were used. Conducting a separate NMA for this subset of patients was not feasible, therefore the HRs generated from the NMA of the ITT population were used to estimate the outcomes of patients treated with other second-line treatments."	The purpose of presenting an additional NMA in an appendix and subsequently supplying a full report for this NMA (as per the ERG's request), was not to provide comparative evidence of abemaciclib versus other second-line treatments for advanced breast cancer. The additional NMA was presented to provide relative OS and PFS estimates for second-line treatments used in the cost-effectiveness model; abemaciclib was not included as a second-line treatment in the cost-effectiveness model. The evaluation of the efficacy of abemaciclib in second-line advanced breast cancer patients is not relevant to this appraisal. Furthermore, as noted in Lilly's response to the ERG's clarification question (A21), the efficacy data for fulvestrant (and abemaciclib plus fulvestrant) included in the NMA analyses in the supplied appendix and report were sourced from the MONARCH 2 ITT population. IPD from a subpopulation of MONARCH 2 receiving second-line treatment	We have updated the text to say that the additional NMA provides relative OS and PFS estimates for second-line treatments included in the cost-effectiveness model. We haven't included the suggested wording about how this was done (i.e. using IPD) as this level of detail isn't appropriate at this part of the Summary.

		were used to inform efficacy estimates for fulvestrant in the model, with HR estimates for other second-line interventions applied to this estimate.	
The estimated study completion date for MONARCH 3 is incorrect. On page 17: "The estimated study completion date is February 2020." Similarly, on page 123: "The effect of abemaciclib on overall survival is currently unclear, as the duration of follow-up is not yet long enough to have measured the required number of events (deaths) needed for the analysis (the estimated study completion date is April 2020)."	It is requested that the statement on page 17 be updated to the following: "The estimated study completion date is July 2021." It is requested that the statement on page 123 be updated to the following: ""The effect of abemaciclib plus an aromatase inhibitor on overall survival is currently unclear, as the duration of follow-up is not yet long enough to have measured the required number of events (deaths) needed for the analysis (the estimated study completion date for MONARCH 3 is July 2021)."	The currently stated estimated study completion date for MONARCH 3 is incorrect.	Updated as requested
The anticipated marketing authorisation wording for abemaciclib is no longer current in the report following receipt of a positive opinion from the CHMP. On page 29, Table 2: "Abemaciclib is expected to be indicated for the treatment of HR+/HER2− locally advanced or metastatic breast cancer: • in combination with an	On page 29, Table 2: It is requested that the wording be updated to the following: "Abemaciclib is expected to be indicated for the treatment of women with HR+/HER2− locally advanced or metastatic breast cancer: • in combination with an aromatase inhibitor as initial endocrine-based therapy (current appraisal) or in women who have received prior endocrine therapy • in combination with fulvestrant as initial	Following positive CHMP opinion, abemaciclib is no longer anticipated to receive marketing authorisation for use as monotherapy in patients who have progressed after endocrine therapy and one or two chemotherapy regimens in the metastatic setting. The final licence wording specifies that abemaciclib is for use in women only.	Updated as requested

aromatase inhibitor as initial endocrine-based therapy (current appraisal) or in women who have received prior endocrine therapy • in combination with fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy • as monotherapy following disease progression after endocrine therapy and one or two chemotherapy regimens in the metastatic setting" Similarly, on page 23, Table 1 footnote: "[a] dose reductions for monotherapy not presented here"	endocrine-based therapy, or in women who have received prior endocrine therapy" On page 23, Table 1 footnote: It is suggested the footnote be removed.		
On page 32: "The ERG judged the MONARCH 3 trial to have a high risk of selective reporting bias, as the EORTC QLQ-BR23 trial was measured but not reported." This wording is deemed to not accurately reflect the risk of selective reporting bias.	It is suggested that this wording be revised to: "The ERG judged the MONARCH 3 trial to have a risk of selective reporting bias, as the EORTC QLQ-BR23 trial was measured but not reported."	The EORTC QLQ-BR23 is a minor health-related quality of life (HRQoL) outcome that is not pivotal to the appraisal. Furthermore, results from two instruments (EORTC QLQ-C30 and EQ-5D-5L) were reported in the submission to provide evidence on HRQoL in patients treated with abemaciclib plus an aromatase inhibitor.	We have removed the word high from this sentence. We agree that omission of the EORTC QLQ-BR23 isn't likely to impact the overall clinical effectiveness and cost effectiveness results.
On page 69:	It is suggested that the wording be revised to:	The BSA input used in the cost-	Updated as suggested

"To estimate drug doses for intravenous treatments, a body surface area (BSA) of 1.70 m^2 were assumed. Given that BSA data were not collected directly from the MONARCH 3 trial, height and body weight were used to estimate BSA. An average weight of 67.99kg and a height of 158.41cm were used for this estimation." The description of the methodology used to calculate BSA is inaccurate.	"To estimate drug doses for intravenous treatments, a body surface area (BSA) of 1.70 m^2 was calculated indirectly. Given that BSA data were not collected directly from the MONARCH 3 trial, height and body weight were used to calculate BSA using the Du Bois formula.[1] An average weight of 67.99kg and a height of 158.41cm were used for this calculation."	effectiveness model was not assumed, but calculated with the Du Bois BSA formula[1] using height and body weight data from the MONARCH 3 trial.	

Issue 2 Confidential Marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 60: The hazard ratio for the random effects OS estimate for palbociclib + NSAI is not marked as academic in confidence.	Please mark the hazard ratio for the random effects OS estimate for palbociclib + NSAI with yellow highlighting and underlining, to indicate that this number is academic in confidence.	This piece of data has not yet been published and was erroneously not marked in the submission. Lilly therefore request this number be treated as academic in confidence.	We cannot find the hazard ratio that is being referred to.
On page 62: The incidence of grade 4 anaemia events is not marked as academic in confidence.	Please mark the incidence of grade 4 anaemia adverse events with yellow highlighting and underlining, to indicate that this number is academic in confidence.	This number has not yet been published. Lilly therefore request this number be treated as academic in confidence.	Marking updated
On page 78, Table 18: The median hazard ratios and credible intervals for abemaciclib	Please mark the median hazard ratios and credible intervals for abemaciclib + NSAI, palbociclib + NSAI and ribociclib + NSAI with yellow highlighting and underlining, to indicate	These data have not yet been published and were erroneously not marked in the submission. Lilly therefore request that these data be	Marking updated

+ NSAI, palbociclib + NSAI and ribociclib + NSAI are not marked as academic in confidence.	that these numbers are academic in confidence.	treated as academic in confidence.	
On page 91, Table 22: The adverse event rates for NSAI are not marked as academic in confidence.	Please mark the adverse event rates for NSAI with yellow highlighting and underlining, to indicate these data are academic in confidence.	These data have not yet been published and were erroneously not marked in the submission. Lilly therefore request that these data be treated as academic in confidence.	Marking updated
On page 98, Table 26: The time to discontinuation of first-line treatment for ABE+NSAI and NSAI has not been published.	Please mark the time to discontinuation of first-line treatment for ABE+NSAI and NSAI with yellow highlighting and underlining, to indicate that this number is academic in confidence.	This number has not yet been published. Lilly therefore request this number be treated as academic in confidence.	Marking updated
On page 98, Table 26: The time to discontinuation of second-line treatment for FUL has not been published.	Please mark the time to discontinuation of second-line treatment for FUL with yellow highlighting and underlining, to indicate that this number is academic in confidence.	This number has not yet been published. Lilly therefore request this number be treated as academic in confidence.	Marking updated
On page 100, Table 28: The 'per cycle' and 'per month' drug cost for abemaciclib has not been marked as commercial in confidence. Similarly, the dose intensity values sourced from the MONARCH 3 and 2 trials should be commercial in confidence (ABE, LTZ, ANAS and FUL).	Please mark the 'per cycle' and 'per month' drug cost for abemaciclib with blue highlighting and underlining, to indicate that these values are commercial in confidence. Please mark the dose intensity values for ABE, LTZ, ANAS and FUL with blue highlighting and underlining, to indicate that these values are commercial in confidence.	The list price for abemaciclib is not yet available to the public. Dose intensity data for MONARCH 2 and 3 is not available to the public.	Marking updated

Issue 3 General Errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
An incorrect abbreviation is used for progesterone receptor. On page 20: "The majority of HR+ tumours are both ER+ and PR+, while around 15% to 20% are ER+ only."	It is suggested that the abbreviation be corrected as follows: "The majority of HR+ tumours are both ER+ and PgR+, while around 15% to 20% are ER+ only."	To ensure the correct abbreviation for the progesterone receptor is used.	Corrected
On page 62: "At grade 3 or higher, the most commonly experienced TEAEs in the abemaciclib + NSAI arm were neutropenia ([redacted] grade 3 / [redacted] grade 4); diarrhoea ([redacted] grade 3 / [redacted] grade 4, see below for more details of diarrhoea); leukopenia ([redacted] grade 3 / [redacted] grade 4); infections and infestations ([redacted] grade 3 / [redacted] grade 4) and anaemia ([redacted] grade 3 / [redacted] grade 4), Table Y."	Please replace "Table Y" with the relevant table number.	It is currently unclear which table the ERG report is referring to with regards to these adverse event data.	Corrected
On page 90: "To achieve this target, the calibration weights are: 1.22 for ABE+NSAI; 1.41 for PAL+NSAI; 1.45 for RIBO+NSAI; and 1 for the reference treatment NSAI (CS Table 25, CS section B.3.3.7)."	Please correct the calibration weights for PAL+NSAI and RIBO+NSAI to following values: • PAL+NSAI: 1.16 • RIBO+NSAI: 1.25	The currently reported calibration weights are incorrect.	Corrected

Incorrect calibration weights are reported for PAL+NSAI and RIBO+NSAI.			
On page 93: The standard error for model 1 PPS utility estimate is incorrect.	Please update the standard error for the model 1 PPS utility estimate to [redacted].	The currently reported standard error for the model 1 PPS utility estimate is incorrect.	Corrected
On pages 111–114, Table 35: It appears that many but not all scenarios have incremental and pairwise ICERs in the wrong order compared with the list of treatments on the left-hand side.	Please re-visit this table to ensure values are presented in the correct cells.	Incorrect incremental and pairwise ICERs are presented versus the treatments on the left-hand side in many of the scenarios in Table 35.	We have corrected this table.

References

1. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. Nutrition 1989;5:303-11; discussion 312-3.

Additional errors identified by the ERG:

Table 26 - ERG erratum: correction to labelling of HRs for TTD1: only ABE+NSAI is relative to NSAI, PAL+NSAI and RIBO+NSAI are calculated relative to ABE+NSAI

Table 37 - Final row of table for second-line drug use has been deleted (this is not part of our preferred analysis, but it is a scenario).

Table 38 - Table corrected for errors in ERG preferred analysis. Firstly, we had rounded utility values to 3 decimal places. Secondly, we had included the ERG clinical scenario for usage of drugs at second and third line in our preferred analysis, rather than treating it as a scenario.

CONFIDENTIAL UNTIL PUBLISHED

Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Abemaciclib with an aromatase inhibitor for untreated advanced hormone receptor-positive, HER2-negative breast cancer

ERRATUM

Replacement pages following the factual accuracy check by Eli Lilly and Company

Produced by Southampton Health Technology Assessments Centre (SHTAC)

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Date completed 17th August 2018

SUMMARY

Scope of the company submission

The company submission (CS) assesses the clinical effectiveness and cost effectiveness of abemaciclib (ABE) in combination with a non-steroidal aromatase inhibitor (NSAI) in women with hormone-receptor positive (HR+), human epithelial growth factor receptor 2-negative (HER2-) advanced breast cancer. The comparators are palbociclib with an NSAI and ribociclib with an NSAI.

The decision problem accords with the NICE scope.

Summary of submitted clinical effectiveness evidence

A good quality systematic literature review of clinical effectiveness identified one randomised controlled trial (RCT) of abemaciclib relevant to the decision problem. The MONARCH 3 trial was a double blind, phase III RCT of abemaciclib (150 mg taken orally twice daily) and NSAI (ABE+NSAI) versus (vs) placebo+NSAI (n=493 patients randomised). The NSAIs used were either letrozole or anastrozole (investigator choice). A small number of patients from the UK ([redacted]) were enrolled in the trial. MONARCH 3 was judged by the ERG to be of reasonable methodological quality, though the possibility of unblinding, imbalance in drop-outs and selective reporting of outcomes increasing the risk of bias. The ERG believes that the company has identified all the relevant available RCTs of abemaciclib.

The CS presents interim results from MONARCH 3 (pre-specified and previously published) at a median follow-up of 17.8 months (data cut-off 31st January 2017), and results at the final progression free survival (PFS) assessment (from a confidential clinical study report) at a median follow-up of [redacted] months (data cut-off 3rd November 2017). Analyses were from an intention-to-treat (ITT) population for the majority of outcomes. The primary outcome of PFS (defined as the date of randomisation to objective progression or death) was investigator-assessed at the interim and final analysis. An independent review of PFS was also undertaken at both assessments.

There are no known trials of ABE+NSAI compared with the scoped comparators palbociclib (PAL) and ribociclib (RIBO). The CS present a Bayesian network meta-analysis (NMA) using published methods to perform indirect comparisons with these (and other) comparators (we refer to this as the 'first-line treatment NMA' in this report). A broad range of (non-scoped) comparator treatments were eligible from the SLR informing the NMA to allow a fully connected network. The NMA included a total of 18 RCTs, though only four of these were directly relevant to the decision problem: The MONARCH 3 trial of abemaciclib; the MONALEESA-2 trial of ribociclib; the PALOMA-1/TRIO-18 and PALOMA-2 trials of palbociclib (all with respective NSAIs). The ERG believes the SLR has identified all relevant RCTs. OS and PFS results from this NMA are used to inform the economic model: PFS results inform the time to first progression estimate and OS results inform the estimate of deaths before first progression (see below for a description of the economic model).

The company also briefly presents an additional NMA (in an appendix) to provide relative OS and PFS estimates for second line treatments included in the cost-effectiveness model. The phase III MONARCH 2 RCT, which compares abemaciclib and fulvestrant to placebo and fulvestrant, is indirectly compared with trials of other endocrine therapies for patients who have progressed following first-line treatment for advanced breast cancer. This NMA (referred to in this report as the 'second-line treatment' NMA) was necessary as the OS data from the MONARCH 3 trial are immature and the economic model therefore includes a PFS2 health state to estimate OS from abemaciclib indirectly via the effects of second-line and subsequent treatment lines.

In the MONARCH 3 trial at the final PFS analysis:
Investigator assessed median PFS was [redacted] months in the ABE+NSAI group compared with [redacted] in the placebo+NSAI group; HR [redacted] (95% CI [redacted], 2-sided [redacted]), giving a reduction in the risk of progression of disease or death of 46%. Expert clinical advice to the ERG is that these results are clinically meaningful.

Median OS was [redacted], HR [redacted] (95% CI [redacted] 2-sided stratified log-rank [redacted]). [redacted] the OS rate at 24 months (ABE+NSAI [redacted] vs placebo+NSAI [redacted] OS data are currently immature ([redacted] events recorded, with final OS analysis to be done after 315 events)

- progression on first-line treatment. We note, however, that the first line NMA indicated similar treatment effects for abemaciclib, ribociclib and palbociclib. This conflicts with the larger advantage predicted for abemaciclib when estimated directly from MONARCH 3 data. A similar issue arises when estimating the first-line pre-progression death rate, but in the opposite direction: direct estimation from MONARCH 3 for ABE+NSAI (jointly estimated with NSAI) gives a higher mortality rate than when this parameter is estimated from the NMA relative effects. Given that the decision problem is focussed on comparison between abemaciclib, ribociclib and palbociclib, it is important that comparators are modelled in a consistent way, and the NMAs are best source of evidence to judge relative treatment effects.
- At second-line, the company use data from a sub-set of patients in the MONARCH 2 trial to estimate PFS and OS for second-line fulvestrant, with other drugs modelled relative to these survival curves using NMA results. As noted above, we have concerns over heterogeneity of the second-line trials and hence over the robustness of the NMA.
- The company choose to model second-line OS with an exponential curve fitted to the fulvestrant arm of MONARCH 2, and long-term extrapolation based on the CONFIRM trial. We disagree with this approach. Firstly, because the exponential curve had a poor fit to the MONARCH 2 data. Secondly, because very little information is provided to justify the fitting of the Weibull survival curve to the CONFIRM trial data. Based on evidence of goodness-of-fit and consideration of the plausibility of extrapolations, we consider the Gompertz or Log-logistic curves fitted to MONARCH 2 data are likely to be more reliable.
- Regarding the company's utility estimates in the base case, we suggest that the value used for second-line progression-free survival (0.69) in the final version of the TA496 appraisal looks more realistic than the original estimate, which is higher than the company's estimated for first-line utility.
- Our main concern over resource use assumptions: that the estimated use of second and third-line treatments does not reflect current NHS practice. In particular, the company includes fulvestrant which is not recommended by NICE in this context.

Summary of additional work undertaken by the ERG

We identified four minor errors in the coding of the model, which we correct. These made very little difference to the company's results. We also ran a range of scenario analyses to test

1 Introduction to the ERG Report

This report is a critique of the company's submission (CS) to NICE from Eli Lilly and Company Limited on the clinical effectiveness and cost effectiveness of abemaciclib with an aromatase inhibitor for untreated advanced hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) breast cancer. It identifies the strengths and weaknesses of the CS. Clinical experts were consulted to advise the Evidence Review Group (ERG) and to help inform this report.

Clarification on some aspects of the CS was requested from the company by the ERG via NICE on (11th July 2018). A response from the company via NICE was received by the ERG on 26th July 2018 and this can be seen in the NICE committee papers for this appraisal.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The company presents an accurate overview of breast cancer and its pathogenesis in CS section B.1.3. Breast cancer is the most common cancer amongst women in the UK (age-standardised incidence rate of 95.0 per 100,000[1]) and is responsible for 7% of all cancer deaths in the UK (mortality rate of 17.1 per 100,000[1, 2]). The annual breast cancer incidence in England and Wales is 0.08% (~46,700 women),[3-5] of which approximately 90% of patients are diagnosed with invasive breast cancer.[3] The majority of these women (95%) are estimated to have early and locally advanced disease,[3] in which the cancer has not spread to other parts of the body. Approximately 35% of these women progress to advanced metastatic breast cancer,[3] where the disease has spread (metastasised) to other parts of the body (e.g. bones, liver, and lungs) or has grown into tissues and is unable to be removed completely by surgery.[6] An estimated 13% of women in the UK have advanced breast care at diagnosis.[3, 7] Advanced breast cancer is associated with poorer outcomes and is incurable, with a median overall survival (OS) of 2–3 years.[8]

The population of relevance to this appraisal is people with untreated advanced HR+ and HER2- breast cancer. Breast tumours are tested for oestrogen receptors (ER) and progesterone receptors (PgR), which stimulate tumour growth. ER+ or PgR+ tumours are commonly referred to as being HR+. The majority of HR+ tumours are both ER+ and PgR+, while around 15% to 20% are ER+ only. Patients with HR+ breast cancer generally have an improved prognosis.

The ERG queried with clinical experts whether the inclusion of locoregionally recurrent breast cancer would potentially exclude patients with newly occurring (de novo) locally advanced breast cancer. The experts clarified that in routine practice the majority of these patients would be treated with chemotherapy in an attempt to downstage them and they would then receive surgery. The patients are unlikely to be entered into palliative treatment trials such as those relevant to this appraisal.

The company's decision problem reflects the patient population in the pivotal clinical trial of abemaciclib included in the CS (MONARCH 3[13] - see Table).

2.3.2 Intervention

The description of the intervention (abemaciclib + non-steroidal AI [ABE+NSAI]), is appropriate to the NHS and the NICE scope. Abemaciclib is a selective dual inhibitor of cyclin-dependent kinase 4 and 6 (CDK4 and 6). The starting dose of abemaciclib is 150 mg twice daily, reflecting the recommended dose of abemaciclib in the draft Summary of Product Characteristics (SmPC) when used in combination with endocrine therapy.[14] Abemaciclib should be taken continuously as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs. Dose interruption and/or dose reduction due to adverse events are recommended (see Table 1), such as for hematologic toxicities, diarrhoea and increased alanine aminotransferase levels.

Table 1 Dose adjustment recommendations for adverse reactions

Draft SmPC[14]	**Abemaciclib dose combination therapy**
Recommended dose	150 mg twice daily
1st dose adjustment	100 mg twice daily
2nd dose adjustment	50 mg twice daily
3rd dose adjustment	-

The decision problem states that either anastrozole or letrozole can be chosen as the NSAI to be used in combination with abemaciclib.

2.3.3 Comparators

The comparators are palbociclib + NSAI (PAL-NSAI) (letrozole) and ribociclib + NSAI (RIB+NSAI) (letrozole). These are appropriate for the NHS and reflect the NICE scope. Clinical experts advising the ERG consider palbociclib and ribociclib equivalent in effectiveness and safety, and the choice between them would be down to patient and clinician preference.

2.3.4 Outcomes

The outcomes stated in the CS scope are overall survival (OS), progression-free survival (PFS), tumour response rate, adverse effects of treatment and health-related quality of life (HRQoL). These are standard outcomes measured in cancer treatment trials and reflect those in the NICE scope.

2.3.5 Economic analysis

The economic analysis described in the decision problem is appropriate for the NHS. Cost-effectiveness is expressed in terms of the incremental cost per quality-adjusted life years (QALY) and costs are considered from the perspective of the NHS and personal social services (PSS), with a 35-year time horizon, using a Markov state-transition model with a fixed 'pay-off' for post-progression survival (see section **Error! Reference source not found.** of this report for further description of the economic analysis).

2.3.6 Other relevant factors

The NICE scope does not contain any patient subgroups. The CS presents a summary of subgroup analyses of PFS and OS from the MONARCH 3 trial of abemaciclib (CS Appendix E). These are discussed in further detail in section 3.1.6 and section 3.3.6 of this report.

The company does not identify inequality issues that could be associated with the introduction or provision of abemaciclib (CS Section B.1.4).

Around 40% of patients had de novo metastatic disease (slightly higher in the ABE+NSAI arm, Table 3) and approximately 44% had prior endocrine therapy in the neo(adjuvant) setting (slightly higher use of (neo)adjuvant NSAI in the placebo+NSAI arm).

The CS summarises selected categories of concomitant medication use (Table 3). Nearly all the patients received concomitant medication regardless of treatment allocation (ABE+NSAI [redacted], placebo+NSAI [redacted]), with details only reported for treatment received in [redacted] of patients. Differences between the treatment arms existed in the use of loperamide (an antidiarrhoeal) (ABE+NSAI [redacted] vs placebo+NSAI [redacted]) and therefore also in the antidiarrhoeal category (ABE+NSAI [redacted] vs placebo+NSAI [redacted], both [redacted] in patients receiving abemaciclib. Use of ≥1 antiemetics + anti-nauseants, erythropoietic agents, granulocyte-colony stimulating factor and granulocyte-macrophage colony stimulating factor [redacted] in patients receiving abemaciclib compared with placebo.

Table 2 Population as defined in the NICE scope, MONARCH 3, company decision problem and anticipated marketing authorisations

NICE final scope	Trial inclusion (MONARCH 3)	Company decision problem	Anticipated EMA marketing authorisation (CS p10)[b]
People with advanced HR+/HER2− breast cancer that has not been previously treated with endocrine therapy	Postmenopausal women (≥18 years) with HR+/HER2− locoregionally recurrent or metastatic breast cancer who had no prior systemic therapy in the advanced setting Exclusion criteria: prior (neo) adjuvant ET with a disease free interval of ≤12 months from completion of treatment	Postmenopausal women with advanced HR+/HER2− locoregionally recurrent or metastatic breast cancer who have had no prior systemic therapy for advanced disease (patients who have received treatment with endocrine therapy in the (neo)adjuvant [a] setting with a disease-free interval >12 months from completion of ET are included).	Abemaciclib is expected to be indicated for the treatment of women with HR+/HER2− locally advanced or metastatic breast cancer: • in combination with an aromatase inhibitor as initial endocrine-based therapy (current appraisal) or in women who have received prior endocrine therapy • in combination with fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy"

[a] As defined in the MONARCH 3 trial

[b] Updated from the CS following the positive opinion for abemaciclib from the Committee for Medicinal Products for Human Use (CHMP) on 26th July 2018.

[a] Race was self-reported; [b] Data was missing for remaining patients; [c] Percentage does not equal 100% as the result of rounding; [d] For one patient in the placebo+NSAI arm, HR status and HER2 status were missing. The patient was not treated; [e] Treatment-free interval was calculated only for patients with prior endocrine therapy.

3.1.4 Description and critique of the approach to validity assessment

Quality assessment of MONARCH 3 was undertaken by the company using NICE recommended criteria. A comparison of the company and ERG judgements for MONARCH 3 can be seen in Table 4.

Table 4 Company and ERG assessment of trial quality for MONARCH 3

NICE QA Criteria for RCT[a]	CS response	ERG response
1. Was the method used to generate random allocations adequate?	Low	Low
2. Was the allocation adequately concealed?	Low	Low
3. Were the groups similar at the outset of the study in terms of prognostic factors, e.g. severity of disease?	Low	Low (for most characteristics but not duration of disease or treatment-free interval, see section 3.1.1)
4. Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Low	Unclear: adequate blinding described but high frequency of adverse events such as diarrhoea in the ABE+NSAI arm could lead to unblinding.
5. Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Low	High: [redacted]
6. Is there any evidence to suggest that the authors measured more outcomes than they reported?	Low	Low. However, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Breast 23 (EORTC QLQ-BR23) was measured in MONARCH 3, but this is not mentioned in the CS or trial publication (mentioned in the CSR).
7. 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	Low

[a] Low = low risk of bias, high = high risk of bias, unclear = uncertain risk of bias.

The ERG agrees with most of the company's judgements for MONARCH 3, but notes that the higher frequency of adverse events such as diarrhoea in the ABE+NSAI arm could have led to unblinding of patients and care providers. This may potentially increase the risk of performance bias and detection bias (particularly affecting self-reported outcomes such as HRQoL). The reasons for discontinuation were not presented by trial arm in the CS; these were requested by the ERG and provided in clarification response A3. [redacted]

[redacted]. The ERG judged the MONARCH 3 trial to have a risk of selective reporting bias, as the EORTC QLQ-BR23 trial was measured but not reported. The ERG obtained these results from the CSR.

3.1.5 Description and critique of company's outcome selection

The outcomes selected by the company are appropriate to the NICE scope and are commonly measured in a cancer trial. The details in the CS generally concur with those reported in the MONARCH 3 trial publication[13] and CSR except where stated below. The ERG consider that the outcomes appear to have been predefined.

The primary outcome of the MONARCH 3 trial was investigator-assessed PFS as defined by RECIST (RECIST: Response Evaluation Criteria in Solid Tumours) version 1.1.[15] PFS was measured from the date of randomisation to the date of objective progression or death due to any cause. A randomly selected subset of scans (number of scans not stated) was independently and blindly reviewed by a panel of radiologists at the interim analysis, and at the final analysis a full independent review of PFS was performed. The CS provides results for both investigator and independently reviewed PFS at both interim and final analysis, which the ERG considers appropriate.

Baseline tumour measurements (RECIST 1.1) were performed within 28 days of randomisation and then on Day 21–28 of every second cycle (approximately every eight weeks) between cycle 2 and cycle 18 and on day 21–28 of every third cycle (approximately every 12 weeks) after cycle 18, and then within 14 days of clinical progression. The finding of a new lesion was required to be unequivocal and not attributable to something other than a tumour. In the non-measurable, bone only disease cases, appearance of one or more new lesions (in bone or outside of bone), or unequivocal progression of existing bone lesions was required.

- For those patients with locoregionally recurrent disease (around 3%) the CS states that in those in whom surgery was performed while on study with evidence of residual disease postoperatively, new baseline measurements should have been assessed. The CSR also describes that in [redacted]

- Proportions with at least one TEAE related to treatment as judged by the investigator ([redacted] abemaciclib + NSAI vs [redacted] placebo + NSAI);
- Proportions with grade ≥3 TEAEs (abemaciclib + NSAI arm [redacted] vs placebo + NSAI arm [redacted], with [redacted] and [redacted] considered related to study treatment as judged by the investigator, respectively);
- Proportions with at least one serious adverse event (SAE) (abemaciclib + NSAI arm [redacted] vs placebo + NSAI arm [redacted]);
- Serious adverse events considered related to study treatment as judged by the investigator (abemaciclib + NSAI group [redacted] placebo + NSAI group [redacted];
- Discontinuations of all study treatments (abemaciclib plus NSAI arm [redacted] vs placebo plus NSAI arm 3.1%).

The CS provides details of TEAEs (grades 1-4 and all grades) occurring in at least 15% of participants in CS Table 16 (CS p69), not reproduced here. All TEAS, with the exception of arthralgia and back pain, occurred more frequently in the abemaciclib + NSAI arm. At any grade, diarrhoea ([redacted]), infections/infestations ([redacted]), neutropenia ([redacted]), fatigue ([redacted]) and nausea ([redacted]) were the most frequently experienced TEAEs in the abemaciclib plus NSAI arm. Infections/infestations ([redacted]), fatigue ([redacted]), diarrhoea ([redacted]), nausea ([redacted]) and arthralgia ([redacted]) were the most frequently experienced TEAEs of any grade in the placebo plus NSAI arm. At grade 3 or higher, the most commonly experienced TEAEs in the abemaciclib + NSAI arm were neutropenia ([redacted] grade 3 / [redacted] grade 4); diarrhoea ([redacted] grade 3 / [redacted] grade 4, see below for more details of diarrhoea); leukopenia ([redacted] grade 3 / [redacted] grade 4); infections and infestations ([redacted] grade 3 / [redacted] grade 4) and anaemia ([redacted] grade 3 / [redacted] grade 4) Table 14. Rates of grade 3 or 4 TEAEs in the placebo + NSAI arm were low; there were no events that were reported more commonly than others, see **Error! Reference source not found.** for those most commonly reported in the abemaciclib + NSAI arm.

Specific TEAEs related to study treatment were not reported in the CS but were identified in the CSR addendum from the final analysis. Any grade diarrhoea made up the majority of these events in both the abemaciclib + NSAI arm ([redacted]) and the placebo + NSAI arm ([redacted]); the majority of which were grade 1 or 2. Rates of other TEAEs related to study treatment that were commonly experienced included any grade neutropenia ([redacted] and [redacted] in the abemaciclib + NSAI arm and placebo + NSAI groups respectively, with [redacted] of ≥grade 3 in the former group) fatigue ([redacted] and [redacted] in the abemaciclib + NSAI arm and

4.3.2 Decision problem

4.3.2.1 Population

While the NICE scope considers a broad population of people with advanced HR+/HER2- breast cancer, the decision problem addressed by the company is narrowed to address postmenopausal women with advanced HR+/HER2− locoregionally recurrent or metastatic breast cancer who have had no prior systemic therapy for advanced disease. No patient subgroups are included in the NICE scope of the CS.

The modelled cohort is women of 65 years and above. To estimate drug doses for intravenous treatments, a body surface area (BSA) of 1.70 m^2 was calculated indirectly. Given that BSA data were not collected directly from the MONARCH 3 trial, height and body weight were used to estimate BSA using a published formula. An average weight of 67.99kg and a height of 158.41cm were used for this estimation.

4.3.2.2 Interventions and comparators

The comparators in the model are palbociclib or ribociclib with an aromatase inhibitor, which are currently licensed for use in the UK NHS and correspond to the NICE scope.

The first-line NMA and economic model treat the NSAIs letrozole and anastrozole as a single class (i.e. similar in efficacy and safety). This reflects conclusions in previous NICE appraisals that in clinical practice AIs are considered to be equivalent, with similar effectiveness and acquisition costs (NICE TA495 and TA496).

In the previous NICE appraisals TA495 and TA496, the committees also considered NSAI monotherapy as a comparator for ribociclib + NSAI and palbociclib + NSAI. However, NSAI monotherapy is not specified as a comparator in the scope for this current appraisal. The company includes NSAI as a reference treatment in the first-line NMA and in the economic model. We therefore report input parameters and results for NSAI to provide context for the included comparators.

4.3.4.3.4 Overall survival calibration

A 'partial surrogacy' assumption is applied by calibrating the time spent in the fixed-pay-off sub-model until a desired ratio between median PFS gain and median OS gain for the first-line comparators relative to NSAI is achieved. The target for the calibration is 27.5% in the company base case. To achieve this target, the calibration weights are: 1.22 for ABE+NSAI; 1.16 for PAL+NSAI; 1.25 for RIBO+NSAI; and 1 for the reference treatment NSAI (CS Table 25, CS section B.3.3.7). For each comparator, the same weight is applied to all second-line event rates (progressions, deaths before progression and deaths after progression), thus holding the proportion of time spent in the three second-line health states (PFS2, PPS and death) constant. The calibration is implemented using the Excel 'goal seek' function. This is also applied within each PSA iteration; so, a different set of calibration factors is estimated for each iteration. Uncertainty over the calibration target itself is not reflected in the PSA. The company conducts a scenario analysis with 'full surrogacy' (i.e. calibration weights of 1 for all comparators).

The base case target of 27.5% surrogacy reflects the 'lower bound' specified by the committee for the NICE appraisal of palbociclib (TA495), based on fitting an exponential curve to final OS and PFS data from the PALOMA-1 trial. The TA495 committee concluded that the extension of PFS1 is likely to result in some improvement in OS, although the choice between the lower bound (27.5%) and upper bound (100%) is a source of uncertainty. The NICE DSU reviewed evidence on the relationship between PFS and OS, concluding that evidence on full surrogacy is 'inconclusive'.[39] Similarly, the NICE committee for appraisal TA496 concluded that ribociclib + NSAI improves PFS, that this is likely to result in some improvement in OS, that a degree of partial surrogacy is 'probably more likely' than full surrogacy, but that the magnitude of the relationship is highly uncertain.

> **ERG conclusion**: We consider that the company have correctly implemented the calibration and that they test an appropriate the range of assumptions about the magnitude of the surrogacy relationship between OS and PFS, as requested by previous NICE appraisal committees TA495 and TA496 (from 27.5% to 100% surrogacy). We also test the conservative assumption of no surrogacy and other intermediate values in our analyses.

4.3.5 Health related quality of life

4.3.5.1 Health state utilities

The company report a systematic literature review of utility studies (CS B.3.4.1 and Appendix H) but conclude that studies found were not representative of the population of interest. Instead, utilities for the model are estimated from analysis of EQ-5D-5L data from MONARCH 3 and MONARCH 2 and from previous NICE appraisals – reported in CS Tables 26, 27 and 28 (B.3.4.2). We summarise sources in Table 23 and discuss further below.

Table 23 Health state utility estimates

Source	PFS1	PFS2[a]	PPS	Comments
Company analysis				
Base case	[redacted] Overall	0.745[a]	[redacted]	MONARCH 3 Model 1 for PFS1. Others from TA496
Scenario 1	[redacted] NSAI	0.745[a]	0.505	Treatment specific PFS1 from MONARCH 3 (Model 2)
	[redacted] Other			
Scenario 2	0.774	0.745[a]	0.505	PFS1 assumed equal to PFS2 (without chemotherapy)
Scenario 3	[redacted]	[redacted][a]	0.505	PFS2 from MONARCH 2 pre-progression utility
Scenario 4	[redacted]	0.745[a]	[redacted]	PPS estimated from MONARCH 3 progression disutility applied to PFS1[c]
Company estimates form trial data [b]				
MONARCH 3	[redacted] Overall	[redacted]		EQ-5D-5L adjusted for repeated measures, baseline utility and progression, with / without treatment arm
	[redacted] NSAI			
	[redacted] ABE+NSAI			
MONARCH 2		[redacted]	[redacted]	As above, without treatment
Previous NICE appraisals				
TA495 (palbociclib)	0.72 Overall	0.505	0.505	PALOMA 2 EQ-5D-3L, mean baseline values for PFS1. Estimated from Lloyd et al.[37] by ERG.[51]
	0.71 NSAI			
	0.74 PAL+NSAI			
TA496 (ribociclib)	Redacted in committee papers	0.774 initial 0.690 final, suggested by DSU	0.505	PFS1 from MONALEESA-2 EQ-5D-5L mixed model for repeated measures. PFS2 based on Lloyd et al. model [37] adjusted for BOLERO-2 age and response. DSU proposed reduction.[39]

Exemestane	37.0%	6.2%	15%	5%
Tamoxifen	18.5%	7.7%	20%	10%
Everolimus + exemestane	**8.0%**	**0.0%**	**40%**	**10%**
No treatment	**0.0%**	**45.6%**	**0%**	**15%**

These are based on assumptions in the NICE appraisal of fulvestrant for untreated HR+ advanced breast cancer (TA503)[57] and the company's assumption that NSAIs would not be used following use at first line.

ERG conclusion: Clinical advice to ERG suggests that these distributions do not reflect current NHS practice and policy. Fulvestrant is not used at second or third line, because it is not recommended by NICE (TA239) and fewer patients have exemestane monotherapy now that everolimus + exemestane are recommended by NICE (TA421). At third-line, a greater proportion of patients have chemotherapy (around 50%), with few patients receiving no treatment (10-15%). NSAIs may also be used sometimes at third-line. We test the impact of a scenario based on this clinical advice in ERG analyses.

4.3.6.2 Duration of treatment

We summarise methods used to model treatment duration in Table 26. For first- and second -line treatments, similar methods are used as for TTP and PFS: with parametric survival curves fitted to MONARCH 3 (NSAI and ABE+NSAI) and MONARCH 2 (FUL), adjusted for other comparators with hazard ratios. However, as time to discontinuation is not reported in trial publications, hazard ratios were estimated based on reported median treatment durations. Third line treatment is only included in the model as a cost, applied for a fixed proportion of time spent in the PPS health state.

Table 26 Time to treatment discontinuation

		Treatment	**Base case**		**Source**
TTD1	Time to discontinuation of first-line treatment	NSAI ABE+NSAI	Gamma survival curves (joint fit)		MONARCH 3, IC-adjusted (CS Figures 24 & 25)
		[redacted]	[redacted]		Hazard ratios estimated from median times on treatment (CS Appendix M Table 68 M.2.4)
		[redacted]	[redacted]	[redacted] [a]	
		PAL+NSAI	19.8 months	HR 0.81 [b]	
		RIBO+NSAI	20.3 months	HR 0.79 [b]	
TTD2	Time to discontinuation of second-line treatment	FUL			
		[redacted]	[redacted]		Hazard ratios relative to fulvestrant, estimated from median times on treatment (CS Appendix M Table 78 M.2.4)
		ANAS	5.6 months	HR 1.43	
		LTZ	5.9 months	HR 1.36	
		EXE	4.4 months	HR 1.84	
		TMX	4.4 months	HR 1.84	
		EVE+EXE	7.8 months	HR 1.03	
		CAP	4.8 months	HR 1.66	

		PAC	4.8 months	HR 1.66	
		DOC	4.8 months	HR 1.66	
Third line: proportion of time in PPS spent on treatment			37%		

[a] Relative to NSAI. Not used in company base case (included here for reference).

[b] Relative to ABE+NSAI.

Time to discontinuation of first-line treatment (TTD1) with ABE+NSAI and NSAI is estimated using parametric survival models fitted to MONARCH 3. Estimation methods are similar to those for TTP1 (see CS section B.3.3.5 and CS Appendix M.1.2 and M.2.4). The company concludes that treatment effects are multiplicative over time, rather than proportional, and that the log-normal, gamma and Gompertz models provide a good fit to the observed data. However, as treatment continuation is constrained by progression (modelled as an exponential), the company ruled out the log-normal and Gompertz curves for the base case (they 'overshoot' progression). They therefore chose the gamma distribution for TTD1, with log-normal, Gompertz and exponential curves used as scenarios. Note the model does also constrain time to discontinuation to not exceed time to progression. Time to discontinuation of the other first-line comparators (PAL+NSAI and RIBO+NSAI) was estimated relative to NSAI using hazard ratios estimated from median times to discontinuation. The resulting TTD1 extrapolation curves are shown in CS Figure 26.

The process for fitting time to discontinuation of second-line treatment (TTD2) was similar to that for PFS2 (CS section B.3.3.6 and CS Appendix M.1.5 and M.2.8). Joint parametric survival curves were fitted to MONARCH 2 data, although only the curve for the fulvestrant curve was used in the model. The company concluded that there was no evidence of violation of the proportional hazards assumption and that the Gompertz curve has the best fit to trial data. However, this overshoots progression, modelled with an exponential curve. The company decided to use an exponential curve for TTD2 in the base case and Gompertz and log-logistic curves for scenario analysis. Consideration of CS Figure 37, which shows the fitted parametric curves in relation to the Kaplan-Meier curve for the fulvestrant arm of MONARCH 2, indicates that exponential does provide a reasonable fit for TTD2.

4.3.6.2.1 Duration of third-line treatment

The company estimates time on third-line therapy, calculated based on an assumption that patients spend approximately 37% of their time on treatment after progression from second-

Table 35 Company scenario results (ERG corrected)

Scenarios	Treatments	Total costs (£)	Total QALYs	Incremental ICER (£/QALY)	Pairwise ICER ABE+NSAI vs. comparator
Discount rates: 0.00%	NSAI	63,783	3.381	Referent	£212,804
	PAL+NSAI	170,307	3.721	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	172,946	3.735	Dominated	ABE+NSAI Dominant
	ABE+NSAI	144,531	3.760	£212,804	-
Discount rates: 6.00%	NSAI	51,717	2.774	Referent	£279,586
	PAL+NSAI	141,688	3.014	Dominated	ABE+NSAI Dominant
	ABE+NSAI	120,879	3.021	£279,586	-
	RIBO+NSAI	143,775	3.025	£6,988,613	£6,988,613
ABE+NSAI treatment effects for PFS: NMA	NSAI	56,152	2.997	Referent	£341,663
	ABE+NSAI	130,514	3.215	£341,663	-
	PAL+NSAI	152,268	3.273	Ex Dominated	£376,720
	RIBO+NSAI	154,559	3.285	£343,915	£343,915
Interval censoring unadjusted	NSAI	56,152	2.997	Referent	£250,352
	PAL+NSAI	152,268	3.273	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	154,559	3.285	Dominated	ABE+NSAI Dominant
	ABE+NSAI	129,590	3.291	£250,352	-
Covariate and interval censoring adjusted	NSAI	58,122	3.127	Referent	£223,086
	RIBO+NSAI	161,058	3.400	Dominated	ABE+NSAI Dominant
	PAL+NSAI	159,934	3.400	Dominated	ABE+NSAI Dominant
	ABE+NSAI	142,262	3.504	£223,086	-
TTP1 Weibull	NSAI	56,305	3.018	Referent	£240,299
	PAL+NSAI	155,494	3.311	Dominated	ABE+NSAI Dominant
	ABE+NSAI	129,213	3.322	£240,299	-
	RIBO+NSAI	158,148	3.327	£5,606,781	£5,606,781
TTP1 Gompertz	NSAI	56,506	3.051	Referent	£215,479
	ABE+NSAI	127,893	3.382	£215,479	-
	PAL+NSAI	162,059	3.396	£2,469,570	£2,469,570
	RIBO+NSAI	165,016	3.399	£935,832	£2,184,412
PFS2 Weibull	NSAI	55,987	3.007	Referent	£256,648
	PAL+NSAI	152,229	3.273	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	154,529	3.285	Dominated	ABE+NSAI Dominant
	ABE+NSAI	129,528	3.294	£256,648	-
PFS2 Gompertz	NSAI	55,226	3.045	Referent	£278,905
	PAL+NSAI	152,010	3.284	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	154,329	3.295	Dominated	ABE+NSAI Dominant
	ABE+NSAI	129,214	3.310	£278,905	-
OS2 Exp.	NSAI	71,084	3.584	Referent	£282,820
	RIBO+NSAI	167,238	3.801	Dominated	ABE+NSAI Dominant
	PAL+NSAI	165,287	3.804	Dominated	ABE+NSAI Dominant
	ABE+NSAI	142,943	3.838	£282,820	-
OS2 Log-logistic	NSAI	57,047	3.031	Referent	£246,160
	PAL+NSAI	153,251	3.322	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	155,397	3.327	Dominated	ABE+NSAI Dominant
	ABE+NSAI	130,419	3.329	£246,160	-
	NSAI	40,049	2.350	Referent	£197,123

Scenarios	Treatments	Total costs (£)	Total QALYs	Incremental ICER (£/QALY)	Pairwise ICER ABE+NSAI vs. comparator
OS2 Gompertz	ABE+NSAI	117,466	2.743	£197,123	-
	RIBO+NSAI	142,614	2.750	Dominated	£3,292,916
	PAL+NSAI	140,748	2.761	£1,250,081	£1,250,081
TTD1 Gompertz	NSAI	56,150	2.997	Referent	£263,915
	PAL+NSAI	151,324	3.273	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	153,716	3.285	Dominated	ABE+NSAI Dominant
	ABE+NSAI	133,567	3.291	£263,915	-
TTD1 Log-normal	NSAI	56,152	2.997	Referent	£254,995
	PAL+NSAI	152,038	3.273	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	154,263	3.285	Dominated	ABE+NSAI Dominant
	ABE+NSAI	130,952	3.291	£254,995	-
TTD1 Exp	NSAI	56,148	2.997	Referent	£224,015
	PAL+NSAI	136,447	3.273	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	139,204	3.285	Dominated	ABE+NSAI Dominant
	ABE+NSAI	121,861	3.291	£224,015	-
TTD2: Log-logistic	NSAI	56,152	2.997	Referent	£250,352
	PAL+NSAI	152,268	3.273	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	154,559	3.285	Dominated	ABE+NSAI Dominant
	ABE+NSAI	129,590	3.291	£250,352	-
TTD2 Gompertz	NSAI	56,152	2.997	Referent	£250,352
	PAL+NSAI	152,268	3.273	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	154,559	3.285	Dominated	ABE+NSAI Dominant
	ABE+NSAI	129,590	3.291	£250,352	-
TTD2 vs 2nd line PFS	NSAI	56,728	2.997	Referent	£248,834
	PAL+NSAI	152,179	3.273	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	154,444	3.285	Dominated	ABE+NSAI Dominant
	ABE+NSAI	129,720	3.291	£248,834	-
Treatment specific utility	NSAI	56,152	3.009	Referent	£270,232
	PAL+NSAI	152,268	3.263	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	154,559	3.275	Dominated	ABE+NSAI Dominant
	ABE+NSAI	129,590	3.281	£270,232	-
PPS MONARCH 2	NSAI	56,152	3.425	Referent	£412,280
	PAL+NSAI	152,268	3.597	Dominated	ABE+NSAI Dominant
	ABE+NSAI	129,590	3.603	£412,280	-
	RIBO+NSAI	154,559	3.608	£5,621,400	£5,621,400
PFS utility MONARCH 2	NSAI	56,152	2.992	Referent	£249,002
	PAL+NSAI	152,268	3.269	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	154,559	3.281	Dominated	ABE+NSAI Dominant
	ABE+NSAI	129,590	3.287	£249,002	-
PPS LOS MONARCH 3	NSAI	57,858	2.997	Referent	£248,787
	PAL+NSAI	153,562	3.273	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	155,846	3.285	Dominated	ABE+NSAI Dominant
	ABE+NSAI	130,836	3.291	£248,787	-

Scenarios	Treatments	Total costs (£)	Total QALYs	Incremental ICER (£/QALY)	Pairwise ICER ABE+NSAI vs. comparator
Relative dose intensity	NSAI	55,697	2.997	Referent	£196,802
	PAL+NSAI	145,059	3.273	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	141,672	3.285	Dominated	ABE+NSAI Dominant
	ABE+NSAI	113,427	3.291	£196,802	-
PFS1 utility = PFS2 utility	NSAI	56,152	3.077	Referent	£209,834
	PAL+NSAI	152,268	3.406	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	154,559	3.419	Dominated	ABE+NSAI Dominant
	ABE+NSAI	129,590	3.427	£209,834	-
PPS BOLERO-2	NSAI	49,909	2.660	Referent	£183,093
	ABE+NSAI	122,096	3.055	£183,093	-
	PAL+NSAI	144,078	3.113	Ex Dominated	£372,986
	RIBO+NSAI	145,475	3.138	£278,607	£278,607
Full surrogacy	NSAI	56,152	2.997	Referent	£159,395
	ABE+NSAI	133,339	3.481	Ex Dominated	-
	PAL+NSAI	159,387	3.633	Ex Dominated	£171,930
	RIBO+NSAI	162,269	3.674	£156,794	£150,253
Utility source EQ5D-5L	NSAI	56,152	2.997	Referent	£250,352
	PAL+NSAI	152,268	3.273	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	154,559	3.285	Dominated	ABE+NSAI Dominant
	ABE+NSAI	129,590	3.291	£250,352	-
Diarrhoea Hosp. and loperamide	NSAI	56,196	2.997	Referent	£251,371
	PAL+NSAI	152,320	3.273	Dominated	ABE+NSAI Dominant
	RIBO+NSAI	154,648	3.285	Dominated	ABE+NSAI Dominant
	ABE+NSAI	129,933	3.291	£251,371	-

4.4.3 ERG preferred assumptions and scenario analyses

Error! Reference source not found. below summarises ERG preferred assumptions and scenario analyses, as discussed earlier in this report

4.4.4 Results from ERG analysis

4.4.4.1 ERG preferred assumptions

Table 37 reports the company's original base case results, the ERG's corrected company base case results and, cumulatively, a series of ERG preferred assumptions. The final part of the table (labelled 'ERG 2L drug use') represents the ERG's base case results. As can be seen, abemaciclib + NSAI remains dominant.

Table 37 Cumulative ERG assumptions – deterministic at list prices

Analysis	Treatments	Total costs	Total QALYs	Incremental ICERs (£/QALY)	Pairwise ICERs ABE vs. comparator
Company original base case	NSAI	£56,449	2.997	Referent	£250,065
	PAL+NSAI	£145,266	3.225	Dominated	ABE+NSAI dom.
	RIBO+NSAI	£148,170	3.222	Dominated	ABE+NSAI dom.
	ABE+NSAI	£129,803	3.291	£250,065	-
ERG corrected company base case	NSAI	£56,152	2.997	Referent	£250,352
	PAL+NSAI	£152,268	3.273	Dominated	ABE+NSAI dom.
	RIBO+NSAI	£154,559	3.285	Dominated	ABE+NSAI dom.
	ABE+NSAI	£129,590	3.291	£250,352	-
+ ABE+NSAI TTP1 from NMA	NSAI	£56,152	2.997	Referent	£341,663
	ABE+NSAI	£130,514	3.215	£341,663	-
	PAL+NSAI	£152,268	3.273	Ext. dom.	£376,720 (SW)
	RIBO+NSAI	£154,559	3.285	£343,915	£343,915 (SW)
+ ABE+NSAI PFD1 from NMA	NSAI	£56,152	2.997	Referent	£289,982
	PAL+NSAI	£152,268	3.273	Dominated	ABE+NSAI dom.
	ABE+NSAI	£138,597	3.282	£289,982	-
	RIBO+NSAI	£154,559	3.285	£4,909,402	£4,909,402 (SW)
+ OS2 Gompertz	NSAI	£40,049	2.350	Referent	£208,333
	RIBO+NSAI	£142,614	2.750	Dominated	ABE+NSAI dom.
	PAL+NSAI	£140,748	2.761	Dominated	ABE+NSAI dom.
	ABE+NSAI	£127,062	2.768	£208,333	-
+ PFS2 utility 0.69 (TA496 final value)	NSAI	£40,049	2.283	Referent	£192,356
	RIBO+NSAI	£142,614	2.719	Dominated	ABE+NSAI Dom.
	PAL+NSAI	£140,748	2.727	Dominated	ABE+NSAI Dom.
	ABE+NSAI	£127,062	2.735	£192,356	-

SW = South West quadrant of the cost-effectiveness plane (ABE+NSAI less expensive and less effective than comparator).

Table 2 reports the results of the ERG's scenario analyses.

Table 2 ERG preferred assumptions - deterministic

ERG scenario		Treatment	Total Costs (£)	Total QALYs	Incremental ICER (£/QALY)	Pairwise ICERs ABE+NSAI vs. comparator
ERG preferred		NSAI	£40,049	2.283	Referent	£192,356
		RIBO+NSAI	£142,614	2.719	Dominated	ABE+NSAI Dominant
		PAL+NSAI	£140,748	2.727	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£127,062	2.735	£192,356	-
1	**Not IC adjusted**	NSAI	£40,049	2.283	Referent	£192,356
		RIBO+NSAI	£142,614	2.719	Dominated	ABE+NSAI Dominant
		PAL+NSAI	£140,748	2.727	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£127,062	2.735	£192,356	-
2	**IC and baseline adjusted**	NSAI	£41,483	2.389	Referent	£201,960
		ABE+NSAI	£128,490	2.820	£201,960	-
		RIBO+NSAI	£149,959	2.875	Dominated	£386,131
		PAL+NSAI	£148,835	2.875	£365,922	£365,922
3	**TTP1 - Joint model (M3)**	NSAI	£40,049	2.283	Referent	£156,468
		RIBO+NSAI	£142,614	2.719	Dominated	ABE+NSAI Dominant
		PAL+NSAI	£140,748	2.727	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£127,711	2.843	£156,468	-
4	**TTP1 - Weibull**	NSAI	£40,247	2.306	Referent	£177,263
		PAL+NSAI	£144,368	2.785	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£147,055	2.802	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£128,583	2.804	£177,263	-
5	**TTP1 - Gompertz**	NSAI	£40,542	2.343	Referent	£153,780
		PAL+NSAI	£151,630	2.903	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£129,688	2.922	£153,780	-
		RIBO+NSAI	£154,998	2.926	£6,462,870	£6,462,870 (SW)
6	**PFS1 HRs - CS Figure 10**	NSAI	£40,049	2.283	Referent	£192,356
		RIBO+NSAI	£142,106	2.721	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£127,062	2.735	£192,356	-
		PAL+NSAI	£141,488	2.742	£2,106,830	£2,106,830 (SW)
7	**PFS1 HRs - ABE+NSAI 0.5**	NSAI	£40,049	2.283	Referent	£174,272
		RIBO+NSAI	£142,614	2.719	Dominated	ABE+NSAI Dominant
		PAL+NSAI	£140,748	2.727	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£127,141	2.783	£174,272	-
8	**PFS1 HRs - ABE+NSAI 0.55**	NSAI	£40,049	2.283	Referent	£198,512
		RIBO+NSAI	£142,614	2.719	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£126,886	2.720	£198,512	-
		PAL+NSAI	£140,748	2.727	£1,983,190	£1,983,190 (SW)
9	**PFS1 HRs - ABE+NSAI: 0.60**	NSAI	£40,049	2.283	Referent	£258,764
		ABE+NSAI	£124,830	2.611	Ex Dominated	-
		RIBO+NSAI	£142,614	2.719	Dominated	£163,426 (SW)
		PAL+NSAI	£140,748	2.727	£226,580	£136,293 (SW)
10	**PF Deaths**	NSAI	£40,049	2.283	Referent	£192,356
		RIBO+NSAI	£142,614	2.719	Dominated	ABE+NSAI Dominant
		PAL+NSAI	£140,748	2.727	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£127,062	2.735	£192,356	-

ERG scenario		Treatment	Total Costs (£)	Total QALYs	Incremental ICER (£/QALY)	Pairwise ICERs ABE+NSAI vs. comparator
11	**PFS2 Weibull**	NSAI	£39,910	2.286	Referent	£195,229
		RIBO+NSAI	£142,600	2.716	Dominated	ABE+NSAI Dominant
		PAL+NSAI	£140,735	2.724	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£127,049	2.732	£195,229	-
12	**PFS2 Gompertz**	NSAI	£39,369	2.289	Referent	£197,231
		RIBO+NSAI	£142,595	2.717	Dominated	ABE+NSAI Dominant
		PAL+NSAI	£140,713	2.725	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£127,034	2.733	£197,231	-
13	**OS2 Log-logistic**	NSAI	£57,047	2.963	Referent	£259,329
		PAL+NSAI	£153,251	3.273	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£155,397	3.278	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£139,562	3.281	£259,329	-
14	**OS2 Exp + CONFIRM**	NSAI	£56,152	2.929	Referent	£269,236
		PAL+NSAI	£152,268	3.226	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£138,597	3.236	£269,236	-
		RIBO+NSAI	£154,559	3.238	£5,455,056	£5,455,056 (SW)
15	**BOLERO 2 PFS2 & OS2**	NSAI	£49,909	2.610	Referent	£187,366
		PAL+NSAI	£144,078	3.027	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£130,558	3.041	£187,366	-
		RIBO+NSAI	£145,475	3.042	£13,923,475	£13,923,475 (SW)
16	**OS/PFS surrogacy - 10%**	NSAI	£40,049	2.283	Referent	£221,645
		PAL+NSAI	£138,769	2.633	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£141,012	2.644	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£125,673	2.669	£221,645	-
17	**OS/PFS surrogacy - 50%**	NSAI	£40,049	2.283	Referent	£165,508
		PAL+NSAI	£142,126	2.801	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£144,299	2.801	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£128,643	2.818	£165,508	-
18	**OS/PFS surrogacy - 100%**	NSAI	£40,049	2.283	Referent	£125,080
		PAL+NSAI	£144,768	2.998	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£147,146	3.001	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£131,236	3.012	£125,080	-
19	**TTD1 lognormal**	NSAI	£40,049	2.283	Referent	£126,355
		PAL+NSAI	£144,538	2.998	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£146,851	3.001	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£132,166	3.012	£126,355	-
20	**TTD1 Gompertz**	NSAI	£40,048	2.283	Referent	£129,407
		PAL+NSAI	£143,824	2.998	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£146,304	3.001	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£134,389	3.012	£129,407	-
21	**TTD1 exp.**	NSAI	£40,046	2.283	Referent	£111,295
		PAL+NSAI	£128,947	2.998	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£131,792	3.001	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£121,182	3.012	£111,295	-

ERG scenario		Treatment	Total Costs (£)	Total QALYs	Incremental ICER (£/QALY)	Pairwise ICERs ABE+NSAI vs. comparator
22	**TTD2 log-logistic**	NSAI	£40,049	2.283	Referent	£125,080
		PAL+NSAI	£144,768	2.998	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£147,146	3.001	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£131,236	3.012	£125,080	-
23	**TTD2 Gompertz**	NSAI	£40,049	2.283	Referent	£125,080
		PAL+NSAI	£144,768	2.998	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£147,146	3.001	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£131,236	3.012	£125,080	-
24	**TTD3 - 10%**	NSAI	£37,754	2.283	Referent	£125,391
		PAL+NSAI	£142,660	2.998	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£144,985	3.001	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£129,167	3.012	£125,391	-
25	**TTD3 - 50%**	NSAI	£41,154	2.283	Referent	£124,931
		PAL+NSAI	£145,782	2.998	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£148,187	3.001	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£132,232	3.012	£124,931	-
26	**AE rates diarrhoea**	NSAI	£41,154	2.283	Referent	£124,931
		PAL+NSAI	£145,782	2.998	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£148,187	3.001	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£132,232	3.012	£124,931	-
27	**AE rates leukopenia**	NSAI	£41,154	2.283	Referent	£124,935
		PAL+NSAI	£145,782	2.998	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£148,187	3.001	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£132,235	3.012	£124,935	-
28	**AE rates neutropenia**	NSAI	£41,154	2.283	Referent	£124,941
		PAL+NSAI	£145,782	2.998	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£148,187	3.001	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£132,240	3.012	£124,941	-
29	**Utility PFS1 0.69**	NSAI	£41,154	2.229	Referent	£131,629
		PAL+NSAI	£145,782	2.909	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£148,187	2.911	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£132,232	2.921	£131,629	-
30	**Utility PFS1 0.774**	NSAI	£41,154	2.363	Referent	£116,113
		PAL+NSAI	£145,782	3.131	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£148,187	3.136	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£132,232	3.147	£116,113	-
31	**Utility PFS2 (ET/ targeted) 0.505**	NSAI	£41,154	2.173	Referent	£124,549
		PAL+NSAI	£145,782	2.889	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£148,187	2.898	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£132,232	2.905	£124,549	-
32	**Utility PFS2 (ET/ targeted) 0.724**	NSAI	£41,154	2.303	Referent	£125,000
		PAL+NSAI	£145,782	3.018	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£148,187	3.020	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£132,232	3.031	£125,000	-

ERG scenario		Treatment	Total Costs (£)	Total QALYs	Incremental ICER (£/QALY)	Pairwise ICERs ABE+NSAI vs. comparator
33	**Utility PFS2 (chemotherapy) 0.505**	NSAI	£41,154	2.318	Referent	£125,053
		PAL+NSAI	£145,782	3.033	Dominated	ABE+NSAI Dominant
		RIBO+NSAI	£148,187	3.034	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£132,232	3.046	£125,053	-
34	**Utility PFS2 (chemo) 0.724**	NSAI	£41,154	2.363	Referent	£125,210
		RIBO+NSAI	£148,187	3.076	Dominated	ABE+NSAI Dominant
		PAL+NSAI	£145,782	3.078	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£132,232	3.090	£125,210	-
35	**Second and third line therapies**	NSAI	£48,437	2.399	Referent	£129,215
		PAL+NSAI	£152,351	3.094	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£138,626	3.097	£129,215	-
		RIBO+NSAI	£155,046	3.111	£1,200,827	£1,200,827 (SW)
36	**Hospitalisation for diarrhoea**	NSAI	£41,199	2.350	Referent	£125,576
		RIBO+NSAI	£148,277	3.064	Dominated	ABE+NSAI Dominant
		PAL+NSAI	£145,835	3.065	Dominated	ABE+NSAI Dominant
		ABE+NSAI	£132,575	3.078	£125,576	-

5 END OF LIFE

The CS does not present a justification for NICE's end of life criteria to be applied.

6 INNOVATION

The company provides a justification for abemaciclib to be considered a treatment innovation on the following basis:

- Abemaciclib delays disease progression and thus the need for cytotoxic chemotherapy to be given. Expert clinical opinion to the ERG is that the increase in PFS is clinically meaningful.
- Abemaciclib has a favourable safety profile which permits continuous dosing. The CS notes that palbociclib and ribociclib are associated with higher levels of neutropenia which requires regular blood count monitoring and treatment gaps at the end of each 21 day cycle. Expert clinical advice to the ERG is that reduced neutropenia-associated myelosupression would be a minor advantage when choosing a between abemaciclib and palbociclib / ribociclib.

7 DISCUSSION

7.1 Summary of clinical effectiveness issues

The MONARCH 3 trial showed a gain of [redacted] months in median PFS for the combination of abemaciclib and NSAI compared to NSAI alone. This is regarded to be a clinically meaningful benefit and is in-keeping with PFS gains for the other CDK 4/6 inhibitors ribociclib (and NSAI) (median difference 9.3 months[19, 29]) and palbociclib (and NSAI) (median difference 13.1 months[21, 49]). The indirect comparison of these treatments showed no statistically significant differences between them.

Abemaciclib can therefore be considered similar in effects to existing NICE recommended treatments in delaying cancer progression, one of the key treatment goals for patients with advanced breast cancer. The effect of abemaciclib on overall survival is currently unclear, as the duration of follow-up is not yet long enough to have measured the required number of events (deaths) needed for the analysis (the estimated study completion date is July 2021). A similar lack of follow-up of survival also applies to the palbociclib and ribociclib pivotal phase III trials. Thus, the clinical effectiveness of these CDK 4/6 inhibitors in

treatments based on the odds of an event is given for the response outcomes of ORR and CBR in Appendix G).[17] The networks comprise comparisons that are informed by both direct and indirect evidence (closed loops) as well as comparisons only informed by indirect evidence.

9.2.3 Statistical methods

The statistical approach used is similar to that used to conduct the first-line treatment NMA (as described in more detail in section 3.1.7 of this report). In brief:

- A Bayesian generalised linear model is used, based on NICE DSU guidelines.[24]
- Fixed and random effects modelling is undertaken with selection of model according to best fit (based on DIC values). Both random effects and fixed effects model are presented for PFS, but only fixed effects results are presented for OS as there was evidence of the prior around the random effects standard deviation dominating the posterior estimates (it is not stated why). Given the observed clinical heterogeneity in the networks (see section 9.2.4 below) the ERG considers the random effects model would have been more appropriate in principle.
- Vague prior distributions were chosen for treatment and study-specific term, in accordance with DSU methodological guidance.[24]
- OpenBUGS software was used to run the analysis (the code is provided in Appendix E the NMA report). A Markov chain Monte Carlo simulator was run for 50,000 burn-in simulations with a further 100,000 simulations for convergence to the posterior distribution (Brooks-Gelman-Rubin plots).

The ERG notes that OS data are immature (median OS not reached in at least one arm) in eight of the trials, including the MONARCH 2 trial. (The final OS analysis of this trial will be conducted at 441 OS events. The estimated study completion date is July 2021.[16] However, none of the remaining seven trials included comparisons that were used in the economic model.

An inconsistency assessment was performed to determine the level of consistency between direct and indirect evidence in the NMA networks, based on the approach recommended by the NICE DSU.[26] For PFS and OS both the total residual deviance and DIC values remained similar (<5 point difference) between consistency and inconsistency models, indicating no inconsistency.