ERG REPORT v2

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Palbociclib in combination with fulvestrant for treating advanced oestrogen-receptor positive, HER2-negative breast cancer [ID916]

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UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Palbociclib in combination with fulvestrant for treating advanced oestrogen-receptor positive, HER2-negative breast cancer [ID916]

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LIST OF ABBREVIATIONS

AE	adverse event
BSC	best supportive care
CBR	clinical benefit response
CDK 4/6	cyclin-dependent kinases 4 and 6
CI	confidence interval
CrI	credible interval
CS	company submission
CSR	clinical study report
DIC	Deviance Information Criterion
DR	duration of response
EORTC	European Organisation for Research and Treatment
EPAR	European Public Assessment Report
EQ-5D	EuroQol-5 dimensions
ER-positive	oestrogen-receptor positive
ERG	Evidence Review Group
FP	fractional polynomial
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
HR-positive	hormone-receptor positive
HRQoL	health-related quality of life
ICER	incremental cost effectiveness ratio
IPD	individual patient data
ITT	intention to treat
K-M	Kaplan-Meier
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
OR	objective response
OS	overall survival
PFS	progression-free survival
PgR	progesterone-receptor
PH	proportional hazards
PSA	probabilistic sensitivity analysis
QALY	Quality adjusted life year
QoL	Quality of Life
QLQ-BR23	Quality of Life Questionnaire-Breast cancer module
QLQ-C30	Quality of Life Questionnaire-Core 30
RCT	randomised controlled trial
RPSFT	rank-preserving structural-failure time
SAE	serious adverse event
STA	Single Technology Appraisal
TSAP	trial statistical analysis plan
TTD	time to treatment discontinuation

1 EXECUTIVE SUMMARY

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the Single Technology Appraisal (STA) process. Clinical and economic evidence have been submitted to NICE by the company (Pfizer) in support of the use of palbociclib (IBRANCE®) in combination with fulvestrant in women with hormone-receptor positive (HR-positive), human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer that has progressed during or soon after completing endocrine therapy received in the (neo)adjuvant or advanced/metastatic setting.

1.1 Critique of the decision problem in the company's submission

As highlighted in Section 2.3 of this ERG report, the decision problem addressed by the company is in accordance with the final scope issued by NICE, with a few minor differences as summarised in Table 1.

Table 1 Differences in final scope issued by NICE and decision problem addressed by the company

Parameter	Final scope issued by NICE	Decision problem
Population	People with HR-positive/HER2-negative locally advanced or metastatic breast cancer who have received prior endocrine therapy	The company considers that treatment of HR-positive HER2-negative advanced breast cancer is not viewed in clinical practice by specific lines of therapy, but rather by whether patients are 'endocrine resistant' or 'endocrine sensitive' (although there is no consensus on the definitions of these terms). Palbociclib plus fulvestrant is considered by the company to be a treatment option for patients with 'endocrine resistant' disease
Comparator(s)	Exemestane, everolimus plus exemestane, tamoxifen, fulvestrant, chemotherapy	The company only provided cost effectiveness evidence for the comparison of palbociclib plus fulvestrant versus everolimus plus exemestane. The company considers that everolimus plus exemestane is the treatment most commonly used in clinical practice and, therefore, is the most appropriate comparator. This view is supported by the conclusions reached by NICE Appraisal Committees during recent and ongoing Single Technology Appraisals (TA579 and ID318), and has been confirmed by clinical advice to the ERG
Outcomes	OS, PFS, response rate, AEs, HRQoL	Data, for all five outcomes were available, from the PALOMA-3 trial, for the comparison of the effectiveness of palbociclib plus fulvestrant versus placebo plus fulvestrant The company conducted NMAs to generate PFS and OS results for the comparison of the effectiveness of palbociclib plus fulvestrant with everolimus plus exemestane

AE=adverse effect of treatment; HER2=human epidermal growth factor receptor 2; HR=hormone-receptor; HRQoL=health-related quality of life; NMA=network meta-analysis; OS=overall survival; PFS=progression-free survival

1.2 Summary of the key issues in the clinical effectiveness evidence

Overall, the ERG considers the methods used to conduct the company's systematic review of clinical effectiveness evidence to be of a good standard (Section 3.1 of this ERG report).

The only randomised controlled trial (RCT) that includes an arm in which patients are treated with palbociclib plus fulvestrant that was identified by the company's systematic review is the PALOMA-3 trial (Section 3.2.1 of this ERG report). The PALOMA-3 trial is an international, multicentre, 2:1 randomised, double-blind, placebo-controlled, parallel-group, Phase 3 clinical trial of palbociclib plus fulvestrant (N=347) versus placebo plus fulvestrant (N=174).

The PALOMA-3 trial is a well-designed, good quality trial with an appropriate and pre-defined statistical approach to the analysis of efficacy, patient reported outcomes and safety (Section 3.2.2 of this ERG report). An examination of the eligibility criteria for trial entry suggests that the trial population is typical of patients who would be considered for treatment for 'endocrine resistant' advanced breast cancer in clinical practice in England and Wales (Section 3.2.1 of this ERG report).

As highlighted in Section 3.3 of this ERG report, as everolimus plus exemestane was not a comparator in the PALOMA-3 trial, the company carried out network meta-analyses (NMAs) to indirectly estimate PFS and OS for the comparison of the effectiveness of palbociclib plus fulvestrant versus everolimus plus exemestane. The NMAs incorporated data from five trials: the PALOMA-3 trial, the BOLERO-2 trial, the CONFIRM trial, the EFECT trial and the SoFEA trial. The ERG considers that the largest potential sources of heterogeneity between the populations of the included trials are HER2 status, prior treatments and 'sensitivity' or 'resistance' to endocrine therapy. In addition, the ERG notes, that the PALOMA-3 trial was the only trial to include women of premenopausal or perimenopausal status.

The PH assumption was violated for PFS data in two trials and for OS data in two trials. The company, therefore, carried out PFS and OS NMAs using a Bayesian fractional polynomials (FPs) modelling approach (Sections 3.4.1 and 3.4.2 of this ERG report). The ERG considers that there is substantial uncertainty around the reliability of the PFS and OS results generated by this approach (namely the estimated survival and HR functions). The ERG is therefore unable to select a suitable FP model with any degree of confidence to inform the comparison of palbociclib plus fulvestrant versus everolimus plus exemestane.

The most frequent treatment-related Grade ≥3 AEs reported by patients treated with palbociclib plus fulvestrant in the PALOMA-3 trial were haematological AEs, in particular, neutropenia ([redacted]) (Section 3.6 of this ERG report). No formal comparison of AEs between

palbociclib plus fulvestrant and everolimus plus exemestane was performed by the company. The ERG notes that in the palbociclib plus fulvestrant arm of the PALOMA-3 trial, frequencies of treatment-related Grade ≥3 AEs and treatment discontinuation were [redacted] and [redacted], respectively. The ERG further notes that in the everolimus plus exemestane arm of BOLERO-2 trial, frequencies of treatment-related Grade ≥3 AEs and treatment discontinuation were 40.9% and 29.0%, respectively.

1.3 Summary of the key issues in the cost effectiveness evidence

There is no direct evidence comparing the effectiveness of treatment with palbociclib plus fulvestrant versus everolimus plus exemestane. The ERG considers that the company's estimates of relative effectiveness generated by the PFS FP and OS FP NMAs cannot be used to inform the comparison of palbociclib plus fulvestrant versus everolimus plus exemestane. (Section 6.2.1).

Clinical advice to the ERG is that treatment with everolimus plus exemestane is at least as effective as fulvestrant. On this basis, the ERG has generated alternative cost effectiveness results using data from the placebo plus fulvestrant arm of the PALOMA-3 trial as a proxy for the effectiveness of treatment with everolimus plus exemestane (Section 6.2.2). The implication of this assumption is that the effectiveness of treatment with everolimus plus exemestane is (i) [redacted] than treatment with placebo plus fulvestrant in terms of PFS and (ii) as there is no statistically significant difference in OS between the two arms of the PALOMA-3 trial, is equivalent to treatment with palbociclib plus fulvestrant in terms of OS.

In the company model, time to treatment discontinuation (TTD) for patients treated with palbociclib plus fulvestrant is estimated using a ratio of TTD to PFS from the PALOMA-3 trial; for patients receiving everolimus plus exemestane, data from the PFS FP NMA are used to model TTD (Section 6.2.1).

When implementing revisions to the company model, the ERG used the TTD Kaplan-Meier data for palbociclib plus fulvestrant from the PALOMA-3 trial and assumed that TTD for patients receiving everolimus plus exemestane can be represented by TTD data from the placebo plus fulvestrant arm of the PALOMA-3 trial (Section 6.2.2).

In addition, based on clinical advice, the ERG considers:

- On average, patients receive more than two lines of subsequent therapy (Section 6.3.1)

- Company assumptions around drug wastage are not realistic; this means that the modelled costs of treatment with everolimus, exemestane and tamoxifen (the latter is a subsequent therapy) are too high (Section 6.3.2)

- Company assumptions about the frequency of appointments with a consultant oncologist are too low (Section 6.3.2).

1.4 Summary of ERG's preferred assumptions and resulting ICER

The ERG made six separate revisions to the company model (Section 6.4):

1. Estimating OS using (pooled) OS data from the PALOMA-3 trial to represent the experience of patients treated with palbociclib plus fulvestrant and patients treated with everolimus plus exemestane

2. Estimating PFS using data from the placebo plus fulvestrant arm of the PALOMA-3 trial as a proxy for the experience of patients treated with everolimus plus exemestane

3. Estimating TTD using data from the placebo plus fulvestrant arm of the PALOMA-3 trial as a proxy for the experience of patients treated with everolimus plus exemestane

4. Amending the company assumptions around time spent on subsequent treatments and the proportion of patients proceeding to subsequent lines of therapy

5. Removing daily oral drug wastage

6. Increasing the frequency of consultant oncologist appointments.

The cost effectiveness results, generated by the company model, after implementing all of the ERG amendments are displayed in Table 2. These results have been generated using the Patient Access Scheme discounted price for palbociclib and list prices for all other treatments. The results show that treatment with palbociclib plus fulvestrant is less expensive and more effective than everolimus plus exemestane.

Table 2 ICER resulting from ERG's preferred assumptions

	Total costs	Total QALYs	∆ costs	∆ QALYs	ICER £/QALY
Palbociclib plus fulvestrant	[redacted]	[redacted]			
Everolimus plus exemestane	[redacted]	[redacted]	[redacted]	[redacted]	Dominates

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

The cost effectiveness results, generated by the company model, after separately implementing each of the ERG amendments listed in Table 2, are displayed in Table 3.

Table 3 Exploratory analyses undertaken by ERG

ERG revision	Section in main ERG report	Technology		Comparator		ICER £/QALY
		Costs	QALYs	Costs	QALYs	
R1) Estimating OS (pooled) from the PALOMA-3 trial	Section 6.2.2	[redacted]	[redacted]	[redacted]	[redacted]	Dominates
R2) Estimating PFS from the PALOMA-3 trial	Section 6.2.2	[redacted]	[redacted]	[redacted]	[redacted]	£8,180
R3) Estimating TTD from the PALOMA-3 trial	Section 6.2.2	[redacted]	[redacted]	[redacted]	[redacted]	£8,731
R4) Amend subsequent therapy assumptions	Section 6.3.1	[redacted]	[redacted]	[redacted]	[redacted]	Dominates
R5) Remove daily oral drug wastage	Section 6.3.2	[redacted]	[redacted]	[redacted]	[redacted]	Dominates
R6) Include monthly oncologist consultation in every health state	Section 6.3.2	[redacted]	[redacted]	[redacted]	[redacted]	Dominates

ICER=incremental cost effectiveness ratio; OS=overall survival; PFS=progression-free survival; QALY=quality adjusted life year; TTD=time to treatment discontinuation

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

Advanced breast cancer (comprising locally advanced or metastatic breast cancer) is an incurable life-threatening disease. Therefore, treatment goals are to delay disease progression, maintain health-related quality of life, alleviate symptoms and improve overall survival (OS).

The majority of patients who are diagnosed with breast cancer have tumours that are HR-positive and/or HER2-negative. A patient's tumour is categorised as being HR-positive if the tumour is found to be oestrogen-receptor positive (ER-positive) and/or progesterone receptor positive (PgR-positive) tumours. Clinical advice to the ERG is that the vast majority of patients whose tumours are described as HR-positive are also ER-positive.

Endocrine therapies are common treatment options for patients with HR-positive/HER2-negative breast cancer in the (neo)adjuvant and advanced settings. The company submission (CS) only provides evidence for palbociclib in combination with fulvestrant for patients who the company describe as a population resistant to endocrine therapy.

Within this ERG report, the ERG has referred to the CS in many places. Unless stated otherwise, the ERG is referring to the company's document B, which is the company's full evidence submission.

It is important to note that there is no standardised definition for endocrine therapy resistance.[1] Hence, definitions used in recent trials such as the PALOMA-3 trial[2] and BOLERO-2 trial[3] have included an 'endocrine resistant' population. In these trials, **patients (deemed to be 'endocrine resistant') were required to have disease recurrence during or within 12 months of endocrine therapy in the adjuvant setting or progression during or within 1 month of ending treatment for advanced disease.**

2.2 Background

2.2.1 Treatment pathway for advanced HR-positive/HER2-negative advanced breast cancer

The treatment pathway for early disease has an impact on the treatment pathway for advanced disease since treatment choices in the advanced setting take into account treatment received in the early setting. The ERG has presented a brief overview of treatment options in the early setting, with a focus on endocrine therapies, in Appendix 1 (Section 9.1) to this ERG report.

2.2.2 Treatment pathway for HR-positive/HER2-negative advanced breast cancer

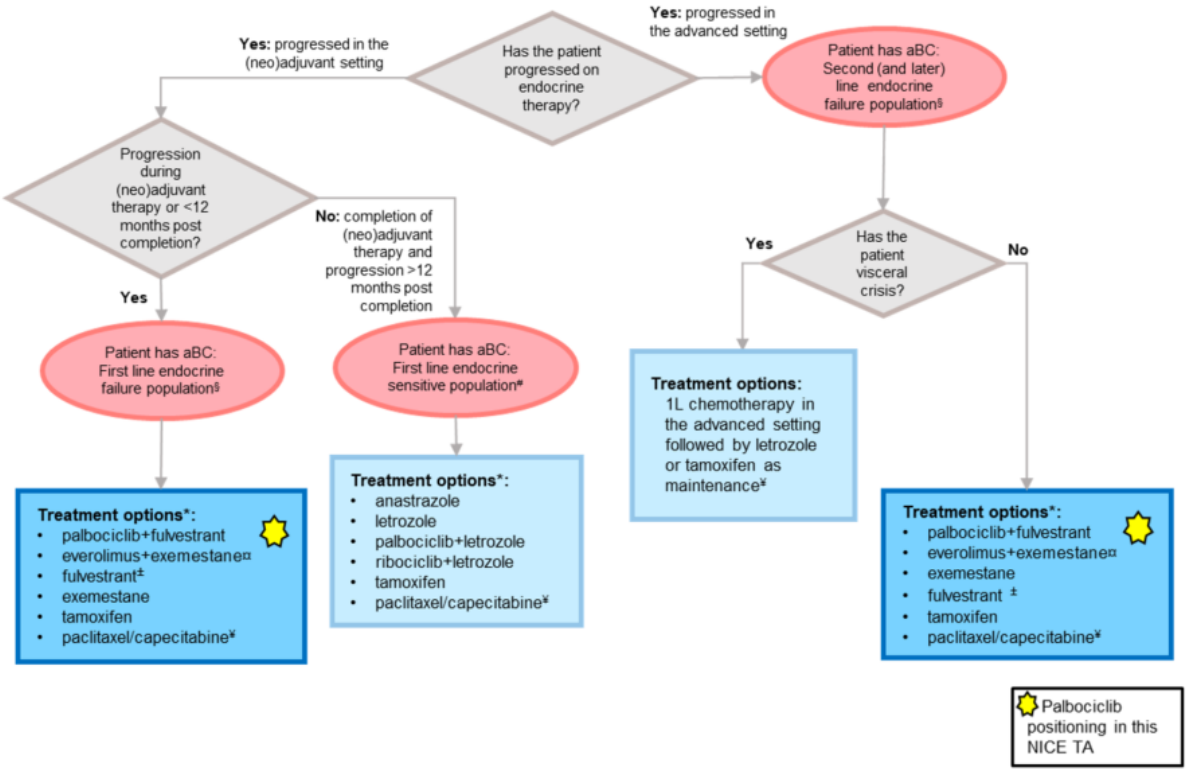
In NICE guidelines it is recommended that: “endocrine therapy is offered as first-line treatment for the majority of patients with ER-positive advanced breast cancer.”[4] For these patients, licensed endocrine therapies include anti-oestrogen therapies (tamoxifen or fulvestrant), non-steroidal aromatase inhibitors (anastrozole or letrozole) and steroidal aromatase inhibitors (exemestane). However, fulvestrant has not been recommended by NICE.[5] Tamoxifen is the endocrine therapy recommended by NICE for men.[4] Tamoxifen is also recommended for premenopausal and perimenopausal women with ER-positive advanced breast cancer not previously treated with tamoxifen. Ovarian suppression is recommended for premenopausal and perimenopausal women who have previously been treated with tamoxifen. An aromatase inhibitor (either non-steroidal or steroidal) is recommended for postmenopausal women with no prior history of endocrine therapy or who have been previously treated with tamoxifen.

However, as highlighted in the CS, (Section B.1.1, p11): “the current standard of care treatments are not specific to line of treatment” but depends on whether a patient is sensitive to endocrine therapy or resistant to endocrine therapy.

As with ‘endocrine resistance’, there is no standard definition of endocrine therapy sensitivity. Recent trials of cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors (palboclib, ribociclib or abemaciclib) in combination with an aromatase inhibitor (for example, the PALOMA-1 trial,[6] PALOMA-2 trial,[7] MONALEESA-2 trial[8,9] and MONARCH-3 trial)[10,11] have included only patients who could be described as ‘endocrine sensitive’. In these trials, ‘endocrine sensitive’ patients had a disease-free interval of 12 months or more following treatment with endocrine therapy in the (neo)adjuvant setting and/or patients had not received any prior endocrine therapy for advanced disease. In recent trials for ‘endocrine resistant’ patients (such as PALOMA-3 and BOLERO-2[3]), previous sensitivity to prior endocrine therapy was defined as at least 24 months of endocrine therapy before recurrence in the adjuvant setting or a response for at least 24 weeks of endocrine therapy for advanced disease.

The treatment pathways for both the ‘endocrine sensitive’ and the ‘endocrine resistant’ populations are illustrated by the company in the CS. The ERG considers Figure 1 of the CS presents an accurate picture of the treatment pathway (reproduced as Figure 1 of this ERG report). It should be noted that in this figure, the term ‘endocrine failure’ is used instead of ‘endocrine resistance’. The ERG further notes that abemaciclib in combination with fulvestrant is now also recommended as a treatment option by NICE for use within the Cancer Drugs Fund[12] but is not shown in this figure. Abemaciclib in combination with fulvestrant would be considered as a treatment option for the ‘endocrine resistant’ population. Like palbociclib and

ribociclib, abemaciclib is a CDK4/6 inhibitor. Ribociclib plus fulvestrant is not currently a NICE recommended treatment option for the 'endocrine resistant' population but the ERG notes that the appraisal for ribociclib in combination with fulvestrant is ongoing (ID1318).[13]



aBC=advanced breast cancer (comprising locally advanced or metastatic)
¤ Everolimus can only be prescribed to postmenopausal women or women who had ovarian oblation. Everolimus can only be used after 1 endocrine therapy
* Therapy with the same agent cannot be repeated if given previously and the disease-free interval was <12 months. In any case, treatment with CDK4/6 or everolimus or exemestane cannot ever be repeated.
± Fulvestrant is licensed for use after anti-oestrogen treatment (e.g. tamoxifen), not recommended by NICE[5] but is variably commissioned by CCGs
Refers to the first licensed indication for palbociclib, namely. 'in combination with an aromatase inhibitor'. The use of palbociclib for this indication has been recommended by NICE[14]
§ Refers to the second licensed indication for palbociclib, namely "in combination with fulvestrant in women who have received prior endocrine therapy"
¥ Chemotherapy used in visceral crisis or high tumour burden: capecitabine and paclitaxel commonly used
NB In this figure, endocrine failure = endocrine resistant

Figure 1 Current treatment pathway for HR-positive HER2-negative advanced breast cancer in England and Wales

Source: CS, Figure 1

The company states (CS, p20) that: "Everolimus [a mammalian target of rapamycin inhibitor] plus exemestane is the most commonly prescribed endocrine based treatment in the endocrine resistant population who do not have life-threatening disease (i.e. who should not receive chemotherapy)." However, the company notes that discussions with clinical experts suggest that the use of everolimus plus exemestane is potentially lower than expected due to its toxicity profile and therefore clinicians at present are sometimes choosing to use "less efficacious" therapy to mitigate these issues (CS, p21). For example, clinical advice to the ERG from Professor Andrew Wardley is that capecitabine (a type of chemotherapy) may often

be used instead of everolimus plus exemestane because the toxicity of capecitabine is more predictable (personal communication, 24 June 2019). In addition, the company (CS, Table 6) and ERG (Table 4) highlights that everolimus plus exemestane is only licensed for use following treatment with a non-steroidal aromatase inhibitor,[15] not following treatment with tamoxifen.

Table 4 Key elements of the drug licences for the 'endocrine resistant' population

Drug	Menopausal status of patients	Previous endocrine therapy
Palbociclib plus fulvestrant	Postmenopausal **or** premenopausal or perimenopausal (providing fulvestrant is combined with luteinizing hormone-releasing hormone)	Aromatase inhibitor **or** anti-oestrogen
Everolimus plus exemestane	Postmenopausal	Aromatase inhibitor
Fulvestrant monotherapy	Postmenopausal	Anti-oestrogen therapy
Exemestane monotherapy	Postmenopausal	Anti-oestrogen therapy
Tamoxifen	Any	Aromatase inhibitor **or** anti-oestrogen therapy
Chemotherapy[a]	Any	Aromatase inhibitor **or** anti-oestrogen therapy

[a] Clinical advice to the ERG is that capecitabine or paclitaxel are the most commonly used chemotherapies

Consistent with the conclusions reached in other appraisals,[12,13] clinical advice to the ERG is that fulvestrant monotherapy (an anti-oestrogen endocrine therapy) although not recommended by NICE,[5] is used by clinicians where it is available. In addition, as noted by the company (CS, Table 6) and ERG (Table 4), fulvestrant is only licensed following treatment with anti-oestrogen therapy,[16] not following treatment with an aromatase inhibitor. However, in clinical practice, and as in the PALOMA-3 trial,[17] fulvestrant is also used for patients whose cancer has relapsed on or after treatment with aromatase inhibitors.

In accordance with NICE guidelines,[4] exemestane monotherapy, tamoxifen and chemotherapy are additional treatment options for the 'endocrine resistant' population. Clinical opinion to the ERG is that these treatments are used less frequently than everolimus plus exemestane or, where available, fulvestrant. Clinical advice to the ERG is that (i) exemestane monotherapy is typically used for patients who have shown a relatively good response to a prior aromatase inhibitor or who are medically unfit to receive exemestane in combination with everolimus (ii) tamoxifen may be used after treatment with everolimus plus exemestane and (iii) chemotherapy remains a treatment option largely for visceral crisis or high tumour burden or when lines of endocrine therapy have been exhausted.

It is important to note that currently in clinical practice, a patient who has previously been treated with a CDK4/6 inhibitor, would not be retreated with a CDK4/6 inhibitor. Thus, for

example, if a patient previously considered sensitive to endocrine therapy received a CDK4/6 inhibitor plus an aromatase inhibitor, they would not be treated with a CDK4/6 inhibitor again.

The length of treatment with endocrine therapy and CDK4/6 inhibitors is typically until disease progression. The same is also true for patients treated with everolimus plus exemestane although clinical advice to the ERG is that some patients stop taking everolimus due to toxicity, typically continuing to take exemestane. The length of treatment with chemotherapy depends on the type of chemotherapy used and may also be until disease progression (particularly with capecitabine).

2.2.3 Estimated number of patients potentially eligible for treatment with palbociclib plus fulvestrant

The company estimates the number of patients diagnosed with advanced breast cancer each year to be 16,600 (CS, Table 3). This figure includes those presenting with de novo advanced breast cancer and has been calculated using the assumption that 30% of early breast cancer cases recur, based on a paper published in 2005 by O'Shaughnessy.[18] The company estimates approximately 9,300 (56%) patients are expected to have HR-positive/HER2-negative tumours, based on a survey of physicians based in the UK, Germany, France, Spain and Italy.[19] The number of patients considered to be resistant to endocrine therapy is not provided by the company in the CS.

2.3 Critique of company's definition of decision problem

Table 1 summarises the decision problem, described by the company in the CS, in relation to the final scope issued by NICE.[20]

Table 5 Summary of decision problem

Parameter	Final scope issued by NICE[a]	Decision problem addressed in the company submission[b]	Rationale if different from the final NICE scope[b]	ERG comment
Population	People with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer who have received prior endocrine therapy	Palbociclib plus fulvestrant, in women with disease that progressed during or soon after completing the endocrine therapy they received in the (neo)adjuvant or advanced/metastatic setting	Clinical experts have indicated they do not view this population by specific lines of therapy, but rather as the group of patients who have already received, and become resistant to, prior endocrine therapy. In line with this, the current standard of care treatments are not specific to line of treatment but rather to the endocrine resistant group as one population. As such, the approach in this submission is to evaluate the cost-effectiveness of palbociclib plus fulvestrant for patients who have become resistant to prior endocrine therapy, defined as the 'endocrine resistant' population. The company submission differs from the final NICE scope, to reflect the current treatment pathway and NICE recommendations	The company has noted that this submission is for a subset of the licensed population for palbociclib, i.e. patients who have received prior endocrine therapy and who are 'endocrine resistant' Palbociclib is also licensed as a treatment in combination with an aromatase inhibitor. Palbociclib in combination with an aromatase inhibitor is also used in clinical practice following recommendation by NICE for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer in December 2017 (TA496).[14] Although patients had to be previously untreated in the advanced setting, they may have been treated in the (neo)adjuvant setting as long as they were considered 'endocrine sensitive' (See Section 2.2.2 of this ERG report for further details regarding 'endocrine resistant' and 'endocrine sensitive' populations)

Parameter	Final scope issued by NICE[a]	Decision problem addressed in the company submission[b]	Rationale if different from the final NICE scope[b]	ERG comment
Intervention	Palbociclib plus fulvestrant	Same as NICE final scope	Not applicable	Palbociclib is self-administered orally at a dose of 125mg each day for the first 21 days of a 28-day cycle. In the event of significant treatment-related toxicity, palbociclib dosing may be interrupted or delayed and/or reduced (palbociclib is also available as 100mg and 75mg tablets). Palbociclib is administered alongside 500mg of fulvestrant on days 1, 15, and once monthly thereafter. Fulvestrant is given as two slow intramuscular injections in the gluteal area. Treatment with palbociclib plus fulvestrant is stopped only on disease progression, or if patients can no longer tolerate the combination

Parameter	Final scope issued by NICE[a]	Decision problem addressed in the company submission[b]	Rationale if different from the final NICE scope[b]	ERG comment
Comparator(s)	• Exemestane • Everolimus plus exemestane • Tamoxifen • Fulvestrant [During the scope consultation it was noted that fulvestrant is not routinely available as a second-line treatment] • Chemotherapy (in accordance with NICE guidance CG81)	• Everolimus plus exemestane	Everolimus plus exemestane is the most relevant comparator in the endocrine resistant population. Expert opinion has fed back that tamoxifen and exemestane monotherapy are used in some patients who cannot tolerate exemestane plus everolimus, but this is infrequent and not enough to be considered the standard of care in the NHS. Fulvestrant is not recommended by NICE[5] and is only variably commissioned by CCGs [Clinical Commissioning Groups] across the country, so is not a relevant comparator for the NHS. Chemotherapy would usually only be used after other less toxic options had been exhausted or if they were not suitable, so is not a relevant comparator. These opinions are aligned with the committee conclusion in the recent appraisal on abemaciclib with fulvestrant for treating HR-positive/HER2-negative aBC [advanced breast cancer] after endocrine therapy.[12]	Clinical opinion received by the ERG is that everolimus plus exemestane is probably the most relevant comparator for this patient population, as concluded by (i) the NICE Appraisal Committee for abemaciclib with fulvestrant for treating HR-positive/HER2-negative aBC after endocrine therapy[12] and (ii) the NICE Appraisal Committee for ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer[13] Clinical opinion received by the ERG is that the other comparators specified in the final scope issued by NICE[20] are also all used in clinical practice but in most centres, to a lesser extent than everolimus plus exemestane (with fulvestrant only available in a limited number of NHS Trusts) Clinical effectiveness evidence is also presented by the company for palbociclib plus fulvestrant versus placebo plus fulvestrant from the PALOMA-3 trial

Parameter	Final scope issued by NICE[a]	Decision problem addressed in the company submission[b]	Rationale if different from the final NICE scope[b]	ERG comment
Outcomes	The outcome measures to be considered include: • overall survival [OS] • progression free survival [PFS] • response rate • adverse effects of treatment • health-related quality of life [HRQoL]	The outcome measures included in this submission are: • PFS • OS • Objective response (OR) • Clinical benefit response (CBR) • Duration of response (DR) • Adverse effects of treatment (AEs) • HRQoL • Time to treatment discontinuation (TTD)	The tumour response variables [OR, CBR, DR] were analysed as secondary outcomes in the pivotal trial for this indication and provide useful insights into the clinical profile of palbociclib over time and its direct effect on the cancer treated	The outcomes specified in the final scope issued by NICE[20] are standard outcomes used in oncology clinical trials and are the most important outcome measures for this appraisal To compare palbociclib plus fulvestrant with everolimus plus exemestane, the company conducted network meta-analyses (NMAs). The focus of this ERG report is on the outcomes that are most relevant to understanding the clinical effectiveness data and also to the cost effectiveness data submitted by the company for this appraisal, i.e. OS, PFS (the two outcomes generated by the NMAs), AEs and HRQoL

Parameter	Final scope issued by NICE[a]	Decision problem addressed in the company submission[b]	Rationale if different from the final NICE scope[b]	ERG comment
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the comparator technologies will be taken into account.	Same as final scope issued by NICE	Not applicable	As specified in the final scope issued by NICE,[20] the cost effectiveness of treatments was expressed in terms of the incremental cost per quality adjusted life year (QALY) gained. Outcomes were assessed over a 40-year time period (equivalent to a lifetime horizon) and costs were considered from an NHS perspective While the company only presents cost effectiveness evidence for palbociclib plus fulvestrant versus everolimus plus exemestane, clinical effectiveness evidence is also presented by the company for palbociclib plus fulvestrant versus placebo plus fulvestrant from the PALOMA-3 trial. The ERG requested cost effectiveness evidence for all of the comparators included in the final scope issued by NICE[20] during the clarification process. However, the company responded that it did not agree this was necessary (the company considers everolimus plus exemestane to be the most appropriate comparator, see clarification response, B3)
Subgroups	No subgroups specified	This submission is for a subset of the licensed population. No other subgroups are to be considered in the appraisal, in line with the final scope	Not applicable	No subgroups were specified in the final scope issued by NICE[20]

Parameter	Final scope issued by NICE[a]	Decision problem addressed in the company submission[b]	Rationale if different from the final NICE scope[b]	ERG comment
Other considerations	No special considerations specified	No special considerations	Not applicable	No special considerations, including issues related to equity or equality, were highlighted in the final scope issued by NICE[20] Palbociclib and everolimus are both available to the NHS at discounted prices via the Patient Access Scheme (PAS). Only the PAS price for palbociclib is known to the company (and included in the base case economic analysis)

[a]Text in this column is taken directly from NICE scope
[b]Text in this column is taken directly from CS, Table 1 (except for population, which is taken from Section B.1.1, pp10-11)
Source: CS, adapted from Table 1 and Section B.1.1, pp10-11 and final scope issued by NICE[20]

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

Full details of the company's process and methods used to identify and select the clinical evidence relevant to the technology being appraised are presented in Appendix D to the CS. The ERG considered whether the review was conducted in accordance with key features of the systematic review process, as summarised in Table 6.

Table 6 ERG appraisal of systematic review methods

Review process	ERG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	See CS, Appendix D.1.2, Table 22
Were appropriate sources searched?	Yes	Sources included MEDLINE, Embase, the Cochrane Library and searches of conference abstracts and trial registries for ongoing trials
Was the timespan of the searches appropriate?	Yes	The search was originally run 23 January 2015 for a review published by Chirila 2017[21] and updated 28 April 2016 for another review,[22] 26 January 2018 for a second update and most recently, 15 February 2019
Were appropriate search terms used?	Yes	-
Were the eligibility criteria appropriate to the decision problem?	Yes	As one of the published reviews[22] had a different focus to that of the current appraisal, RCTs excluded in that review were re-screened for the current review
Was study selection applied by two or more reviewers independently?	Yes	-
Was data extracted by two or more reviewers independently?	Possibly	In Appendix D.4.3 of the CS, it is stated that data extracted were verified by a second researcher
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	-
Was the quality assessment conducted by two or more reviewers independently?	Unclear	Responsibility for quality assessment is not reported
Were attempts to synthesise evidence appropriate?	Yes	For full details of the network meta-analysis, see Sections 3.3 and 3.4 of this ERG report

RCT=randomised controlled trial

Overall, the ERG considers the methods used to conduct the company's systematic review of clinical effectiveness evidence to be of a good standard. Nonetheless, the ERG observes that the searches failed to identify a poster presentation of a relevant study[23] which presented OS results for the EFECT trial; these OS data should, therefore, have been included in the company's NMA for OS (see Section 3.3 of this ERG report). This poster was not identified by the searches since it was a presentation from 2007 and only conference abstracts from the

previous 3 years had been searched initially (23 January 2015) and then again during each update. Thus, only conference presentations from 2012 onwards could have been considered. This approach to searching conference abstracts is not uncommon. It is not clear why the OS results presented in the 2007 poster were not subsequently published in a peer reviewed journal.

In addition to a search for RCT evidence, the company also searched for ongoing studies and non-RCTs of palbociclib plus fulvestrant on 23 January 2015, 28 April 2016 and 26 January 2018. The search for ongoing studies and non-RCTs was not however repeated on 15 February 2019 (when all other searches were repeated); thus, any studies deemed relevant that have been published since January 2018 were "identified internally" (CS, Section B.2.11.1). The ERG has only focussed on RCT evidence in this report as this evidence is considered to represent the best level of evidence.[24]

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation

3.2.1 Included studies

Only one trial was identified that presented evidence for the clinical effectiveness of palbociclib plus fulvestrant, the PALOMA-3 trial. An overview of the trial is presented in the CS (Table 7). The trial was an international, multicentre, 2:1 randomised, double-blind, placebo-controlled, parallel-group, Phase 3 clinical study of palbociclib plus fulvestrant (N=347) versus placebo plus fulvestrant (N=174). Data for the outcomes presented in the CS have been analysed from five different data-cuts (Table 7).

Table 7 Data-cuts from PALOMA-3

Data-cut	Description	Outcomes reported in CS	Median follow-up	CSR available?	Publications[a]
1	Primary analysis of primary PFS endpoint[b] 5 December 2014	None (PFS reported in the CS is from the fourth data-cut)	5.6 months	Yes – Pfizer 2015[2]	Turner 2015[25]
2	Exploratory analysis 16 March 2015	HRQoL: EORTC QLQ-C30 and EORTC QLQ-BR23	8.9 months	No	Cristofanilli 2016[26] Harbeck 2016[27] Verma 2016[28] Iwata 2017[29] Loibl 2017[30]
3	Safety data 31 July 2015	AEs	Not reported	No - data from the supplemental New Drug Application (sNDA) 90-Day Safety Update[31]	None
4	Exploratory analysis 23 October 2015	PFS ORR CBR DR HRQoL: EQ-5D	PAL+FUL: 15.8 months FUL: 15.3 months	Yes (PFS update for European Union) - Pfizer 2016[17]	Loibl 2016[32] Turner 2016[33] Cristofanilli 2018[34] Turner 2018[35] Masdua 2019[36]
5	Most recent analysis 13 April 2018	OS Time to subsequent chemotherapy	44.8 months	Yes (abbreviated CSR) - Pfizer[37]	Turner 2018[38]

[a] Publications cited in the CS. Two other publications are also cited by the company. These present analyses in relation to deoxyribonucleic acid [39,40]
[b] Interim analysis which became the primary analysis due to rapid enrolment and high event rate observed in the study
AE=adverse event; EORTC=European Organisation for Research and Treatment; EQ-5D=Five-dimension EuroQol; OS=overall survival; PFS=progression-free survival; QLQ-BR23=Quality of Life Questionnaire-Breast cancer module; QLQ-C30=Quality of Life Questionnaire-Core 30

An examination of the eligibility criteria for PALOMA-3 trial entry suggests that the patients would be typical of patients who would be considered for treatment for 'endocrine resistant' advanced breast cancer in clinical practice in England and Wales. With the possible exception of involved disease site, baseline characteristics were well balanced between the two arms (CS, Table 10). [redacted] metastases were [redacted] found in patients in the palbociclib plus fulvestrant arm than in the placebo plus fulvestrant arm ([redacted]), the [redacted] for liver metastases (36.6% versus 46.6%, respectively). Although the trial only included [redacted] patients from the UK (clarification response, A7), the ERG considers the majority of the characteristics of the patients to be typical of patients with HR-positive/HER2 negative 'endocrine resistant' disease who would be seen in clinical practice in England and Wales (Table 8).

Table 8 Summary of baseline characteristics of patients in the PALOMA-3 trial

Characteristics	ERG comment
Race	Most patients were classified as white (73.9%) or Asian (20.2%). These patients are similar to patients in clinical practice in England and Wales
Age	The median age of patients was 56 to 57 years (placebo plus fulvestrant and palbociclib plus fulvestrant, respectively). Most patients (75.2%) were aged <65 years which is a higher proportion than the proportion of patients aged <65 years seen in clinical practice in the UK (51.7%).[41] However, clinical trials typically include younger patients than patients in clinical practice
Menopausal status	Most patients were postmenopausal (79.3%). This is what would be expected in clinical practice in England and Wales.
Disease at presentation	All patients had advanced cancer (LABC: 14.2% or MBC: 85.8%) and most patients had measurable disease (77.9%). Most commonly, the site of disease included the bone (75.6%), liver (>39.9%) and [redacted]. This is similar to what would be expected in clinical practice in England and Wales. Most patients had visceral disease (59.7%). A [redacted] proportion of patients had Stage IV disease at initial diagnosis [redacted] than typically seen in clinical practice in England (5%)[41]
Performance status	Most patients had Eastern Cooperative Oncology Group (ECOG) PS0 61.8%) and all patients had ECOG PS0-1. Typically, clinical trials mostly include patients with ECOG PS0-1 (See Table 12, Section 3.3 of this ERG report). However, clinical advice to the ERG is that patients with ECOG PS2 and possible some patients with ECOG PS >2 would be candidates for treatment in clinical practice in England and Wales
Prior endocrine therapy	All patients had received prior endocrine therapy with the majority having been previously considered sensitive to prior endocrine therapy (78.7%).* Typically, patients had received [redacted] and most patients had already received at least one endocrine therapy in the advanced setting (88.1%). Many patients had received an aromatase inhibitor only (39.7%) or an aromatase inhibitor and tamoxifen (46.1%), with only 14.2% having received tamoxifen only. It was uncommon for the most recent therapy patients had received to be an endocrine therapy (aromatase inhibitor 0.8%; tamoxifen 16.5%). Overall, previous endocrine therapy received by patients was similar to what would be expected in clinical practice in England and Wales
Prior chemotherapy	A high proportion of patients had also received chemotherapy for their primary diagnosis [redacted], either in the (neo)adjuvant setting only [redacted] or in the advanced setting [redacted]. Overall, most patients received two or more regimens prior to trial entry ([redacted]). The purpose of the most recent treatment was more often for treating advanced disease (77.9%) than early disease (21.9%). It is not uncommon for endocrine resistant patients to receive chemotherapy for their advanced disease in clinical practice in England and Wales

LABC=locally advanced breast cancer; MBC=metastatic breast cancer
* Patients were defined as having sensitivity to prior endocrine therapy if they had a relapse after 24 months of adjuvant endocrine therapy or had a clinical benefit (objective response [complete or partial] or stable disease lasting ≥24 weeks) from prior endocrine therapy in the context of advanced disease. The ERG notes that this is a more conservative definition of 'endocrine sensitive' than that employed by the company in the CS (p10). The ERG further notes that patients considered sensitive to prior endocrine therapy in clinical practice may now receive a CDK4/6 inhibitor. Patients were excluded from the trial if they had received a prior CDK4/6 inhibitor. At the time of the PALOMA-3 trial, CDK4/6 inhibitors were not standard of care for patients.
Source: data on baseline characteristics taken from CS, Table 10, Turner 2015,[25] Table 1, Cristofanilli 2016,[26] Table 1 and Loibl 2017,[30] Table 1

3.2.2 Risk of bias assessment in the PALOMA-3 trial

The company performed a quality assessment of the PALOMA-3 trial using the University of York Centre for Reviews and Dissemination guidance (Table 15 of the CS).[42] The ERG generally agrees with the company's assessment presented in Table 15 of the CS; however, the ERG does not consider patients who discontinue treatment due to disease progression to be 'drop-outs.' Examining the PALOMA-3 trial patient disposition at the end of treatment (Table 14, CS), the ERG considers that, other than disease progression or relapse, reasons for

discontinuing treatment are relatively well balanced between the two arms (11% discontinued palbociclib plus fulvestrant and 9% discontinued placebo plus fulvestrant). Furthermore, the ERG considers that there is no evidence that the authors measured more outcomes than they reported. All outcomes listed in the protocol are reported within trial publications[25,26,38] and on the ClinicalTrials.gov page of the trial.[43] Therefore, the ERG considers the PALOMA-3 trial to be at low risk of bias.

3.2.3 ERG critique of the statistical approach of the PALOMA-3 trial

A summary of the additional checks made by the ERG in relation to the pre-planned statistical approach used by the company to analyse data from the PALOMA-3 trial is provided in Table 9 of this ERG report. Information relevant to the statistical approach taken by the company has been extracted from the CS, the CSRs,[2,17,37] the trial protocols and trial statistical analysis plans (TSAPs) which were available as online supplementary documents to the PALOMA-3 trial publications.[25,26,38]

Having carried out these checks, the ERG considers that the pre-planned statistical approach employed by the company is adequate but highlights that, as acknowledged by the company in the company response to question A3 of the ERG clarification letter, it is unlikely that the proportional hazards (PH) assumption holds for the PFS analyses. Therefore, all HRs for PFS presented from the PALOMA-3 trial have no meaningful interpretation without the assumption of PH. The ERG notes that a third amendment to the PALOMA-3 protocol was data driven, related to the interim analysis results for PFS conducted on 5 December 2014. However, the ERG acknowledges that this protocol amendment was necessary and made at the request of a Data Monitoring Committee and based on Health Authorities requirements.

Table 9 ERG assessment of statistical approach used to analyse data from the PALOMA-3 trial

Item	Statistical approach with ERG comments
Were all analysis populations clearly defined and pre-specified?	The analysis populations are reported in Table 11 of the CS (p31). The ERG is satisfied that these analysis populations (ITT, as-treated, PRO and safety) are clearly defined and pre-specified in the PALOMA-3 TSAP version 2.1 (Section 5, p13).
Was an appropriate sample size calculation pre-specified?	The sample size calculation of the PALOMA-3 trial relating to PFS is reported in Table 12 of the CS. The ERG is satisfied that this sample size calculation is appropriate and pre-specified in the PALOMA-3 TSAP version 2.1 (Section 4.2.1, p12). The ERG also notes that this sample size calculation for PFS allows for assessment of the difference in secondary endpoint OS (PALOMA-3 TSAP version 2.1, Section 4.2.2, p12).
Were all protocol amendments carried out prior to analysis?	The original protocol of the PALOMA-3 trial, plus three amended protocols with a list of all amendments made and the rationale for these amendments was available as supplement to the final trial publication.[38] Most amendments were administrative or related to minor language changes (for example, to clarify inclusion and exclusion criteria). The largest amendment within protocol amendment 3 related to the changes to efficacy and safety analyses following interim analysis of PFS (05 December 2014) and additional analyses of safety conducted to comply with Health Authorities requirements. The ERG is satisfied with the rationale for all amendments and that amendments made to the first two amended versions were made before the data cut-off date used for interim analysis (05 December 2014) and therefore not driven by any results. The ERG acknowledges that the third amendment of the protocol was related to results of the interim analysis of PFS, but notes that this amendment was made upon the request of a data monitoring committee and based on Health Authorities requirements and that the general definitions and statistical analysis approach of the efficacy and safety outcomes remained the same in protocol amendment 3. Therefore the ERG does not consider that the analyses conducted at the subsequent data cuts of 16th March 2015, 23 October 2015 and 13 April 2018 for efficacy outcomes and 31 July 2015 and 12 April 2018 for safety outcome are likely to have been influenced by the third amendment.
Were all primary and secondary efficacy outcomes pre-defined and analysed appropriately?	The primary (PFS) & secondary efficacy outcomes (OR, CBR, DR, OS) outcomes are defined in Table 8, Table 9 and Section 2.3.2.1 of the CS. The statistical analysis approach for the primary and secondary efficacy outcomes is reported in Table 12 of the CS. The ERG is satisfied that the primary and secondary efficacy outcome definitions and analysis approaches were pre-defined in the PALOMA-3 TSAP version 2.1 (definitions: Section 6.1, pp14-16 and analysis approaches: Section 8.1, pp25-26) and that the definitions and analysis approaches are appropriate. Results of primary and secondary efficacy outcomes are further discussed in Section 3.2.4 of this ERG report. The ERG notes that TTD and time to chemotherapy are defined in Table 9 of the clinical effectiveness section of the CS and the statistical analysis approach of the TTD is described in Table 12 of the CS, but no statistical approach for the analysis of time to chemotherapy is provided in the CS. The ERG cannot find pre-specification of TTD or time to chemotherapy within any version of the protocol or TSAP for the PALOMA-3 trial.
Was the analysis approach for PROs appropriate and pre-specified?	PROs measured were EOTRC QLQ-C30, EOTRC QLQ-BR23, EQ-5D and time to deterioration. These outcomes are defined in Table 9 and Section 2.3.2.1 of the CS. The ERG is satisfied that the safety outcome definitions and analysis approaches were pre-defined in the PALOMA-3 TSAP version 2.1 (definitions: Section 6.4.3, pp22-23 and analysis approaches: Section 8.2.7, pp42-43) and that the definitions and analysis. approaches are appropriate. Results of PROs are further discussed in Section 3.5 of this ERG report.

Item	Statistical approach with ERG comments
Was the analysis approach for AEs appropriate and pre-specified?	AEs were assessed using the MedDRA v17.1 classification system with severity graded according to the CTCAE version 4.0 and emphasis was placed on treatment-related AEs. Further details of the definition and statistical approach for safety outcomes is provided in Table 9 and Table 12 respectively of the CS. The ERG is satisfied that the safety outcome definitions and analysis approaches were pre-defined in the PALOMA-3 TSAP version 2.1 (definitions: Section 6.3, p18 and analysis approaches: Section 8.2.6, pp39-41) and that the definitions and analysis approaches are appropriate. The ERG is also satisfied that all summary tables of AEs are provided in the PALOMA-3 CSR (pp183-220);[37] all AEs, AEs of special interest, AEs leading to permanent or temporary treatment discontinuation, SAEs and deaths are presented and summarised by grade and by treatment arm. Treatment-related AEs are further discussed in Section 3.6 of this ERG report.
Were modelling assumptions (e.g. proportional hazards) assessed?	It was pre-specified in the PALOMA-3 TSAP version 2.1 (Section 8.1.1, p25) that PFS and OS would be analysed using a Cox PH model. Log-cumulative hazard plots provided in Appendix D.2 of the CS, in addition to plots and statistical tests of Schoenfeld residuals provided in the company's response to question A3 of the ERG clarification letter demonstrate that the PH assumption may not hold for PFS, but does appear to hold for OS (CS, Section 2.9.2). The ERG acknowledges the importance of employing pre-specified statistical analysis methods to ensure the validity of clinical trial results. However, it should be noted that a HR estimated from a Cox PH model has no meaningful interpretation when the PH assumption is violated.
Was a suitable approach employed for handling missing data?	The company's approach to handling missing data for dates of any efficacy or safety assessments, tumour assessments, PFS derivation and PROs is described in Table 150, Appendix N of the CS. The ERG is satisfied that the approach to handling missing data was pre-defined in the PALOMA-3 TSAP version 2.1 (Section 7, pp23-24) and that all approaches are suitable.
Were all subgroup and sensitivity analyses pre-specified?	The ERG is satisfied that all of the subgroup analyses defined in Table 8 and presented in Figure 13 and Figure 14 of the CS and were pre-specified in the PALOMA-3 TSAP version 2.1 (Section 8.2.3, p25). No sensitivity or supportive analyses are presented within the CS. The ERG notes that eight sensitivity analyses and six supportive analyses of PFS or secondary efficacy outcomes (OR and DR) were pre-specified in the PALOMA-3 TSAP version 2.1 (Section 8.3, pp50-51). Results of these sensitivity and supportive analyses are reported in Table 20 of the PALOMA-3 CSR.[37] Numerical results of the sensitivity analysis are very similar to one or two decimal places to those of the primary analysis and result in no change to the conclusions of the PALOMA-3 trial or to the clinical effectiveness section of the CS.

AE=adverse event; CBR=clinical benefit response; CSR=clinical study report; CTCAE=common terminology criteria for adverse events; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer quality of life questionnaire; EORTC QLQ-BR23=European Organisation for Research and Treatment of Cancer quality of life questionnaire breast cancer module; EQ-5D=EuroQoL five dimensions score; ITT=intention to treat; MedDRA=medical dictionary for regulatory activities; PFS=progression-free survival; PH=proportional hazards; PRO=patient reported outcome; OR=objective response; OS=overall survival; SAE= serious adverse event; TSAP=trial statistical analysis plan; TTD = time to treatment discontinuation
Source: adapted from the CS, Table 8, Table 9, Table 11, Table 12, Table 150 (Appendix N), Figure 13, Figure 14, Section 2.3.2.1; PALOMA-3 CSRs,[2,17,37] PALOMA-3 trial protocol and TSAPs (online supplementary file to the PALOMA-3 publications[25,26,38]), the company's response to question A3 of the ERG clarification letter, and ERG comment

3.2.4 Efficacy results from the PALOMA-3 trial

Patient disposition

Patient disposition during the study and at end of treatment are summarised in Figure 4 and in Table 14 of the CS respectively. A total of 521 patients were randomised in a 2:1 ratio in the PALOMA-3 trial and were included in the intention to treat (ITT) population; 347 to palbociclib plus fulvestrant and 174 to placebo plus fulvestrant. Using data from the fourth cut-off date of 23 October 2015, the most common reasons for discontinuation of treatment was objective response or relapse (including progressive disease); 56.2% of patients in the palbociclib plus fulvestrant arm and 73.0% of patients in the placebo plus fulvestrant arm (Table 14 of the CS). As described in Section 3.2.2 of this ERG report, the ERG considers that discontinuations for other reasons are reasonably balanced between treatment arms.

Primary outcome: investigator-assessed PFS

Three analyses of PFS were conducted using data from several cut-off dates: 5 December 2014 (interim analysis which became the primary analysis due to rapid enrolment and high event rate observed in the study), 16 March 2015 (previous updated analysis) and 23 October 2015 (current updated analysis). Results using data from the latest cut-off date were presented within the CS and are summarised by the ERG in Table 10. The median length of follow-up was 15.8 months in the palbociclib plus fulvestrant arm and 15.3 months in the placebo plus fulvestrant arm. Further details of the PFS analysis is provided in Table 16 of the CS and a Kaplan-Meier (K-M) curve of PFS is shown in Figure 5 of the CS.

Table 10 Summary of PFS results in the PALOMA-3 trial (data cut-off 23 October 2015)

PFS results	PAL+FUL	PBO+FUL
Duration of follow-up: median (95% CI)	15.8 (15.5 to 16.2) months	15.3 (15.0 to 15.9) months
Objective progression or death events: n (%)	200 (57.6%)	133 (76.4%)
Median PFS (95% CI)	11.2 (9.5 to 12.9) months	4.6 (3.5 to 5.6) months
Stratified HR (95% CI); stratified one-sided p-value	0.497 (0.398 to 0.620); p<0.0001	

CI=confidence interval; FUL=fulvestrant; HR=hazard ratio; PAL=palbociclib; PBO=placebo; PFS=progression free survival
Source: adapted from CS, Table 16 and Section 2.6.2.

Local investigator-assessment of progression only was conducted for all patients and a blinded independent central review (BICR) of progression for 211 (40%) randomised patients was conducted as a supportive analysis. Results of this supportive analysis are reported to be consistent with the investigator assessment.[25,26]

Efficacy results using earlier data-cuts are provided in Appendix O, Table 151 of the CS. The ERG considers that the PFS results across the three data-cuts are very similar numerically and all reach the same conclusion. Results for pre-specified subgroup analyses of PFS are

provided in Figure 13 of the CS. The ERG considers that PFS results for all pre-specified subgroups are generally consistent with the PFS results presented within Table 10 of this ERG report but notes that the imprecision of these results should be taken into account when drawing conclusions due to small sample sizes and imbalances within some of the subgroups. The ERG also emphasises that a HR estimated from a Cox PH model has no meaningful interpretation when the PH assumption is violated and there is evidence that the PH assumption does not hold for PFS.

Secondary outcome: OS

The final OS analysis conducted using data from the fifth and most recent cut-off date of 13 April 2018 is presented in the CS and the ERG summarises the results in Table 11. The median length of follow-up was 44.8 months across both treatment arms.

Table 11 Summary of OS results in the PALOMA-3 trial (data cut-off 13 April 2018)

OS results	PAL+FUL	PBO+FUL
Objective progression or death events: n (%)	201 (57.9%)	109 (62.6%)
Median OS (95% CI)	34.9 (28.8 to 40.0) months	28.0 (23.6 to 34.6) months
Stratified HR (95% CI); stratified p-value	0.81 (0.64 to 1.03); p=0.09	

CI=confidence interval; FUL=fulvestrant; HR=hazard ratio; PAL=palbociclib; PBO=placebo; OS=overall survival
Source: adapted from CS, Table 17 and Section 2.6.4.

The ERG notes there is no statistically significant difference in OS between the palbociclib plus fulvestrant and placebo plus fulvestrant arms.

Further details of the OS analysis is provided in Table 17 of the CS and a K-M curve of OS is shown in Figure 6 of the CS. Results for pre-specified subgroup analyses of OS are provided in Figure 14 of the CS. As for PFS, the ERG considers that OS results over all pre-specified subgroups are generally consistent with the OS results presented within Table 11 of this ERG report but notes that the imprecision of these results should be taken into account when drawing conclusions due to small sample sizes and imbalances within some of the subgroups.

The ERG notes that while cross-over between treatment arms in the PALOMA-3 trial was not permitted, 27(15.5%) of the 174 patients randomised to placebo plus fulvestrant received palbociclib and/or other cyclin-dependent kinases 4 and 6 (CDK 4/6) inhibitors as post-progression subsequent treatment after completion of the trial intervention. Results from a sensitivity analysis were reported in the PALOMA-3 trial publication for OS[38] using the rank-preserving structural-failure time (RPSFT) method to correct for the cross-over which suggested a small decrease in OS in the placebo plus fulvestrant arm. The results using the RPSFT method were similar to the unadjusted results. Thus, there were no changes to conclusions compared to the original OS results presented.[38]

Secondary outcomes: OR, CBR, DR and time to subsequent chemotherapy

Using data from the fourth cut-off date of 23 October 2015, analysis of OR, CBR and DR favoured palbociclib plus fulvestrant versus placebo plus fulvestrant. Further details are provided in Section B.2.6.3 of the CS and results using data from previous data cut-off dates are provided in Appendix O of the CS. From the most recent data-cut (13 April 2018), time to subsequent chemotherapy is delayed in the palbociclib plus fulvestrant arm compared to the placebo plus fulvestrant arm. Further details are provided in Section B.2.6.5 of the CS.

3.3 Critique of trials identified and included in the company's network meta-analyses

In the absence of direct clinical evidence, the company carried out network meta-analyses (NMAs) to indirectly estimate PFS and OS for the comparison of palbociclib plus fulvestrant versus everolimus plus exemestane.

In addition to the PALOMA-3 trial, the company identified four relevant trials for inclusion in the NMAs (BOLERO-2,[44,45] CONFIRM,[46,47] EFECT[48] and SoFEA[49]). The company included RCTs with K-M data for PFS or time to disease progression (TTP) in the PFS network (thus assuming equivalence of the two measures) and RCTs with HR data available for OS in the OS network. Within the CS, the company reported that four of the five identified trials were eligible for inclusion in the OS NMA as OS data had not been reported for the EFECT trial. The ERG identified a conference poster for the EFECT trial in which OS data had been reported[23] and, as part of the clarification process, asked the company to update the OS NMA with these data. Therefore, the resulting NMAs for both PFS and OS included data from all five identified trials.

The company considered the heterogeneity of the trials included in the NMAs in terms of risk of bias (CS, Appendix D.1.3, Table 28), baseline patient characteristics (Table 29 of Appendix D.1.4), interventions (CS, Appendix D.1.4, Table 30), prior endocrine and chemotherapy treatment (CS, Appendix D.1.4, Table 31), HR and HER2 status (CS, Appendix D.1.4, Table 32), blinding of studies and accounting for crossover (CS, Appendix D.1.4, Table 33).

The ERG generally agrees with the company's summary of the trials included in the NMAs from Appendix D.1.3 and Appendix D.1.4 of the CS but notes the following:

- Methodological information for the CONFIRM trial[46,47] and EFECT trial[23,48] are limited; both trials are described as randomised and double-blind but no further details of randomisation or blinding methods are reported.

- The company reports that the SoFEA trial[49] is double-blinded. The ERG considers that blinding in the SoFEA trial was performed only for the two fulvestrant arms in the trial, (placebo plus fulvestrant or fulvestrant plus anastrozole, the latter of which is not relevant to the NMA). The ERG notes that the comparison relevant to the NMA within the SoFEA trial[49] (fulvestrant versus exemestane) is not blinded.

- The company reports that cross-over after progression was not permitted in any of the five trials. However, the ERG notes that cross-over to subsequent therapy was permitted post-progression in the PALOMA-3 trial and a sensitivity analysis using the RPSFT method was conducted to correct for the cross-over of 27 patients randomised to placebo plus fulvestrant, showing similar results to the OS results from the PALOMA-3 trial.[38]

- Furthermore, the ERG notes that, in the CONFIRM trial, following the first analysis of OS (after approximately 50% of patients had had an event),[46] an independent Data Monitoring Committee advised investigators to offer fulvestrant 500mg to ongoing fulvestrant 250mg patients. It is reported that, subsequently,[47] eight patients crossed over to fulvestrant 500mg (2.1% of patients ongoing on fulvestrant 250mg) for the updated OS analysis after approximately 75% of patients had an event. This updated analysis in which 2.1% of patients crossed over[47] is used in the OS NMA. The ERG considers the small proportion of patients crossing over in the PALOMA-3 and CONFIRM trials[35,47] is unlikely to have impacted on the overall results of the OS NMA.

The ERG considers that the characteristics of the eligible populations of the included studies, with regards to endocrine resistance, HR status, HER2 status and previous therapies in an advanced setting, are likely to be the largest potential sources of heterogeneity within the NMAs. The ERG summarises these population characteristics in Table 12.

Table 12 Population characteristics of the five trials included in the NMAs for PFS and OS

Trial	Population characteristics	HR+ status	HER2- status	Prior therapy in the advanced setting
PALOMA-3	• Women, 18 years or older, of any menopausal status with HR+ and HER2- advanced breast cancer not amenable to curative therapy • Progressed during or within 12 months of completion of (neo) adjuvant endocrine therapy or progressed during or within 1 month of completion of prior endocrine therapy for advanced breast cancer (i.e. all patients are 'endocrine resistant') • Randomisation was stratified by sensitivity to previous endocrine therapy, where sensitivity is defined as documented clinical benefit from at least one endocrine therapy in the metastatic setting or treatment with at least 24 months of adjuvant therapy before disease recurrence • 79% of the PAL+FUL arm and 78% of the PBO+FUL arm were defined as sensitive to previous endocrine therapy • All patients had ECOG PS 0-1	PAL+FUL=100% PBO+FUL=100%	PAL+FUL=100% PBO+FUL=100%	• 79% of the PAL+FUL arm and 76% of the PBO+FUL arm had received their most recent treatment in the advanced setting • 33% of the PAL+FUL arm and 39% of the PBO+FUL arm had received chemotherapy in an advanced setting • Patients had previously received NSAIs, tamoxifen or both but it is not stated how many patients received these treatments in the advanced setting
BOLERO-2	• Adult postmenopausal women with HR+ advanced breast cancer not amenable to surgery or radiotherapy and progressing after anastrozole or letrozole • Progression was defined as disease recurrence during or within 12 months of end of adjuvant treatment or progression during or within 1 month of end of treatment for advanced disease (i.e. all patients are 'endocrine resistant') • Randomisation was stratified by sensitivity to previous endocrine therapy, where sensitivity is defined as documented clinical benefit (CR, PR or SD for at least 24 weeks) to at least one prior endocrine therapy in the advanced setting or at least 24 months of adjuvant endocrine therapy prior to recurrence • 84% of both the EVE+EXE and PBO+EXE arms were defined as sensitive to previous endocrine therapy • 98% of patients had ECOG PS ≥0-1	EVE+EXE=100% PBO+EXE=100%	EVE+EXE=100% PBO+EXE=100%	• 79% of the EVE+EXE arm and 84% of the PBO+EVE arm had received prior therapy in the advanced setting • 26% of each arm had received chemotherapy in an advanced setting • Anastrozole, letrozole, fulvestrant and tamoxifen listed as previous endocrine therapies but it is not stated how many patients received these treatments in the advanced setting
CONFIRM	• Postmenopausal women with ER+ advanced breast cancer • Eligible patients had experienced relapse during or within one year of completing of adjuvant endocrine therapy (53%), relapse after more than one year of completion of adjuvant endocrine therapy (12%), or de-novo advanced disease and experiencing progression on first-line endocrine therapy (35%) (i.e. 88% of patients are 'endocrine resistant') • PS of patients not reported	FUL 500mg=100% FUL 200mg=100%	HER2 status not reported	• Not stated how many patients had received chemotherapy or endocrine therapy in the advanced setting

Trial	Population characteristics	HR+ status	HER2- status	Prior therapy in the advanced setting
EFECT	• Postmenopausal women with incurable advanced breast cancer whose disease had relapsed during treatment with (or within 6 months of discontinuation of) an adjuvant NSAI, or whose advanced disease progressed during treatment with a NSAI • Patients were categorised as NSAI sensitive if the investigator determined that the patient had a CR, PR or SD for at least 6 months during treatment with the NSAI in the advanced setting (63% of total patients randomised) • All other patients, including all those who received the NSAI as adjuvant therapy, were defined as NSAI resistant (37% of total patients randomised) • 95% of patients had ECOG PS 0-1	EXE=98.2% FUL=98.3%	HER2 status not reported	• 22% of the EXE arm and 25% of the FUL arm had received chemotherapy in the advanced setting • 86% of the EXE arm and 89% of the FUL arm had received endocrine therapy in the advanced setting
SoFEA	• Postmenopausal women of HR+ status (ER+ or PgR+ positive, or both) were eligible if they relapsed or progressed to advanced breast cancer on an NSAI • NSAI had to have been given as adjuvant treatment for at least 12 months, or as first-line treatment for advanced breast cancer for at least 6 months • Patients could have previously received tamoxifen and chemotherapy in the adjuvant or neo-adjuvant setting or chemotherapy as first-line treatment for advanced breast cancer followed by an NSAI alone for at least 6 months • All patients had WHO PS 0-2 but numbers of patients by WHO PS not reported	EXE=99% FUL+PBO=100%	All patients: EXE=57% FUL+PBO=61% Patients for whom HER2 status was known:* EXE=89% FUL+PBO=91%	• 67% of the EXE arm and 74% of the FUL+PBO arm had received an endocrine therapy (tamoxifen) in the advanced setting • It is not stated how many patients received chemotherapy in the advanced setting

* Not all patients were tested for HER2 status in this trial, the numbers tested being 159 (64%) in the EXE arm and 155 (67%) in the FUL+PBO arm

CR=complete response; ECOG=Eastern Cooperative Oncology Group; ER+=oestrogen receptor positive; EVE=everolimus; EXE=exemestane; FUL=fulvestrant; HER2-human epidermal growth receptor 2 negative; HR+=hormone receptor positive, mg = milligrams; NSAI=nonsteroidal aromatase inhibitor; PAL=palbociclib; PBO=placebo; PgR+=progesterone receptor positive; PR=partial response; PS=performance status; SD=stable disease; WHO=World Health Organization

Source: CS, adapted from Table 10; CS, Appendix D.1.3 (Table 27, Table 31 and Table 32), selected trial publications of PALOMA-3,[25,26,38] BOLERO-2,[3,44,45] CONFIRM,[46,47] EFECT[23,48] and SoFEA[49]

Using a definition of disease recurrence during or within 12 months of end of adjuvant treatment or progression during or within 1 month of end of treatment for advanced disease, the 'endocrine resistant' population was 100% in the PALOMA-3 trial and BOLERO-2 trial.[44,45] The vast majority (99.2%) of the patients in the CONFIRM trial[46,47] had also progressed within 12 months of adjuvant therapy or on first-line endocrine therapy for advanced disease (with 0.8% described as 'other'). However, in the EFECT trial,[23,48] a large proportion (62.6%) of patients were described as having aromatase inhibitor 'sensitive disease'. The authors of the EFECT trial discussed that the proportion of patients resistant to endocrine therapy may in fact have been higher, noting that there was no central confirmation of resistance or sensitivity in the trial.[48] The ERG could not find information on resistance or sensitivity described in the SoFEA trial,[49] although the authors of this trial publication[49] stated that the population was similar to that of the BOLERO-2 trial[44,45] in terms of previous endocrine sensitivity.

The ERG notes that almost all (over 98%) of patients within the five included trials had HR-positive disease and, where reported, the proportions of included patients who had received previous endocrine therapy or chemotherapy in an advanced setting were similar across trials. However, reported details of previous therapies in an advanced setting were limited, particularly in the CONFIRM trial.[46,47]

The PALOMA-3 trial and BOLERO-2 trial[44,45] reported recruiting only patients with HER2-negative disease, the SoFEA trial[49] reported that 61% and 57% of patients in the fulvestrant and exemestane arms had HER2-negative disease (but of those where HER2 status was known, the proportions were 89% and 91%, respectively) and HER2 status was not reported in the CONFIRM trial[46,47] or EFECT trial.[23,48] Therefore, the ERG considers that HER2 status is an area of uncertainty for the PFS and OS NMAs.

The company emphasises (CS, p21) that the PALOMA-3 trial contains the largest pre/peri-menopausal population in a Phase 3 study of an 'endocrine resistant' population. Furthermore, the company highlights that the European Medicines Agency has not issued licences to allow either fulvestrant or everolimus to be used to treat pre/peri- menopausal women (CS, p21). The ERG notes that this wider population of women of any menopausal status in the PALOMA-3 trial compared to the postmenopausal populations in the other four included trials may also act as a source of heterogeneity in the NMAs. Indeed, this wider population (20.7% of the patients in the PALOMA-3 trial are of pre/peri menopausal status) is reflected by the slightly lower median age of 57 years in the PALOMA-3 trial compared to median ages of between 61 and 66 years in the other four trials recruiting only postmenopausal populations (CS, Table 29 of Appendix D.1.4).

The ERG summarises the definitions and median follow-up times for the data-cuts included in the PFS and OS NMAs for the five included trials in Table 13. The ERG notes that the definitions of PFS are very similar across the five trials, including the EFECT trial[23,48] which measures TTP as the primary outcome rather than PFS. PFS was investigator-assessed for all patients in the PALOMA-3 trial (with blinded central assessment for a random sample of approximately 40% of randomised patients), both investigator-assessed and centrally reviewed PFS results were reported in the BOLERO-2 trial[44] and it was not reported whether PFS was investigator-assessed or centrally assessed in the CONFIRM trial,[46] EFECT trial[48] or SoFEA trial.[49] The median duration of follow-up for PFS was similar in the PALOMA-3 trial, BOLERO-2 trial[44] and EFECT trial[48] (approximately 13 to 17 months), substantially longer in the SoFEA trial[49] (approximately 38 months) and not reported in the CONFIRM trial.[46] The ERG considers that the potential variability in measurement of PFS (investigator or central assessment) and median follow-up could also be an area of uncertainty in the PFS NMA.

The ERG notes that the definitions of OS are also very similar across the five trials. However, the ERG notes further variability and uncertainty in the median duration of follow-up for OS, ranging from approximately 21 to 48 months in the PALOMA-3 trial, BOLERO-2 trial[45] and EFECT trial[23] and not reported in the CONFIRM trial[47] or SoFEA trial,[49] which could also be an area of uncertainty in the OS NMA.

The ERG also notes that due to the lack of a closed loop within the network (CS, Figure 15 and Figure 16) results generated by the NMAs are based on indirect evidence. Therefore, the fundamental methodological assumptions of consistency of the direct and indirect evidence within the NMAs cannot be investigated statistically. The ERG considers that the validity of the consistency assumption is unknown and that this should be taken into account when interpreting numerical results from the indirect comparison of palbociclib plus fulvestrant versus everolimus plus exemestane where no direct evidence exists.

Overall, while the ERG acknowledges trial differences do increase uncertainty with regard to the reliability and robustness of the results, the ERG does not consider that the differences across trials introduce sufficient heterogeneity to preclude the conduct of meaningful NMAs.

Table 13 Definitions and median follow-up time for PFS and OS in the five trials included in the company NMAs

Trial	PFS definition	Median PFS follow-up	OS definition	Median OS follow-up
PALOMA-3	• The time for the date of randomisation to the date of first documentation of objective progressive disease or death due to any cause in the absence of documented progressive disease, whichever occurred first • PFS data were censored on the date of the last tumour assessment for patients who did not have objective tumour progression and who did not die during the study • PFS was investigator assessed only for all patients, blinded central assessment of PFS was conducted for a random sample of 40% of randomised patients	PAL+FUL=15.8 months (95% CI: 15.5 to 16.2 months) PBO+FUL=15.3 months (95% CI 15.0 to 15.9 months)	• Date of randomisation to the date of all-cause death • Patients last known to be alive were censored at the last contact date	44.8 months (both treatment arms)
BOLERO-2	• The time from date of randomisation to the date of first documented progression or death due to any cause. • If a patient has not had an event, PFS is censored at the date of last adequate tumour assessment. • Both investigator assessed and blinded central assessment	17.7 months; range 10.9 to 28.6 months (both treatment arms)	• Time from date of randomisation to the date of death due to any cause • If a patient is not known to have died, survival will be censored at the last date of contact	39.3 months (both treatment arms)
CONFIRM	• The time elapsing between the date of random assignment and the date of earliest evidence of objective disease progression or death from any cause before documented disease progression. • Unclear if PFS investigator assessed or centrally assessed	Not stated	• Number of days from randomisation to death from any cause • Patients who died after the data cut-off date or who were known to be alive after data cut-off date were right-censored at the date of the data cut-off	Not stated

Trial	PFS definition	Median PFS follow-up	OS definition	Median OS follow-up
EFECT	• TTP was defined as the number of days from the date of random assignment until the date of objective disease progression, as per RECIST criteria. If the patient died without documented disease progression, and the date of death was no more than 6 months from the last disease assessment per RECIST, then death was regarded as a progression event • For patients who had not experienced disease progression at the time of data cut-off, data were right censored to the date of the last RECIST assessment • Unclear if PFS was investigator assessed or centrally assessed	Approx. 13 months (both treatment arms)	• Time from randomisation to death from any cause • The date of last evaluation for patients who were alive at data cut-off date.	20.9 months (both treatment arms)
SoFEA	• Time from randomisation to progression of exiting disease, new sites of disease, second primary cancer if change in systemic treatment was necessary or death from any cause. • Unclear if PFS was investigator assessed or centrally assessed	37.9 months; IQR 23.1 to 50.8 (all treatment arms)*	• Time from randomisation to death from any cause	37.9 months; IQR 23.1 to 50.8 (all treatment arms)*

* Unclear if this median follow-up reported is applicable to both PFS and OS. Also this median follow-up time includes a treatment arm of fulvestrant plus anastrozole included in the SoFEA trial which is not relevant to the NMAs

CI=confidence interval; FUL=fulvestrant; IQR=inter-quartile range; NMA=network meta-analysis; OS=overall survival; PAL=palbociclib; PBO=placebo; PFS=progression-free survival; RECIST=Response evaluation criteria in solid tumours; TTP=time to disease progression

Source: CS, adapted from CS, Table 10 and Table 12, selected trial publications of PALOMA-3,[25,26,38] BOLERO-2,[3,44,45] CONFIRM,[46,47] EFECT[23,48] and SoFEA[49]

3.4 Critique of the company's network meta-analyses

3.4.1 Proportional hazards (PH) assumption

Within the CS (Section 2.9.2 and Appendix D.2), the company judged that the PH assumption for PFS in the PALOMA-3 trial did not hold. This conclusion was reached after visual inspection of a log-cumulative hazard plot. The validity of the PH assumption was not considered in the other five trials due to violation of the PH assumption in the PALOMA-3 trial. The company presented an NMA using fractional polynomials (FPs) for PFS, an approach which does not rely on the PH assumption (see Section 3.4.2 of this ERG report for further details).

The company judged that the PH assumption was held for all five trials included within the OS NMA; this judgement was based on visual inspection of a log-cumulative hazard plot. The company carried out a traditional Bayesian NMA for OS under the assumption of PH.

The ERG considers that any decisions made after visual inspection of log-cumulative hazard plots are subjective and, therefore, this approach may not always be an adequate method for judging the validity of the PH assumption. During the clarification process, the ERG asked the company to also perform a statistical test of the PH assumption for PFS and OS for all of the five trials included in the PFS and OS NMAs. In the response to question A3 of the ERG clarification letter, the company presented plots and a statistical test of Schoenfeld residuals for PFS and OS for all five included trials. Schoenfeld residuals suggest that the PH assumption holds if a plotted flat line with no systematic trend is observed and the statistical test shows a p-value>0.05. The ERG also requested that an NMA using FPs be performed for OS if evidence of violation of the PH assumption was found for any of the five trials.

For PFS, the ERG agrees with the company assessment of PFS, i.e., that PH seems to be violated for at least one trial [redacted]

The company judged that, for OS, PH can be assumed to hold in all trials "despite some evidence of slight deviations," notably:

- The ERG notes that the p-values from the test of Schoenfeld residuals suggested that PH had been violated for the BOLERO-2 trial[45] (p=0.001) and for the EFECT trial[23] (p=0.007), but the company argued that PH can be assumed to hold as the variation in the log-cumulative hazard plots occurred only at the beginning of the plot (for the first couple of months).

- The company considered that the PH assumption was 'borderline' for the SoFEA trial[49] as the K-M curves and log-cumulative hazard plots cross many times. The company also argued that, as the observed HR in the SoFEA trial[49] was close to 1, and as there was no difference between the treatments, PH was not violated (CS, Appendix D.2.2).

For the SoFEA trial,[49] the ERG agrees with the company that the interpretation of the plots is difficult and notes the non-significant p-value from the test of Schoenfeld residuals (p=0.551). The ERG does not agree with the company's argument that PH is not violated as the HR is close to 1. The ERG considers that the PH assumption is related to whether the HR can be assumed to be a constant value or whether the HR changes over time. Therefore, the numerical value of the HR is not relevant when assessing whether the PH assumption holds.

The ERG does not consider that it is valid to assume that PH holds if the lines appear parallel for a proportion of the plot as the PH assumption applies to the entire analysis time-frame. Therefore, in the BOLERO-2 trial[45] and the EFECT trial,[23] considering both the log-cumulative hazard plots as well as the plots and a statistical test of Schoenfeld residuals, the ERG judges that the PH assumption has been violated for OS.

Due to the ERG judgement that the PH assumption has been violated for at least one trial for both PFS and OS, the ERG presents and critiques only the NMA results generated from a FP modelling approach to estimate comparative PFS and OS effectiveness (Section 3.4.3 and Section 3.4.4 of this report).

3.4.2 Fractional polynomial approach

In the absence of PH, the company took a Bayesian FP modelling approach to the NMAs for PFS and OS according to the methods of Jansen 2011.[50] Under the assumption of PH, the HR is represented as a single parameter (i.e., a number and a 95% Credible Interval [CrI]) which is assumed to be constant over time. This alternative approach using FPs is designed to model the hazard function with multiple parameters as a function of time, allowing the HR to change over time in the presence of non-PH. FP models of any 'order' can be fitted to time-to-event data to capture the shape of the hazard functions; 1st order FP models model time as a function with one additional parameter (i.e., a model of two parameters in total in which the shape of the hazard function can change once), 2nd order FP models model time as a function with two additional parameters (i.e., a model of three parameters in total in which the shape of the hazard function can change twice), and so on. However, as the order of the FP model increases, so too does the statistical complexity required to fit the model and issues with convergence of the model become more likely. The company considered only 1st and 2nd order FP models across all combinations of powers across the range: -2.0, -1.0, -0.5, 0.0, 0.5, 1.0,

2.0, 3.0. The company fitted both fixed-effects and random-effects FP models to individual patient data (IPD) from the PALOMA-3 trial and re-created IPD by digitising published K-M data from the other four trials. FP models were extrapolated up to 60 cycles, where a cycle was defined as 28 days.

The company used the Deviance Information Criterion (DIC) to compare the goodness-of-fit of different 1st and 2nd order FP models of different powers and to compare FP models fitted with fixed or random-effects. The model with the lowest DIC was considered to provide the 'best fit' and other models with a DIC within 3-5 points were also considered as candidates for the 'best' fitting model, along with 'visual inspection of the fit and plausibility of the predictions… with each treatment' (CS, p64).

Further details of the Bayesian FP modelling approach taken by the company is provided in Section B.2.9.4.1 and in Appendix D.3.1 to the CS.

Theoretically, the ERG considers the statistical approach taken by the company in the absence of PH to be reasonable in principle and that the company has applied the methods described by Jansen[50] appropriately. However, the ERG notes that, within the CS, a graphical representation of only the 'best fitting' FP model is provided for PFS (2nd order model, powers -1, -1) and very limited information is provided within the CS or in Appendix D.2 and D.3 to the CS relating to any of the other FP models applied for the PFS NMA. The ERG was unable to find numerical results of the beta parameters of the 'best fitting' FP model for PFS or an interpretation of the results of this model in terms of the comparison of the effectiveness of treatment with palbociclib plus fulvestrant versus everolimus plus exemestane anywhere within the CS or the appendices to the CS. During the clarification process (question A4 and A5 of the ERG clarification letter), the company provided numerical results (including 95% CrIs) of the beta parameters for all fitted FP models that converged for the PFS and OS NMAs to allow the ERG to further understand the FP modelling approach that had been carried out.

The ERG considers that the DIC is a measure of the statistical fit of a model and therefore should not be used alone to select or rule out an FP model when the generated model outputs from an NMA are intended to be used to inform a clinical decision. The ERG considers that it is essential that any FP model outputs (i.e., the survival and HR functions) derived from an NMA for clinical application are also shown to be clinically and numerically plausible, regardless of model fit according to DIC.

3.4.3 Results of PFS FP NMA

Using data provided during the clarification process, the ERG presents graphical representations of the survival and HR functions for the company's three 'best fitting' FP models according to the DIC statistic for the PFS NMA in Appendix 2, Section 9.2.1 of this ERG. All of these models are 2nd order fixed-effects FP models.

Despite showing the best statistical model fit according to the lowest DIC statistic, from visual inspection of the survival and HR functions of the company's three 'best fitting' 2nd order FP models, the ERG considers that these models for the survival functions of palbociclib plus fulvestrant and everolimus plus exemestane are likely to be overfitted to the data. In other words, the survival function model is fit too closely to the specific data used within the PFS FP NMA, and therefore may not be suitable for making inferences. Specifically, the ERG considers that these 2nd order FP models [redacted]

Due to these visual observations, the ERG has not considered any of the other 2nd order FP models applied by the company. Instead, the ERG has presented graphical representations of the survival and HR functions for all 1st order FP models applied by the company in Appendix 2, Section 9.2.1 of this ERG report. The 1st order FP models are less statistically complex and therefore may be less likely to overfit the data.

From visual inspection of the 1st order FP models, [redacted]

However, the [redacted] survival and HR functions generated by the 1st order FP models are quite variable and there is potentially a large amount of uncertainty around these estimated survival and HR functions (see approximate CrIs graphically represented in Appendix 2, Section 9.2.1 of this ERG report). The ERG considers that the extrapolation of the trial data up to 60 cycles may also have introduced uncertainty and the ERG notes that all results are presented with fixed-effects. If FP models fitted with random-effects to the NMA had also been presented by the company, the uncertainty around these survival and HR functions would be even larger than those associated with the fixed-effects models.

[redacted] generated by the company's 1st and 2nd order FP models, the ERG considers that treatment with palbociclib plus fulvestrant may lead to better PFS results than treatment with everolimus plus exemestane. However, the ERG notes that the statistical significance and the magnitude of this observed advantage cannot be tested.

For the reasons described within this section, the ERG cannot select a suitable FP model with any degree of confidence to inform the relative comparison of the clinical effectiveness of treatment with palbociclib plus fulvestrant versus everolimus plus exemestane.

3.4.4 Results of OS FP NMA

Using data provided during the clarification process, the ERG presents graphical representations of the survival and HR functions for the two 'best fitting' FP models according to the DIC statistic for the OS FP NMA in Appendix 2, Section 9.2.2 of this ERG report. Both of these models are 2nd order fixed-effects FP models.

As per the PFS PF NMA, despite showing the best statistical model fit according to the lowest DIC statistic, from visual inspection of the survival and HR functions of the two 'best fitting' 2nd order FP models, [redacted] the ERG has not considered any of the other 2nd order FP models applied by the company.

From visual inspection of the four 1st order FP models for the OS FP NMA (see Appendix 2, Section 9.2.2 of this ERG report), the ERG notes that different conclusions could be drawn from these four 1st order FP models. In other words, [redacted].

The ERG notes the variability of the conclusions that could be drawn from the survival and HR functions generated by the 1st and 2nd order FP models for the OS FP NMA; [redacted]

[redacted]

The ERG also notes that there is, potentially, a large amount of uncertainty around the company's OS FP NMA results, namely the estimated survival and HR functions (see approximate CrIs graphically represented in Appendix 2, Section 9.2.2 of this ERG report) and the extrapolation of the trial data up to 60 cycles. Furthermore, all presented results have been generated using fixed-effects; if FP models had been fitted using random-effects the uncertainty around the survival and HR functions would be even larger.

Therefore, as per the PFS FP NMA, the ERG cannot select a suitable FP model with any degree of confidence to inform the relative comparison of the effectiveness of treatment with palbociclib plus fulvestrant versus everolimus plus exemestane. The ERG considers that the evidence generated by the company FP NMA does not demonstrate that, in terms of OS, treatment with palbociclib plus fulvestrant delivers better results than treatment with everolimus plus exemestane.

3.5 Patient reported outcomes (health-related quality of life)

3.5.1 Measures of HRQoL in the PALOMA-3 trial

HRQoL data were collected in the PALOMA-3 trial using three instruments (as described in Table 7). The data were analysed from two data-cuts (as also described in Table 7).

Table 14 Measures of health-related quality of life in PALOMA-3 trial

Instrument, data-cut	Measures of HRQoL		
QLQ-C30, second data-cut, 16 March 2015	Single item symptom scales:[a] 1. Dyspnoea 2. Sleep disturbance 3. Appetite loss 4. Constipation 5. Diarrhoea 6. Financial impact of cancer Multi-item symptom scales (4-point Likert scales):[a] 1. Fatigue ***2. Nausea/vomiting*** ***3. Pain***	Multi-item functional subscales (4-point Likert scales):[b] 1. Physical 2. Role ***3. Emotional*** 4. Cognitive 5. Social functioning	***Global QoL/health status subscale (7-point Likert scale)[b]***
QLQ-BR23, second data-cut, 16 March 2015	Symptom scales:[a] 1. Systemic side effects 2. Breast symptoms 3. Arm symptoms ***4. Upset by hair loss***	Functional scales:[b] 1. Body image 2. Sexual functioning 3. Sexual enjoyment 4. Future perspective	
EQ-5D-3L, fourth data-cut, 23 October 2015	***Index derived from descriptors of current health state:[c]*** 1. Mobility 2. Self-care 3. Usual activities 4. Pain/discomfort 5. Anxiety/depression		VAS:[d] Self-rated health status

EQ-5D=EuroQol-5 dimensions 3 level; HRQoL=health-related quality of life; QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; QLQ-BR23=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer module; QoL=quality of life; VAS= visual analogue scale
[a] For symptom-oriented scales, a higher score represents higher symptoms severity
[b] For functional and global QoL/health status scales, higher scores represent a better level of functioning/QoL
[c] Scores range from 0 to 1 with low scores representing a higher level of dysfunction and 1 as perfect health
[d] Self-rated health status on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state)
Measures in bold italics were reported to be statistically significant over time from a longitudinal repeated measures mixed model (2-sided) approach adjusting for specified covariates
Source: CS, adapted from Table 9 (p33) and pp50-58; Harbeck et al 2016[27] and Loibl et al 2017[30]

Patients completed the HRQoL instruments on day 1 of the first four treatment cycles and then on day 1 of every other subsequent cycle, starting with cycle 6 (and then at the end-of study treatment).[27,30] The ERG notes that at baseline, in both arms of the trial, symptom severity scores were low,[27] functioning levels were high,[27] and global quality of life (QoL) was "moderately high" (CS, p50). Nonetheless, as noted by Harbeck et al 2016,[27] global QoL/health status was within range of reference values published previously.[51] The ERG further notes that the baseline global QoL/health status scores are similar to those in reported in an analysis of HRQoL data from the BOLERO-2 trial.[52]

Change from baseline scores were compared between the treatment arms using a longitudinal repeated measures mixed model (2-sided) approach adjusted for specified covariates. As detailed in the CS (pp50-56 and shown in bold italics in Table 7 of this ERG report), statistically significant differences in HRQoL over time favouring treatment with palbociclib plus fulvestrant

versus placebo plus fulvestrant were observed for some (but not all) measures, namely nausea/vomiting (QLQ-C30), pain (QLQ-C30), emotional functioning (QLQ-C30), global QoL/health status (QLQ-C30) and EQ-5D Index. Statistically significantly higher scores were observed among patients reporting hair loss (QLQ-BR23) in the palbociclib plus fulvestrant arm than in the placebo plus fulvestrant arm i.e. favouring placebo plus fulvestrant. It is reported by the company that the overall changes within each treatment arm, based on interpretation of the 95% CIs of the change from baseline analysis, indicated that global QoL/health status was maintained in the palbociclib plus fulvestrant arm and significantly deteriorated in the placebo plus fulvestrant arm (CS, p50). It is not reported in either the CS or relevant published paper[52] until what time period the change has been measured but is assumed by the ERG to be until end-of study treatment.

Given the high incidence of neutropenia associated with treatment with palbociclib plus fulvestrant (see Section 3.6.1 of this ERG report), the impact of this AE on EQ-5D scores was also explored by the company (CS, pp55-57); no statistically significant differences were observed in the overall EQ-5D index score and change from baseline on treatment within the palbociclib plus fulvestrant arm between patients with or without neutropenia.

3.5.2 Completion rates of HRQoL instruments in the PALOMA-3 trial

As patients only completed the HRQoL instruments when on treatment and at the end of treatment, over time, the number of eligible patients decreased as patients' disease progressed. This was particularly the case in the placebo plus fulvestrant arm where median PFS was lower than that in the palbociclib plus fulvestrant arm. Thus, while completion rates (defined as answering at least one question) at each cycle were reported to be high ([redacted] for any given instrument at any given cycle), the numbers of eligible patients decreased notably over time (for response data from the first data-cut, 5 December 2014, see Table 15 of this ERG report). Thus, the results from later cycles may not be as reliable as those from earlier cycles due to greater variation in scores around the mean and median values.

Table 15 Number of eligible patients who completed each HRQoL instrument by cycle

Cycle	QLQ-C30, n (%)*		QLQ-BR23, n (%)*		EQ-5D, n (%)*	
	PAL+FUL	PBO+FUL	PAL+FUL	PBO+FUL	PAL+FUL	PBO+FUL
ITT population	347	174	347	174	347	174
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle2 Day1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle3 Day1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle4 Day1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle6 Day1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle8 Day1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle10 Day1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle12 Day1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle14 Day1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EOT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Proportion is calculated using n in the previous row as the denominator, with the exception of EOT where the denominator is the number of patients in the ITT population
EOT=end-of-treatment; HRQoL=health-related quality of life; ITT=intention-to-treat; PAL+FUL=palbociclib plus fulvestrant; PBO+FUL=placebo plus fulvestrant;
Source: adapted from CSR for first data-cut,[2] Table 14.5.1.1.1, Table 14.5.1.2.1 and Table 14.5.2.1

3.5.3 Other PALOMA-3 trial patient reported outcomes

Time to deterioration in the pain and global QoL/health status subscales of QLQ-C30 were estimated from the second data-cut (16 March 2015).[27] "Deterioration was defined as an increase in score of 10 points or greater from baseline" (CS, Table 9, p33). It is unclear if a similar definition of deterioration has been used to define deterioration in pain, i.e., a decrease in score of 10 points or greater from baseline (since for global QoL/health status, lower scores represent lower levels of QoL whereas for the pain scale, higher scores represent higher symptoms severity). However, the ERG considers this may be the case since time to deterioration in global QoL/health status has been defined as a decrease of 10 points or more in the BOLERO-2 trial[52] (see Section 3.5.4 of this ERG report).

In addition, the company highlights in Sections B.2.6.5, B.2.13.3 and B.3.11.6 of the CS that delaying chemotherapy and its associated toxicities is an important aspect of HRQoL which is not captured by instruments such as the EQ-5D questionnaire. Therefore, data from the most recent (i.e. fifth) data-cut (13 April 2018), are presented for time to subsequent chemotherapy (Section B.2.6.5 of the CS).

Of these additional outcomes, only time to deterioration in the pain subscale of QLQ-C30 was a pre-specified outcome. The company states (CS, p32) that estimates of the time to deterioration in the pain subscale were derived using survival analysis methods, although the ERG notes limited information regarding these methods has been provided (Section 3.2.3, Table 9 of this ERG report).

Results for the time to deterioration in the pain and in the global QoL/health status subscale of QLQ-C30 and time to subsequent chemotherapy are reported as medians and the results from the two PALOMA-3 trial arms compared using HRs. The ERG highlights that as with other time to event outcomes, such as PFS and OS, for the HR to be meaningful for any trial results, the PH assumption must hold. It is not reported if the PH assumption had been tested for any of the aforementioned outcomes.

Time to deterioration in the pain and in the global QoL/health status subscales of QLQ-C30 in the PALOMA-3 trial (second data-cut, 16 March 2015)

Median time to deterioration in pain was 8 months (95% CI: 5.6 months to not estimable) in the palbociclib plus fulvestrant arm compared with 2.8 months (95% CI: 2.3 months to 5.4 months) in the placebo plus fulvestrant arm (HR=0.642; 95% CI: 0.487 to 0.846; p<0.001) (CS, p52).

While median time to deterioration in global QoL/health status had not been reached in either arm, it is reported that there was a statistically significantly greater delay in deterioration of global QoL/health status for patients randomised to the palbociclib plus fulvestrant arm compared with those randomised to the placebo plus fulvestrant arm (HR=0.641; 95% CI: 0.451 to 0.910; p=0.0065).

Time to subsequent chemotherapy in the PALOMA-3 trial (fifths data-cut, 13 April 2018)

Treatment with palbociclib plus fulvestrant delayed the time to subsequent chemotherapy by an additional 8.8 months compared with treatment with placebo plus fulvestrant (median delay 17.6 months [95% CI: 15.2 to 19.7] and 8.8 months [95% CI: 7.3to 12.7] respectively). The difference was reported to be statistically significant (HR=0.58; 95% CI: 0.47 to 0.73; p<0.001).

3.5.4 HRQoL in the BOLERO-2 trial

The company has not presented any HRQoL data from patients treated with everolimus plus exemestane. The ERG notes that few HRQoL from the BOLERO-2 trial have been published. However, time to deterioration in global QoL/health status data for patients in this trial treated with everolimus plus exemestane are available.[52] In the BOLERO-2 trial, time to deterioration in global QoL/health status was defined as a 5% decrease in the score relative to baseline. In a sensitivity analysis, it was defined as a 10 point decrease in global QoL/health status compared with baseline. The reported results[52] were as follows:

- Primary analysis (5% decrease): The median time to deterioration was 8.3 months (95% CI: 7.0 to 9.7 months) in the everolimus plus exemestane arm and 5.8 months

(95% CI: 4.2 to 7.2 months) in the exemestane arm (HR=0.74; 95%CI 0.58 to 0.95; p=0084 by the log-rank test).

- Sensitivity analysis (minimum 10 points decrease): The median time to deterioration was 11.7 months (95% CI: 9.7 to 13.3 months) in the everolimus plus exemestane arm and 8.4 months (95% CI: 6.6 to 12.5 months) in the exemestane arm (HR=0.8; 95% CI: 0.61 to 1.06; p=0.1017 by the log-rank test).

It is not reported if the PH assumption had been tested for any of the outcomes.

3.6 Safety

3.6.1 Adverse events reported in the PALOMA-3 trial

A total of 345 patients in the palbociclib plus fulvestrant arm and 172 patients in the placebo plus fulvestrant arm of the PALOMA-3 trial received at least one dose of the assigned intervention (safety population). All AE data reported in the CS from the PALOMA-3 trial were taken from the 31 July 2015 data-cut. The ERG notes that some AE data from the most recent-data cut (12 April 2018) have been published in a supplementary appendix to the Turner et al 2018 paper.[35] However, these data are for all treatment-emergent AEs and not specifically treatment-related AEs. Furthermore, no data are presented by Turner et al 2018[35] for serious adverse events (SAEs), treatment discontinuations, dose reductions or deaths arising from AEs. Therefore, in this section, the ERG has reported data from the CS.

Treatment-related adverse events

The company has provided a list of the treatment-related AEs, experienced by ≥5% of patients that were considered to be related to study treatment (CS, Table 19). [redacted] patients who received palbociclib plus fulvestrant experienced a treatment-related AE ([redacted]) than those who received placebo plus fulvestrant ([redacted]). Compared with treatment with placebo plus fulvestrant, Grade 3 treatment-related AEs were [redacted] for patients treated with palbociclib plus fulvestrant ([redacted] versus [redacted]), as were Grade 4 treatment-related AEs ([redacted] versus [redacted]).

Neutropenia was the most frequently reported Grade ≥3 treatment-related AE experienced by patients in the palbociclib plus fulvestrant arm ([redacted] Grade 3 and [redacted] Grade 4). The company highlights that neutropenia occurred less often with increasing number of treatment cycles (CS, p71). Numbers of patients who experienced neutropenia of maximum severity Grade 3 or Grade 4 in all cycles is provided in Table 22 in the CS. In the palbociclib plus fulvestrant arm, only [redacted] of patients with Grade 3 neutropenia and [redacted] of patients with Grade 4 neutropenia and, in the placebo plus fulvestrant arm, only [redacted] patients with Grade 3

neutropenia, developed febrile neutropenia and there were no cases of neutropenic sepsis or infection.

Other haematological AEs experienced by patients in the palbociclib plus fulvestrant arm included decreased neutrophil count ([redacted] Grade 3 and [redacted] Grade 4), leukopenia ([redacted] Grade 3 and [redacted] Grade 4), decreased white blood cell count ([redacted] Grade 3 and [redacted] Grade 4) and anaemia ([redacted] Grade 3 and [redacted] Grade 4). Non-haematological AEs were predominantly of Grade 1 and Grade 2 severity.

The most common ([redacted]) Grade ≥3 treatment-related AEs experienced by [redacted] patients in the placebo plus fulvestrant arm were fatigue ([redacted]) and anaemia ([redacted]). No patients in the placebo plus fulvestrant arm experienced Grade ≥3 neutropenia.

Serious adverse events

As of 31 July 2015, the proportions of patients experiencing a SAE were [redacted]: [redacted] in the palbociclib plus fulvestrant arm and [redacted] in the placebo plus fulvestrant arm (CS, Appendix R3, Table 156). [redacted] QTc interval prolongation is highlighted by the company (CS, p71) as a SAE experienced by [redacted] in the palbociclib plus fulvestrant arm. It is reported that [redacted] palbociclib therapy was temporarily discontinued and subsequently restarted at a reduced dose of 100mg.

Treatment discontinuation and dose reductions due to adverse events

The frequency of treatment-related AEs leading to temporary treatment discontinuation in the palbociclib plus fulvestrant arm ([redacted]) was [redacted] than in the placebo plus fulvestrant arm ([redacted]). Neutropenia was the most common reason for temporary discontinuation in the palbociclib plus fulvestrant arm ([redacted]), followed by decreased neutrophil count ([redacted]) and decreased white cell count ([redacted]). Of patients who had experienced treatment-related AEs associated with temporary discontinuation from treatment with palbociclib plus fulvestrant, [redacted] subsequently permanently discontinued treatment ([redacted] of all patients treated with palbociclib plus fulvestrant). Only [redacted] of patients in the placebo plus fulvestrant arm experienced permanent discontinuation from treatment due to AEs.

Dose reductions and regimen changes were reported in the CS; [redacted] of patients had their palbociclib dose reduced and [redacted] of patients had their palbociclib dose regimen changed (from 3 weeks on/1 week off to [redacted].

Treatment-related hospitalisations

During the clarification process (response to question A7iii), the company presented data showing that, in the PALOMA-3 trial, [redacted]

Treatment-related deaths

There were [redacted] treatment-related deaths [redacted] of the PALOMA-3 trial.

3.6.2 Adverse events reported for everolimus plus exemestane

The CS did not include specific details about the AEs experienced by patients receiving everolimus plus exemestane. Rather, the safety profile of everolimus was informed by pooled data from 2,672 patients across ten clinical studies (CS, Section B.2.10.8.2, p72). It is unclear from the CS which studies were included, but the ERG notes that in the European Public Assessment Report for everolimus,[15] pooled data are presented for 2,879 patients in 11 clinical studies (five double-blind, placebo controlled phase III RCTs, including BOLERO-2, and six open-label phase I and phase II studies), related to all the approved indications for everolimus. The additional 207 patients referred to in the EPAR but not referred to in the CS appear to be from the BOLERO-6 trial[53] in which patients with advanced HR-positive/HER2-negative breast cancer were randomised to everolimus plus exemestane (n=104), everolimus alone (n=103) or capecitabine (n=102). Pooled data referred to in the CS and EPAR therefore include RCT data for everolimus monotherapy for neuroendocrine tumours of pancreatic origin (RADIANT-3,[54] n=207) neuroendocrine tumours of gastrointestinal or lung origin (RADIANT-4,[55] n=205) and renal cell carcinoma (RECORD-1,[56] n=278). No information is provided in the EPAR regarding the other six studies (n=1497).

Given the pooled data in the CS only includes a minority of patients randomised to treatment with HR-positive/HER2-negative advanced breast cancer treated with everolimus plus exemestane (n=485), the ERG highlights the following results from analyses of safety data from patients in the BOLERO-2 trial treated with everolimus plus exemestane (most recent data-cut, 3 October 2013; 39.3 months' median study follow up):[45]

- Just over half (55.2%) of all patients experienced Grade ≥3 AEs; the most common AEs reported from an earlier data-cut (15 December 2011; 17.7 months' median study follow up)[44] were stomatitis (8%), increased gamma-glutamyl transferase (7%) and anaemia (7%); other Grade ≥3 AEs experienced by approximately 5% of patients were dyspnoea, fatigue and hyperglycaemia

- Approximately three-quarters of all Grade ≥3 AEs were considered to be treatment-related (40.9% of all patients in the everolimus plus exemestane trial arm)
- 32.6% of patients experienced treatment-emergent SAEs
- Approximately two-fifths of all SAEs were considered to be treatment-related (13.1% of all patients in the everolimus plus exemestane trial arm)
- 29.0% of patients had discontinued treatment because of AEs; from an earlier data-cut (15 December 2011; 17.7 months' median study follow up),[44] the two most common AEs leading to treatment discontinuation were reported to be pneumonitis (5.6%) and stomatitis (2.7%)
- AE-related deaths were reported to be 1.7%.

3.6.3 Safety summary

While treatment-related Grade ≥3 AEs and treatment-related SAEs were [redacted] for patients in the placebo plus fulvestrant arm of the PALOMA-3 trial ([redacted] and [redacted], respectively) than in the palbociclib plus fulvestrant arm ([redacted] and [redacted], respectively), treatment discontinuation rates were [redacted] ([redacted] in the placebo plus fulvestrant arm, [redacted] in the palbociclib plus fulvestrant arm). The ERG further notes that the AE data for the placebo plus fulvestrant arm of the PALOMA-3 trial are consistent with data reported in other RCTs of fulvestrant (CONFIRM[46,47] EFECT[23,48] and SOFEA[49]).

The ERG notes that the proportion of treatment-related Grade ≥3 AEs was [redacted] in the palbociclib plus fulvestrant arm of the PALOMA-3 trial ([redacted]) than in the everolimus plus exemestane arm of the BOLERO-2 trial (40.9%).[45] However, the proportion of patients with treatment-related SAEs in the palbociclib plus fulvestrant arm of the PALOMA-3 trial ([redacted]) was [redacted] to the proportion of patients with treatment-related SAEs in the everolimus plus exemestane arm of the BOLERO-2 trial (13.1%).[45] Furthermore, treatment discontinuation from the palbociclib plus fulvestrant arm of the PALOMA-3 trial was [redacted] ([redacted]) than treatment discontinuation from the everolimus plus exemestane arm of the BOLERO-2 trial (29.0%).[45]

The company concluded that treatment with palbociclib plus fulvestrant was generally well-tolerated and resulted in very few permanent treatment discontinuations. The primary toxicity of asymptomatic neutropenia was generally manageable with dose modification, interruption or cycle delay, which enabled patients to remain on treatment without affecting treatment duration. Discontinuation due to toxicity was uncommon. In addition, neutropenia associated

with palbociclib plus fulvestrant appears to be reversible and manageable and results in few permanent treatment discontinuations.

3.7 Conclusions of the clinical effectiveness section

The company's decision problem is appropriate for addressing the final scope issued by NICE.[20] The company states that, of all the comparators listed in the final scope,[20] everolimus plus exemestane is the most commonly used in clinical practice and is therefore the most appropriate comparator. This statement is supported by the conclusions reached in recent and ongoing appraisals by NICE Appraisal Committees[12,13] and confirmed by clinical advice to the ERG.

Overall, the ERG considers the methods used to conduct the company's systematic review of clinical effectiveness evidence to be of a good standard.

The only RCT of palbociclib plus fulvestrant identified by the company's systematic review is the PALOMA-3 trial. The comparator in the PALOMA-3 trial was placebo plus fulvestrant (not everolimus plus exemestane). The PALOMA-3 trial is well-designed and is a good quality trial with an appropriate and pre-defined statistical approach to the analysis of efficacy, patient reported outcomes and safety. The patient population also appears to be broadly comparable to the population likely to be treated in clinical practice in England and Wales, meaning the trial results should be generalisable to patients in the NHS.

Results from the PALOMA-3 trial demonstrated that the absolute difference in median OS and PFS between patients who received palbociclib plus fulvestrant and patients who received placebo plus fulvestrant was 6.9 months and 6.6 months, respectively. The difference in OS between trial arms was not statistically significant. Furthermore, interpreting the statistical significance of the PFS difference is challenging; the company highlighted that the PH assumption was violated and thus the HR estimated from a Cox PH model has no meaningful interpretation.

In the absence of direct clinical evidence, the company carried out NMAs to indirectly estimate PFS and OS for the comparison of palbociclib plus fulvestrant versus everolimus plus exemestane. To conduct the analyses, each of the NMAs included five trials, including PALOMA-3 and BOLERO-2[44,45] (the only trial to study everolimus plus exemestane).

Due to the violation of the PH assumption for PFS in two trials and for OS in two trials, the company carried out FP NMAs as this method does not require the assumption of PH to hold. The ERG considers that there is considerable variability in terms of the specific outputs of the FP models, including some numerically implausible results and that there is, potentially, a large amount of uncertainty around the results (namely the estimated survival and HR functions) for both PFS and OS. The ERG was, therefore, unable to select a suitable FP model with any degree of confidence to inform the comparison of palbociclib plus fulvestrant versus everolimus plus exemestane.

Patient-reported outcomes of HRQoL from the PALOMA-3 trial suggested that HRQoL may be better for patients treated with palbociclib plus fulvestrant than for patients treated with placebo plus fulvestrant. No comparisons of HRQoL between patients who receive palbociclib plus fulvestrant and patients who receive other comparators have been carried out by the company. However, to the ERG's knowledge, the only HRQoL data reported for everolimus plus exemestane from the BOLERO-2 trial[52] describe time to deterioration in global QoL.[52]

Data from the PALOMA-3 trial showed treatment with palbociclib plus fulvestrant resulted in proportionately more treatment-related Grade ≥3 AEs than placebo plus fulvestrant; however, the proportions of SAEs and treatment withdrawals between arms were similar. No treatment-related deaths from AEs were reported in either arm of the trial. The most frequent treatment-related Grade ≥3 AEs reported by patients treated with palbociclib plus fulvestrant were haematological AEs, in particular, neutropenia ([redacted]); febrile neutropenia, however, was uncommon ([redacted]). No formal comparison of AEs between palbociclib plus fulvestrant and everolimus plus exemestane was presented by the company. The ERG notes, from a simple naïve comparison, that the proportion of treatment-related Grade ≥3 AEs was [redacted] in the palbociclib plus fulvestrant arm of the PALOMA-3 trial ([redacted]) than in the everolimus plus exemestane arm of the BOLERO-2 trial[45] (40.9%). On the other hand, treatment discontinuation in the palbociclib plus fulvestrant arm in the PALOMA-3 trial was [redacted] ([redacted]) than treatment discontinuation in the everolimus plus exemestane arm in the BOLERO-2 trial (29.0%). Overall, therefore, treatment with palbociclib plus fulvestrant was considered to be generally well-tolerated.

4 COST EFFECTIVENESS

4.1 Critique of the methods of review(s)

Full details of the company's process and methods used to identify and select the cost effectiveness evidence relevant to the technology being appraised are presented in Appendix G of the CS. The ERG considered whether the review was conducted in accordance with key features of the systematic review process, as summarised in Table 16.

Table 16 ERG appraisal of systematic review methods

Review process	ERG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	See CS, Appendix G, Table 98
Were appropriate sources searched?	Yes	Sources included MEDLINE, Embase, the Cochrane Library (specifically the Health Technology Assessment [HTA] database and NHS Economic Evaluation Database) and EconLit. The company also searched conference abstracts and HTA websites.
Was the timespan of the searches appropriate?	Yes	The search was originally run on 20 January 2016 and updated on 5 February 2018
Were appropriate search terms used?	Yes	-
Were the eligibility criteria appropriate to the decision problem?	Yes	-
Was study selection applied by two or more reviewers independently?	Yes	-
Was data extracted by two or more reviewers independently?	N/A	No relevant studies identified
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	N/A	No relevant studies identified
Was the quality assessment conducted by two or more reviewers independently?	N/A	No relevant studies identified
Were attempts to synthesise evidence appropriate?	N/A	No relevant studies identified

RCT=randomised controlled trial

The ERG considers the methods used to conduct the company's systematic review of cost effectiveness evidence to be of a good standard. Details provided in Appendix G of the CS suggest that the databases were last accessed in February 2018 and it was not stated whether the search has been updated. The company did not identify any relevant cost effectiveness studies as a result of the systematic review.

Overall, the ERG is satisfied that the company has not missed any relevant economic studies.

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

4.2.1 NICE Reference Case checklist and Drummond checklist

Table 17 NICE Reference Case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	None
Perspective on costs	NHS and PSS	Only NHS costs considered
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	None
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	None
Synthesis of evidence on health effects	Based on systematic review	The company carried out NMAs to indirectly estimate PFS and OS in the absence of direct clinical effectiveness data comparing PAL+FUL versus EVE+EXE. The ERG does not consider the clinical effectiveness evidence generated by the company NMAs to be appropriate for use in the economic model
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults	None
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	HRQoL data used in the economic model were reported by patients in the PALOMA-3 trial. No HRQoL data were available for patients treated with EVE+EXE, so the company used HRQoL from the PLA+FUL arm of the PALOMA-3 trial as a proxy
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Utility values for the post-progression state were derived from an algorithm based on a study[57] of general population preferences of health states of people with metastatic breast cancer described by vignettes, rather than patient derived health states valued using general population preference
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	None
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	(i) Costs associated with first-line treatment with PAL+FUL are based on adjusted TTD estimates from the PALOMA-3 trial and costs associated with first-line treatment with EVE+EXE were based on estimates of PFS, which the ERG considers to be inconsistent (ii) Wastage costs included for oral drugs are not well justified by the company and the ERG considers them inappropriate (iii) The company has underestimated resource use associated with oncologist appointments. (iv) The ERG considers resource use in the post-progression state to be uncertain due to overestimation of the time patients spend in best supportive care.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	None

EQ-5D= Five-dimension EuroQol (standardised instrument for use as a measure of health outcome); HRQoL=health-related quality of life; OS=overall survival; PFS=progression-free survival; PSS=Personal Social Services; QALYs=quality-adjusted life years; TTD=time-to-treatment discontinuation

4.2.2 Summary of the company's economic evaluation

Model structure (CS, Section B.3.2.2)

The company developed a *de novo* lifetime (40 years) partitioned survival model in MS Excel to compare treatment with palbociclib plus fulvestrant versus treatment with everolimus plus exemestane for HR-positive/HER2-negative advanced breast cancer that has become resistant to previous endocrine therapy.

The model extends the standard three-state partitioned-survival structure (pre-progression, post-progression and death) by subdividing the post-progression state into subsequent treatment lines (first subsequent treatment, second subsequent treatment and best supportive care [BSC]). All patients enter the model in the pre-progression state and can either stay in this state or move to a worse health state in each cycle. Patients who enter the post-progression state either receive six cycles of first active subsequent therapy (75%) or move immediately to BSC (25%). After six cycles of a first active subsequent therapy, patients either move to a second subsequent therapy (75%) or to BSC (25%). After six cycles of a second subsequent therapy, all patients move to BSC. The model schematic is shown in Figure 2.

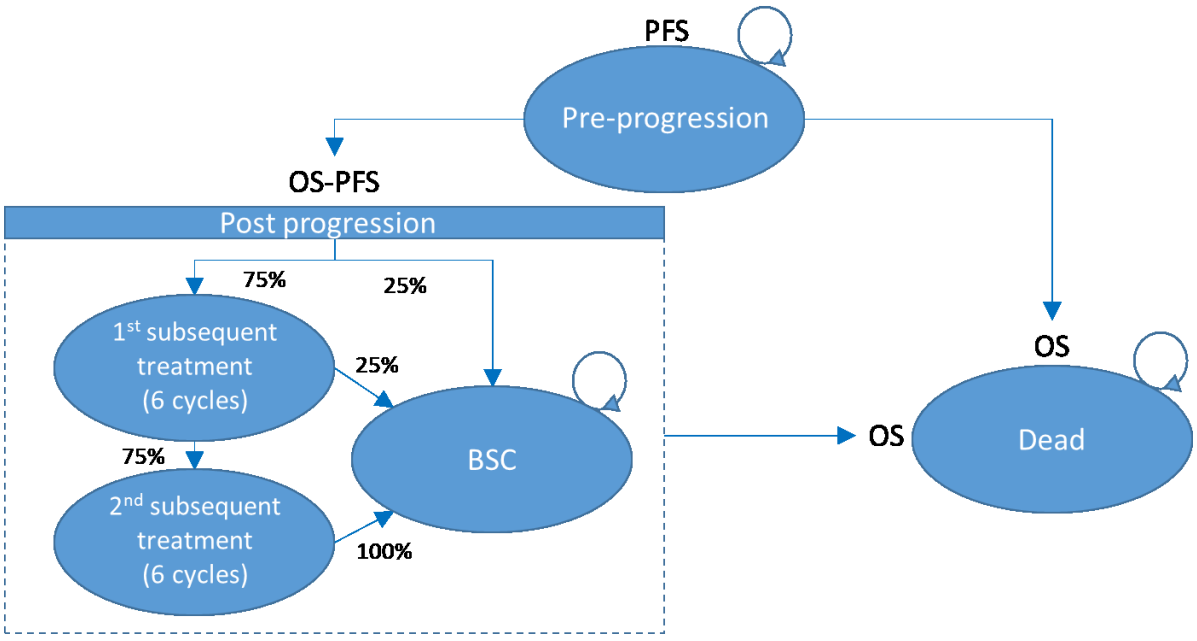


Figure 2 Model schematic

Source: Adapted from CS, Figure 18
BSC=best supportive care; OS=overall survival; PFS=pre-progression survival

The model is built from the perspective of the NHS and Personal Social Services (PSS). The model cycle length is 28 days and includes a half-cycle correction. Costs and benefits are discounted at 3.5%.

Clinical parameters (CS, Section B.3.3.1 to B.3.3.3)

Progression-free survival (CS, Section B.3.3.1)

Company base case PFS estimates for both the intervention and comparator were calculated using the results of the company's FP NMA (Section 3.4 of this report). Second-order FP model parameters from the PFS FP NMA were used to create PFS curves over the model time horizon for treatment with palbociclib plus fulvestrant and with everolimus plus exemestane. These curves were used directly in the model to estimate PFS transition probabilities over time. Mean PFS in the company base case is [redacted] months for treatment with palbociclib plus fulvestrant and [redacted] months with everolimus plus exemestane (gain=[redacted] months). The PFS curves used in the base case analysis are shown in Figure 17 of the CS.

Overall survival (CS, Section B.3.3.2)

Company base case OS estimates for treatment with palbociclib plus fulvestrant were calculated using a Weibull curve fitted to the OS data from the PALOMA-3 trial. Company base case OS for treatment with everolimus plus exemestane was estimated by applying the HR (HR=[redacted]; 95% CI [redacted] to [redacted]) generated by company's Bayesian NMA (Section 3.4 of this report) to the OS estimates for treatment with palbociclib plus fulvestrant. Mean OS in the company base case is [redacted] months for treatment with palbociclib plus fulvestrant and [redacted] months with everolimus plus exemestane (gain=[redacted]months). The OS curves used in the base case analysis are shown in Figure 20 of the CS.

Time to treatment discontinuation (CS, Section B.3.3.3)

Company base case time to treatment discontinuation (TTD) for treatment with palbociclib plus fulvestrant was estimated by applying a HR to PFS. To estimate the HR, the company first appended exponential curves to the end of the PFS and TTD K-M data from the PALOMA-3 trial, then calculated mean PFS and TTD using these models. The ratio of mean TTD to mean PFS using the K-M plus exponential models ([redacted]) was then applied as a HR to the model base case PFS. Company base case TTD for treatment with everolimus plus exemestane was set equal to PFS for treatment with everolimus plus exemestane. Mean TTD in the company base case is [redacted] months for treatment with palbociclib plus fulvestrant and [redacted] months with everolimus plus exemestane (difference=[redacted]months). The OS curves used in the base case analysis are shown in Figure 23 of the CS.

Health-related quality of life (CS, Section B.3.4)

Pre-progression utility values for treatment with palbociclib plus fulvestrant and treatment with placebo plus fulvestrant were derived from EQ-5D data collected during the PALOMA-3 trial from patients whilst on treatment. Pre-progression utility values for treatment with fulvestrant in the PALOMA-3 trial were used as a proxy for pre-progression utility values for treatment with everolimus plus exemestane. Index scores for the pre-progression health state were calculated using a repeated measures mixed-effects regression model.

Post-progression utility values were calculated using an algorithm published by Lloyd et al 2006.[57] Utility values used in the base case model are the same for each post-progression state (first subsequent line, second subsequent line and BSC).

Age-related utility decrements are applied in each cycle of the model. These decrements are calculated using the model described by Ara and Brazier 2010.[58] Baseline utility values, before the application of age-related decrements, are shown in Table 18.

Table 18 Baseline utility values used in the company base case model

Health state	Palbociclib plus fulvestrant	Everolimus plus exemestane	Source
	Mean value (95% CI)	Mean value (95% CI)	
Pre-progression	0.74 (0.72 to 0.76)	0.69 (0.67 to 0.72)	PALOMA-3
Post-progression	0.56 (0.50 to 0.60)		Lloyd et al 2006[57]

Source: CS, Table 29
CI=confidence interval

First-line drug acquisition, administration and monitoring (CS, Section B.3.5.2)

The company base case analysis includes the PAS price for palbociclib and list prices for fulvestrant, everolimus plus exemestane. Everolimus is also subject to a confidential PAS, which is not used in the company analysis. First-line drug costs are shown in Table 30 of the CS.

The company has assumed no wastage costs for palbociclib plus fulvestrant, but includes wastage costs for everolimus, exemestane and tamoxifen. Wastage for everolimus plus exemestane is a function of the 28-day model cycle and 30-tablet pack sizes available for each of the drugs. For example, the company has assumed two tablets are wasted each model cycle for everolimus plus exemestane, which amounts to wastage costs of £178.20 and £0.25 per model cycle respectively.

Monitoring costs are included for palbociclib and everolimus. No monitoring costs are included for fulvestrant and exemestane. Monitoring costs are shown in Table 31 and Table 32 of the CS.

The company does not include administration costs for palbociclib, everolimus or exemestane, as they are oral therapies self-administered by the patient. Administration costs for fulvestrant were weighted based on the proportion of patients expected to receive a dose in a primary care (33.3%) or outpatient (66.7%) setting. This approach was also used in NICE TA503 (Fulvestrant for untreated locally advanced or metastatic oestrogen-receptor positive breast cancer).[59] Administration costs for fulvestrant are shown in Table 33 of the CS.

Health-state resource use and costs (CS, Section B.3.5.3)

Resource use in the company base case is dependent on health state and subsequent treatment line. Health-state costs increase as patients move through the model predominantly due to the company assumption that worse health states would incur more frequent GP and clinical nurse specialist visits. A terminal care cost is applied on death to account for extra resource use in the final 2 weeks of life (Table 19). Costs for the terminal care phase were calculated using data from NICE CG81 Package 3, uplifted from 2006/07 to 2017/18 values.[4] Detailed health-state resource use and unit costs are shown in Table 34, Table 35 and Table 36 of the CS.

Table 19 Company base case health-state costs per cycle and terminal care costs

	Cost per cycle
Pre-progression	£282.26
Post-progression: 1st subsequent therapy	£493.89
Post-progression: 2nd subsequent therapy	£721.46
Post-progression: BSC	£1,284.56
	One-off cost
Terminal care	£4519.57

BSC=best supportive care
Source: Company model

Adverse event resource use and costs (CS, Section B.3.5.4)

Costs for AEs are applied as a one-off cost in the first cycle of the model. Incidence of any Grade ≥3 event in the palbociclib plus fulvestrant arm of the PALOMA-3 trial was used to estimate the proportion of patients who would experience an AE following treatment with palbociclib plus fulvestrant ([redacted]). Costs for all Grade 3+ events were assumed to be equal to the cost of the most frequent Grade 3+ AE in the palbociclib plus fulvestrant arm of the PALOMA-3 trial (neutropenia). The cost of treating neutropenia was estimated as the cost of one oncologist visit using NHS Reference Costs.[60] Although [redacted] patients in the palbociclib arm of the PALOMA-3 trial developed febrile neutropenia, [redacted].[2]

Incidence of the most common Grade 3+ event in the everolimus plus exemestane arm of the BOLERO-2 trial (stomatitis, [redacted]) was used to estimate the proportion of patients who would experience any Grade ≥3 AE following treatment with everolimus plus exemestane. Costs for all Grade 3+ events following treatment with everolimus plus exemestane were assumed to be equal to the cost of treating Grade 3+ stomatitis. The cost of treating Grade 3+ stomatitis was assumed to be equal to the cost of a 3 day hospital stay using NHS Reference Costs.[60] Adverse event resource use and unit costs are shown in Table 37 of the CS.

Subsequent treatment costs (CS, Section B.3.5.5)

The company model includes two active lines of subsequent therapy following progression. Subsequent treatment costs were calculated using a basket of therapies. The type and distribution of therapies included in the basket were taken from a scenario provided by the ERG in NICE TA563 (Abemaciclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer).[61] The proportions of patients treated with each therapy in the 'basket' differs according to whether patients had initially received treatment with palbociclib plus fulvestrant or everolimus plus exemestane. The distribution of subsequent therapies by initial treatment is presented in Table 39 of the CS. The subsequent therapies included in the model do not match those received in the PALOMA-3 trial (company clarification response A7ii); the ERG notes that in some instances, the proportion of each subsequent therapy received in the PALOMA-3 trial likely does not match clinical practice, for example, no patients in the trial received tamoxifen in subsequent lines. The company estimated the mean duration of each subsequent treatment to be six cycles based on data from a retrospective review of UK medical records carried out in 2015.[62] Mean time spent on active subsequent therapy in the company model is [redacted] months for treatment with palbociclib plus fulvestrant and [redacted] months for treatment with everolimus plus exemestane ([redacted] and [redacted] respectively of time spent in the post-progression state).

5 SUMMARY OF THE RESULTS OF THE COMPANY'S ECONOMIC EVALUATION

Base case analysis (CS, Section B.3.7)

The results of the company base case analysis indicate that treatment with palbociclib plus fulvestrant costs less and generates more benefits than everolimus plus exemestane when using the PAS price for palbociclib and list price for fulvestrant, everolimus plus exemestane (Table 20). Clinical outcomes and disaggregated results of the model are given in Appendix J of the CS.

Table 20 Results of company base case economic analysis (PAS price for palbociclib, list price for all other drugs)

Technologies	Total			Incremental			ICER versus baseline (£/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	
EVE+EXE	[redacted]	[redacted]	[redacted]				-
PAL+FUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

LYG=life years gained; QALY=quality adjusted life year; ICER=incremental cost effectiveness ratio
Source: CS, Table 40

Probability sensitivity analysis (CS, Section B.3.8.1)

The company performed a probabilistic sensitivity analysis (PSA) to explore the effect of uncertainty in key model parameters. The results of the company PSA indicate that there is an approximately [redacted] probability of palbociclib plus fulvestrant being cost effective in comparison to everolimus plus exemestane at a willingness to pay threshold of £30,000 per QALY gained when using the PAS price for palbociclib and list prices for all other drugs. The cost effectiveness acceptability curve for treatment with palbociclib plus fulvestrant versus everolimus plus exemestane using the PAS price for palbociclib and list prices for all other drugs is shown in Figure 3.

Figure 3 Cost effectiveness acceptability curve of treatment with palbociclib plus fulvestrant versus everolimus plus exemestane using the PAS price for palbociclib and list prices for all other drugs

Source: Company model

Deterministic sensitivity analysis (CS, Section B.3.8.2)

The company conducted one-way sensitivity analyses (OWSA) for key variables in the model. The results of the company's OWSA indicate that incremental costs are most affected by varying administration costs, health-care professional resource use and health-care professional unit costs. Incremental QALYs are most affected by the utility value for the progressed disease state and the utility value for the pre-progression state. The company did not present ICERs per QALY gained from the OWSA.

Model validation and face validity check

The company states clinical outcomes from the model were compared against clinical trial evidence to validate results. It also states that input from clinical experts was sought to estimate and validate resource use, AE management and patient monitoring inputs. Additionally, internal quality control was undertaken by the model developers on behalf of the company.

6 ERG ADDITIONAL ANALYSES

6.1 Key issues in the company model

The company provided a model built in MS Excel. The ERG's summary of the structure of the company model and the data used to populate it are provided in Section 4.2 of this ERG report. The ERG considers that the submitted model is generally well built, and produces the ICERs per QALY gained that are presented in the CS.

The ERG is concerned about the reliability of the company's estimates of the relative clinical effectiveness of treatment with palbociclib plus fulvestrant versus everolimus plus exemestane. These results have been estimated using results from the company's NMAs. Details about the ERG's concerns relating to the company's NMAs are provided in Section 3.4 of this report. The ERG has also identified the following areas of uncertainty:

1. Amending subsequent treatment assumptions
2. Removing assumptions relating to daily oral drug wastage
3. Amending resource use to increase frequency of appointments with an oncologist.

In addition, the ERG has identified some minor issues relating to other aspects of the company model. Resolution of these issues does not have a large impact on the size of the ICER per QALY gained and therefore only a description of these issues has been provided (see Appendix 3, Section 9.3).

The company base case cost effectiveness results have been generated using the PAS price for palbociclib and the list prices for fulvestrant, everolimus plus exemestane. All ERG scenario results presented in this report have been generated using these prices. The company's base case results, and results from the ERG's scenarios, generated using PAS prices for palbociclib and everolimus are provided in Confidential Appendix 1.

6.2 Estimating clinical effectiveness in the company model

6.2.1 Company approach to estimating clinical effectiveness

Overall survival

The ERG highlights that the PH assumption is violated in at least one of the trials included in the company's standard Bayesian NMA for OS; the ERG therefore considers that the HR produced is unreliable. At clarification (question A5), the company presented results from a NMA for OS using FP methods. The ERG notes that [redacted]

[redacted] Therefore, the ERG does not consider it possible to confidently choose a single set of results from the range of OS FP NMA results presented by the company.

Progression-free survival

The company has modelled PFS for patients receiving everolimus plus exemestane using results from the PFS FP NMA. The ERG does not consider it possible to confidently choose a single set of results from the range of PFS FP NMA results presented in the CS. [redacted]

Time to treatment discontinuation

In the company model, TTD for patients treated with palbociclib plus fulvestrant is estimated using a ratio of TTD to PFS from the PALOMA-3 trial. The company states that this is due to the extrapolation of TTD not being in line with their extrapolation of PFS data. The ERG considers the company approach to adjusting TTD to be arbitrary and therefore does not consider that this approach generates a reliable estimate of the time that patients receiving palbociclib plus fulvestrant spend on treatment. This approach means that the number of patients receiving the treatment is always lower than the number of patients who are progression free.

In the absence of TTD data for everolimus plus exemestane, the company has assumed that TTD is equal to the PFS estimated using the results of the company's PFS FP NMA. The ERG considers that the company approach of using TTD data to represent the experience of patients treated with palbociclib plus fulvestrant and using PFS data to represent time on treatment for patients receiving everolimus plus exemestane is an unfair comparison.

6.2.2 ERG approach to measuring clinical effectiveness

The company states (CS, p73) that: "… PFS and OS [are higher] for everolimus plus exemestane than fulvestrant". The ERG asked the company during the clarification process to provide evidence to substantiate their claim (CS, p73) that treatment with everolimus plus exemestane is clinically superior to fulvestrant monotherapy (question A6).

The company made the case in their clarification response (question A6) that, in terms of PFS, everolimus plus exemestane is clinically superior to fulvestrant monotherapy; this assertion is

based on the results of a published NMA (Bachelot et al. 2014).[63] However, during the clarification period, the company conducted PH testing (question A3) which demonstrated a violation of the PH assumption for PFS [redacted] (see Section 3.4 of this report for more details). The ERG therefore considers that the results of the published NMA[63] cannot be used to demonstrate that treatment with palbociclib plus fulvestrant delivers superior PFS results compared with treatment with everolimus plus exemestane.

However, clinical advice to the ERG is that treatment with everolimus plus exemestane is generally considered to be more effective than treatment with fulvestrant. The ERG has therefore generated alternative cost effectiveness results using PFS data from the placebo plus fulvestrant arm of the PALOMA-3 trial as a proxy for the experience of patients treated with everolimus plus exemestane. The ERG recognises that this is a conservative approach.

In terms of OS, the company did not provide any evidence to support its claim that everolimus plus exemestane is clinically superior to fulvestrant monotherapy. Clinical advice to the ERG is that treatment with everolimus plus exemestane is generally considered to be more effective than treatment with fulvestrant and results from the PALOMA-3 trial show that there is no statistically significant difference in terms of OS between treatment with palbociclib plus fulvestrant versus placebo plus fulvestrant. The ERG has therefore pooled the data from both arms of the PALOMA-3 trial (5th data cut) and used this pooled data set as the basis for modelling OS for both patients treated with palbociclib plus fulvestrant and for patients treated with everolimus plus exemestane.

The implications of the ERG's approach are that (i) PFS associated with treatment with everolimus plus exemestane is [redacted] than treatment with placebo plus fulvestrant and (ii) OS associated with treatment with everolimus plus exemestane is [redacted] than treatment with placebo plus fulvestrant. In this instance, given that there is no statistically significant difference in OS between the two arms of the PALOMA-3 trial, the implication is that treatment with everolimus plus exemestane is [redacted] than treatment with palbociclib plus fulvestrant.

The ERG has used TTD data from the palbociclib plus fulvestrant and placebo plus fulvestrant arms of the PALOMA-3 trial to model TTD for patients receiving palbociclib plus fulvestrant and everolimus plus exemestane respectively (in the absence of TTD data for everolimus plus exemestane). The ERG acknowledges that this may not appropriately represent TTD for patients receiving everolimus plus exemestane since substantially more patients discontinue treatment with everolimus plus exemestane than fulvestrant monotherapy due to AEs (Section 3.6).

ERG revised modelling of OS

The ERG has used pooled PALOMA-3 trial OS data from the 5th data cut directly in the model up until 40 months. The ERG prefers to use K-M data from trials directly in the model, when available, rather than only using a parametric function as the K-M data represent real patient experience. Appraisal of the cumulative hazard plot for pooled OS data from the PALOMA-3 trial indicates that a constant hazard trend (a straight line) is apparent from about [redacted] months (Figure 4).This indicates that it is appropriate to extrapolate available data using an exponential function. The ERG, therefore, appended an exponential projection to the pooled OS K-M data. Using this approach, the mean OS for patients, irrespective of treatment, is [redacted] months. The ERG's revised OS survival curves are presented in Figure 5 alongside those used to generate the company's base case results.

K-M=Kaplan-Meier; OS=overall survival

Figure 4 ERG pooled overall survival cumulative hazard plot

Figure 5 Company and ERG modelled OS survival curves

The ERG's exponential extrapolation extends mean OS for both treatment arms, thus resulting in higher costs and QALYs for both arms. The pooled OS data suggest better survival than the company base case representation for patients treated with everolimus plus exemestane; thus, the magnitude of change in costs and QALYs are greater in this arm than for patients treated with palbociclib plus fulvestrant.

Compared with the company's base case results, assuming OS is equal for palbociclib plus fulvestrant and everolimus plus exemestane leads to a ( ) decrease in incremental QALYs (and a decrease in incremental costs of meaning that palbociclib plus fulvestrant remains dominant over everolimus plus exemestane.

ERG revised modelling of progression-free survival

The ERG represented PFS for patients treated with palbociclib plus fulvestrant using PFS K-M data from the 4th data cut of the PALOMA-3 trial directly until months and then appended an exponential tail. Similarly, when modelling PFS for patients treated with everolimus plus exemestane, the ERG used the PALOMA-3 trial placebo plus fulvestrant data for months and then appended an exponential tail. The ERG considered that it was appropriate to fit exponential tails as examination of the cumulative hazard plot for PFS from the PALOMA-3 trial indicates that a constant hazard trend (a straight line) is apparent from about months for the palbociclib plus fulvestrant arm and from months for the placebo plus fulvestrant arm

(Figure 6). The ERG's revised PFS survival curves are presented, alongside those used to generate the company's base case results, in Figure 7.

KM Kaplan-Meier; PAL plus FUL=palbociclib+fulvestrant; PFS=progression-free survival; PLA+FUL=placebo plus fulvestrant;

Figure 6 Progression-free survival cumulative hazard plot

EVE+ EXE=everolimus plus exemestane; PAL+ FUL=palbociclib plus fulvestrant

Figure 7 Company and ERG modelled PFS

Using the ERG's approach to modelling PFS generated an estimated mean duration in the progression-free health state of [redacted] months for patients treated with palbociclib plus fulvestrant and a mean of [redacted] months for patients treated with everolimus plus exemestane.

Compared with the company base case, this approach leads to a ([redacted]) increase in incremental QALYs ([redacted] and an increase in incremental costs of [redacted] This results in an ICER per QALY gained of £8,180.

ERG revised modelling of time to treatment discontinuation

The ERG explored TTD using data from the 5th data cut of the PALOMA-3 trial; however, the ERG noted unusual censoring of these data, which began at the time of the 4th data cut and lasted for around 20 months, where there was no censoring in either arm. As a result, the ERG has used data from the 4th data cut to model TTD.

Appraisal of the cumulative hazard plot of TTD data from the PALOMA-3 trial indicates that a constant hazard trend (a straight line) is apparent from about [redacted] month for patients treated with palbociclib plus fulvestrant and from [redacted] months for patients treated with placebo plus fulvestrant (Figure 8), meaning it is appropriate to extrapolate trial data using an exponential function. The ERG, therefore, used the TTD K-M data from the 4th data cut directly from the PALOMA-3 trial until 13 months for both arms, and then appended an exponential function separately to each arm.

KM Kaplan-Meier; PAL+FUL=palbociclib+fulvestrant; PLA+FUL=placebo plus fulvestrant; TTD=time to treatment discontinuation

Figure 8 TTD PALOMA-3 KM cumulative hazard plots

In the company model, a half-cycle correction is applied to estimates of TTD. The ERG considers the application of a half-cycle correction to be inappropriate as the cost of the drugs and the other resources associated with the drugs are likely to occur at the beginning of each cycle. The ERG's revised TTD estimates do not include a half-cycle correction. The ERG's revised estimates of TTD are presented alongside the company base case estimates in

Figure 9.

Figure 9 Company and ERG modelled TTD

Compared with the company base case, the ERG's revision using PALOMA-3 trial data as the basis for estimating TTD leads to an increase in incremental costs of [redacted] There is no change to incremental QALYs. This results in an ICER per QALY gained of £8,731.

The ERG notes that, in the PALOMA-3 trial, whilst PFS exceeds TTD for the palbociclib plus fulvestrant arm, TTD and PFS are almost identical for the placebo plus fulvestrant arm. As described in Section 3.6 of this report, treatment discontinuation due to AEs was higher for everolimus plus exemestane in BOLERO-2[45] (29%) than for palbociclib plus fulvestrant in the PALOMA-3 trial (2.9%). This suggests that TTD may be less than PFS by a greater degree for everolimus plus exemestane than for palbociclib plus fulvestrant. Without published evidence of TTD for everolimus plus exemestane, however, the ERG cannot be certain as to the relationship between TTD and PFS for patients receiving this treatment. If the use of the placebo plus fulvestrant TTD data from the PALOMA-3 trial overestimates the everolimus plus exemestane drug costs, then the ICER per QALY gained for palbociclib plus fulvestrant versus everolimus plus exemestane would be higher.

Impact of implementing ERG OS, PFS and TTD revisions to the company base case

A summary of the sources of the estimates of the clinical evidence used in the company base case, and in the ERG revisions is provided in Table 21.

Table 21 Source of estimates

	Base case		ERG revision	
	PAL+FUL	**EVE+EXE**	**PAL+FUL**	**EVE+EXE**
OS	PAL+FUL from PALOMA-3 (full Weibull curve)	HR from NMA applied to PAL+FUL OS	Pooled from PALOMA-3 (K-M data plus exponential tail)	Pooled from PALOMA-3 (K-M data plus exponential tail)
PFS	Results of FP NMA	Results of FP NMA	PAL+FUL from PALOMA-3 (K-M data plus exponential tail)	PLA+FUL from PALOMA-3 (K-M data plus exponential tail)
TTD	PAL+FUL TTD from PALOMA-3 with a ratio applied calculated from TTD & PFS	PFS results of FP NMA	PAL+FUL from PALOMA-3 (K-M data plus exponential tail)	PLA+FUL from PALOMA-3 (K-M data plus exponential tail)

AEs=adverse events; OS=overall survival; PFS=progression-free survival; TTD=time to treatment discontinuation

Compared with the company base case cost effectiveness results, using the ERG estimates of OS, PFS and TTD leads to a decrease in incremental QALYs of [redacted] and change in incremental costs of [redacted] for the comparison of treatment with palbociclib plus fulvestrant versus everolimus plus exemestane.

6.3 Other areas of uncertainty

6.3.1 Amend subsequent treatment assumptions

Company approach

In the company model, at the point of progression, patients can proceed to subsequent therapy or BSC. After the first-line of subsequent therapy patients can, again, proceed to another line of therapy or move to BSC, i.e., patients can receive up to two lines of subsequent therapy (and each line of therapy can last for up to six model cycles).

NICE guidelines for advanced breast cancer[4] include three lines of therapy; clinical advice to the ERG is that, on average, patients receive several subsequent lines of therapy.

In the company base case analysis, the maximum duration of treatment for each line of subsequent treatment is set to six cycles, patients spend approximately [redacted] months in total receiving subsequent treatments, and [redacted] months in the BSC health state. This is in contrast to published evidence from the PALOMA-3 trial[38] which shows that the median time patients spent receiving their first subsequent treatment was 4.9 months. The ERG, therefore, considers that, in the company base case, the mean time spent receiving subsequent therapies is an underestimate and that the mean time spent in BSC is an overestimate.

In the company model, it is assumed that, once the maximum duration of first line subsequent therapy has been reached, 25% of remaining patients proceed to BSC rather than receive a

second line of subsequent therapy. The company has not provided any evidence to justify using this figure and clinical advice to the ERG is that fewer than 25% of patients will be unfit for, or will refuse, each available subsequent treatment.

ERG revised approach to modelling subsequent lines of therapy

The ERG has made two revisions to the company model to more accurately reflect the experience of NHS patients than the company base case. However, the structure of the company model has limited the extent of the ERG revisions and the ERG is only able to use the results of these changes to indicate the direction of travel of the model outcomes.

The company has assumed that patients can only receive a maximum of six cycles of two subsequent lines of treatment. The model structure allows patients to receive up to nine cycles of each treatment. As post-progression in the company model is made up of two lines of subsequent therapy and BSC health states, extending the duration of subsequent therapy results in a reduction in the time spent in BSC. When the maximum duration of each subsequent treatment is set to nine model cycles, the mean duration of subsequent therapies is [redacted] months. Clinical advice to the ERG is that this is an underestimate of the time NHS patients with advanced breast cancer receive subsequent treatments.

To present a scenario with the shortest time spent in the BSC health state, the ERG has assumed 100% (rather than 75%) of patients proceed to the next line of therapy. The ERG is aware this may not represent clinical practice, but it allows the impact of decreasing the time spent in the BSC heath state to be explored.

Increasing the duration of each subsequent treatment to nine cycles and reducing the time spent in the BSC health state leads to patients spending approximately [redacted] months receiving subsequent therapies, and [redacted] months in the BSC health state. Based on clinical advice to the ERG, these changes still represent an underestimate of the time spent receiving subsequent therapies and, therefore, an overestimate of time spent in the BSC health state.

Compared with the company base case cost effectiveness results, using a maximum duration of each cycle of subsequent treatment of nine cycles and assuming all patients who are alive at the point when the maximum duration of a line of treatment has been reached are eligible for each additional line of treatment, changes incremental costs by [redacted]). There is no change to incremental QALYs. Treatment with palbociclib plus fulvestrant remains dominant over treatment with everolimus plus exemestane.

6.3.2 Resource use

Drug wastage

The company model cycle length is 28 days. The company has assumed that, for oral drugs that are dispensed in packs that contain more than 28 daily doses, that any drugs remaining after 28 days are wasted. Everolimus, exemestane and tamoxifen are dispensed in packs that include the drugs necessary for 30 days of treatment; thus, in the company model, two tablets (two days of drugs) per month are wasted. Clinical advice to the ERG is that the vast majority of patients use all of one pack of medications before opening the next and, therefore, there is no reason for the cycle length in the company model to induce any artificial wastage assumptions.

The ERG considers the most appropriate method for adjusting the pack size to the cycle size is to calculate the cost per mg and use this value to estimate the cost for 28 days. The company has followed this method to estimate the drug costs per cycle but adds the cost of the remaining two drugs in each pack as wastage. The ERG revision removes the additional cost of wastage from the calculations of the costs of everolimus, exemestane and tamoxifen (a subsequent therapy).

Compared with the company base case cost effectiveness results, removing the cost of oral daily drug wastage changes incremental costs by [redacted]). Incremental QALYs do not change. Palbociclib plus fulvestrant remains dominant over everolimus plus exemestane.

Number of appointments with a consultant oncologist

In the company model, it is assumed that, in the progression-free health state, patients have an appointment with a consultant oncologist every 6 months and that whilst receiving the first-line of subsequent therapy patients have an appointment with a consultant oncologist every 2 months. Clinical advice to the ERG is that these assumptions are underestimates and that, in the NHS, patients have appointments with a consultant oncologist once per month, irrespective of health state. The ERG has amended the model resource use assumptions to include a monthly appointment with a consultant oncologist in both the progression-free and progressed disease health states (which include two lines of subsequent treatment and BSC).

Compared with the company base case, increasing the frequency of consultant visits to once per month irrespective of heath state changes incremental costs by [redacted]. There is no change to incremental QALYs. Palbociclib plus fulvestrant remains dominant over everolimus plus exemestane.

6.4 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The ERG has made six revisions to the company base case:

1. Estimating OS using (pooled) OS data from the PALOMA-3 trial to represent the experience of patients treated with palbociclib plus fulvestrant and those treated with everolimus plus exemestane

2. Estimating PFS using data from the placebo plus fulvestrant arm of the PALOMA-3 trial as a proxy for the experience of patients treated with everolimus plus exemestane

3. Estimating TTD using data from the placebo plus fulvestrant arm of the PALOMA-3 trial as a proxy for the experience of patients treated with everolimus plus exemestane

4. Amending the company assumptions around time spent on subsequent treatments and the proportion of patients proceeding to subsequent lines of therapy

5. Removing daily oral drug wastage

6. Increasing the frequency of consultant oncologist appointments.

The ERG's revised ICERs per QALY gained are shown in Table 22. These results have been generated using the PAS price for palbociclib and the list prices for fulvestrant, everolimus plus exemestane. The company's base case results, and results from the ERG's scenarios, generated using PAS prices for palbociclib and everolimus are provided in Confidential Appendix 1.

Details of all Microsoft Excel revisions carried out by the ERG to the company model are provided in Appendix 4, Section 9.4.

Table 22 ERG adjustments to company base case: palbociclib (including PAS) plus fulvestrant versus everolimus plus exemestane

ERG revision	PAL+FUL			EVE+EXE			Incremental			*ICER*
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates
R1) Estimating OS (pooled) from the PALOMA-3 trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates
R2) Estimating PFS from the PALOMA-3 trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,180
R3) Estimating TTD from the PALOMA-3 trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,731
R4) Amend subsequent therapy assumptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates
R5) Remove daily oral drug wastage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates
R6) Include monthly oncologist consultation in every health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates
All ERG revisions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates

ICER=incremental cost effectiveness ratio; OS=overall survival; PFS=progression-free survival; QALY=quality adjusted life year; TTD=time to treatment discontinuation

6.5 ERG's preferred assumptions

The ERG prefers to combine all of the six revisions detailed in Section 6.4. The ERG presents the results of combining these revisions alongside each revision singularly in Table 22.

6.6 Conclusions of the cost effectiveness section

The company base case cost effectiveness results have been generated using the PAS price for palbociclib and the list prices for fulvestrant, everolimus plus exemestane. The company's base case cost effectiveness results show that treatment with palbociclib plus fulvestrant dominates treatment with everolimus plus exemestane. The ERG's revised ICERs per QALY gained range between dominant and £8,731. When all of the ERG revisions are combined, treatment with palbociclib plus fulvestrant dominates treatment with everolimus plus exemestane.

7 END OF LIFE

A technology meets NICE End of Life criteria[64] if (i) life expectancy with standard of care treatments for the target population is under 24 months and (ii) the increase in life expectancy with the technology being appraised is at least 3 months.

The company has not explicitly made a case that treatment with palbociclib plus fulvestrant meets the NICE End of Life criteria. However, the company argues (CS, p83): "Given the benefits attributable to palbociclib, and the PAS which is already being offered to the NHS, we believe it reasonable that flexibility in the traditional threshold is considered by the committee given the large relative survival gain."

The NICE End of Life criteria[64] and a summary of the relevant data from the clinical and cost effectiveness evidence presented by the company is presented in Table 43.

Table 23 End of Life criteria

NICE End of Life criteria	Data presented by the company and ERG
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	• Based on the evidence provided by the company, the ERG does not consider the short life expectancy criteria to be met • In the PALOMA-3 trial, median OS for patients who received placebo plus fulvestrant was 28.0 months (95% CI: 23.6 to 34.6 months) (Section 3.2.4, Table 11 of this ERG report) • In the BOLERO-2 trial,[45] median OS for patients who received everolimus plus exemestane was 31.0 months (95% CI: 28.0 to 34.6 months)
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	• The ERG does not consider that the company has provided any robust evidence of an OS gain for palbociclib plus fulvestrant compared to everolimus plus exemestane • The gain in median OS in the PALOMA-3 trial for palbociclib plus fulvestrant versus placebo plus fulvestrant was 6.9 months (Section 3.7 of this ERG report). However, this gain is not statistically significantly different. The ERG therefore does not consider there to be sufficient evidence to meet the life extension criteria

OS=overall survival

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9 APPENDICES

9.1 Appendix 1 HR-positive/HER2-negative early breast cancer

Based on the patient population in the PALOMA-3 trial, the company envisages palbociclib plus fulvestrant as a treatment option for patients with HR-positive/HER2-negative advanced breast cancer who are resistant to endocrine therapy. Since endocrine therapies are common treatment options for patients with HR-positive/HER2-negative breast cancer in both the early and advanced settings, and since the definitions of 'endocrine sensitive' and 'endocrine resistant' refer to the early and advanced settings, a brief outline of the treatment pathway starting from early disease has been provided below.

All the information about the treatment of early breast cancer presented in this appendix is taken from NICE Guideline 101[65] and relates to advice issued when treating people with ER-positive early breast cancer.

9.1.1 Surgery

People diagnosed with early breast cancer who are deemed to be operable undergo either breast-conserving surgery (removal of the tumour) or mastectomy (removal of the breast).

9.1.2 Neoadjuvant therapy

Where surgery is not an initial option, patients may receive neoadjuvant therapy with the goal of reducing the size of the tumour and removing cancerous cells. Neoadjuvant therapies used in clinical practice include chemotherapy (anthracycline plus platinum) and endocrine therapy. The endocrine therapies that are used include aromatase inhibitors (anastrozole or letrozole) and anti-oestrogen endocrine therapy (tamoxifen). In premenopausal women, neoadjuvant chemotherapy may be more likely to produce a clinical response than neoadjuvant endocrine therapy. It is recommended that endocrine therapy should be used to treat postmenopausal women when there is no definite indication for treating them with chemotherapy.

9.1.3 Adjuvant therapy

Endocrine therapy

Following surgery, patients typically receive adjuvant therapy to minimise the risk of disease recurrence. The vast majority of people with HR-positive breast cancer receive endocrine therapy in the adjuvant setting. The length of treatment with an endocrine therapy may initially be up to 5 years.

Tamoxifen is recommended as initial endocrine therapy for men and premenopausal women. For premenopausal women, it is recommended that ovarian function suppression is

considered in addition to endocrine therapy. Premenopausal women who have been on tamoxifen for 5 years may be considered for 5 years of additional therapy with tamoxifen.

Tamoxifen is also recommended for postmenopausal women if they are at low risk of disease recurrence. An aromatase inhibitor is recommended for postmenopausal women at medium or high risk of disease recurrence. Typically, the aromatase inhibitors used in the adjuvant setting are anastrozole or letrozole.

Postmenopausal women who have been on tamoxifen for 2 to 5 years may be offered the option of switching to an aromatase inhibitor for up to a further 5 years. For postmenopausal women, switching to an aromatase inhibitor may be more effective at reducing recurrence than continuing with tamoxifen.

Other adjuvant therapies

Other adjuvant therapies used in clinical practice and recommended by NICE[65] include treatment for 9 to 12 weeks with a chemotherapy regimen that contains both a taxane (docetaxel or paclitaxel) and an anthracycline, radiotherapy (for a minimum of 5 years) and bisphosphonates (sodium clodronate and zoledronic acid, (typically used 6-monthly for 3 years [clinical advice to the ERG]). Bisphosphonates are only recommended for postmenopausal women. Biological therapy is not recommended for patients with HER2-negative disease.

9.2 Appendix 2 Fractional polynomial models

Based on the numerical results for the beta parameters of the FP models provided by the company in the response to the ERG clarification letter for the fixed-effects NMAs for PFS and OS, the ERG presents graphical representations of the survival and HR functions generated from the median of the beta parameters and also graphical representation with approximate 'credible intervals' around the median beta parameters to demonstrate the uncertainty associated with the estimated beta parameters. These intervals were constructed based on all of the 2.5% CrIs of the beta parameters and all of the 97.5% CrIs of the beta parameters, therefore the ERG emphasises that the approximate credible intervals presented should be interpreted as approximate 'best-case' and 'worst-case' scenario intervals, rather than an exact 95% confidence region around the curves.

9.2.1 Graphical results of PFS NMA (fixed effects)

The ERG presents the three 'best fitting' 2nd order FP models as judged by the company and all 1st order FP models, except for the Weibull model which assumes PH. Graphical results are presented in ascending order from the FP model with the lowest DIC statistic.

[redacted]

[redacted]

CI=credible interval; DIC=deviance information criterion; FP=fractional polynomial; HR=hazard ratio; PFS=progression free survival
Source: adapted from Table 4 of the company response to the ERG clarification letter

[redacted]

[redacted]11

CI=credible interval; DIC=deviance information criterion; FP=fractional polynomial; HR=hazard ratio; PFS=progression free survival
Source: adapted from Table 3 of the company response to the ERG clarification letter

[redacted]

[redacted]12

CI=credible interval; DIC=deviance information criterion; FP=fractional polynomial; HR=hazard ratio; PFS=progression free survival
Source: adapted from Table 5 of the company response to the ERG clarification letter

[redacted]

[redacted]13

CI=credible interval; DIC=deviance information criterion; FP=fractional polynomial; HR=hazard ratio; PFS=progression free survival
Source: adapted from Table 16 of the company response to the ERG clarification letter

[redacted]

[redacted]14 CI=credible interval; DIC=deviance information criterion; FP=fractional polynomial; HR=hazard ratio; PFS=progression free survival
Source: adapted from Table 17 of the company response to the ERG clarification letter

15 CI=credible interval; DIC=deviance information criterion; FP=fractional polynomial; HR=hazard ratio; PFS=progression free survival
Source: adapted from Table 18 of the company response to the ERG clarification letter

16 CI=credible interval; DIC=deviance information criterion; FP=fractional polynomial; HR=hazard ratio; PFS=progression free survival
Source: adapted from Table 20 of the company response to the ERG clarification letter

17 CI=credible interval; DIC=deviance information criterion; FP=fractional polynomial; HR=hazard ratio; PFS=progression free survival
Source: adapted from Table 21 of the company response to the ERG clarification letter

9.2.2 Graphical results of OS NMA (fixed effects)

The ERG presents the two 'best fitting' 2nd order FP models as judged by the company and all 1st order FP models, except for the Weibull model which assumes PH. Graphical results are presented in ascending order from the FP model with the lowest DIC statistic.

[redacted][18] CI=credible interval; DIC=deviance information criterion; FP=fractional polynomial; HR=hazard ratio; OS=overall survival
Source: adapted from Table 24 of the company response to the ERG clarification letter

[redacted][19] CI=credible interval; DIC=deviance information criterion; FP=fractional polynomial; HR=hazard ratio; OS=overall survival
Source: adapted from Table 23 of the company response to the ERG clarification letter

20 CI=credible interval; DIC=deviance information criterion; FP=fractional polynomial; HR=hazard ratio; OS=overall survival
Source: adapted from Table 31 of the company response to the ERG clarification letter

21 CI=credible interval; DIC=deviance information criterion; FP=fractional polynomial; HR=hazard ratio; OS=overall survival
Source: adapted from Table 35 of the company response to the ERG clarification letter

[redacted]

[redacted]22[redacted]CI=credible interval; DIC=deviance information criterion; FP=fractional polynomial; HR=hazard ratio; OS=overall survival
Source: adapted from Table 38 of the company response to the ERG clarification letter

[redacted]

[redacted]23[redacted]CI=credible interval; DIC=deviance information criterion; FP=fractional polynomial; HR=hazard ratio; OS=overall survival
Source: adapted from Table 39 of the company response to the ERG clarification letter

9.3 Appendix 3 ERG economic critique: minor issues

The ERG considers the following issues to have little effect on the ICER per QALY gained estimates, so provides a description of the issues only.

9.3.1 Utility values: post-progression health state

The utility value used within the company model to estimate HRQoL in the post-progression health state is calculated using an algorithm and coefficients published in a paper by Lloyd et al, 2006.[57] In the company model, the same value is used for patients treated with palbociclib plus fulvestrant and everolimus plus exemestane.

The ERG notes that, the Lloyd et al, 2006 paper[57] is based on general population preferences of health states of people with metastatic breast cancer described by vignettes, rather than patient derived health states valued using general population preference, as is preferred in the NICE Reference Case.[64]

9.3.2 AEs at the beginning of treatment

Within the economic model, AEs are assumed to occur at the beginning of treatment and all events are treated simultaneously. Clinical advice to the ERG is that neutropenia can occur at any time whilst on treatment therefore the assumption that AEs only occur at the beginning of treatment is not strictly correct. The ERG however considers that as AE costs as a proportion of overall costs within the economic model are small, and the impact of allocating costs over the duration of treatment would only mean a change to the discounting allocated, the ERG does not consider it necessary to amend this assumption within the company economic model.

9.3.3 Proportion of everolimus plus exemestane AEs

In the company economic model, the rate of AEs modelled for treatment with palbociclib plus fulvestrant is the total number of Grade ≥3 events in the PALOMA-3 trial (69.9%). However, for everolimus plus exemestane it is only the number of patients experiencing a Grade ≥3 stomatitis event (8%) (Section 3.6.2).

Additionally, the proportion of patients receiving everolimus plus exemestane who experienced Grade ≥3 AEs in the BOLERO-2 trial is reported as 55% in Piccart et al, 2014.[45] The ERG considers this to mean that the AEs for everolimus plus exemestane are underestimated in comparison to the palbociclib plus fulvestrant AEs.

9.3.4 AE resource use

The company estimated resource use for AEs in the economic model from the most frequent Grade ≥3 AEs from the palbociclib plus fulvestrant arm of the PALOMA-3 trial and the

everolimus plus exemestane arm of the BOLERO-2 trial.[44] For palbociclib plus fulvestrant the most frequent AE was neutropenia and for everolimus plus exemestane the most frequent AE was stomatitis. The company then estimated what would be required to treat neutropenia and stomatitis and used this resource use estimate for all AEs in that associated arm of the economic model. The resource use estimated to treat neutropenia is one oncologist visit compared to three days in hospital to treat the stomatitis.

Clinical advice to the ERG is that the company estimates of resource use to manage AEs may be underestimated for treatment with palbociclib plus fulvestrant and overestimated for treatment with everolimus plus exemestane. Clinical advice to the ERG is that whilst some patients only require an assessment with an oncologist followed by a dose reduction or treatment break to manage neutropenia, other patients may in fact need to be hospitalised, although hospitalisation is rare. The ERG also received clinical advice that an estimate of three days in hospital for any Grade ≥3 stomatitis seems an overestimate. Clinical advice to the ERG is that an antiseptic mouthwash may be prescribed and an assessment by an oncologist necessary for severe stomatitis, but that a hospital stay is rarely necessary. The ERG also considers that estimating resource use for each SAE would be more appropriate.

9.3.5 Drug monitoring

The company's economic model includes some assumptions about the level of resource use required to monitor patients being treated with palbociclib plus fulvestrant and everolimus plus exemestane. In the company model, a chest x-ray is assumed to be necessary once every two months whilst being treated with everolimus plus exemestane. Clinical advice to the ERG is that this is an overestimate as chest x-rays are only necessary for patients who have symptoms of breathlessness.

9.4 Appendix 4 ERG revisions to company's model

All revisions are activated by a logic switch with:

0 = unchanged

1 = apply ERG modification

Logic switches are indicated by named range variables Mod_*letter* where letter = A - F.

A menu of revisions and Mod names appears below and on the 'Results_Deterministic' worksheet together with summary results as used to transfer to the ERG report.

Revision #	Modification name	Switch	Description
R1)	Mod_A	0	Estimating OS (pooled) from the PALOMA-3 trial
R2)	Mod_B	0	Estimating PFS from the PALOMA-3 trial
R3)	Mod_C	0	Estimating TTD from the PALOMA-3 trial
R4)	Mod_D	0	Amend subsequent therapy assumptions
R5)	Mod_E	0	Remove daily oral drug wastage
R6)	Mod_F	0	Include monthly oncologist consultation in every health state

Instructions for modifying the company model

1. Include discounted prices in the Control sheet (Cell B10 for palbociclib and Cell B14 for everolimus)
2. Move all sheets from *palbo 916_ERG additional model data.xlsx* into company model
3. Create named switches for each of the modifications mod_A to mod_F
4. For each sheet given in the 'Sheet' column below:
    - copy formulae from the 'Modified formulae' column in the table below
    - paste formulae into the cells referred to in the 'Cells' column in the table below

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
R1) Use pooled OS from the PALOMA-3 trial	Mod_A	OS_inputs	Q64 copy down to Q584	Use pooled PALOMA-3 OS for PAL+FUL =IF(mod_A=1,ERG_OS!D4,CHOOSE(OS_model_PAL_and_FLV,K64,L64,M64,N64,O64))
			X64 copy down to X584	Use pooled PALOMA-3 OS for EVE+EXE =IF(mod_A=1,ERG_OS!D4,CHOOSE(OS_model_comps,S64,T64,U64,V64))
R2) Use PFS data from PALOMA-3	Mod_B	PFS_Inputs	R62 copy down to R582	Use PALOMA-3 PFS for PAL+FUL =IF(mod_B=1,ERG_PFS!D4,CHOOSE(PFS_model_PAL_and_FUL,K62,L62,M62,N62,O62,P62))
			Y62 copy down to Y582	Use PALOMA-3 PFS for PLA+FUL as proxy for EVE+EXE =IF(mod_B=1,ERG_PFS!E4,CHOOSE(PFS_model_comps,T62,U62,V62,W62))

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
R3) Use TTD data from PALOMA-3 (without mid-cycle correction)	Mod_C	TTD_Inputs	Q12 copy down to Q533	Use PALOMA-3 TTD for PLA+FUL as proxy for EVE+EXE =IF(mod_C=1,ERG_TTD!D4,IF(TTD_source=1,CHOOSE(AnalysisControl!C13,MIN(F12,M12),MIN(F12,M12),F12,MIN(F12,M12)),(EnginePAL_FLV!E11^(1/TTDAdjPAL))))
		EngineEVE_EXE	AP11	Amend drug costs to use TTD (1st cycle) =IF(mod_C=1,ERG_TTD!E4*AP9,E11*AP9)
			AP12 copy down to AP531	Amend drug costs to use TTD (subsequent cycles) =IF(mod_C=1,ERG_TTD!E5*AP10,E12*AP10)
			AQ11 copy down to AQ531	Amend drug wastage to use TTD =IF(mod_C=1,ERG_TTD!E4*AQ$9,E11*AQ$9)
			AR11 copy down to AR531	Amend drug administration to use TTD =IF(mod_C=1,ERG_TTD!E4*AR$9,E11*AR$9)
			AS11 copy down to AS531	Amend drug monitoring to use TTD =IF(mod_C=1,ERG_TTD!E4*AS$9,E11*AS$9)
			AT11	Amend AEs to use TTD =IF(mod_C=1,ERG_TTD!E4*AT9,E11*AT9)
R4) Amend subsequent therapy assumptions	Mod_D	Sequences	C19 copy down to C20	Set maximum number of cycles in subsequent therapy to the highest possible within the model (9) =IF(mod_D=1,9,CHOOSE(K19,D19,H19,I19,J19))
			C27 copy down to C28	Assume all patients are eligible for subsequent therapy lines =IF(mod_D=1,1,CHOOSE(K27,D27,H27,I27,J27))

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
R5) Remove daily oral drug wastage (everolimus, exemestane and tamoxifen)	Mod_E	Cost_drug	O21 copy down to O23	Remove 2 days per cycle of everolimus wastage =IF(mod_E=1,0,L21*(I21-M21))
			O17	Remove 2 days per cycle of tamoxifen (10mg) wastage =IF(mod_E=1,0,L17*(I17-M17))
			O18	Remove 2 days per cycle of tamoxifen (20mg) wastage =IF(mod_E=1,0,L18*2)
			O24	Remove 2 days per cycle of exemestane wastage =IF(mod_E=1,0,L24*(I24-M24))
R6) Amend health states to each include a monthly visit with a consultant	Mod_F	Cost_HS_resource	C55	Amend oncologist consultation in the pre-progression health state =IF(mod_F=1,1,IF(D55="",E55,D55))
			C71	Amend oncologist consultation in the 1st line of subsequent therapy health state =IF(mod_F=1,1,IF(D71="",E71,D71))