NICE National Institute for Health and Care Excellence

Cancer Drugs Fund Review

Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy [ID2727]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CANCER DRUGS FUND REVIEW

Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy [ID2727]

Contents:

The following documents are made available to consultees and commentators:

Link to TA579
Link to Final Scope and Final Matrix

1. **Company submission** from Eli Lilly and Company Ltd.

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Breast Cancer Now

4. **Public Health England Study Report**

5. **Evidence Review Group report** prepared by BMJ-TAG

6. **Evidence Review Group report – factual accuracy check**

7. **Technical engagement response from company**

8. **Technical engagement responses from experts:**
   a. Dr Mark Verrill, Consultant Medical Oncologist – clinical expert, nominated by the UK Breast Cancer Group
   b. Holly Heath, Policy Manager – patient expert, nominated by Breast Cancer Now

9. **Evidence Review Group critique of company response to technical engagement** prepared by BMJ-TAG
   a. Addendum

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund Review of TA579

Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy [ID2727]

Company evidence submission for committee

24th September 2020

File name	Version	Contains confidential information	Date
Abemaciclib NICE CDF Review_Final Submission_240920	Final	Yes	24/09/2020

Instructions for companies

This is the template you should use for your evidence submission to the National Institute for Health and Care Excellence (NICE) as part of the Cancer Drugs Fund (CDF) review process. This document will provide the appraisal committee with an overview of the important aspects of your submission for decision-making.

This submission should not be longer than 25 pages, excluding the pages covered by this template. If it is too long it will not be accepted.

Provide supportive and detailed methodological or investigative evidence in an appendix to this submission.

When cross referring to evidence in the original submission or appendices, please use the following format: Document, heading, subheading (page X).

For all figures and tables in this summary that have been replicated, cross refer to the evidence from the main submission or appendices in the caption in the following format: Table/figure name – document, heading, subheading (page X).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.

Highlighting in the template (excluding the contents list)

Square brackets and [redacted] highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [redacted] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Grey highlighted text in the footer does not work as an automatic form field, but serves the same purpose – as prompt text to show where you need to fill in relevant details. Replace the text highlighted in [redacted] in the header and footer with appropriate text. (To change the header and footer, double click over the header or footer text. Double click back in the main body text when you have finished.)

Contents

Tables and figures

Cancer Drugs Fund review submission

A.1 Background

Following TA579, abemaciclib plus fulvestrant (ABE-FUL) is recommended for use within the Cancer Drugs Fund (CDF) as an option for treating hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2−) locally advanced or metastatic breast cancer in people who have had endocrine therapy only if:

- Exemestane plus everolimus (EXE-EVE) would be the most appropriate alternative and
- The conditions in the managed access agreement for ABE-FUL are followed

Incremental cost-effectiveness ratios (ICERs) presented to the committee in TA579 included a simple discount of [redacted] There was a confidential simple discount for EVE at the time of appraisal. The committee noted that the company's ICERs were within the range usually considered a cost-effective use of National Health Service (NHS) resources. However, the committee was concerned that the ICERs were very uncertain.

The committee highlighted the following key uncertainties during the appraisal:

- That the survival evidence was uncertain given the immaturity of the data presented
- The time-on-treatment estimates were uncertain in the company's base case
- The most appropriate method for conducting the network meta-analysis (NMA) is uncertain

The committee considered that, on the basis of the cost-effectiveness analyses including all commercial discounts, there was plausible potential that ABE-FUL would be cost-effective compared with EXE-EVE, if subsequent data confirm the company's preferred assumptions, leading to the recommendation for use within the CDF.

A.2 Key committee assumptions

The committee's preferred assumptions from TA579 are detailed in Table 1. The requests for the CDF review (highlighted bold in Table 1) are all discussed subsequently in this submission.

Table 1: Key committee assumptions

	Committee Preferred Assumptions
Comparators	• The committee concluded that the most relevant comparator was EXE-EVE. EXE or TMX would be a relevant comparator for some people who cannot tolerate EXE-EVE. FUL is not routinely commissioned but is sometimes used • The committee noted that ABE-FUL was not cost effective in people who would otherwise have treatments other than EXE-EVE and therefore committee did recommend that ABE-FUL only be used when EXE-EVE is the alternative • **The CDF review should only include a comparison with EXE-EVE**
NMA	• The company's original NMA to compare PFS and OS across the treatments were based on hazard ratios. The ERG highlighted that for some of the studies included in the network, the proportional hazards (PH) assumption was not met. The ERG therefore presented an NMA that was based on a fractional polynomial (FP) method and a modified network • Both the company's and the ERG's preferred networks (which were not the same) included trials that had different eligibility criteria to MONARCH 2 and the analyses for OS were very uncertain because of the immaturity of the

	OS data from MONARCH 2 • **The company should update the NMA and should explore the most appropriate trials to include and the most appropriate method to compare PFS and OS across the treatments**
Model	• The committee concluded that the model structure is appropriate for decision making
Treatment duration	• The company estimated time to treatment discontinuation for ABE-FUL and FUL by jointly fitting Weibull curves to the time to treatment discontinuation data from the ITT population in MONARCH 2 • The ERG considered joint curve fitting to be inappropriate because the proportional hazards assumption was not met. It preferred to use an alternative method using the PFS curves from its FP NMA. The ERG also highlighted the effect of the protocol amendment in MONARCH 2 (in which the starting dose of ABE was reduced) and more people who started on the 200 mg dose of ABE stopped treatment early than people who started on the 150 mg dose • **The company should explore the most appropriate method and extrapolation of ToT data for those who start on a twice daily 150 mg dose of ABE (post amendment population)**
Post-progression utilities	• The utility value from MONARCH 2, or the value derived from Mitra et al. and used in the ERG's base case were methodologically preferable to the value from Lloyd et al. because they used EQ-5D to measure health-related quality of life in people with breast cancer, however the utility value for post-progression survival does not have a big effect on the cost-effectiveness results compared with EXE-EVE • **The company should provide analyses using both approaches**
Subsequent treatments	• **The company should use the ERG's changes to modelling of subsequent treatments**
Most plausible ICER	• When the confidential discount for EVE was included, the company's base-case ICER compared with EXE-EVE was below £30,000 per QALY gained, and the ERG's base-case ICER was above £30,000 per QALY gained • The committee noted that if alternative hazard ratios were used to estimate the time-to-discontinuation curve from PFS for ABE-FUL, this increased the ERG base case ICER estimates
End of life	• ABE-FUL does not meet the end-of-life criteria

Abbreviations: ABE: abemaciclib; CDF: Cancer Drugs Fund; ERG: Evidence Review Group; EVE: everolimus; EXE: exemestane; FP: fractional polynomial; FUL: fulvestrant; HER2−: human epidermal growth factor receptor 2 negative; HR+: hormone receptor positive; ICER: incremental cost-effectiveness ratio; ITT: intention-to-treat; NMA: network meta-analysis; OS: overall survival; PFS: progression-free survival; QALY: quality adjusted life year; TMX: tamoxifen; ToT: time on treatment.

A.3 Other agreed changes

In accordance with the NICE process for CDF review, no additional changes or evidence have been included in this submission other than detailed above.

A.4 The technology

A summary of abemaciclib is provided in Table 2.

Table 2: A summary of the technology

UK approved name and brand name	Abemaciclib (Verzenios®)

Mechanism of action	Abemaciclib is a selective dual inhibitor of CDK4 and 6
Marketing authorisation/CE mark status	EMA marketing authorisation was granted on the 26th September 2018.[1]
Indications and any restriction(s) as described in the summary of product characteristics	Abemaciclib is indicated for the treatment of women with HR positive, HER2 negative locally advanced or metastatic breast cancer in combination with … fulvestrant …, and in women who have received prior endocrine therapy. In pre- or peri-menopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.[1]
Method of administration and dosage	• The dose for abemaciclib in this indication is one 150 mg oral tablet twice daily (a total of 300 mg daily) on a continuous 28-day cycle, in combination with fulvestrant (500 mg on Days 1 and 15 of the first cycle, and on Day 1 of subsequent 28-day cycles). • Dose adjustment and/or dose interruption are recommended for the management of some adverse reactions (such as haematological toxicities, diarrhoea, increased ALT), and when given in combination with CYP3A inhibitors. • 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 tests or investigations are required to determine eligibility for abemaciclib beyond those routinely conducted in NHS clinical practice.
List price and average cost of a course of treatment	List price of abemaciclib: £2,950.00 per 28-day cycle *The mean ToT, and cost per mean ToT, have been updated following the availability of additional data:* Mean ToT: [redacted] months (modelled, using ToT data for the post amendment population in MONARCH 2) Cost per mean ToT (based on list price): £[redacted]
Commercial arrangement (if applicable)	A patient access scheme has been agreed for abemaciclib. The abemaciclib with-PAS price is £[redacted] per 28-day cycle.
Date technology was recommended for use in the CDF	March, 2019
Data collection end date	June 2019 (MONARCH 2) December 2019 (SACT)

Abbreviations: ALT: alanine aminotransferase; CDF: Cancer Drugs Fund; CDK: cyclin-dependent kinase; EMA: European Medicines Agency; HER2−: human epidermal growth factor receptor 2 negative; HR+: hormone receptor positive; LHRH: luteinising hormone-releasing hormone; NHS: National Health Service; PAS: patient access scheme; SACT: Systemic Anti-Cancer Therapy; ToT: time on treatment.

A.5 Clinical effectiveness evidence

The data collection agreement specifies the terms of data collection during the period of managed access. In summary:

- Further follow-up from MONARCH 2 provides longer-term OS data for the ITT population and time-on-treatment data for patients in the post amendment population in MONARCH 2
- The ongoing data collection has also resulted in updated data from MONARCH 2 for

PFS, time to second disease progression (PFS2), chemotherapy-free survival (CFS), time to discontinuation (TTD) and safety

- Real-world data collected within the CDF by Public Health England (SACT data) provides evidence of the time on treatment (ToT) as well as OS data for patients who received ABE-FUL in clinical practice. Based on the limitations discussed in Section A.6.3 the OS data collected from the SACT cohort were not incorporated in the updated economic analyses

A.6 Key results of the data collection

A.6.1 MONARCH 2

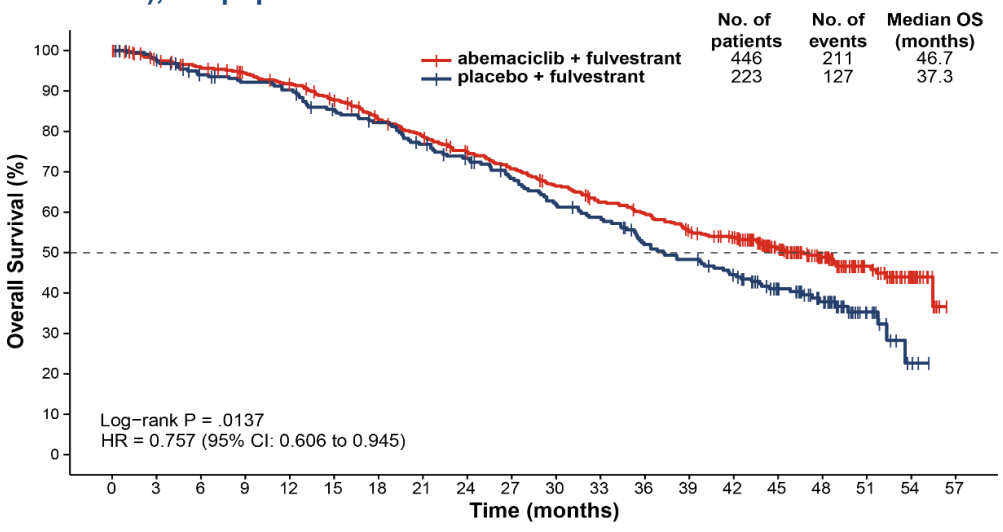
The updated clinical effectiveness results detailed below are taken from the OS interim analysis in MONARCH 2 (data cut-off [DCO] date 20th June 2019). Full details of the MONARCH 2 study design can be found in TA579 Document B, Section B.2.3 and Section B.2.4 (Pages 30–45).

Overall survival (ITT population)

At the time of the primary PFS analysis (DCO 14th February 2017), the OS data were still immature, with 85 (19.1%) events (deaths) in the ABE-FUL arm and 48 (21.5%) events in the PBO-FUL arm, resulting in a hazard ratio (HR) of [redacted] (95% confidence intervals [CI]: [redacted]; as described in TA579 Document B, Section B.2.6.2 [Pages 51–54]). The median follow-up times were similar across treatment arms ([redacted] months [ABE-FUL] and [redacted] months [PBO-FUL]).

By the time of the updated DCO (20th June 2019), a total of 338 patients experienced an OS event, including 211 patients (47.3%) in the ABE-FUL arm and 127 patients (57.0%) in the placebo plus fulvestrant (PBO-FUL) arm, with a median follow-up time of 47.7 months. A statistically significant and clinically meaningful improvement in OS was observed in the ABE-FUL arm compared to the PBO-FUL arm, with a HR of 0.757 (95% CI: 0.606, 0.945; 2-sided p = 0.0137). These results correspond to a 24.3% reduction in the risk of death. Median OS was improved by 9.47 months, with a median OS of 46.7 months in the ABE-FUL arm and 37.3 months in the PBO-FUL arm. A Kaplan-Meier plot for OS at the OS interim analysis is presented in Figure 1, and a full summary of OS results is presented in Table 10 (Appendix 1).

Figure 1: Kaplan-Meier plot of OS for ABE-FUL vs PBO-FUL at the OS interim analysis (DCO 20th June 2019), ITT population



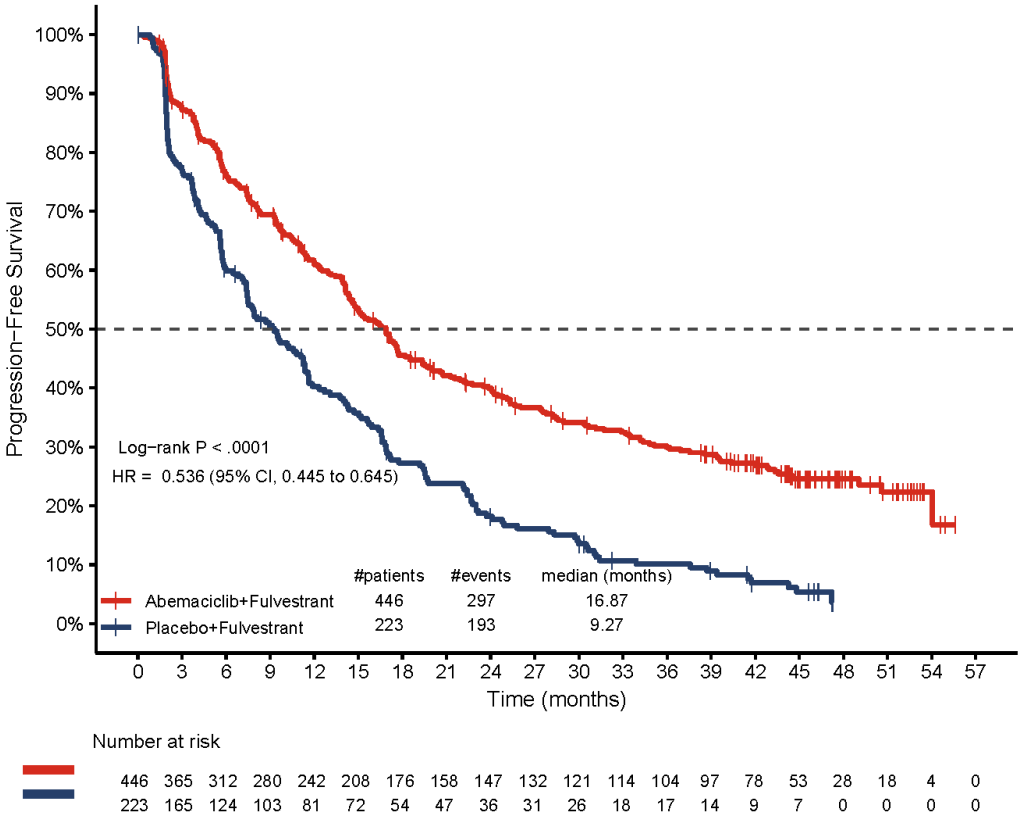
Abbreviations: ABE: abemaciclib; DCO: data cut-off; FUL; fulvestrant; HR: hazard ratio; ITT: intention-to-treat; OS: overall survival; PBO: placebo.

Progression free survival (ITT population)

At the time of the primary PFS analysis (DCO 14th February 2017), a total of 379 patients experienced PFS events, with an increased median PFS of 16.4 months in the ABE-FUL arm compared to 9.3 months in the PBO-FUL arm, a statistically significant and clinically meaningful improvement (HR=0.553 [95% CI: 0.449 to 0.681], p<0.001) (as presented in TA579 Document B, Section B.2.6.1, Pages 48–50).[2]

Consistently, at the time of the OS interim analysis (DCO 20th June 2019), PFS was significantly improved for patients receiving ABE-FUL compared to PBO-FUL (HR: 0.536, 95% CI: 0.445, 0.645; 2-sided p-value [redacted]). A total of 490 patients experienced PFS events, including 297 patients (66.6%) in the ABE-FUL arm and 193 patients (86.5%) in the PBO-FUL arm. A Kaplan-Meier plot for PFS at the OS interim analysis is presented in Figure 2 and a full summary of the updated PFS results is presented in Table 11 (Appendix 1).

Figure 2: Kaplan-Meier plot of PFS for ABE-FUL vs PBO-FUL at the OS interim analysis (DCO 20th June 2019), ITT population



Abbreviations: ABE: abemaciclib; CI: confidence interval; DCO: data cut-off; FUL; fulvestrant; ITT: intention-to-treat; OS: overall survival; PBO: placebo; PFS: progression free survival.

Extent of exposure (ITT population)

At the time of the updated DCO (20th June 2019), the median number of cycles of ABE received per patient was [redacted] cycles (mean [redacted] cycles) compared to [redacted] cycles (mean [redacted] cycles) in the PBO-FUL arm. The median time to discontinuation of ABE/PBO with or without FUL was [redacted] months in the ABE-FUL arm and [redacted] months in the PBO-FUL arm. Kaplan-Meier and Weibull plots for TTD at the OS interim analysis are presented in Figure 3. A full summary of drug exposure to ABE or PBO is presented in Table 12 (Appendix 1).

Figure 3: Weibull and KM plots of time to discontinuation for ABE or PBO, ITT population

Abbreviations: ABE: abemaciclib; ITT: intention-to-treat; PBO: placebo.

Extent of exposure (post amendment population)

The results below are presented for the post amendment population in MONARCH 2 who received at least one dose of study drug at a starting dose of 150 mg.

The Kaplan-Meier summary of the time to treatment discontinuation for ABE or PBO at the time of the updated DCO (20th June 2019) is presented in Figure 4. Using the Kaplan-Meier method, the median time to discontinuation of ABE/PBO with or before FUL was [redacted] months (95% CI: [redacted], [redacted]) in the ABE-FUL arm, and [redacted] months (95% CI: [redacted], [redacted]) in the PBO-FUL arm. A full summary of drug exposure to ABE or PBO is presented in Table 13 (Appendix 1).

Figure 4: Kaplan-Meier summary of time to treatment discontinuation for ABE or PBO (post amendment population)

Notes: [a] Unstratified HR. [b] P-value (2-sided) – logrank unstratified for comparing with PBO.
Abbreviations: ABE: abemaciclib; HR: hazard ratio; PBO: placebo.

Additional efficacy outcomes (ITT population)

The results of the OS interim analysis (DCO 20th June 2019) additionally showed that PFS2 (median 23.1 months vs 20.6 months), time to chemotherapy (median, 50.2 months vs 22.1

months) and chemotherapy-free survival (median, 25.5 months vs 18.2 months) were also statistically significantly improved for patients treated with ABE-FUL compared to PBO-FUL.[3]

Safety (ITT population)

The results of the OS interim analysis (DCO 20th June 2019) showed that the safety profile for ABE-FUL was consistent with the primary PFS analysis (14th February 2017), with respect to incidence, type and severity of AEs. No new safety signals were observed with longer follow-up.[3]

A.6.2 Systemic Anti-Cancer Therapy (SACT) Data

Baseline characteristics

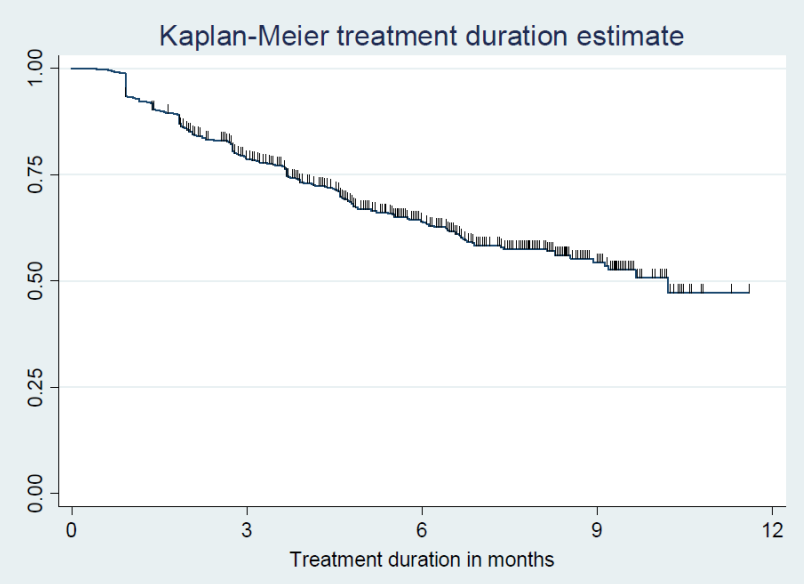
A summary of the key baseline characteristics and demographic factors for patients treated with ABE-FUL in the SACT dataset is presented in Table 14 (Appendix 2).

Treatment duration

In total, 298 patients (24%) were identified as having completed treatment by the latest date of follow-up in the SACT dataset (31st December 2019).[4] Patients were assumed to have completed treatment if they have died, have an outcome summary recorded in the SACT dataset or if they have not received treatment with ABE-FUL in at least three months.[4] The median follow-up time in the SACT dataset was 4.4 months (133 days), with a maximum follow-up of 10 months.[4]

Figure 5 presents the Kaplan-Meier curve for treatment duration with ABE-FUL. The median treatment duration for all patients was 10.2 months (310 days).[4] At six months, 64% (95% CI: 60%, 67%) of patients were still receiving treatment, with 46% (95% CI: 37%, 56%) of patients still receiving treatment at 12 months.[4]

Figure 5: Kaplan Meier treatment duration estimates for patients receiving ABE-FUL



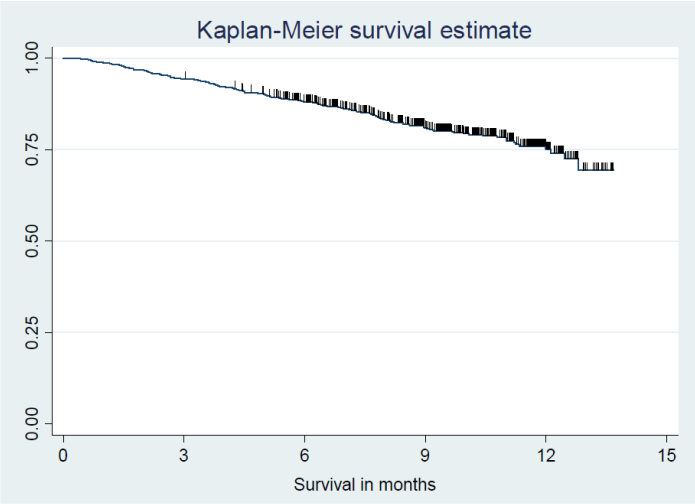
Source: Public Health England SACT Data Review[4]

Overall survival

The median OS was not reached for the SACT dataset.[4] At six months, OS was 88% (95% CI: 86%, 90%), and at 12 months, OS was 75% (95% CI: 70%, 79%).[4] The median follow-up time in SACT was 8.5 months (258 days).[4] The OS results from the SACT dataset demonstrate

decreased OS in comparison to ITT MONARCH 2 results (75% vs 91.8% of patients surviving at 12 months).[3, 4]

Figure 6: Kaplan-Meier overall survival estimates for patients receiving ABE-FUL



Source: Public Health England SACT Data Review[4]

A.6.3 Differences between SACT and MONARCH 2

Lilly contends that there are a number of reasons that the OS outcomes for patients in the SACT cohort are different compared to those reported in the MONARCH 2 trial. These reasons limit interpretation of the SACT data and are discussed in detail below.

Patient selection

The analysis cohort used for the SACT report included patients with a Blueteq® application for ABE-FUL and a matched report in SACT during the period from 2nd April 2019 to 15th December 2019 (with a possible follow-up through the SACT snapshot date of 4th April 2020). As a result, the data in the report only include patients initiating ABE-FUL during the first nine months of its availability in the CDF.

It has previously been observed that early users of a newly available product may not be representative of the product's eventual user population, due to the selective prescribing of the new product to patients who are not responding well to existing therapies.[5-8] These early patients may be different from the later use population with regard to characteristics which affect likelihood of response (with the inclusion of patients with more severe, treatment-refractory disease).

The selection of patients with more severe clinical characteristics early after product launch has also been demonstrated in an observational study of ABE utilisation shortly after launch in the USA.[9] Within the early post-marketing observation period, it is possible that lack of experience from physicians in treating patients with ABE-FUL may have contributed to the over-representation of severe patients into this study.

Baseline characteristics

A comparison of the key baseline characteristics for patients in the SACT cohort and patients in MONARCH 2 is presented in Table 3 below.

The SACT dataset represents a frailer, older patient population than observed in MONARCH 2 – the median age of the SACT dataset was higher than MONARCH 2 (median 65 years vs 59 years), while an increased proportion of patients had an Eastern Cooperative Oncology Group

(ECOG) Performance Status (PS) of 1 (47% vs 40%), 2 (8% vs [redacted]) or missing (13% vs [redacted]) in comparison to MONARCH 2. Proportionally, more patients in the SACT dataset were treated with ABE-FUL after progressing on first line treatment for metastatic breast cancer (62%) than in MONARCH 2 (38%). The patient profile of the SACT cohort is therefore consistent with the above considerations regarding the potential for patient selection for products on launch to over-represent patients with more severe, treatment-refractory disease relative to the ultimate end use population.

Lilly are also aware of anecdotal reports from NHS workers that patients within the SACT dataset may also have received prior chemotherapy for metastatic breast cancer due to the lack of a specific exclusion factor within the CDF criteria. In contrast, prior treatment with chemotherapy in the locally advanced or metastatic setting (except for neoadjuvant/adjuvant chemotherapy) was an exclusion criterion in MONARCH 2 (detailed in TA579 Document B, Section B.2.3.2, Table 4, Page 31). Pre-treatment of the SACT cohort with chemotherapy for metastatic disease would create further difficulty in interpreting the comparison of outcomes between the SACT cohort and MONARCH 2, as this is likely to negatively impact outcomes for patients in the SACT cohort.

Table 3: Key baseline characteristics of patients receiving ABE-FUL in the SACT dataset and in MONARCH 2

Characteristics	Patients receiving ABE-FUL	
	SACT (n = 876)	MONARCH 2 (n = 446)
Median age, years (range)	65	59 (32 to 91)
Performance status, n (%)		
0	273 (31)	264 (59.2)
1	416 (47)	176 (39.5)
2	66 (8)	[redacted]
Missing	116 (13)	[redacted]
Previous ET, n (%)	876 (100)	–
Progressive disease whilst still receiving adjuvant or neoadjuvant ET for early breast cancer with no subsequent ET received following disease progression	302 (34)	–
Progressive disease within 12 or less months of completing adjuvant ET for early breast cancer with no subsequent ET received following disease progression	32 (4)	–
Progressive disease on first line ET for advanced/metastatic breast cancer with no subsequent ET received following disease progression	542 (62)	–
Most recent ET, n (%)		
(Neo)adjuvant	–	263 (59.0)
Metastatic	–	171 (38.3)
Endocrine resistance, n (%)		
Primary endocrine resistance	–	111 (24.9)
Secondary endocrine resistance	–	326 (73.1)

Abbreviations: ABE: abemaciclib; ET: endocrine therapy; FUL; fulvestrant; SACT: Systemic Anti-Cancer Therapy.
Source: Lilly Data on File (Clinical Study Report P117). 2017[10]; Public Health England SACT Data Review[4]

Relative treatment effect

The absence of a comparator or control group in the SACT cohort means that it is not possible to undertake a meaningful comparison of ABE-FUL versus FUL alone to determine a relative treatment difference – only an absolute efficacy estimate is provided. This means that further assumptions of causality, or comparison of the absolute benefit of ABE-FUL in the SACT cohort with the results of MONARCH 2 should be interpreted with caution.

In comparison, MONARCH 2 was designed to estimate the relative treatment effect of ABE-FUL versus FUL, and included prespecified subgroups such as age, previous endocrine treatment and ECOG PS for treatment effect analysis. Consistent relative treatment benefits for ABE-FUL versus FUL alone were observed across these subgroups, including for patients with poor prognostic factors. Consequently, had a corresponding cohort of patients received FUL alone in the SACT dataset, Lilly does not see any reason to assume that the results would reflect anything other than a similar relative treatment effect for ABE-FUL compared to FUL alone.

Data immaturity

For OS, the median follow-up of the SACT report population is 8.5 months (258 days). Lilly believe that interpretation of the OS results will meaningfully change when events have accrued, similarly to what was observed between DCOs for MONARCH 2 (presented for MONARCH 2 in Section A.6.1).

For time on treatment, the median follow-up was 4.4 months (133 days). Lilly is concerned that this short patient follow-up may mean that early discontinuations of treatment are over-reported in the SACT cohort.

Treatment exposure

In the SACT cohort, patients discontinued both ABE and FUL at the same time, whereas in MONARCH 2 patients were permitted to discontinue the two treatments independently. For example, the MONARCH 2 posology means that physicians could discontinue ABE but maintain treatment with FUL while patients derived clinical benefit. While this was applicable for few patients, Lilly believes this is important to consider when interpreting the SACT cohort results.

In addition, treatment exposure to ABE was not reported in the SACT cohort, complicating comparison of the reported outcomes across SACT and MONARCH 2.

Treatment options for population

Lilly are aware that other CDK4/6-inhibitors were made available to patients and physicians for the population in question on the CDF. Lilly are concerned that the availability of multiple products with overlapping indications may have had the potential to cause patient selection to be not at random for one or more of these products. Specifically, this could mean that the population of patients receiving ABE-FUL on the CDF represents a selected sample of the patient population in MONARCH 2 for whom there were no other treatment options available.

As the other SACT reports were not available to Lilly at the time of writing, it has not been possible to further assess this potential difference.

Concluding remarks

Lilly acknowledges the findings in the SACT cohort and suggests that they support that ABE-FUL is a treatment option that can offer improved outcomes for patients, consistent with what has been discussed in other sections of the dossier. Lilly recommend that the totality of evidence be considered in the commissioning decision-making, and that appropriate weight be given to the

randomised controlled trial (RCT) evidence from MONARCH 2 relative to the real-world data from the early post-marketing setting of the SACT cohort.[11]

A.7 Evidence synthesis

A.7.1 NMA methodology

Overview

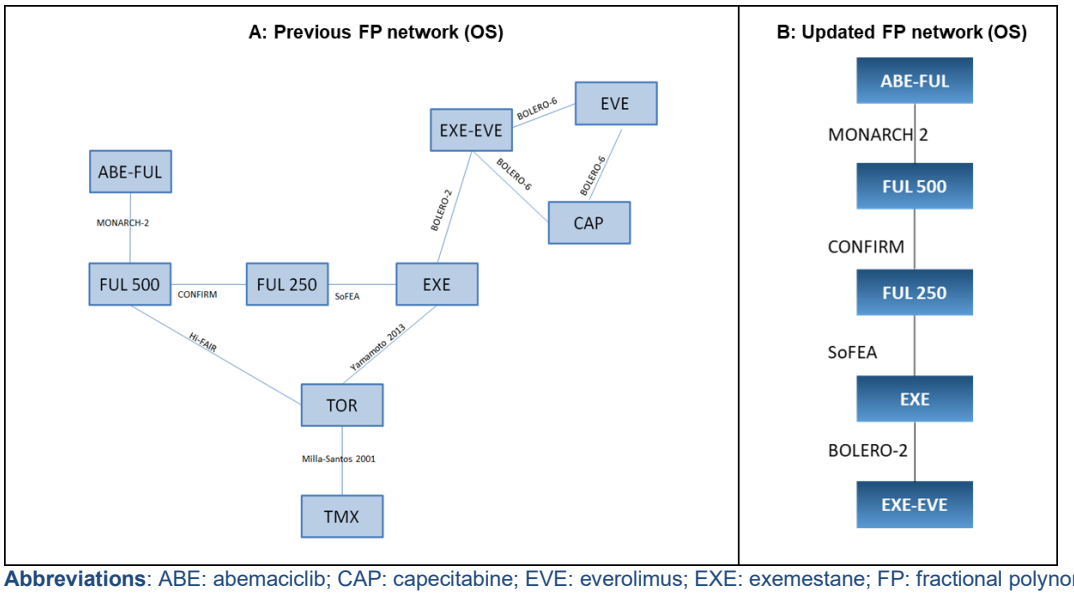
In the original appraisal (TA579), the indirect treatment comparisons were originally conducted using a proportional hazards (PH) NMA (TA579 Document B, Section B.2.9, Pages 60–71) Subsequently an alternative fractional polynomial (FP) NMA was conducted in response to the ERG Clarification Questions (presented in the Company Response to Abemaciclib Clarification Questions, 18th December 2018, Question A3b, Pages 7–11, as some of the trials in the PH NMA did not meet the PH assumption. In line with the committee's preferred assumptions for this CDF review, an updated FP NMA, using an updated methodology, is presented below for the indirect treatment comparison of ABE-FUL and EXE-EVE.

Alongside an updated methodology, the updated FP NMA incorporates the additional PFS and OS data from the most recent DCO (20th June 2019) of MONARCH 2, as described in Section A.6.1 , including OS data which are now mature.

OS network of evidence

In comparison to the OS network of evidence used in the original company FP NMA (presented in TA579 Company Response to Abemaciclib Clarification Questions, 18th December 2018, Figure 4, Page 9), the network has been simplified for this submission, as shown in Figure 7. According to the committee's preferred assumptions, the network only includes the minimum number of trials required to connect ABE-FUL and EXE-EVE. Consequently, BOLERO-6, Hi-FAIR, Yamamoto et al. (2013) and Milla-Santos et al. (2001) have been removed from the network, removing EVE monotherapy, capecitabine (CAP), toremifene (TOR) and tamoxifen (TMX) as treatments that are considered.

Figure 7: OS network of evidence used in the (A) original FP NMA and (B) updated FP NMA

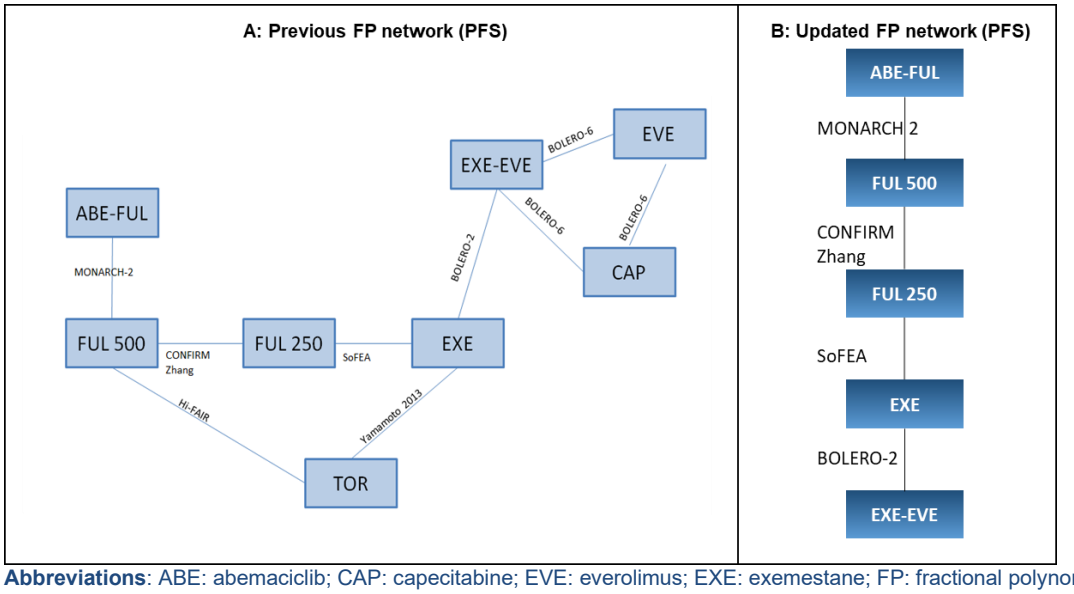


Abbreviations: ABE: abemaciclib; CAP: capecitabine; EVE: everolimus; EXE: exemestane; FP: fractional polynomial; FUL: fulvestrant; NMA: network meta-analysis; OS: overall survival; TOR: toremifene; TMX: tamoxifen.

PFS network of evidence

Similarly, in comparison to the PFS network of evidence used in the original company FP NMA (presented in TA579 Company Response to Abemaciclib Clarification Questions, 18th December 2018, Figure 3 Page 8 [Page 262 of the TA579 Committee Papers]), the network has been simplified for this submission, as shown in Figure 8. According to the committee's preferred assumptions, the network now contains only the minimum number of trials required to connect ABE-FUL and EXE-EVE (Figure 8). Consequently, BOLERO-6, Hi-FAIR and Yamamoto et al. (2013) have been removed from the network, removing EVE monotherapy, CAP and TOR as treatments that are considered.

Figure 8: PFS network of evidence used in the (A) original FP NMA and (B) updated FP NMA



Abbreviations: ABE: abemaciclib; CAP: capecitabine; EVE: everolimus; EXE: exemestane; FP: fractional polynomial; FUL: fulvestrant; NMA: network meta-analysis; PFS: progression-free survival; TOR: toremifene.

Curve selection methodology

The methodology of the company FP NMA is based on the methods described by Jansen (2011)[12], and is very similar to the methodology detailed previously (TA579 Company Response to Abemaciclib Clarification Questions, 18th December 2018, Pages 9–10 [Page 255 of the TA579 Committee Papers]). A brief summary of the original methodology is provided below:

"*An FP approach was taken to account for violation in the proportional hazards assumption. Unlike the standard NMA approach to time-to-event data considering HR data, the FP does not require that the proportional hazards assumption holds.*

A FP function of first or second order can be utilised to estimate the natural logarithm of the hazard function per treatment arm in each study, defined as $ln(h(t)) = \beta_0 + \beta_1 t^{p1}$ *and* $ln(h(t)) = \beta_0 + \beta_1 t^{p1} + \beta_2 t^{p2}$ *with t0=log t. If* p_1=p_2=p*, the model becomes a repeated powers model, defined as* $y = \beta_0 + \beta_1 t^p + \beta_2 t^p \, log \, t$.

The power of the linear predictors p_1 *and* p_2 *are chosen from a set; different choices correspond to different hazard functions, allowing a range of different shapes. In oncology, usually values in the set {-2,-1,-0.5,0,0.5,1,2,3} are considered to result in best fit to time-to-event data.*

An NMA is then performed on the parameters of the fractional polynomials from each study to obtain an overall set of estimated parameters for each treatment. The survival curves can then be generated from these parameters.

For the purposes of the analysis of OS and PFS the following models were fitted:

- *First order (*β_2*=0) and second order fractional polynomials fixed effects (FE) and random effects (RE) models with powers* p_1 *and* p_2 *from the set {-2,-1,-0.5,0,0.5,1,2,3}.*
- *The RE models accounted for heterogeneity for* d_0 *(treatment effect under the proportional hazard model) only (constant heterogeneity of log HR over time).*

If various FP models showed similar deviance information criterion (DIC) values (e.g. within 5 points), the selection was further informed by visual inspection of the fit of the observed data, carefully examining the tails of the distributions and plausibility of long-term extrapolation. Second-order models showed better fit than first-order models throughout, both in terms of DIC and visual inspection of the curves. For OS, the FE second-order model with p_1=0, p_2=1 *showed best fit, whereas for PFS, the RE second-order model with* p_1=0.5, p_2=1 *fitted best.*

For a number of combinations of p_1 *and* p_2 *in the second-order FP models, we experienced issues with convergence and autocorrelation. This may occur due to the data being in conflict with the structural form implied by these combinations. As a consequence, the Gibbs sampler is unable to visit the relevant areas of the parametric space and cannot converge to the corresponding posteriors, even if the number of simulations is increased to 200,000 or more.*

Analyses were conducted using OpenBUGS version 3.2.3, and R version 3.4.4. The package 'R2OpenBUGS' was used to run OpenBUGS from within R. Analyses were run with 30,000 iterations of which 12,000 were discarded as burn in, and a thinning parameter of 4, with 2 chains, to identify the parameter combinations with best fit. Once identified, the best-fitting models were rerun with 200,000 iterations of which 50,000 were discarded as burn in, with the same thinning parameter and number of chains as described above.

Minimally informative priors were used for all parameters, corresponding to a multivariate normal distribution with zero mean and covariance and 10,000 variance for d and μ parameters and a uniform distribution in the range of [0,2] for σ."

Compared to the original FP NMA, the updated FP NMA analyses were run with 100,000 iterations, of which 20,000 were discarded as burn in. For model selection, 50,000 iterations were considered, and then an increased number were considered after model selection to reduce any uncertainty due to observed variance. However, these additional iterations did not impact the model selection and only reduced uncertainty.

A thinning parameter was used with two chains to identify the parameter combinations with best fit. Also, when choosing the power of the linear predictor's p_1 and p_2, in addition to the values usually used in oncology and used in the original company FP NMA: {−2, −1, −0.5, 0, 0.5, 1, 2, 3}, an additional value of −1.5 was also tested in the available data to determine if this resulted in improved fits, in line with the ERG's previous assumptions.

Consistent with the original analyses, a number of combinations of p_1 and p_2 did not converge and tended towards infinity. This may occur due to the data being in conflict with the structural form implied by these combinations.

Initial curve fitting was conducted based on criteria proposed by Janssen et al in their original paper.[12] Both first order and second order models were assessed with multiple combinations for p_1 and p_2. Second order models were found to be statistically good fits to the clinical data. However, on visual inspection of the tails of extrapolations, the second order models consistently overfitted the changes in hazards between ABE-FUL and FUL between 40 and 60 months. This produced extrapolations which consistently proposed cure models for ABE-FUL. However, Lilly are not aware of any evidence to support such long-term extrapolations and cure models.

To resolve this issue, the DIC selection criteria were relaxed from within five points to within 20 points of best statistical fit based on DIC in order to choose models with plausible long-term projections. Generally, these were first order models, suggesting the second order models were overfitting to the data. Lilly believes this is consistent with critique of the Company NMA in the original FP NMA (TA579) and similar to the ERG's approach to focus on a subset of possible extrapolations.

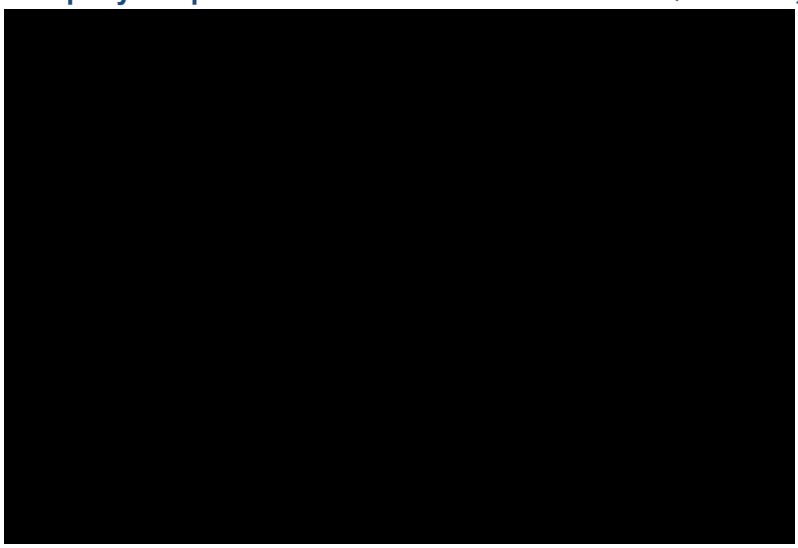
The chosen extrapolations for OS and PFS were chosen based on ability to reasonably predict observed trial data and a plausible incremental improvement of survival in the tails. However, one limitation (discussed in detail in Section A.7.3) is that all of the plausibly well-fitting PFS curves intersect all of the plausibly well-fitting OS curves. This is a result of potential overfitting of the tail of the PFS extrapolation to observed PFS outcomes in MONARCH 2, combined with the fact that outcome extrapolation is conducted independently for PFS and OS in the FP NMA.

A.7.2 NMA results

OS extrapolations and summary statistics

The OS DIC results of the FP NMA showed that, among the models which were within 20 DIC from the best statistical fit and clinically plausible (i.e. where the extrapolation of OS or PFS did not tend towards a cure), the first-order FE model with $p_1 = -1.0$ showed best fit (a full summary of fitting statistics can be found in Appendix 3, Table 19). The corresponding time-to-event curves are presented in Figure 10, and a range of OS summary statistics are presented in Table 4. For comparison, the OS time-to-event curves (up to Month 80) from the original company FP NMA are presented in Figure 9 below.

Figure 9: OS Time-To-Event Curves up to Month 80 (original FP NMA) (Figure 5, TA579 Company Response to Abemaciclib Clarification Questions, 18th December 2018, Page 11)



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

Figure 10: OS time-to-event curves (updated FP NMA)

Note: The curves presented above include a combined FUL extrapolation (combining data from both FUL 500 mg and FUL 250 mg) in line with the methodology used in the economic analysis, rather than the separate FUL 500 and FUL 250 curves that directly result from the NMA.
Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; NMA: network meta-analysis; OS: overall survival.

The FP NMA shows that ABE-FUL has a higher median OS in comparison to EXE-EVE (months vs months respectively) (Table 4). The order of treatments is consistent across both median and mean OS estimates (Table 4). For patients receiving treatment with ABE-FUL, approximately % of patients were surviving at 12 months, % at 60 months and % at 120 months.

Table 4: OS summary statistics from the updated FP NMA

	FUL	EXE	EXE-EVE	ABE-FUL
Mean OS, months	[redacted]	[redacted]	[redacted]	[redacted]
Median OS, months	[redacted]	[redacted]	[redacted]	[redacted]
Alive at 12 months, %	[redacted]	[redacted]	[redacted]	[redacted]
Alive at 60 months, %	[redacted]	[redacted]	[redacted]	[redacted]
Alive at 120 months, %	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FP: fractional polynomial; FUL: fulvestrant; NMA: network meta-analysis; OS: overall survival.

The original FP NMA reports median OS estimates of [redacted] months for patients treated with ABE-FUL and [redacted] months for patients treated with EXE-EVE. In comparison, the updated company FP NMA reported median OS of [redacted] months for patients treated with ABE-FUL, and [redacted] months for patients treated with EXE-EVE.

PFS extrapolations and summary statistics

The PFS DIC results of the FP NMA showed that, among the models which were clinically plausible, the first-order FE model with $p_1 = 0$ showed the most reasonable fit (fitting statistics can be found in Appendix 3, Table 20).

The time-to-event curves of the updated company FP NMA are presented in Figure 12, and a range of PFS summary statistics for the updated FP NMA are presented in Table 5. For comparison, the PFS time-to-event curves from the original company FP NMA are presented in Figure 11.

Figure 11: PFS Time-To-Event Curves to Month 80 (original FP NMA – Figure 5, TA579 Company Response to Abemaciclib Clarification Questions, 18th December 2018, Page 11)

Abbreviations: ABE: abemaciclib; CAP: capecitabine; EVE: everolimus; EXE: exemestane; FP: fractional polynomial; FUL: fulvestrant; NMA: network meta-analysis; PFS: progression-free survival; TOR: toremifene.

Figure 12: PFS Time-To-Event Curves (Updated FP NMA)

Note: The curves presented above include a combined FUL extrapolation (combining data from both FUL 500 and FUL 250) in line with the methodology used in the economic analysis, rather than the separate FUL 500 and FUL 250 curves that directly result from the NMA.
Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FP: fractional polynomial; FUL: fulvestrant; NMA: network meta-analysis; PFS: progression-free survival.

Table 5: PFS summary statistics from the FP NMA

	FUL	EXE	EXE-EVE	ABE-FUL
Median PFS, months	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free at 12 months, %	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free at 60 months, %	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free at 120 months, %	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABE: abemaciclib; CI: confidence interval; EVE: everolimus; EXE: exemestane; FP: fractional polynomial; FUL: fulvestrant; NMA: network meta-analysis; PFS: progression-free survival.

The original FP NMA reports median PFS estimates of [redacted] months for patients treated with ABE-FUL and [redacted] months for patients treated with EXE-EVE. In comparison, the updated company FP NMA reported median PFS of [redacted] months for patients treated with ABE-FUL, and [redacted] months for patients treated with EXE-EVE.

A.7.3 Uncertainties

Overall, the updated FP NMA is able to substantially reduce the uncertainty of the results when compared to the original PH and FP NMAs, as it incorporates updated OS and PFS data from MONARCH 2, utilises the preferred FP methodology and carefully considers clinical plausibility of extrapolations alongside statistical fit. The use of the FP NMA methodology does result in all of the plausibly well-fitting PFS curves intersecting all of the plausibly well-fitting OS curves, due to potential overfitting of the PFS extrapolations to the observed PFS outcomes from MONARCH 2. However, the interactions between PFS and OS in the respective best fitting curves occurs after approximately [redacted] years, when approximately only [redacted]% of the cohort is alive, and consequently the updated FP NMA methodology results in substantially improved clinical plausibility in comparison to the cure model extrapolations that resulted from the original company FP NMA.

The updated FP NMA does not fully resolve some minor uncertainties from the original NMAs. While the simplification of the OS and PFS networks of evidence does reduce some of the original heterogeneity, nonetheless some heterogeneity in the patient populations of the included trials remains, particularly in regard to treatment with prior chemotherapy or endocrine therapy. Furthermore, the BOLERO-2 trial included patients that were refractory to either letrozole or

anastrozole (i.e. patients had previously received an aromatase inhibitor) and based on clinical expert opinion this could have overestimated the benefit of EXE-EVE relative to EXE by potentially biasing against the control arm. Therefore, the effect of this bias is conservative with respect to estimation of the relative effectiveness of ABE-FUL versus EXE-EVE (i.e. potentially results in underestimation of the relative effectiveness of ABE-FUL).

A.7.4 Conclusions

The results of the updated FP NMA support the conclusions from TA579, but with substantially reduced uncertainty surrounding the long-term extrapolation of the clinical outcomes from MONARCH 2 through the use of updated mature OS data.

In line with the data submitted in the original appraisal, the data from the updated DCO (20th June 2019) in MONARCH 2 did not support the application of a PH NMA. Consequently, the updated OS and PFS data were incorporated into an updated FP NMA. First order NMA extrapolations for OS and PFS were chosen as the best fitting models. All of the best fitting models continued to result in overfitting of PFS data, although the final extrapolations of the FP NMA are substantially more clinically plausible in comparison to the original FP NMA. Considering the improved clinical plausibility of the extrapolations, as well as the increased follow-up of the OS and PFS data from MONARCH 2 (including OS data which are now mature), the FP NMA substantially reduces the uncertainty surrounding long-term extrapolation of clinical outcomes for ABE-FUL vs. relevant comparators compared to the original appraisal.

A.8 Incorporating collected data into the model

A.8.1 Overall survival

The original economic analysis, based on the original company PH NMA, used OS inputs that were estimated by fitting standard parametric distributions to the immature OS data from MONARCH 2, as detailed in TA579 Document B, Section B.3.3.5 (Pages 108–113). A Weibull distribution using data from MONARCH 2 was used to model OS for ABE-FUL and FUL; however, these estimates were considered to be uncertain regarding long-term extrapolation and treatment-effect. Consequently, extrapolations of OS for both arms were informed using long-term external data from the CONFIRM trial after [redacted] months, in line with the maximum follow-up on the ABE-FUL arm of the MONARCH 2 trial. In addition, the treatment effect for ABE-FUL vs FUL was tapered from [redacted] months to gradually reach 1.00 at the time point of extrapolation ([redacted] months) due to the uncertainty regarding the long-term treatment effect between ABE-FUL and FUL alone.

In comparison, in the updated economic analyses based on the original company FP NMA and now the updated company FP NMA, the OS for ABE-FUL and all comparators was estimated based on the survival output for the FP NMA, as detailed in Section 7. Briefly, an NMA was performed on the beta parameters of the FP for the reference treatment, fulvestrant, which was modelled using data from MONARCH 2 and CONFIRM as both include FUL 500 mg. For the relative effect, a deviance from the reference treatment is estimated (for example, for trial A/C d_{AC}) in the form of a time-varying hazard from each treatment to obtain an overall set of estimated parameters for each treatment. The time varying HRs can then be combined with the reference treatment to generate survival functions for each comparator. The base case extrapolations for all treatments are presented in Figure 9 (for the original company FP NMA) and Figure 10 (for the updated company FP NMA, incorporated in the new company base case) in Section A.7.2 above.

In addition to the methodology that has been changed since the original appraisal, the updated FP NMA incorporates additional, mature OS data from MONARCH 2, based on a later DCO (20th June 2019). In comparison, the original economic analyses based on the original company PH and FP NMAs used OS data from the previous DCO in MONARCH 2 (DCO 14th February 2017),

as described in Section A.6.1 and Table 10 (Appendix 1). The inclusion of mature OS data reduces the uncertainty around the long-term treatment-effect for ABE-FUL vs FUL alone.

A.8.2 Duration of therapy

For this updated economic analysis, the duration of therapy for ABE-FUL and FUL have been estimated based on data from the MONARCH 2 trial, in line with the previous appraisal. However, in line with the committee's preferred assumptions for this review, time to discontinuation has now been modelled considering the post amendment patient population in MONARCH 2, while the ITT population was used in the original submission.

For EXE and EXE-EVE, the duration of therapy has been estimated based on the median duration of therapy estimates reported in the primary publications that were used to inform PFS and OS. Using the median duration of therapy and median PFS (from these publications) a HR was estimated to reflect the difference in the medians, and hence the relationship between reported duration of therapy and PFS. This HR was then applied to the PFS distribution in the cost effectiveness model to attain relative estimates of duration of therapy for the comparators.

This approach, in line with the original appraisal, was necessary to derive an extrapolation profile for duration of treatment with the comparators, given that only median duration of therapy data (not Kaplan Meier plots) were reported in the publications. Lilly continues to believe that the relation of the ToT to the difference in published median PFS and ToT represents the most appropriate methodology to replicate the difference in PFS and ToT from the literature, especially considering differences in definitions of treatment time outcomes.

It is important to note that the approach used in the base case analysis, which includes analysis of the MONARCH 2 ToT data using a time to event framework, should be considered conservative (with regard to cost-effectiveness), as all treatment pauses for patients receiving ABE-FUL are modelled as carrying forth a treatment cost.

As a most conservative alternative scenario (with regard to cost-effectiveness), the economic model allows for an extrapolation to be selected where the ToT is set as equal to PFS for ABE-FUL, increasing the ToT for patients treated with ABE-FUL. However, Lilly does not believe that this scenario is clinically plausible – as detailed in Table 11 (Appendix 1), at the time of the OS interim analysis (DCO 20th June 2019), patients treated with ABE-FUL had a median PFS of 16.87 months (95% CI: 14.53, 18.51). In comparison, patients in the post amendment population and ITT population had median ToT estimates of [redacted] months and [redacted] months respectively, notably lower than the median PFS estimate.

A.8.3 Progression free survival

Similarly to OS, the original economic analysis, based on the original company PH NMA, used PFS estimates for ABE-FUL and FUL that were based on fitting standard joint parametric models to the investigator-assessed PFS data from the MONARCH 2 trial, as detailed in TA579 Document B, Section B.3.3.5 (Pages 108–113). A Weibull distribution was selected to model PFS for ABE-FUL and FUL in the base case analysis. For the comparators, PFS for EXE and EXE-EVE was estimated by applying the relative treatment effects generated by the company PH NMA to the FUL PFS curve based on the MONARCH 2 trial.

In comparison, in the updated economic analyses, based on the original company FP NMA and now the updated company FP NMA, use PFS estimates for ABE-FUL and all comparators that have been estimated using the FP NMA, as detailed in Section 7. As discussed in Section A.8.1 for OS, time varying HRs can be combined with the reference treatment from the FP NMA to generate survival functions for each treatment. The base case extrapolations for all treatments are presented in Figure 10 in Section A.7.2 above.

In addition to the methodology that has been changed since the original appraisal, the updated FP NMA incorporates additional PFS data from MONARCH 2, based on a later DCO (20th June 2019), in comparison to the original economic analyses based on either the original company PH or FP NMAs (DCO 14th February 2017), as described in Section A.6.1 and Table 11 (Appendix 1).

A.8.4 Adverse events

The results of the OS interim analysis (DCO 20th June 2019) showed that the safety profile for ABE-FUL was consistent with the primary analysis, with respect to incidence, type and severity of AEs. No new safety signals were observed with longer follow-up. Consequently, as safety did not represent a key uncertainty in the original appraisal of TA579, and alongside the consistent safety profile, safety data were not updated in the economic model.

A.9 Key model assumptions and inputs

The updated economic model continued to use a partitioned survival approach including three health states, which the committee previously concluded was appropriate for decision making. The key model assumptions and inputs that have been changed in the base case of the economic model following the CDF data collection period are detailed in Table 6. All other parameters and assumptions remain unchanged from the economic model submitted to NICE during TA579.

Table 6: Key model assumptions and inputs

Model input and cross reference	Original parameter /assumption according to the Company FP NMA (TA579) (Table 24, TA579 Company Response to ERG Clarification Questions, Wave C, 18th December 2018, Page 44 [Page 298 of the TA579 Committee Papers])	Updated parameter /assumption	Source/Justification
Modelling of OS	OS estimates for ABE-FUL and all comparators were derived from the survival output of the original company FP NMA, as detailed in Section 7. The OS data incorporated in the FP NMA were based on the primary DCO (14th February 2017) of MONARCH 2 (TA579 Document B, Section B.2.6.2, Page 51).	OS estimates beyond the MONARCH 2 trial follow-up period have now been estimated and included, based on the survival output of the updated FP NMA, as described in Section 7. The updated FP NMA used an amended methodology and considered a restricted evidence network compared to the original company FP NMA. Additionally, the OS data incorporated in the FP NMA is based on a later DCO (20th June 2019), compared to the original appraisal, now including mature OS data, as detailed in Section A.6.1 and Table 10 (Appendix 1).	The updated DCO does not support application of a PH NMA, so the updated base case uses an FP NMA methodology. Based on criteria discussed in Section 7, first order FP NMA extrapolations of long-term OS outcomes have been chosen, with corrections for interaction with PFS. The use of the FP NMA is aligned with the committee's preferred assumptions from the original appraisal.
Modelling of PFS	PFS estimates for ABE-FUL and all comparators were derived from the survival output of the original company FP NMA, as detailed in Section 7. The PFS data incorporated in the original company FP NMA were based on the primary DCO (14th February 2017) of MONARCH 2 (TA579, Document B, Section B.2.6.1, Page 48).	PFS estimates for ABE-FUL and all comparators were estimated using the survival output of the updated company FP NMA, as detailed in Section 7. The updated FP NMA used an amended methodology and considered a restricted evidence network compared to the original company FP NMA (Section 7).	The updated DCO (20th June 2019) in MONARCH 2 does not support the application of a PH NMA, so the updated base case uses an FP NMA methodology Within the FP NMA methodology, based on the criteria discussed in Section 7, first order FP NMA extrapolations of long-term outcomes for PFS have been chosen, with corrections for interaction with OS.

		The PFS data incorporated in the FP NMA are based on a later DCO (20th June 2019) compared to the original appraisal, as detailed in Section A.6.1 and Table 11 (Appendix 1).	The use of the FP NMA is aligned with the committee's preferred assumptions from the original appraisal.
Duration of therapy and TTD	Duration of therapy and TTD for ABE-FUL and FUL were estimated by jointly fitting Weibull curves to the ToT discontinuation data from the ITT population in MONARCH 2	Duration of therapy and TTD for ABE-FUL and FUL were estimated by jointly fitting Weibull curves to the ToT discontinuation data from the post amendment population in MONARCH 2, resulting in increased costs and ICERs compared to the consideration of the ITT population. Alternative analyses using the ITT population of MONARCH 2 are presented for reference in Table 21 (Appendix 4).	The use of the post amendment population in MONARCH 2 is aligned with the committee's preferred assumption.
	For EXE-EVE and EXE, the duration of therapy was estimated based on published median duration of therapy estimates and median PFS estimates. The HR between the two was then applied to the modelled PFS extrapolations to estimate duration of therapy.	For EXE-EVE, the duration of therapy was estimated based on published median duration of therapy estimates and median PFS estimates. The HR between the two was then applied to the modelled PFS extrapolations to estimate duration of therapy.	Due to the extrapolation approach for PFS taken, Lilly believes it is most appropriate to relate the ToT to the difference in published median PFS and ToT so that modelled ToT attempts to replicate the difference in PFS and ToT from literature. Alternative approaches such as relating the modelled PFS to ToT without accounting for differences between PFS and ToT appears to overestimate cost for the ABE-FUL.
Post-progression utilities	The previous base case based on the original company FP NMA used a post progression utility decrement value derived from Lloyd et al. (2006).	The updated base case uses a utility value derived from Mitra et al. An alternative scenario analysis is provided using the post progression utility decrement value derived from MONARCH 2 in Table 22 (Appendix 4).	The exploration of utility values derived from Mitra et al. and MONARCH 2 is in line with the committee's preferred assumptions.
Subsequent therapy	The previous base case based on the original company FP NMA used the company's original assumptions for subsequent therapy, including the assumption that the proportion	The updated base case is fully aligned with the ERG's preferred changes to the modelling of subsequent treatments.	The use of the ERG's preferred changes is in line with the committee's preferred assumptions.

	of time spent on subsequent treatment during post-progression would be 37% of post-progression time.		
Resource use	The base case based on the original company FP NMA included the company's assumption for health state costs which were critiqued by ERG.	The updated base case uses the ERG's health state costs and the updated average costs per item. The updated model allows replication of both company and ERG health state costs with either updated average costs per item or original costs	The use of the ERG's preferred changes is in line with the committee's preferred assumptions.

Abbreviations: ABE: abemaciclib; DCO: data cut-off; ERG: Evidence Review Group; FP: fractional polynomial; FUL; fulvestrant; HR: hazard ratio; ITT: intention-to-treat; NMA; network meta-analysis; OS; overall survival; PBO: placebo; PFS: progression free survival; PH: proportional hazards; ToT: time on treatment; TTD: time to discontinuation.

A.10 Cost-effectiveness results (deterministic)

The updated economic analyses are presented in Table 7. The analyses using the original company FP NMA and the ERG FP NMA are presented in cost-effectiveness analyses 1a and 1b respectively. Cost-effectiveness analysis 2 presents an intermediate step considering the updated PFS and OS data from MONARCH 2 (as well as updated ToT data for the post amendment population) in the updated company FP NMA but using the company's original preferred cost and resource use assumptions. The revised base case for this appraisal, considering the updated company FP NMA and the ERG's preferred cost and resource assumptions is presented in cost-effectiveness analysis 3.

Taken together, the various analyses noted above therefore provide an iterative demonstration of the impact of model changes to reach the final revised base case for this appraisal (cost-effectiveness analysis 3). Additional intermediate analyses can be provided upon request.

A range of sensitivity and scenario analyses are provided in the below sections. Alternative analyses considering ToT data for the ITT population in MONARCH 2 are presented in Table 21 (Appendix 4), and an analysis using the post progression utility decrement from MONARCH 2 is presented in Table 22 (Appendix 4).

The parameters selected in the economic model for each of the analyses below are detailed in Table 23 (Appendix 5).

Table 7: Cost-effectiveness results (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs for ABE-FUL vs. each comparator (£)	Incremental LYG for ABE-FUL vs. each comparator	Incremental QALYs for ABE-FUL vs. each comparator	Incremental ICER (£/QALY) for ABE-FUL vs. comparator
Cost-effectiveness analysis 1a: Original company FP NMA (Table 24, TA579 Company Response to ERG Clarification Questions, Wave C, 18th December 2018, Page 44 [Page 298 of the TA579 Committee Papers])							
ABE-FUL	[redacted]	4.57	[redacted]	[redacted]	0	[redacted]	NA
EXE-EVE	[redacted]	2.34	[redacted]	[redacted]	2.23	[redacted]	£23,374
Cost-effectiveness analysis 1b: ERG FP NMA (Scenario 13, Table 55, TA579 ERG Report, Page 192 [Page 571 of the TA579 Committee Papers])							
ABE-FUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA
EXE-EVE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Cost-effectiveness analysis 2: Using the updated PFS and OS data from MONARCH 2 in the updated company FP NMA (as well as updated ToT data for the post amendment population) but the original company cost and resource use assumptions							

ABE-FUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA
EXE-EVE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,870
Cost-effectiveness analysis 3: Updated company base-case							
ABE-FUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA
EXE-EVE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,012

Abbreviations: ABE: abemaciclib; CDF: Cancer Drugs Fund; ERG: Evidence Review Group; EVE: everolimus; EXE: exemestane; FP: fractional polynomial; FUL: fulvestrant; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NA: not applicable; NMA: network meta-analysis; PH: proportional hazards; QALYs, quality-adjusted life years.

A.11 Probabilistic sensitivity analysis

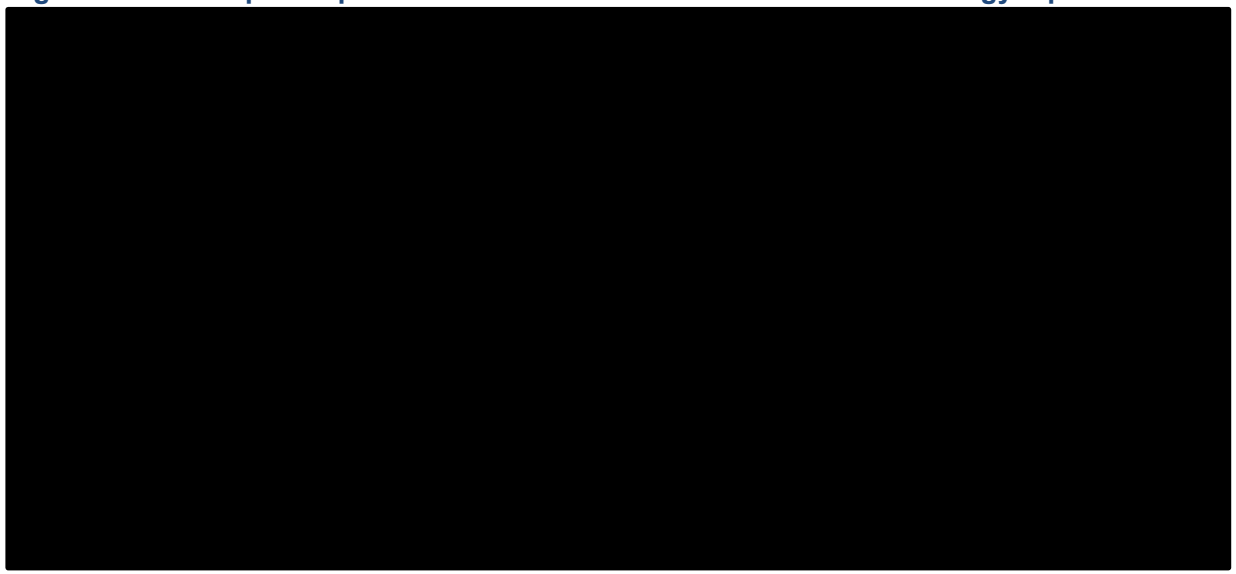
The updated probabilistic base case results evaluating the cost-effectiveness of ABE-FUL versus EXE-EVE are presented in Table 8. The accompanying scatterplot of probabilistic results is presented in Figure 13. The probabilistic sensitivity analyses have been conducted in line with the ERG critique of original methodology, as reported in TA579 Document B, Section B.3.8 (Page 156).

Table 8: Updated base-case results (probabilistic) – in line with the methodology reported in TA579 Document B, Section B.3.8 (Page 156)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
ABE-FUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA
EXE-EVE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,932

Abbreviations: ABE: abemaciclib; ERG: Evidence Review Group; EVE: everolimus; EXE: exemestane; FP: fractional polynomial; FUL: fulvestrant; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NA: not applicable; NMA: network meta-analysis; PH: proportional hazards; QALYs, quality-adjusted life years.

Figure 13: Scatterplot of probabilistic results – in line with the methodology reported in TA579 Document B, Section B.3.8 (page 158)



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

A.12 Key sensitivity and scenario analyses

Sensitivity analyses

Deterministic sensitivity analyses can be provided upon request.

Scenario analyses

Table 9 presents a number of key scenario analyses, using alternative parameters, in order to investigate key areas of uncertainty around the base case cost-effectiveness results. Additional scenario analyses are available within the economic model, and upon request.

Table 9: Key scenario analyses

Scenario and cross reference	Scenario detail	Brief rationale	ICER for ABE-FUL vs EXE-EVE
Base case	NA		£24,012

Fulvestrant Cost Discounts			
Fulvestrant 50% discount	A 50% discount is applied to the drug acquisition cost of FUL, meaning that FUL has a price of £261.21 per 28-day cycle.	The loss of exclusivity for fulvestrant is anticipated to occur at a similar time to the anticipated date for routine commissioning of ABE-FUL. Therefore, while the base case analysis considers the list price of FUL, it is reasonable to suggest that the loss of exclusivity will result in a reduced FUL price, which could plausibly result in increased cost-effectiveness for ABE-FUL in comparison to EXE-EVE.	£11,946
Fulvestrant 80% discount	An 80% discount is applied to the drug acquisition cost of FUL, meaning that FUL has a price of £104.48 per 28-day cycle.		£4,707
Alternative networks			
OS	This scenario uses the first order RE model with $p_1 = -1.0$ as an alternative for the long-term extrapolation of OS.	In order to explore the uncertainty around the best fitting extrapolations, scenarios have been conducted using alternative extrapolations for PFS, OS and both.	£25,009
PFS	This scenario uses the first order RE model with $p_1 = -0.5$ as an alternative for the long-term extrapolation of PFS.		£22,999
OS and PFS	This scenario combines the two alternative extrapolations for PFS and OS described above.		£22,903
Utility Values			
MONARCH 2 utility values	This scenario explores the use of a post progression utility decrement value derived from MONARCH 2	As part of the original appraisal, the company noted that the utility value from MONARCH 2 or the value derived from Mitra et al. were methodologically preferable. In line with the committee's preferred assumptions, a scenario analysis using the utility value from MONARCH 2 has been provided alongside the base case analysis using the value from Mitra et al.	£23,727

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; ICER: incremental cost-effectiveness ratio; NA: not applicable; PFS: progression-free survival; OS: overall survival.

A.13 Key issues and conclusions based on the data collected during the CDF review period

The updated DCO (20th June 2019) of MONARCH 2 represents the key data collected during the CDF review period, informing the update to the economic model. At the time of the updated DCO, ABE-FUL was associated with a statistically significant and clinically meaningful improvement in OS compared to PBO-FUL (HR: 0.757; 95% CI: 0.606, 0.945; 2-sided p = 0.0137). ABE-FUL resulted in a median OS improvement of 9.47 months, with a median OS of 46.7 months in the ABE-FUL and 37.3 months in the PBO-FUL arm (median follow-up time of 47.7 months). The mature OS data continued to demonstrate the anticipated trend presented during the original submission, reducing the uncertainty around the long-term extrapolation of OS.

The updated DCO also demonstrated a consistent PFS improvement (HR: 0.536) compared with the primary analysis (HR: 0.553). ABE-FUL showed statistically significant improvements for PFS2, time to chemotherapy and CFS in comparison to PBO-FUL, with a safety profile that was consistent with the primary analysis.

The SACT cohort provides further data on ABE-FUL. Lilly believes that the findings of the SACT cohort are consistent with the results observed in MONARCH 2 in terms of supporting that ABE-FUL can offer improved survival for patients versus current treatment options, although consideration of a frailer, older, early-use patient population and the absence of a control group or data on treatment adherence mean that there are limitations with any further interpretation. Lilly believes appropriate weight should be given to the RCT evidence from MONARCH 2 relative to the SACT real-world data from an early use setting.

In line with the original appraisal, the updated DCO in MONARCH 2 did not support the application of a PH NMA. Consequently, the updated OS and PFS data were incorporated into an updated FP NMA. First order NMA extrapolations for OS and PFS were chosen as the best fitting models that were also reasonably clinical plausible. All of the best fitting models continued to result in overfitting of PFS data, although the final extrapolations of the FP NMA are substantially more clinically plausible in comparison to the original FP NMA. As a result of this and the increased follow-up of the OS and PFS data from MONARCH 2, the FP NMA is able to substantially reduce the uncertainty surrounding the long-term extrapolation of the clinical outcomes of MONARCH 2 in comparison to the original appraisal.

The results of the updated economic analysis found that greater LY and QALY gains were observed for ABE-FUL ([redacted] and [redacted]) compared to EXE-EVE ([redacted] and [redacted]), indicating that ABE-FUL provides greater clinical benefit for women with HR+, HER2− locally advanced or metastatic breast cancer who have received prior endocrine therapy compared with EXE-EVE. The extended follow-up and maturity of the OS data means that the uncertainty around the long-term clinical benefit of ABE-FUL is substantially reduced compared to the previous economic analysis.

The model estimates that ABE-FUL at the with-PAS price is associated with a higher total cost (£[redacted]) compared to EXE-EVE at list price (£[redacted]), when considering the clinical data described above and the ERG's preferred assumptions for cost and resource use. The incremental cost of ABE-FUL was predominantly driven by increased costs for subsequent, third-line treatments and the administration cost for ABE-FUL vs EXE-EVE. The anticipated loss of exclusivity for FUL at a similar time as the anticipated date for routine commissioning of ABE-FUL is expected to result in a reduced FUL price, which could plausibly reduce the total costs associated with ABE-FUL.

Based on the price of ABE with the proposed PAS, the base case analysis produced a pairwise ICER for ABE-FUL of £24,012 per QALY gained compared to EXE-EVE, indicating that ABE-FUL represents a cost effective treatment option at a threshold of £30,000 per QALY.

References

1. European Medicines Agency (EMA). Verzenios. Available at https://www.ema.europa.eu/en/medicines/human/EPAR/verzenios. [Accessed 14 April 2020], 2020.
2. Sledge GW, Jr., Toi M, Neven P, et al. MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. J Clin Oncol 2017;35:2875-2884.
3. Sledge GW, Jr, Toi M, Neven P, et al. The Effect of Abemaciclib Plus Fulvestrant on Overall Survival in Hormone Receptor–Positive, ERBB2-Negative Breast Cancer That Progressed on Endocrine Therapy—MONARCH 2: A Randomized Clinical Trial. JAMA Oncology 2020;6:116-124.
4. Public Health England (PHE). Abemaciclib with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer after endocrine therapy – data review. , 2020.
5. Rassen JA, Schneeweiss S. Newly marketed medications present unique challenges for nonrandomized comparative effectiveness analyses. Journal of Comparative Effectiveness Research 2012;1:109-111.
6. Schneeweiss S, Gagne JJ, Glynn RJ, et al. Assessing the comparative effectiveness of newly marketed medications: methodological challenges and implications for drug development. Clin Pharmacol Ther 2011;90:777-90.
7. Petri H, Urquhart J. Channeling bias in the interpretation of drug effects. Stat Med 1991;10:577-81.
8. Eichler HG, Abadie E, Breckenridge A, et al. Bridging the efficacy-effectiveness gap: a regulator's perspective on addressing variability of drug response. Nat Rev Drug Discov 2011;10:495-506.
9. Carter GC, Sheffield KM, Gossai A, et al. Abstract P2-08-12: Initial real world treatment patterns and outcomes of Abemaciclib for the treatment of HR+, HER2-metastatic breast cancer: AACR, 2020.
10. Eli Lilly Data on File. Clinical Study Report [MONARCH 2]. 2017.
11. Duke Margolis. White Paper. Adding Real-World Evidence to a Totality of EVidence Approach for Evaluating Marketed Product Effectiveness, 2019.
12. Jansen JP. Network meta-analysis of survival data with fractional polynomials. BMC Medical Research Methodology 2011;11:61.
13. Eli Lilly Data on File. Clinical Study Report [MONARCH 2]: Interim Overall Survival Analysis, 2019.

Appendix 1: Updated data collection results (MONARCH 2)

OS

A full summary of OS by investigator assessment is presented in Table 10.

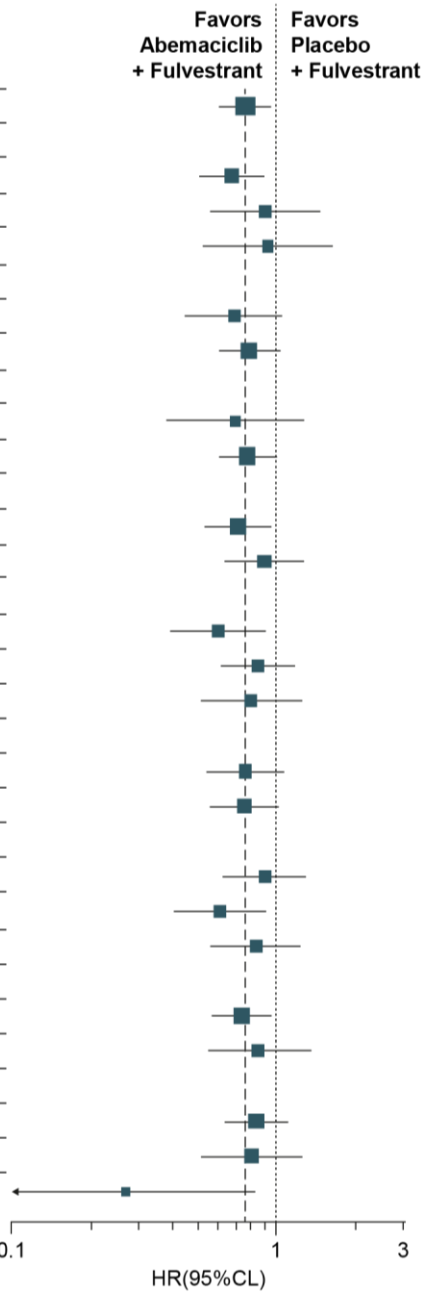
Table 10: OS for ABE-FUL vs PBO-FUL at the OS interim analysis (DCO 20th June 2019), ITT population

	ABE-FUL (n = 446)	PBO-FUL (n = 223)	Treatment Effect/Difference/ p-value[c]
Number of deaths, n (%)	211 (47.3)	127 (57.0)	[redacted]
Number of patients censored, n (%)	[redacted]	[redacted]	[redacted]
Alive	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]
Withdrawal by patient	[redacted]	[redacted]	[redacted]
Median (95% CI)	46.72 [redacted]	37.25 [redacted]	9.47
p-value (2-sided) – log rank test stratified[a]	[redacted]	[redacted]	0.0137
Hazard ratio (95% CI) – stratified[a]	[redacted]	[redacted]	0.757 (0.606, 0.945)
Survival rate, % (95% CI)			
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]
48 months	[redacted]	[redacted]	[redacted]

Quartiles and OS rates were estimated using the Kaplan-Meier method. Corresponding 95% CIs were estimated using the methods of Brookmeyer and Crawley (1982) and Greenwood (1926) respectively;
[a] P values and hazard ratios stratified by IWRS sensitivity to endocrine therapy and IWRS nature of disease. [b] 95% Cis and 2-sided p values for the difference between rates were calculated based on normal approximation. [c] Treatment effect/difference/p-values are computed based on comparator placebo.
Abbreviations: ABE: abemaciclib; CI: confidence interval; DCO; data cut-off; FUL: fulvestrant; ITT: intention-to-treat; IWRS: interactive web response system; NA: not applicable; OS: overall survival; PBO: placebo.
Source: Sledge et al., 2020[3]; Lilly Data on File (JPBL Clinical Study Report Addendum for the Interim Overall Survival Analysis) 2020[13]

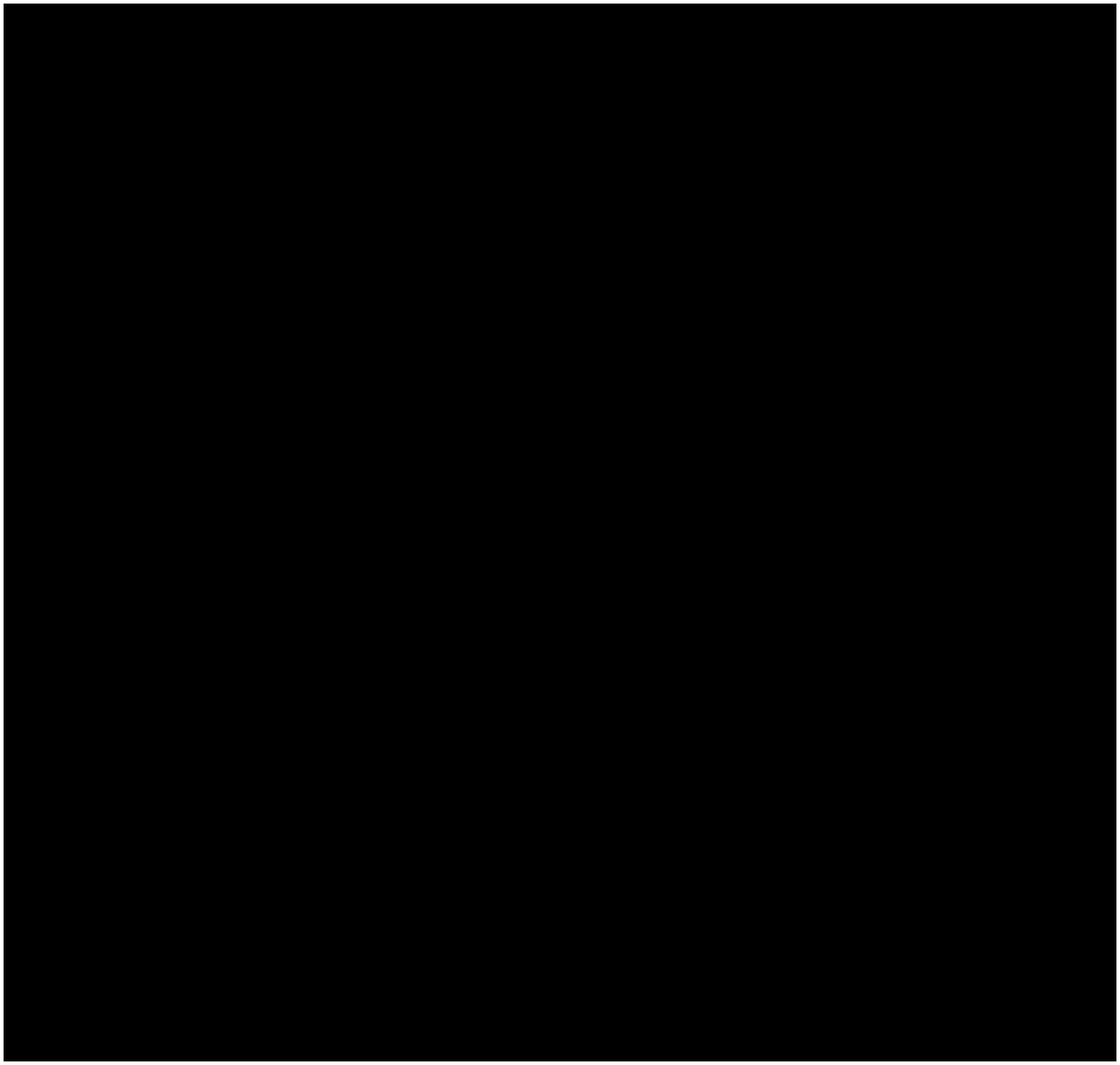
Figure 14: Forest plot of OS by pre-specified subgroups in MONARCH 2 (ITT population)

Subgroup	No. of Patients	No. of Events	HR (95%CL)
Overall	669	338	0.757 (0.606-0.945)
Nature of disease			
Visceral	373	210	0.675 (0.511-0.891)
Bone only	180	76	0.907 (0.564-1.457)
Other	113	52	0.928 (0.528-1.632)
ET resistance			
Primary resistance	172	94	0.686 (0.451-1.043)
Secondary resistance	488	241	0.787 (0.606-1.021)
Menopausal status			
Premenopausal or perimenopausal	114	44	0.689 (0.379-1.252)
Postmenopausal	551	293	0.773 (0.609-0.980)
Age group, years			
<65	424	200	0.710 (0.532-0.948)
≥65	245	138	0.898 (0.638-1.263)
Geographical region			
North America	178	96	0.596 (0.393-0.901)
Europe	279	153	0.848 (0.613-1.173)
Asia	212	89	0.798 (0.515-1.235)
ECOG PS			
1	264	152	0.757 (0.544-1.053)
0	400	184	0.750 (0.557-1.010)
Organs involved, No.			
≥3	203	126	0.900 (0.628-1.289)
2	200	101	0.609 (0.409-0.906)
1	263	111	0.832 (0.562-1.231)
Measurable disease			
Yes	483	255	0.734 (0.569-0.945)
No	183	83	0.853 (0.545-1.336)
Race			
White	373	214	0.834 (0.633-1.098)
Asian	214	90	0.802 (0.518-1.239)
Other	42	12	0.264 (0.085-0.818)



Note: OS HRs and 95% Cis are indicated by diamonds and the crossing horizontal lines, respectively. HRs for overall and within subgroups are unstratified; subgroup HRs are estimated with the adjustment of arm*subgroup interaction. The factor levels that consisted of less than 5% of randomised patients were omitted from the analysis.
Abbreviations: CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; ITT: intention-to-treat; OS: overall survival; PS: performance status.
Source: Adapted from Sledge et al. (2020)[3]

Figure 15: Forest plot of OS by additional subgroups of interest in MONARCH 2 (ITT population)



Note: OS HRs and 95% CIs are indicated by diamonds and the crossing horizontal lines, respectively. HRs for overall and within subgroups are unstratified; subgroup HRs are estimated with the adjustment of arm*subgroup interaction. The factor levels that consisted of less than 5% of randomised patients were omitted from the analysis.
Abbreviations: CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; ITT: intention-to-treat; OS: overall survival; PS: performance status.
Source: Lilly Data on File (JPBL Clinical Study Report Addendum for the Interim Overall Survival Analysis) 2020[13]

PFS

A full summary of PFS by investigator assessment is presented in Table 10.

Table 11: PFS for ABE-FUL vs PBO-FUL at the OS interim analysis (DCO 20th June 2019), ITT population

	ABE-FUL (n = 446)	PBO-FUL (n = 223)	Treatment Effect/Difference/p-value[c]
Number of events, n (%)	297 [redacted]	193 [redacted]	[redacted]
Death without PD	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]
Median (95% CI)	16.87 [redacted]	9.27 [redacted]	[redacted]
p-value (2-sided) – log rank test stratified[a]	[redacted]	[redacted]	[redacted]
Hazard ratio (95% CI) – stratified[a]			0.536 (0.445, 0.645)
Survival rate, % (95% CI)[b]			
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
36 months	29.9 [redacted]	10.1 [redacted]	[redacted]

Quartiles and OS rates were estimated using the Kaplan-Meier method. Corresponding 95% Cis were estimated using the methods of Brookmeyer and Crawley (1982) and Greenwood (1926) respectively;
[a] P values and hazard ratios stratified by IWRS sensitivity to endocrine therapy and IWRS nature of disease. [b] 95% CIs and 2-sided p values for the difference between rates were calculated based on normal approximation. [c] Treatment effect/difference/p-values are computed based on comparator placebo.
Abbreviations: ABE: abemaciclib; CI: confidence interval; DCO: data cut-off; FUL: fulvestrant; ITT: intention-to-treat; IWRS: interactive web response system; OS: overall survival; PBO; placebo; PD: progressed disease; PFS; progression free survival.
Source: Sledge et al., 2020[3]; Lilly Data on File (JPBL Clinical Study Report Addendum for the Interim Overall Survival Analysis) 2020[13]

Extent of exposure (ITT population)

A summary of the drug exposure to ABE or PBO for patients in MONARCH 2 (ITT population) is presented in Table 12.

Table 12: Summary of drug exposure for ABE or PBO at the OS interim analysis (DCO 20th June 2019) (ITT population)

Number of Patients	ABE (n = 441)	PBO (n = 223)
Number of patients who received abemaciclib or placebo, n (%)[a]	[redacted]	[redacted]
Cycles received per patient[b]		
Median	[redacted]	[redacted]
Q1-Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]

Duration of therapy (weeks)		
Median	[redacted]	[redacted]
Q1-Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Cumulative dose (mg)		
Median	[redacted]	[redacted]
Q1-Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]

Footnotes: [a] Number of patients who received at least 1 dose of abemaciclib or placebo, either partial or complete. [b] Patient was considered to have received a treatment cycle after receiving at least 1 dose of abemaciclib or placebo, either partial or complete.
Abbreviations: ABE: abemaciclib; ITT: intention-to-treat; Max: maximum; min: minimum; N: number of patients in the safety population; n: number of patients in the specified category; Q1-Q3: interquartile range; SD: standard deviation.
Source: Lilly Data on File (JPBL Clinical Study Report Addendum for the Interim Overall Survival Analysis) 2020[13]

Extent of exposure (post-amendment population)

A summary of the drug exposure to ABE or PBO for patients in MONARCH 2 (ITT population) is presented in Table 13.

Table 13: Drug exposure for ABE or PBO at the OS interim analysis (DCO 20th June 2019 (post-amendment population)

Number of Patients	ABE (n = 320)	PBO (n = 166)
Number of patients who received abemaciclib or placebo, n (%)[a]	[redacted]	[redacted]
Cycles received per patient[b]		
Median	[redacted]	[redacted]
Q1-Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Duration of therapy (weeks)		
Median	[redacted]	[redacted]
Q1-Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Cumulative dose (mg)		
Median	[redacted]	[redacted]
Q1-Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]

Footnotes: [a] Number of patients who received at least 1 dose of abemaciclib or placebo, either partial or complete. [b] Patient was considered to have received a treatment cycle after receiving at least 1 dose of abemaciclib or placebo, either partial or complete.

Abbreviations: ABE: abemaciclib; ITT: intention-to-treat; Max: maximum; min: minimum; N: number of patients in the safety population; n: number of patients in the specified category; Q1-Q3: interquartile range; SD: standard deviation.
Source: Lilly Data on File

Appendix 2: Updated data collection results (SACT dataset)

Baseline characteristics

Baseline characteristics of patients in the SACT cohort are presented in Table 14.

Table 14: Baseline characteristics of patients receiving abemaciclib with fulvestrant

Characteristics	Patients receiving abemaciclib with fulvestrant (n = 876)
Gender	
Female, n (%)	865 (99)
Age	
<40, n (%)	21 (2)
40–49, n (%)	92 (11)
50–59, n (%)	208 (24)
60–69, n (%)	235 (27)
70–79, n (%)	248 (28)
≥80, n (%)	72 (8)
Median age (overall), years	65
Median age (women)	64
Median age (men)	68
Performance status	
0	273 (31)
1	416 (47)
2	66 (8)
3	4 (<1)
4	1 (<1)
Missing	116 (13)
Previous endocrine therapy, n (%)	876 (100)
Progressive disease whilst still receiving adjuvant or neoadjuvant endocrine therapy for early breast cancer with no subsequent endocrine therapy received following disease progression	302 (34%)
Has progressive disease within 12 or less months of completing adjuvant endocrine therapy for early breast cancer with no subsequent endocrine therapy received following disease progression	32 (4)
Has progressive disease on first line endocrine therapy for advanced/metastatic breast cancer with no subsequent endocrine therapy received following disease progression	542 (62)

Source: Public Health England SACT Data Review[4]

Treatment duration

Treatment status and treatment outcomes for patients that received ABE-FUL in the SACT cohort are presented in Table 15 and Table 16 respectively.

Table 15: Treatment status of all patients that received ABE-FUL

Patient status	Patients receiving abemaciclib with fulvestrant (n = 876)
Patient died (not on treatment), n (%)	142 (16)
Patient died (on treatment), n (%)	26 (3)
Treatment stopped, n (%)	130 (15)
Treatment ongoing, n (%)	578 (66)

Source: Public Health England SACT Data Review[4]

Table 16: Treatment outcomes for patients that have ended treatment

Patient status	Patients receiving abemaciclib with fulvestrant (n = 298)
Stopped treatment	298 (100)
Progression of disease	105 (35)
Acute chemotherapy toxicity	63 (21)
Patient choice	19 (6)
Died not on treatment	61 (20)
Died on treatment	26 (9)
No treatment in at least three months	24 (8)

Source: Public Health England SACT Data Review[4]

Overall survival

Table 17 and Table 18 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 13.5 months (410 days). All patients were traced on 22 May 2020.

Table 17: Number of SACT patients at risk, by quarterly breakpoints

Time intervals, months	0-15	3-15	6-15	9-15	12-15
Number at risk	876	825	711	381	86

Source: Public Health England SACT Data Review[4]

Table 18 shows that, out of all patients in the SACT dataset who received treatment, 708 were still alive (censored) at the date of follow-up and 168 had died (events).

Table 18: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints

Time intervals, months	0-15	3-15	6-15	9-15	12-15
Censored, n	708	707	647	362	83

Events, n	168	118	64	19	3

Source: Public Health England SACT Data Review[4]

Appendix 3: NMA results

OS

Table 19 presents fitting statistics for the OS FP NMA extrapolations of the updated company FP NMA, as described in Section A.7.1

Table 19: FP NMA OS DIC results

P1	P2	Fixed Effects			Random Effects		
		Dbar	pD	DIC	Dbar	pD	DIC
0	0	[redacted]					
0	0.5	[redacted]					
0	1	[redacted]					
0	2	[redacted]					
0	3	[redacted]					
0.5	0.5	[redacted]					
0.5	1	[redacted]					
0.5	2	[redacted]					
0.5	3	[redacted]					
-0.5	0	[redacted]					
-0.5	0.5	[redacted]					
-0.5	-0.5	[redacted]					
-0.5	1	[redacted]					
-0.5	2	[redacted]					
-0.5	3	[redacted]					
1	1	[redacted]					
1	2	[redacted]					
1	3	[redacted]					
-1	0	[redacted]					
-1	0.5	[redacted]					

P1	P2	Fixed Effects			Random Effects		
		Dbar	pD	DIC	Dbar	pD	DIC
-1	-0.5	[redacted]					
-1	1	[redacted]					
-1	-1	[redacted]					
-1	2	[redacted]					
-1	3	[redacted]					
2	2	[redacted]					
2	3	[redacted]					
-2	0	[redacted]					
-2	0.5	[redacted]					
-2	-0.5	[redacted]					
-2	1	[redacted]					
-2	-1	[redacted]					
-2	2	[redacted]					
-2	-2	[redacted]					
-2	3	[redacted]					
3	3	[redacted]					
0		[redacted]					
0.5		[redacted]					
-0.5		[redacted]					
1		[redacted]					
-1		[redacted]					
2		[redacted]					
-2		[redacted]					
3		[redacted]					

Abbreviations: Dbar: posterior mean of the differences; DIC: deviance information criterion; FP: fractional polynomial; NA: not applicable; OS: overall survival; pD: posterior mean of the deviance minus the deviance of the posterior means.

PFS

Table 20 presents fitting statistics for the PFS FP NMA extrapolations for the updated company FP NMA, as described in Section A.7.1

Table 20: FP NMA PFS DIC results

P1	P2	Fixed Effects			Random Effects		
		Dbar	pD	DIC	Dbar	pD	DIC
0	0	[redacted]					
0	0.5	[redacted]					
0	1	[redacted]					
0	2	[redacted]					
0	3	[redacted]					
0.5	0.5	[redacted]					
0.5	1	[redacted]					
0.5	2	[redacted]					
0.5	3	[redacted]					
-0.5	0	[redacted]					
-0.5	0.5	[redacted]					
-0.5	-0.5	[redacted]					
-0.5	1	[redacted]					
-0.5	2	[redacted]					
-0.5	3	[redacted]					
1	1	[redacted]					
1	2	[redacted]					
1	3	[redacted]					
-1	0	[redacted]					
-1	0.5	[redacted]					
-1	-0.5	[redacted]					
-1	1	[redacted]					
-1	-1	[redacted]					

P1	P2	Fixed Effects			Random Effects		
		Dbar	pD	DIC	Dbar	pD	DIC
-1	2	[redacted]					
-1	3	[redacted]					
2	2	[redacted]					
2	3	[redacted]					
-2	0	[redacted]					
-2	0.5	[redacted]					
-2	-0.5	[redacted]					
-2	1	[redacted]					
-2	-1	[redacted]					
-2	2	[redacted]					
-2	-2	[redacted]					
-2	3	[redacted]					
3	3	[redacted]					
0		[redacted]					
0.5		[redacted]					
-0.5		[redacted]					
1		[redacted]					
-1		[redacted]					
2		[redacted]					
-2		[redacted]					
3		[redacted]					

Abbreviations: Dbar: posterior mean of the differences; DIC: deviance information criterion; FP: fractional polynomial; NA: not applicable; pD: posterior mean of the deviance minus the deviance of the posterior means; PFS: progression-free survival.

Appendix 4: Additional cost-effectiveness results

Cost-effectiveness analyses using updated ToT data for the ITT population in MONARCH 2

Table 21: Cost-effectiveness results (deterministic) – MONARCH 2 ITT population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs for ABE-FUL vs. each comparator (£)	Incremental LYG for ABE-FUL vs. each comparator	Incremental QALYs for ABE-FUL vs. each comparator	Incremental ICER (£/QALY) for ABE-FUL vs. comparator
Updated company FP NMA (TA579), using the updated clinical data from MONARCH 2 (including ToT data for the ITT population) but the original company cost and resource use assumptions (MONARCH 2 ITT population)							
ABE-FUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA
EXE-EVE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Updated company base-case (MONARCH 2 ITT population)							
ABE-FUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA
EXE-EVE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,356

Note: As detailed in the original appraisal (TA579 Document B, Section B.3.5.2, Page 134) the rate of hospitalisation is assumed to be the same for EXE-EVE as ABE-FUL, and is based on data from MONARCH 2. Consequently, switching between the ITT and post-amendment populations in MONARCH 2 also results in minor changes to the total costs for EXE-EVE.
Abbreviations: ABE: abemaciclib; CDF: Cancer Drugs Fund; ERG: Evidence Review Group; EVE: everolimus; EXE: exemestane; FP: fractional polynomial; FUL: fulvestrant; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NA: not applicable; NMA: network meta-analysis; PH: proportional hazards; QALYs, quality-adjusted life years.

Cost-effectiveness analyses using the post progression utility value decrement from MONARCH 2

Table 22: Cost-effectiveness results (deterministic) – using the post progression utility value decrement from MONARCH 2

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs for ABE-FUL vs. each comparator (£)	Incremental LYG for ABE-FUL vs. each comparator	Incremental QALYs for ABE-FUL vs. each comparator	Incremental ICER (£/QALY) for ABE-FUL vs. comparator
Cost effectiveness analysis using the same settings as the updated company base case (cost effectiveness analysis 3 in Table 7 above), but using the post progression utility value decrement from MONARCH 2							
ABE-FUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA
EXE-EVE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,727

Abbreviations: ABE: abemaciclib; CDF: Cancer Drugs Fund; ERG: Evidence Review Group; EVE: everolimus; EXE: exemestane; FP: fractional polynomial; FUL: fulvestrant; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NA: not applicable; NMA: network meta-analysis; PH: proportional hazards; QALYs, quality-adjusted life years.

Appendix 5: Settings to replicate previous economic analyses

Table 23: Settings in the economic model to replicate the economic analyses described in Section A.10

	Cost-effectiveness analysis			
Parameter in the economic model	**1a: Original company FP NMA**	**1b: ERG FP NMA**	**2: Updated company FP NMA using updated PFS and OS, but original company cost and resource assumptions**	**3: Updated company base case**
Overview_2020				
Use FP NMA	Yes	Yes	Yes	Yes
Use 2020 NMA	No	No	Yes	Yes
2020 – OS Network	NA	NA	Overall survival – NICE network	Overall survival – NICE network
2020 – PFS Network	NA	NA	Progression free survival – NICE network	Progression free survival – NICE network
Selected costs	Original	Original	Original	Updated
ToT: Use 2020 data	No	No	Yes	Yes
ToT: Selected approach – MONARCH 2	NA	NA	Calibration (modelled PFS to trial ToT)	Calibration (modelled PFS to trial ToT)
MONARCH 2 trial data: Use 2020 data	No	No	No	No
MONARCH 2 trial data: interval censored adjustment	NA	NA	NA	NA
MONARCH 2 trial data: curve for PFS	NA	NA	NA	NA
MONARCH 2 trial data: curve for OS	NA	NA	NA	NA
Proportion of PPS on treatment	37%	37%	37%	37%
CAP administrations and dose	False	True	False	True
FUL loading dose admin correction from £43 to £172	False	True	False	True
Post-progression treatment distributions	False	True	False	True
ABE discount	[redacted]	[redacted]	[redacted]	[redacted]
EVE discount	0%	0%	0%	0%
FUL discount	0%	0%	0%	0%

	Cost-effectiveness analysis			
Parameter in the economic model	**1a: Original company FP NMA**	**1b: ERG FP NMA**	**2: Updated company FP NMA using updated PFS and OS, but original company cost and resource assumptions**	**3: Updated company base case**
ERG's analysis (2)				
PPS utility from MONARCH 2	False	False	False	False
PPS utility from Mitra 2016	False	True	False	True
Remove AE-related disutilities	False	True	False	False
Age-related utility decrements	False	True	False	False
Post-progression treatment distributions	False	True	False	True
Capping the time patients could spend on FUL and EXE-EVE as subsequent treatments	False	True	False	True
Post-progression treatment in PPS from 37% up to 3 months before death	False	True	False	True
TA496 health state costs	False	True	False	True
TA496 FUL administration costs (loading dose and subsequent)	False	True	False	False
ABE starting dose (34 days for 27.5% of patients)	False	False	False	False
TMX dose (40 mg to 20 mg)	False	False	False	False
Removing non-AE-related hospitalisation costs	False	True	False	False
CAP administrations and dose	False	True	False	True
FUL loading dose admin correction from £43 to £172	False	True	False	True
FUL loading dose acquisition cost from £130 to £522	False	True	False	True

	Cost-effectiveness analysis			
Parameter in the economic model	**1a: Original company FP NMA**	**1b: ERG FP NMA**	**2: Updated company FP NMA using updated PFS and OS, but original company cost and resource assumptions**	**3: Updated company base case**
ERG's analysis				
Use FP NMA PFS	No	Yes	No	No
Alternative OS	No	No	No	No
Base case OS	No	Yes	No	No
Remove half-cycle correction	No	Yes	No	No
Dashboard				
Population (MONARCH 2)	ITT	ITT	Subgroup 150 mg starting dose ABE	Subgroup 150 mg starting dose ABE
PFS = min (PFS, OS)	On	On	On	On
Source of post-progression utility decrement	Lloyd 2006	Lloyd 2006	Lloyd 2006	Mitra

Abbreviations: ABE: abemaciclib; AE: adverse event; CAP: capecitabine; ERG: Evidence Review Group; EVE: everolimus; EXE; exemestane; FUL: fulvestrant; ITT: intention-to-treat; NMA: network meta-analysis; OS: overall survival; PFS: progression free survival; TMX: tamoxifen

Appendix 6: Data collection agreement

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund – Data Collection Arrangement

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

Company name: Eli Lilly and Company Limited

Primary source of data collection: Ongoing clinical study, MONARCH 2

Secondary source of data collection: Public Health England routine population-wide cancer data sets, including Systemic Anti-Cancer Therapy data set

NICE Agreement Manager	Carla Deakin
NHS England Agreement Manager	Peter Clark
Public Health England Agreement Manager	Rebecca Smittenaar
Eli Lilly and Company Limited Agreement Manager	[redacted]

1 Purpose of data collection arrangement

The purpose of the agreement is to describe the arrangements and responsibilities for further data collection for abemaciclib with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer after endocrine therapy (ID1339) (TA579). A positive recommendation within the context of a managed access agreement has been decided by the appraisal committee.

2 Commencement and period of agreement

This data collection arrangement shall take effect on publication of the managed access agreement. The data collection period is anticipated to conclude in

December 2021 (see section 5.1). The process for exiting the Cancer Drugs Fund will begin at this point and the review of the NICE guidance will start.

As part of the managed access agreement, the technology will continue to be available through the Cancer Drugs Fund after the data collection period has ended and while the guidance is being reviewed. This assumes that the data collection period ends as planned and the review of guidance follows the standard timelines described in the addendum to NICE's methods and processes when appraising cancer technologies.

3 Patient eligibility

Abemaciclib with fulvestrant is recommended for use within the Cancer Drugs Fund as an option for treating locally advanced or metastatic, hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer in people who have had endocrine therapy if they might otherwise be considered for exemestane plus everolimus

Key patient eligibility criteria for the use of abemaciclib in the Cancer Drugs Fund include:

- Application for abemaciclib in combination with fulvestrant is made by and the first cycle of abemaciclib plus fulvestrant will be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy.
- Patient has histologically or cytologically documented oestrogen receptor positive and HER-2 negative breast cancer.
- Patient has metastatic breast cancer or locally advanced breast cancer which is not amenable to curative treatment
- Patient is male or is female and if female is either post-menopausal or if pre- or peri-menopausal has undergone ovarian ablation or suppression with LHRH agonist treatment

- Patient has an ECOG performance status of 0 or 1 or 2.
- Patient has received previous therapy according to one of the three populations as set out below as these are the only groups for which there was evidence submitted to NICE for the use of abemaciclib plus fulvestrant.
    - has progressive disease whilst still receiving adjuvant or neoadjuvant endocrine therapy for early breast cancer with no subsequent endocrine therapy received following disease progression or
    - has progressive disease within 12 or less months of completing adjuvant endocrine therapy for early breast cancer with no subsequent endocrine therapy received following disease progression or
    - has progressive disease on 1st line therapy for advanced/metastatic breast cancer with no subsequent endocrine therapy received following disease progression.
- Patient has had no prior treatment with a CDK 4/6 inhibitor unless either abemaciclib has been received as part of any compassionate use scheme for the combination of abemaciclib plus fulvestrant and the patient meets all the other criteria set out here
- Patient has had no prior treatment with fulvestrant
- Patient has had no prior treatment with everolimus
- Abemaciclib will only be given in combination with a fulvestrant.
- Treatment will continue until there is progressive disease or excessive toxicity or until the patient chooses to discontinue treatment, whichever is the sooner
- Treatment breaks of up to 6 weeks are allowed, but solely to allow toxicities to settle

- Abemaciclib and fulvestrant will be otherwise used as set out in its Summary of Product Characteristics (SPC)

[redacted]

The estimated patient numbers per year are shown in the table below. These are the estimated patient numbers expected to be treated within the Cancer Drugs Fund during the managed access arrangement period. These estimates include assumptions of uptake and market share.

Table 1: Number of people in England expected to start treatment of abemaciclib with fulvestrant

	Company estimate (NHS Year)
Year 1	[redacted]
Year 2	[redacted]
Year 3	[redacted]

Mean time on treatment is [redacted] months (modelled). Median time on treatment is [redacted] months (modelled). Duration of therapy from the study was [redacted] months. Overall survival estimates (using economic model) were mean [redacted] months and median [redacted] months (Company submission table 67, page 168).

4 Area(s) of clinical uncertainty

The key clinical uncertainties identified by the appraisal committee are:

- Immaturity of the survival data from MONARCH 2: The committee considered that the survival data were immature impacted on the uncertainty of the survival extrapolations in the economic model. The committee were aware of the ongoing clinical trial (MONARCH 2) and

considered that further data cut might provide greater clarity in this long term outcome.

Estimate of time-on-treatment: The committee agreed that the time to treatment discontinuation was uncertain. The committee considered that more data might be collected on time on treatment

5 Source(s) of data collection

Phase III trial: MONARCH 2

It is anticipated that the clinical uncertainty concerning the immaturity of the survival data from MONARCH 2 will be addressed through the publication of OS data from the phase III clinical trial (MONARCH 2).

[redacted].

Other data

NHS England's Blueteq database captures the CDF population. NHS England shares Blueteq data with Public Health England for the CDF evaluation purposes. That sharing is governed by a data sharing agreement between NHS England and Public Health England.

Public Health England identifies, collects, collates, quality-assures and analyses large population-level datasets for specific diseases and conditions, including cancer. These datasets include the Systemic Anti-cancer Therapy (SACT) dataset, which is a mandated dataset as part of the Health and Social Care Information Standards. Public Health England will use the routinely-captured data collected during the period of the data collection arrangement to provide analyses as defined in sections 6.2 and 7.2.

Public Health England will collect data, including via the SACT dataset, alongside the primary source of data collection.

6 Outcome data

Clinical trial

Overall survival is the outcome of interest and is a reported outcome from the MONARCH 2 trial. The final data cut will provide further evidence of overall survival in the trial population.

Other data, including SACT

During the managed access agreement period, Public Health England will collect data to provide information on overall survival and duration of therapy unless it is determined by the SACT Operational Group that no meaningful data will be captured in during the period of data collection.

7 Data analysis plan

Clinical trials

MONARCH 2

[redacted] The final analysis will follow the analysis plan outlined in the trial protocol.

Other data

At the end of the data collection period Public Health England will provide a final report for NHS England based on routinely collected population-wide data, including that collected via SACT. The report will present depersonalised summary data, including the total number of patients starting treatment, overall survival and treatment duration. The necessary controls will be put in place to ensure that patient confidentiality is not put at risk. The report will be shared with Eli Lilly and Company Limited in advance of the planned review of guidance.

Completeness of SACT dataset reporting will be shared with NHS England and Eli Lilly and Company Limited at regular intervals during the data collection period. Public Health England will provide summary results for treatment duration and overall survival to NHS England and Eli Lilly and Company Limited on an annual basis, to check the continuing validity of the period of the data collection arrangement.

8 Ownership of the data

For all clinical trial data listed above, Eli Lilly and Company Limited will be the owner]

The data analysed by Public Health England is derived from patient-level information collected by the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the National Cancer Registration and Analysis Service, which is part of Public Health England. Access to the data was facilitated by the Public Health England Office for Data Release Eli Lilly and Company Limited will not have access to the Public Health England patient data, but will receive de-personalised summary data, with appropriate controls in place to cover this. Public Health England will provide a report to NHS England and Eli Lilly and Company Limited at the end of the managed access period.

The SACT dataset is a mandated dataset as part of the Health and Social Care Information Standards. All necessary governance arrangements through SACT, and other datasets brought together by Public Health England, have been established with NHS Trusts and NHS England.

Blueteq's CDF system data is owned by NHS England. NHS England is responsible for implementing Blueteq data collection and generally for analysis of these data. NHS England, however, shares Blueteq data with Public Health England for CDF evaluation purposes. That sharing is governed by a data sharing agreement between NHS England and Public Health England.

9 Publication

The details/authorship of any proposed publications arising from these studies will be planned with the publication of the final study results.

Publication of the analysis results of data collected by Public Health England, including through SACT and the data from Blueteq's CDF system, will be planned and implemented by Public Health England.

10 Data protection

The terms of clause 7 (data protection) of the managed access agreement, as apply between NHS England and Eli Lilly and Company Limited, shall also apply between the parties to this data collection arrangement in relation to the performance of their obligations under this data collection arrangement

11 Equality considerations

Do you think there are any equality issues raised in data collection?

☐ Yes ☒ **No**

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund review

Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy [ID2727]

Clarification questions

October 2020

File name	Version	Contains confidential information	Date
ID2727 abemaciclib clarification response 201020	**3**	**Yes**	**201020**

Notes for company

Highlighting in the template

Square brackets and [redacted] highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [redacted] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

A1. Priority question: Please confirm if MONARCH 2 PFS data presented in the company submission and informing the FP NMA are unadjusted for interval censoring? If the data used are adjusted, please re-run the analyses using the unadjusted data.

As discussed in the clarification teleconference on Friday Oct 9th, the company has not adjusted K-M curves for interval censoring in the company submission.

A2. Priority question: Please provide PFS and OS results for the post amendment population (abemaciclib starting dose of 150 mg) for the latest data cut (DCO 20 June 2019) from MONARCH 2.

Please provide the number of events, median, mean, and KM-plots.

Please provide PFS results unadjusted for interval censoring.

Summary

The separate analysis of the post-amendment population is inappropriate for the following reasons:

- Intention of protocol change
- Treatment time before protocol change
- Dose intensity
- Adjustment for multiplicity and confounding factors
- Baseline characteristic and prognostic factors
- Pre- and post-amendment control arm
- Regulatory review

Consequently, Lilly will not use the post amendment population due to the many compelling statistical and methodological issues with excluding the patients treated in pre-amendment. We have explained these in more detail below.

Protocol change

In response to this question, Lilly believes it is important to highlight that the MONARCH 2 pre- and post-amendment subgroups do not represent any comparison between two different doses of abemaciclib (ABE). The protocol was amended, and trial expanded to account for the observed tolerability of 200mg dose. The ITT analysis represents the efficacy of patients treated with ABE-FUL as compared to PBO-FUL.

Treatment time before protocol change

Patients enrolled prior to the protocol amendment only received a median of [redacted] days of treatment at the 200 mg starting dose. All patients (ABE-fulvestrant [FUL] or placebo [PBO]-FUL) had their dose or matching placebo reduced to 150 mg.

Dose intensity

The short treatment duration at the 200 mg dose means that patients in the pre- and post-amendment subgroups had [redacted] median dose intensities of [redacted] and [redacted], respectively. Lilly [redacted], and contend that starting dose is not a treatment effect modifier. Dose adjustments were allowed in the protocol and implemented for [redacted] patients treated with ABE ([redacted] %) and [redacted] patients ([redacted]%) treated with PBO in MONARCH 2. Lilly has not heard from advisors that this represents a concern for the ITT efficacy results presented.

Differences in baseline characteristics and prognostic factors

Instead, it is likely that [redacted], as well as

[redacted] a [redacted] was observed between the pre- and post-amendment subgroups ([redacted]). However, it is important to note that this analysis was not adjusted for multiplicity or confounding factors and [redacted] to dose intensity.

In order to adjust for confounding effects, a multivariate analysis of OS was performed based on ten pre-specified subgroup variables.

A stepwise selection method was used, as detailed in the PFS Sensitivity Analysis 4 in Section 11.4.3.3.2 of the MONARCH 2 full CSR was considered. The final model included: treatment arm; starting dose; number of organs at baseline; region and baseline ECOG PS. The subgroup analyses for each of the 10 pre-specified variables were rerun with these 5 main effects as the subgroup by treatment interaction term included. After accounting for these prognostic main effects, [redacted]

Pre- and post-amendment in control arm

The need to consider multiple prognostic baseline characteristics as potential confounders (for OS) is highlighted by [redacted] for patients receiving PBO-FUL in the pre- and post-amendment subgroups [redacted]

To further investigate the impact of key baseline characteristics on OS between the pre- and post-amendment subgroups, a series of OS analyses by prespecified subgroups, as well as menopausal status, comparing pre- versus post-amendment subgroups receiving PBO-FUL were undertaken. The results are shown in Table 1.

In general, OS was [redacted] across each of the prespecified subgroups for patients in the pre-amendment subgroup compared to those in the post-amendment subgroup, with [redacted] for almost all subgroups of patients in the pre-amendment subgroup. The only exceptions were for the subgroups of [redacted] where the median OS [redacted] in the pre- versus post-amendment subgroups. [redacted] of these variables were observed, [redacted]

Overall, there were [redacted]

The [redacted] should be interpreted with caution, considering the small sample size ([redacted] patients in the pre-amendment subgroup and [redacted] patients in the post-amendment subgroup), as well as the immaturity of the data ([redacted] in the pre-amendment subgroup; [redacted] in the post-amendment subgroup, [redacted]

Table 1: Summary of overall survival for patients receiving PBO-FUL in MONARCH 2 in the pre- and post-amendment subgroups

	Pre-Amendment Group (N=57)				Post-Amendment Group (N=166)				Pre- versus Post-Amendment Group Comparison	
Subgroup	**n**	**Events**	**Median, months**	**95% CI**	**n**	**Events**	**Median, months**	**95% CI**	**HR[a] (95% CI)**	**Interaction p-value[b]**
Overall	[redacted]									
Nature of disease										
Visceral	[redacted]									
Bone-only	[redacted]									
Other	[redacted]									
Sensitivity to endocrine therapy										
Primary resistance	[redacted]									
Secondary resistance	[redacted]									
Measurable disease at baseline										
Yes	[redacted]									
No	[redacted]									
Number of organs at baseline										
≥ 3	[redacted]									
2	[redacted]									
1	[redacted]									
Progesterone receptor status										
Negative	[redacted]									
Positive	[redacted]									
Baseline ECOG PS										
1	[redacted]									
0	[redacted]									

	Pre-Amendment Group (N=57)				Post-Amendment Group (N=166)				Pre- versus Post-Amendment Group Comparison	
Subgroup	**n**	**Events**	**Median, months**	**95% CI**	**n**	**Events**	**Median, months**	**95% CI**	**HR[a] (95% CI)**	**Interaction p-value[b]**
Menopausal status										
Pre-menopausal										
Post-menopausal										
Pooled age group										
< 65 years										
≥ 65 years										
Geographic region										
North America										
Africa										
Europe										
Pooled race group										
Caucasian										
Asian										
Other										

Footnotes: [a] Pre-amendment subgroup versus post-amendment subgroup. [b] The p-value the interaction term is from a model with arm, the subgroup variable and arm multiplied by subgroup interaction term. The factor levels that consist less than 5% of randomised patients were omitted from the analysis.
Abbreviations: CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; PS: performance status.

In summary, these results demonstrate a [redacted] in the pre- versus post-amendment subgroups. [redacted] As noted above, [redacted] the interaction p-value for patients receiving ABE-FUL in the pre- and post-amendment subgroups [redacted]

Regulatory review

The global regulatory community including EMA, FDA and Canadian regulators, have assessed the evidence generated from the MONARCH 2 trial. Based on these reviews, the efficacy data presented to healthcare professionals in UK and globally in summary of product characteristics remains the ITT population.

Conclusion

Due to the totality of evidence, Lilly does not consider it appropriate to evaluate the efficacy of ABE-FUL by separating the results of the pre- or post-amendment subgroups in MONARCH 2. As such, Lilly have chosen to continue to apply the appropriately powered and selected ITT population results for efficacy.

A3. Priority question: Please run the FP NMA for PFS and OS using the post amendment population of MONARCH 2 (abemaciclib starting dose of 150 mg).

> Please provide means, medians, % alive or progression-free, and survival curves.
>
> Please use PFS data unadjusted for interval censoring as requested in A2.

Lilly does not accept that the post-amendment subgroup represents an appropriate approach to describe the efficacy for ABE-FUL, for the reasons discussed in the response to Question A2 above.

A4. Please provide a short description of the methods and the results of the assessment of proportional hazards (PHs) for PFS and OS in MONARCH 2, and for any other outcomes it has been tested for.

The assessment of PH was aligned with the original appraisal where for each trial within the network-meta analysis and for OS and PFS, the PH assumption was assessed by:

- Log cumulative hazard plots (log cumulative hazard over log time, referred to as a log–log plot)
- Schoenfeld residual plots
- Weighted residual test based on standardised Schoenfeld residuals.

The assessment demonstrated that the assumption held across the majority of studies, however as the trial data for BOLERO-2 had not changed the findings of non-proportional hazards remained.

A5. Please provide mean PFS for the FP NMA presented in the CS.

The mean PFS estimates derived from the FP NMA are presented in Table 2.

Table 2: Mean PFS values for the company FP NMA

	FUL	EXE	EXE-EVE	ABE-FUL
Mean PFS, months	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABE: abemaciclib; EXE: exemestane; EVE: everolimus; FP: fractional polynomial; FUL: fulvestrant; NMA: network meta-analysis; PFS: progression free survival.

While these PFS estimates are the direct outputs of the FP NMA, these are slightly different to the PFS estimates used in the company base case analysis. The company base case sets the PFS equal to the minimum value out of PFS or OS, in order to increase the clinical plausibility of the PFS extrapolations.

The mean PFS estimates used in the company base case are presented in Table 3.

Table 3: Mean PFS values used in the Company Base Case

	FUL	EXE	EXE-EVE	ABE-FUL
Mean PFS, months	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABE: abemaciclib; EXE: exemestane; EVE: everolimus; FP: fractional polynomial; FUL: fulvestrant; NMA: network meta-analysis; PFS: progression free survival.

A6. Assuming the FP NMA results for fulvestrant in the company submission are referring to the 500mg dose please provide the FP NMA results for 250mg fulvestrant for PFS and OS.

The FP NMA results for fulvestrant in the company submission refer to a combined FUL 500 extrapolation. The time-to-event curves with separate data for FUL 250 and FUL 500 are presented in Figure 1 (PFS) and Figure 2 (OS) below respectively, with the corresponding summary statistics for FUL 500 and FUL 250 presented in Table 4 (PFS) and Table 5 (OS).

Figure 1: PFS time-to-event curves up to Month 120, with separate curves for FUL 500 and FUL 250 (ITT)

Abbreviations: ABE: abemaciclib; EXE: exemestane; EVE: everolimus; FP: fractional polynomial; FUL: fulvestrant; ITT: intention-to-treat population; NMA: network meta-analysis; PFS: progression free survival.

Table 4: PFS summary statistics for the FUL 250 and FUL 500 (ITT)

	FUL 250	FUL 500
Median PFS, months	[redacted]	[redacted]
Progression-free at 12 months, %	[redacted]	[redacted]
Progression-free at 60 months, %	[redacted]	[redacted]
Progression-free at 120 months, %	[redacted]	[redacted]

Abbreviations: FP: fractional polynomial; FUL: fulvestrant; ITT: intention-to-treat; NMA: network meta-analysis; PFS: progression-free survival.

Figure 2: OS time-to-event curves up to Month 120, with separate curves for FUL 500 and FUL 250 (ITT)

Abbreviations: ABE: abemaciclib; EXE: exemestane; EVE: everolimus; FP: fractional polynomial; FUL: fulvestrant; NMA: network meta-analysis; OS: overall survival.

Table 5: OS summary statistics for the FUL 250 and FUL 500 for the FP NMA (ITT)

	FUL 250	FUL 500
Median OS, months	[redacted]	[redacted]
Alive at 12 months, %	[redacted]	[redacted]
Alive at 60 months, %	[redacted]	[redacted]
Alive at 120 months, %	[redacted]	[redacted]

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FP: fractional polynomial; FUL: fulvestrant; ITT: intention-to-treat; NMA: network meta-analysis; OS: overall survival

A7. Please provide a clinical rationale for why prior treatment with letrozole or anastrozole in BOLERO-2 could lead to an overestimation of the benefit of EXE-EVE relative to EXE. Please also provide a discussion around how progression on prior non-steroidal aromatase inhibitors, such as letrozole and anastrozole, may impact on the results of SoFEA and the overall results of the NMA.

The BOLERO-2 trial is a phase 3, double blind, randomized international trial comparing everolimus plus exemestane versus placebo in post-menopausal women with HR+, advanced breast cancer with recurrence/progression during or after NSAI. Patients were randomised according to stratification factors including previous endocrine sensitivity defined as “at least 24 months of endocrine therapy before recurrence in the adjuvant setting or a response or stabilization for at least 24 weeks of endocrine therapy for advanced disease”, which is akin to ESMO definition of

secondary endocrine resistance. 84% of the BOLERO-2 population were considered to be endocrine sensitive (i.e. secondary resistance) by this definition.

After progression on a NSAI a proportion of patients retain sensitivity to endocrine therapy. A phase II study of exemestane after NSAI in postmenopausal women with HR+ ABC, or determined as HR sensitive based upon previous treatment if ER status not known, demonstrated that under a quarter of patients (24.3%) achieved a durable overall success rate (Complete Response + Partial Response + No change for≥24 weeks) (1). Sequential single agent endocrine therapies are associated with only modest clinical benefit, compared to endocrine and targeted combination regimens which provide greater treatment benefit, supported by data from several large, recently conducted, RCTs (MONARCH 2, PALOMA 3 and BOLERO-2). However single agent endocrine therapy may be favourably considered by clinicians in terms of their tolerability profile compared with chemotherapy or targeted combination regimens.

Based on clinical opinion received by Lilly, the benefit of EVE-EXE relative to EXE could have been overestimated by potentially biasing against the control arm. Notably the number of patients achieving an objective response was far lower in the EXE arm vs. the EXE-EVE arm (4/239 [1.7%] vs. 61/485 [12.6%] respectively). Similarly, mPFS on the basis of central assessment was much lower at 4.1 months in the EXE arm, compared to 10.6 months in the EXE-EVE arms (hazard ratio, 0.36; 95% CI, 0.27 to 0.47; P<0.001). Additionally, it has been questioned if EXE is an appropriate treatment for patients that have previously failed on an aromatase inhibitor; and whether the results would have been as favourable if a stronger comparator had been used in the study. (2)

The SoFEA trial compared fulvestrant plus anastrazole to fulvestrant plus placebo versus exemestane in postmenopausal patients who had relapsed or progressive HR+ ABC on an NSAI. This trial, though now demonstrated to use a suboptimal unlicensed dose of fulvestrant demonstrated a median PFS of 4.4months, 4.8 months and 3.4 months in the respective arms. The authors concluded that after loss

of response to NSAIs in postmenopausal women with HR+ ABC maximum double endocrine treatment was no better than with fulvestrant or exemestane alone.

Interpreted in combination, Lilly believes these considerations supports the treatment ranking produced by the FP NMA methodology discussed in the submission. Lilly acknowledges that the SoFEA trial design suffers from a similar potential bias for FUL as BOLERO-2 does for EXE-EVE, which could bias the results in favour of FUL.

1. Lønning PE, Bajetta E, Murray R, et al: Activity of exemestane in metastatic breast cancer after failure of nonsteroidal aromatase inhibitors: A phase II trial. J Clin Oncol 18::2234,2000-224

2. Gupta S. Progression-free or overall survival...revisited in BOLERO-2. Indian J Med Paediatr Oncol. 2014;35(1):1-2.

A8. Please provide a table with the numbers at risk, along with the number of patients censored and number with an event for each of the timepoints in:

Figure 1 for OS;

Figure 2 for PFS; and

Figure 4 for TTD.

The numbers at risk and with event can be found in the updated file in sheet AtRisk. In addition, these numbers can be found for the Excel generated graphs of PFS, OS and TTD in sheet KM for the respective curve.

Section B: Clarification on cost-effectiveness data

[Add subheadings as needed]

B1. Priority question. Please confirm that when the population chosen in the model (tab "Dashboard", cell J22) is set to the 150mg starting dose population in MONARCH 2, the data inputs affected in the model are the TTD curves and the utility data from MONARCH 2. Please provide information about other parameters that are affected by using the 150mg population in the model.

> Please use the OS and unadjusted PFS NMA betas for the post amendment population, updated data cut from MONARCH 2 (requested in question A3) in the model when the population chosen in the model (tab "Dashboard", cell J22) is set to the 150mg starting dose population.

When the setting on the dashboard is set to 150mg the model uses population specific data for TTD, utility values and hospitalisation rates and length of stay. The data for hospitalisation is available on the 'Hosp' tab column AA and onwards.

B2. Priority question. Please add the following data to the tab "KM" in the economic model, for ABE+FUL and FUL:

1. KM PFS data for the post amendment population (150mg population) from the updated data cut from MONARCH 2 (20th June 2019) unadjusted for interval censoring;
2. KM PFS data for the post amendment population (150mg population) from the updated data cut from MONARCH 2 (20th June 2019) adjusted for interval censoring;
3. KM OS data for the post amendment population (150mg population) from the updated data cut from MONARCH 2 (20th June 2019);
4. KM TTD data for the post amendment population (150mg population) from the updated data cut from MONARCH 2 (20th June 2019).

As discussed in the clarification teleconference on Friday Oct 9th, the Lilly did not adjust K-M curves for interval censoring in the company submission. As discussed in question A2 above, Lilly does not agree that points 1, 2 and 3 in question B2 represents appropriate analysis of treatment effect from the MONARCH 2 trial.

The excel chart for point 4 is available in the KM tab, in columns CT to DD to use for cost implication. This chart is also presented below.

B3. Priority question. Please explain why the KM TTD for ABE+FUL and FUL curves were jointly fitted in the model (for the spost amendment population; data cut 20 June 2019), especially considering that only the ABE+FUL curve is of interest to the updated economic analysis and that PHs in the previous data cut did not hold for TTD data. Please consider independently fitting a survival curve to the ABE+FUL KM TTD data.

The analysis was conducted using the same methodology as the PFS and OS analysis conducted for this analysis and previous analysis. It is best practice to use the same model approach across endpoints. Additionally, this selection isn't used in the base case.

B4. Priority question. Please explain why a Weibull (and an alternative gamma curve) were deemed the most appropriate curves to model the post amendment KM TTD data (data cut 20 June 2019), based on the curve choice criteria provided in the DSU document 14.

> Please provide (in Excel format and included in the model) the alternative curves (i.e. lognormal;log logistic;exponential;gompertz;etc) considered for fitting the TTD KM data from MONARCH 2 for the post amendment population (data cut 20 June 2019).

Lilly provided alternative extrapolation for TTD in the file "ID2727 Abemaciclib NICE CDF Review_Final 240920" in sheet TOT_2020, range C29 to AK29. "ID2727 Abemaciclib NICE CDF Review_Final 151020" has not changed the location of extrapolations.

The curve selection was based on the goodness of fit statistics and visual inspection. However additional consideration was made to align with the survival analysis of other endpoints as suggested in the DSU guidelines, where the same parametric survival model should be used across endpoints to prevent bias.

While not used in the submission, Lilly provided extrapolations consistent with previous appraisal. Lilly acknowledges Weibull and Gamma extrapolations can be criticised based on fit statistics.

The additional models for extrapolation of results from the ITT population and considered both fit statistics and the tails of curves generated. In summary, log normal, log logistic and gamma provide similar fit statistics for BIC.

Model	N	Log likelihood (null)	Log likelihood (model)	df	AIC	BIC
Exponential	**669**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	**669**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	**669**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LLogistic	**669**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	**669**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	**669**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The best statistical fit based on AIC and BIC was lognormal with [redacted] and [redacted], respectively. However, from the extrapolations generated, Lilly is concerned that the extrapolations [redacted] time to discontinuation after approx. [redacted] months for the PBO-FUL arm and potentially underestimates ABE-FUL from approx. [redacted] months.

Gamma provides [redacted] fit statistics based on AIC ([redacted]) and [redacted] fit based on BIC ([redacted]). The extrapolation generated fits the observed data [redacted] until approx. [redacted] months for PBO-FUL, at which point gamma extrapolation [redacted] the time to discontinuation (TTD). For ABE-FUL, the extrapolation [redacted] TTD until approx. [redacted] months. After [redacted] months, the extrapolation [redacted] TTD, which could bias the cost-effectiveness results for ABE-FUL.

B5. Priority question. For scenario 2 used to estimate TTD for EVE-EXE in the model, please provide an alternative analysis where the methodology proposed by the ERG in their original report is used. More specifically, please use the PFS curve from BOLERO 2 to estimate survival in the PFS curve at the point of median TTD (also taken from BOLERO 2) - please see Table 26 in the ERG's original report, where a HR of 1.16 was used for EVE-EXE.

The option to apply the proposed ration has been implemented on Overview_2020 in cell F14. Lilly notes this value is based on median duration of exposure as reported by Yardley et al (2013). Lilly are unable to verify that this value was derived from a KM analysis of treatment survival. We therefore believe the most appropriate value to compare BOLERO-2's 6.8 months median duration of exposure is median duration of therapy (weeks) in the post amendment group as reported in Table 13 of the company submission. From taking the PFS proportion at median duration of therapy from the PFS KM curve, the comparable ration for ABE-FUL is log(0.5)/log( ) = . Therefore, ERG's preferred HR also applies this HR for ABE-FUL unless disabled.

Applying these in the model yields an incremental cost of £ and an ICER per QALY of £12,011.

Cost-effectiveness - Pairwise results

Comparator	Costs	LYs	QALYs	ICER (per QALY) ABE-FUL vs. EXE-EVE
ABE-FUL	[redacted]	[redacted]	[redacted]	-
EXE-EVE	[redacted]	[redacted]	[redacted]	-
Incremental	[redacted]	[redacted]	[redacted]	£12,011

B6. Priority question. Please include an option in the model where the TTD curve for ABE+FUL is estimated through fitting a parametric survival curve to the KM data in the post amendment TTD data (data cut 20 June 2019) AND the TTD curve for EVE+EXE is estimated as requested in B5. Please cap the ABE+FUL TTD curve by the ABE+FUL PFS curves if the curves cross.

This option is available in the model, the selection of curves is selected through J43 for ABE-FUL. The approach is selected within the option of J44.

B7. Priority question. Please plot together the KM PFS and the KM TTD data from MONARCH 2 for ABE+FUL and FUL (separately) for the post amendment data (data cut 20 June 2019) and describe if the shape and relationship between the PFS and TTD curves is as expected given the MONARCH 2 trial protocol.

From the trial protocol, Lilly expects patients to discontinue ABE-FUL before or with their progression-free survival. This is true for all time points except, approx. 0 to 3 months where ToT crosses PFS.

B8. Priority question. The tab "costs_2020" in the model reports changes in multiple cost input parameters that have not been reported or justified in the CS. If the company wishes to incorporate

these new inputs in their updated base case analysis please justify the amendments proposed for each cost input in this tab.

Lilly acknowledges the ERG's proposal for original costs and agrees to proceed with these for the base case analysis.

B9. Priority question. In tab "costs_2020" in the model; cell M116 the company does not allow for the ERG's preferred cost parameter to be used (£59). The ERG notes that this estimate is necessary to replicate the ICER reported by the company in analysis 1b (Table 7 of CS). Please include the use of this parameter as an option in the model.

Lilly have added a selection of therapist cost to cell H10 on sheet Overview_2020 (Overview_2020!H10). Please note, original cost must be selected from cell D9 for this to be applied.

B10. Priority question. The ERG would like the company to note the changes (in red) described in the table below (replicated from Table 23 from the CS). Based on the table below, can the company please:

1. Confirm the changes on the 4th column (in red) are correct;
2. Re-run analysis 3 in the company's submission (ERG's original assumptions with company's new data) based on the changes proposed on column 5, and provide an updated deterministic and probabilistic ICER for this scenario;
3. Re-run analysis 2 if deemed necessary in light of the changes proposed by the ERG in the table.

Table 23: Settings in the economic model to replicate the economic analyses described in Section A.10

	Cost-effectiveness analysis			
Parameter in the economic model	1a: Original company FP NMA	1b: ERG FP NMA	2: Updated company FP NMA using updated PFS and OS, but original company cost and resource assumptions	3: Updated company base case
Overview_2020				

Use FP NMA	Yes	Yes	Yes	Yes
Use 2020 NMA	No	No	Yes	Yes
2020 – OS Network	NA	NA	Overall survival – NICE network	Overall survival – NICE network
2020 – PFS Network	NA	NA	Progression free survival – NICE network	Progression free survival – NICE network
Selected costs	Original	Original	Original	Original
ToT: Use 2020 data	No	No	Yes	Yes
ToT: Selected approach – MONARCH 2	NA	NA	Calibration (modelled PFS to trial ToT PFS difference) according to labeling of option 1 and option 2 in tab "TOT_2020".	For the ERG's original preferred assumptions: calibration (modelled PFS to median ToT) + please see question B5 for EXE+EVE. For the ERG's updated preferred approach: please see question B6.
MONARCH 2 trial data: Use 2020 data	No	No	No	No
MONARCH 2 trial data: interval	NA	NA	NA	NA

censored adjustment				
MONARCH 2 trial data: curve for PFS	NA	NA	NA	NA
MONARCH 2 trial data: curve for OS	NA	NA	NA	NA
Proportion of PPS on treatment	37%	37%	37%	37%
CAP administrations and dose	False	True	False	True
FUL loading dose admin correction from £43 to £172	False	True	False	True
Post-progression treatment distributions	False	True	False	True
ABE discount	[redacted]	[redacted]	[redacted]	[redacted]
EVE discount	0%	0%	0%	0%

FUL discount	0%	0%	0%	0%
ERG's analysis (2)				
PPS utility from MONARCH 2	False	False	False	False
PPS utility from Mitra 2016	False	True	False	True
Remove AE-related disutilities	False	True	False	True
Age-related utility decrements	False	True	False	True
Post-progression treatment distributions	False	True	False	True
Capping the time patients could spend on FUL and EXE-EVE as subsequent treatments	False	True	False	True
Post-progression treatment in PPS from 37% up to 3 months before death	False	True	False	True

TA496 health state costs	False	True	False	True
TA496 FUL administration costs (loading dose and subsequent)	False	True	False	True
ABE starting dose (34 days for 27.5% of patients)	False	False	False	False
TMX dose (40 mg to 20 mg)	False	False	False	False
Removing non-AE-related hospitalisation costs	False	True	False	True
CAP administrations and dose	False	True	False	True
FUL loading dose admin correction from £43 to £172	False	True	False	True
FUL loading dose acquisition cost from £130 to £522	False	True	False	True

ERG's analysis				
Use FP NMA PFS	No	Yes	No	No
Alternative OS	No	No	No	No
Base case OS	No	Yes	No	No
Remove half-cycle correction	No	Yes	No	No
Dashboard				
Population (MONARCH 2)	ITT	ITT	Subgroup 150 mg starting dose ABE	Subgroup 150 mg starting dose ABE
PFS = min (PFS, OS)	On	On	On	On
Source of post-progression utility decrement	Lloyd 2006	Mitra	Lloyd 2006	Mitra
ToT calculation	Calibration (modelled PFS to trial ToT PFS difference)	Calibration (modelled PFS to median ToT)	Calibration (modelled PFS to trial ToT PFS difference)	Calibration (modelled PFS to median ToT)

[redacted]

Response

1. Lilly has responded to questions B5 and B6 above. Lilly acknowledges the correction for EXE-EVE. However, Lilly believes it is inappropriate to extrapolate ToT independently of FP NMA PFS for ABE-FUL. As discussed in B5, a ratio based on comparable methodology to what was used by ERG has been developed based on PFS proportion at median duration of therapy.
In terms of PPS utility applied in scenario 1b, Lilly confirms this was mistaken referred to as Lloyd 2006 in the submission. The selection for PPS utility from Mitra 2016 was set to true. Lilly believes Calibration (modelled PFS to trial ToT PFS difference) from Dashboard was required to replicate the scenario discussed.

For scenarios 2b and 3, Lilly would like to clarify that ERG values selected from sheet ERG's analysis (2) is applied in the model. As an example, proportion of time in PPS on treatment uses only ERG's preferred assumption and not 37 % as originally proposed by Lilly.

B10.2) *Re-run analysis 3 in the company's submission (ERG's original assumptions with company's new data) based on the changes proposed on column 5, and provide an updated deterministic and probabilistic ICER for this scenario;*

The deterministic cost-effectiveness results for B10.2 (analysis 3, column 5 of ERG table 23) are presented in the below table.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
ABE-FUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA
EXE-EVE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,746

Abbreviations: ABE: abemaciclib; ERG: Evidence Review Group; EVE: everolimus; EXE: exemestane; FP: fractional polynomial; FUL: fulvestrant; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NA: not applicable; NMA: network meta-analysis; PH: proportional hazards; QALYs, quality-adjusted life years.

The probabilistic cost-effectiveness analysis results for B10.2 (analysis 3, column 5 of ERG table 23) are presented in the below table.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
ABE-FUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA
EXE-EVE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,539

Abbreviations: ABE: abemaciclib; ERG: Evidence Review Group; EVE: everolimus; EXE: exemestane; FP: fractional polynomial; FUL: fulvestrant; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NA: not applicable; NMA: network meta-analysis; PH: proportional hazards; QALYs, quality-adjusted life years.

The scatterplot of the probabilistic results for B10.2 (analysis 3, column 5 of ERG table 23) are presented below.

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

B10.3) *Re-run analysis 2 if deemed necessary in light of the changes proposed by the ERG in the table.*

The deterministic cost-effectiveness results for B10.3 (analysis 2, column 4 of ERG table 23) are presented in the below table.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
ABE-FUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA
EXE-EVE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,028

Abbreviations: ABE: abemaciclib; ERG: Evidence Review Group; EVE: everolimus; EXE: exemestane; FP: fractional polynomial; FUL: fulvestrant; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NA: not applicable; NMA: network meta-analysis; PH: proportional hazards; QALYs, quality-adjusted life years.

The probabilistic cost-effectiveness analysis results for B10.3 (analysis 2, column 4 of ERG table 23) are presented in the below table.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
ABE-FUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA
EXE-EVE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,645

Abbreviations: ABE: abemaciclib; ERG: Evidence Review Group; EVE: everolimus; EXE: exemestane; FP: fractional polynomial; FUL: fulvestrant; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NA: not applicable; NMA: network meta-analysis; PH: proportional hazards; QALYs, quality-adjusted life years.

The scatterplot of the probabilistic results for B10.3 (analysis 2, column 4 of ERG table 23) are presented below.

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

Appendix 1 – Additional extrapolation curves for question B4

NICE National Institute for Health and Care Excellence

Patient organisation submission

Abemaciclib in combination with fulvestrant for treating advanced hormone receptor-positive, HER2-negative breast cancer (CDF review of TA579) [ID2727]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Breast Cancer Now
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Breast Cancer Care and Breast Cancer Now merged on 1 April 2019 to create one charity – Breast Cancer Now. From research to care, our charity has people affected by breast cancer at its heart – providing support for today and hope for the future. United, we'll have the ability to carry out even more world-class research, provide even more life-changing support and campaign even more effectively for better services and care. Breast Cancer Now's main sources of income are individual giving and corporate partnerships. 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.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	Breast Cancer Now does not receive any pharmaceutical funding for our Policy, Evidence and Influencing work. Our work on access to drugs is independent of any funding we may receive from the pharmaceutical industry and is based on the evidence of the clinical effectiveness of drugs. In 2019/20 Breast Cancer Now has either received or been pledged the following funding from pharmaceutical companies which are listed in the matrix for this appraisal: - Eli Lilly, £21,065 - Living with Secondary Breast Cancer Service Sponsorship (other industry have also supported this service) - Eli Lilly, £20,000 – Helpline - Eli Lilly, £30,000 – UK Interdisciplinary Breast Cancer Symposium 2020 sponsorship (along with a number of other pharmaceutical sponsors)

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None.
5. How did you gather information about the experiences of patients and carers to include in your submission?	At Breast Cancer Now we utilise our various networks of those affected by breast cancer to gather information about patient experience. This included people who had experience of abemaciclib with fulvestrant since it was recommended for use on the Cancer Drugs Fund.
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?	Secondary (also known as advanced, metastatic 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 secondary breast cancer. Treatment aims to control and slow the spread of the cancer, relieve any symptoms, and maintain health, wellbeing and a good quality of life for as long as possible. A patient can be diagnosed with secondary breast cancer right from the start, or they can develop the condition months or years after treatment for their primary breast cancer has ended. Being diagnosed with secondary breast cancer is extremely difficult to come to terms with both for patients and their family and friends. Everyone's experience of being diagnosed and living with secondary breast cancer is different. Many people will feel overwhelmed, upset and shocked or anxious, as well as

	angry and alone. The uncertainty of living with secondary breast cancer can be the hardest part for many people, with people telling us it has fundamentally changed their perspective on life and they feel they are living on borrowed time. These common feelings can have a huge impact on people's mental health. A diagnosis of secondary breast cancer can also affect people's relationship with those closest to them which can be particularly difficult to cope with. People living with secondary breast cancer have told us: "How confused and scared I am all the time; even when I'm happy it's always there in the back of your mind". "It is scary. I am permanently scared about my future and what my family will have to deal with without me". As well as the huge emotional toll of living with secondary breast cancer, patients often have to cope with numerous practical concerns, such as managing their day to day activities, which may include working, household and parental responsibilities as well as travelling to and from hospital appointments. People living with secondary breast cancer have shared the following: "It totally and completely affects your life after diagnosis. Endless doctors' appointments can begin to wear you down in no time at all". "My treatment goes on for as long as it works and this is my life now. Constant 'scanxiety', endless hospital appointments and the struggle with day to-day living that others either don't see or understand". The symptoms of secondary breast cancer can vary depending on where the cancer has spread to. For example, if it has spread to the bones the main symptoms can include pain in the bones or bone fractures. If breast cancer has spread to the lungs, someone may experience symptoms such as breathlessness or continuous pain and tightness in the chest. Also all breast cancer treatments can cause some side effects

	and although everyone reacts differently to drugs, for those people who experience more side effects than others, it can cause a significant impact on their day to day lives and health and wellbeing. Patients are keen to find treatments that will halt progression and extend life for as long as possible. As patients' time is limited, people tell us that quality of life is just as important to take into account as length of life, as this enables them to spend quality time with their loved ones. Therefore, the type and severity of treatment side effects are also important for patients when considering their treatment decisions.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	The introduction of abemaciclib with fulvestrant (and other CDK 4/6 inhibitors) into NHS use via the Cancer Drugs Fund was hugely welcomed by the patient community. These offer a new treatment option for patients with hormone receptor positive, HER2 negative locally-advanced or metastatic breast cancer after prior endocrine therapy. CDK 4/6 inhibitors with fulvestrant opened the door for thousands of women who had received prior endocrine therapy to benefit from the innovative CDK 4/6 inhibitor which had previously only been available to newly diagnosed patients with locally advanced or metastatic breast cancer. Prior to CDK 4/6 inhibitors, this patient group could receive exemestane, tamoxifen or exemestane plus everolimus. However, it was suggested in the initial appraisal of abemaciclib with fulvestrant that exemestane plus everolimus can have adverse events which may limit its use in clinical practice.
8. Is there an unmet need for patients with this condition?	Yes there was an unmet for this patient group. Patients who progressed on an AI could not benefit from the introduction of CDK 4/6 inhibitors. Treatments that improve the time before progression, delay chemotherapy are much needed for this group of patients. Interim analysis also now suggests this treatment combination could improve overall survival.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	For patients, the advantages of abemaciclib in combination with fulvestrant are: • Pre-planned interim overall survival (OS) shows a significant benefit with abemaciclib with fulvestrant of 9.4 months which would be a crucial benefit to this patient group. • A significant improvement in progression free survival (PFS). The latest data from the MONARCH 2 study demonstrated that abemaciclib plus fulvestrant improves progression free survival (PFS) compared with fulvestrant alone, with a median PFS of 16.9 months compared to 9.3 months. We know patients value this extra time, as delaying disease progression means more quality time to spend with their relatives and friends. Maintaining a high quality of life for as long as possible is currently the best outcome for this patient group. • Delaying progression and improving overall survival can also have a positive impact on patients' emotional wellbeing and mental health, as it may mean that the patient can continue doing the activities they enjoy and leading a more or less normal daily life. • Increasing the time until a patient's disease progresses and improving overall survival is also likely to bring some comfort to their relatives and friends, as this is the best possible outcome for an incurable disease. This in turn could help to reduce any stress the patient is experiencing as a result of worrying about any burden on their friends and family. • The use of this technology could also delay patients having to start on systemic (non-targeted) chemotherapy. Chemotherapy is traditionally associated with more severe and gruelling side effects which can result in a poorer quality of life for patients and people are often particularly fearful and anxious about being moved onto chemotherapy. One patient told us "If this treatment had not been available, I would have had to go on chemotherapy, which was something I wanted to avoid as long as possible. My scan results with abemaciclib and fulvestrant still show no significant active cancer or progression to other organs/bones. I've been on this treatment combination for over 15 months now. So that shows the treatment is keeping things under control, which is the main thing!"

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Abemaciclib plus fulvestrant is associated with some increased side effects compared to fulvestrant alone. MONARCH 2 reported that the most common adverse events of any grade were diarrhoea, neutropenia, nausea, fatigue and abdominal pain. Apart from neutropenia, these side effects occurred mostly at grade 1 or 2 severity. Although diarrhoea was the most common side effect of abemaciclib in combination with fulvestrant, it is noted that diarrhoea events typically occurred in the first treatment cycle and that in most cases, it was effectively managed using antidiarrheal medications and with dose adjustments. A patient told us "I have experienced some difficult side effects from abemaciclib. To begin with, I was put on the highest dose. I think I managed 3 or 4 cycles at this dose. But by then I was having unpleasant and debilitating diarrhoea and feeling nauseous and unwell. I had lost my appetite and found it difficult to go out in case I suddenly needed the toilet. My oncologist suggested that I have my dose reduced and I was pleased to do this. I still have diarrhoea and nausea……but I found the treatment more tolerable. I manage the diarrhoea when it occurs….However, I rarely feel really well. However, I would rather be on this treatment than chemotherapy". Every treatment for breast cancer has some side effects and each patient's situation will be different and the side effects will affect some patients more than others. Patients' willingness to take treatments will vary, however, as long as all the side effects are clearly discussed with the patient, they will be able to make their own choice as to the level of risk they will be willing to take. Patients would also need to attend hospital or in some places a GP surgery for fulvestrant to be administered, as this is given as an injection. However, for many patients, any inconvenience caused by attending hospital or GP appointments for the administration of fulvestrant will be outweighed by an increase in progression free survival.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	None that we are aware of.
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?	None.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- In the MONARCH 2 trial, abemaciclib in combination with fulvestrant showed significant benefits in progression-free survival and overall survival compared to fulvestrant alone.
- These outcomes are important to patients as it enables patients to spend quality time with their friends and families as well as continue with their daily activities, which can improve the emotional wellbeing of both patients and their loved ones.
- There are some increased side effects from abemaciclib in combination with fulvestrant, compared to fulvestrant alone. However, not all patients will experience side effects. As long as the benefits and risks of a treatment are clearly discussed with the patient, they can make the decision that is right for them.
- This treatment adds to the drug options available for patients with this type of breast cancer which cannot be cured. Any new treatments that can delay the need to start on chemotherapy which is generally associated with more severe side effects and a poorer quality of life is welcomed by patients.
- The introduction of this treatment into NHS practice (via the Cancer Drugs Fund) was a significant step forward in the treatment of this type of breast cancer and was welcomed amongst patients and the clinical community. It is critical we now do not take a step back and that this treatment is able to be routinely approved for NHS use.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

Public Health England

Protecting and improving the nation's health

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

Commissioned by NHS England and NHS Improvement

About Public Health England

Public Health England exists to protect and improve the nation's health and wellbeing and reduce health inequalities. We do this through world-leading science, knowledge and intelligence, advocacy, partnerships and the delivery of specialist public health services. We are an executive agency of the Department of Health and Social Care, and a distinct delivery organisation with operational autonomy. We provide government, local government, the NHS, Parliament, industry and the public with evidence-based professional, scientific and delivery expertise and support.

Public Health England
Wellington House
133-155 Waterloo Road
London SE1 8UG
Tel: 020 7654 8000
www.gov.uk/phe
Twitter: @PHE_uk
Facebook: www.facebook.com/PublicHealthEngland

Published September 2020
PHE publications
gateway number: GW-1485

PHE supports the UN
Sustainable Development Goals

Contents

Executive summary

Introduction

The National Institute for Health and Care Excellence (NICE) appraised the clinical and cost effectiveness of abemaciclib with fulvestrant for advanced hormone-receptor positive, HER2-negative breast cancer. The appraisal committee highlighted clinical uncertainty around estimates of overall survival (OS) in the evidence submission. As a result, they recommended commissioning of abemaciclib with fulvestrant through the Cancer Drugs Fund (CDF) to allow a period of managed access, supported by additional data collection to answer the clinical uncertainty.

NHS England and NHS Improvement commissioned Public Health England (PHE) to evaluate the real-world treatment effectiveness of abemaciclib with fulvestrant in the CDF population during the managed access period. This report presents the results of the use of abemaciclib with fulvestrant in clinical practice, using the routinely collected Systemic Anti-Cancer Therapy (SACT) dataset.

This report, and the data presented, demonstrate the potential within the English health system to collect real-world data to inform decision-making about patient access to cancer treatments via the CDF. The opportunity to collect real-world data enables patients to access promising new treatments much earlier than might otherwise be the case, whilst further evidence is collected to address clinical uncertainty.

The NHS England and NHS Improvement and PHE partnership for collecting and following up real-world SACT data for patients treated through the CDF in England has resulted in analysis being carried out on 91% of patients and 79% of patient outcomes reported in the SACT dataset. PHE and NHS England and NHS Improvement are committed to providing world first high-quality real-world data on CDF cancer treatments to be appraised alongside the outcome data from the relevant clinical trials.

Methods

NHS England and NHS Improvement's Blueteq® system was used to provide a reference list of all patients with an application for abemaciclib with fulvestrant for advanced hormone-receptor positive, HER2-negative breast cancer in the CDF. Patient NHS numbers were used to link Blueteq applications to PHE's routinely collected SACT data to provide SACT treatment history.

Between 2 April 2019 and 15 December 2019, 1,113 applications for abemaciclib with fulvestrant were identified in NHS England and NHS Improvement's Blueteq system. Following appropriate exclusions (see Figures 1 and 2), 876 unique patients who received treatment were included in these analyses. All patients were traced to obtain their vital status using the personal demographics service (PDS)[1].

Results

876 (91%) unique patients with CDF applications were reported in the SACT dataset.

Median treatment duration was 10.2 months[a], (310 days). 64% [95% CI: 60%,67%] of patients were receiving treatment at 6 months and 46% [95% CI: 37%, 56%] of patients were receiving treatment at 12 months.

At data cut off, 34% (N=298) of patients were identified as no longer being on treatment; 35% (N=105) of patients stopped treatment due to progression, 11% (N=63) of patients stopped treatment due to acute toxicity, 6% (N=19) of patients chose to end their treatment, 20% (N=61) of patients died not on treatment, 9% (N=26) of patients died on treatment and 8% (N=24) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment.

The median overall survival was not reached. OS at 6 months was 88% [95% CI: 86%, 90%], OS at 12 months was 75% [95% CI: 70%, 79%].

A sensitivity analysis was conducted for a cohort with at least 6 months data follow-up in the SACT dataset. Results for treatment duration and survival were consistent with the full analysis cohort.

Conclusion

This report analyses SACT real world data for patients treated with abemaciclib with fulvestrant for advanced hormone-receptor positive, HER2-negative breast cancer in the CDF. It evaluates treatment duration, overall survival, treatment outcomes for all patients treated with abemaciclib with fulvestrant for this indication.

[a] Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced

Introduction

Breast cancer (C50) accounts for 15% of all cancer diagnoses in England. In 2017, 46,109 patients were diagnosed with breast cancer (females 45,790, males 319)[2].

Abemaciclib with fulvestrant is recommended for use within the Cancer Drugs Fund as an option for treating hormone receptor-positive, human epidermal growth factor receptor 2 (HER2) - negative locally advanced or metastatic breast cancer in people who have had endocrine therapy only if:

- exemestane plus everolimus would be the most appropriate alternative and
- the conditions in the managed access agreement for abemaciclib with fulvestrant are followed[3].

Background to this report

The Public Health England and NHS England and NHS Improvement partnership on cancer data – using routinely collected data to support effective patient care

High quality and timely cancer data underpin NHS England NHS Improvement and Public Health England's (PHE's) ambitions of monitoring cancer care and outcomes across the patient pathway. The objective of the PHE and NHS England and NHS Improvement partnership on cancer data is to address mutually beneficial questions using Systemic Anti-Cancer Therapy (SACT) data collected by PHE. This includes NHS England and NHS Improvement commissioning PHE to produce routine outcome reports on patients receiving treatments funded through the Cancer Drugs Fund (CDF) during a period of managed access.

The CDF is a source of funding for cancer drugs in England[4]. From the 29th July 2016 NHS England implemented a new approach to the appraisal of drugs funded by the CDF. The new CDF operates as a managed access scheme that provides patients with earlier access to new and promising treatments where there is uncertainty as to their clinical and cost effectiveness. During this period of managed access, ongoing data collection is used to answer the uncertainties raised by the NICE committee and inform drug reappraisal at the end of the CDF funding period[5].

PHE will analyse data derived from patient-level information collected in the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the National Cancer Registration and Analysis Service, which is part of PHE.

NICE Appraisal Committee review of abemaciclib with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer after endocrine therapy [TA579].

The NICE Appraisal Committee reviewed the clinical and cost effectiveness of abemaciclib with fulvestrant (Lilly) in treating advanced hormone-receptor positive, HER2-negative breast cancer [TA579] and published guidance for this indication in May 2019[6]

Due to the clinical uncertainties identified by the committee and outlined below, the committee recommended commissioning of abemaciclib with fulvestrant through the CDF for a period of 32 months, from April 2019 to December 2021, this date has since been amended as per the company's request.

During the CDF funding period, results from an ongoing clinical trial evaluating abemaciclib with fulvestrant in the licensed indication is likely to answer the main clinical uncertainties raised by the NICE committee. The ongoing trial to support the evaluation of abemaciclib with fulvestrant is MONARCH 2[7]. Data collected from the MONARCH 2 clinical trial would be the primary source of data collection.

Analysis of the SACT dataset would provide information on real-world treatment patterns and outcomes for abemaciclib with fulvestrant for advanced hormone-receptor positive, HER2-negative breast cancer in England, during the CDF funding period. This would act as a secondary source of information alongside the results of the MONARCH 2[7].

The committee identified the key areas of uncertainty below for re-appraisal at the end of the CDF data collection;

- **Overall survival**
- **Treatment duration**

Approach

Upon entry to the CDF, representatives from NHS England and NHS Improvement, NICE, PHE and the company (Lilly) formed a working group to agree the Data Collection Agreement (DCA)[6]. The DCA set out the real-world data to be collected and analysed to support the NICE re-appraisal of abemaciclib with fulvestrant. It also detailed the eligibility criteria for patient access to abemaciclib with fulvestrant through the CDF and CDF entry and exit dates.

This report includes patients with approved CDF applications for abemaciclib with fulvestrant, approved through Blueteq® and followed-up in the SACT dataset collected by PHE.

Methods

CDF applications - identification of the cohort of interest

NHS England and NHS Improvement collects applications for CDF treatments through their online prior approval system (Blueteq®). The Blueteq application form captures essential baseline demographic and clinical characteristics of patients needed for CDF evaluation purposes. Where appropriate, Blueteq data are included in this report.

Consultants must complete a Blueteq application form for every patient receiving CDF funded treatment. As part of the application form, consultants must confirm that a patient satisfies all clinical eligibility criteria to commence treatment. PHE has access to the Blueteq database and key data items such as NHS numbers, primary diagnosis and drug information of all patients with an approved CDF application (which therefore met the treatment eligibility criteria).

The lawfulness of this processing is covered under Article 6(1)(e) of the EU General Data Protection Regulations (GDPR) (processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller). The processing of special categories of personal data is also covered under article 9(2)(h) of EU GDPR (processing is necessary for the purposes of preventive or occupational medicine). As NHS E & I do not have an exemption to the Common Law Duty of Confidentiality, NHS E & I cannot access the identifiable data directly. PHE, through the National Cancer Registration and

Analysis Service have permission to process confidential patient information though Regulation 2 of The Health Service (Control of Patient Information) Regulations 2002.

PHE collates data on all SACT prescribed drugs by NHS organisations in England, irrespective of the funding mechanism. The Blueteq extract is therefore essential to identify the cohort of patients whose treatment was funded by the CDF.

Abemaciclib with fulvestrant clinical treatment criteria

- Application for abemaciclib in combination with fulvestrant is made by and the first cycle of abemaciclib plus fulvestrant will be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
- Patient has histologically or cytologically documented oestrogen receptor positive and HER-2 negative breast cancer
- Patient has metastatic breast cancer or locally advanced breast cancer which is not amenable to curative treatment
- Patient is male or is female and if female is either post-menopausal or if pre- or peri-menopausal has undergone ovarian ablation or suppression with LHRH agonist treatment
- Patient has an ECOG performance status of 0 or 1 or 2.
- Patient has received previous therapy according to one of the three populations as set out below as these are the only groups for which there was evidence submitted to NICE for the use of abemaciclib plus fulvestrant
    - has progressive disease whilst still receiving adjuvant or neoadjuvant endocrine therapy for early breast cancer with no subsequent endocrine therapy received following disease progression or
    - has progressive disease within 12 or less months of completing adjuvant endocrine therapy for early breast cancer with no subsequent endocrine therapy received following disease progression or
    - has progressive disease on 1st line therapy for advanced/metastatic breast cancer with no subsequent endocrine therapy received following disease progression.
- Patient has had no prior treatment with a CDK 4/6 inhibitor unless either abemaciclib has been received as part of any compassionate use scheme for the combination of abemaciclib plus fulvestrant and the patient meets all the other criteria set out here
- Patient has had no prior treatment with fulvestrant
- Patient has had no prior treatment with everolimus
- Abemaciclib will only be given in combination with fulvestrant
- Treatment will continue until there is progressive disease or excessive toxicity or until the patient chooses to discontinue treatment, whichever is the sooner
- Treatment breaks of up to 6 weeks are allowed, but solely to allow toxicities to settle
- Abemaciclib and fulvestrant will be otherwise used as set out in its Summary of Product Characteristics (SPC)

CDF applications - de-duplication criteria

Before conducting any analysis on CDF treatments, the Blueteq data is examined to identify duplicate applications. The following de-duplication rules are applied:

- If two trusts apply for abemaciclib with fulvestrant for the treatment of advanced hormone-receptor positive, HER2-negative breast cancer for the same patient (identified using the patient's NHS number), and both applications have the same approval date, then the record where the CDF trust (the trust applying for CDF treatment) matches the SACT treating trust is selected.

- If two trusts apply for abemaciclib with fulvestrant for the treatment of advanced hormone-receptor positive, HER2-negative breast cancer for the same patient, and the application dates are different, then the record where the approval date in the CDF is closest to the regimen start date in SACT is selected, even if the CDF trust did not match the SACT treating trust.

- If two applications are submitted for abemaciclib with fulvestrant for the treatment of advanced hormone-receptor positive, HER2-negative breast cancer and the patient has no regimen start date in SACT capturing when the specific drug was delivered, then the earliest application in the CDF is selected.

Initial CDF cohorts

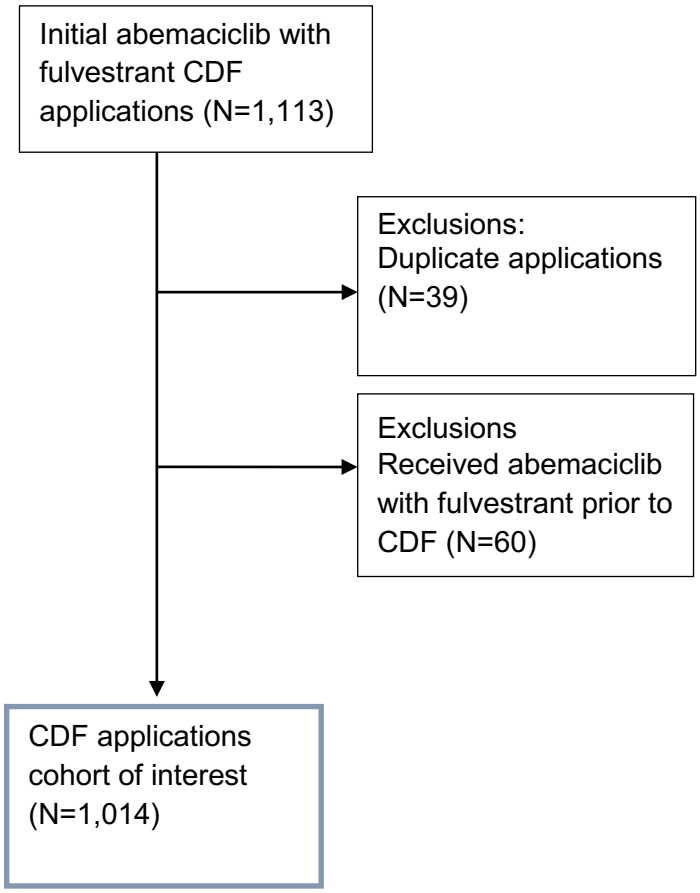
The analysis cohort is limited to the date abemaciclib with fulvestrant entered the CDF for this indication, onwards. Any treatments delivered before the CDF entry date are excluded as they are likely to be patients receiving treatment via an Early Access to Medicines Scheme (EAMS) or a compassionate access scheme run by the pharmaceutical company. These schemes may have different eligibility criteria compared to the clinical treatment criteria detailed in the CDF managed access agreement for this indication.

The CDF applications included in these analyses are from 2 April 2019 to 15 December 2019. A snapshot of SACT data was taken on 4 April 2020 and made available for analysis on 14 April 2020. The snapshot includes SACT activity up to the 31 December 2019. Tracing the patients' vital status was carried out on 22 May 2020 using the personal demographics service (PDS)[1].

There were 1,113 applications for CDF funding for abemaciclib with fulvestrant for advanced hormone-receptor positive, HER2-negative breast cancer between 2 April 2019 and 15 December 2019 in the NHS England and NHS Improvement Blueteq database. Following de-duplication this relates to 1,074 unique patients.

Sixty patients were excluded from these analyses as they appeared to have received abemaciclib with fulvestrant prior to the drug being available through the CDF.

Figure 1: Derivation of the cohort of interest from all CDF (Blueteq) applications made for abemaciclib with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer between 2 April 2019 and 15 December 2019



Linking CDF cohort to SACT

NHS numbers were used to link SACT records to CDF applications for abemaciclib with fulvestrant in NHS England and NHS Improvement's Blueteq system. Information on treatments in SACT were examined to ensure the correct SACT treatment records were matched to the CDF application; this includes information on treatment dates (regimen, cycle and administration dates) and primary diagnosis codes in SACT.

Addressing clinical uncertainties

Treatment duration

Treatment duration is calculated from the start of a patient's treatment to their last known treatment date in SACT.

Treatment start date is defined as the date the patient started their CDF treatment. This date is identified as the patient's earliest treatment date in the SACT dataset for the treatment of interest. Data items[8] used to determine a patient's earliest treatment date are:

- Start date of regimen – SACT data item #22
- Start date of cycle – SACT data item #27
- Administration date – SACT data item #34

The earliest of these dates is used as the treatment start date.

The same SACT data items (#22, #27, #34)[8] are used to identify a patient's final treatment date. The latest of these three dates is used as the patient's final treatment date.

Additional explanation of these dates is provided below:

Start date of regimen
A regimen defines the drugs used, their dosage and frequency of treatment. A regimen may contain many cycles. This date is generally only used if cycle or administration dates are missing.

Start date of cycle
A cycle is a period of time over which treatment is delivered. A cycle may contain several administrations of treatment, after each treatment administration, separated by an appropriate time delay. For example; a patient may be on a 3-weekly cycle with treatment being administered on the 1st and 8th day, but nothing on days 2 to 7 and days 9 to 20. The 1st day would be recorded as the "start day of cycle". The patient's next cycle would start on the 21st day.

Administration date
An administration is the date a patient is administered the treatment, which should coincide with when they receive treatment. Using the above example, the administrations for a single 3-week cycle would be on the 1st and 8th day. The next administration would be on the 21st day, which would be the start of their next cycle.

The interval between treatment start date and final treatment date is the patient's time on treatment.

All patients are then allocated a 'prescription length' which is a set number of days added to the final treatment date to allow for the fact that they are effectively still 'on treatment' between administrations. The prescription length should correspond to the typical interval between treatment administrations.

If a patient dies between administrations, then their censor date is their date of death and these patients are deemed to have died on treatment unless an outcome summary is submitted to the SACT database confirming that the patient ended treatment due to disease progression or toxicity before death.

Abemaciclib with fulvestrant is administered orally, treatment is generally prescribed in a healthcare facility and healthcare professionals are able to confirm that the prescribing of treatment has taken place on a specified date. A duration of 28-days has been added to final treatment date for all patients; this represents the duration from a patient's last cycle to their next[9]. Abemaciclib with fulvestrant is a 28-day cycle consisting of one administration.

Treatment duration is calculated for each patient as:
Treatment duration (days) = (Final treatment date – Treatment start date) + prescription length (days).

Once a patient's treatment duration has been calculated, the patient's treatment status is identified as one of the following:

No longer receiving treatment (event), if:

- the patient has died.
- the outcome summary (SACT data item #41) detailing the reason for stopping treatment has been completed.
- there is no further SACT records for the patient following a three-month period.

If none of the above apply, the patient is assumed to still be on treatment and is censored.

Overall survival (OS)

OS is calculated from the CDF treatment start date, not the date of a patient's cancer diagnosis. Survival from the treatment start date is calculated using the patient's earliest treatment date, as described above, and the patient's date of death or the date the patient was traced for their vital status.

All patients in the cohort of interest are submitted to the PDS to check their vital status (dead/alive). Patients are traced before any analysis takes place. The date of tracing is used as the date of follow-up (censoring) for patients who have not died.

OS is calculated for each patient as the interval between the earliest treatment date where a specific drug was given to the date of death or date of follow-up (censoring).

OS (days) = Date of death (or follow up) – treatment start date

The patient is flagged as either:

Dead (event):
At the date of death recorded on the PDS.

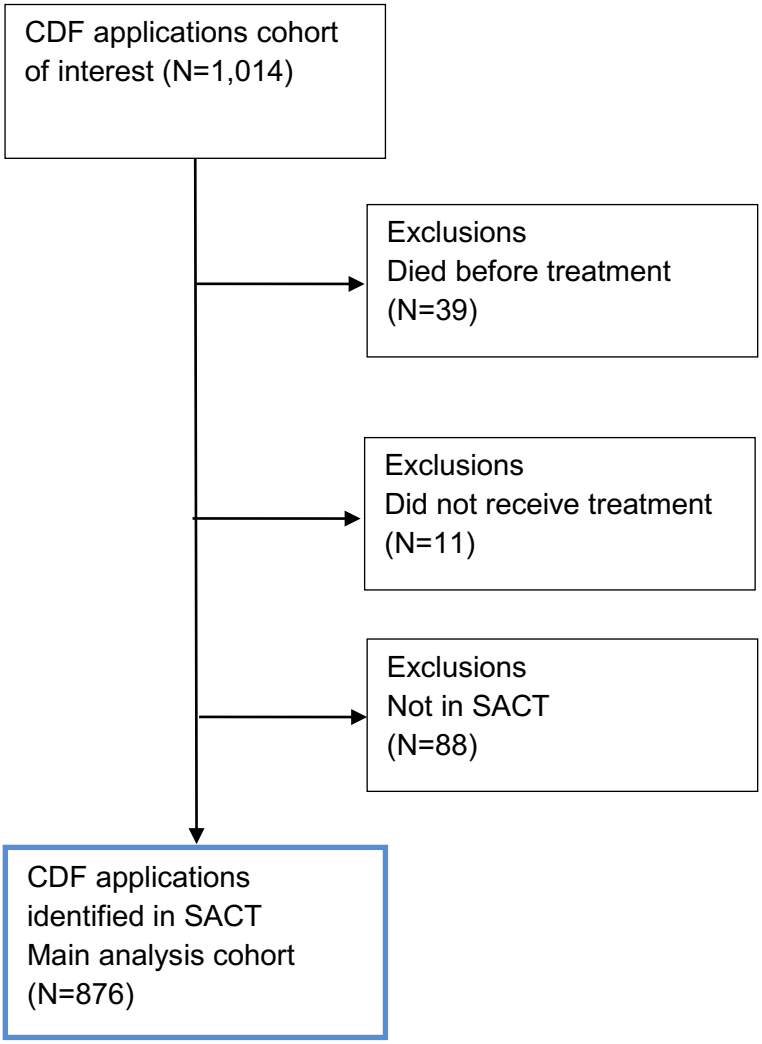
Alive (censored):
At the date patients were traced for their vital status as patients are confirmed as alive on this date.

Results

Cohort of interest

Of the 1,014 new applications for CDF funding for abemaciclib with fulvestrant for advanced hormone-receptor positive, HER2-negative breast cancer, 11 patients did not receive treatment, of which, three patients went on to receive urgent chemotherapy treatment instead, 39 patients died before treatment and 88 patients were missing from SACT[b] (see Figure 2).

Figure 2: Matched cohort - SACT data to CDF (Blueteq®) applications for abemaciclib with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer between 2 April 2019 and 15 December 2019



[b] The 11 patients that did not receive treatment, eight were confirmed by the relevant trust by the PHE data liaison team and three patients started a different therapy within a month of their CDF application form. of the 39 that died before treatment, 13 have been confirmed by the relevant trusts by the PHE data liaison team.

A maximum of 964 abemaciclib with fulvestrant records are expected in SACT for patients who were alive, eligible and confirmed to have commenced treatment (Figure 2). 91% (876/964) of these applicants for CDF funding have a treatment record in SACT.

Completeness of SACT key variables

Table 1 presents the completeness of key data items required from SACT. Completeness is 100% for primary diagnosis, date of birth, gender and treatment dates. Performance status at the start of regimen is 87% complete.

Table 1: Completeness of key SACT data items for the abemaciclib with fulvestrant cohort (N=876)

Variable	Completeness (%)
Primary diagnosis	100%
Date of birth (used to calculate age)	100%
Sex	100%
Start date of regimen	100%
Start date of cycle	100%
Administration date	100%
Performance status at start of regimen	87%

Table 2 presents the completeness of regimen outcome summary. A patient's outcome summary, detailing the reason why treatment was stopped, is only captured once a patient has completed their treatment. Therefore, the percentage completeness provided for outcome summary is for records where we assume treatment has stopped and an outcome is expected. Outcomes are expected if a patient has died, has an outcome in SACT stating why treatment has ended or has not received treatment with abemaciclib with fulvestrant in at least three months. These criteria are designed to identify all cases where a patient is likely to have finished treatment. Based on these criteria, outcomes are expected for 298. Of these, 234 (79%) have an outcome summary recorded in the SACT dataset.

Table 2: Completeness of outcome summary for patients that have ended treatment (N=298)

Variable	Completeness (%)
Outcome summary of why treatment was stopped	79%

Completeness of Blueteq key variables

Table 3 presents the completeness of key data items required from Blueteq. Previous endocrine therapy is 100% complete (876/876).

Table 3: Previous endocrine therapy (N=876)

Variable	Completeness (%)
Previous endocrine therapy	100%

Patient characteristics

The median age of the 876 patients receiving abemaciclib with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer was 65 years. The median age in females and males was 64 and 68 years respectively.

Table 4: Patient characteristics (N=876)

Patient characteristics[c]			
		N	**%**
Sex	Female	865	99%
	Male	11	1%
Age	<40	21	2%
	40-49	92	11%
	50-59	208	24%
	60-69	235	27%
	70-79	248	28%
	80+	72	8%
Performance status	0	273	31%
	1	416	47%
	2	66	8%
	3	4	<1%
	4	1	<1%
	Missing	116	13%

[c] Figures may not sum to 100% due to rounding.

Blueteq data items

Previous endocrine therapy

The distribution of previous endocrine therapy in Table 5 shows that 34% (N=302) of patients have progressive disease whilst receiving adjuvant or neoadjuvant therapy, 4% (N=32) of patients have progressive disease within 12 or less months of completing adjuvant therapy and 62% (N=542) of patients have progressive disease on 1st line endocrine.

Table 5: Distribution of previous endocrine therapy in Blueteq (N=876)

Previous endocrine therapy	N	%
Has progressive disease whilst still receiving adjuvant or neoadjuvant endocrine therapy for early breast cancer with no subsequent endocrine therapy received following disease progression	302	34%
Has progressive disease within 12 or less months of completing adjuvant endocrine therapy for early breast cancer with no subsequent endocrine therapy received following disease progression	32	4%
has progressive disease on 1st line endocrine therapy for advanced/metastatic breast cancer with no subsequent endocrine therapy received following disease progression	542	62%
Total	**876**	**100%**

Treatment duration

Of the 876 patients with CDF applications, 298 (34%) were identified as having completed treatment by 31 December 2019 (latest follow up in SACT dataset). Patients are assumed to have completed treatment if they have died, have an outcome summary recorded in the SACT dataset or they have not received treatment with abemaciclib with fulvestrant in at least three months (see Table 9). The median follow-up time in SACT was 4.4 months (133 days).

Presently, 94% (N=132) of trusts submit their SACT return to the submission portal two months after the month's treatment activity has ended; this provides a maximum follow-up period of nine months. 6% (N=9) of trusts submit their SACT return to the submission portal one month after the month's treatment activity has ended; this provides the maximum follow-up period of ten months. SACT follow-up ends 31 December 2019.

Table 6: Breakdown by patients' treatment status[d,e,f]

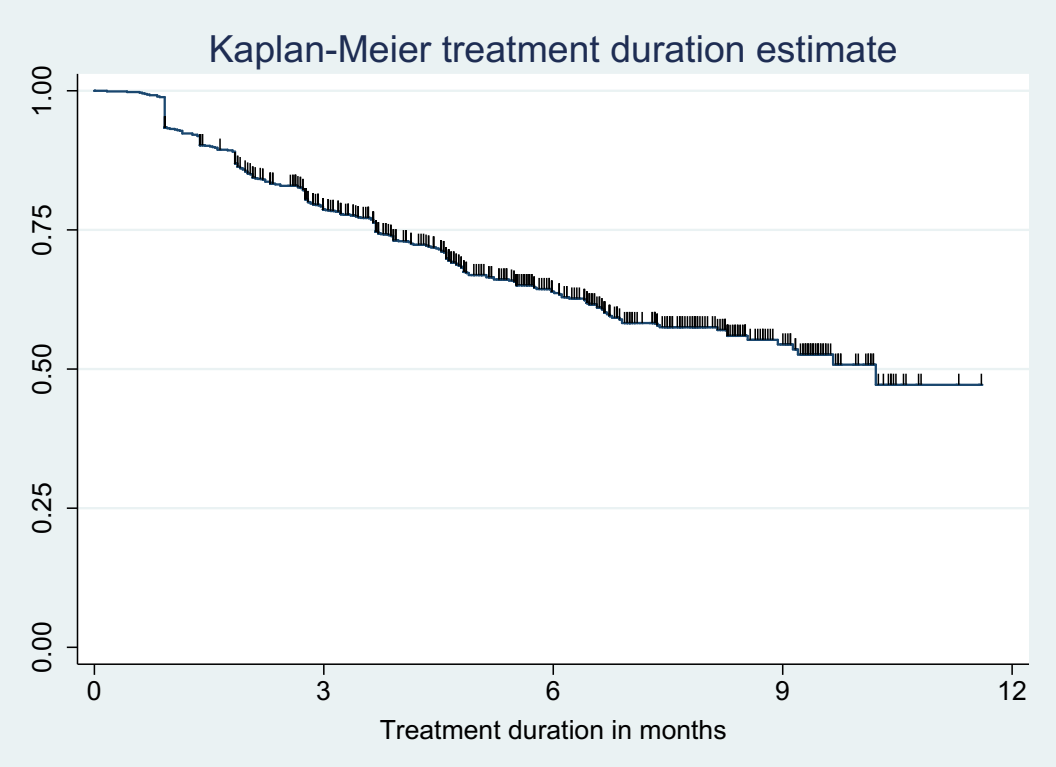
Patient status	Frequency (N)	Percentage (%)
Patient died – not on treatment	142	16%
Patient died – on treatment	26	3%
Treatment stopped	130	15%
Treatment ongoing	578	66%
Total	**876**	**100%**

[d] Figures may not sum to 100% due to rounding.
[e] Table 9 presents the outcome summary data reported by trusts. This includes patients from Table 6 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[f] 'Deaths on treatment' and 'deaths not on treatment are explained in the methodology paper available on the SACT website: http://www.chemodataset.nhs.uk/nhse_partnership/

The Kaplan-Meier curve for ongoing treatment is shown in figure 3. The median treatment duration for all patients was 10.2 months[g], (310 days) (N=876).

64% of patients were still receiving treatment at 6 months [95% CI: 60%,67%], 46% of patients were still receiving treatment at 12 months [95% CI: 37%, 56%].

Figure 3: Kaplan-Meier treatment duration (N=876)



Tables 7 and 8 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was nine months (273 days). SACT contains more follow-up for some patients.

Table 7: Number of patients at risk, by quarterly breakpoints.

Time intervals (months)	0 - 12	3 - 12	6 - 12	9 - 12
Number at risk	876	577	261	64

[g] Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced

Table 8 shows that for all patients who received treatment, 578 were still on treatment (censored) at the date of follow-up and 298 had ended treatment (events).

Table 8: Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored).

Time intervals (months)	0 - 12	3 - 12	6 - 12	9 - 12
Censored	578	458	230	60
Events	298	119	31	4

Table 9 gives a breakdown of a patient's treatment outcome recorded in SACT when a patient's treatment has come to an end. 34% (N=298) of patients had ended treatment at 31 December 2019.

Table 9: Treatment outcomes for patients that have ended treatment (N=298)[h,i]

Outcome	Frequency (N)	Percentage (%)
Stopped treatment – progression of disease	105	35%
Stopped treatment – acute chemotherapy toxicity	63	21%
Stopped treatment – patient choice	19	6%
Stopped treatment – died not on treatment[j]	61	20%
Stopped treatment – died on treatment	26	9%
Stopped treatment – no treatment in at least 3 months	24	8%
Total	**298**	**100%**

[h] Figures may not sum to 100% due to rounding.
[i] Table 9 presents the outcome summary data reported by trusts. This includes patients from Table 6 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[j] 'Deaths on treatment' and 'deaths not on treatment are explained in the methodology paper available on the SACT website: http://www.chemodataset.nhs.uk/nhse_partnership/

Table 10: Treatment outcomes and treatment status for patients that have ended treatment (N=298)

Outcome[k]	Patient died [l] not on treatment	Treatment stopped	Patient died on treatment
Stopped treatment – progression of disease	63	42	
Stopped treatment – acute chemotherapy toxicity	12	51	
Stopped treatment – patient choice	6	13	
Stopped treatment – died not on treatment	61		
Stopped treatment – died on treatment			26
Stopped treatment – no treatment in at least 3 months		24	
Total	**142**	**130**	**26**

[k] Relates to outcomes submitted by the trust in table 9.

[l] Relates to treatment status in table 6 for those that have ended treatment.

Overall survival

Of the 876 patients with a treatment record in SACT, the minimum follow-up was five months (152 days) from the last CDF application. Patients were traced for their vital status on 22 May 2020. This date was used as the follow-up date (censored date) if a patient is still alive.

The median follow-up time in SACT was 8.5 months (258 days). Figure 4 provides the Kaplan-Meier curve for overall survival, censored at 22 May 2020. The median survival was not reached. Survival at 6 months was 88% [95% CI: 86%, 90%], 12 months survival was 75% [95% CI: 70%, 79%].

Figure 4: Kaplan-Meier survival plot (N=879)

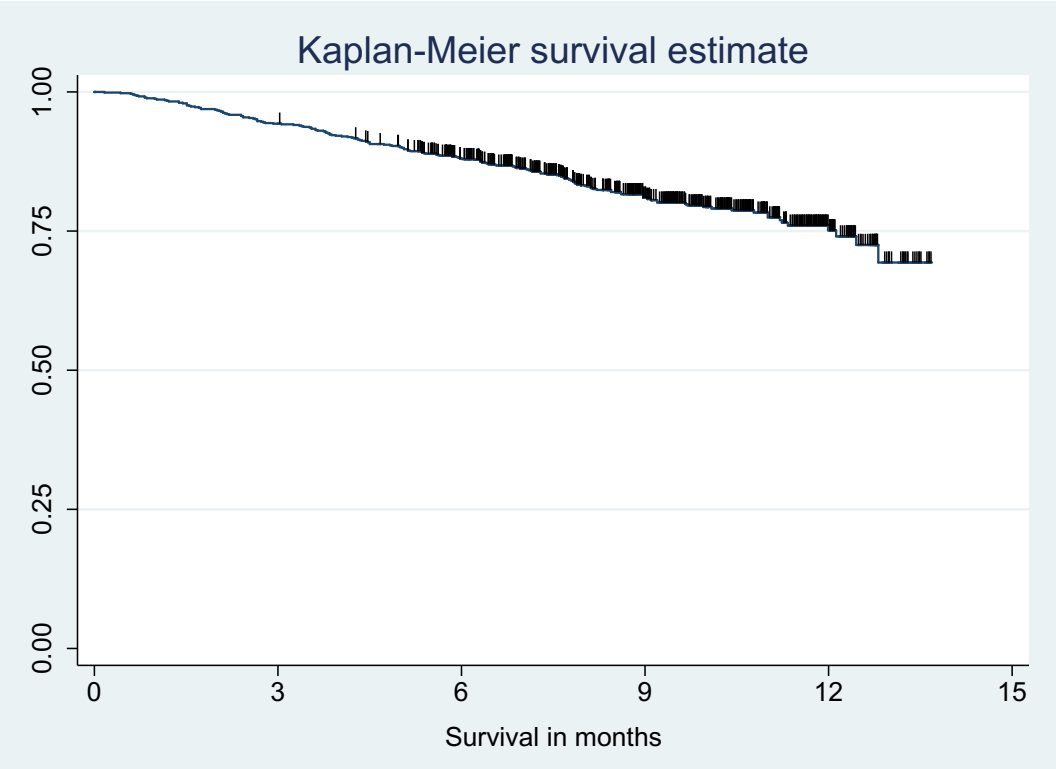


Table 11 and 12 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 13.5 months (410 days), all patients were traced on 22 May 2020.

Table 11: Includes the number of patients at risk, by quarterly breakpoints.

Time intervals (months)	0-15	3-15	6-15	9-15	12-15
Number at risk	876	825	711	381	86

Table 12 shows that for all patients who received treatment, 708 were still alive (censored) at the date of follow-up and 168 had died (events).

Table 12: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints.

Time intervals (months)	0-15	3-15	6-15	9-15	12-15
Censored	708	707	647	362	83
Events	168	118	64	19	3

Sensitivity analyses

Cohort 1: 6-month SACT follow up

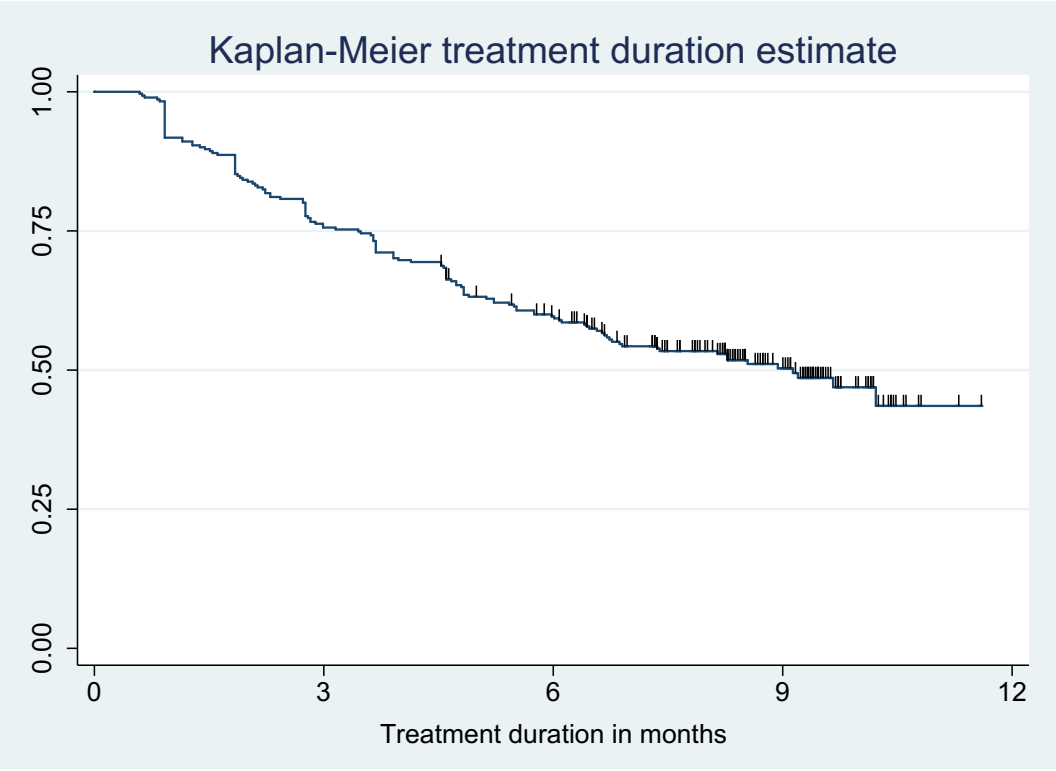
Treatment duration

Sensitivity analyses was carried out on a cohort with at least 6 months follow-up in SACT. To identify the treatment duration cohort, CDF applications were limited from 27 July 2018 to 30 June 2019 and SACT activity was followed up to the 31 December 2019.

Following the exclusions above, 291 patients (33%) were included in these analyses. The median follow-up time in SACT was 6.6 months (200 days)

The Kaplan-Meier curve for ongoing treatment is shown in figure 5. The median treatment duration for patients in this cohort was 9.1 months[m] (276 days) (N=291).

Figure 5: Kaplan-Meier treatment duration plot (N=291)



[m] Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced

Tables 13 and 14 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was nine months (273 days).

Table 13: Includes the number of patients at risk, by quarterly breakpoints.

Time intervals (months)	0 - 3	3 - 6	6 - 9	9 - 12
Number at risk	291	220	166	62

Table 14 shows that for all patients who received treatment, 149 were still on treatment (censored) at the date of follow-up and 142 had ended treatment (events).

Table 14: Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored).

Time intervals (months)	0 - 3	3 - 6	6 - 9	9 - 12
Censored	149	149	141	58
Events	142	71	25	4

Overall survival

Sensitivity analyses was also carried out for overall survival on a cohort with at least 6 months follow-up in SACT. To identify the cohort, CDF applications were limited from 27 July 2018 to 22 November 2019.

Following the exclusions above, 826 patients (94%) were included in these analyses. The median follow-up time in SACT was 8.6 months (261 days)

Figure 6 provides the Kaplan-Meier curve for overall survival, censored at 22 May 2020. The median survival was not reached.

Figure 6: Kaplan-Meier survival plot (N=826)

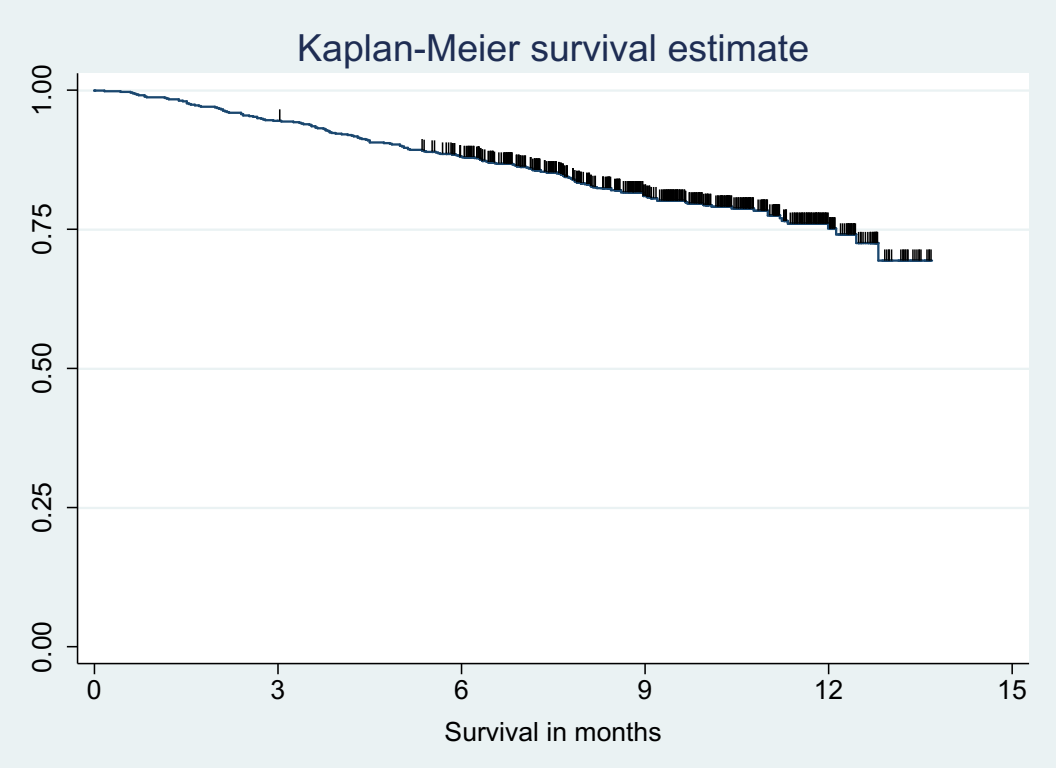


Table 15 and 16 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 13.5 months (410 days), all patients were traced on 22 May 2020.

Table 15: Includes the number of patients at risk, by quarterly breakpoints.

Time intervals (months)	0-15	3-15	6-15	9-15	12-15
Number at risk	826	780	709	381	86

Table 16 shows that for all patients who received treatment, 664 were still alive (censored) at the date of follow-up and 162 had died (events).

Table 16: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints.

Time intervals (months)	0-15	3-15	6-15	9-15	12-15
Censored	664	663	645	362	83
Events	162	117	64	19	3

Table 17: Median treatment duration and overall survival, full cohort and sensitivity analysis[n].

Metric	Standard analysis: Full cohort	Sensitivity analysis: 6 months follow-up cohort: treatment duration	Sensitivity analysis: 6 months follow-up cohort: OS
N	876	291	826
Median treatment duration	10.2 months (310 days)	9.1 months (276 days)	
OS	Not reached		Not reached

[n] Confidence intervals could not be produced for treatment duration as there was an insufficient number of events at the time this report was produced

Conclusions

967 patients received abemaciclib with fulvestrant for the treatment of advanced hormone-receptor positive, HER2-negative breast cancer [TA579] through the CDF in the reporting period (2 April 2019 and 15 December 2019). 876 patients were reported to the SACT dataset, giving a SACT dataset ascertainment of 91%. An additional eight patients with a CDF application did not receive treatment and 38 patients died before treatment. Not all were confirmed by the trust responsible for the CDF application by the team at PHE.

Patient characteristics from the SACT dataset show that 99% (N=865) of patients that received abemaciclib with fulvestrant for advanced hormone-receptor positive, HER2-negative breast cancer were female, 1% (N=11) of patients were male. Most of the cohort was aged between 50 and 79 years (79%, N=691) and 81% (N=711) of patients had a performance status between 0 and 2 at the start of their regimen.

At data cut off, 34% (N=298) of patients were identified as no longer being on treatment; 35% (N=105) of patients stopped treatment due to progression, 11% (N=63) of patients stopped treatment due to acute toxicity, 6% (N=19) of patients chose to end their treatment, 20% (N=61) of patients died not on treatment, 9% (N=26) of patients died on treatment and 8% (N=24) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment.

Median treatment duration was 10.2 months[o], (310 days). 64% [95% CI: 60%,67%] of patients were receiving treatment at 6 months and 46% [95% CI: 37%, 56%] of patients were receiving treatment at 12 months.

The median overall survival was not reached. OS at 6 months was 88% [95% CI: 86%, 90%], OS at 12 months was 75% [95% CI: 70%, 79%].

Sensitivity analyses were carried out to evaluate a cohort for which all patients had a minimum follow-up of six months. Results for treatment duration showed a difference of 1.1 months but this was not statistically significant (full cohort = 10.2 months; sensitivity analysis cohort = 9.1 months). The median overall survival was not reached in in the full or sensitivity analysis.

[o] Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced

References

1. The Personal Demographics Service (PDS) [Internet]. NHS Digital: 2020 [cited 2020 Jun]. Available from: https://digital.nhs.uk/Demographics

2. Office for National Statistics. Cancer Registration Statistics, England: 2017. 2020 [cited 2020 Jun]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland

3. National Institute for Health and Care Excellence: 2019 [cited 2020 Jun]. Available from: https://www.nice.org.uk/guidance/ta579/chapter/1-Recommendations

4. Cancer Drugs Fund. [Internet]. NHS England and NHS Improvement: 2017 [cited 2020 Jun]. Available from: https://www.england.nhs.uk/cancer/cdf/

5. Appraisal and funding of Cancer Drugs. NHS England and NHS Improvement: 2016 [cited 2020 Jun]. Available from: https://www.england.nhs.uk/wp-content/uploads/2013/04/cdf-sop.pdf

6. National Institute for Health and Care Excellence: 2019 [cited 2020 Jun]. Available from: https://www.nice.org.uk/guidance/ta579/chapter/3-Committee-discussion

7. MONARCH 2 clinical trial: 2018 [cited 2020 Jun] Available from: https://clinicaltrials.gov/ct2/show/NCT02107703

8. Systemic Anti-Cancer Therapy [Internet]: SACT: 2019 [cited 2020 Jun]. Available from: http://www.chemodataset.nhs.uk/home/SACT

9. CDF analytical methods. [Internet]. PHE: 2019 [cited 2020 Jun]. Available from: http://www.chemodataset.nhs.uk/nhse_partnership/

BMJ TAG

Abemaciclib with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer after endocrine therapy (CDF review of TA579)

Cancer Drugs Fund Review

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 13/12/15T.

Title:	Abemaciclib with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer after endocrine therapy (CDF review of TA579)
Produced by:	BMJ Technology Assessment Group (BMJ TAG)
Authors:	Steve Edwards, Director of Health Technology Assessment, BMJ-TAG, London Charlotta Karner, HTA Analyst Manager, BMJ-TAG, London Mariana Bacelar, Principal Health Economist, BMJ-TAG, London
Correspondence to:	Steve Edwards, BMJ TAG, BMJ, BMA House, Tavistock Square, London, WC1H 9JR.
Date completed:	29/10/2020
Source of funding:	This report was commissioned by the NIHR Evidence Synthesis Programme as project number 13/12/15T.
Declared competing interests of the authors	No competing interests were declared which affect the impartiality of this report. BMJ Technology Assessment Group (BMJ-TAG) and the editorial team of The BMJ work independently to one another. The views and opinions expressed in this report are those of the BMJ-TAG.
Acknowledgments:	The ERG would like to thank Dr Alicia Okines, Consultant Medical Oncologist at The Royal Marsden NHS Foundation Trust and Dr Rob Stein, Professor of Breast Oncology & Consultant Medical Oncologist at UCLH, for providing clinical advice for the project.
Rider on responsibility for report:	The views expressed in this report are those of the authors and not necessarily those of the NIHR Systematic Reviews Programme. Any errors are the responsibility of the authors.
Report reference:	Edwards SJ, Karner C, Bacelar M. Abemaciclib with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer after endocrine therapy: A CDF review of TA579. BMJ-TAG, 2020.

Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Charlotta Karner	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; validation of the companies FP NMAs; critical appraisal of the clinical evidence and drafted the clinical sections
Mariana Bacelar	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

All authors read and commented on draft versions of the ERG report.

Table of Contents

List of Tables

List of Figures

1 Executive summary

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.2 provides an overview of the key issues. Section 1.3 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.4 and 1.5 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

1.1 Critique of the adherence to committees preferred assumptions from the Terms of Engagement in the company's submission

In general, the ERG considers that the company has adhered to the committee's preferred assumptions from the Terms of Engagement (ToE), although the company did not provide full results for the subgroup of patients in MONARCH 2 who were given the licenced dose of abemaciclib (150mg), hereafter referred to as the post-amendment subgroup.

The clinical data presented by the company includes the latest data cut from the company's randomised controlled trial (RCT), MONARCH 2, comparing abemaciclib plus fulvestrant (ABE-FUL) and placebo plus fulvestrant (PBO-FUL). In line with the committee's preferred assumptions for this CDF review, the company has also presented updated fractional polynomial (FP) network meta-analyses (NMAs), enabling a comparison of ABE-FUL with the key comparator exemestane with everolimus (EXE-EVE). The company has performed the NMAs using the updated MONARCH 2 data for the ITT population but has not provided results using the updated MONARCH 2 data for the post-amendment subgroup.

Also, in line with the with the committee's preferred assumptions for this CDF review, the company has used the updated, post-amendment data from MONARCH 2 to estimate TTD for ABE-FUL in the model.

In addition, the company presented a summary of the observational data that has been collected by Public Health England during the period of managed access for ABE-FUL through the Cancer Drugs Fund (CDF), hereafter referred to as the Systemic Anti-Cancer Therapy (SACT) cohort. Overall survival (OS) data were reported for the SACT cohort but median follow up for OS was only 8.5 months and OS data were immature.

1.2 Overview of the ERG's key issues

Table 1 provides a summary of the ERG's key issues.

Table 1. Summary of key issues

Issue number	Summary of issue	Report sections
Issue 1	**Abemaciclib starting dose:** The clinical and cost effectiveness of the licenced dose of abemaciclib, based on the post amendment subgroup, have not been explored.	3.1.1
Issue 2	**Outcome validation using SACT data:** Validation limited as data from SACT cohort are immature.	3.1.2
Issue 3	**ITC of ABE-FUL and EXE-EVE:** Heterogeneity within the ITC network persists.	3.1.3
Issue 4	**Estimation of TTD for ABE-FUL**: The company's approach to estimating TTD for ABE-FUL results in underestimating the costs of abemaciclib.	4.1.4.3
Issue 5	**Estimation of TTD for EXE-EVE**: The company's approach to estimating TTD for EXE-EVE results in overestimating the costs of the comparator treatment.	4.1.4.2
Issue 6	**Prices used in the model**: The ERG found several discrepancies between the NHS reference codes to the cost estimates updated to the 2018/19 cost year (previously a 2016/17 cost year). Furthermore, some costs were not inflated, such as terminal care costs or drug costs.	4.1.6

Abbreviations: ABE-FUL, abemaciclib and fulvestrant; ERG, evidence review group; EXE-EVE, exemestane and everolimus; ITC, indirect treatment comparison; SACT, Systemic Anti-Cancer Therapy; TTD time to treatment discontinuation

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are the choice of population to run the NMA; and the methods used to derive TTD for both treatments in the model.

1.3 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Generating a survival benefit compared to EXE-EVE;
- Generating a delay in time to progression compared with EXE-EVE;

Overall, the technology is modelled to affect costs by:

- Its higher unit cost compared with EXE-EVE;
- Being better tolerated by patients than EXE-EVE, therefore prolonging the time on treatment (and time to progression) with ABE-FUL compared with EXE-EVE;
- Being administered intravenously in hospital (fulvestrant only), where EXE-EVE are administered orally.

The modelling assumptions that have the greatest effect on the ICER are:

- The OS and PFS curves derived through the FP NMA using the ITT population in MONARCH 2;
- The modelling approach used to estimate TTD for ABE-FUL;
- The HR used to estimate TTD for EXE-EVE.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

The ERG's key issues that relate to the clinical effectiveness evidence are detailed below in Table 2 to Table 3.

Table 2. Issue 1 Subgroup data by abemaciclib starting dose not explored

Report section	3.1.1
Description of issue and why the ERG has identified it as important	More mature data for the post-amendment subgroup show [redacted] in OS with ABE-FUL (HR [redacted]). In comparison, the ITT analysis shows a statistically significant improvement in OS with ABE-FUL (HR 0.757, 95% CI: 0.606 to 0.945). Due to the large difference between these results, the subgroup results are likely to have a large impact on the cost effectiveness of ABE-FUL. The company has not explored the robustness of the subgroup results or the impact of the subgroup results on the cost effectiveness of abemaciclib. Furthermore, the underlying population for OS and PFS outcomes in the economic analysis which are based on the ITT population from MONARCH 2, does not match the post-amendment population used for the estimation of TTD outcomes. Importantly, the ITT population also does not reflect the licensed treatment dose for abemaciclib and costed in the model.
What alternative approach has the ERG suggested?	The ERG strongly encourages the company to provide full subgroup data and to explore the cost effectiveness of abemaciclib 150mg using the same approach used by the company for the ITT data.
What is the expected effect on the cost-effectiveness estimates?	As the subgroup data has not been provided by the company, no cost-effectiveness estimates have been calculated. However, as the efficacy of ABE-FUL compared with PBO-FUL seems to be substantially lower in the post amendment subgroup than in the ITT population, it is reasonable to assume that ABE-FUL will be less cost-effective in this population.
What additional evidence or analyses might help to	The ERG strongly encourages the company to provide full subgroup data

resolve this key issue?	and to explore the cost effectiveness of abemaciclib 150mg. The ERG also encouraged the company to further explore the robustness of the subgroup analysis. That is, not the difference between the pre- and post-amendment subgroups but any reasons for why the subgroup results would not be reliable. This is in light of MONARCH 2 being a placebo controlled RCT of good quality and the post-amendment subgroup, which constitutes a large proportion of the overall trial population (~75%), having an adequate sample size to be powered to detect a significant difference between ABE-FUL and PBO-FUL.

Abbreviations: ABE-FUL, abemaciclib and fulvestrant; ERG, evidence review group; EXE-EVE, exemestane and everolimus; HR, hazard ratio; ITT, intention to treat; OS, overall survival; PBO-FUL, placebo and fulvestrant; PFS, progression-free survival; RCT, randomised controlled trial; TTD time to treatment discontinuation.

Table 3. Issue 3 Heterogeneity within the indirect treatment comparison network

Report section	3.1.3
Description of issue and why the ERG has identified it as important	The network for the ITC has been trimmed down to only include trials needed to link ABE-FUL with EXE-EVE. This is likely to decrease the clinical heterogeneity across the network, however, the heterogeneity has not been eliminated. Therefore, there is still uncertainty around the clinical efficacy of ABE-FUL compared with EXE-EVE, which continues to impact on the uncertainty around the cost effectiveness.
What alternative approach has the ERG suggested?	The ERG does not have a suggested alternative approach as the data are limited by the patient characteristics reported for the trials in the network.
What is the expected effect on the cost-effectiveness estimates?	The ERG is unable to predict what the impact on the ICER is likely to be.
What additional evidence or analyses might help to resolve this key issue?	The ERG does not consider it unlikely that additional information from the trials other than MONARCH 2 included in the network, will become available to help resolve this issue of potential unknown heterogeneity. In addition, where there are known differences between the trials in the network, the ERG does not consider adjustments can be reasonably undertaken to help resolve this issue.

Abbreviations: ABE-FUL, abemaciclib and fulvestrant; ERG, evidence review group; EXE-EVE, exemestane and everolimus; ITC, indirect treatment comparison.

1.5 The cost-effectiveness evidence: summary of the ERG's key issues

Table 4 to Table 6 present the ERG's key issues with the company's cost-effectiveness analysis.

Table 4. Issue 4 TTD estimated for ABE-FUL

Report section	4.1.4.1
Description of issue and why the ERG has identified it as important	The company's approach to estimating TTD for ABE-FUL results in underestimating the costs of abemaciclib. The company did not comply with the ERG's request, at the clarification stage, for PFS data for the post amendment population in MONARCH 2,

	therefore the ERG could not compare TTD and PFS for ABE-FUL in the same population. However, the TTD KM curve (post amendment population) tracks closely to the PFS KM curve for the ITT population. If the 200mg population were excluded from the ITT PFS curve (therefore resulting in a PFS curve for the post amendment population), it is likely that the PFS KM curve for the post amendment population would track much closer (or even on top) of the KM TTD curve for the same population, as the post amendment population received a lower and potentially less effective dose of ABE-FUL. The modelled PFS and TTD curves for ABE-FUL show a wide separation after month 6 in the model, which is not supported by the available TTD and PFS data.
What alternative approach has the ERG suggested?	The ERG has assumed that patients receiving 150mg BID of ABE-FUL only discontinue treatment upon progression (i.e. TTD equals PFS in the model).
What is the expected effect on the cost-effectiveness estimates?	Assuming that TTD equals PFS in the ABE-FUL of the model increased the ICER from £13,746 to £44,281 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	The company should provide the PFS KM data for the post amendment population from MONARCH 2 (20th June 2019 data cut) for comparison with the TTD KM data for the same population.

Abbreviations: Abbreviations: ICER, incremental cost-effectiveness ratio; KM, Kaplan Meier; TTD, time to treatment discontinuation

Table 5. Issue 5 TTD estimated for EXE-EVE

Report section	4.1.4.24.1.4.2
Description of issue and why the ERG has identified it as important	The company's approach to estimating TTD for EXE-EVE results in overestimating the costs of the comparator treatment. In BOLERO 2, median TTD for EXE and EVE in the EXE-EVE arm was 6.8 and 5.5 months, respectively. The ERG acknowledges that in its original report it recommended that the median time on treatment for EXE was used to dictate time on treatment as patients will not discontinue the intervention (i.e. the combination treatment) until both treatments are discontinued. However, clinical expert opinion provided to the ERG during the CDF review informed that in clinical practice, most patients discontinue EVE due to its toxicity, but carry on treatment with EXE. Given that EXE is considerably less expensive than EVE, assuming 6.8 instead of 5.5 months in the model would overestimate the treatment costs for EXE-EVE, considering the model's inability to cost treatment durations separately in the EXE-EVE arm. Time on treatment with EXE-EVE was estimated by applying a HR of 1.53 to the updated FP NMA PFS curve for EXE-EVE. The company estimated the HR with the formula: log(0.5)/log(0.64) = 1.53; where 0.64 represents the percentage of patients in the updated FP NMA PFS curve for EXE-EVE at 6.8 months (the median time on treatment with EXE in the EXE-EVE arm in BOLERO 2).
What alternative approach has the ERG suggested?	The ERG proposes that 5.5 months is a more robust estimate for calculating treatment costs with EXE-EVE. Furthermore, using the PFS curve from BOLERO 2 would have been more appropriate than using the updated FP NMA PFS curve to estimate the percentage of patients free from progression at the time of median TTD. Therefore, the ERG derived a HR by diving the cumulative hazard for median TTD [i.e. log(0.5)] by the cumulative hazard for the KM PFS curve

	from BOLERO 2 at the time of median TTD in the same trial (5.5 months) - log(0.5)/log(0.65) = 1.61; where 0.65 represents the percentage of patients in the KM PFS curve for EXE-EVE at 5.5 months.
What is the expected effect on the cost-effectiveness estimates?	Using the ERG's estimated HR increased the ICER from £13,746 to £18,032 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	The availability of KM data to model TTD for EXE and EVE separately.

Abbreviations: Abbreviations: ICER, incremental cost-effectiveness ratio; KM, Kaplan Meier; TTD, time to treatment discontinuation

Table 6. Issue 6 Prices used in the model

Report section	4.1.6
Description of issue and why the ERG has identified it as important	The ERG concluded that the company provided new cost estimates in their CDF review model which reflect NHS reference costs for the 2018/19 cost year (previously a 2016/17 cost year). Nonetheless, when trying to match the NHS reference codes to the cost estimates, the ERG found several discrepancies. Furthermore, the ERG notes that the company was inconsistent as it did not, for example, inflate costs such as terminal care costs or drug costs. It is important that the costs used in the analysis reflect the more up to date NHS reference costs.
What alternative approach has the ERG suggested?	The ERG replaced the NHS reference costs to match the NHS reference code but notes that due to time constraints it could not undertake a systematic review of all cost parameters.
What is the expected effect on the cost-effectiveness estimates?	The most likely impact of updating the costs is that costs in both treatment arms will increase.
What additional evidence or analyses might help to resolve this key issue?	The ERG recommends that the company provides an input sheet with all NHS reference costs appropriately referenced and costed, together with all 2016/2017 prices uplifted to 2018/2019 costs using the consumer price index.

Abbreviations: Abbreviations: NHS, national health system

1.6 Other key issues: summary of the ERG's view

Table 7. Subsequent treatments in MONARCH 2

Report section	4.1.4.3
Description of issue and why the ERG has identified it as important	The latest data cut from MONARCH 2 provided more mature subsequent treatment data. Overall, the proportion of progressed patients who received subsequent treatments was similar across trial arms, with [redacted] of patients receiving a second line treatment. The proportion of patients receiving second line chemotherapy ([redacted] for ABE-FUL and FUL, respectively) is [redacted] to the company's proposition that ABE-FUL will provide an additional treatment option for primary or secondary ET-resistant patients therefore, allowing the postponement of chemotherapy. Although MONARCH 2 data have demonstrated that ABE-FUL delays disease progression (63% of ABE-FUL patients progressed, while 83% of FUL patients progressed in the same time interval), therefore, delaying the beginning of subsequent therapy, the observed subsequent treatment

	regimens [redacted] the proposition that ABE-FUL has an advantage over FUL, with regards to allowing other treatment options before chemotherapy. This analysis needs to be caveated by the fact that the data on subsequent therapies in MONARCH 2 are slightly incomplete (33% of patients in the ABE-FUL arm, and 13% of patients in the FUL arm had not progressed or died at the end of the follow-up period) and so it is unknown what treatments these patients would receive after they progressed. Interestingly, the proportion of patients receiving additional lines of therapy in the FUL arm was always [redacted] when compared to ABE-FUL, all the way through the 11 subsequent lines of therapy reported in the CSR.
What alternative approach has the ERG suggested?	There is no need for an alternative approach, only consideration from the committee.
What is the expected effect on the cost-effectiveness estimates?	This issue relates to the company's value proposition for ABE-FUL, but not directly with the cost-effectiveness of the drug.
What additional evidence or analyses might help to resolve this key issue?	More mature data on subsequent treatments would help painting a more complete picture, however the data maturity is reasonably good.
Abbreviations: Abbreviations: ICER, incremental cost-effectiveness ratio; KM, Kaplan Meier; TTD, time to treatment discontinuation	

Table 8. Updated quality of life data from MONARCH 2

Report section	4.1.5
Description of issue and why the ERG has identified it as important	The EQ-5D data from MONARCH 2 were reasonably mature at the earlier data cut: 211 (47.3%) patients in the ABE-FUL arm had had a progression event. However, the latest and more mature dataset shows that 63% of patients in the ABE-FUL arm had a progression event (280 out of 446 patients). The company did not present information on the quality of life data collected in the updated clinical study report (CSR) for MONARCH 2 (20th June 2019 data cut), therefore the ERG cannot ascertain what new data might have been available to conduct the analysis.
What alternative approach has the ERG suggested?	If there are more mature quality-of life data for the post-amendment population in MONARCH 2, the ERG suggests that these data should be used in the economic model.
What is the expected effect on the cost-effectiveness estimates?	The impact on the cost-effectiveness estimates will be related to the change in the utility estimates derived from the more mature data.
What additional evidence or analyses might help to resolve this key issue?	If more mature quality of life data from MONARCH 2 (post-amendment population) are available, the ERG suggests that the company provides these, and uses these in the economic analysis.
Abbreviations: Abbreviations: ICER, incremental cost-effectiveness ratio; KM, Kaplan Meier; TTD, time to treatment discontinuation	

1.7 Summary of ERG's preferred assumptions and resulting ICER

The common preferred assumptions for the economic model are listed below:

1. Removal of the half-cycle correction from the model (Section 4.1.3);
2. Assuming that TTD is the same as PFS for ABE-FUL (Section 4.1.4.2);
3. Applying the 1.61 HR to the EXE-EVE PFS curve to obtain a TTD curve for EXE-EVE (Section 4.1.4.3);
4. Using the post-progression utility from MONARCH 2 (Section 4.1.5);
5. Using the company's updated costs (with ERG's corrections - Section 4.1.6).

When the ERG's preferred assumptions are combined in the model, the ICER results in £46,225 per QALY gained (Table 9). The ERG notes the following caveats in its analysis:

1. The ERG has assumed that ABE-FUL is given until treatment discontinuation, and that patients receiving 150mg BID abemaciclib do not discontinue treatment before progression. The ERG reiterates that without the company providing the post amendment PFS data for ABE-FUL it is not possible to fully validate this assumption in the model;
2. The HR derived by the ERG to estimate TTD for EXE-EVE is based on a comparison of medians. This is a reasonably weak approach, as equivalence (or difference) in median survival estimates does not inform the difference in the curves' shape and doesn't necessarily translate into an accurate picture of differences in mean survivals. Nonetheless, given that TTD data were not available for the comparator treatments, the use of median TTD estimates was necessary;
3. The costs included in the ERG's analysis need revision, and updating by the company, as explained in Section 4.1.6.

Table 9. ERG's preferred model assumptions

Scenario	Incremental costs	Incremental QALYs	ICER
Company base case	[redacted]	[redacted]	£13,746
Removal of the half-cycle correction from the model	[redacted]	[redacted]	£13,263
Assuming that TTD is the same as PFS for ABE-FUL	[redacted]	[redacted]	£44,281
Applying the 1.61 HR to the EXE-EVE PFS curve to obtain a TTD curve	[redacted]	[redacted]	£18,032
Using the post-progression utility from MONARCH 2	[redacted]	[redacted]	£13,580
Using the company's updated costs	[redacted]	[redacted]	£12,436

ERG's preferred base case	[redacted]	[redacted]	£46,225

Abbreviations: ICER, incremental cost-effectiveness ratio; HR, hazard ratio; PFS, progression free survival; PPS, post-progression survival; QALY, quality adjusted life year

2 Introduction and background

2.1 Introduction

Abemaciclib with fulvestrant (ABE-FUL) have been approved for use in England since May 2019 through the Cancer Drugs Fund (CDF) as a treatment option for hormone receptor-positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced breast cancer.[1]

Advanced breast cancer (aBC) encompasses locally advanced breast cancer that is not amenable to curative surgery, and metastatic cancer.[2] Although aBC is incurable multiple treatments are available with the aim to manage pain and symptoms, improve quality of life and prolong life. Treatment options depend on multiple histological and genetic factors, including the expression of HR and HER2.[2] HR+/HER2− breast cancer, which is the population of interest for this appraisal, is the most common type (64% of women with metastatic breast cancer in the UK).[3]

Abemaciclib (brand name Verzenios©), which was granted marketing authorisation in October 2018,[4] is a small molecule inhibitor of cyclin-dependent kinase (CDK)4 and CDK6. CDK 4/6 inhibitors such as abemaciclib inhibit DNA synthesis and cell proliferation leading to suppression of tumour growth. Fulvestrant is a competitive oestrogen receptor (ER) antagonist that acts by down-regulation of ERs.[5] The combination of abemaciclib and fulvestrant for aBC has been evaluated in the RCT MONARCH 2. This report comprises a review of the latest clinical and cost-effectiveness evidence on abemaciclib in combination with fulvestrant based on MONARCH 2 and real-world data collected within the CDF by Public Health England.

2.2 Background

An overview of the treatment pathway for aBC and the positioning of ABE-FUL in the pathway for the population relevant to this appraisal are presented in Figure 1 below.

For HR+/HER2- breast cancer the treatment strategy comprises endocrine therapies (ETs) such as tamoxifen, fulvestrant and aromatase inhibitors (AIs), that disrupt hormone production or otherwise interfere with intracellular oestrogen signalling.[2] Some HR+ tumours do not respond to initial ET or develop resistance to ET over time. HR+/HER2− aBC can therefore be subdivided into patients with sensitivity or resistance to ET. ET-sensitive patients include those with no prior treatment with ET (*de novo* advanced), and those who have relapsed more than one year after completion of adjuvant ET with curative intent.[2] Endocrine resistance is defined as patients who either relapse during ET, or patients who initially respond to ET, yet later become unresponsive.[2] Resistance is a continuum and these definitions are mainly used in clinical trials and not necessarily clinical practice.

The predominant treatment of choice for ET-resistant aBC that is available through routine commissioning is everolimus plus exemestane (EXE-EVE). ABE-FUL is proposed as a treatment alternative for women who have relapsed or progressed on or after prior ET, that is, for women with ET-resistant breast cancer for whom EXE-EVE would be the most appropriate alternative (Figure 1).

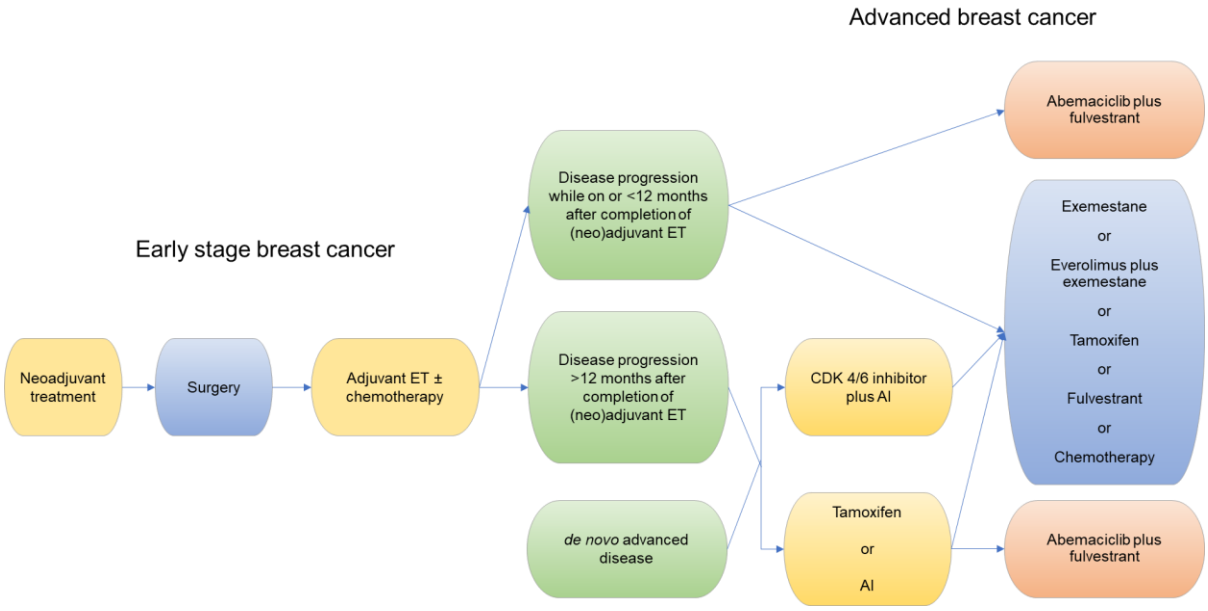
Other CDK 4/6 inhibitors, palbociclib and ribociclib, in combination with fulvestrant are also available through the CDF for this patient population but as they are not available through routine commissioning they are not considered relevant comparators for this review.[6, 7]

ABE-FUL is unlikely to be offered to patients who have received another CDK 4/6 inhibitor plus AI because of the intensity of following a combination treatment with another combined regimen, and because of the lack of evidence of reversal of ET resistance. If a CDK 4/6 inhibitor plus AI is used first-line, subsequent treatment would most likely be a monotherapy, typically fulvestrant (if available) or single agent chemotherapy.

At this time, CDK4/6 inhibitors plus AI is the preferred first-line choice of treatment for patients with ET sensitive disease, that is, *de novo* aBC and patients who have relapsed more than one year after completion of adjuvant ET.[2] Use of ABE-FUL second line is therefore likely to be limited. However, according to the ESO-ESMO guideline for aBC, it remains unclear if CDK4/6 inhibitors should be preferably administered in the first- or second-line setting.[2] Dependent on the patient, AI monotherapy might be given as a first-line treatment and ABE-FUL might be given subsequently at second-line, although the number of patients this applies to is likely to be small.

Thus, the main place for ABE-FUL in the treatment pathway is likely to be as a first line treatment alternative to EXE-EVE for patients who have progressed on or within 12 months after completion of adjuvant ET. Although some patients, who progress while receiving first-line endocrine monotherapy in the advanced setting, are also likely to receive ABE-FUL.

Figure 1. Treatment pathway for early and advanced HR+/HER2- breast cancer after introduction of abemaciclib



Abbreviation: ET, endocrine therapy

The clinical-effectiveness evidence for ABE-FUL in the original company submission (CS) for TA579[1] were derived from one randomised controlled trial (RCT), MONARCH 2, designed to evaluate the efficacy and safety of ABE-FUL in women with HR+/HER2− aBC who had progressed while receiving (neo)adjuvant ET, ≤ 12 months from the end of adjuvant therapy, or while receiving first-line ET in the advanced setting. The population eligible for ABE-FUL in MONARCH 2 is consistent with the company's proposed positioning of ABE-FUL therapy in clinical practice; however, the comparator in MONARCH 2 is fulvestrant monotherapy and therefore an indirect treatment comparison (ITC) is necessary to compare ABE-FUL with EXE-EVE. Key uncertainties during the original appraisal were around the most appropriate method for conducting the ITC of ABE-FUL and EXE-EVE, time-on-treatment and overall survival estimates, which were immature at the time. This report provides a critique of the updated evidence and analyses the company has provided to relieve these uncertainties.

2.3 Critique of company's adherence to committees preferred assumptions from the Terms of Engagement

In general, the ERG considers that the company has adhered to the committee's preferred assumptions from the Terms of Engagement. The ERG's critique of the company's adherence to the committee's preferred assumptions from the Terms of Engagement is provided in Table 10.

Table 10. Preferred assumptions from Terms of Engagement

Assumption	Terms of Engagement	Addressed by the company submission	Rationale if different	ERG comment
Comparator	Key comparator is exemestane with everolimus	Yes.	NA	The company has adhered to the assumption
Extrapolating overall survival beyond KM	Extrapolations were uncertain due to divergence in results between Company Submission and ERG report, and immature overall survival data.	Yes.	In accordance with the Terms of Engagement, Lilly will investigate the preferred extrapolation for overall survival using the minimal numbers of trials in the network required to connect MONARCH-2 with BOLERO-2. Lilly will apply the fractional polynomial NMA methodology and select the preferred extrapolation assumption(s) based on goodness of fit statistics, visual inspection and clinical plausibility. Company preferred assumption(s) not available at the time of writing.	The company has provided more mature data for MONARCH 2 for PFS, OS, and time-on-treatment. The latest data from MONARCH 2 have informed the updated FP NMA, in order to compare ABE-FUL and EXE-EVE. The company has not provided full data for the post-amendment subgroup with an abemaciclib starting dose of 150 mg or provided results from the updated FP NMA informed by these subgroup data.
Treatment duration	Time on treatment was underestimated in the company's model and was a key area of uncertainty. The company was to use the post-amendment population from MONARCH 2 to estimate TTD.	Yes, however, the company used the PFS ITT data (instead of the PFS post-amendment data) to conduct some of the calculations in the TTD analysis.	The company considered that PFS outcomes from the post-amendment population were not appropriate to use in the analysis.	The ERG strongly recommends that the company provides the PFS and OS data for the post-amendment population from MONARCH 2 (latest data cut).

Utility used in the post-progressed health state	Investigate Mitra *et al* [8] and MONACRH 2 as sources for post-progression utility.	Yes, however, it is unclear to the ERG if more mature quality of life data (20th June 2019 data cut) were available to conduct an updated analysis.	NA	The ERG advises that the company clarifies if more mature data are available and update their quality of life analysis if these data are available.
Subsequent treatments	The company should use the ERG's changes to the modelling of subsequent treatments	Yes.	NA	NA
Abbreviations: TTD, time to treatment discontinuation; PFS, progression free survival; QALY, quality adjusted life year				

3 Critique of new clinical evidence

In accordance with the data collection agreement, the company provided the following data and updated analyses:

- Further follow-up from MONARCH 2 provided for PFS, OS, time-on-treatment and other outcomes;
- SACT dataset - real-world evidence (RWE) collected within the CDF by Public Health England, providing evidence of the time on treatment (ToT) as well as OS data for patients who received ABE-FUL in clinical practice;
- Updated NMA with the more mature data cut for MONARCH 2.

3.1.1 MONARCH 2

In the original submission, data for MONARCH 2 were presented based on the primary PFS analysis, data cut-off (DCO) 14th February 2017. The updated clinical effectiveness results are taken from the interim OS analysis with DCO 20th June 2019.

The company has indicated that the proportional hazards (PHs) assumption is not fulfilled in the MONARCH 2 trial. For outcomes for which the PHs assumption does not hold, the ERG highlights that resulting HRs are challenging to interpret and potentially misleading as they infer a constant relative treatment effect throughout which is not the case. The ERG considers it more appropriate to focus on the Kaplan-Meier (KM) curves, means and % event-free at different time intervals. It is unclear for which outcomes the PHs assumption has been explored and, therefore, the ERG assumes that PHs may not hold for any of the outcomes and that although HRs are presented here (Figure 2 and Figure 3), these should be interpreted with caution.

At the time of the OS interim analysis (DCO 20th June 2019) of MONARCH 2, median follow up was 47.7 months and both median PFS and OS had been reached. The updated data cut confirms the analyses seen at the primary PFS analysis (DCO 14th February 2017), showing a clear and sustained benefit with ABE-FUL over fulvestrant monotherapy for PFS and OS (Figure 2 and Figure 3). Median PFS was 16.87 months with ABE-FUL compared with 9.27 months with fulvestrant monotherapy, and median OS was 46.72 months and 37.25 months for ABE-FUL and FUL, respectively (Table 11).

The company reports that the safety profile for ABE-FUL was consistent with the primary PFS analysis (14th February 2017). The type and relative frequency of AEs remained consistent with those in the primary analysis. No new safety signals were observed with longer follow-up.

The company provided results of pre-specified subgroup analyses from MONARCH 2 for OS. Consistently, a relative treatment benefit for ABE-FUL versus FUL alone were observed across these subgroups (Appendix 9.1). The subgroup analyses included one comparing the starting dose of abemaciclib, which was changed due to a protocol amendment that lowered the starting dose from 200 mg to 150 mg; the lower dose representing the approve starting dose in the marketing authorisation. Just over a quarter of the trial population (26.6%) were enrolled prior to the change in abemaciclib starting dose and 73.3% of patients were enrolled after the protocol amendment; 121 patients received a starting dose of 200 mg and 325 patients received abemaciclib at the 150 mg starting dose.

The relative treatment effect in favour of ABE-FUL over PBO-FUL was [redacted] in the 200 mg subgroup (HR [redacted], 95% CI: [redacted]) compared with the 150mg subgroup (HR [redacted], 95% CI: [redacted]), and the interaction between the subgroups was [redacted]([redacted]). This is despite patients enrolled prior to the amendment only receiving a median of [redacted] days of treatment before all patients still at the 200 mg starting dose had their dose reduced to 150 mg and median dose intensities were comparable between the groups; the pre- and post amendment subgroups had median dose intensities of [redacted] mg/day and [redacted] mg/day, respectively. The ERG notes that mean dose intensities, which may be considerably different, were not reported.

As the lower starting dose represents the approve starting dose in the marketing authorisation, the ERG considers the post amendment subgroup to be of particular interest for this appraisal. The ERG requested the full PFS and OS results for the post amendment subgroup but the company did not provide these, stating that a separate analysis of the post amendment population would be inappropriate. The ERG stresses that without being able to see the data and more information around the subgroup analysis, the ERG is not able to validate the company's conclusion. Likewise, the committee will not have complete information around the subgroup analyses, which, judging by the size of effect of the OS subgroup data, is likely to have a substantial impact on the cost effectiveness.

The company states that the difference between the pre- and post amendment subgroup results for OS is likely to be due to [redacted]. The company reports [redacted] in OS for patients receiving PBO-FUL in the pre- and post-amendment subgroups; [redacted], respectively, which the company states is strongly indicative of an imbalance in baseline prognostic factors between the two subgroups.

In order to account for potential [redacted] and performed multivariate analysis of OS based on the same 10 pre-specified subgroup variables.[9] [redacted]. The company reports that the interaction p-value between the pre- and post-amendment subgroups based on the multivariate analysis of OS was [redacted]

The company also presents results of a series of OS analyses comparing pre- versus post-amendment subgroups receiving PBO-FUL in order to investigate the impact of key baseline characteristics. [redacted]), and, as the company comments, [redacted] However, OS was [redacted] across most of the prespecified subgroups for patients in the pre-amendment subgroup compared to those in the post-amendment subgroup.

The ERG notes that the imbalances in baseline prognostic factors between the pre- and post-amendment subgroups indicate that patient selection is likely to have been systematically different pre- and post-amendment; i.e. whether protocol-driven and/or clinician-driven, it seems plausible that the differences pre- and post-amendment could be due to patient selection bias. Potentially systematically different patients, that still met the inclusion/exclusion criteria, were selected for the trial post-amendment based on the issue with tolerability in the pre-amendment population.

More importantly, although the company has highlighted that there are differences in baseline characteristics between the pre-and post-amendment subgroups, it is unclear if there are differences also between treatment arms within these subgroups. Due to the relatively small size of the pre-amendment subgroup it may suffer some imbalances in patient characteristics but the post-amendment subgroup, which was expanded in order for the trial to be powered to detect a difference in PFS in this subgroup, should be balanced unless the randomisation process was flawed. The study initially planned to enrol 450 patients, however, after the protocol amendment changing the starting dose of abemaciclib from 200 mg to 150 mg, the sample size was increased to 630 patients to ensure that at least 450 patients were enrolled at the 150 mg dose. The ERG notes that the differences between the pre- and post-amendment populations, highlighted by the company, indicates that it may not be appropriate to pool the populations as is done in the ITT analysis.

The ERG is therefore very concerned about the company's decision not to provide OS and PFS data for the post-amendment population from the more mature MONARCH 2 data. Consequently, the ERG has not been able to validate the company's conclusions or evaluate the subgroup results. As highlighted above, the post-amendment subgroup, which makes up almost three quarters of the trial population and which was powered to detect a difference between ABE-FUL and PBO-FUL, were given the abemaciclib dose which reflects the marketing authorisation and the dose that will be used in clinical practice. This highlights the importance of evaluating the clinical and cost effectiveness of ABE-FUL in the post-amendment population.

In order for the committee to make an informed decision about the robustness and importance of these subgroup results, the ERG strongly encourages the company to present the requested data as well as baseline characteristics for the included patients.

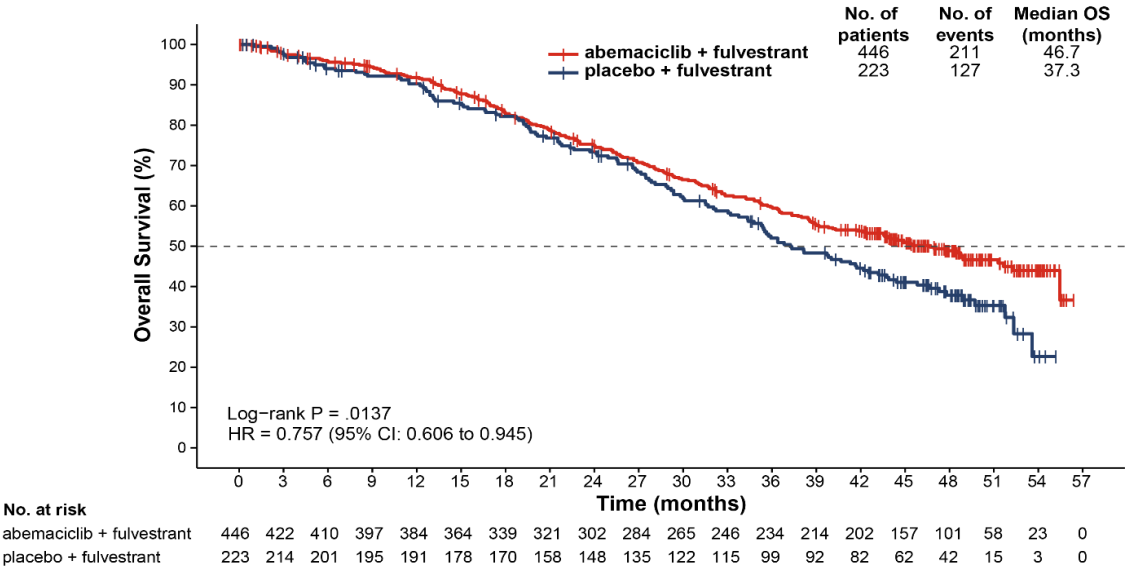
Table 11. Summary of results from MONARCH 2 (DCO 20th June 2019)

		ABE-FUL	PBO-FUL
ITT	n	446	223
OS	Events n (%)	211 (47.3)	127 (57.0)
	Median OS months (95% CI)	46.72 [redacted]	37.25 [redacted]
Survival rate	12 months % (95% CI)	[redacted]	[redacted]
	24 months % (95% CI)	[redacted]	[redacted]

	36 months % (95% CI)	[redacted]	[redacted]
	48 months % (95% CI)	[redacted]	[redacted]
PFS	Events n (%)	297 (66.6)	193 (86.5)
	Median PFS months	16.87 [redacted]	9.27 [redacted]
Survival rate	12 months % (95% CI)	[redacted]	[redacted]
	24 months % (95% CI)	[redacted]	[redacted]
	36 months % (95% CI)	29.9 [redacted]	10.1 [redacted]
exposure	Median cycles of ABE n	[redacted]	[redacted]
	Mean cycles of ABE n (SD)	[redacted]	[redacted]
	median time to discontinuation of ABE/PBO months	[redacted]	[redacted]
150mg subgroup	n	325	166
exposure	Median cycles of ABE n	[redacted]	[redacted]
	Mean cycles of ABE n (SD)	[redacted]	[redacted]
	median time to discontinuation of ABE/PBO months (95% CI)	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])

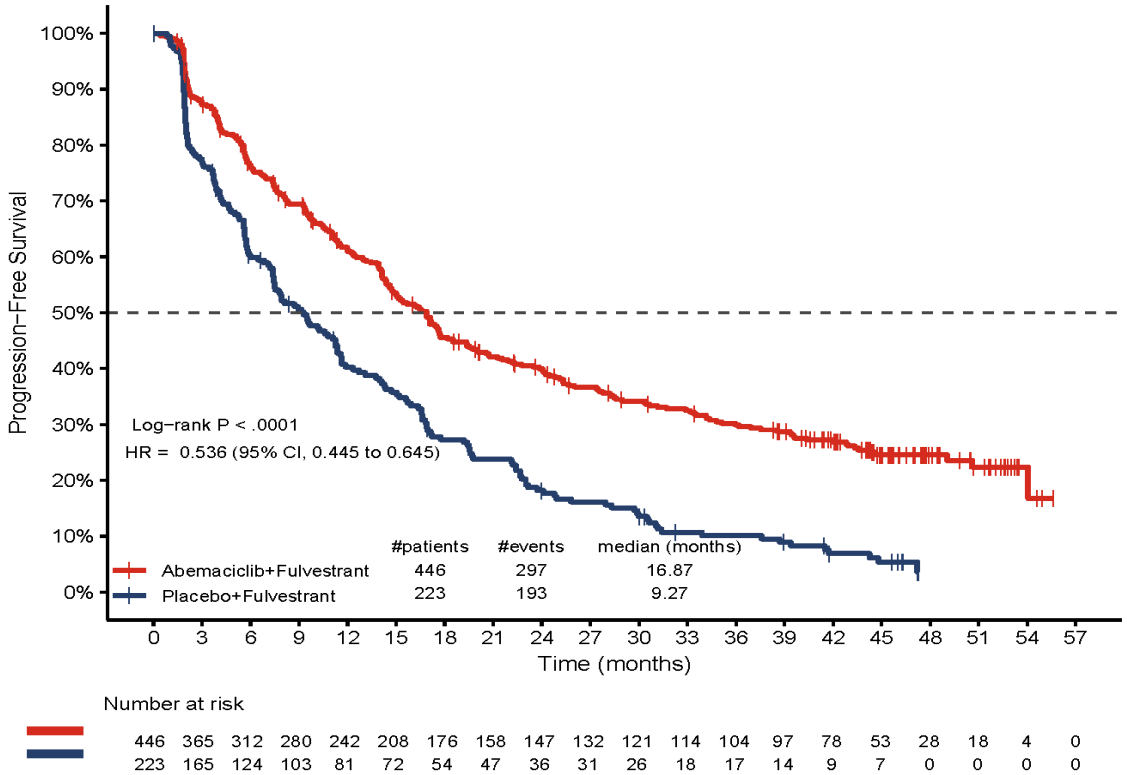
Abbreviations: ABE-FUL, abemaciclib with fulvestrant; CI, confidence interval; ITT, intention to treat; OS, overall survival; PBO-FUL, placebo with fulvestrant; PFS, progression-free survival; SD, standard deviation

Figure 2. Kaplan-Meier plot of OS for ABE-FUL vs PBO-FUL at the OS interim analysis (DCO 20th June 2019), ITT population (reproduced from CS, Figure 1)



Abbreviations: ABE: abemaciclib; DCO: data cut-off; FUL; fulvestrant; HR: hazard ratio; ITT: intention-to-treat; OS: overall survival; PBO: placebo.

Figure 3. Kaplan-Meier plot of PFS for ABE-FUL vs PBO-FUL at the OS interim analysis (DCO 20th June 2019), ITT population (reproduced from CS, Figure 2)



Abbreviations: ABE: abemaciclib; CI: confidence interval; DCO: data cut-off; FUL; fulvestrant; ITT: intention-to-treat; OS: overall survival; PBO: placebo; PFS: progression free survival.

3.1.2 Systemic Anti-Cancer Therapy (SACT) data

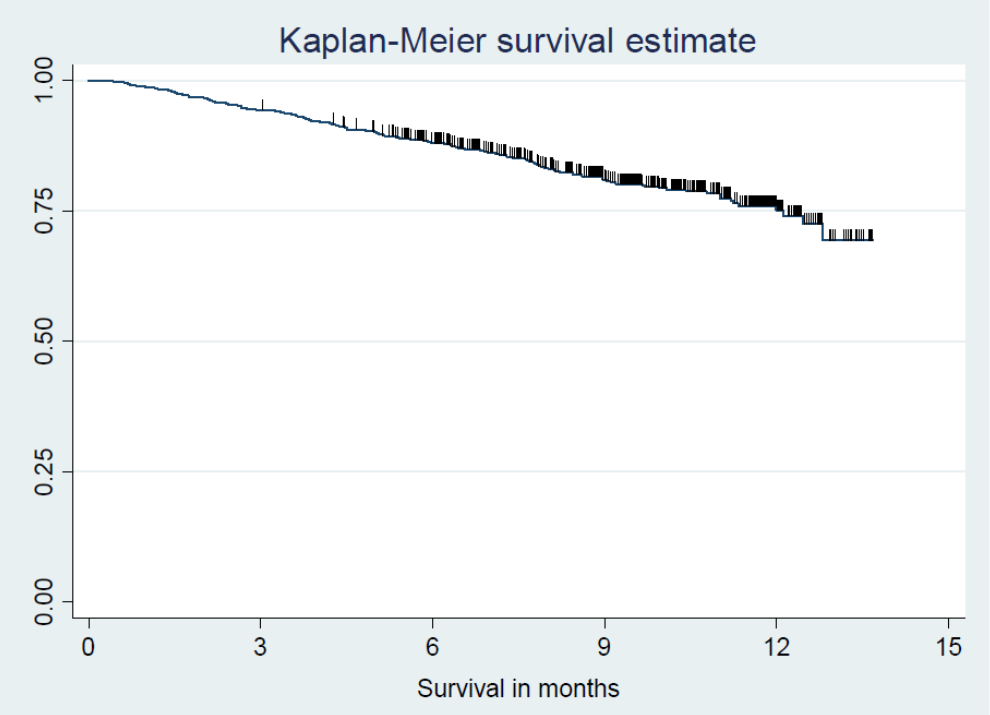
SACT data has been collected for 876 patients who have received ABE-FUL treatment through the CDF. A summary of the key baseline characteristics and demographic factors for patients treated with ABE-FUL in the SACT dataset is presented in the CS, Table 14 (Appendix 2). By the latest date of follow-up (31st December 2019) 24% of patients had completed treatment, that is, they had not received treatment with ABE-FUL in at least three months, had an outcome summary recorded in the SACT dataset or they had died. At the time of this data cut, the median duration of treatment with ABE-FUL was 10.2 months. Median follow up for OS for the SACT cohort was 8.5 months and median OS was not reached, but the survival rates show that 88% were alive at 6 months, which decreased to 75% at 12 months (Figure 4, Table 12).[10]

Table 12. Summary of results from the SACT cohort (DCO 31st December 2019)

Outcome		ABE-FUL
OS	% alive at 6 months (95% CI)	88 (86 to 90)
	% alive at 12 months (95% CI)	75 (70 to 79)
exposure	median time to discontinuation of ABE months	10.2

Abbreviations: ABE, abemaciclib; DCO, data cut-off; FUL, fulvestrant

Figure 4. Kaplan-Meier overall survival estimates for patients receiving ABE-FUL in SACT cohort (reproduced from CS Figure 6)



Source: Public Health England SACT Data Review[10]

The OS outcomes of patients in the SACT cohort are [redacted] than for the ITT population in MONARCH 2 with only 75% of patients in the SACT cohort alive at 12 months compared with [redacted] in MONARCH 2 (Table 11 and Table 12). Similarly, median duration of treatment with ABE-FUL was [redacted] in the SACT cohort, at 10.2 months, compared with [redacted] in MONARCH 2.

There are several factors likely to explain the observed differences in result between the SACT cohort and the MONARCH 2 trial, which are summarised and discussed below. Based on these factors, the company did not incorporate data from the SACT cohort in the updated economic model.

Patient selection

The SACT cohort include patients initiating treatment with ABE-FUL during the first nine months of its availability through the CDF. The company comments that early users of a newly available product may not be representative of the product's eventual user population and suggests that patients receiving ABE-FUL during this initial data collection for the SACT cohort may have more severe, treatment-refractory disease than would be expected when ABE-FUL has become more established as a treatment option. In the SACT cohort 62% of patients received ABE-FUL after progression on first line ET compared with 38% of patients in MONARCH 2. That is, a larger proportion of patients were at a later stage in the treatment pathway, which is indicative more severe, treatment-refractory disease. The ERG's clinical experts comment that this may be due to the timing of approval of CDK4/6 inhibitors with AI as first line therapy options, rather than early users of ABE-FUL generally being different from patients receiving ABE-FUL when the treatment has become more established. This may have led to a larger proportion of patients in the SACT cohort missing the opportunity of receiving a CDK4/6 inhibitor with AI first line, than would be expected as these combination therapies become more available.

Baseline characteristics and data immaturity

The SACT cohort constitute a slightly older and more frail (higher proportion of patients with performance status 2) population than that of MONARCH 2, as can be expected when comparing a controlled clinical trial and real world evidence (RWE). The company concludes that the absolute outcomes of patients in the SACT cohort are therefore likely to be slightly worse than what is observed in MONARCH 2, which the ERG agrees with. However, it is striking that the 12-month survival rate for the SACT cohort is [redacted] than for MONARCH 2, even though the SACT data are very immature with only 16% of patients having had an event and a median follow up for OS of just 8.5 month.

Treatment exposure

The company states that patients included in the SACT cohort who discontinued therapy discontinued both abemaciclib and fulvestrant at the same time, whereas in MONARCH 2 patients could discontinue one or the other treatment separately. The ERG's clinical experts comment that patients who discontinue both treatments at the same time are only likely to do so due to progression. In clinical practice, patients who come off abemaciclib due to toxicities will continue

fulvestrant therapy and be offered to change to another CDK 4/6 inhibitor with a different safety profile. That is, within clinical practice, it is likely that patients will receive a CDK 4/6 inhibitor until disease progression but that it may not be the same CDK 4/6 inhibitor throughout this period for all patients.

Treatment options

The company is concerned that patient selection for the different CDK 4/6 inhibitors that have been available through the CDF may not have been at random for one or more of these products. This could mean that the population of patients receiving ABE-FUL on the CDF represents a selected sample of the patient population in MONARCH 2. The ERG's clinical experts comment that because of the different safety profiles of the different CDK 4/6 inhibitors their use is likely to be tailored to slightly different patient groups. Palbociclib has been shown to have no or very little GI toxicity, whereas abemaciclib has been shown to be effective in patients with visceral disease (in MONARCH 2 more than half of patients had visceral metastases) and may therefore be prioritised for patients with liver metastases. That is, the use of CDK 4/6 inhibitors through the CDF is likely to reflect who would receive them in clinical practice, assuming all CDK 4/6 inhibitors are approved for routine commissioning.

Relative treatment effect

Although there is a clear difference in the absolute results between the SACT cohort and the ITT population of MONARCH 2, it is unclear if the differences between the patient cohorts and settings will have an effect on the relative efficacy between ABE-FUL and fulvestrant monotherapy. The MONARCH 2 trial remains the most robust and the only estimate of the comparative efficacy of ABE-FUL and FUL but the ERG highlights that there is a degree of uncertainty around the generalisability of the MONARCH 2 data as MONARCH 2 may not be fully reflective of clinical practice.

Conclusions

The SACT dataset provides important RWE of the efficacy of ABE-FUL in UK clinical practice, but the company has not incorporated it in the updated economic model for this appraisal, mainly because of the short follow up and therefore data immaturity, and that it is non-comparative. In comparison, MONARCH 2 provides more mature data and an estimate of the efficacy of ABE-FUL compared with fulvestrant.

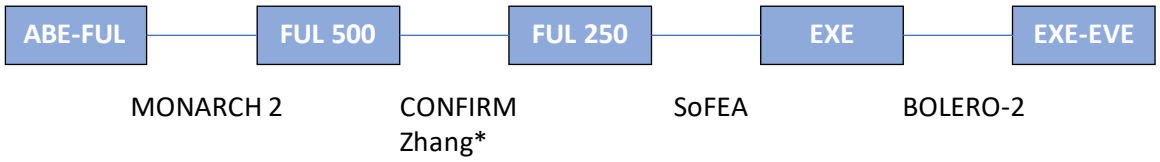
3.1.3 Indirect treatment comparison

In line with the committee's preferred assumptions for this CDF review, the company performed FP NMAs following similar methods to the original appraisal, incorporating the additional PFS and OS data for the ITT population from the most recent DCO (20th June 2019) of MONARCH 2.

In order to evaluate the clinical and cost effectiveness of ABE-FUL in the post-amendment population, which were given the 150 mg abemaciclib dose reflecting the marketing authorisation and the dose that will be used in clinical practice, the ERG requested that the company update the FP NMA using the post amendment subgroup data for MONARCH 2. The purpose of this request was also to match the source of clinical data used for TTD outcomes to the source of clinical data used to estimate OS and PFS outcomes in the economic model (see Section 4.1.4). For the reasons described in Section 3.1.1, the company did not provide the requested analyses.

The company simplified the network compared with the original NMAs, only including the minimum number of trials required for the indirect comparison of ABE-FUL and EXE-EVE (Figure 5).

Figure 5. Network used in the updated FP NMAs



*Zhang et al. is included in the PFS NMA but not the OS NMA

In the original networks for PFS and OS there was clinical heterogeneity across the trials due to population differences and differences in reporting between the trials. Although the updated network has been limited to fewer trials, the issue of clinical heterogeneity within the network has not been resolved. Because of the linear shape of the network and as there is only one trial for each comparison, it is not possible to assess statistical heterogeneity or incoherence in the network. Below is a summary of the main potential sources of clinical heterogeneity across the included trials.

HER2– status was only an eligibility criterion in BOLERO-2 and MONARCH 2. In SoFEA the proportion of patients with HER2– was 59%, whereas CONFIRM and Zhang 2016 did not report HER2 status of the participants. The populations enrolled in CONFIRM, SoFEA and Zhang 2016 could therefore have a worse prognosis than those recruited to the MONARCH 2 and BOLERO-2 where all or almost all patients were HER2–.

MONARCH 2, CONFIRM and Zhang 2016 enrolled patients with up to one prior ET for aBC, whereas BOLERO-2 and SoFEA allowed enrolment of patients who had received more than one prior line of therapy for aBC. BOLERO-2 reports that about 50% of people had received three or more previous treatments, including treatment in the adjuvant setting. MONARCH 2 did not allow prior chemotherapy in the advanced setting whereas CONFIRM, BOLERO-2, Zhang 2016 and SoFEA allowed one prior line of chemotherapy.

The company comments that the results of BOLERO-2 may have overestimated the benefit of EXE-EVE relative to EXE as the trial only enrolled patients that were refractory to aromatase inhibitors (letrozole or anastrozole). At the clarification stage the company explained that sequential single agent endocrine therapies are associated with only modest clinical benefit and that it has been questioned if EXE, which as a steroidal AI, is an appropriate treatment for patients that have previously failed on an AI. The ERG highlights that all patients also in SoFEA had progressed on a prior NSAI. If the efficacy of EXE monotherapy is underestimated in a population that have progressed on prior AI, the efficacy of FUL 250 is likely to be overestimated in SoFEA. With a possible overestimation of FUL 250 in SoFEA and of EXE-EVE in BOLERO-2 it is not possible to anticipate the overall direction of the impact of this across the whole network and ultimately for the comparison of ABE-FUL versus EXE-EVE.

Methods

The company based their methods for the updated FP NMA on those described by Jansen *et al*. 2011[11], as in the original STA, but for the updated methods the company has also taken on board the suggestions by the ERG in the original appraisal. Both the original and the updated methods are provided in the CS, Section A.7.1.

Compared with the original FP NMA, the most important updates to the methods are:

- Tested increased granularity of powers. An additional value of −1.5 was tested in the available data, in line with the ERG's previous assumptions;
- Relaxed DIC criterion, from within five points to within 20 points of best statistical fit based on DIC, to allow more plausible long-term projections;
- Increased the importance of clinical plausibility based on visual inspection of curves. Second order models for which the extrapolation resulted in a clinically implausible plateau, indicating a cure, were excluded.

For model selection, the company ran 50,000 iterations, then an increased number (100,000 iterations, of which 20,000 were discarded as burn in) were considered after model selection to reduce any uncertainty due to observed variance. The company states that the additional iterations did not impact the model selection and only reduced uncertainty. Though it is unclear if that would be the case for all powers unless both have been run and compared.

Results

Among the models which were within 20 DIC from the best statistical fit and which were clinically plausible, the first-order, fixed effect (FE) models p1 = −1.0 and p1 = 0 showed best fit for OS and PFS, respectively. The company's chosen FP model for PFS (p1 = 0) based on the updated data from MONARCH 2 is the same as that chosen by the ERG in the original appraisal based on the interim MONARCH 2 data. For OS there was a different power chosen by the company based on the updated dataset compared with that chosen by the ERG in the original appraisal, although both were first order powers.

The ERG has validated the company's chosen models, which has been confirmed by the ERG's clinical experts to be plausible extrapolations of the KM data. Due to the restricted timelines for the CDF review the ERG has not validated all powers within 20 DIC from the best fitting one.

Both the PFS and OS analyses show that ABE-FUL treatment leads to a longer event-free period than EXE-EVE. However, the order of effectiveness among the comparators differed between OS and PFS. For OS treatment with ABE-FUL resulted in the longest median OS, followed by fulvestrant monotherapy, EXE-EVE and least effective was exemestane monotherapy (Table 12). The order of the treatments was mostly sustained over time in the survival curves (

Figure 6).

Based on median PFS, ABE-FUL is the most effective treatment, followed by EXE-EVE, fulvestrant monotherapy and exemestane monotherapy (Table 14). There was considerable overlap of the PFS curves up to around 20 months after which the ABE-FUL curve was clearly above the curve for EXE-EVE (

Figure 7).

Although the PFS and OS curves seem clinically plausible when viewed separately, the PFS curves crossed the OS curves, which is not plausible. This may be due to due to overfitting of the PFS extrapolations to the tail of the KM-data for the trials when the number of patients at risk were low.

Figure 6. OS time-to-event curves (updated FP NMA) (reproduced from CS Figure 10)

Note: The curves presented above include a combined FUL extrapolation (combining data from both FUL 500 mg and FUL 250 mg) in line with the methodology used in the economic analysis, rather than the separate FUL 500 and FUL 250 curves that directly result from the NMA.

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; NMA: network meta-analysis; OS: overall survival.

Table 13. OS summary statistics from the updated FP NMA (adapted from CS Table 4)

	FUL*	EXE	EXE-EVE	ABE-FUL
Mean OS, months	[redacted]	[redacted]	[redacted]	[redacted]
Median OS, months	[redacted]	[redacted]	[redacted]	[redacted]
Alive at 12 months, %	[redacted]	[redacted]	[redacted]	[redacted]
Alive at 60 months, %	[redacted]	[redacted]	[redacted]	[redacted]
Alive at 120 months, %	[redacted]	[redacted]	[redacted]	[redacted]

*Data presented for FUL is combining data from FUL 500 mg and FUL 250 mg in line with the economic analysis, rather than the separate FUL 500 and FUL 250 data that directly result from the NMA

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FP: fractional polynomial; FUL: fulvestrant; NMA: network meta-analysis; OS: overall survival.

Figure 7. PFS Time-To-Event Curves (Updated FP NMA) (reproduced from CS, Figure 12)

Note: The curves presented above include a combined FUL extrapolation (combining data from both FUL 500 and FUL 250) in line with the methodology used in the economic analysis, rather than the separate FUL 500 and FUL 250 curves that directly result from the NMA.

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FP: fractional polynomial; FUL: fulvestrant; NMA: network meta-analysis; PFS: progression-free survival.

Table 14. PFS summary statistics from the FP NMA (adapted from CS Table 5)

	FUL[$]	EXE	EXE-EVE	ABE-FUL
Median PFS, months	[redacted]	[redacted]	[redacted]	[redacted]
Mean PFS, months**	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free at 12 months, %	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free at 60 months, %	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free at 120 months, %	[redacted]	[redacted]	[redacted]	[redacted]

[$]Data presented for FUL is combining data from FUL 500 mg and FUL 250 mg in line with the economic analysis, rather than the separate FUL 500 and FUL 250 data that directly result from the NMA

*Reported in weeks in the CS, changed to months by the ERG

**Provided by the company at the clarification stage. The values are slightly different to the PFS estimates used in the company base case analysis. In the company's base case PFS is equal to the minimum value out of PFS or OS, in order to increase the clinical plausibility of the PFS extrapolations.

Abbreviations: ABE: abemaciclib; CI: confidence interval; EVE: everolimus; EXE: exemestane; FP: fractional polynomial; FUL: fulvestrant; NMA: network meta-analysis; PFS: progression-free survival.

3.2 Conclusions of the clinical effectiveness section

The company has taken on board the committees preferred assumptions as stated in the terms of engagement and the evidence submitted by the company reflects the decision problem in the final scope. The key uncertainties identified at the original appraisal were around the survival evidence, which was very immature, and the most appropriate method for conducting the NMA. The company has provided more mature data for MONARCH 2 which generally confirm the results and decrease the uncertainty compared with the original data cut.

During the initial appraisal of ABE-FUL PFS subgroup data by starting dose (pre- and post-amendment) showed a larger relative treatment effect in favour of ABE-FUL in the pre-amendment subgroup compared with post-amendment subgroup (subgroup interaction test not statistically significant). Based on the latest data cut, comparing OS in the pre- and post-amendment group show a [redacted] ([redacted]), with ABE-FUL leading to [redacted] OS relative to PBO-FUL in the pre-amendment population (HR [redacted], 95% CI: [redacted]) compared with the post-amendment population (HR [redacted], 95% CI: [redacted]). The company considers [redacted]

The ERG notes that although there are differences in baseline characteristics between the pre-and post-amendment subgroups, it is unclear if there are differences also between treatment arms within these subgroups. Due to the relatively small size of the pre-amendment subgroup it may suffer some imbalances in patient characteristics but the post-amendment subgroup, which was expanded in order for the trial to be powered to detect a difference in PFS in this subgroup, should be balanced. The ERG also highlights that the post-amendment subgroup was given the abemaciclib dose which reflects the marketing authorisation and the dose that will be used in clinical practice. It is therefore of importance to evaluate the clinical and cost effectiveness of ABE-FUL in this population.

The ERG is therefore very concerned about the company's decision not to provide baseline characteristics, OS and PFS data for the post-amendment population. Consequently, the ERG has not been able to validate the company's conclusions around the validity of the subgroup results.

The ERG strongly encourages the company to present the requested data as well as baseline characteristics for the included patients, in order for the committee to make an informed decision about the robustness and importance of these subgroup results.

To enable the comparison of ABE-FUL and the key comparator EXE-EVE, the company performed FP NMAs incorporating the MONARCH 2 data for PFS and OS from the updated data cut for the ITT population. The ERG requested that the company also update the FP NMA to include the post-amendment subgroup data in order to evaluate the clinical and cost effectiveness of the licenced dose of abemaciclib and to match the source of clinical data used for TTD, OS and PFS in the economic model, but the company did not provide these.

The company's analyses using the updated dataset for the ITT population confirm the results and reduced the uncertainty around the ERG's FP NMA of the original appraisal. The company has utilised the FP NMA methodology preferred by the ERG, giving more weight to clinical plausibility of extrapolations alongside statistical fit. The FP NMAs for PFS and OS show that treatment with ABE-FUL leads to a longer event-free period compared with the key comparator, EXE-EVE. It is important to note that the heterogeneity between the trials in the network is likely to persist compared with the original appraisal. This includes factors such as number of lines of prior therapy, proportion of patients who had received prior AI, HER- status, primary and secondary ET resistance and prior chemotherapy. It is not possible to predict the overall direction of or quantify the impact of any potential bias, which should be kept in mind when interpreting the results. The ERG considers the results of the company's FP NMAs to provide the best available estimates of ABE-FUL versus EXE-EVE for the ITT population but notes the uncertainty around the results and the lack of FP NMA results based on the post-amendment population for MONARCH 2.

SACT data has been collected for 876 patients who have received ABE-FUL treatment through the CDF. Median follow up for OS for the SACT cohort was 8.5 months and median OS was not reached. The OS outcomes of patients in the SACT cohort are [redacted] than for the ITT population in MONARCH 2 with only 75% of patients in the SACT cohort alive at 12 months compared with [redacted] in MONARCH 2. The SACT dataset provides important RWE of the efficacy of ABE-FUL in UK clinical practice, but the company has not incorporated it in the updated economic model for this appraisal, mainly because of the short follow up and therefore data immaturity, and that it is non-comparable. In comparison, MONARCH 2 provides more mature data and an estimate of the relative efficacy of ABE-FUL compared with fulvestrant.

4 Cost effectiveness

4.1 Summary and critique of the company's submitted economic evaluation by the ERG

For the purpose of presenting and discussing the results of the several analyses used throughout TA579 and the CDF review, the ERG defined the result sets as follows:

- Company's base case results from TA579 – the base case ICER put forward by the company in TA597 (post clarification);
- Company's CDF review base case results – the base case ICER put forward by the company as a result of the CDF review;
- Company's CDF review updated base case results – the updated base case ICER put forward by the company as a result of the CDF review post clarification;
- ERG's base case results from TA579 – the base case ICER put forward by the ERG in TA597;
- ERG's CDF review base case results – the updated base case ICER put forward by the ERG as a result of the CDF review.

As a result of the clarification stage, the company updated the assumptions used in their submission for the CDF review. The key changes made in the company's economic CDF review base case results (after clarification) were as follows:

- The only comparator included in the analysis is exemestane in combination with everolimus (EXE-EVE);
- The updated FP NMA using a later data cut and the ITT population from MONARCH 2 (20th June 2019), described in Section 3, was used to derive OS and PFS curves in the model;
- The time on treatment with ABE-FUL was estimated by applying a HR of [redacted] to the updated FP NMA PFS curve for ABE-FUL;
- The time on treatment with EXE-EVE was estimated by applying a HR of 1.53 to the updated FP NMA PFS curve for EXE-EVE;
- The pre-progression utilities used in the model were those collected in the post amendment population (which included patients who started the trial on a twice daily 150 mg dose of abemaciclib) from MONARCH 2 (February 2017 data cut);
- Hospitalisation rates and length of stay were also updated in the model to reflect those collected in the post amendment population from MONARCH 2;

- Use of a post-progression utility from Mitra *et al.*; [8]
- Removal of AE-related disutilities;
- Inclusion of age-related utility decrements;
- Inclusion of fulvestrant administration costs (loading dose and subsequent doses);
- The subsequent treatment use was modelled according to the ERG's proposed method in the ERG TA579 report;
- The company accepted the ERG's proposed changes (from TA579) to the resource use and heath state costs in the model.

During the clarification stage, the ERG asked the company to explain the new cost parameters included in the model (question B8). The company did not provide a justification and instead, reverted to using its original costs from TA579. Upon closer inspection of the model, the ERG could ascertain that some of the costs provided in the company's CDF review model are updated costs to reflect the 2018/19 cost year. Nonetheless, the ERG found several problems with the updated costs estimates, which are discussed in Section 4.1.6.

As a result of the clarification stage, the company updated their CDF review base case results. These are presented in Table 15, alongside the company's base case results from TA579. All results presented in this report are inclusive of the company's patient access scheme (PAS) simple discount of [redacted] for abemaciclib.

Table 15. Company's base case results

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Company's base case results from TA579							
EXE-EVE	[redacted]	[redacted]	[redacted]	-	-	-	-
ABE-FUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
CDF review updated base case results							
EXE-EVE	[redacted]	[redacted]	[redacted]	-	-	-	-
ABE-FUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,746

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

4.1.1 Population

The population considered by the company for this CDF review comprises women with HR+/HER2- aBC who had progressed according to at least one of the following criteria:

1. While receiving (neo)adjuvant ET;
2. Less than or equal to 12 months from the end of adjuvant ET;
3. While receiving first-line ET for metastatic disease.

In the company's base case analysis from TA579, the modelled population was based on the FUL and ABE-FUL arms of the ITT population in MONARCH 2. The CDF review updated model includes the more mature data for the ITT population from MONARCH 2 for OS and PFS outcomes, while TTD outcomes; utility data; and hospitalisation data for ABE-FUL were estimated using the post amendment population, which included patients who started the trial on a twice daily 150 mg dose of abemaciclib.

During the clarification stage, the ERG requested that the company updated their FP NMA to include the post amendment data for OS and PFS outcomes from MONARCH 2 (instead of the ITT data used by the company). The company did not carry the analysis requested by the ERG nor did it provide the requested KM OS and PFS data for the post amendment population from MONARCH 2 (data cut 20th June 2019). This issue is further discussed in Section 3 and Section 4.1.4.

4.1.2 Interventions and comparators

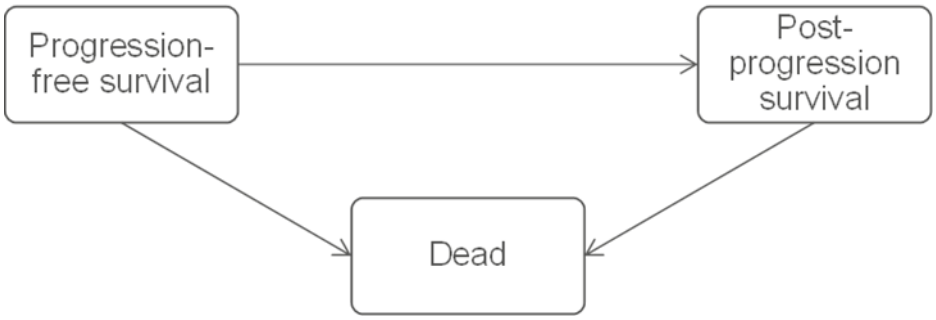
The company modelled the recommended dose for abemaciclib 150mg capsules daily on a 28-day cycle. The cost for fulvestrant (in combination with abemaciclib) was based on the recommended dose of 500mg given as an intramuscular injection at intervals of one month, with an additional 500mg dose given two weeks after the initial dose. As per the committee conclusions in TA579, the comparator included in the analysis was EXE 25mg + EVE 10mg.

The ERG notes that the company modelled the recommended dose in the final Summary of Product Characteristics (SmPC) for abemaciclib is 150mg twice daily. However, the modelled dose does not entirely reflect the clinical effectiveness data used in the analysis, as the ITT population from MONARCH 2 includes patients who received a higher dose of 200mg BID for abemaciclib.

4.1.3 Modelling approach and model structure

The company's model structure remains unchanged from TA579. The cohort-based partitioned survival model (presented in Figure 8) includes three health states: progression-free survival (PFS), progressed disease (PD), and death. The company used a lifetime horizon of 20 years and discretised time into weekly cycles, with a half-cycle correction applied. The analysis was carried out from an NHS and Personal Social Services (PSS) perspective. Costs and health effects are discounted at an annual rate of 3.5%, in line with the NICE Reference Case.

Figure 8. Model structure



As originally stated by the ERG in TA579, considering the short duration of the model cycles (seven days), the ERG does not see the need for the half-cycle correction applied by the company. Therefore, the ERG removed the half-cycle correction from the model as an exploratory analysis and presents the results of the analysis in Section 6.

4.1.4 Treatment effectiveness

The main changes in the company's estimation of treatment effectiveness in the model relate to the FP NMA undertaken to derive PFS and OS (discussed in Section 3); and to the estimation of time to treatment discontinuation (TTD) in the model.

As a result of the committee recommendations in TA579, the company used the post amendment population from MONARCH 2, which only included patients who started the trial on a twice daily 150 mg dose of abemaciclib, to estimate TTD in the model for ABE-FUL. The ERG notes that utility and hospitalisation data for the post amendment population were also used in the company's CDF review analysis.

During the clarification stage, the ERG requested that the company updated their FP NMA to include the post amendment data for OS and PFS outcomes from MONARCH 2 (instead of the ITT data used by the company). The purpose of this request was to match the source of clinical data used for PFS and OS outcomes to the source of clinical data used to estimate TTD (as well as utility and hospitalisation data from MONARCH 2). The ERG also notes that the recommended dose in the final SmPC for abemaciclib is 150mg twice daily, therefore, this is the dose used in clinical practice and should be the dose reflected in the clinical effectiveness data used in the analysis. Finally, the ERG reiterates that the post-amendment subgroup was pre-specified (via a protocol amendment) in MONARCH 2 and appropriately powered for a difference in PFS, therefore, making the use of the post-amendment data in the NMA a robust approach.

The company did not carry out the analysis requested by the ERG nor did it provide the requested KM OS and PFS data for the post amendment population from MONARCH 2 (data cut 20th June 2019). The ERG is extremely concerned with the company's refusal to provide the OS and PFS data for the post amendment population from the more mature MONARCH 2 data, especially when the limited data shared by the company suggests that the results in the post amendment population are worse than those observed in the ITT population, which included patients who received the unlicensed higher dose of 200mg for abemaciclib. This issue is discussed in more detail in Section 3 of the report.

4.1.4.1 Time to treatment discontinuation with ABE-FUL

Time on treatment with ABE-FUL was estimated by applying a HR of [redacted] to the updated FP NMA PFS curve for ABE-FUL. The HR was derived by dividing the cumulative hazard for median TTD (i.e. log[0.5]) by the cumulative hazard for the KM PFS curve from MONARCH 2 (data cut 20th June 2019) at the time of median TTD. The company's approach can be more simply demonstrated by the formula log(0.5)/[redacted]; where [redacted] represents the percentage of patients in the KM PFS curve for ABE-FUL at [redacted] months (when median TTD was reached in the ABE-FUL arm).

The ERG disagrees with the company's approach to estimating TTD for ABE-FUL, given that it results in underestimating the costs of abemaciclib (Figure 9).

Figure 10 shows the ABE-FUL TTD KM data from MONARCH 2 (post amendment population, data cut 20th June 2019), compared with the KM PFS data for the ITT population (same data cut). The ERG notes that the direct comparison of these two curves is not adequate (as the populations for both outcomes are not the same); however, the company did not comply with the ERG's request of PFS data for the post amendment population in MONARCH 2 (questions B2 and B7 in the clarification document). Nonetheless,

Figure 10 shows how the TTD KM curve tracks closely to the PFS KM curve for the ITT population. If the 200mg population were excluded from the ITT PFS curve (therefore resulting in a PFS curve for the post amendment population), it is likely that the PFS curve would shift down, given that patients in the post amendment population received a lower and potentially less effective dose of ABE-FUL. Therefore, the ERG considers that the PFS KM curve for the post amendment population would track even closer (or even on top) of the KM TTD curve for the same population.

In contrast, the modelled PFS and TTD curves for ABE-FUL (Figure 11) show a wide separation after month 6 in the model, and do not track close together until approximately 16 years later. The ERG notes that there are no data to support that patients on 150mg ABE-FUL discontinue treatment before progression to the same extent seen in Figure 11, and advises the committee on the extreme importance of comparing the TTD KM curve with the PFS KM curve for the same population (i.e. the post amendment population in MONARCH 2). Finally, the ERG notes that the curves in Figure 11 benefit ABE-FUL as these result in lower costs for abemaciclib without compromising on the treatment relative effectiveness.

Figure 9. Company's modelled TTD curve and KM TTD for ABE-FUL, post amendment population, data cut 20th June 2019, MONACRH 2 trial

Figure 10. PFS KM ITT data and TTD KM data for the post amendment group in MONARCH 2

Figure 11. PFS KM and PFS modelled ITT curves and TTD KM and TTD modelled curves for the post amendment group in MONARCH 2

Ideally, given the availability of mature TTD KM data from MONARCH 2, the ERG would have recommended fitting TTD curves in the model. Using MONARCH 2 data would have allowed the company to make use of trial data for the right population (i.e. the post amendment group), and not having to rely on the use of an estimated HR between the PFS and TTD ABE-FUL curves (for which the assumption of proportion hazards has not been assessed). The ERG asked the company to independently fit a survival curve to the ABE-FUL TTD KM data from MONARCH 2 (post amendment population, data cut 20th June 2019). However, the company did not provide the requested analysis and considered it inappropriate to extrapolate TTD independently of the FP NMA PFS curve for ABE-FUL.

Therefore, the ERG explored the option of using the KM TTD data to fit and extrapolate a TTD curve for ABE-FUL in the model. The ERG independently fitted the following distributions to the KM TTD data from MONARCH 2: exponential, Weibull, Gompertz, lognormal, log-logistic, and generalised gamma. The AIC and BIC (Table 23 in the Appendix) were calculated using the standard *stats* package included in *R,* and, in combination with a visual plot of the resulting curves, were used to determine the best fitting distributions for both treatment groups.

Based on AIC and BIC statistics and visual fit of the curves (Figure 19 in the Appendix), the ERG chose the lognormal distribution to estimate TTD for ABE-FUL in the model (

Figure 20 in the Appendix). Nonetheless, when the ERG compared the TTD fitted curve with the FP NMA PFS curve for ABE-FUL, it noted that using a fitted TTD curve would result in an overestimation of abemaciclib costs. As seen in

Figure 12, the fitted lognormal TTD curve is above the FP NMA PFS curve for approximately 20 months at the beginning of the model, suggesting that patients would continue treatment with ABE-FUL after progression. The ERG acknowledges that patients discontinued treatment upon progression in MONARCH 2 and so these curves might not represent a clinically plausible scenario. The ERG notes, again, the importance of having the company share the PFS KM data for the post amendment population in MONARCH 2 to understand how PFS and TTD related in the trial.

Given the lack of access to the PFS data for the post amendment population, and the likelihood that the PFS KM curve for the post amendment population would track very close (or even on top) of the KM TTD curve for the same population, the ERG assumed TTD to be the same as PFS in the ABE-FUL arm of the model. The alternative approach available to the ERG of modelling TTD would be using the fitted TTD curves; however, this is likely to overestimate the treatment costs given the use of the FP NMA PFS curve in the model. The impact of assuming TTD is the same as PFS for ABE-FUL in the model is reported in Section 6.

Figure 12. Fitted lognormal TTD curve and FP NMA PFS curve

4.1.4.2 Time to treatment discontinuation with EXE-EVE

Time on treatment with EXE-EVE was estimated by applying a HR of 1.53 to the updated FP NMA PFS curve for EXE-EVE. The HR was derived by using the same methodology employed to estimate the HR for ABE-FUL (see Section 4.1.4.1). The company estimated the HR with the formula: log(0.5)/log(0.64) = 1.53; where 0.64 represents the percentage of patients in the updated FP NMA PFS curve for EXE-EVE at 6.8 months (the median time on treatment with EXE in the EXE-EVE arm in BOLERO 2).

In BOLERO 2, median TTD for EXE and EVE in the EXE-EVE arm was 6.8 and 5.5 months, respectively. The ERG acknowledges that in its original report it recommended that the median time on treatment for EXE-EVE was based on EXE, as patients will not discontinue the intervention (i.e. the combination treatment) until both treatments are discontinued. However, clinical expert opinion provided to the ERG during the CDF review informed that in clinical practice, most patients discontinue EVE due to its toxicity, but carry on treatment with EXE. Given that EXE is considerably less expensive than EVE, assuming 6.8 instead of 5.5 months in the model would overestimate the treatment costs for EXE-EVE given the model's inability to cost treatment durations separately in the EXE-EVE arm. Therefore, as a modelling simplification, the ERG proposes that 5.5 months is a more robust estimate for calculating treatment costs with EXE-EVE.

Furthermore, given that the point of this adjustment exercise is to assess if PFS and TTD curves (or medians) are similar within treatments, using the PFS curve from BOLERO 2 would have been more

appropriate than using the updated FP NMA PFS curve to estimate the percentage of patients free from progression at the time of median TTD.

As a result, the ERG derived a HR by diving the cumulative hazard for median TTD [i.e. log(0.5)] by the cumulative hazard for the KM PFS curve from BOLERO 2 at the time of median TTD in the same trial (5.5 months) - log(0.5)/log(0.65) = 1.61; where 0.65 represents the percentage of patients in the KM PFS curve for EXE-EVE at 5.5 months. Results of this analysis are reported in Section 6.

Figure 13 shows that when the 1.61 HR is used in the model, the TTD EXE-EVE curve lies below the PFS EXE-EVE curve, which satisfies the ERG's clinical experts' opinion that patients usually discontinue treatment with EVE before progression, given the drug's toxicity profile.

Overall, assuming that TTD and PFS for ABE-FUL are similar, while having EXE-EVE patients discontinuing treatment before progression in the model, is consistent with clinical expert opinion that an advantage of ABE-FUL is its increased tolerability when compared with EXE-EVE.

Figure 13. Modelled PFS and TTD curves for EXE-EVE

4.1.4.3 Subsequent treatments

The latest data cut from MONARCH 2 provided more mature subsequent treatment data. Overall, the proportion of progressed patients who received subsequent treatments was [redacted] who received first-line subsequent [redacted] the company's proposition that ABE-FUL will provide an

additional treatment option for primary or secondary ET-resistant patients therefore, allowing the postponement of chemotherapy. Although MONARCH 2 data have demonstrated that ABE-FUL delays disease progression (63% of ABE-FUL patients progressed, while 83% of FUL patients progressed in the same time interval), therefore, delaying the beginning of subsequent therapy, the observed subsequent treatment regimens [redacted]. This analysis needs to be caveated by the fact that the data on subsequent therapies in MONARCH 2 are slightly incomplete (33% of patients in the ABE-FUL arm, and 13% of patients in the FUL arm had not progressed or died at the end of the follow-up period) and so it is unknown what treatments these patients would receive after they progressed.

Interestingly, the proportion of patients receiving additional lines of therapy in the FUL arm was [redacted] when compared to ABE-FUL, all the way through the 11 subsequent lines of therapy reported in the CSR.

Table 16. Subsequent treatments received in MONARCH 2 (data cut 20th June 2019) – edited by the ERG from the CSR

	Abemaciclib+fulvestrant arm (N=446)	Fulvestrant arm (N=223)
Patients with disease progression (n)	[redacted]	[redacted]
Proportion (%) of subsequent therapies received in relation to number of patients with first progression		
Patients receiving 1st subsequent line	[redacted]	[redacted]
CHEMOTHERAPY	[redacted]	[redacted]
EXEMESTANE	[redacted]	[redacted]
FULVESTRANT	[redacted]	[redacted]
LETROZOLE	[redacted]	[redacted]
TAMOXIFEN	[redacted]	[redacted]
EVEROLIMUS+EXEMESTANE	[redacted]	[redacted]
BEVACIZUMAB	[redacted]	[redacted]
EVEROLIMUS	[redacted]	[redacted]
PALBOCICLIB	[redacted]	[redacted]
Patients receiving 2nd subsequent line	[redacted]	[redacted]
CHEMOTHERAPY	[redacted]	[redacted]
EXEMESTANE	[redacted]	[redacted]

FULVESTRANT	[redacted]	[redacted]
INVESTIGATIONAL	[redacted]	[redacted]
BEVACIZUMAB	[redacted]	[redacted]
EVEROLIMUS	[redacted]	[redacted]
PALBOCICLIB	[redacted]	[redacted]
Patients receiving 3rd subsequent line	[redacted]	[redacted]
CHEMOTHERAPY	[redacted]	[redacted]
EXEMESTANE	[redacted]	[redacted]
FULVESTRANT	[redacted]	[redacted]
BEVACIZUMAB	[redacted]	[redacted]
EVEROLIMUS	[redacted]	[redacted]
Patients receiving 4th subsequent line	[redacted]	[redacted]
CHEMOTHERAPY	[redacted]	[redacted]
BEVACIZUMAB	[redacted]	[redacted]
EVEROLIMUS	[redacted]	[redacted]
PALBOCICLIB	[redacted]	[redacted]
Patients receiving 5th subsequent line	[redacted]	[redacted]
CHEMOTHERAPY	[redacted]	[redacted]
EXEMESTANE	[redacted]	[redacted]
FULVESTRANT	[redacted]	[redacted]
LETROZOLE	[redacted]	[redacted]
EVEROLIMUS	[redacted]	[redacted]
PALBOCICLIB	[redacted]	[redacted]
Patients receiving 6th subsequent line	[redacted]	[redacted]
CHEMOTHERAPY	[redacted]	[redacted]

4.1.5 Health-related quality of life

The company changed the pre-progression utility values derived from the safety population in MONARCH 2 to those estimated in the post amendment population (both sets of analysis using the old data cut of February 2017). The ERG is unclear if the more recent data cut included more mature EQ-5D data. The post amendment utility values used in the company's CDF review base case analysis are similar to those obtained for the safety population (Table 17).

For the post-progression utility value, the company used the Mitra *et al*. estimate, and provided a scenario analysis using the utility value derived in the post amendment population (February 2017 data cut) (Table 17).

In the original ERG report, the ERG expressed a preference for the use of trial data to estimate the post-progression utility in the model as this would match the source for the utility values used in the pre-progression state. The company did not use the post-progression utility data from MONARCH 2 in their base case analysis in TA579 as these data were deemed too immature.

The ERG reiterates its original view that EQ-5D data from MONARCH 2 were reasonably mature at the earlier data cut as [redacted] patients in the ABE-FUL arm had had a progression event and, more importantly, the latest and more mature dataset shows that [redacted] of patients in the ABE-FUL arm had a progression event ([redacted] out of 446 patients). The company did not present information on the quality of life data collected in the updated clinical study report (CSR) for MONARCH 2 (20th June 2019 data cut), therefore the ERG cannot ascertain what new data might have been available to conduct the analysis.

Table 17. Utility values used in the model

Health state	Mean utility	
	Company's original model (safety population, February 2017data cut)	Company's CDF model (post amendment population, February 2017data cut)
PFS	[redacted]	[redacted]
PPS (Mitra *et al.*)	0.670	0.670
PPS (MONARCH 2 – scenario analysis)	[redacted]	[redacted]
Abbreviations: PFS, post-progression survival; PPS, post-progression survival		

4.1.6 Resource use and costs

The company's changes to the estimation of resource use and costs in the model have been listed in Section 4.1.

The ERG concluded that the company provided new cost estimates in their CDF review model which reflect NHS reference costs for the 2018/19 cost year (previously a 2016/17 cost year).[12, 13] Nonetheless, when trying to match the NHS reference codes to the cost estimates, the ERG found several discrepancies. Furthermore, the ERG notes that the company was inconsistent as it did not, for example, inflate costs such as terminal care costs or drug costs. The ERG replaced the NHS reference costs to match the NHS reference codes (results presented in Section 6) but notes that due to time constraints it could not undertake a systematic review of all cost parameters.

Therefore, the ERG recommends that the company provides an input sheet with all NHS reference costs appropriately referenced and costed, together with all 2016/2017 prices uplifted to 2018/2019 costs using the consumer price index.

5 Cost effectiveness results

5.1.1 Company's cost effectiveness results

As a result of the clarification stage, the company updated their base CDF review results. The company's deterministic results are presented in Table 18.

Table 18. Company's base case deterministic results

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
CDF updated base case results							
EXE-EVE	[redacted]	[redacted]	[redacted]	-	-	-	-
ABE-FUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,746

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

The company provided a PSA based on 10,000 simulations, to assess the impact of parameter uncertainty when all parameters are varied simultaneously in the economic model. The results of the PSA are given in Table 19, and cost-effectiveness planes and cost-effectiveness acceptability curves are presented in

Figure 14 and Figure 15.

Table 19. Company's base case probabilistic results

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
CDF updated base case results							
EXE-EVE	[redacted]	[redacted]	[redacted]	-	-	-	-
ABE-FUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,539

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

Figure 14. Cost-effectiveness plane

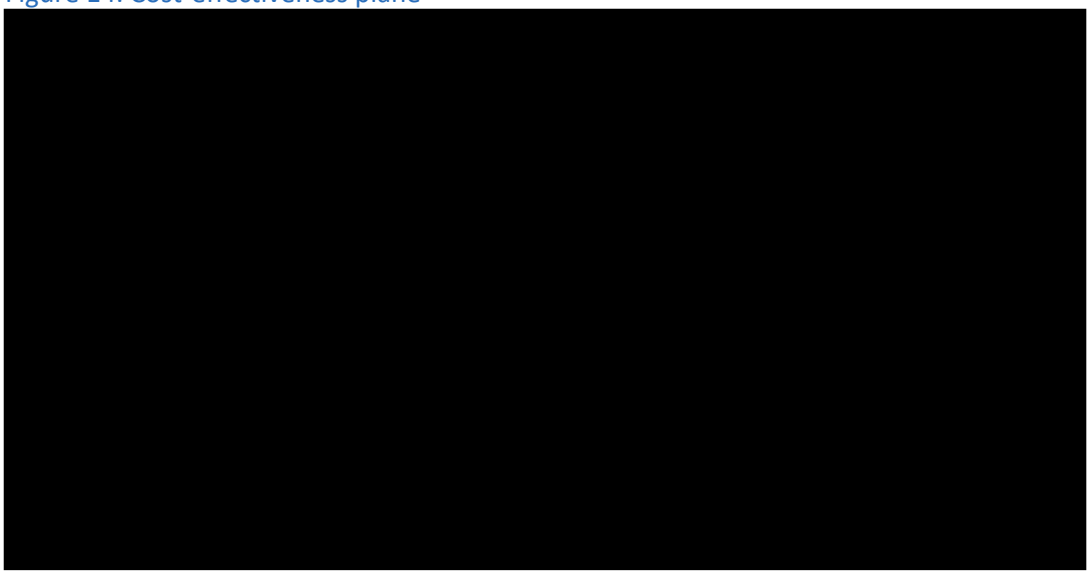


Figure 15. Cost-effectiveness acceptability curve

5.1.2 Company's sensitivity analyses

The company conducted a range of scenario analyses to assess the impact of varying model parameters. Results of the company's scenario analyses can be found in Table 9 of the company CDF

review submission document (Section A.12). These consisted mainly on applying different discounts for FUL; using alternative networks for the NMA and using the MONARCH 2 data to estimate post progression utilities in the model.

6 Additional economic analysis undertaken by the ERG

6.1 Exploratory and sensitivity analyses undertaken by the ERG

The scenario analyses undertaken by the ERG are explained throughout Section 4 of the report. Results of the exploratory analyses are reported in Table 20 and consist on the following changes to the model:

1. Removal of the half-cycle correction from the model (Section 4.1.3);
2. Assuming that TTD is the same as PFS for ABE-FUL (Section 4.1.4.2);
3. Applying the 1.61 HR to the EXE-EVE PFS curve to obtain a TTD curve for EXE-EVE (Section 4.1.4.3);
4. Replacing the NHS reference costs to match the right NHS reference codes.

The TTD estimation for ABE-FUL is the main key driver of the economic analysis (leading to increase in the ICER from £13,746 to £44,281), followed by the TTD estimated for EXE-EVE. The ERG notes that even though the FP NMA curves for OS and PFS were not varied in the ERG's analysis (as the post-amendment data were not available to update the NMA), these are likely to be the primary key drivers of the model. As a result, the ERG reiterates the importance of running the NMA with PFS and OS data for the post amendment population, so that the appropriate curves can be used in the economic analysis.

Table 20. Results of ERG's exploratory analysis

	Results per patient	ABE-FUL	EXE-EVE	Incremental value
0	Company's CDF base case post clarification			
	Total costs	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£13,746
1	Removal of the half-cycle correction from the model			
	Total costs	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£13,263
2	Assuming that TTD is the same as PFS for ABE-FUL			

	Total costs	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£44,281
3	Applying the 1.61 HR to the EXE-EVE PFS curve to obtain a TTD curve			
	Total costs	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£18,032
4	Replacing NHS reference costs			
	Total costs	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£12,436

Abbreviations: ICER, incremental cost-effectiveness ratio; HR, hazard ratio; PAIC, population adjusted indirect comparison; PFS, progression free survival; PPS, post-progression survival; QALY, quality adjusted life year

6.2 ERG preferred assumptions

The common preferred assumptions for the economic model are listed below:

1. Removal of the half-cycle correction from the model (Section 4.1.3);
2. Assuming that TTD is the same as PFS for ABE-FUL (Section 4.1.4.2);
3. Applying the 1.61 HR to the EXE-EVE PFS curve to obtain a TTD curve for EXE-EVE (Section 4.1.4.3);
4. Using the post-progression utility from MONARCH 2 (Section 4.1.5);
5. Using the ERG's corrected company's updated costs (Section 4.1.6).

When the ERG's preferred assumptions are combined in the model, the ICER results in £46,225 per QALY gained (Table 21). The ERG notes the following caveats in its analysis:

- The ERG has assumed that ABE-FUL is given until treatment discontinuation, and that patients receiving 150mg BID abemaciclib do not discontinue treatment before progression. The ERG reiterates that without the company sharing the post amendment PFS data for ABE-FUL it is not possible to fully validate this assumption in the model;

- The HR derived by the ERG to estimate TTD for EXE-EVE is based on a comparison of medians. This is a reasonably weak approach, as equivalence (or difference) in median survival estimates does not inform the difference in the curves' shape and doesn't necessarily translate an accurate picture of differences in mean survivals. Nonetheless, given that TTD data were not available for the comparator treatments, the use of median TTD estimates was necessary;
- The costs included in the ERG's analysis need revision, and updating by the company, as explained in Section 4.1.6.

The ERG's probabilistic ICER amounts to £49,733 per QALYs gained. The biggest uncertainty in the results comes from the effectiveness parameters (Figure 16). The ERG notes the following caveats in its PSA analysis:

- The HR derived by the ERG to estimate TTD for EXE-EVE was not varied in PSA, as that would entail having the KM PFS data from BOLERO 2, in order to match the different probabilistic median TTDs to the PFS values in the KM curve. Due to time constraints, the ERG could not digitise the PFS KM curve from BOLERO 2 , however, suggests that the company conducts this analysis during technical engagement;
- Given the computation burden of running PSA, the ERG only ran 1,000 simulations (which took 2 hours). This compares to the 10,000 simulations ran by the company.

Table 21. ERG's preferred model assumptions

Scenario	Incremental costs	Incremental QALYs	ICER
Company base case	[redacted]	[redacted]	£13,746
Removal of the half-cycle correction from the model	[redacted]	[redacted]	£13,263
Assuming that TTD is the same as PFS for ABE-FUL	[redacted]	[redacted]	£44,281
Applying the 1.61 HR to the EXE-EVE PFS curve to obtain a TTD curve	[redacted]	[redacted]	£18,032
Using the post-progression utility from MONARCH 2	[redacted]	[redacted]	£13,580
Using the company's updated costs	[redacted]	[redacted]	£12,436

ERG's preferred base case	[redacted]	[redacted]	£46,225

Abbreviations: ICER, incremental cost-effectiveness ratio; HR, hazard ratio; PFS, progression free survival; PPS, post-progression survival; QALY, quality adjusted life year

Table 22. ERG's base case probabilistic results

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
CDF updated base case results							
EXE-EVE	[redacted]	[redacted]	[redacted]	-	-	-	-
ABE-FUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£49,733

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

Figure 16. Cost-effectiveness plane (ERG's analysis)

Figure 17. Cost-effectiveness acceptability curve (ERG's analysis)

6.3 Conclusions of the cost effectiveness sections

One of the key objectives of the CDF review was that the company used the post amendment population data to estimate TTD in the model. As the MONARCH 2 data matured, more reliable PFS and OS data also became available, nonetheless, the ERG only had access to the ITT OS and PFS outcomes. The latter were used by the company to update their FP NMA.

The TTD estimation for ABE-FUL is the main key driver of the CDF review economic analysis, followed by the TTD estimated for EXE-EVE. The ERG notes that even though the FP NMA curves for OS and PFS were not varied in the ERG's analysis, these are likely to remain the primary key drivers of the model.

The ERG's results should be interpreted with caution as the underlying population for OS and PFS outcomes in the economic analysis is based on the ITT population from MONARCH 2, which does not match the post amendment population used for the estimation of TTD outcomes. Importantly, the ITT population also does not reflect the treatment dose recommended for abemaciclib in its marketing authorisation. As explained in Section 3, the ERG has reasons to believe that clinical outcomes for the post amendment population would be worse than those observed in the ITT population, therefore, using the post amendment outcomes in the analysis could potentially lead to a decrease in the relative treatment effectiveness of ABE-FUL, and ultimately in an increase in the final ICER.

Although MONARCH 2 data have demonstrated that ABE-FUL delays disease progression (63% of ABE-FUL patients progressed, while 83% of FUL patients progressed in the same time interval), therefore, delaying the beginning of subsequent therapy, the observed subsequent treatment regimens [redacted]. Overall, assuming that TTD and PFS for ABE-FUL are similar, while having EXE-EVE patients discontinuing treatment before progression in the model, is consistent with clinical expert opinion that an advantage of ABE-FUL is its increased tolerability when compared with EXE-EVE.

7 End of Life

As reported by the company, and agreed by the ERG, ABE-FUL does not meet the end-of-life criteria.

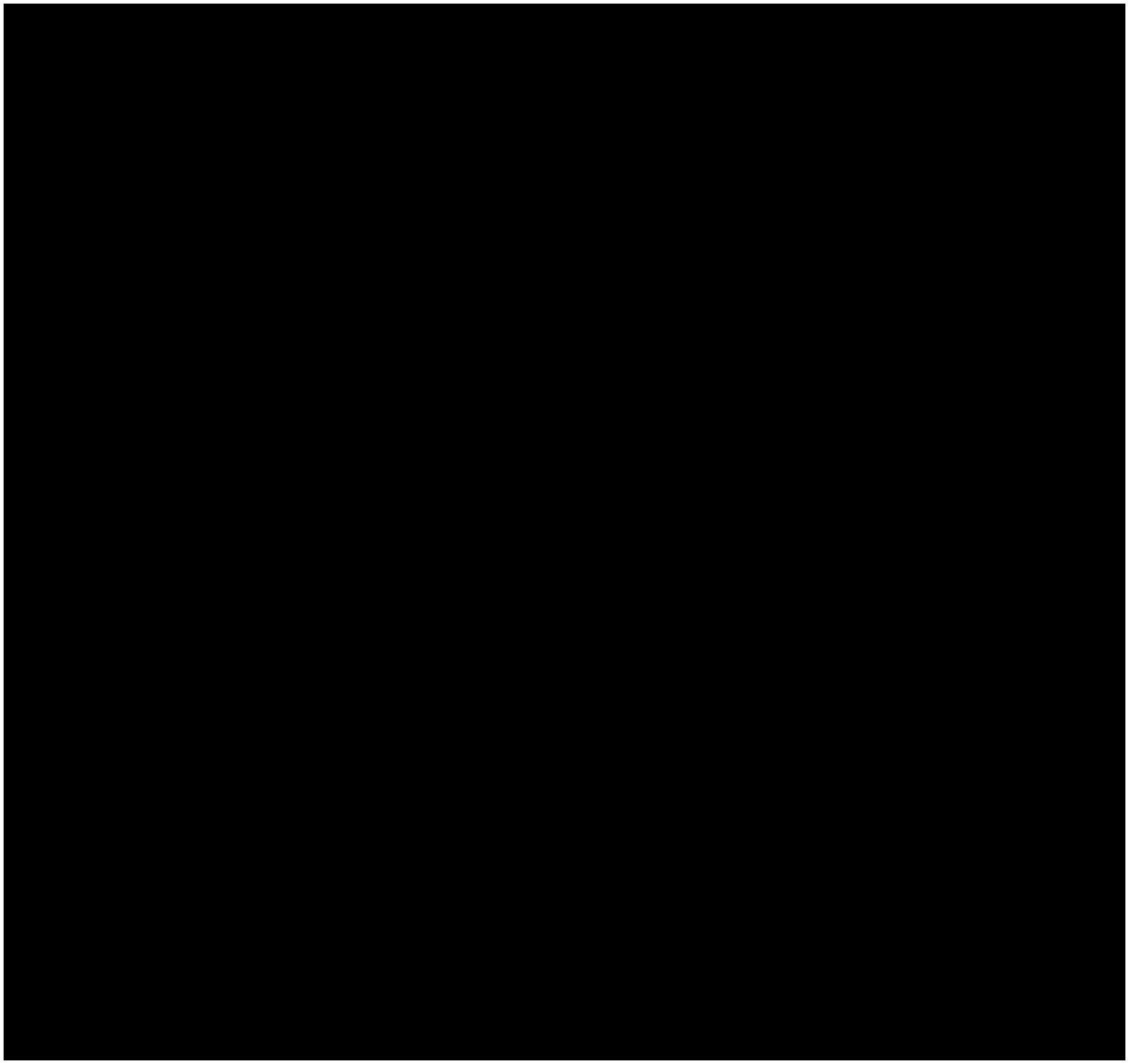
8 References

1. NICE. Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy [TA579]. Available at: https://www.nice.org.uk/guidance/TA579 (Accessed 09.05.19). 2019.
2. F. Cardoso SP-S, E. Senkus, G. Curigliano, M.S. Aapro, F. André, C.H., Barrios JB, G.S. Bhattacharyya, L. Biganzoli, F. Boyle, M.-J. Cardoso, L.A., Carey JC, N.S. El Saghir, M. Elzayat, A. Eniu, L. Fallowfield, P.A. Francis,, K. Gelmon JG, R. Haidinger, N. Harbeck, X. Hu, B. Kaufman, R. Kaur,, B.E. Kiely S-BK, N.U. Lin, S.A. Mertz, S. Neciosup, B.V. Offersen, S. Ohno,, O. Pagani AP, F. Penault-Llorca, H.S. Rugo, G.W. Sledge, C. Thomssen, D.A., et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Ann Oncol* 2020.
3. DeKoven M, Bonthapally V, Jiao X, Ganguli A, Pathak P, Lee WC, et al. Treatment pattern by hormone receptors and HER2 status in patients with metastatic breast cancer in the UK, Germany, France, Spain and Italy (EU-5): results from a physician survey. *J Comp Eff Res* 2012; **1**: 453-63.
4. (EMA) EMA. Verzenios: Assessment report, 2018. Available from: https://www.ema.europa.eu/documents/assessment-report/verzenios-epar-public-assessment-report_en.pdf. Date accessed: 9 Nov 2018.
5. (EMA) EMA. Faslodex: EPAR - Product Information, 2009. Available from: https://www.ema.europa.eu/documents/product-information/faslodex-epar-product-information_en.pdf. Date accessed: 9 Nov 2018.
6. NICE. Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer [TA593]. Available at: https://www.nice.org.uk/guidance/ta593 (Accessed 25.09.20). 2019.
7. NICE. Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer [TA619]. Available at: https://www.nice.org.uk/guidance/ta619 (Accessed 25.09.20). 2019.
8. Mitra D, Wood R, De Courcy J, Iyer S. Patient Reported Health Utility in HR+/HER2- Advanced/Metastatic Breast Cancer. *Value in Health* 2016; **A347 – A766**.
9. Lilly E. Data on File. Clinical Study Report [MONARCH 2]. . 2017.
10. Public Health England (PHE). Abemaciclib with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer after endocrine therapy – data review. . 2020.
11. Jansen JP. Network meta-analysis of survival data with fractional polynomials. *BMC Med Res Methodol* 2011; **11**: 61.
12. Curtis LB, A. Unit Costs of Health and Social Care 2019, 2019. Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019/. Date accessed: Oct 2020.
13. Improvement N. National Cost Collection: National Schedule of NHS costs - Year 2018-19 - NHS trust and NHS foundation trusts, 2020. Available from: https://www.england.nhs.uk/national-cost-collection/. Date accessed: Oct 2020.
14. Centre for Reviews and Dissemination (CRD). CRD's guidance for undertaking reviews in healthcare. *Available at https://wwwyorkacuk/media/crd/Systematic_Reviewspdf (Accessed 21 March 2016)* 2011.
15. Sledge GW, Jr, Toi M, Neven P, Sohn J, Inoue K, Pivot X, et al. The Effect of Abemaciclib Plus Fulvestrant on Overall Survival in Hormone Receptor–Positive, ERBB2-Negative Breast Cancer That Progressed on Endocrine Therapy—MONARCH 2: A Randomized Clinical Trial. *JAMA Oncology* 2020; **6**: 116-24.

9 Appendices

9.1 Pre-specified subgroup analyses

Figure 18: Forest plot of OS by pre-specified subgroups in MONARCH 2 (ITT population)



Note: OS HRs and 95% CIs are indicated by diamonds and the crossing horizontal lines, respectively. HRs for overall and within subgroups are unstratified; subgroup HRs are estimated with the adjustment of arm*subgroup interaction. The factor levels that consisted of less than 5% of randomised patients were omitted from the analysis.
Abbreviations: CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; ITT: intention-to-treat; OS: overall survival; PS: performance status.
Source: Lilly Data on File (JPBL Clinical Study Report Addendum for the Interim Overall Survival Analysis) 2020

9.2 ERG's survival analysis results

Table 23. Goodness-of-fit statistics for ABE-FUL TTD fitted curves

Distribution	AIC	BIC
Exponential	2172.134	2175.918
Weibull	2172.054	2179.622
Lognormal	2142.57	2150.137
Log-logistic	2148.394	2155.962
Gompertz	2158.628	2166.195
Generalized gamma	2143.250	2154.601
Abbreviations in table: AIC, Akaike information criterion; BIC, Bayesian information criterion		

Figure 19. ABE-FUL KM plot and fitted curves for TTD

Figure 20. ABE-FUL KM TTD data and ERG's fitted lognormal curve

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy [ID2727]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 9 November 2020** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

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

Issue 1 Incorrect description of fulvestrant administration

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 12 "Being administered intravenously in hospital (fulvestrant only)"	**"**Being administered via intramuscular injection (fulvestrant only)"	Fulvestrant is administered via intramuscular injection, not intravenously – this description is incorrect. Furthermore, not all patients will receive fulvestrant in hospital – some people will be able to receive injections in the community.	The ERG has amended the text as suggested by the company.

Issue 2 Omission of detail

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 28, Table 11 Table 11 has the following row headings, for both the ITT and post-amendment populations: • "Median cycles of ABE" • "Mean cycles of ABE"	• Median cycles of ABE **or PBO** • Mean cycles of ABE **or PBO**	These rows present results for both ABE-FUL and PBO-FUL (median and mean cycles of ABE or PBO, respectively). Therefore, the row headings should be amended to state ABE or PBO.	The row headings have been amended as suggested.

Issue 3 Omission of detail

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 49–50 "the proportion of progressed patients who received subsequent treatments was [redacted]"	"the proportion of progressed patients who received subsequent treatments was [redacted]"	This statement is not correct – [redacted] of patients who received PBO-FUL received a subsequent treatment. This statement should be amended to note the percentages for both arms.	The statement has been amended as requested.

Issue 4 Omission of detail

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 50: [redacted] who received first-line subsequent [redacted]…"	[redacted] who received first-line subsequent **treatment** [redacted]	"treatment" is missing from this sentence, and should be included.	The ERG amended the text as suggested by the company.

Issue 5 Calculation error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 51, Table 16 – The proportion of patients in the ABE-FUL arm who received 2nd line subsequent treatment with bevacizumab is listed as [redacted]	The proportion of patients in the ABE-FUL arm who received 2nd line subsequent treatment with bevacizumab should be listed as [redacted]	The current value of [redacted] has been calculated as a percentage of the total patients in MONARCH 2: [redacted]/446*100 = [redacted] To be consistent with the other values in the table, this should be calculated based on the number of patients with disease progression ([redacted]). [redacted]*100 = [redacted] This value should be listed as [redacted].	The ERG agrees with the company and has replaced [redacted] by [redacted].

Issue 6 Omission of detail

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 15: The ERG recommends that the company provides an input sheet with all NHS reference costs appropriately referenced and costed, together with all 2016/2017 prices uplifted to 2018/2019 costs using the consumer price index. **Page 58:** Therefore, the ERG recommends that the company provides an input sheet with all NHS reference costs appropriately referenced and costed, together with all 2016/2017 prices uplifted to 2018/2019 costs using the consumer price index.	**Page 15:** The ERG recommends that the company provides an input sheet with all NHS reference costs appropriately referenced and costed, together with all 2016/2017 prices uplifted to 2018/2019 costs using the consumer price index **(health), or the NHSCII Pay and Price Index published in the PSSRU."**. **Page 58:** "Therefore, the ERG recommends that the company provides an input sheet with all NHS reference costs appropriately referenced and costed, together with all 2016/2017 prices uplifted to 2018/2019 costs using the consumer price index **(health), or the NHSCII Pay and Price Index published in the PSSRU."**	The general consumer price index is not an appropriate source for the inflation of healthcare costs. Lilly believes that it would be more appropriate to use an index more specific to health care costs, such as the specific consumer price index for health, or the NHSCII Pay and Price Index (published in the PSSRU).	The ERG agrees with the company and has amended the text as suggested.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy [ID2727]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments 4th December 2020

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted], and all information submitted under [redacted] in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Eli Lilly and Company Limited
Disclosure	

Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Subgroup data by abemaciclib starting dose not explored	YES	Lilly notes the ERG's desire to review the subgroup data for the post-amendment (PA) population. Lilly has already provided the baseline characteristics for the PA population, and has provided these again for reference in Appendix 1 (Key Issue 1) below. Lilly has now also provided the PFS and OS data at the time of the OS interim analysis (DCO 20th June 2019) for the PA population, in order to any uncertainty to be explored. These data can also be found in in Appendix 1 (Key Issue 1). Lilly maintains that it is not appropriate to evaluate the efficacy of ABE-FUL compared to PBO-FUL by separating the results of the pre-amendment or PA subgroups in MONARCH 2; as outlined in Question A2, Pages 3–8 of the ERG Clarification Questions response v3_201020. Clinical expert opinion was sought by Lilly as input to this response. The clinical expert view was that is that it is not appropriate to analyse these populations separately. To do so, and disregard the overall ITT population, would not reflect the intention of the MONARCH 2 trial. The full statement from the clinical expert has been provided as additional evidence alongside this response. The lifetime survival extrapolations presented in Appendix 1 (Table 10) show that the estimated [redacted]

		Considering the above, Lilly maintains that the use of the ITT PFS and OS data in the company's base case analysis remains the most appropriate approach. Alternative results incorporating the PA data are provided as an exploratory scenario analysis.
Key issue 2: Outcome validation using SACT data	NO	Lilly is in agreement with the ERG's judgement that validation of the SACT data is limited, as the data are immature. As discussed with the ERG and the NICE Technical Team, Lilly agrees that these data cannot be incorporated into the economic analysis for this appraisal.
Key issue 3: Heterogeneity within the indirect treatment comparison network	NO	Lilly acknowledges there is some heterogeneity remaining within the indirect treatment comparison network. This heterogeneity has been reduced from the original submission, following the simplification of the network to only include the minimum number of trials needed to connect ABE-FUL and EXE-EVE. Lilly agrees with the ERG's judgement that there is nothing further than can be done to eliminate the remaining uncertainty in the network without the individual patient data for the comparator trials. Lilly acknowledges this is a minor limitation of the analysis.
Key issue 4: Time to treatment discontinuation (TTD) estimated for abemaciclib plus fulvestrant (ABE-FUL)	YES	Lilly believes that the extremely conservative HR of 1.0 between PFS and TTD for ABE-FUL lacks face validity, and does not represent a clinically plausible assumption. This was chosen in the ERG's base case to illustrate the potential impact associated with the PA population. A HR of 1.0 assumes that all patients will receive treatment with ABE-FUL until disease progression, and that no patients will discontinue ABE-FUL for other reasons (including but not limited to treatment-related toxicity). While clinical expert opinion sought by the ERG has indicated that ABE-FUL has an improved tolerability profile compared to EXE-EVE, it is not clinically plausible to assume that no patients will discontinue treatment prior to disease progression. The safety data for both the ITT and PA populations presented in the original MONARCH 2 CSR (DCO 14th February 2017) shows that a small but notable number of patients discontinued treatment for reasons other than disease progression. While Lilly acknowledges that the HR of [redacted] used in the company submission base case, in line with the ERG's preferred methodology, may be subject to some degree of uncertainty, Lilly believes there is clear evidence to demonstrate that the ERG's HR of 1.0 reflects an extremely conservative assumption, when considering the totality of the clinical evidence from MONARCH 2. Moreover, this assumption is inconsistent with the disclosed evidence from all other MONARCH trials to date.

		In order to explore the uncertainty of the relationship between ABE-FUL PFS and TTD, Lilly has conducted two further analyses in Appendix 1 (Key Issue 4). Three separate ratios were considered for ABE-FUL TTD: the ratio of ITT PFS to ITT TTD, the ratio of ITT PFS to PA TTD and the ratio of PA PFS to PA TTD. The additional analyses included both a lifetime survival extrapolation, as well as a scenario analysis using a restricted mean methodology (comparing the areas under the curves [AUC]). This restricted mean approach is less reliant on the shape of the curve and the HR at a single point on the curve; helping to characterise the possible uncertainty around the base case HR of [redacted]. Curve selection for both analyses, was based on statistical and visual fit; with log normal extrapolations selected for all four extrapolations. A lifetime survival analysis resulted in the following HRs between PFS and TTD (Appendix 1, Table 12): • ITT PFS vs ITT TTD: [redacted] • ITT PFS vs PA TTD: [redacted] • PA PFS vs PA TTD: [redacted] These HRs provide strong supportive evidence for the HR of [redacted] between ABE-FUL PFS and TTD that is used in the company base case analysis. This value was previously calculated in line with the ERG's requested method, using the logarithm of the cumulative PFS at the point of median duration of exposure (as detailed in QB5, Page 18 of the abemaciclib clarification response v3_201020). Lilly also compared the same three sets of populations using the aforementioned restricted mean analysis (Appendix 1, Table 13): • ITT PFS vs ITT TTD: [redacted] • ITT PFS vs PA TTD: [redacted] • PA PFS vs PA TTD: [redacted]

		Lilly strongly believes that these analyses represent a very conservative scenario, where the lowest of [redacted] (from the restricted mean comparison of [redacted]), is more plausible than the ERG's proposed implausible analysis using a HR of 1.0. Considering the above, the company base case analysis remains unchanged (HR of [redacted]), as Lilly believes that this represents the most appropriate assumption based on the totality of evidence available. A rate of [redacted] would represent an appropriate assumption for a very conservative scenario analysis. Of note, both estimates are aligned to the ERG's expert opinion that ABE-FUL is better tolerated by patients compared to EXE-EVE. Based on all of the analyses presented, Lilly does not believe that there is any plausible rationale to consider a HR of 1.0 between ABE-FUL PFS and TTD.
Key issue 5: Time to treatment discontinuation (TTD) estimated for exemestane with everolimus (EXE-EVE)	YES	Lilly acknowledges the ERG's concerns regarding the approach used to estimate the TTD for EXE-EVE in the company's base case analysis. As subsequently requested by the ERG, Lilly digitised the BOLERO-2 PFS KM curve to allow probabilistic analysis of the EXE-EVE HR for ToT. With digitised curve and dynamic look-up, the ERG's preferred HR is 1.58 rather than 1.61, as proposed in the ERG report. Lilly notes that a limitation of both the company's and ERG's analyses is that while treatment with EVE is assumed to be so burdensome that patients discontinue EVE at significantly higher rates than ABE(-FUL), this is modelled without applying any decrement to QoL during ongoing EVE treatment. Lilly believes this should be considered by the Committee. However, as agreed with the ERG and the NICE Technical Team, Lilly believes that there are a number of alternative methodologies that should be explored to estimate TTD for EXE-EVE, in order to best explore the uncertainty around the assumptions, in the absence of individual patient data from the BOLERO-2 trial. In the parallel Technical Engagement step for the concurrent RIB-FUL Cancer Drugs Fund review of TA593, which considers a similar decision problem (a CDK4&6 inhibitor in combination with fulvestrant in comparison to EXE-EVE) and which is to be considered by the same Committee as this appraisal, different methods have been proposed to model EXE-EVE TTD in than those used in this appraisal. The alternative methods to model EXE-EVE TTD used in the comparison with RIB-FUL are described below:

		1. Based on clinical expert feedback sourced in the CDF review of TA593, an alternative scenario assumes that approximately 20% of patients will discontinue EVE six months after the initiation of treatment but will continue to receive EXE until disease progression. Lilly believes that this scenario is more clinically plausible than the first scenario. 2. Clinical expert opinion sourced in the CDF review of TA593 also indicated that a large proportion of patients remaining on EVE would require a dose reduction from 10 mg daily to 5 mg daily. Therefore, another alternative scenario proposed in the RIB-FUL CDF review assumed that 20% of patients will discontinue EVE six months after the initiation of treatment, and will continue to receive EXE until disease progression. Of the patients remaining on EVE, 70% will have their dose reduced from 10 mg daily to 5 mg daily at month six, in line with clinical expert opinion. Lilly believes that this scenario represents the most clinically plausible assumption for the estimation of EXE-EVE TTD. 3. The final alternative scenario assumes that all patients receiving EXE-EVE are treated until disease progression, in line with the original appraisal. However, Lilly acknowledges that this scenario is likely to overestimate the costs of treatment with EXE-EVE, when considering the toxicity burden associated with EVE. In order to explore the effect of these alternative approaches, Lilly have implemented them as additional scenario analyses in the model. The corresponding impact of each of these steps on the ICER is detailed below (considering the effect on the company's base case after technical engagement – the impact on the base before technical engagement is provided below): Company Base Case ICER After Technical Engagement: £6,593 <u>Scenario 1</u> Incremental costs: [redacted] Incremental QALYs: [redacted] ICER: Dominant <u>Scenario 2:</u> Incremental costs: [redacted]

		Incremental QALYs: [redacted] ICER: Dominant <u>Scenario 3:</u> Incremental costs: [redacted] Incremental QALYs: [redacted] ICER: Dominant Lilly believes that the current methodology used in the ERG base case may not represent the most clinically plausible methodology for modelling EXE-EVE TTD. Lilly believes that this analysis may not actually be based on the KM median time to treatment discontinuation for EVE. Instead, this may reflect a naïve value for median time of treatment for EVE. As such, the alternative scenarios detailed above may be more clinically plausible, and aligned with their considerations in the concurrent RIBO-FUL appraisal.
Key issue 6: Prices used in the model	YES	Lilly acknowledges the ERG's concerns regarding some of the prices used in the model. These costs have been updated and incorporated into the revised base case analysis. Additional details on the updates can be found in Appendix 1 (Key Issue 6).
Key issue 7 (un-numbered in ERG report but summarised in Table 7 of ERG report): Subsequent treatments in MONARCH 2	YES	Lilly notes the ERG's statements regarding subsequent treatment. Lilly strongly believes that while similar numbers of patients treated with ABE-FUL or PBO-FUL may ultimately receive cytotoxic chemotherapy, MONARCH 2 demonstrated that ABE-FUL postpones the need for subsequent cytotoxic chemotherapy. The time-to-event analyses presented in the CDF review submission document (Section A.6.1, Page 12) provide clear evidence of this. At the time of the OS interim analysis (DCO 20th June 2019), ABE-FUL resulted in a statistically significant improvement versus PBO-FUL with respect to time to second disease progression (PFS2; median, 23.1 months vs 20.6 months), time to chemotherapy (median, 50.2 months vs 22.1 months), and chemotherapy free-survival (CFS; median, 25.5 months versus 18.2 months). KM plots for PFS2, time to chemotherapy and CFS are presented in the Appendix of Additional Evidence (Key Issue 7), and demonstrate an early and sustained benefit for patients treated with ABE-FUL vs PBO-FUL with regard to all three metrics.

		These differences represent an important and clinically meaningful benefit for patients. The initiation of cytotoxic chemotherapy is associated with a significantly worsened side effect profile and impaired HRQoL compared to endocrine therapy alone, while patients may also require an increased level of care due to the potential toxicity burden associated with chemotherapy.[1] As a result, strategies to delay cytotoxic chemotherapy and allow patients to maintain a good HRQoL are crucial aspects of breast cancer care.[2] The burden associated with chemotherapy has been detailed in the original company submission (Document B, Section B.1.3.1, page 17–18).
Key issue 8 (un-numbered in ERG report but summarised in Table 8 of ERG report): Updated quality of life data from MONARCH 2	NO	Additional quality of life data are not available from MONARCH 2, and so cannot be presented as part of this submission. However, as agreed with the ERG and the NICE Technical Team, Lilly does not consider this to be a key area of uncertainty, and does not believe that any further data would be able to resolve any remaining uncertainty relating to quality of life. Any updated utility data collected in MONARCH 2 would not constitute 'more mature' data. In MONARCH 2, utility data were collected at one month following disease progression and no further utility values were collected at later points in the trial. Therefore, any potential collection of utility data at the OS interim analysis would only provide a small number of additional observations, and not extended follow up for the utility values that have already been recorded and incorporated in the current economic analysis. Therefore, Lilly does not believe that it is a particular concern that further quality of life data are not available. Additionally, Lilly would note that scenario analyses have been included using alternative utility values, including Mitra et al. 2016 and Lloyd et al. 2006, in order to explore any uncertainty around quality of life, and have demonstrated that ABE-FUL remains a cost-effective treatment option.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do not use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Anticipated fulvestrant discount due to fulvestrant loss of exclusivity	NA	**YES**	Lilly does not believe it is appropriate to assume that the NHS will incur the cost of the current FUL list price, as a result of the imminent loss of exclusivity for FUL, and the likely availability of significantly lower cost generic formulations. Consequently, Lilly has chosen to apply an assumed discount percentage of [redacted] to the list price of FUL in its revised base case analysis. While the exact discount price is unknown, Lilly believes that this estimate is more realistic than not applying a discount, while still representing a conservative assumption.

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

<table>
<tr><th>Key issue(s) in the ERG report that the change relates to</th><th>Company's base case before technical engagement</th><th>Change(s) made in response to technical engagement</th><th>Impact on the company's base-case ICER</th></tr>
<tr><td colspan="4">Company's base case before technical engagement:
<table>
<tr><th>Technologies</th><th>Total costs (£)</th><th>Total LYG</th><th>Total QALYs</th><th>Incremental. costs (£)</th><th>Incremental LYG</th><th>Incremental QALYs</th><th>Incremental ICER (£/QALY)</th></tr>
<tr><td>ABE-FUL</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>NA</td></tr>
<tr><td>EXE-EVE</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£13,746</td></tr>
</table></td></tr>
<tr><td>Issue 5</td><td>Lilly applied the proposed ERG method to generate a HR for EXE-EVE.</td><td>Lilly digitised the BOLERO 2 KM PFS curve and applied a dynamic look-up of PFS at median time-on-treatment in BOLERO 2.

Lilly has also conducted additional scenario analyses using methodology aligned with the concurrent CDF review of TA593 (for RIBO-FUL) to inform time on treatment for EXE-EVE:</td><td>Updated incremental costs: [redacted]
Change from previous base case: [redacted]
Updated Incremental QALYs: [redacted]
Change from previous base case: [redacted]
Updated ICER: £16,683
Change: £2,937
<u>Scenario 1 (using all other original base case settings)</u>
Incremental costs: [redacted]
Incremental QALYs: [redacted]
ICER: Dominant</td></tr>
</table>

		1. 20% of patients discontinue EVE at month 7 2. In line with scenario 1, but assuming that 70% of patients that continue on EVE have their treatment dose reduced 3. This scenario sets PFS equal to TOT	Scenario 2 (using all other original base case settings) Incremental costs: [redacted] Incremental QALYs: [redacted] ICER: Dominant Scenario 3 (using all other original base case settings) Incremental costs: [redacted] Incremental QALYs: [redacted] ICER: Dominant
Issue 6	Lilly acknowledges the ERG's concerns with some of the prices used in the economic model.	Lilly has updated the resource cost and cost codes used in the original submission with National Schedule of NHS cost 2018-2019, or inflated the cost based on the consumer price index (CPI) or health price index (HPI) to 2019. BNF and eMIT were also checked for updated drug prices.	Updated incremental costs: [redacted] Change from previous base case: [redacted] Updated Incremental QALYs: [redacted] Change from previous base case: [redacted] Updated ICER: £13,587 Change: − £159
Additional Issue 1	Lilly did not assume a rebate for FUL in the base case.	As an estimate for the FUL price following loss of exclusivity, Lilly have assumed a [redacted] price reduction. From historic examples, the	Updated incremental costs: [redacted] Change from previous base case: [redacted] Updated Incremental QALYs: [redacted]

		realised price reduction could be considerably larger.	Change from previous base case: [redacted] Updated ICER: £3,893 Change: − £9,853
Other Changes	Lilly used a post-progression utility value from Mitra et al. (2016) in the company's base case before technical engagement.	Lilly used the post-progression utility value based on data derived from MONARCH 2 in the updated base case.	Updated incremental costs: £[redacted] Change from previous base case: [redacted] Updated Incremental QALYs: [redacted] Change from previous base case: [redacted] Updated ICER: £13,580 Change from previous base case: − £166
Company's preferred base case following technical engagement *(incorporating changes from issue 5, 6 and additional issue 1, as well as the M2 post-progression utility decrement)*	Incremental QALYs: [redacted]	Incremental costs: [redacted]	Company's preferred base case ICER: £6,593

Summary of Lilly's Preferred Base Case After Technical Engagement

Deterministic Cost-Effectiveness Results

Table 1: Updated company base case cost-effectiveness results (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)

ABE-FUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
EXE-EVE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,593

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FP: fractional polynomial; FUL: fulvestrant; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NA: not applicable; NMA: network meta-analysis; PH: proportional hazards; QALYs, quality-adjusted life years.

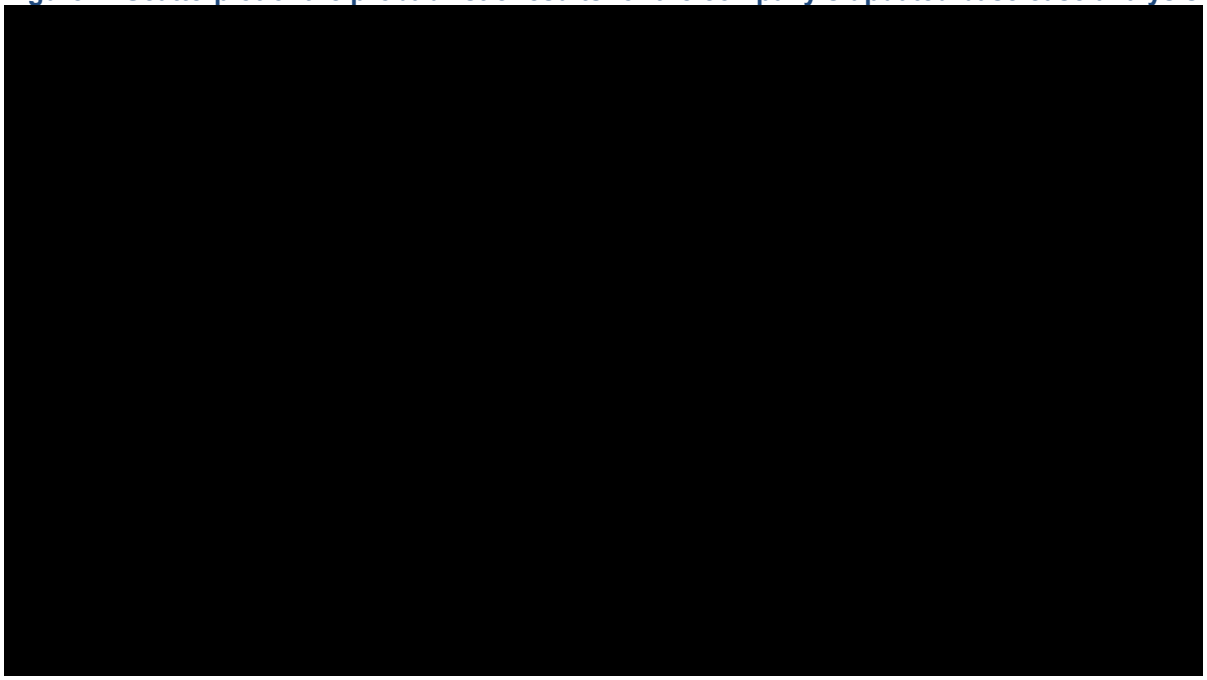
Probabilistic Cost-Effectiveness Results

Table 2: Updated company base case cost-effectiveness results (probabilistic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
ABE-FUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
EXE-EVE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,119

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FP: fractional polynomial; FUL: fulvestrant; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NA: not applicable; NMA: network meta-analysis; PH: proportional hazards; QALYs, quality-adjusted life years.

Figure 1: Scatterplot of the probabilistic results for the company's updated base case analysis



Appendix of Additional Evidence

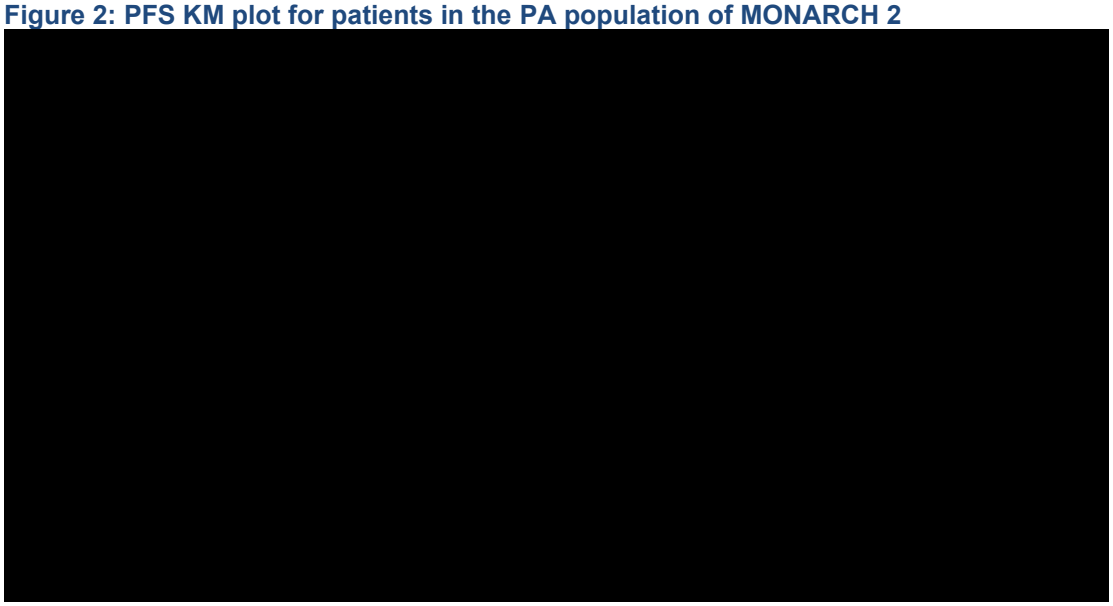
Key Issue 1: Post-Amendment Data

Post-Amendment Data from MONARCH 2

The baseline characteristics for the PA population are detailed in Section 13.1 of the original MONARCH 2 CSR (DCO 14th February 2017), and presented in Table 3 for convenience.

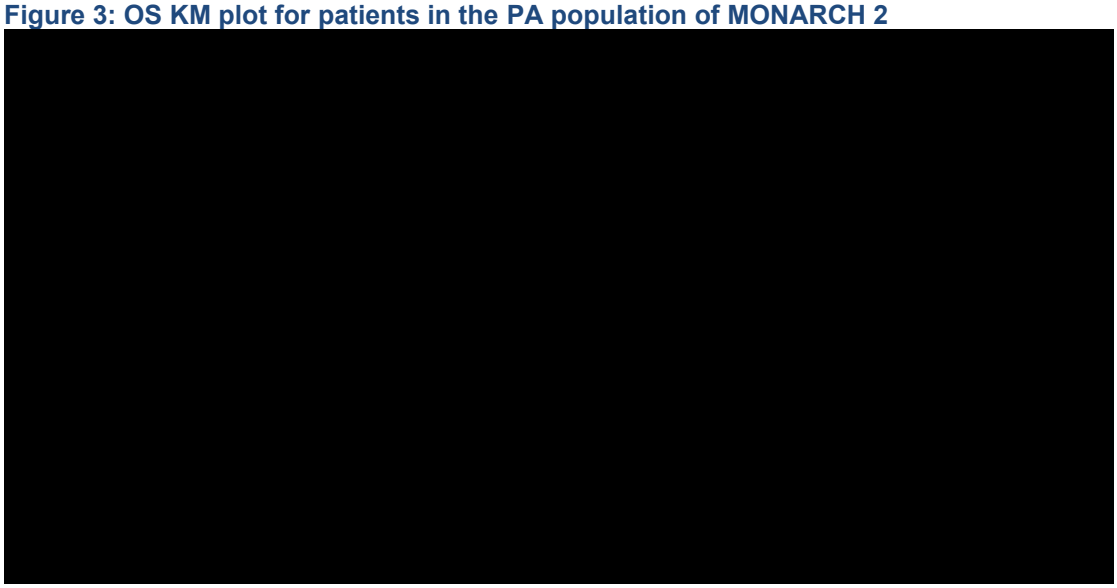
The relevant KM curves for the PA population in MONARCH 2 are presented in Figure 2 (PFS) and Figure 3 (OS).

Figure 2: PFS KM plot for patients in the PA population of MONARCH 2



Abbreviations: ABE: abemaciclib; FUL: fulvestrant; KM: Kaplan-Meier; PA: post-amendment; PFS: progression-free survival.

Figure 3: OS KM plot for patients in the PA population of MONARCH 2



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

Table 3: Baseline characteristics for the pre-amendment and PA populations in MONARCH 2

	Pre-amendment population		PA population		ITT Population	
	Abemaciclib 200 mg	Placebo 200 mg	Abemaciclib 150 mg	Placebo 150 mg	Abemaciclib	Placebo
Key baseline characteristics (N)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median age (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race ≥10%, n (%)						
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Menopausal status, n (%)						
Postmenopausal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre or perimenopausal (ovarian suppression)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Primary resistance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visceral disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bone only disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; NA; not applicable; ORR: overall response rate; PA: post-amendment; PFS: progression-free survival; Q1-Q3: interquartile range.

Incorporation of PA data in the FP NMA

The PA data have been incorporated into the FP NMA, in line with the methodology detailed in Section A.7 (Pages 17–22) of the Abemaciclib NICE CDF Review_Final Submission_240920. The models with the most reasonable fit were the same as those chosen for the ITT analysis. For PFS, the first-order FE model with $p_1 = 0$ showed the most reasonable fit, while for OS, the first-order FE model with $p_1 = -1.0$ showed best fit.

The corresponding time-to-event curves and summary statistics can be found in Figure 4 and Table 4 (OS), and Figure 5 and Table 5 (PFS).

Figure 4: OS time-to-event curves (FP NMA, PA population)

Note: The curves presented above include a combined FUL extrapolation (combining data from both FUL 500 mg and FUL 250 mg) in line with the methodology used in the economic analysis, rather than the separate FUL 500 and FUL 250 curves that directly result from the NMA.
Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; NMA: network meta-analysis; OS: overall survival.

Table 4: Estimated OS summary statistics from the FP NMA including the PA population data

	FUL	EXE	EXE-EVE	ABE-FUL
Mean OS, months	[redacted]	[redacted]	[redacted]	[redacted]
Median OS, months	[redacted]	[redacted]	[redacted]	[redacted]
Alive at 12 months, %	[redacted]	[redacted]	[redacted]	[redacted]
Alive at 60 months, %	[redacted]	[redacted]	[redacted]	[redacted]
Alive at 120 months, %	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FP: fractional polynomial; FUL: fulvestrant; NMA: network meta-analysis; OS: overall survival.

Figure 5: Estimated PFS time-to-event curves (FP NMA, PA population)

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FP: fractional polynomial; FUL: fulvestrant; NMA: network meta-analysis; PFS: progression-free survival.

Table 5: Estimated PFS summary statistics from the FP NMA

	FUL	EXE	EXE-EVE	ABE-FUL
Mean PFS, months	[redacted]	[redacted]	[redacted]	[redacted]
Median PFS, months	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free at 12 months, %	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free at 60 months, %	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free at 120 months, %	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FP: fractional polynomial; FUL: fulvestrant; NMA: network meta-analysis; PFS: progression-free survival.

Key Issue 4: ABE-FUL TTD

Summary and fitting statistics for a range of extrapolations for PFS and TTD for both the ITT and PA populations are presented in the tables below.

Table 6: Fit statistics for a range of extrapolations for PFS (ITT population)

ITT – PFS	AIC	BIC
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Log Logistic	[redacted]	[redacted]
Log Normal	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; ITT: intention-to-treat; PFS: progression free survival.

Table 7: Fit statistics for a range of extrapolations for TTD (ITT population)

ITT – TTD	AIC	BIC
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Log Logistic	[redacted]	[redacted]
Log Normal	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; ITT: intention-to-treat; TTD: time to discontinuation.

Table 8: Fit statistics for a range of extrapolations for PFS (PA population)

PA - PFS	AIC	BIC
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Log Logistic	[redacted]	[redacted]
Log Normal	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PA: post-amendment; PFS: progression free survival.

Table 9: Fit statistics for a range of extrapolations for TTD (PA population)

PA - TTD	AIC	BIC
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Log Logistic	[redacted]	[redacted]
Log Normal	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PA: post-amendment population; TTD: time to discontinuation.

In all cases, log-normal extrapolations provided the best statistical fit (according to AIC/BIC). Log-normal also provide good visual fit with regard to clinical plausibility, and as such have been selected as the most appropriate extrapolations for the subsequent analyses. The alternative extrapolations are presented in the economic model (in the PFS_ITT, PFS_PA, TTD_ITT and TTD_PA tabs).

As discussed above, in order to investigate the uncertainty around ABE-FUL TTD, Lilly has explored two approaches in order to determine the HR between PFS and TTD for ABE-FUL to be incorporated in the economic analysis: a lifetime survival analysis, as well as a restricted mean methodology comparing the AUCs between PFS and TTD.

Lifetime Survival Analysis

Table 10: Estimated mean and median PFS and TTD for ABE-FUL in the ITT and PA population in MONARCH 2 based on a lifetime survival analysis using a log normal extrapolation

Extrapolation	ITT - PFS	PA - PFS	ITT - TTD	PA - TTD
Mean	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]

A summary of the respective HRs derived from the ratio of the means between the extrapolated ITT or PA PFS and the extrapolated ITT or PA TTD data are presented in Table 11.

Table 11: Hazard ratios between PFS and TTD for patients treated with ABE-FUL in the ITT or PA population (based on a log normal extrapolation)

	ITT PFS versus ITT TTD	ITT PFS versus PA TTD	PA PFS vs PA TTD
HR between PFS and TTD	[redacted]	[redacted]	[redacted]

Abbreviations: ABE: abemaciclib; FUL: fulvestrant; HR: hazard ratio; ITT: intention-to-treat; PA: post-amendment; PFS: progression-free survival; TTD: time-to-discontinuation.

Restricted Mean Methodology

As discussed above, Lilly also considered an alternative methodology using a restricted mean approach that compared the ratio between the AUC for both PFS and TTD. The mean was restricted at a time point of 54 months, which reflects the length of observed data that is currently available from MONARCH 2 at the time of the OS interim analysis (DCO 20th June 2019).

Table 12: Mean PFS and TTD for ABE-FUL in the ITT and PA population in MONARCH 2 using a restricted mean analysis at 54 months

Extrapolation	ITT - PFS	ITT - TTD	PA - PFS	PA - TTD
Mean	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABE: abemaciclib; FUL: fulvestrant; HR: hazard ratio; ITT: intention-to-treat; PA: post-amendment; PFS: progression-free survival; TTD: time-to-discontinuation.

Table 13: Hazard ratios between PFS and TTD for patients treated with ABE-FUL in the ITT or PA population using an AUC methodology

	ITT PFS versus ITT TTD	ITT PFS versus PA TTD	PA PFS vs PA TTD
Log normal	[redacted]	[redacted]	[redacted]

Abbreviations: ABE: abemaciclib; AUC: area under the curve; FUL: fulvestrant; HR: hazard ratio; ITT: intention-to-treat; PA: post-amendment; PFS: progression-free survival; TTD: time-to-discontinuation.

Key Issue 6: Updated Costs

A number of costs have been updated from the original economic analysis. For any costs which have been changed, the original and updated costs are summarised below, as well as the sources, and justification for all changes that have been made.

Table 14: Original and updated treatment costs

Treatment	Drug	Units (mg/mL)	Pack/vial size (mg/mL)	Original Price	Original Source	Updated Price	Source	Justification
EXE	EXE	25	30	£3.69	eMIT, 12 month period to end June 2017	£6.39	eMIT , accessed: Dec-2020	Updated price from latest eMIT.
EXE-EVE	EXE	25	30	£3.69	eMIT, 12 month period to end June 2017	£6.39	eMIT , accessed: Dec-2020	Updated price from latest eMIT.
TMX	TMX	10	30	£7.02	eMIT, 12 month period to end June 2017	£6.10	eMIT , accessed: Dec-2020	Updated price from latest eMIT.
TMX	TMX	20	30	£1.59	eMIT, 12 month period to end June 2017	£1.70	eMIT , accessed: Dec-2020	Updated price from latest eMIT.
CAP	CAP	150	60	£3.97	eMIT, 12 month period to end June 2017	£4.17	eMIT , accessed: Dec-2020	Updated price from latest eMIT.
CAP	CAP	500	120	£21.76	eMIT, 12 month period to end June 2017	£25.76	eMIT , accessed: Dec-2020	Updated price from latest eMIT.
CAP	CAP	150	60	£3.97	eMIT, 12 month period to end June 2017	£4.17	eMIT , accessed: Dec-2020	Updated price from latest eMIT.
CAP	CAP	500	120	£21.76	eMIT, 12 month period to end June 2017	£25.76	eMIT , accessed: Dec-2020	Updated price from latest eMIT.
PAC	PAC	300	50	£19.68	eMIT, 12 month period to end June 2017	£39.32	eMIT , accessed: Dec-2020	Updated price from latest eMIT.

VNB	VNB	50	5	£22.58	eMIT, 12 month period to end June 2017	£13.33	eMIT , accessed: Dec-2020	Updated price from latest eMIT.
LTZ	LTZ	2.5	28	£2.71	eMIT, 12 month period to end June 2017	£1.03	eMIT , accessed: Dec-2020	Updated price from latest eMIT.
EXE	EXE	25	30	£3.69	eMIT, 12 month period to end June 2017	£6.39	eMIT , accessed: Dec-2020	Updated price from latest eMIT.
CYC	CYC	2000	1	£25.99	eMIT, 12 month period to end June 2017	£27.50	eMIT , accessed: Dec-2020	Updated price from latest eMIT.
CYC	EPI	50	25	£5.62	eMIT, 12 month period to end June 2017	£4.84	eMIT , accessed: Dec-2020	Updated price from latest eMIT.
CYC	FLU	2500	100	£3.59	eMIT, 12 month period to end June 2017	£2.84	eMIT , accessed: Dec-2020	Updated price from latest eMIT.
GEM	GEM	2000	52.6	£15.92	eMIT, 12 month period to end June 2017	£20.35	eMIT , accessed: Dec-2020	Updated price from latest eMIT.

Table 15: Original and Updated Administration Costs

Treatment	Drug	Original Mean Cost	Original Source	Updated Mean Cost	Updated Source	Justification
ABE-FUL	FUL	£0.00		£103.00	PSSRU 2019 and NHS Reference Cost 2018-19	Overwritten by ERG Analysis selection.
ABE-FUL.LD	FUL.LD	£172.67		£181.91	NHS Reference costs, 2018-19; WF01B Non-admitted F2F	Overwritten by ERG Analysis selection.

					attendance, First, Service Code 370 (Medical Oncology)	
FUL	FUL	£0.00		£103.00	PSSRU 2019 and NHS Reference Cost 2018-19	Overwritten by ERG Analysis selection.
FUL.LD	FUL.LD	£172.67		£181.91	NHS Reference costs, 2018-19; WF01B Non-admitted F2F attendance, First, Service Code 370 (Medical Oncology)	Overwritten by ERG Analysis selection.
CAP	CAP	£163.82	National Schedule of Reference Cost 2016-17, SB11Z,Deliver Exclusively Oral Chemotherapy, outpatient	£185.71	NHS reference costs 2018-19, SB11Z Deliver exclusively oral chemo (outpt only based no activity)	Updated with corresponding 2018-19 National Schedule of Reference cost
CAP	CAP	£163.82	National Schedule of Reference Cost 2016-17, SB11Z, Deliver Exclusively Oral Chemotherapy, outpatient	£185.71	NHS reference costs 2018-19, SB11Z Deliver exclusively oral chemo (outpt only based no activity)	Updated with corresponding 2018-19 National Schedule of Reference cost
PAC	PAC	£259.76	National Schedule of Reference Cost 2016-17, SB12Z, Deliver Simple Parenteral Chemotherapy at First Attendance, daycase	£254.14	NHS reference costs 2018-19, SB12Z Deliver simple parenteral chemo at first attendance (daycase only based on activity)	Updated with corresponding 2018-19 National Schedule of Reference cost
VNB	VNB	£163.82	National Schedule of Reference Cost 2016-17, SB11Z,Deliver Exclusively Oral	£183.54	NHS reference costs 2018-19, SB12Z Deliver simple parenteral chemo at first attendance (outpatient)	Activity originally costed as delivery of oral chemo in outpatient setting. This is inappropriate for an injectable chemo. Due to time constraints, Lilly has assumed this

			Chemotherapy, outpatient			can be delivered as outpatient chemo in absence of more detailed cost information.
ERI	ERI	£259.76	National Schedule of Reference Cost 2016-17, SB12Z, Deliver Simple Parenteral Chemotherapy at First Attendance, daycase	£254.14	NHS reference costs 2018-19, SB12Z Deliver simple parenteral chemo at first attendance (daycase only based on activity)	Updated with corresponding 2018-19 National Schedule of Reference cost
FUL	FUL	£0.00		£103.00	As per pre-progression	Overwritten by ERG Analysis selection.
FUL.LD	FUL.LD	£172.67		£181.91	As per pre-progression	Updated with corresponding 2018-19 National Schedule of Reference cost
CYC	CYC	£310.00	National Schedule of Reference Cost 2016-17, SB13Z, Deliver more Complex Parenteral Chemotherapy at First Attendance, daycase	£314.36	NHS reference costs 2018-2019, SB13Z, Deliver complex chemo at first attendance, daycase based on activity	Updated with corresponding 2018-19 National Schedule of Reference cost
GEM	GEM	£259.76	National Schedule of Reference Cost 2016-17, SB12Z, Deliver Simple Parenteral Chemotherapy at First Attendance, daycase	£254.14	NHS reference costs 2018-19, SB12Z Deliver simple parenteral chemo at first attendance (daycase only based on activity)	Updated with corresponding 2018-19 National Schedule of Reference cost
BEV	BEV	£205.09	National Schedule of Reference Cost 2016-17, SB15Z, Deliver Subsequent Elements of	£223.00	NHS reference costs 2018-19, Subsequent treatment cycles: SB15Z - delivery subsequent elements of a chemotherapy cycle (chemotherapy outpatient)	Updated with corresponding 2018-19 National Schedule of Reference cost

			a Chemotherapy Cycle, outpatient			

Table 16: Original and updated costs for BSC

BSC Component	Drug	Dose	Pack/vial size	Original Cost Per Pack	Original Source	Updated Cost Per Pack	Updated Source	Justification
Antiemesis or antinauseants	Ondansetron	4	30	£2.43		£3.72	BNF, accessed: Dec-2020	Updated with latest cost

Table 17: Original and updated AE costs

AE	Original Cost	Original Source	Updated Cost	Updated Source	Justification
Anaemia	£270.00	NHS Reference Cost 16-17 SA44A, outpatient, service code 370, Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over	£247.23	NHS Reference Cost 2018-19, 370, OPROC, SA44A, Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over	Updated with latest average from NHS Reference Cost 2018/19, accessed: dec-2020
Dyspnoea	£389.64	NHS Reference Costs for AEs DZ19L, DZ19M and DZ19N for Other Respiratory Disorders without Interventions	£358.60	NHS Reference Cost 2018-19, Average of DZ19 L, M & N in non-elective short stay, Other Respiratory Disorders without Interventions	Updated with latest average from NHS Reference Cost 2018/19, accessed: dec-2020
Hyperglycemia	£434.91	NHS Reference Costs for AEs KB02G, KB02H, KB02J and KB02K for Diabetes with Hyperglycaemic Disorders	£438.89	NHS Reference Cost 2018-19, Average of KB02G, H, J, & K in Non-elective short stay,	Updated with latest average from NHS Reference Cost

				Diabetes with Hyperglycaemic Disorders	2018/19, accessed: dec-2020
Leukopenia	£173.00	NHS Reference Cost 16-17 WF01A service code 370 Medical Oncology Non-Admitted Face to Face Attendance, Follow-up	£190.64	NHS Reference Cost 2018-19, 370, OPROC, WF01A, Non-Admitted Face-to-Face Attendance, Follow-up	Updated with latest average from NHS Reference Cost 2018/19, accessed: dec-2020
Neutropenia	£173.00	NHS Reference Cost 16-17 WF01A service code 370 Medical Oncology Non-Admitted Face to Face Attendance, Follow-up	£190.64	NHS Reference Cost 2018-19, 370, OPROC, WF01A, Non-Admitted Face-to-Face Attendance, Follow-up	Updated with latest average from NHS Reference Cost 2018/19, accessed: dec-2020
Stomatitis	£482.28	NHS Reference Costs for AEs FD10J, FD10K, FD10L and FD10M for Non-Malignant Gastrointestinal Tract Disorders without Interventions	£443.09	NHS Reference Cost 2018-19, Average of FD10 J, K, L, & M in non-elective short stay, Non-Malignant Gastrointestinal Tract Disorders without Interventions	Updated with latest average from NHS Reference Cost 2018/19, accessed: dec-2020

Table 18: Original and Updated Costs Associated with Resource Use Pre and Post Progression

PFS Resource	Original Cost	Original Source	Updated Cost	Updated Source	Justification
Pre Progression					
CT scan	£112.07	NHS Reference costs, RD24Z, CT of 2 areas with contrast, outpt setting	£103.47	NHS Reference costs, IMAG, IMAGOP, RD24Z, CT of 2 areas with contrast, outpt setting	Updated with cost from National schedule of Reference Cost 2018/19, accessed: dec-2020
MRI scan	£204.57	NHS Reference costs, RD05Z, MRI of 2 areas with contrast, outpt setting	£206.36	NHS Reference costs, IMAG, IMAGOP, RD05Z,	Updated with cost from National schedule of Reference Cost 2018/19, accessed: dec-2020

				MRI of 2 areas with contrast, outpt setting	
PET scan	£478.79	NHS Reference costs, RN 07A, PET, 19 years and over outpt setting	£814.86	NHS Reference costs, NM, IMAGOP, RN 07A, PET, 19 years and over outpt setting	Updated with cost from National schedule of Reference Cost 2018/19, accessed: dec-2020
X-ray	£0.00	Assumed no cost	£22.00	NHS Reference Costs 2018-2019, IMAG, IMAGOP, PF, Plain Film in Outpatient setting	Updated with cost from National schedule of Reference Cost 2018/19, accessed: dec-2020
Electrocardiogram	£256.35	NHS Reference costs, 2016-17, EY51Z, Electrocardiogram monitoring or stress testing, Service Code 370 (Medical Oncology)	£195.61	NHS Reference costs, 2018-19, OPROC, 370, EY51Z, Electrocardiogram monitoring or stress testing	Updated with cost from National schedule of Reference Cost 2018/19, accessed: dec-2020
Complete blood count	£3.06	NHS Reference costs, 2016-17, DAPS05, Haematology	£2.79	NHS Reference costs, 2018-19, DAPS05, Haematology	Updated with cost from National schedule of Reference Cost 2018/19, accessed: dec-2020
Serum chemistry	£1.13	NHS Reference costs, 2016-17,DAPS04, Clinical biochemistry	£1.10	NHS Reference costs, 2018-19, DAPS04, Clinical biochemistry	Updated with cost from National schedule of Reference Cost 2018/19, accessed: dec-2020
Oncologist consultation	£172.67	NHS Reference costs, 2016-17, WF01A Non-admitted F2F attendance, First, Service Code 370 (Medical Oncology)	£194.17	NHS Reference costs, 2018-19, OPROC, WF01A Non-admitted F2F attendance, First, Service Code 370 (Medical Oncology)	Updated with cost from National schedule of Reference Cost 2018/19, accessed: dec-2020
GP visit	£38.00	PSSRU, 2017, Per patient contact lasting 9.22 with	£39.00	PSSRU, Unit Costs of Health and Social Care 2019, Community Based	Updated with cost from PSSRU 2019, accessed: dec-2020

		qualifications minutes		Health Care Staff 2019, Per patient contact lasting 9.22 with qualifications minutes incl direct care staff costs	
Community nurse	£36.00	PSSRU, 2017, Community Nurse, Band 5, Cost per working hour	£37.00	PSSRU, Unit Costs of Health and Social Care 2019, Community Nurse, Band 5, Cost per working hour	Updated with cost from PSSRU 2019, accessed: dec-2020
Clinical nurse specialist	£44.00	PSSRU, 2017, Community Nurse, Band 6, Cost per working hour	£46.00	PSSRU, Unit Costs of Health and Social Care 2019, Community Nurse, Band 6, Cost per working hour	Updated with cost from PSSRU 2019, accessed: dec-2020
Post Progression					
CT scan	£112.07	NHS Reference costs, RD24Z, CT of 2 areas with contrast, outpt setting	£103.47	NHS Reference costs, RD24Z, CT of 2 areas with contrast, outpt setting	Updated with cost from NHS Reference Cost 2018/19, accessed: dec-2020
MRI scan	£204.57	NHS Reference costs, RD05Z, MRI of 2 areas with contrast, outpt setting	£206.36	NHS Reference costs, RD05Z, MRI of 2 areas with contrast, outpt setting	Updated with cost from NHS Reference Cost 2018/19, accessed: dec-2021
PET scan	£478.79	NHS Reference costs, RN 07A, PET, 19 years and over outpt setting	£814.86	NHS Reference costs, RN 07A, PET, 19 years and over outpt setting	Updated with cost from NHS Reference Cost 2018/19, accessed: dec-2022
Electrocardiogram	£256.35	NHS Reference costs, 2016-17, EY51Z, Electrocardiogram monitoring or stress testing, Service Code 370 (Medical Oncology)	£195.61	NHS Reference costs, 2018-19, OPROC, 370, EY51Z, Electrocardiogram monitoring or stress testing	Updated with cost from NHS Reference Cost 2018/19, accessed: dec-2023

Complete blood count	£3.06	NHS Reference costs, 2016-17, DAPS05, Haematology	£2.79	NHS Reference costs, 2018-19, DAPS05, Haematology	Updated with cost from NHS Reference Cost 2018/19, accessed: dec-2024
Serum chemistry	£1.13	NHS Reference costs, 2016-17,DAPS04, Clinical biochemistry	£1.10	NHS Reference costs, 2018-19, DAPS04, Clinical biochemistry	Updated with cost from NHS Reference Cost 2018/19, accessed: dec-2025
Oncologist consultation	£172.67	NHS Reference costs, 2016-17, WF01A Non-admitted F2F attendance, First, Service Code 370 (Medical Oncology)	£194.17	NHS Reference costs, 2018-19, OPROC, WF01A Non-admitted F2F attendance, First, Service Code 370 (Medical Oncology)	Updated with cost from NHS Reference Cost 2018/19, accessed: dec-2026
GP visit	£38.00	PSSRU, 2017, Per patient contact lasting 9.22 with qualifications minutes	£39.00	PSSRU, Unit Costs of Health and Social Care 2019, Community Based Health Care Staff 2019, Per patient contact lasting 9.22 with qualifications minutes incl direct care staff costs	Updated with cost from PSSRU 2019, accessed: dec-2020
Community nurse	£36.00	PSSRU, 2017, Community Nurse, Band 5, Cost per working hour	£37.00	PSSRU, Unit Costs of Health and Social Care 2019, Community Nurse, Band 5, Cost per working hour	Updated with cost from PSSRU 2019, accessed: dec-2021
Clinical nurse specialist	£44.00	PSSRU, 2017, Community Nurse, Band 6, Cost per working hour	£46.00	PSSRU, Unit Costs of Health and Social Care 2019, Community Nurse, Band 6, Cost per working hour	Updated with cost from PSSRU 2019, accessed: dec-2022

Therapist	£59.00	PSSRU, 2017, Community Occupational Therapist, cost per working hour	£65.00	PSSRU, 2019, Community Occupational Therapist, Band 8a, Cost per working hour	Updated with cost from PSSRU 2019, accessed: dec-2023

Table 19: Original and Updated Costs Associated with terminal care resource use

Resource	Original Cost	Original Source	Updated Cost	Updated Source	Justification
Terminal care- in hospital	£5,695.05	NICE clinical guideline 81 (package 3 estimates inflated to 2017 prices)	£5,989.20	NICE clinical guideline 81 (package 3 estimates inflated to 2019 prices with HPI)	Inflation adjusted cost based on user selected method.
Terminal care- in a hospice	£7,100.06	NICE clinical guideline 81 (package 3 estimates inflated to 2017 prices)	£7,466.77	NICE clinical guideline 81 (package 3 estimates inflated to 2019 prices with HPI)	Inflation adjusted cost based on user selected method.
Terminal care- at home with community support	£2,938.29	NICE clinical guideline 81 (package 3 estimates inflated to 2017 prices)	£3,090.05	NICE clinical guideline 81 (package 3 estimates inflated to 2019 prices with HPI)	Inflation adjusted cost based on user selected method.

Table 20: Original and Updated Costs associated with hospitalisation

Resource	Original Cost	Mean length of stay, days	Original Source	Updated Cost	Mean length of stay, days	Updated Source	Justification
Hospitalisation	£3,481.54	7.78	NHS Reference costs, JD12D-L, Malignant breast disorders with / without interventions, non-elective long stay	£3,661.36	7.78	Inflated from original cost with HPI	Inflation adjusted cost based on user selected method.

Key Issue 7: Additional Data for PFS2, time to chemotherapy and CFS

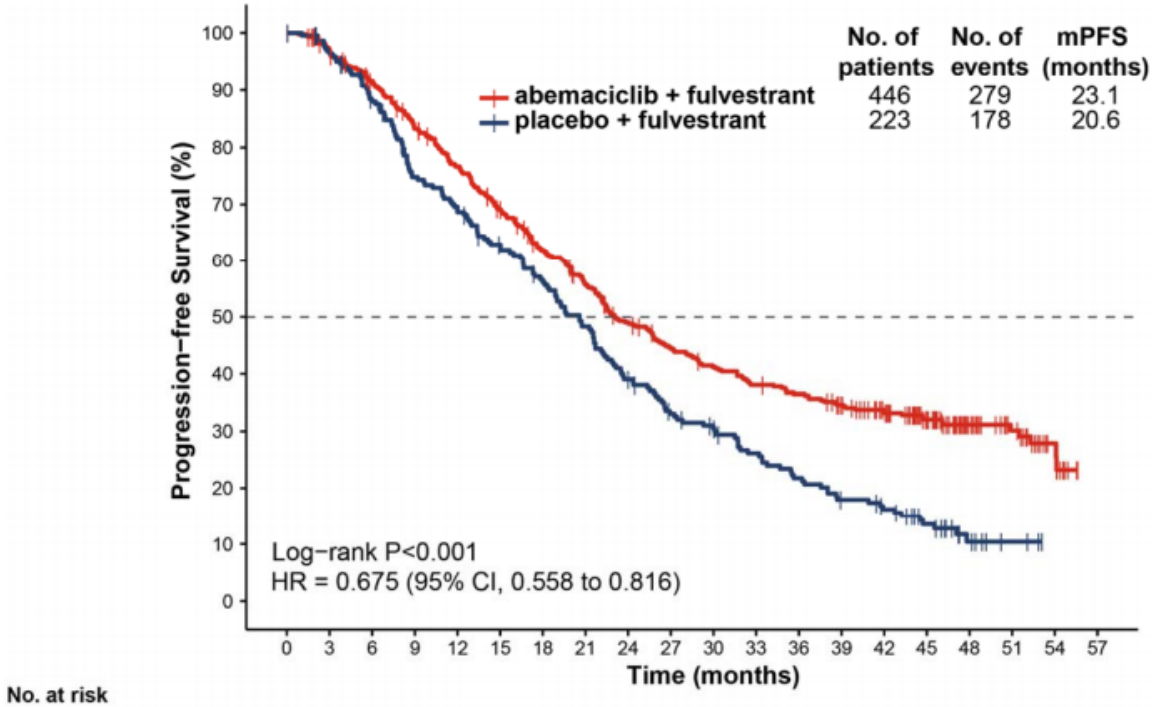
KM plots for time to second disease progression (PFS2), time-to-chemotherapy and chemotherapy free survival (CFS) for the ITT population are presented in Figure 6 and Figure 7.

PFS2 was defined as the time from randomisation to the discontinuation date of next-line treatment (first line of post discontinuation treatment), or the starting date of the second line of post-discontinuation treatment or death from any cause, whichever was earlier.

Time to chemotherapy was defined as the time from randomisation to initiation on first post discontinuation chemotherapy (censoring patients who died prior to initiation of chemotherapy).

CFS was defined as the time from randomisation to initiation of first post-discontinuation chemotherapy or death.

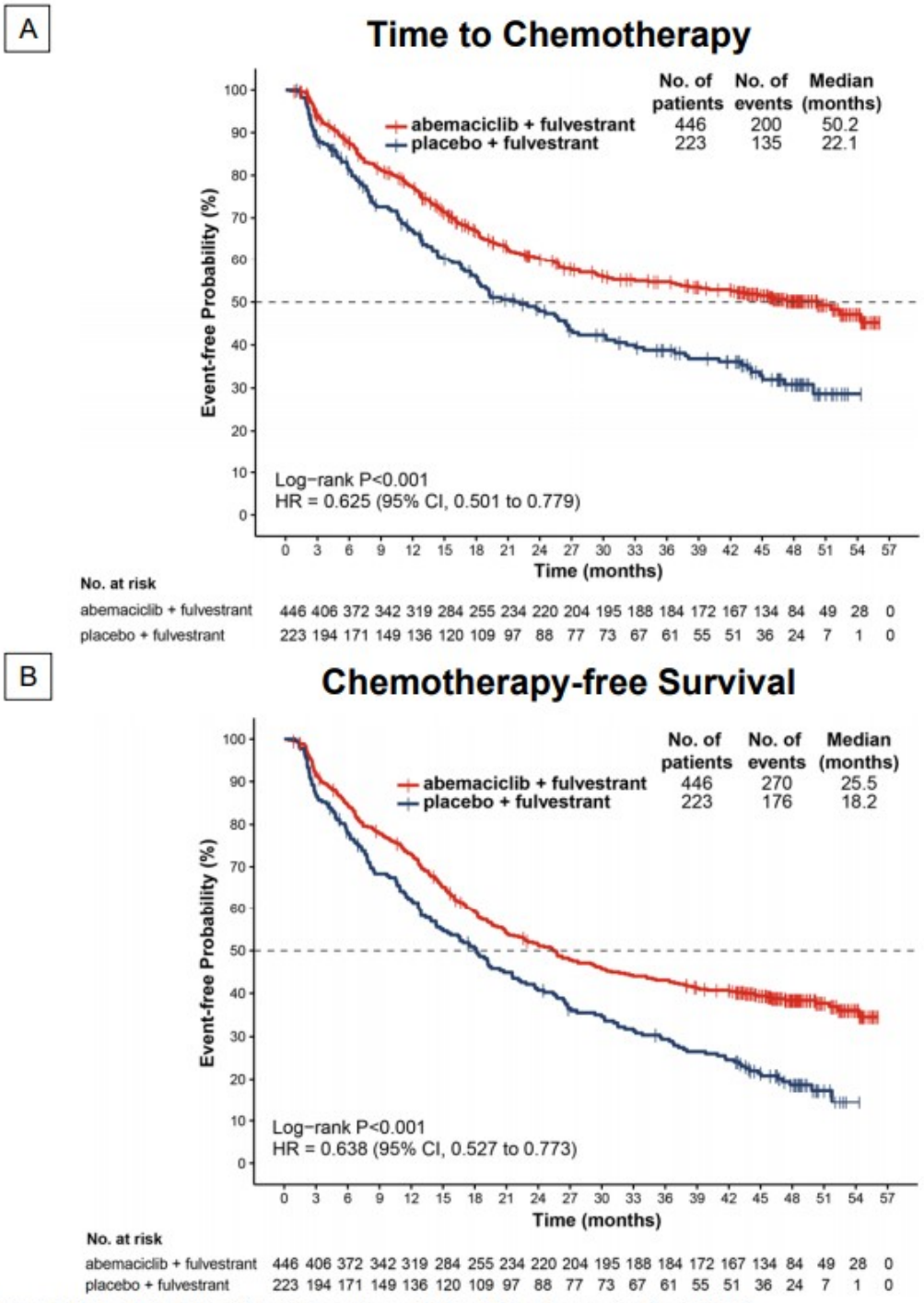
Figure 6: KM-Plot of Time to Second Disease Progression (PFS2) for the ITT population in MONARCH 2



eFigure 3: Kaplan-Meier Plot of Time to Second Disease Progression (PFS2)
PFS2 was defined as the time from randomization to the discontinuation date of next-line (first line of post discontinuation treatment), or starting date of the second line of post discontinuation treatment or death from any cause, whichever was earlier. CI, confidence interval; HR, hazard ratio; mPFS, median PFS; No., number; P, p-value

Source: Sledge et al. (2020)[3]

Figure 7: KM-Plot of Time to Chemotherapy and Chemotherapy Free Survival for the ITT population in MONARCH 2



eFigure 4: Kaplan-Meier Plots of Time to Chemotherapy (TTC) and Chemotherapy-free Survival (CFS)
Panel A, TTC was defined as the time from randomization to initiation on first post discontinuation chemotherapy (censoring pts who died prior to initiation of chemotherapy). Panel B, CFS was defined as the time from randomization to initiation of first post discontinuation chemotherapy or death. CI, confidence interval; HR, hazard ratio; No., number; P, p-value

Source: Sledge et al. (2020)[3]

References

1. Gupta S, Zhang J, Jerusalem G. The association of chemotherapy versus hormonal therapy and health outcomes among patients with hormone receptor-positive, HER2-negative metastatic breast cancer: experience from the patient perspective. Expert Rev Pharmacoecon Outcomes Res 2014;14:929-40.
2. Walker MS, Hasan M, Yim YM, et al. Retrospective study of the effect of disease progression on patient reported outcomes in HER-2 negative metastatic breast cancer patients. Health Qual Life Outcomes 2011;9:46.
3. Sledge GW, Jr, Toi M, Neven P, et al. The Effect of Abemaciclib Plus Fulvestrant on Overall Survival in Hormone Receptor–Positive, ERBB2-Negative Breast Cancer That Progressed on Endocrine Therapy—MONARCH 2: A Randomized Clinical Trial. JAMA Oncology 2020;6:116-124.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Abemaciclib in combination with fulvestrant for treating advanced hormone receptor-positive, HER2-negative breast cancer (CDF review of TA579) [ID2727]

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	**Mark Verrill**
2. Name of organisation	**The Newcastle upon Tyne Hospitals NHS Foundation Trust/UK Breast Cancer Group**

3. Job title or position	**Consultant Medical 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? ☐ 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)	**X** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the	☐ yes

rest of this form will be deleted after submission.)	
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To control locally advanced and metastatic Oestrogen receptor positive and HER2 negative breast cancer after prior treatment with an antiendocrine therapy. Compared to the comparator arm in the relevant clinical trial for this indication, the addition of Abemaciclib produced a clinically meaninigful extension of progression free and overall 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.)	The accepted definition of a Partial Response (PR) is a reduction in the sum of the diameters of representative tumour deposits by 30%. However, the ability to stabilise disease without progression is also a worthwhile goal. The combination of Fulvestrant with Abemaciclib produced a partial response in 48% of patients with measurable disease (Sledge GW Jr, et al. J Clin Oncol 2017;35:2875–84).
9. In your view, is there an unmet need for patients and	In this indication, the combination of exemestane with everolimus is available but has not been shown to extend overall survival and is associated with significant clinical toxicity which is frequently dose limiting.

healthcare professionals in this condition?	
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Clinical guidance was developed as part of the Cancer Drugs Fund provisional authorisation of Fulvesttrant and Abemaciclib and remain relevant to the NICE TA.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is clearly defined in license and existing CDF guidance. There is a building consensus that this treatment facilitates delay of the use of chemotherapy, although there are some circumstances where clinicians may favour chemotherapy before the use of fulvestrant with Abemaciclib. Either sequence is permitted in both the license and CDF rules although prior chemotherapy was an exclusion in the registration study for the technology.
• What impact would the technology have on the current pathway of care?	Because of the prior CDF approval of the combination of fulvestrant with Abemaciclib, the current pathway of care will not be affected if any NICE approval maps on to the CDF criteria.

11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Because of the prior CDF approval of the combination of fulvestrant with Abemaciclib, the current pathway of care will not be affected if any NICE approval maps on to the CDF criteria.
• How does healthcare resource use differ between the technology and current care?	See above
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This is a specialist systemic anticancer therapy and should be supervised by appropriately trained non-surgical oncology specialists.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Because this treatment extends life and requires close supervision, there will be additional service/resource requirements including clinician, nursing and pharmacy time. There will be a small impact on SACT delivery service for the monthly fulvestrant injection (but it does not need to be given in a chemotherapy facility). Abemaciclib is an oral therapy taken at home by patients.
12. Do you expect the technology to provide clinically	We have already seen in a clinical setting the advantage for patients of this combination provided through the CDF, including less chemotherapy use and longer periods of disease control and overall survival.

meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	Yes – already seen following CDF approval
• Do you expect the technology to increase health-related quality of life more than current care?	Yes – avoidance of cytotoxic chemotherapy with the additional die effect burden (please note fulvestrant monotherapy is not NICE approved and so not an option in place of the combination).
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This is only relevant to people with ER+ HER2- disease. It is not appropriate for ER- or HER2+ people. It is not indicated in "visceral crisis" – the presence of immediately life threatening visceral disease with compromised organ function or patients with poor performance status (WHO/ECOG 3 or 4).
The use of the technology	
14. Will the technology be easier or more difficult to use	The technology requires clinical supervision. There are monthly fulvestrant injections. Once established on treatment many patients require minimal medical intervention but as with all other patients on SACT

for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	require regular response evaluation. People taking Abemaciclib are provided with loperamide in case of diarrhoea but there are no other routine concomitant medications. There ae no special tests associated with the use of the technology.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Rules should map on to clinical trial stopping rules including progression, unacceptable toxicity and patient choice.
16. Do you consider that the use of the technology will result in any substantial health-	The technology will result in the delay of chemotherapy for a substantial cohort of patients – QOL has not been compared directly with chemotherapy in the clinical trials conducted to date.

related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	The CDK 4/6 inhibitors are the most significant advance in this sub-group of patients (ER+, HER2- advanced disease) since the Aromatase inhibitors were first used 20 years ago.
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes – effective and tolerable therapy in patients with disease that is resistant to the aromatase inhibitors.

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?	In a small subset of patients receiving this treatment, diarrhoea can be troublesome but is controlled in the majority. At present under CDF rules there is the option to switch to either ribociclib or Palbociclib if toxicity is problematic in the first 6 months of treatment. There is good evidence that the ability to control disease with this class of drug is closely correlated to maintenance of quality of life.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes – the monarch 2 trial maps closely onto the clinical scenario where this technology will be used.
• 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?	Overall and progression free survival. Tolerability compared to chemotherapy. QOL vs. chemotherapy was not tested in the registration study. (Sledge GW Jr et al. JAMA Oncology doi:10.1001/jamaoncol.2019.4782)
• If surrogate outcome measures were used, do they adequately predict	OS data are available and reflect the gold standard outcome.

long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes – the FDA has issued a warning that all of the CDK 4/6 inhibitors have a rare toxicity of drug induced interstitial lung disease.
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 [TAXXX]?	N/A
22. How do data on real-world experience compare with the trial data?	The real world date with this drug class are likely to show more modest gains compared to the trial based on patient selection and the use of chemotherapy prior to fulvestrant + Abemaciclib in the real world setting

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.	
24. In up to 5 bullet points, please summarise the key messages of your statement. • Overall Survival advantage in tightly defined trial population of > 9 months comared to control arm • Overall response rate of 48% in patients with measurable disease. • Progression free survival advantage of > 7 months compared to control • Chemotherapy delayed • Efficacy in patients with documented resistance to endocrine therapy – most commonly aromatase inhibitors	

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.

.....

NICE National Institute for Health and Care Excellence

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy [ID2727]

Thank you for agreeing to give us your views on this treatment 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.

About this Form

In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **4th December 2020**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important 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 want 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 15 pages.

PART 1 – Living with or caring for a patient with hormone receptor-positive, HER2-negative advanced breast cancer and current treatment options	
About you	
1.Your name	**Holly Heath**
2. Are you (please tick all that apply):	☐ a patient with hormone receptor-positive, HER2-negative advanced breast cancer? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with hormone receptor-positive, HER2-negative advanced breast cancer? ☒ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	Breast Cancer Now
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☒ I agree with it and **do not wish to** complete this statement

	☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience. ☐ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with hormone receptor-positive, HER2-negative advanced breast cancer? If you are a carer (for someone with hormone receptor-positive, HER2-negative advanced breast cancer) please share your experience of caring for them.	

Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for hormone receptor-positive, HER2-negative advanced breast cancer on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	
8. If there are disadvantages for patients of **current NHS treatments** for hormone receptor-positive, HER2-negative advanced breast cancer (for example how everolimus with exemestane is given or taken, side effects of treatment etc) please describe these	
Advantages of this treatment	
9a. If there are advantages of abemaciclib with fulvestrant over current treatments on the NHS please describe these. For example, the impact on your Quality of Life, your ability to continue work, education, self-care, and care for others?	

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does abemaciclib with fulvestrant help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	
Disadvantages of this treatment	
10. If there are disadvantages of abemaciclib with fulvestrant over current treatments on the NHS please describe these? For example, are there any risks with abemaciclib with fulvestrant? If you are concerned about any potential side effects you have heard about, please describe them and explain why.	
Patient population	
11. Are there any groups of patients who might benefit more from abemaciclib with fulvestrant or any	

who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
Equality	
12. Are there any potential equality issues that should be taken into account when considering hormone receptor-positive, HER2-negative advanced breast cancer and abemaciclib with fulvestrant? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics	

More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	

PART 2 – Technical engagement questions for patient experts
Issues arising from technical engagement
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
15. Key issue 1: Subgroup data by abemaciclib starting dose not explored	
16. Key issue 3: Heterogeneity within the indirect treatment comparison network	
17. Key issue 4: Time to treatment discontinuation (TTD) estimated for abemaciclib plus fulvestrant (ABE-FUL)	
18. Key issue 5: Time to treatment discontinuation (TTD) estimated for exemestane with everolimus (EXE-EVE)	We are aware through anecdotal evidence that given the adverse effects associated with everolimus such as mouth ulcers that the clinical use of this treatment combination can be limited in practice or patients may stop with everolimus soon after commencing treatment or experience a dose reduction. If people are unable to tolerate everolimus they may have exemestane monotherapy.

19. Key issue 6: Prices used in the model	
20. Key issue 7 (un-numbered in ERG report but summarised in Table 7 of ERG report): Subsequent treatments in MONARCH 2	
Key issue 8 (un-numbered in ERG report but summarised in Table 8 of ERG report): Updated quality of life data from MONARCH 2	
21. Are there any important issues that have been missed in ERG report?	As set out in the technical engagement call in response to a question, it is crucial that a number of CDK 4/6 inhibitors are available given the different side effect profile. Having this choice is crucial for clinicians and patients and we now hope this treatment will be able to be approved for routine use on the NHS.
PART 3 -Key messages	
22. In up to 5 sentences, please summarise the key messages of your statement:	

- As set out in original patient organisation submission
-
-
-
-

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.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

Abemaciclib with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer after endocrine therapy (CDF review of TA579)

Cancer Drugs Fund Review

ERG critique of the company's response to the technical engagement process

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 13/12/15T.

1 Introduction

This document provides a review and critique of the company's response to technical engagement (TE). The company's response addressed nine issues, which the ERG discusses in turn below.

1.1 Issue 1: Subgroup data by abemaciclib starting dose

The company maintains that it is not appropriate to evaluate the efficacy of ABE-FUL compared with PBO-FUL in the post-amendment subgroup in MONARCH 2. Despite this the company has kindly provided PFS and OS data for the post-amendment subgroup. Cost-effectiveness results based on these data have not been presented by the company, but the ERG has provided these in Section 2 of this report.

As highlighted in the ERG report (Section 3.1.1), the post-amendment subgroup was given the abemaciclib dose which reflects the marketing authorisation and the dose of abemaciclib that will be used in clinical practice. In addition, the pre- and post-amendment subgroup analyses were pre-specified, and the post-amendment subgroup had an adequate sample size to be powered to detect a significant difference in PFS between ABE-FUL and PBO-FUL. The study initially planned to enrol 450 patients; however, after the protocol amendment changing the starting dose of abemaciclib from 200 mg to 150 mg, the sample size was increased to 630 patients to ensure that at least 450 patients were enrolled at the 150 mg dose. As such, the ERG considers the post-amendment subgroup to be methodologically robust and provide the most appropriate results to inform this appraisal.

The company highlights that [redacted] The figures below show the KM-curves for ABE-FUL and PBO-FUL for the ITT population and post-amendment subgroup in the same graph for PFS (Figure 1) and OS (Figure 2), respectively. [redacted] The figures also show that, during the observed period, [redacted]

Figure 1. PFS KM curves for ABE-FUL and PBO-FUL in the post amendment population and the ITT population (latest data cut)

[figure redacted]

Figure 2. OS KM curves for ABE-FUL and PBO-FUL in the post amendment population and the ITT population (latest data cut)

[figure redacted]

The ERG notes that information is only available for a limited number of baseline characteristics for the post-amendment subgroup in the CSR and the table provided by the company at technical engagement (company response Table 1). These include nature of disease (visceral, bone or other)

and primary/secondary ET resistance, which were stratification factors at randomisation in MONARCH 2. [redacted]

OS subgroup data for MONARCH 2 show a small numerical difference in efficacy of ABE-FUL versus FUL based on primary and secondary ET resistance but with wide and overlapping 95% confidence intervals (CI); primary resistance HR 0.686 (95% CI: 0.451 to 1.043) and secondary resistance HR 0.787 (95% CI: 0.606 to 1.021). The imbalance in the proportion of patients with primary ET resistance is therefore unlikely to explain [redacted] pre- and post-amendment subgroup (pre-amendment OS HR [redacted] 95% CI: [redacted] to [redacted]; post-amendment OS HR [redacted] 95% CI: [redacted] to [redacted]). The ERG notes that there may be imbalances in other baseline characteristics, but because of the limited reporting, this remains unknown.

MONARCH 2 is a placebo controlled RCT of good quality and the post-amendment subgroup is a pre-specified subgroup of adequate sample size to detect a significant difference between ABE-FUL and PBO-FUL. The ERG does therefore not consider that reasons have been presented to question the reliability or validity of the post-amendment subgroup. As the post-amendment subgroup was given the abemaciclib dose reflective of the marketing authorisation, the ERG considers it important for the committee to consider the clinical and cost effectiveness results of both the ITT population and the post-amendment subgroup. Though the ERG considers the post-amendment subgroup the most relevant for this appraisal and the ERG's exploratory analysis in response to technical engagement is therefore based on this subgroup.

Fractional polynomial NMA using post-amendment subgroup data

The company also provided results of the FP NMAs based on the post-amendment subgroup. These show a [redacted] of ABE-FUL therapy compared with EXE-EVE throughout the time horizon (Figure 3), and a PFS [redacted] with ABE-FUL from [redacted] months (Figure 5). The PFS and OS benefit with ABE-FUL are [redacted] in the post-amendment population than for the ITT population for both outcomes (Figure 4 and Figure 6, Table 1 and Table 2) and taking into account the heterogeneity and uncertainty across the network (see Issue 3), the [redacted] is highly uncertain.

The company followed the same methodology as described in the CDF submission for the ITT population; however, it is unclear if the company explored the same selection of powers for the FP NMA using the post-amendment subgroup as for the ITT population, or a limited selection. The company concluded that the models with the most reasonable fit for the post-amendment subgroup were the same as those chosen for the ITT analysis; that is, a first-order FE model with p1 = 0 for PFS and with p1 = −1.0 for OS.

Figure 3. OS time-to-event curves, FP NMA, MONARCH 2 post-amendment population (reproduced from the company's technical engagement response Figure 3)

[figure redacted]

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; NMA: network meta-analysis; OS: overall survival.

Figure 4. OS time-to-event curves, FP NMA, MONARCH 2 ITT population (reproduced from CS Figure 10)

[figure redacted]

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FUL: fulvestrant; NMA: network meta-analysis; OS: overall survival.

Figure 5. PFS time-to-event curves, FP NMA, MONARCH 2 post-amendment population (reproduced from the company's technical engagement response Figure 4)

[figure redacted]

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FP: fractional polynomial; FUL: fulvestrant; NMA: network meta-analysis; PFS: progression-free survival.

Figure 6. PFS Time-To-Event Curves, FP NMA, MONARCH 2 ITT population (reproduced from CS Figure 12)

[figure redacted]

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FP: fractional polynomial; FUL: fulvestrant; NMA: network meta-analysis; PFS: progression-free survival.

Table 1. Estimated OS summary statistics from the FP NMA

	Post-amendment population				ITT population			
	FUL	EXE	EXE-EVE	ABE-FUL	FUL	EXE	EXE-EVE	ABE-FUL
Mean OS, months	[redacted]							
Median OS, months	[redacted]							
Alive at 12 months, %	[redacted]							
Alive at 60 months, %	[redacted]							
Alive at 120 months, %	[redacted]							

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FP: fractional polynomial; FUL: fulvestrant; ITT, intention to treat; NMA: network meta-analysis; OS: overall survival.

Table 2. Estimated PFS summary statistics from the FP NMA

	post-amendment population				ITT population			
	FUL	EXE	EXE-EVE	ABE-FUL	FUL	EXE	EXE-EVE	ABE-FUL
Mean PFS, months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median PFS, months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free at 12 months, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free at 60 months, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free at 120 months, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FP: fractional polynomial; FUL: fulvestrant; ITT, intention to treat; NMA: network meta-analysis; PFS, progression-free survival.

1.2 Issue 2: Outcome validation using the SACT data

The ERG agrees with the company that, although the SACT dataset provides important real-world evidence of the efficacy of ABE-FUL in UK clinical practice, outcome validation using SACT data is limited because of the short follow up and data immaturity (discussed in the ERG report, Section 3.1.2).

1.3 Issue 3: Heterogeneity within the indirect treatment comparison network

As discussed in the ERG report, Section 3.1.3, there is clinical heterogeneity across the indirect treatment comparison network and therefore uncertainty around the clinical efficacy of ABE-FUL compared with EXE-EVE. However, the remaining uncertainty is unlikely to be resolved without more data available for the comparator trials. The ERG therefore considers the results of the company's FP NMAs to provide the best available estimates of ABE-FUL versus EXE-EVE for the post-amendment population but notes that it is not possible to predict the overall direction of or quantify the impact of any potential bias across the network, which should be kept in mind when interpreting the results of the FP NMAs.

1.4 Issue 4: Time to treatment discontinuation with ABE-FUL

The company disagreed with the ERG's original modelling assumption that patients in the post amendment population received treatment with ABE-FUL until disease progression. The company

used the MONARCH 2 trial data (earliest data cut February 2017) to justify that in the post amendment population a "*small but notable*" proportion of patients discontinued treatment for reasons other than disease progression.

The ERG notes that in the clinical study report (CSR) for the early, less mature, data from MONARCH 2 there were [redacted] of patients discontinuing treatment with ABE-FUL in the post amendment population. Out of these discontinuation events, [redacted] were due to disease progression and [redacted] due to death. The remaining [redacted] of discontinuations were due to adverse events ([redacted]); withdrawal from the study ([redacted]); non-compliance to study drug or clinician's decision ([redacted]). Therefore, the ERG reiterates that the majority of events leading to treatment discontinuation in MONARCH 2 were events captured in the PFS curve (i.e. disease progression or deaths), amounting to [redacted] of the total number of events leading to treatment discontinuation, and with AEs amounting to only [redacted].

This analysis is caveated by the fact that it is based on a less mature data cut, and that the only data available in the CSR were discontinuation events prior to dose reductions, instead of total number of discontinuation events in the trial.

As a response to TE, the company provided the PFS KM figure for the post amendment population in MONARCH 2. The ERG digitised the curve and used the PFS KM data to compare these to the TTD post amendment data in the latest data cut, to ascertain how discontinuation and progression events related in the 150mg group. As discussed in Section 1.1 (Issue 1), the PFS KM curves for the post amendment population [redacted] from the ITT PFS curves, with the post amendment PFS curve for ABE-FUL being [redacted] than that for the ITT population (Figure 7).

Figure 7. TTD KM curve for ABE-FUL in the post amendment population, and PFS KM curves for ABE-FUL in the ITT and in the post amendment populations (latest data cut)

[figure redacted]

In Section 4.1.4.1 of the ERG report, it was discussed how the company's base case HR of [redacted] used to estimate a TTD curve for ABE-FUL (by applying the HR to the updated FP PFS NMA curve) was likely to underestimate the costs of abemaciclib. The ERG was concerned that there were no data to support that patients on 150mg ABE-FUL discontinued treatment before progression to the same extent as seen in the company's modelled curves (Figure 11 in the ERG report).

The company still proposes that the HR of [redacted] is used in their post TE model. The ERG reiterates its original concerns that the use of a HR of [redacted] leads to a separation between modelled PFS and TTD curves that is not substantiated by the separation seen in the PFS and TTD KM curves for the post amendment population (Figure 8). The modelled PFS and TTD curves for ABE-FUL show a wide separation throughout the model time horizon, and do not track close together until approximately 16 years later. The ERG notes that for example, at month 18, the TTD KM and the PFS KM curves come close together for ABE-FUL patients, while the modelled curves show a difference of approximately 12% between the curves. Therefore, the company's methodology results in lower costs for abemaciclib without compromising on the treatment relative effectiveness.

As part of their response to TE, the company investigated different approaches to estimate the HR between TTD and PFS for ABE-FUL. The company provided results for three sets of data comparisons: ITT PFS data compared to post amendment TTD data; ITT PFS data compared to ITT TTD data; and post amendment PFS data compared to post amendment TTD data. For reasons discussed in the original ERG report, only the latter comparison (i.e. TTD and PFS data for the post

amendment group) is considered valid by the ERG. Furthermore, the company employed two different methodologies to estimate the HRs: the one used in the original CDF review submission (described in Section 4.1.4.1 of the ERG report); and a new one using a restricted means methodology, where areas under fitted PFS and TTD curves were compared. The first methodology produced a HR of [redacted] (Figure 9); while the second produced a HR of [redacted] (Figure 10). Visual inspection of the curves shows, as expected, that using a HR of [redacted] yields similar curves to those obtained using a HR of [redacted]. Therefore, the ERG concerns remain when this HR is used. However, when the [redacted] HR is used, the relative positioning of the TTD and PFS modelled curves seems to be more aligned to the relative positioning of the TTD and PFS KM curves.

In light of the new data provided by the company (shown in Figure 7), the ERG agrees that there is not enough evidence to substantiate that ABE-FUL is given until progression for all patients. Out of all the new HRs proposed by the company to capture the relationship between PFS and TTD for ABE-FUL, the ERG considers that the HR of [redacted] is likely to be the most robust. Therefore, the ERG replaced its original assumption of treatment until progression with ABE-FUL by the use of the [redacted] HR in the model. The ERG applied this HR to the post amendment FP NMA PFS curve for ABE-FUL to obtain a TTD curve. Results of this approach are provided in Section 2.

Figure 8. PFS KM post amendment and PFS modelled NMA post amendment curves; and TTD KM and TTD modelled curves for the post amendment group in MONARCH 2 (HR of [redacted])

[figure redacted]

Figure 9. PFS KM post amendment and PFS modelled NMA post amendment curves; and TTD KM and TTD modelled curves for the post amendment group in MONARCH 2 (HR of [redacted])

[figure redacted]

Figure 10. PFS KM post amendment and PFS modelled NMA post amendment curves; and TTD KM and TTD modelled curves for the post amendment group in MONARCH 2 (HR of [redacted])

[figure redacted]

1.5 Issue 5: Time to treatment discontinuation with EXE-EVE

Clinical expert opinion provided to the ERG during the CDF review informed that in clinical practice, a high proportion of patients discontinue everolimus due to its toxicity but continue treatment with exemestane. Given that EXE is considerably less expensive than everolimus, using the median TTD for EXE (6.8 months) instead of the median TTD for everolimus (5.5 months) to estimate the EXE-EVE costs in the model would overestimate the comparators' treatment costs considering the model's inability to cost treatment durations separately in the EXE-EVE arm. Therefore, as a modelling simplification, the ERG proposed that 5.5 months was used for calculating treatment costs with EXE-EVE.

The ERG derived a HR to be applied to the FP NMA PFS EXE-EVE curve in order to estimate the EXE-EVE TTD curve in the model. The ERG divided the cumulative hazard for median TTD [i.e. log(0.5)] by the cumulative hazard for the KM PFS curve from BOLERO 2 at the time of median TTD in the same trial (5.5 months). The ERG observed the percentage of patients in the BOLERO 2 PFS curve by visually inspecting the curve and concluded that there were 65% of patients in the PFS curve at 5.5. months. Thus, the ERG estimated a HR of 1.61 [log(0.5)/log(0.65)].

As part of their response to TE, the company digitised the EXE-EVE KM curve from BOLERO 2 to allow a more precise matching of the percentage of patients in the PFS curve in BOLERO 2 at the point of median TTD (5.5 months) in the same trial.

As a result of the company's updated method, it was concluded that the percentage of patients in the PFS curve at 5.5. months is 64.54%. Therefore, the ERG-derived HR estimated by diving the cumulative hazard for median TTD [i.e. log(0.5)] by the cumulative hazard for the KM PFS curve from BOLERO 2 at the time of median TTD in the same trial (5.5 months), was updated from 1.61 [(log(0.5)/log(0.65)] to 1.58 [[(log(0.5)/log(0.6454)]. The ERG agrees with the use of the company's updated HR and presents their preferred ICER with this correction implemented in Section 2.

Nonetheless, the company disagreed with the use of this methodology to estimate TTD for EXE-EVE. Therefore, the company proposed three alternative approaches to estimate TTD for EXE-EVE:

1. The company assumed that all patients receiving EXE-EVE are treated until disease progression. The company reported that this scenario is likely to overestimate the costs of treatment with EXE-EVE, when considering the toxicity burden associated with everolimus;
2. Based on clinical expert feedback sourced by the ERG in the CDF review of TA593 (ribociclib with fulvestrant), the company assumed that approximately 20% of patients will discontinue

everolimus 6 months after the initiation of treatment but will continue to receive exemestane until disease progression;

3. Also based on clinical expert feedback sourced by the ERG in the CDF review of TA593, the company assumed that 20% of patients will discontinue everolimus 6 months after the initiation of treatment, and that 70% of the of the patients remaining on everolimus will have their dose reduced from 10 mg daily to 5 mg daily at month six. Patients on exemestane were assumed to stay on treatment until progression.

The company reported that the third scenario analysis was considered the most clinically plausible assumption for the estimation of EXE-EVE TTD. Nonetheless, the company's base case analysis used the updated HR of 1.58 to estimate the TTD curve for EXE-EVE.

The ERG disagrees with the first scenario analysis proposed by the company where EXE-EVE is assumed to be given until disease progression, considering the consistently reported clinical expert opinion (substantiated by the BOLERO 2 data) that most patients do not tolerate a full dose of everolimus until disease progression.

For inclusiveness, the ERG acknowledges the value of assessing the impact of the company's third scenario (which combined scenario 2 with the assumption of dose reductions) on the final ICERs. The ERG found an error in the company's implementation of this scenario as treatment costs with EXE-EVE were being considered after disease progression. This is incorrect as treatment with EXE-EVE stops upon disease progression. The ERG corrected this in the model and presents the results in Section 2.

The cost of EXE-EVE is one of the key drivers of the economic results. Given the lack of available TTD KM data for this comparator, the ERG notes that uncertainty remains around this parameter. The ERG produced Figure 11 which shows the FP NMA PFS curve for EXE-EVE in the model, together with the two options described above to model TTD. The red curve represents the (corrected) approach taken by the ERG in its original report (i.e. using the 1.58 PFS to TTD HR), while the orange dotted curve represents scenario 2 proposed by the company after TE (i.e. assuming that 20% of patients will discontinue EVE at six months after the initiation of treatment, and that 70% of the of the patients remaining on EVE will have their dose reduced from 10 mg daily to 5 mg daily at month six).

Scenario 2 leads to higher treatment costs with EXE-EVE, and therefore, to lower ICERs. Costs with exemestane have been estimated until disease progression in both scenario 2 and in the scenario where the 1.58 HR is used to estimate TTD. The ERG recommends that the committee

discusses the plausibility of the curves provided in Figure 11 to determine which curve is likely to be a more plausible representation of TTD with everolimus in clinical practice in the UK.

Figure 11. PFS curve for EXE-EVE and alternative modelled curves for TTD on everolimus

[figure redacted]

1.6 Issue 6: Prices used in the model

As a result of TE, the company updated the resource and cost codes used with the National Schedule of NHS cost 2018-2019, and inflated the costs based on the consumer price index (CPI) or health price index (HPI) to 2019 where needed. The company reports that the BNF and eMIT were also checked for updated drug prices.

The ERG found some discrepancies in the NHS codes used to cost adverse events, as the company choose non-elective short-stay codes instead of day cases codes without justification. Nonetheless, using the day case (lower) costs had a minimal impact on the ICER.

The company has incorporated the updated costs in their base case, therefore there were no additional analysis required from the ERG.

1.7 Issue 7: Subsequent treatments in MONARCH 2

The company provided new data to substantiate their proposition that ABE-FUL delays time to subsequent cytotoxic chemotherapy when compared to fulvestrant.

As mentioned in the ERG original report, the ERG agrees that there is evidence available to suggest that ABE-FUL delays progression, thus delaying time to subsequent treatments. Issue 7 discussed by

the ERG in their original report referred to the proportion of progressed patients in MONARCH 2 who received subsequent treatments and how the latter was similar across trial arms, with [redacted] of patients receiving a second line treatment in the ABE-FUL arm; and [redacted] of patients receiving subsequent treatment in the FUL arm. The proportion of patients receiving second line chemotherapy was [redacted] for ABE-FUL and FUL, respectively.

1.8 Issue 8: Updated quality of life data from MONARCH 2

The ERG was unclear whether the latest data from MONARCH 2 (20th June 2019 data cut) included more mature EQ-5D data. In their response to TE, the company clarified that additional quality of life data were not collected during the prolonged follow-up period of the trial.

The ERG maintains its preference for the use of trial data to estimate the pre- and post-progression utility in the model for the post amendment population. The company has incorporated the ERG's preferred values in their base case, therefore there were no additional analysis required from the ERG.

1.9 Issue 9: Fulvestrant discount due to loss of exclusivity

The company's base case ICER post TE includes a 50% discount on the list price of fulvestrant given the drugs' imminent loss of exclusivity.

The ERG has been informed of the new confidential patient access scheme (PAS) agreed by NHS England for fulvestrant. Therefore, the ERG results presented in this report include the fulvestrant list price, while a confidential appendix provides the results of the ERG's analysis with the fulvestrant confidential PAS.

2 Results from ERG's original analysis and new exploratory analysis

In this section the ERG provides the results of the new exploratory analysis conducted after TE. The ERG's preferred assumptions, which remain unchanged after TE and have not been adopted by the company in their post TE base case results, are the following:

1. Removal of the half-cycle correction from the model (Section 4.1.3 of the ERG report).

In light of the company's reply to TE, the ERG made the following changes to the model:

2. Removal of fulvestrant discount from the analysis (Section 1.9);
3. Using the updated NMA with the post amendment data (Section 1.1 and Section 1.3);

4. Using the HR of [redacted] to estimate TTD for ABE-FUL in the model (Section 1.4).

In addition to assumptions 1 to 4, the ERG combined the latter with two alternative scenarios to model TTD for EXE-EVE:

a) Applying the 1.58 HR to the EXE-EVE PFS curve to obtain a TTD curve for EXE-EVE in order to cost treatment with everolimus, and assuming that exemestane was given until disease progression (Section 1.5);
b) Assuming that 20% of progression-free patients receiving EVE-EXE will discontinue everolimus at six months after the initiation of treatment, and that 70% of the of the patients remaining on everolimus will have their dose reduced from 10 mg to 5 mg daily at month six (and applying the model correction described in Section 1.5). Patients were also assumed to receive exemestane until disease progression in this scenario.

Results of the ERG's exploratory analyses are reported in Table 3 for the comparison of ABE-FUL with EXE-EVE. As discussed in Section 1.5 and Section 1.6, the key drivers of the economic results remain the assumptions made to cost treatment with ABE-FUL and with EXE-EVE.

Table 3. Results of ERG's exploratory analysis

Scenario		Incremental costs	Incremental QALYs	ICER
0	Company base case	[redacted]	[redacted]	£6,593
1	Removing fulvestrant discount	[redacted]	[redacted]	£16,327
2	Removal of the half-cycle correction from the model	[redacted]	[redacted]	£15,850
3	Using the company's NMA PFS and OS curves for the post amendment population	[redacted]	[redacted]	£10,146
4	Applying the [redacted] HR to the ABE-FUL NMA PFS curve to obtain a TTD curve	[redacted]	[redacted]	£33,906
a	Applying the 1.58 HR to the EXE-EVE PFS curve to obtain a TTD curve for EXE-EVE and costing EXE until disease progression	[redacted]	[redacted]	£15,626
b	Assuming that 20% of patients receiving EVE-EXE will discontinue EVE at six months after the initiation of treatment, and that 70% of the of the patients remaining on EVE will have a dose reduction	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; HR, hazard ratio; PFS, progression free survival; PPS, post-progression survival; QALY, quality adjusted life year

The results of the combined exploratory analysis undertaken by the ERG are presented in **Error! Not a valid bookmark self-reference.**. Depending on the assumption used to cost treatment with everolimus, the ERG combined ICER ranges from £49,556 to dominant (in favour of ABE-FUL). The ERG notes that these results include the PAS for abemaciclib but do not include the PASs available

for everolimus and fulvestrant. Results of the ERG's combined analysis with all PASs included are reported in a confidential appendix.

Table 4. ERG's combined analysis

Scenario		Incremental costs	Incremental QALYs	ICER
0	Company base case	[redacted]	[redacted]	£6,593
1	Removing fulvestrant discount	[redacted]	[redacted]	£16,327
1+2	Removal of the half-cycle correction from the model	[redacted]	[redacted]	£15,850
1+2+3	Using the company's NMA PFS and OS curves for the post amendment population	[redacted]	[redacted]	£9,086
1+2+3+4	Applying the [redacted] HR to the ABE-FUL NMA PFS curve to obtain a TTD curve	[redacted]	[redacted]	£49,879
1+2+3+4+a	Applying the 1.58 HR to the EXE-EVE PFS curve to obtain a TTD curve for EXE-EVE and costing EXE until disease progression	[redacted]	[redacted]	£49,556
1+2+3+4+b	Assuming that 20% of patients receiving EVE-EXE will discontinue EVE at six months after the initiation of treatment, and that 70% of the of the patients remaining on EVE will have a dose reduction	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; HR, hazard ratio; PFS, progression free survival; PPS, post-progression survival; QALY, quality adjusted life year

Abemaciclib with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer after endocrine therapy (CDF review of TA579)

Cancer Drugs Fund Review

Addendum to the ERG critique of the company's response to the technical engagement process

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 13/12/15T.

This document provides an addendum to the ERG's review of the company's response to technical engagement (TE).

Error! Reference source not found. reports the differences in the key model parameters between the ERG's preferred analysis (for scenario a and scenario b as described in Section 2 of the ERG's review of the company's reply to TE) and the company's base case.

Table 1. Key model parameters used in the company's base case and in ERG's preferred analysis

Assumption		Company's base case	ERG's preferred approach
1	Fulvestrant price	50% discount	List price (and PAS in confidential appendix)
2	NMA FP curves used for PFS and OS outcomes in the ABE-FUL and in the EXE-EVE arms	ITT data from MONARCH 2	Post amendment data from MONARCH 2
3	HR applied to the ABE-FUL NMA PFS curve to obtain a TTD curve for ABE-FUL	[redacted]	[redacted]
4	HR applied to the EXE-EVE NMA PFS curve to obtain a TTD curve for EXE-EVE	1.58	ERG scenario a: 1.58 ERG scenario b: Assuming that 20% of patients receiving EVE-EXE will discontinue EVE at six months after the initiation of treatment, and that 70% of the of the patients remaining on EVE will have a dose reduction

Error! Reference source not found. reports the ERG's preferred analysis (scenarios a and b as described in Section 2 of the ERG's review of the company's reply to TE) using the ITT data from MONARCH 2 for PFS and OS FP NMA curves.

Table 2. ERG's combined analysis using the ITT PFS and OS data from MONARCH 2

Scenario		Incremental costs	Incremental QALYs	ICER
0	Company base case	[redacted]	[redacted]	£6,593
1	Removing fulvestrant discount	[redacted]	[redacted]	£16,327
1+2	Removal of the half-cycle correction from the model	[redacted]	[redacted]	£15,850
1+2+4	Applying the [redacted] HR to the ABE-FUL NMA PFS curve to obtain a TTD curve	[redacted]	[redacted]	£33,431
1+2+4+a	Applying the 1.58 HR to the EXE-EVE PFS curve to obtain a TTD curve for EXE-EVE and costing EXE until disease progression	[redacted]	[redacted]	£33,310
1+2+4+b	Assuming that 20% of patients receiving EVE-EXE will discontinue EVE at six months after the initiation of treatment, and that 70% of the of the patients remaining on EVE will have a dose reduction	[redacted]	[redacted]	£9,237

Abbreviations: ICER, incremental cost-effectiveness ratio; HR, hazard ratio; PFS, progression free survival; PPS, post-progression survival; QALY, quality adjusted life year