NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission** from Pfizer

2. **Company response to NICE's request for clarification**

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

4. **Expert personal perspectives** from:
   a. Dr Nicholas Turner – clinical expert, nominated by Pfizer
   b. Holly Heath – patient expert, nominated by Breast Cancer Care and Breast Cancer Now
   c. Stephanie Pollard – patient expert, nominated by Breast Cancer Care and Breast Cancer Now
   d. Dr Anne Rigg – clinical expert, nominated by Pfizer

5. **Evidence Review Group report** prepared by Liverpool Reviews and Implementation Group (LRiG)
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7. **Technical engagement response from company**
   a. Main submission
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8. **Technical engagement responses from experts:**
   a. Dr Nicholas Turner – clinical expert, nominated by Pfizer

9. **Technical engagement responses from consultees and commentators:**
   a. NHS England and Improvement
   b. Novartis

10. **Evidence Review Group critique of company response to technical engagement** prepared by Liverpool Reviews and Implementation Group

(LRiG)
a. Addendum

11. Final Technical Report

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Palbociclib (PD-0332991) in combination with fulvestrant for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer that has become resistant to previous endocrine therapy [ID916]

Document B

Company evidence submission

April 2019

File name	Version	Contains confidential information	Date
ID916_Palbociclib_ DocumentB_18APR19(ACiC)	**FINAL**	**Yes**	**18th April 2019**

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Abbreviations

1L	First line
2L	Second line
aBC	Advanced breast cancer
AE	Adverse event
AI	Aromatase inhibitor
AIC	Akaike information criteria
ALP	Alkalinephosphatase
ALT	Aminotransferase
AST	Aspartate aminotransferase
AT	As-treated
BC	Breast cancer
BIC	Bayesian information criteria
BICR	Blinded Independent Central Review
BMJ	British Medical Journal
BNF	British National Formulary
BSC	Best supportive care
CA	Cancer antigen
CBR	Clinical benefit response
CCG	Clinical commissioning group
CDK	Cyclin dependent kinases
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
cfDNA	Circulating free deoxyribonucleic acid
CG	Clinical guideline
CI	Confidence interval
CNS	Central nervous system
CNSs	Clinical nurse specialists
CR	Complete response
CRF	Case report form
CrI	Credible interval
CT	Computed tomographic
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	Cytochrome P450
DARE	Database of Abstracts of Reviews of Effectiveness
DIC	Deviance Information Criterion
DR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	Electronic market information tool
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC QLQ-BR23	QLQ Breast cancer module
EPAR	European public assessment report
EQ-5D	5-dimension EuroQol questionnaire
ER	Estrogen receptor
ERD	Oestregen receptor down
ESMO	European society for medical oncology
ET	Endocrine therapy
EU	European Union
EVE	Everolimus
EXE	Exemestane
FBC	Full blood count
FP	Fractional polynomial

FSE	Feelings about side effects
FUL	Fulvestrant
GGT	Gamma-glutamyl transferase
GMC	General medical council
GP	General practitioner
GSCF	Granulocyte-colony stimulating factor
HER2-	Human epidermal growth factor receptor 2 negative
HLCI	High limit confidence interval
HR	Hazard ratio
HR+	Hormone receptor positive
HRQoL	Health-related quality of life
HS	Health state
HSUV	Health state utility value
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IM	Intramuscular
IRIS	Ibrance real world insights study
ITT	Intention to treat
IV	Intravenous
KM	Kaplan-Meier
KoL	Key opinion leaders
LHRH	Luteinizing hormone-releasing hormone
LLCI	Low limit confidence interval
LY	Life years
LYG	Life years gained
mBC	Metastatic breast cancer
MedDRA	Medical dictionary for regulatory activities
MHRA	Medicines and Healthcare Products Regulatory Agency
NA	Not available
NCI	National cancer institute
NCRAS	National cancer registration and analysis service
NHS	National health service
NHSE	National health service England
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
ONS	Office for National statistics
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PAL	Palbociclib
PAS	Patient access scheme
PBO	Placebo
PD	Progressed disease
PFS	Progression-free survival
PgR	Progesterone receptor
PH	Proportional hazard
PIM	Promising Innovative medicine
PI3K-mTOR	Phosphoinositide 3 kinase – mammalian target of rapamycin
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PROs	Patient-reported outcomes
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QOL	Quality of life

RCT	Randomized controlled trial
RECIST	Response evaluation criteria in solid tumors
RR	Response rate
RW	Real World
SAE	Severe adverse event
SD	Standard deviation
SD	Stable disease
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SOC	System organ class
SUCRA	Surface Under the Cumulative Ranking curve
TA	Technology appraisal
TEAEs	Treatment-emergent adverse events
SMC	Scottish medicines consortium
STA	Single technology appraisal
SWT	Satisfaction with therapy
TSD	technical support document
TTD	Time to treatment discontinuation
TTD	Time to deterioration
TTP	Time to progression
VAS	Visual analogue scale
WBC	White blood cell
WTP	Willingness to pay

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

B.1.1 Decision problem

IBRANCE® (palbociclib) is indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer (mBC):

- in combination with an aromatase inhibitor;
- in combination with fulvestrant in women who have received prior endocrine therapy.

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

The product's indication can be broken down into two populations for advanced breast cancer (aBC), including locally advanced or metastatic disease, addressed separately in two NICE appraisals:

i. Palbociclib in combination with an aromatase inhibitor is typically a treatment for endocrine sensitive patients. The term "endocrine-sensitive" describes patients who have either never had endocrine therapy and are therefore expected to be "sensitive" to its effects, or patients who have completed a course of endocrine therapy in the (neo)adjuvant setting (e.g. following surgery) and who completed that course and did not relapse within the 12 months period following treatment; due to previously successful treatment, these patients are also expected to be "sensitive" to the effects of endocrine therapy in the advanced setting. This population is captured in palbociclib's phase II PALOMA-1[1] and phase III PALOMA-2[2] trials, and for whom positive recommendation has already been issued by NICE for the use of palbociclib with an aromatase inhibitor (TA495).[3]

ii. Palbociclib in combination with fulvestrant is a treatment that would typically be used in patients who have previously been classed as developing resistance to prior therapy: "endocrine resistant" patients. This would include patients treated in the (neo)adjuvant setting but whose disease is now advanced or metastatic following progression on, or within 12 months of completing, (neo)adjuvant endocrine therapy; these patients could receive palbociclib plus fulvestrant as a first-line treatment in the advanced setting. Also, in the "endocrine resistant" population are those who have previously received endocrine therapy in the advanced setting (such as aromatase inhibitor or anti-oestrogen based therapy) but have experienced disease progression whilst on treatment and so require an alternative therapy for their advanced disease. These second- and later line patients would be eligible to receive palbociclib plus fulvestrant. This endocrine resistant population is covered in palbociclib's phase III PALOMA-3 trial.[4]

Given part (i) of the above is covered by TA495,[3] this current submission focuses on part (ii). 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; Table 1 summarises the decision problem.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Palbociclib in combination with 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.	Same as NICE final scope	N/A
Intervention	Palbociclib in combination with fulvestrant	Same as NICE final scope	N/A
Comparator(s)	Fulvestrant monotherapy Everolimus and exemestane Exemestane Tamoxifen Chemotherapy	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 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 after endocrine therapy.[6]

Outcomes	The outcome measures to be considered include: • progression-free survival (PFS) • overall survival (OS) • response rate (RR) • 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 • HRQoL • Time to treatment discontinuation (TTD)	The tumour response variables 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.
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.	Same as final scope issued by NICE.	N/A
Subgroups to be considered	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.	N/A
Special considerations including issues related to equity or equality	No special considerations	No special considerations	N/A

B.1.2 **Description of the technology being appraised**

Palbociclib is a transformative, first-in-class, orally administered, selective small-molecule inhibitor of the cyclin dependent kinases (CDKs) types 4 and 6, which play a pivotal role in driving the proliferation of breast cancer cells. In 2015, the MHRA recognised the transformative nature of palbociclib with its potential to address the unmet medical need created by limited endocrine therapy (ET) efficacy by awarding it the status of Promising Innovative Medicine (PIM). This designation is awarded to drugs that show major advantages over existing UK therapies in the treatment, diagnosis or prevention of life-threatening or seriously debilitating conditions with high unmet need, such as HR-positive, HER2-negative advanced or metastatic breast cancer, because existing therapies have serious limitations.

In this submission, palbociclib plus fulvestrant is presented for consideration for treating HR-positive, HER2-negative locally advanced or metastatic breast cancer (aBC), in women with disease that progressed during, or within 12 months of completing, prior endocrine therapy whether prior therapy was in the neo-adjuvant, adjuvant, advanced or metastatic setting.

A summary of the technology being appraised is presented in Table 2.

Table 2. Summary of the technology being appraised

UK approved name and brand name	Palbociclib (Ibrance®)
Mechanism of action	Palbociclib is a first in class small molecule inhibitor of the cyclin dependent kinases (CDK) 4 and 6 that synergistically enhances the effect of endocrine therapy leading to a significant improvement in PFS in patients with ER+/HER2- aBC with a generally manageable adverse event profile.[1,2,7,8] Through its mechanism of action palbociclib enhances the anti-proliferative efficacy of endocrine treatments through inhibition of the ER receptor in BC cells.[7]
Marketing authorisation/CE mark status	Palbociclib received a positive opinion from the Committee for Human Medicinal Products on 15th September 2016 collectively for both the indications detailed above in section B.1.1. European Marketing Authorisation was then granted on 9th November 2016 for the same indications. Please refer to Appendix C for the Summary of Product Characteristics (SmPC).
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Palbociclib is indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or in combination with fulvestrant in women who have received prior endocrine therapy. In pre- or peri-menopausal women, the endocrine therapy should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist.
Method of administration and dosage	Forms Palbociclib: Oral Fulvestrant: Intramuscular injection

	Dosage Palbociclib: 125mg (also available in 100mg and 75mg, all priced the same) Fulvestrant: 500mg given as two slow (i.e. 1-2 minutes) intramuscular injections in the gluteal area Dosing Frequency Palbociclib: daily for 21 consecutive days, followed by 7 days off treatment (to complete one 28-day cycle), until disease progression Fulvestrant: on days 1, 15, and once monthly thereafter. Cycle length One cycle of palbociclib plus fulvestrant is 28 days. Within this, the course of palbociclib treatment is for the first 21 consecutive days (then a 7-day break) and for fulvestrant is once per month (but twice in the first 4 weeks).
Additional tests or investigations	None required
List price and average cost of a course of treatment	Palbociclib list price: £2,950 per pack of 21 capsules, which covers a 28-day treatment cycle. Fulvestrant: £522 per month at list price (but double dosed during the first month). At list price, per course the combined price cost is £3,472 (£3,994 in the first course due to fulvestrant's double dose).
Patient access scheme (if applicable)	Palbociclib price with simple Patient Access Scheme: [redacted] per pack of 21 capsules, which covers a 28-day/4-week treatment cycle. With palbociclib's PAS and fulvestrant's list price, the cost per course is [redacted] (or [redacted] in the first 4 weeks).

Abbreviations: aBC, advance breast cancer; BC, breast cancer; CDK, cyclin dependent kinases; ER, oestrogen receptor; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; LHRH, luteinizing hormone-releasing hormone; PAS, patient access scheme; SmPC, Summary of Products Characteristics.

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

B.1.3.1 *Disease overview*

Advanced (aBC) hormone receptor positive, human epidermal growth factor-2 negative (HR-positive HER2-negative) breast cancer (BC) is a terminal disease with an associated average life expectancy under 3 years.[9] There are an estimated 49,200 new cases of BC every year in England and Wales.[10] At the time of diagnosis around 2,661 (5%) are already metastatic, with the remaining cases presenting in stages 1-3. Around 13,949 (30%)[11] of early breast cancers are estimated to progress into the advanced (or metastatic) setting every year. This suggests there are 16,609 new cases of aBC in England and Wales. From these, around 9,301 (56%) are expected to be HR-positive HER2-negative (Table 3).

Table 3. Estimated new cases of ER-positive HER2-negative aBC per year

	Percentage (%)	Population	Source / comment
New breast cancer cases in 2015 across England and Wales		49,003	Breast Cancer Research UK 2018,[10] ONS population estimates mid-2017[12]
Change in incidence of breast cancer, per annum	0.1%		Breast Cancer Research UK 2018[10]
New breast cancer cases in 2019 across England and Wales		49,200	Inflated by annual growth from 2015 to 2019
Breast cancer first diagnosed in stage 1	44%	21,819	Public Health England. National Cancer Registration and Analysis Service (NCRAS). Stage breakdown by CCG 2016[13]
Breast cancer first diagnosed in stage 2	41%	20,248	
Breast cancer first diagnosed in stage 3	9%	4,428	
Breast cancer first diagnosed in stage 4 (de novo metastatic)	5%	2,661	
New cases of early and locally advanced invasive breast cancer per year		46,495	NICE CG81 Costing Template[14]
Recurred early breast cancer that become advanced or metastatic each year	30%	13,949	O'Shaughnessy et al. 2005[11]
New cases of advanced and metastatic breast cancer per year		16,609	Sum of breast cancer first diagnosed in stage 4 (de novo metastatic) and Recurred early breast cancer that become advanced or metastatic each year
New cases of ER-positive HER2-negative advanced and metastatic breast cancer per year	56%	9,301	DeKoven et al. 2012[15]

Abbreviations: CG, Clinical Guideline; CCG, Clinical Commissioning Group; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; NICE, National Institute for Health and Care Excellence; ONS, Office for National Statistics.

Advanced BC is an incurable life-threatening disease; the clinical goals are to delay disease progression whilst maintaining quality of life, alleviating symptoms and improving survival-related outcomes. Most cases of female breast cancer in UK are diagnosed at a relatively early stage or as locally advanced disease, with only approximately 5-6% of women presenting with metastatic disease.[16,17] The disease is stratified clinically into various stages (Table 4).[18] A substantial proportion of patients initially diagnosed with early-stage or locally advanced breast cancer go on to suffer recurrence or metastases. In 2009, NICE estimated that up to 40% of those diagnosed with early breast cancer develop advanced disease within 10 years.[19]

Table 4. Clinical stratification of aBC[18]

Anatomic stage / prognostic groups[a]		
	Node stage	**Metastasis**
Stage IIB		
T2	N1	M0
T3	N0	M0
Stage IIIA		
T0	N2	M0
T1 [b]	N2	M0
T2	N2	M0
T3	N1	M0
T3	N2	M0
Stage IIIB		
T4	N0	M0
T4	N1	M0
T4	N2	M0
Stage IIIC		
Any T	N3	M0
Stage IV		
Any T	Any T	M1

[a]T, tumour; N, node; M, metastases
[b]Anatomic stage M0 includes M0(i+). The designation pM0 is not valid; any M0 should be clinical. If a patient presents with M1 before neoadjuvant systemic therapy, the stage is considered stage IV and remains stage IV regardless of response to neoadjuvant therapy. Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy. Post-neoadjuvant assessment is designated with a 'yc' or 'yp' prefix. Of note, no stage group is assigned if there is a complete pathological response (pCR) to neoadjuvant therapy e.g. ypT0ypN0cM0.
[c]T1 includes T1mi.
[d]T0 and T1 tumours with nodal micro metastases only are excluded from stage IIA and are classified stage IB.

B.1.3.2 *Effects of aBC on patients, carers and society*

As the disease progresses, patients take more time off work and they are more likely to leave employment altogether. Chemotherapy, in particular, may be associated with significant toxicity that can reduce quality of life[20,21] and the ability to work.[22] In a sample of European working-age women with HR-positive HER2−negative aBC, 32% continued to work whilst on first-line chemotherapy. Of the percentage of women who are able to work through subsequent lines of chemotherapy decreases: 13% still work whilst receiving second-line chemotherapy and only 7% when receiving third-line chemotherapy.[22] A study of 19,496 women with mBC found that women treated missed between one and two weeks of work every quarter, with rates of absence increasing with disease progression and subsequent lines of therapy. First-line metastatic patients missed an average of 87 hours per quarter, and at second-line this increased to 112 hours. Further, the study found that women whose cancer progressed were more likely to exit employment all together.[17]

Diagnosis with aBC and subsequent treatment can negatively affect patients psychologically.[23,24] UK clinical experts have indicated that in the face of cancer, one of the primary goals of treatment is to allow patients to carry on living a 'normal' life for as long a period as possible. As metastatic disease is terminal, experts have stressed the importance of enabling the women to retain normality, allowing them to spend as much time as possible looking after their families, children and continuing to work. This relies on a treatment being non-intrusive (i.e. oral therapy), limiting the impact on quality of life (i.e. a manageable safety profile), and halting disease for as long as possible (i.e. PFS). Indeed, research has shown that the negative effects of aBC and potential negative effects of therapy have been found to compromise the ability of women to fulfil their caring duties as partners, friends and mothers.[25]

Friends and family members often play a key role in the care of patients with aBC. In fact, as a consequence of the risk of breast cancer increasing rapidly above the age of 60, many women with aBC may require extensive support from informal caregivers.[26] Diagnosis with aBC and subsequent treatment can negatively affect the caregivers of patients,[27] and such carers are at higher risk of depression and reduced quality of life than the general population.[28] Many patients with aBC are themselves fulfilling care giving roles and the burden of diagnosis of aBC in itself cause significant impacts to their roles and impact their families significantly.

The burden on carers is even greater when the patient's disease progresses as a patient's quality of life falls. The psychological impact on patients of disease progression and of the onset of further treatment can increase the caregiver burden. Deteriorating patient health can require additional caring burden as the ability to complete normal tasks reduces. Unfortunately, the increase in symptoms is often met with the use of chemotherapy and this can cause further caregiver burden due to chemotherapy's association with toxicity, lower quality of life [20,21] and a lower ability to work.[22]

Breast cancer progression is associated with a large increase in healthcare costs, most of which are inpatient costs.[29] According to a 2017 study,[30] the incremental lifetime cost of managing mBC from diagnosis to death in the UK has been estimated at approximately £27,000[30] compared to women without breast cancer. Another study found that the aggregate 5-year cost of treating recurrent breast cancer was £16,640 (2007 basis).[31] These estimates also do not reflect indirect costs related to lost work productivity or burden on families, which for ER-positive HER2-negative mBC patients amount to an average of £28,000 per year.[30] Even though treatment acquisition costs for women with HR-positive HER2-negative aBC patients are lower than for women with other aBC tumour subtypes (due to mostly generic treatment options), the total healthcare costs for this population are large due to the prevalence of this group, the multiple lines of therapy that women typically undergo, and a survival of several years leading to accumulation of supportive care costs.[32-34]

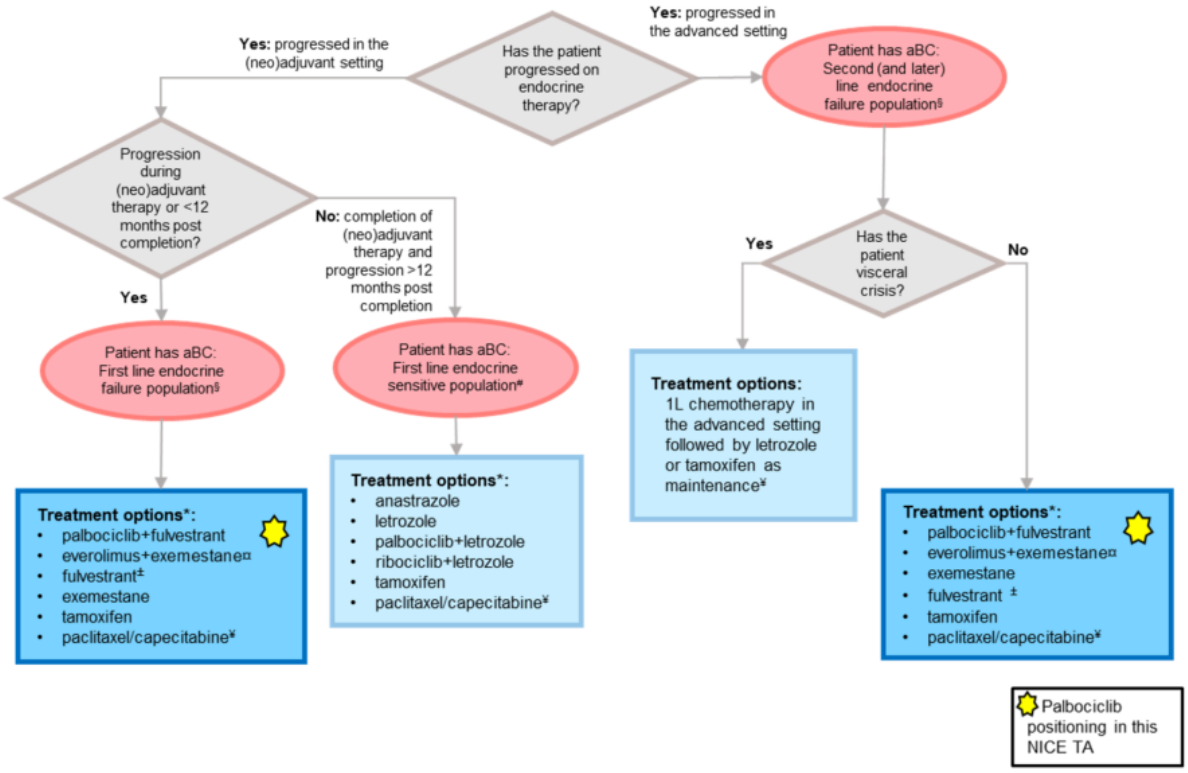
In summary, aBC places a significant psychological and symptomatic burden on patients, a financial burden on patients and employers because of lost work productivity, and a significant psychological burden on informal carers. These burdens are likely intensified for patients on chemotherapy and their carer due to the toxic effects of the therapy, the potential requirement to attend a centre for drug administration, the reduced PFS experienced on chemotherapy and greater involvement of the health system to support the patient. Palbociclib offers aBC patients an innovative treatment that can delay progression (and thereby offering a delay to

chemotherapy), improve quality-of-life and extended clinically meaningful survival, with a tolerable toxicity profile, compared to currently available treatments (Section B.2). All the benefits of palbociclib combined can significantly mitigate these burdens.

B.1.3.3 *The clinical pathway of care that shows the context of the proposed use of the technology.*

The treatment pathway for the endocrine resistant population is summarised in Figure 1. This pathway is broadly consistent with the updated NICE Pathway for management of advanced breast cancer, although fulvestrant is not NICE recommended but is used via variable CCG comissioning.[35] Primarily, palbociclib will be expected to displace everolimus plus exemestane.

Figure 1. Current treatment pathway for HR-positive HER2-negative aBC in England and Wales



Abbreviations: aBC, advance breast cancer (comprising locally advanced or metastatic)
¤ Everolimus can only be prescribed to post-menopausal women or women who had ovarian oblation. Everolimus can only be used after 1 endocrine therapy and 1 chemotherapy.
* 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[3]
§ 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

The comparators in this population are therapies that can be used in patients who have become resistant to prior endocrine therapy. This includes patients who have recently become resistant to (i.e. experienced disease progression) endocrine therapy either whilst on, or within

12 months of completing, (neo)adjuvant treatment (for details, see Section B.1.1). It also includes patients already with advanced disease that have become resistant to endocrine therapy in the advanced setting. In summary, the “endocrine resistant” population in whom palbociclib plus fulvestrant is effective includes both:

- A first line advanced population: patients whose disease progressed whilst on, or within 12 months of completing, endocrine therapy in the (neo-)adjuvant setting;
- A second or later line advanced population: patients who already received endocrine therapy in the advanced/metastatic setting but whose disease has now progressed.

Everolimus 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). Also, in this population NICE currently only recommends everolimus plus exemestane (TA421)[36]. Although discussions with clinical experts suggests 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. In the submission, the standard of care comparator for which cost-effectiveness has been evaluated is everolimus plus exemestane. However, in addition to everolimus plus exemestane, the final scope includes fulvestrant, tamoxifen, exemestane and chemotherapy.

In this endocrine resistant population NHSE note that fulvestrant is not recommended by NICE in these patients (TA239),[5] however it is variably commissioned by CCGs across England and is therefore not considered a relevant comparator for the NHS. In Scotland fulvestrant is recommended by the SMC and clinical experts have indicated its use is more prominent than everolimus plus exemestane due to the toxicity of the latter.

There is no NICE technology appraisal guidance for the use of tamoxifen in this population. Consultation with clinical experts has indicated that tamoxifen would only be used in those who cannot tolerate everolimus plus exemestane, therefore it is used infrequently in these patients and is not considered a standard of care treatment.

Clinical experts also indicated that exemestane monotherapy is used infrequently. This is expected given that monotherapy would only be used if a patient could not tolerate everolimus as it would prevent the use of everolimus plus exemestane, which has been shown to be more effective than the monotherapy and has been approved for use in this population.[36]

Chemotherapy is used in patients who are in visceral crisis or have life-threatening disease. In patients without life-threatening disease, chemotherapy is recommended once endocrine therapies have been exhausted. Palbociclib plus fulvestrant is not expected to be used in this population and therefore, chemotherapy is not a relevant comparator.

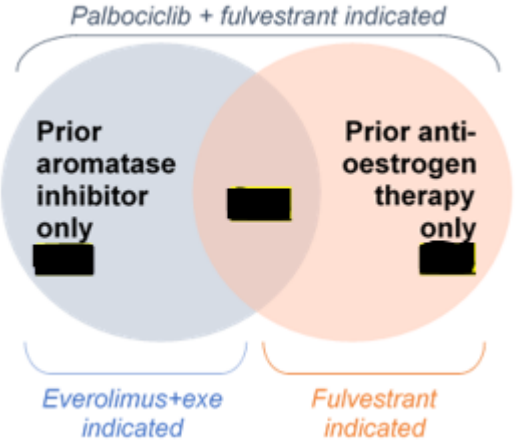
Whilst the regimen of palbociclib combined with fulvestrant is indicated for use in women who have had any type of prior endocrine therapy, both everolimus plus exemestane and fulvestrant have restricted marketing authorisations:

- fulvestrant monotherapy is licensed for use in women who have relapsed or progressed on or after treatment with an anti-oestrogen (e.g. tamoxifen),

- everolimus combined with exemestane is licensed and recommended by NICE for use in treating advanced HER2-negative, HR-positive BC in postmenopausal women without symptomatic visceral disease that has recurred or progressed after a non-steroidal aromatase inhibitor (i.e. letrozole and anastrozole).

The above restrictions do not allow for one treatment to be used across all endocrine resistant patients, thus palbociclib represents a potential option to address this clinical unmet need. The patient population split by the two marketing authorisations is displayed in Figure 2.

Figure 2. Patients included in PALOMA-3 split by prior anti-oestrogen or prior aromatase inhibitor therapy[8]



The PALOMA-3 trial contained the largest pre/peri-menopausal population in a phase 3 study examining this hormone resistant population.[8,37,38] Neither fulvestrant nor everolimus currently hold an EMA license for prescribing within the pre/peri-menopausal population. Although clinicians can prescribe outside of license, the General Medical Council (GMC) have very clear guidelines in when clinicians are able to do this, i.e. when a licensed alternative is not available. Palbociclib has a license to prescribe in this population with the addition of an LHRH inhibitor.

B.1.3.4 *Current relevant guidelines*

The most recently-reviewed and published UK clinical guideline is the BMJ Best Practice guideline (reviewed November 2017),[39] however it only covers aBC, not localised advanced BC. Moreover, with reference to this submission, it only covers the second line endocrine resistant population, not the first line in the advanced/metastatic setting.

The BMJ guideline recommends different agents for endocrine resistant patients, depending on a woman's menopausal status, as shown in Table 5 (note: therapy with the same agent cannot be repeated if given previously and the disease-free interval was < 12 months. In any case, treatment with CDK 4/6 or everolimus or exemestane cannot ever be repeated).

Table 5. Treatment options for women with oestrogen-receptor positive, HER2-negative metastatic breast cancer that has become resistant to first-line endocrine therapy - BMJ Best

Practice guideline and NICE management of advanced cancer pathways[35,39]

Treatment	Post-menopausal population	Pre-menopausal population
Primary options (for women not exposed to CKD4/6 inhibitor therapy in the first-line setting)	**Exemestane** 25mg *PLUS* **everolimus** 10mg once daily until tumour progression *OR* **Fulvestrant** 500mg IM on days 1, 15, 29 then once monthly *PLUS* **palbociclib** 125mg orally once daily on days 1-21 of each cycle followed by 7 days off before repeating	**Anastrozole**: 1 mg orally once daily until tumour progression *OR* **Letrozole**: 2.5 mg orally once daily until tumour progression *OR* **Anastrozole**: 1 mg orally once daily on days 1-28 *OR* **Letrozole**: 2.5 mg orally once daily on days 1-28 *PLUS* **Palbociclib**: 125 mg orally once daily on days 1-21 of each cycle followed by 7 days off before repeating *OR* **ribociclib**: 600 mg orally once daily on days 1-21 of each cycle followed by 7 days off before repeating
Secondary options	**Exemestane**: 25mg orally once daily until tumour progression	**Fulvestrant** (to be considered if an aromatase inhibitor has been taken in the past): 500 mg intramuscularly on days 1, 15, 29, then once monthly until tumour progression
	Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens: 1.23 mg/m2 administered intravenously over 2 to 5 minutes on days 1 and 8 of every 21-day cycle. Eribulin is recommended as an option for treating locally advanced or metastatic breast cancer in adults, after it has progressed after at least 2 chemotherapy regimens (which may include an anthracycline or a taxane, and capecitabine).	

Abbreviations: IM, intramuscular

The NICE Clinical Guideline 81 on managing aBC was revised and re-published in August 2017.[19] It recommends a range of potential treatment options following resistance to endocrine treatment. The main points of the guidance, as well as the treatment options which were considered by NICE, are summarised in Table 6. An important consideration from the NICE guidance for England and Wales is that fulvestrant is not recommended in the endocrine resistant setting, on the grounds of cost-effectiveness.[5]

The recent ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4) guidelines recognise that the addition of a CDK 4/6 inhibitor such as palbociclib to fulvestrant, in patients previously exposed to endocrine therapies show significant improvements in median PFS and QOL and a favourable safety profile. The guidelines concur that a CDK 4/6 inhibitor plus fulvestrant is one of the preferred treatment options if a CDK 4/6 inhibitor was not previously administered in pre- and peri-menopausal women with ovarian function suppression or ablation and post-menopausal women.[40]

Table 6. NICE Clinical Guideline 81 – pharmacological treatments recommended after initial

endocrine therapy resistance[19]

Treatment	Recommended setting[1]
Aromatase inhibitors	Postmenopausal women with ER-positive breast cancer previously treated with tamoxifen.
Chemotherapy	On disease progression, offer systemic sequential therapy to the majority of patients with advanced breast cancer who have decided to be treated with chemotherapy. Consider using combination chemotherapy to treat patients with advanced breast cancer for whom a greater probability of response is important and who understand and are likely to tolerate the additional toxicity. For patients with advanced breast cancer who are not suitable for anthracyclines (because they are contraindicated or because of prior anthracycline treatment either in the adjuvant or metastatic setting), systemic chemotherapy should be offered in the following sequence: • first line: single-agent docetaxel • second line: single-agent vinorelbine or capecitabine • third line: single-agent capecitabine or vinorelbine (whichever was not used as second-line treatment).
Palbociclib	*NICE has not yet evaluated palbociclib in the "endocrine resistant" setting.*
Everolimus	Everolimus, plus exemestane, is recommended within its marketing authorisation, as an option for treating advanced HER2-negative, HR-positive BC in postmenopausal women without symptomatic visceral disease that has recurred or progressed after a non-steroidal aromatase inhibitor. When everolimus was accepted for use via the Cancer Drugs Fund in England, the recommendation stipulated that the following 7 conditions must all be met to approve funding: 1. Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy 2. ER-positive, HER2–positive aBC 3. No symptomatic visceral disease 4. In combination with exemestane 5. Previous treatment with a non-steroidal aromatase inhibitor 6. No previous treatment with exemestane for metastatic breast cancer 7. No more than one line of chemotherapy for the treatment of advanced breast cancer
Fulvestrant	Fulvestrant is not recommended within its licensed indication, as an alternative to aromatase inhibitors for the treatment of oestrogen-receptor-positive, locally advanced or BC cancer in postmenopausal women whose cancer has relapsed on or after adjuvant anti-oestrogen therapy, or who have disease progression on anti-oestrogen therapy. *This non-recommendation is based on cost-effectiveness.*

Notes: 1. Does not document patient access schemes mentioned in recommendations. Only the clinical settings and populations are given. Table entries are restricted to those which are relevant to the current submission. The NICE Clinical Guideline also covers first-line treatment of aBC with endocrine therapy, these entries have been excluded.

B.1.4 Equality considerations

There are no equality considerations to be made.

B.2 *Clinical effectiveness*

B.2.1 **Identification and selection of relevant studies**

Relevant randomised controlled trial (RCT) evidence has been sourced from a systematic literature review (SLR) up to March 2016, conducted by Wilson et al. (2017).[41] Two further updates of the Wilson's SLR up to January 2018 and February 2019 were conducted to identify all relevant clinical data from the published literature regarding the clinical effectiveness of pre/peri/post-menopausal women with HR+, HER2- locally advanced or metastatic breast cancer receiving first- or second-line therapy for their disease and who have been exposed to prior endocrine therapy, either in the (neo)adjuvant or advanced/metastatic setting.

Further details of the SLR are available in Appendix D.

B.2.1.1 *Search strategy*

The systematic reviews (the original search from 2015 and the updates from 2016, 2018 and 2019) were performed in accordance with the methodological principles of conducting systematic reviews as detailed in the University of York Centre for Reviews and Dissemination guidance for undertaking systematic reviews in health care and is reported here following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting checklist.[8, 9]

The following electronic databases were searched for the original systematic review[42] from their inception dates until the date of the search, indicated below:

- MEDLINE, MEDLINE In-Process and MEDLINE Daily Update, 22 January 2015 (using Ovid SP platform)
- Embase, 22 January 2015 (using Elsevier Platform)
- The Cochrane Library (Wiley Online platform), 23 January 2015, specifically the following:
    - The Cochrane Central Register of Controlled Trials (CENTRAL)
    - The Cochrane Database of Systematic Reviews (CDSR)
    - Database of Abstracts of Reviews of Effectiveness (DARE)
    - Health Technology Assessment (HTA) Database

The same databases were searched again on 28 April 2016 as part of the first systematic review update.[41,43] However, the following minor changes were made:

- The Epub Ahead of Print database was searched alongside the MEDLINE databases, using the Ovid SP platform
- Embase was searched using the Ovid SP platform instead of Elsevier. This search was run simultaneously with the MEDLINE search. Search terms were translated and adapted as necessary for use in the Ovid SP platform.

No date limits were applied in the update search; instead, the EndNote library of search results obtained in the April 2016 update was de-duplicated against the library obtained in the January 2015 search, prior to screening of titles and abstracts.

As well as the electronic database searches, the following conference proceedings were searched from 2012–2015 (2012–2014 in the original SLR, and 2015 in the systematic review update):

- American Society of Clinical Oncology (ASCO)
- American Association for Cancer Research (AACR), including the San Antonio Breast Cancer Symposium
- European Society of Medical Oncology (ESMO), including:
    - ESMO
    - IMPAKT-Breast Cancer
    - European Cancer Congress
    - ESMO Asia
    - Immuno-Oncology

As part of the last SLR update, the same databases from Wilson's SLR were searched on 26 January 2018 as part of the SLR update, as well as for the other update on 15 February 2019, with the following minor change: Embase was searched using the Elsevier instead of Ovid SP platform.

In addition, a search of conference proceedings identical to Chirila's SLR was conducted for the years of 2016-2018 and in the update and adaptation in 2019 for the year 2018 and 2019.

Finally, ClinicalTrials.gov and the International Clinical Trials Registry Platform were searched for relevant RCTs of palbociclib in Chirila's SLR. The search was extended to all relevant comparators in the update/adaptation of Wilson's SLR. The FDA website was also searched for the Summary Basis of Approvals in Chirila's SLR and in the update/adaptation of Wilson's SLR.

Full details of the original systematic review and the subsequent updates are presented in Appendix D, including full list of studies which were excluded at the full-text screening stage as well as excluded studies which were identified from clinicaltrials.gov.

B.2.1.2 *Description of identified studies*

A total number of 60 studies were included from Wilson's systematic review. The update/adaptation of Wilson's systematic review also included 38 publications of 23 unique studies, out of which 2 were subgroup analysis and updated publications of studies already included in the previous reviews. The 2019 update resulted in the inclusion of 44 publications, of which 22 unique studies. Of these unique studies, 13 were not identified before. Overall, 142 publications for 94 unique studies were included in the review.

B.2.2 **List of relevant clinical effectiveness evidence**

B.2.2.1 *Palbociclib studies*

The SLR for clinical evidence identified several publications, from one RCT of palbociclib plus fulvestrant in women with HR-positive HER2-negative aBC of any menopausal status who had received and become resistant to prior endocrine therapy PALMOA-3 (NCT01942135). A summary of the PALOMA-3 study and the associated publications between 2015 and 2018 is presented in Table 7.

Table 7. Overview of PALOMA-3

Study	NCT01942135 (PALOMA-3)				
Study design	International, multicentre, 2:1 randomised, double-blind, placebo-controlled, parallel-group, Phase 3 clinical study				
Population	Women 18 years of age or older and of any menopausal status, with HR-positive, HER2-negative aBC not amenable to resection or radiation therapy with curative intent or metastatic breast cancer, whose disease progressed during or soon after completion of prior endocrine therapy received in the (neo)adjuvant or advanced setting.				
Intervention(s)	Palbociclib in combination with fulvestrant				
Comparator(s)	Fulvestrant				
Indicate if trial supports application for marketing authorisation	Yes	✓	Indicate if trial used in the economic model	Yes	✓
	No			No	
Rationale for use/non-use in the model	This is the pivotal study of palbociclib for this population.				
Reported outcomes specified in the decision problem	• PFS, OS, OR, CBR, DR • AEs • HRQoL				
Other reported outcomes	TTD				
Key publication	Turner 2015[4]				
Secondary publications	Cristofanilli 2016[8] Harbeck 2016[44] Turner 2016[45] Loibl 2016[46] Verma 2016[47] Loibl 2017[48] Lwata 2017[49] Turner 2018[50] O'Leary 2018[51] Turner 2018[37] Cristofanilli[52] O'leary 2018[53] Masdua 2019[54]				

Notes: a. Pre- or peri-menopausal women are required to combine the fulvestrant treatment with an LHRH agonist. Abbreviations: aBC, advanced breast cancer; AE, adverse event; CBR, clinical benefit response; DR, duration of response; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; HRQoL, health-related quality-of-life; LHRH, luteinizing hormone-releasing hormone; OR, objective response; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation.

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

B.2.3.1 *PALOMA-3 - Study methods overview*

PALOMA-3[55] is an ongoing[1] international, multicentre, 2:1 randomised, double-blind, placebo-controlled, parallel-group, Phase 3 clinical study with the primary objective of demonstrating the superiority in prolonging PFS of palbociclib plus fulvestrant (Faslodex®) over fulvestrant plus placebo in women 18 years or older of any menopausal status, with HR-positive, HER2-negative aBC not amenable to treatments or interventions with curative intent, whose disease had progressed within 12 months of completion or whilst on endocrine therapy, or whose disease has progressed on previous treatment in the advanced setting. The safety between the two treatment arms was also compared. During study treatment, pre- and perimenopausal women were required to be receiving therapy with the LHRH agonist goserelin acetate (Zoladex® or generic).

A brief overview of PALOMA-3 methodology is provided in Table 8. The complete list of inclusion and exclusion criteria for PALOMA-3 is presented in the Appendix M.

Table 8. Summary of PALOMA-3 methodology[55]

Trial number (acronym)	**PALOMA-3 (study A5481023)**
Location	144 sites in 17 countries across Australia, Canada, Europe, Japan, Russian Federation, Republic of South Korea, Taiwan, Turkey, Ukraine, United States and United Kingdom.
Trial design	Phase 3, multicentre, randomised, double-blind, placebo-controlled, triple masked (Participant, Care Provider, Investigator) study. Treatment is continued until objective demonstration of disease progression, symptomatic deterioration, unacceptable toxic effects, or withdrawal of consent, whichever occurs first. Crossover in the event of disease progression was not allowed.
Method of randomisation	The original estimated enrolment of 417 eligible women was planned to be randomised assigned on a 2:1 basis to receive either palbociclib in combination with fulvestrant (278 women), or placebo in combination with fulvestrant (139 women). The actual enrolment comprised 521 women. Randomisation was stratified according to three factors: • the presence or absence of visceral metastasis§ (Yes vs No); • menopausal status at study entry (postmenopausal vs. pre- or peri-menopausal); • sensitivity to prior endocrine therapy (Yes vs No)#.
Eligibility criteria for participants	Inclusion Criteria (all the following): • Women 18 years or older with aBC not amenable to curative therapy • Any menopausal status

[1] Final PFS and OS results are now available.

	• Histologically or cytologically confirmed diagnosis of HR-positive/HER2-negative aBC with evidence of recurrent (local or metastatic) disease • Progressed during or within 12 months of completion of (neo)adjuvant endocrine therapy or progressed during or within 1 month of completion of prior advanced/metastatic endocrine breast cancer therapy • On an LHRH agonist for at least 28 days, if pre-/peri-menopausal, and willing to switch to goserelin (Zoladex®) at time of randomisation. • Measurable disease defined by RECIST version 1.1, or bone-only disease • ECOG score of 0-1 • Adequate organ and marrow function, resolution of all toxic effects of prior therapy or surgical procedures • Patient must agree to provide tumour tissue from metastatic tissue at baseline Exclusion Criteria (any of the following): • Prior treatment with any CDK inhibitor, fulvestrant, everolimus, or agent that inhibits the PI3K-mTOR pathway • Patients with extensive advanced/metastatic, symptomatic visceral disease, or known uncontrolled or symptomatic CNS metastases • Major surgery or any anti-cancer therapy within 2 weeks of randomisation • Prior stem cell or bone marrow transplantation • Use of potent CYP3A4 inhibitors or inducers
Settings & locations where the data were collected	Multicentre (144 centres in 17 countries).
Trial drugs and method of administration	In this study, palbociclib capsules of 125 mg, matching palbociclib placebo, and fulvestrant in pre-filled syringes (250 mg in 5 ml solution) were used. Palbociclib 125 mg capsules (or matching placebo capsules in the placebo plus fulvestrant group) were taken orally once daily on days 1 to 21 of each 28-day cycle. 500mg of fulvestrant was administered by two consecutive intramuscular injections on Days 1 and 15 of Cycle 1, and every 28 days (±7 days) thereafter starting from Day 1 of Cycle 2. Placebo orally continuously dosed for 3 weeks followed by 1 week off; repeated at each subsequent cycle Patients will continue to receive assigned treatment until one of the following criteria was met (whichever occurred first): • Disease progression • Symptomatic deterioration • Unacceptable toxicity • Death • Withdrawal of consent In the event of significant treatment-related toxicity, palbociclib/placebo dosing may be interrupted or delayed and/or reduced.

	Dose modifications may occur in three ways: • Within a cycle: dosing interruption until adequate recovery followed by dose reduction, if required. • Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start. • At start of the new cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle. Patients experiencing adverse events meeting certain criteria will have their treatment with palbociclib/placebo interrupted/delayed. If the retreatment parameters are met within 3 weeks of treatment interruption palbociclib/placebo may be resumed. In case of a Grade 2 toxicity lasting for >3 weeks or a Grade ≥3 toxicity, dose reduction is recommended for the subsequent cycles. Dose reduction of palbociclib/placebo by one, and, if needed, by two dose levels (see below) is recommended depending on type and severity of the toxicity. Once a dose has been reduced for a given patient, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Dose re-escalation is not allowed. Palbociclib/placebo dose reduction levels (fulvestrant 2 x 250mg/injection): • 125mg/day • 100 mg/day • 75 mg/day Palbociclib/placebo dose de-escalation below 75 mg/d is not allowed, but the schedule may be changed to 75 mg/day two weeks on followed by two weeks off (2/2 schedule). **Fulvestrant** No dose adjustment for fulvestrant is permitted. A single fulvestrant injection can be skipped in case of a fulvestrant-related toxicity or dosing can be delayed. Treatment delay for fulvestrant-related toxicities will be performed as per the investigator's best medical judgment, but by no more than 7 days. If delay of longer than 7 days is required, then the dose should be skipped. In the event of a toxicity requiring dosing delay of palbociclib/placebo, fulvestrant can also be delayed by a maximum of 7 days
Primary outcomes	The primary endpoint was PFS (assessed by the Investigator and up to 12 months) which was defined as the time from the date of randomisation to the date of the first documentation of objective PD or death due to any cause in the absence of documented PD, whichever occurred first.

Secondary and other outcomes	• OS, OR, CBR, DR
	• PROs including:
	  ○ EORTC QLQ-C30 (change from baseline)
	  ○ EORTC QLQ-BR23 (change from baseline)
	  ○ TTD
	  ○ EQ-5D (Index score and VAS)
	• TEAEs
	• Biomarker analyses

Pre-planned subgroups for PFS analysis	• Age (<65 years, ≥65 years) • Race (White, Asian, Black or other) • Region (North America, Europe, Asia Pacific) • Baseline ECOG score (0 or 1)

	• Menopausal status at study entry (pre/peri, post) • Metastatic disease site (visceral, non-visceral) • Sensitivity to prior endocrine therapy (yes, no) • Receptor status (ER+/PgR+, ER+/PgR-) • Disease-free interval (≤24 months, >24 months) • Bone-only disease at baseline (yes, no) • Number of disease sites (1, 2, ≥3) • Prior chemotherapy ((neo)adjuvant only, advanced/metastatic ± (neo)adjuvant, none) • Prior lines of therapy in metastatic setting (0, 1, 2, ≥3) • Most recent therapy by setting ((neo)adjuvant, advanced/metastatic) • Most recent therapy by type of prior endocrine therapy (aromatase inhibitors; anti-oestrogens; other)
Duration of study and follow-up	PALOMA-3 date of first enrolment was 26 September 2013. A total 521 patients had enrolled by 26 August 2014. The primary analysis of the primary PFS endpoint was performed at the data cut-off date of 05 December 2014 after PD or death had been documented in patients for a total of 195 events based on the investigator's assessment (approximately 82% of the total number of PFS events planned for final analysis). At that point, the median duration of follow-up for both treatment arms was 5.6-months. Since the analysis of the December 2014 data cut (published in Turner 2015[4]), two further data cuts and two further analyses have been carried out on PFS, deaths and tumour response: March 2015 – exploratory analysis (Cristofanilli 2016[8]) October 2015 – latest data cut (2016 San Antonio Breast Cancer Symposium[45]; Turner 2018;[50] 2016 European Society for Medical Oncology.[46]) The October 2015 data cut formed the basis for clinical efficacy data in this submission. The analysis was performed after PD or death had been documented for a total of 333 events based on the investigator's assessment. As an indication of data maturity, the ratio of the number of events (N=333) to the number of patients (N=521) reached 64%. The median duration of follow-up was 15.8 months for the palbociclib plus fulvestrant arm and 15.3 months for the placebo plus fulvestrant arm. Results of the analysis performed at the October 2015 cut-off date, representing more mature data, have been submitted to the EU Regulatory Agencies for assessment during the EU Marketing Authorisation Application review. Turner et al. 2018 forms the basis of the OS data analysis from April 13th 2018 datacut.[37]

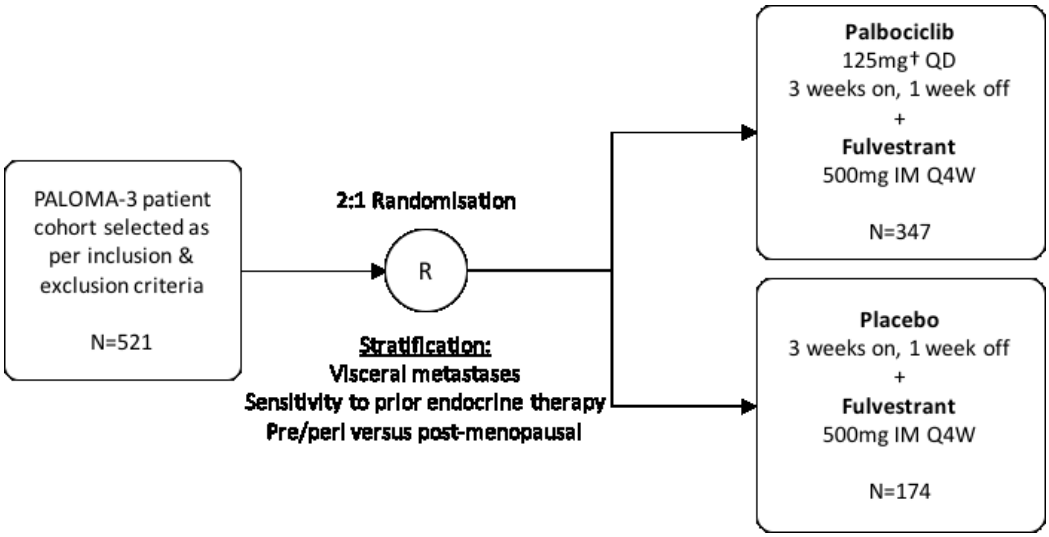
Notes: #In PALOMA-3, patients were defined as sensitive to prior endocrine therapy if they had a relapse after 24 months of adjuvant endocrine therapy or had a clinical benefit (objective response [complete or partial] or stable disease lasting ≥24 weeks) from prior endocrine therapy in the context of advanced disease. §Visceral metastatic disease involvement was defined by evidence of cancer in the lung, liver, brain, pleura, and/or peritoneum.

Abbreviations: aBC, advanced breast cancer; CBR, clinical benefit response; CDK, cyclin-dependent kinase; CNS, central nervous system; CYP3A4, Cytochrome P450 3A4; DR, duration of response; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-BR23, QLQ Breast Cancer Module; EQ-5D, EuroQoL five dimension score; ER, oestrogen receptor; EU, European Union; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LHRH, luteinizing hormone-releasing hormone; OR, objective response; OS, overall survival; PD, progressed disease; PI3K-mTOR, phosphoinositide 3 kinase – mammalian target of rapamycin; PFS, progression-free survival; PgR, progesterone receptor; PRO, patient-reported outcome; RECIST, Response

Evaluation Criteria in Solid Tumours; TEAEs, treatment-emergent adverse events; TTD, time to deterioration in pain score VAS, visual analogue scale.

The randomisation methodology is depicted graphically in Figure 3.

Figure 3. PALOMA-3 study design and randomisation[45]



Notes: † 75 mg, 100 mg or 125 mg;

Abbreviations: QD, once daily; IM, intramuscular injection; Q4W, once every 28 days.

B.2.3.2 *PALOMA-3 - Outcomes reported*

The PALOMA-3 study captured clinical, safety and patient-reported outcomes. Definitions and methods of assessment of primary and secondary outcomes are provided in Table 9.

B.2.3.2.1 *Clinical outcomes*

All primary and secondary endpoints based on radiological (and photographical where applicable) assessments of tumour burden (i.e., PFS, OR, DR, CBR) were derived using the local radiologist's/investigator's assessment.

PFS was the primary outcome in PALOMA-3. PFS was defined as the time from the date of randomisation until either:

- the patient first had documentation of an objective disease progression (PD);
- in the absence of any PD observations, the patient died.

Secondary clinical outcomes collected in PALOMA-3 were overall survival (OS), measures assessing tumour control (OR, CBR and DR), and time to treatment discontinuation (TTD).

Pharmacokinetic analyses were carried out in line with the protocol and are reported in the product SmPC[56] (see Appendix C).

B.2.3.2.2 *Patient-reported outcomes (PROs)*

PROs for functioning, global quality of life and general health status were assessed using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30,[57] Breast Cancer Module (EORTC QLQ-BR23)[58] and EuroQoL-5D (EQ-5D) index score and VAS[59]). Patients completed each instrument at pre-dose on Day 1 of Cycles 1-4, then on Day 1 of every other subsequent cycle starting with Cycle 6 (i.e. cycles 6, 8, 10, etc.), and then at the End-of-treatment visit.

In addition to the above analyses, the time to deterioration in the pain subscale of the QLQ-C30 was examined using survival analysis methods. Deterioration was defined as an increase in score of 10 points or greater from baseline.

Patients were to complete these instruments in the clinic and prior to having any tests or any discussion of their progress with healthcare personnel at the site.

B.2.3.2.3 *Safety*

Safety assessment consisted of monitoring of all adverse events (AEs), including serious AEs (SAEs), regular monitoring of haematology, serum chemistry, and routine monitoring of ECGs, physical examinations, vital signs, ECOG performance status, and chest CTs.

Table 9. Description of outcomes reported in PALOMA-3[55]

Outcome	Description
Primary efficacy outcome	
PFS	PFS was defined as the time from the date of randomisation to the date of the first documentation of objective PD or death due to any cause in the absence of documented PD, whichever occurred first.
Secondary efficacy outcomes	
OR	OR was defined as CR or PR according to RECIST v.1.1[60] recorded from randomisation until disease progression or death due to any cause. The RECIST v1.1 definitions of CR and PR are assessed by MRI. CR corresponds to the disappearance of all target lesions; PR is characterized as a ≥30% decrease in the sum of the longest diameter of target lesions (longest for non-nodal and short axis for nodal target lesions).[60]
CBR	CBR was defined as the overall CR, PR, or SD ≥24 weeks according to the RECIST version 1.1,[60] recorded in the period between randomisation and disease progression or death of any cause. Participants who did not have on-study radiographic tumour re-evaluation, who received anti-tumour treatment other than the study medication prior to reaching a CR or PR, a best response of SD ≥24 weeks, or who died, progressed, or dropped out for any reason prior to reaching a CR or PR and a best response of SD ≥24 weeks were counted as non-responders in the assessment of CBR.
OS	OS was defined as the time from the date of randomisation to the date of all-cause death. Patients last known to be alive were censored at the last contact date. Kaplan-Meier analysis was used to estimate OS probability.

Outcome	Description
DR	DR was defined as the time from the first documentation of objective tumour response (CR or PR) to the first documentation of objective tumour progression or to death due to any cause, whichever occurred first. DR data were censored on the date of the last tumour assessment on study for patients who did not have objective tumour progression and who did not die due to any cause while on study. DR was only calculated for the subgroup of patients with an OR.
Patient reported outcomes (PROs)	
EORTC QLQ-C30	The EORTC-QLQ-C30[57] is a 30-item questionnaire composed of five multi-item functional subscales (physical, role, emotional, cognitive, and social functioning), three multi-item symptom scales (fatigue, nausea/vomiting, and pain), a global QOL subscale, and 6 single item symptom scales assessing other cancer-related symptoms (dyspnoea, sleep disturbance, appetite loss, constipation, diarrhoea, and the financial impact of cancer). The questionnaire includes 4-point Likert scales to assess functioning and symptoms and two 7-point Likert scales for global health and overall QOL. Responses to all items are to be then converted to a 0 to 100 scale using a standard scoring algorithm. For functional and global QOL scales, higher scores represent a better level of functioning/QOL. For symptom-oriented scales, a higher score represents higher symptoms severity.
EORTC QLQ-BR23	The EORTC-QLQ-BR23[58] is a 23-item breast cancer-specific companion module to the EORTC-QLQ-C30 and consists of 4 functional scales (body image, sexual functioning, sexual enjoyment, future perspective) and 4 symptom scales (systemic side effects, breast symptoms, arm symptoms, upset by hair loss).
EQ-5D	The EQ-5D (version 3L[59]) is a brief, self-administered, validated instrument consisting of 2 parts. The first part consists of 5 descriptors of current health state (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression); a patient is asked to rate each state on a three-level scale with higher levels indicating greater severity/impairment. Published weights are available to derive the EQ-5D index, which ranges from 0 to 1 with low scores representing a higher level of dysfunction and 1 as perfect health. The second part consists of the EQ-5D general health status as measured by VAS. The EQ-5D VAS measures the patient's self-rated health status on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state).
Time to deterioration	Time to deterioration in the pain subscale of QLQ-C30 was carried out using survival analysis methods. Deterioration was defined as an increase in score of 10 points or greater from baseline.
Safety	
Safety	AEs were classified using MedDRA v. 17.1 classification system. The severity of the toxicities was graded according to the NCI CTCAE v4.0 whenever possible.[61] AEs were summarised by treatment and by the frequency of patients experiencing TEAEs corresponding to body systems and MedDRA preferred term. AEs were graded by worst NCI CTCAE v4.0 Grade. Detailed information collected for each AE included a description of the event, duration, whether the AE was serious, intensity, relationship to study drug, action taken, and clinical outcome. Emphasis in the analysis was placed on treatment-related TEAEs rather than all-cause TEAEs.
Other	

Outcome	Description
TTD (time to treatment discontinuation)	The term "discontinuation" refers to a patient's withdrawal (temporary or permanent) from the active treatment phase. The reason for discontinuation from treatment was collected on the appropriate CRF. Patients could have been withdrawn from the active treatment phase in the event of: • Disease progression as per RECIST v.1.1 • Symptomatic deterioration (i.e., global deterioration of health status without objective evidence of disease progression as per RECIST v.1.1). • Need for new or additional anticancer therapy not specified in the protocol. • Unacceptable toxicity. • Investigator's conclusion that discontinuing therapy was in the patient's best interest • Lost to follow-up • Patient choice to withdraw from treatment (follow-up permitted by patient) • Withdrawal of patient consent (cessation of follow-up) • Death If a patient opted to discontinue from the active treatment phase as the result of an unacceptable adverse drug reaction. The reason for discontinuation was recorded as "Unacceptable toxicity".
Time to chemotherapy	Time to chemotherapy was defined as the time from randomisation to the receipt of chemotherapy.

Abbreviations: AE, adverse event; AESI, adverse event of special interest; CBR, clinical benefit response; CI, confidence interval; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; CRF, case report form; DR, duration of response; EQ-5D, EuroQoL five dimensions score; HR, hazard ratio; MedDRA, medical dictionary for regulatory activities; MRI, magnetic resonance imaging; NCI, National Cancer Institute; OR, objective response; OS, overall survival; PD, progressed diseases; PFS, progression-free survival; PR, partial response; PRO, patient-reported outcome; QOL, quality of life; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality of life questionnaire; EORTC QLQ-BR23, QLQ Breast Cancer Module; RECIST, Response Evaluation Criteria in Solid Tumours; SAE, serious adverse event; SD, stable disease; TEAE, treatment-emergent adverse event; TTD, time to treatment discontinuation; VAS, visual analogue scale.

B.2.3.3 *PALOMA-3 - Baseline characteristics*

The baseline characteristics of patients randomly assigned to treatment arms in the PALOMA-3 study are summarised in Table 10. These characteristics were well balanced between the two groups. The clinical baseline characteristics of patients' subgroups according to whether their prior endocrine therapy failed either in the (neo)adjuvant setting or in the advanced/metastatic setting are presented in the Appendix P.

Table 10. Summary of baseline characteristics of patients in PALOMA-3 – ITT population[55]

Characteristics	**Palbociclib + Fulvestrant (N=347)**	**Placebo + Fulvestrant (N=174)**
Age median (min-max)	57 (30-88)	56 (29-80)
<65, n (%)	261 (75.2)	131 (75.3)
≥ 65, n (%)	86 (24.8)	43 (24.7)
Race, n (%)		
White	252 (72.6)	133 (76.4)
Black	12 (3.5)	8 (4.6)
Asian	74 (21.3)	31 (17.8)
Other	8 (2.3)	1 (0.6)

Characteristics	Palbociclib + Fulvestrant (N=347)	Placebo + Fulvestrant (N=174)
Unspecified	1 (0.3)	1 (0.6)
Ethnicity, n (%)		
Hispanic/Latino	[redacted]	[redacted]
Not Hispanic/Latino	[redacted]	[redacted]
Unspecified	[redacted]	[redacted]
ECOG performance status, n (%)		
0	206 (59.4)	116 (66.7)
1	141 (40.6)	58 (33.3)
Sensitivity to prior hormonal therapy, [a] n (%)		
Yes	274 (79.0)	136 (78.2)
No	73 (21.0)	38 (21.8)
Visceral metastases, [a] n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Menopausal status, [a,b] n (%)		
Pre-/peri-	72 (20.7)	36 (20.7)
Post-	275 (79.3)	138 (79.3)
Prior systemic therapies, n (%)		
No	[redacted]	[redacted]
Yes	[redacted]	[redacted]
Number of regimens		
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
>3	[redacted]	[redacted]
Previous chemotherapy regimen for primary diagnosis, n (%)		
No	[redacted]	[redacted]
Yes	[redacted]	[redacted]
Oncology treatment types		
Neoadjuvant	[redacted]	[redacted]
Adjuvant	[redacted]	[redacted]
Advanced/metastatic	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Previous hormonal regimen for primary diagnosis, n (%)		
1	[redacted]	[redacted]
>1	[redacted]	[redacted]
Previous anti-hormonal therapy, n (%)		
Tamoxifen	[redacted]	[redacted]
Aromatase inhibitors	[redacted]	[redacted]
Measurable disease present, [c] n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Involved disease site, [a,d] n (%)		
Bone	[redacted]	[redacted]
Breast	[redacted]	[redacted]
Liver	[redacted]	[redacted]
Lung	[redacted]	[redacted]
Lymph node	[redacted]	[redacted]
Other	[redacted]	[redacted]
Disease stage at initial diagnosis, n (%)		
Stage I	[redacted]	[redacted]
Stage IB	[redacted]	[redacted]
Stage II	[redacted]	[redacted]
Stage IIA	[redacted]	[redacted]

Characteristics	Palbociclib + Fulvestrant (N=347)	Placebo + Fulvestrant (N=174)
Stage IIB	[redacted]	[redacted]
Stage III	[redacted]	[redacted]
Stage IIIB	[redacted]	[redacted]
Stage IIIC	[redacted]	[redacted]
Stage IV	[redacted]	[redacted]
Other	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Previous chemotherapy		
Neoadjuvant or adjuvant only	139 (40%)	74 (43%)
Treatment of metastatic disease (with or without adjuvant or neoadjuvant)	113 (33%)	64 (37%)

Notes: a. Based on randomization; b. Postmenopausal status defined by at least 1 of the following criteria: 1) ≥ 60 years of age; 2) <60 years of age and cessation of regular menses for at least 12 consecutive months, with no alternative pathological or physiological cause, and serum estradiol and follicle stimulating hormone level within the laboratory's reference range for postmenopausal women; 3) documented bilateral oophorectomy; or 4) medically confirmed ovarian failure. Pre- or perimenopausal status defined as not meeting the criteria for being postmenopausal; c. At least 1 target lesion ≥ 20 mm by conventional techniques or at least 1 target lesion >10 mm by spiral computed tomography; d. Involved sites included both target and nontarget lesions. Sites with multiple lesions were counted once.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; max, maximum; min, minimum; N, total number of patients in population; n, number of patients meeting pre-specified criteria.

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

Appendix O provides a breakdown of the patient numbers analysed in each of the data cuts generated throughout the PALOMA-3 study period.

B.2.4.1 *PALOMA-3 – Analysis populations*

Information about the study population is presented in Table 11.

Table 11. Summary of population analyses in PALOMA-3[55]

Type of analysis	Study population
ITT population	The ITT population included all patients who were randomised, with study drug assignment designated according to initial randomisation. The ITT population was the primary population for evaluating all efficacy endpoints and patient characteristics.
AT population	The AT population included all patients who received at least 1 dose of study treatment (i.e., palbociclib/placebo or fulvestrant), with treatment assignments designated according to actual study treatment received. The AT population was the primary population for evaluating treatment administration/compliance and safety.
PRO Analysis population	The PRO evaluable population was defined as a subset of ITT patients, who had completed a baseline and at least one post–baseline PRO assessment prior to end of study treatment.
Safety Analysis	The AT population was the primary population for evaluating safety. This population included all patients who received at least one dose of any agent of the combination.

Abbreviations: AT, as-treated; ITT, intention-to-treat; PRO, patient-reported outcome

B.2.4.2 *PALOMA-3 - Approach to efficacy analyses*

Efficacy analyses were conducted on the ITT population. Analysis of DR was based upon the responders (CR or PR) from the ITT population. All analyses were performed using SAS® Version 9.2 or higher.

All primary and secondary endpoints based on radiological (and photographical where applicable) assessments of tumour burden (i.e., PFS, OR, DR, CBR) were derived using the local radiologist's/investigator's assessment. An independent third-party core imaging laboratory performed a Blinded Independent Central Review (BICR) audit which was based on approximately 40% randomly selected patients. This information was used for supportive analyses.

B.2.4.3 *PALOMA-3 - Hypotheses, tests and data management*

Statistical hypotheses (where applicable) and methods in PALOMA-3 are summarised in Table 12 for the primary outcome, PFS, and in Table 13 for secondary outcomes. All analyses were conducted at a 1-sided 0.025 level of significance. Handling of missing data is described in detail in Appendix N.

Table 12. Summary of statistical analysis and data management for the primary outcome of PFS in PALOMA-3[55]

Hypothesis	Statistical analysis	Sample size	Data management
H0: HR=1 versus HA: HR<1, for palbociclib plus fulvestrant compared to placebo plus fulvestrant.	The length of PFS was calculated as PFS time (months) =[progression/death date (censor date) - randomisation date + 1]/30.4.[62] The primary analyses of PFS were performed in the ITT population. A log-rank test (1-sided) stratified by the presence of visceral metastases and sensitivity to prior hormonal therapy was used to compare PFS time between the 2 treatment arms with the overall significance level preserved at 0.025 (1 sided). PFS time associated with each treatment arm was summarised for the ITT population using the Kaplan-Meier method. CIs for the 25th, 50th, and 75th percentiles of the event-free time were reported. The Cox Proportional hazards model was used to compute the HR and the corresponding 95% CI.	The sample size was based on the results of a randomised Phase 2 trial assessing fulvestrant with or without dasatinib in postmenopausal patients with HR-positive metastatic breast cancer previously treated with an aromatase inhibitor.[63] The median PFS for the placebo plus fulvestrant arm was 5.3 months, and the median PFS for the combination arm was 6.0 months. Based on these results, the median PFS for the control arm in this study was assumed to be 6.0 months. Therefore, PALOMA-3 was designed to detect an improvement of 56% to a median PFS of 9.4 months (corresponding to an HR of 0.64). A total of 238 PFS events were needed in the 2 treatment arms (with a 2:1 randomisation) for the study to have a 90% power to detect an HR of 0.64 with a 1-sided significance level of α=0.025. A total sample size of 417 patients (278 in the fulvestrant plus palbociclib arm and 139 in the placebo plus fulvestrant arm) was required.	PFS data were censored on the date of the last tumour assessment on study for patients who did not have objective tumour progression and who did not die while on study. Patients lacking an evaluation of tumour response after randomisation had their PFS time censored on the date of randomisation with the duration of one day. Patients who started a new anticancer therapy prior to documented PD were censored at the date of the last tumour assessment prior to the start of the new therapy. Patients with documentation of PD or death after an unacceptably long interval (i.e., 2 or more incomplete or non-evaluable assessments) since the last tumour assessment were censored at the time of last objective assessment that did not show PD.

Abbreviations: CI, confidence interval; CR, complete response; DFI, disease-free interval; H0, null hypothesis; HA, alternative hypothesis; HR, hazard ratio; ITT, intention to treat; PD, progressed disease; PFS, progression-free survival; PR, partial response.

Table 13. Summary of statistical analysis methods for secondary outcomes in PALOMA-3[55]

Secondary outcome	Statistical analysis and data management
OS	All patients randomised were considered evaluable for OS. OS was hierarchically tested for significance at the time of PFS analysis, provided the primary PFS endpoint was statistically significant at the interim and/or final analyses. The main objective of hierarchical testing was to test PFS (primary) and OS (secondary) hypotheses proposed in this study with the family-wise error rate strongly controlled at level 0.025. A stratified log-rank test (using the same stratification factors as for the PFS analysis) was used to compare OS between the treatment arms. OS for the two treatment arms was assessed using Kaplan-Meier methods and displayed graphically where appropriate. The median event times and 95% CIs were estimated. Cox regression models were used to estimate the HR and its 95% CI. The 1-year survival probability was estimated using the Kaplan-Meier method and a two-sided 95% CI for the log [-log(1-year survival probability)] was calculated using a normal approximation using the Greenwood's formula, and then back-transformed to give a CI for the 1-year survival probability itself. The 2-year and 3-year survival probabilities were estimated similarly.
OR	A patient was considered to have achieved OR if she had a sustained CR or PR according to RECIST v.1.1 definitions.[60] Otherwise, the patient was considered as a non-responder in the OR rate analysis. Additionally, patients with inadequate data for tumour assessment (e.g., no baseline assessment or no follow-up assessments) were considered as non-responders in the OR rate analysis. The OR rate in each randomised treatment arm was estimated by dividing the number of patients with OR (CR or PR) by the number of patients randomised to the respective treatment arm ("response rate"). A 95% CI for the response rates was provided. Response rate comparisons between the 2 treatment arms as randomised were assessed using the Cochran–Mantel–Haenszel (CMH) test with the same stratification factors as for the PFS analysis. Analyses of OR rate were performed on the ITT population based on the investigator's assessment, on the investigator-assessed ITT population with measurable disease at baseline as well as on a randomly sampled audit subset of the ITT population based on the review of the blinded independent third-party core imaging laboratory. In addition, the Best Overall Response for each patient was summarised by treatment arm.
CBR	Analyses for CBR were performed on the ITT population based on the investigator's assessment and on a randomly sampled audit subset of the ITT population based on the review of the blinded independent third-party core imaging laboratory. A 95% CI for the CBR rate was provided. CBR rate comparison between the two treatment arms as randomised was assessed using the CMH test with the same stratification factors as for the PFS analysis.
DR	DR was only calculated for the subgroup of patients with an OR.

Secondary outcome	Statistical analysis and data management
	DR was calculated as [the date response ended (i.e., date of PD or death) - first CR or PR date + 1)]/30.4. DR for the two treatment arms was summarised using Kaplan-Meier methods and displayed graphically, where appropriate. The median event time and 95% CI for the median were provided for each endpoint. The DR was only calculated for the participants with a CR or PR.
PROs	Completion rates were summarised by cycle. Patient reported global QOL, functioning and symptom scores assessed using the EORTC QLQ-C30 and BR-23 and change from baseline scores were compared between the treatment arms using a longitudinal repeated measures mixed model (2-sided) approach adjusting for specified covariates. Statistical significance of within treatment arm change from baseline was interpreted using the 95% CIs of the average change from baseline score. In addition to the above analyses, the time to deterioration in pain was carried out using survival analysis methods. Deterioration was defined as an increase in score of 10 points or greater from baseline. A log-rank test (1-sided) was used to compare time to deterioration between the 2 treatment arms. Time to deterioration in pain associated with each treatment arm was summarised using the Kaplan-Meier method and displayed graphically. The Cox proportional hazards model was used to compute the treatment HR and the corresponding 95% CI. EQ-5D general health status and EQ-5D Index and VAS scores between treatment arms were compared using longitudinal repeated measures models. No adjustments were made for multiple comparisons.

Secondary outcome	Statistical analysis and data management
Safety	The percentage of participants with TEAEs and participants who discontinued was reported according to the AT population analysis. A detailed risk analysis was undertaken.[47] Emphasis in the analysis was placed on AEs classified as treatment-related TEAEs. A 3-tier approach was used to summarise AEs. Tier-1 events: pre-specified events of clinical importance and maintained in a list in the product's Safety Review Plan. Tier-2 events: events that are not Tier-1 but are "common". A MedDRA preferred term is defined as a tier-2 event if there are at least 10% for all grades in any treatment group. For grade 3/4/5 analysis, the events were to be reported in at least 5% patients in any treatment group. Tier-3 events: events that are neither Tier-1 nor Tier-2 events. For Tier-1 events, the MedDRA preferred term, treatment arm, n (%) for each MedDRA preferred term per arm, risk difference, 95% CI and p-values for the risk difference were provided. Graphical format was presented as well in descending p-value order. For Tier-2 events, the MedDRA preferred term, treatment arm, n (%) for each MedDRA preferred term per treatment arm, risk difference and 95% CIs for the risk difference were provided in tabular format. A table of AEs for All Grade and for Grade 3/4/5 was provided. Tier-3 events were presented by observed event proportions. The following was provided: Incidence and grade of treatment-emergent (all-causality, preferred term, and by SOC) AEs for all cycles combined. Incidence and grade of treatment-emergent (all-causality, preferred term) AEs for all cycles combined by descending frequency order. Incidence and grade of treatment-emergent (treatment related, preferred term and by SOC) AEs for all cycles combined. Incidence and grade of treatment-emergent (treatment related, preferred term) AEs for all cycles combined by descending frequency order.
TTD	The analysis of time to permanent discontinuation of treatment was undertaken in the 'As Treated' population For patients who already discontinued from study treatment, each patient had been counted as an event, and the time to treatment discontinuation had been calculated as (last dose date – first dose date)+1. For patients who were still on treatment by the data cut-off date (23 October 2015), each patient had been counted as censored and the time of censoring was calculated as (23 October 2015 – first dose date)+1.

Abbreviations: AE, adverse event; AT, As treated; CBR, clinical benefit response; CI, confidence interval; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DR duration of response; EQ-5D, EuroQoL five dimensions score; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality of life questionnaire; EORTC QLQ-BR23, QLQ Breast Cancer Module; HR, hazard ratio; ITT, intention to treat; NCI, National Cancer Institute; OR, objective response; OS, overall survival; PFS, progression-free survival; PR, partial response; PRO, patient-reported outcome; RECIST, Response Evaluation Criteria in Solid Tumours; SOC, system organ class; TEAE, treatment-emergent adverse event; TTD, time to treatment discontinuation.

B.2.4.4 *PALOMA-3 - Interim analyses and data cuts*

The study was designed to conduct one interim analysis for efficacy. The interim analysis pre-specified early stopping of the study was based upon the primary endpoint PFS. The Haybittle-Peto[64,65] efficacy stopping boundary was pre-specified and used at the interim analysis (α=0.00135).

The planned PFS interim analysis was to be performed after PD or death had been documented for at least 143 patients (approximately 60% of the total events planned for final analysis). Due to the rapid enrolment and the event rate observed in the study, 195 events (approximately 82% of expected total events planned for final PFS analysis) were included in the analysis performed as of 5 December 2014. This analysis was therefore considered the primary analysis for PFS data rather than interim.

Statistical analysis of OS was to be performed at the pre-planned OS interim analysis (approximately 97 deaths) and/or OS final analysis (198 deaths). The number of deaths required to power the final OS analysis was calculated by assuming the median OS for women with advanced or metastatic BC treated with fulvestrant monotherapy to be equal to 24 months. With an overall one-sided α of 0.025 and one interim analysis of OS, the study had approximately 80% power to detect a HR of 0.65 (representing a 54% increase in median OS from 24 months to 37 months) when 198 deaths had occurred.

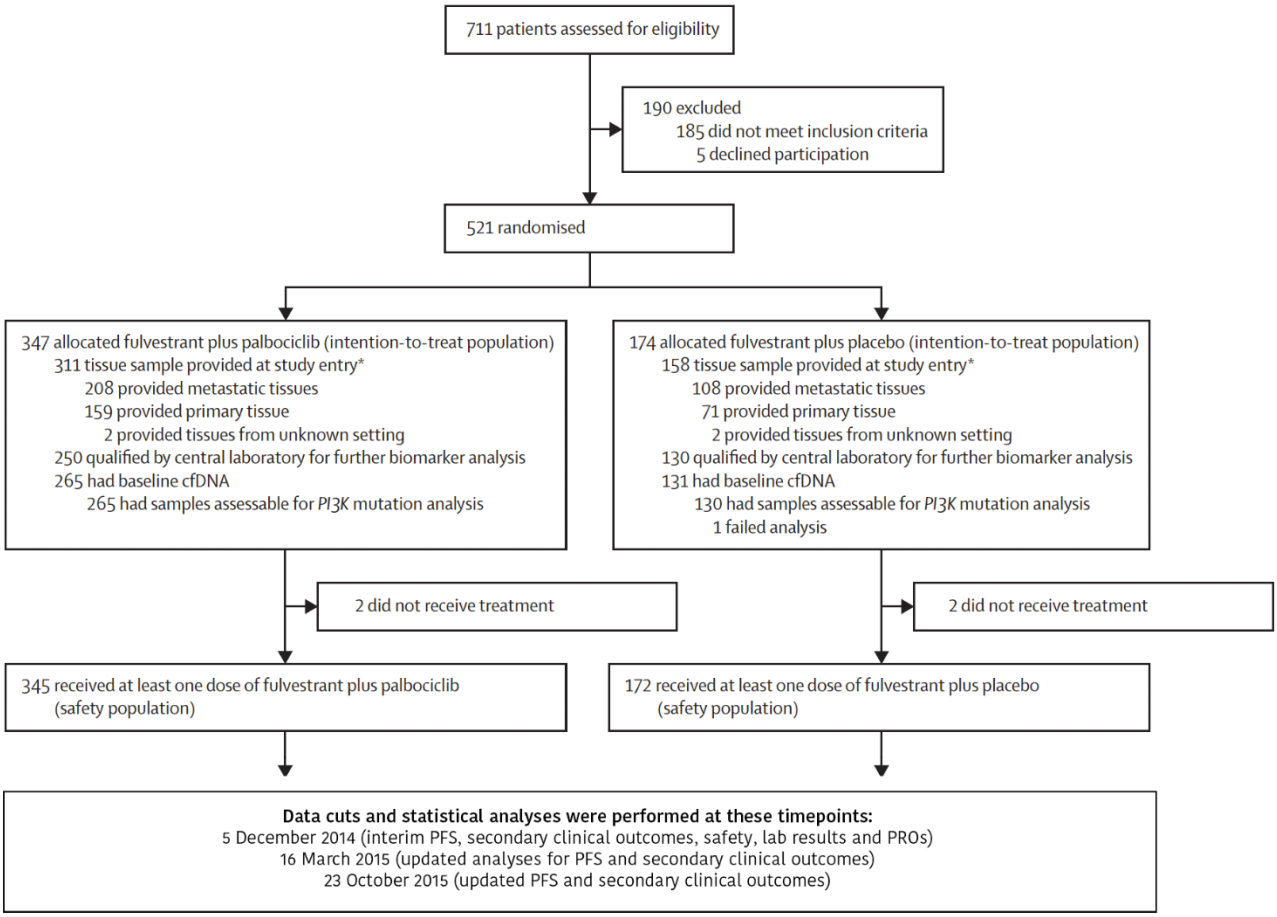
As the trial continued, further data cuts were generated and analysed as of 16 March 2015[8] and 23 October 2015.[16] The latest data cut was chosen as the basis to inform the main efficacy parameters in this submission. A final analysis of OS was conducted on 13 April 2018 where the majority of efficacy outcomes were not updated, however OS (after 310 events had been recorded) as well as time from randomisation to subsequent chemotherapy were evaluated. Efficacy results from the older 5 December 2014 and 16 March 2015 data cuts are presented in Appendix O for comparison. To date, some of the results based on the October 2015 data cut have been disseminated in the form of three publications[8,47,50] and two congress poster presentations.[45,66]

B.2.4.5 *PALOMA-3 - Patient disposition*

Figure 4 provides an overview of the screening, randomisation, assessment, treatment and analyses undertaken in the PALOMA-3 study. Patient disposition data for the ITT population at end of treatment (palbociclib or placebo) as of 23 October 2015 are summarised in Table 14. Between 26 September 2013 and 26 August 2014, a total of 521 patients were randomised of whom 347 were randomised to the palbociclib plus fulvestrant arm and 174 to the placebo plus fulvestrant arm. The 521 patients were randomised at 144 sites in 17 countries.

Two patients in the palbociclib plus fulvestrant arm and two patients in the placebo plus fulvestrant arm were randomised but not treated. Objective progression or relapse, including PD, was the most frequent reason for discontinuation in both treatment arms (56.2% of patients in the palbociclib plus fulvestrant arm and 73.0% of patients in the placebo plus fulvestrant arm).

Figure 4. Patient study entry, screening, allocation and treatment in PALOMA-3[55]



Abbreviations: cfDNA, circulating free deoxyribonucleic acid; PFS, progression-free survival; PRO, patient reported outcome.

Table 14. Patient Disposition at End of Treatment (Palbociclib or Placebo) in PALOMA-3 as of 23 October 2015 — Intent-to-Treat Population[55]

	Number (%) of Patients (N=521)	
Patient category	**Palbociclib + Fulvestrant (N=347)**	**Placebo + Fulvestrant (N=174)**
Ongoing	[redacted]	[redacted]
Treated and discontinued	[redacted]	[redacted]
Randomised not treated	[redacted]	[redacted]
Reason for discontinuation [a]		
Adverse event	[redacted]	[redacted]
Global deterioration of health status	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Medication error without associated adverse event	[redacted]	[redacted]
Objective progression or relapse + progressive disease	[redacted]	[redacted]
Protocol violation	[redacted]	[redacted]
Study terminated by Sponsor	[redacted]	[redacted]
Patient died	[redacted]	[redacted]
Patient refused to continue treatment for reason other than adverse event	[redacted]	[redacted]
Patient started new treatment for disease under study	[redacted]	[redacted]
Withdrew consent	[redacted]	[redacted]
Other [b]	[redacted]	[redacted]

Notes: 1) "Discontinued" or "ongoing" status was determined per the Conclusion-of-Treatment page in the CRF. 2) Doses of 0 mg have not been excluded from the algorithm determining patient status.

a. Includes patients who were discontinued from treatment because of disease progression or any other reason.

b. Other category is specified as "surgery on target lesion" or "subject received palliative radiation and exceeded the allowable amount of marrow exposure; physician's decision: slight bone progression with elevated CA15-3."

Abbreviations: CA, cancer antigen; CRF, Case Report Form; N, total number of patients in population.

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

Critical appraisal of the included clinical trial (PALOMA-3) was conducted using CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination). A summary of the quality assessment is presented below in Table 20.

Table 15. Detailed quality assessment of PALOMA-3 trial

Trial number (acronym)	NCT01942135 (PALOMA-3)
Was randomisation carried out appropriately?	Eligible patients were randomly assigned to receive fulvestrant 500 mg plus palbociclib 125 mg or fulvestrant in a 2:1 ratio via a centralised interactive web-based and voice-based randomisation system on the basis of three stratification factors: sensitivity to previous hormonal therapy, menopausal status at study entry and presence of visceral metastases
Was the concealment of treatment allocation adequate?	Study participants, investigators, and research staff were masked to treatment group assignment. Sponsor personnel or designees involved in the study design and data analysis were also masked to treatment group assignment until the independent data monitoring committee (IDMC) recommended stopping the study at the pre-planned interim analysis
Were the groups similar at the outset of the study in terms of prognostic factors?	Baseline characteristics of the intention-to-treat population did not differ substantially between randomised groups
Were the care providers, participants and outcome assessors blind to treatment allocation?	Study participants, investigators, and research staff were masked to treatment group assignment.
Were there any unexpected imbalances in drop-outs between groups?	128 (37%) of 347 patients discontinued treatment because of disease progression in the fulvestrant plus palbociclib group compared with 107 (61%) of 174 patients in the fulvestrant plus placebo group
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes, see Outcome section from Cristofanilli 2016.[8]
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes – an ITT approach was used. For PFS analysis, no values were imputed for missing data (for details on how missing data were handled in PALOMA-3 please see Appendix N)

Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).
Sources: Cristofanilli et al. 2016;[8] Turner et al. 2018;[37] PALOMA-3 CSR.[55]

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

B.2.6.1 *PALOMA-3 efficacy results*

Overview

- PFS was the primary endpoint in PALOMA-3. A median PFS of 11.2 months in the palbociclib plus fulvestrant arm versus 4.6-months in the placebo plus fulvestrant arm. (HR=0.50; 95% CI: 0.40, 0.62; stratified 1-sided p<0.0001) (Section B.2.6.2).
- The addition of palbociclib to fulvestrant resulted in a 6.9 months median gain in OS (34.9 months median survival for palbociclib plus fulvestrant versus 28.0 months for placebo plus fulvestrant (HR=0.81; 95% CI: 0.64, 1.03, p=0.09). Whilst OS results observed in PALOMA-3 were clinically meaningful, please note that the clinical trial was not optimised for statistical significance in OS (Section B.2.6.4).
- Tumour response was evaluated as a secondary outcome with palbociclib plus fulvestrant associated with improved tumour response versus placebo plus fulvestrant in OR, CBR and DR.
    - OR rate was higher in the palbociclib plus fulvestrant arm ([redacted]) compared to the placebo plus fulvestrant arm ([redacted]). (Section B.2.6.3.1)
    - The CBR rate was [redacted] in the palbociclib plus fulvestrant arm and [redacted]) in the placebo plus fulvestrant arm (odds ratio= [redacted]) (Section B.2.6.3.2).
    - Investigator-assessed median DR was [redacted] in the palbociclib plus fulvestrant arm and [redacted] in the placebo plus fulvestrant arm (Section B.2.6.3.3).
- Adding palbociclib to fulvestrant significantly delayed the time to subsequent chemotherapy by an additional 8.8 months versus placebo plus fulvestrant (median 17.6 months [95% CI: 15.2, 19.7] from randomisation to first subsequent chemotherapy in the palbociclib plus fulvestrant arm compared with 8.8 months in the fulvestrant arm [95% CI: 7.3, 12.7]; HR=0.58; 95% CI: 0.47, 0.73; p<0.001) (Section B.2.6.5).
- Palbociclib plus fulvestrant improved quality of life versus fulvestrant alone. On treatment, the mean EQ-5D index score for palbociclib plus fulvestrant was significantly higher than for placebo plus fulvestrant (Section B.2.6.6). In addition, palbociclib plus fulvestrant demonstrated statistically significant improvements in global health, nausea/vomiting, pain and emotional functioning from baseline and significantly extended the time to deterioration in pain, compared to fulvestrant alone, assessed via the EORTC questionnaires (measuring cancer-related QoL).
- PALOMA-3 demonstrated that adding palbociclib to fulvestrant significantly extends PFS, improves tumour response and provides clinically meaningful improvements in OS. These improvements in comparative efficacy are observed whilst maintaining QoL.

Note: OS and time to subsequent chemotherapy results are presented from a final analysis conducted on 13 April 2018. All other efficacy and safety results presented are based on analyses from the data cut on 23 October 2015. The data-cut on 23 October 2015 was the final cut for PFS. Tabulation of efficacy analysis results from each data cut is provided in the separate Appendix O.

Abbreviations: CBR; CI, confidence interval; DR: duration of response; HR: hazard ratio; NE: not estimable; OR: overall response

B.2.6.2 *Primary endpoint: progression-free survival (PFS)*

At the data cut-off date of 23 October 2015, a total of 333 patients with objective progression or death had been reported: 200 (57.6% of 347 patients) were from the palbociclib plus fulvestrant arm and 133 (76.4% of 174 patients) were from the placebo plus fulvestrant arm. The median duration

of follow-up[2] was 15.8 months (95% CI: 15.5, 16.2) for the palbociclib plus fulvestrant arm and 15.3 months (95% CI: 15.0, 15.9) for the placebo plus fulvestrant arm. Among the censored patients, 109 (31.4%) in the palbociclib plus fulvestrant arm and 25 (14.4%) in the placebo plus fulvestrant arm were still being followed up for disease progression as of 23 October 2015.

The median PFS was 11.2 months (95% CI: 9.5, 12.9) in the palbociclib plus fulvestrant arm and 4.6 months (95% CI: 3.5, 5.6) in the placebo plus fulvestrant arm. The observed HR (stratified analysis) was 0.497 (95% CI: 0.398, 0.620; stratified 1-sided p<0.0001) in favour of palbociclib plus fulvestrant. Kaplan-Meier (KM) curves of PFS assessed by the investigator are shown for both treatment arms in Figure 5. A detailed summary of PFS is provided in Table 16.

Table 16. Progression-related observations and censoring in PALOMA-3[16]

Category	Palbociclib + Fulvestrant (N=347)	Placebo + Fulvestrant (N=174)
Number of patients with event, n (%)	[redacted]	[redacted]
Type of event		
Objective progression	[redacted]	[redacted]
Death without objective progression	[redacted]	[redacted]
Number censored, n (%)	[redacted]	[redacted]
Reason for censorship, n (%)		
No adequate baseline assessments	[redacted]	[redacted]
No on-study disease assessments	[redacted]	[redacted]
Given new anticancer treatment[a] prior to disease progression and after last dose of study treatment	[redacted]	[redacted]
Discontinued study without disease progression or death	[redacted]	[redacted]
Withdrew consent for follow-up	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Other	[redacted]	[redacted]
Unacceptable gap (>20 weeks) between PD or death and the most recent prior adequate assessment	[redacted]	[redacted]
In follow-up for progression	[redacted]	[redacted]
Probability of being event free at Month 6[b] (95% CI)[c]	[redacted]	[redacted]
Probability of being event free at Month 12[b] (95% CI)[c]	[redacted]	[redacted]
Kaplan-Meier estimates of time to event (month)		
Quartiles (95% CI)[d]		
25%	[redacted]	[redacted]
50%	[redacted]	[redacted]
75%	[redacted]	[redacted]

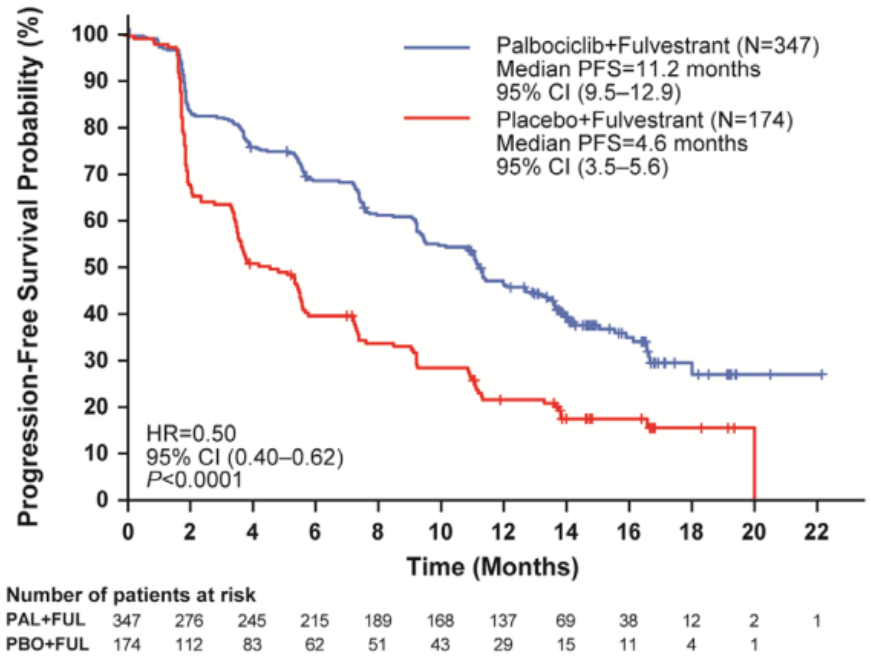
Notes: a. Anticancer treatment includes surgery containing a lesion removal or subsequent anticancer systemic therapies. b. Estimated from Kaplan-Meier curve. c. Calculated using the product-limit method. d. Based on the Brookmeyer and Crowley Method.

Abbreviations: CI, confidence interval; N, total number of patients in population; n, number of patients meeting pre-specified criteria; NE, not estimable.; PD, progressed disease.

Figure 5. Kaplan-Meier Plot of PFS Assessed by the Investigator in PALOMA-3 as of 23 October 2015

[2] Duration of follow-up is calculated as days from randomisation up to the last date of contact alive/dead and presented as months.

– Intent-to-Treat Population[37]



Abbreviations: CI, confidence interval; N, total number of patients in population; PAL+FUL, palbociclib plus fulvestrant arm; PCB+FUL, placebo plus fulvestrant arm; PFS, progression-free survival.

B.2.6.3 *Secondary clinical endpoints*

B.2.6.3.1 *Objective response (OR) rate*

As of the data cut-off date of 23 October 2015, the investigator-assessed OR rate was [redacted] in the palbociclib plus fulvestrant arm and [redacted] in the placebo plus fulvestrant arm. The odds ratio was [redacted] in favour of palbociclib plus fulvestrant treatment, with a stratified 1-sided p-value of [redacted].

In patients with measurable disease at baseline, the investigator-assessed OR rate was [redacted] in the palbociclib plus fulvestrant arm and [redacted] in the placebo plus fulvestrant arm. The odds ratio was [redacted] in favour of palbociclib plus fulvestrant treatment, with a stratified 1-sided p-value of [redacted].

B.2.6.3.2 *Clinical benefit response (CBR)*

As of the data cut-off date of 23 October 2015, the investigator-assessed CBR rate was [redacted] in the palbociclib plus fulvestrant arm and [redacted] in the placebo plus fulvestrant arm. The odds ratio was [redacted] in favour of palbociclib plus fulvestrant treatment, with a stratified 1-sided p-value of [redacted].

B.2.6.3.3 *Duration of objective response (DR)*

As of the data cut-off date of 23 October 2015, the investigator-assessed median DR was [redacted] in the palbociclib plus fulvestrant arm and [redacted] in the placebo plus fulvestrant arm.

B.2.6.4 *Overall survival (OS)*

A total of 310 deaths had occurred on the data cut of 13 April 2018, permitting the planned final analysis of OS. A summary of this analysis is presented in Table 17. Palbociclib plus fulvestrant was associated with a clinically meaningful gain in OS with a median survival gain of 6.9 months compared to placebo plus fulvestrant. The stratified hazard ratio was 0.81 (95% CI: 0.64, 1.03, p= 0.09) improvement in OS associated with palbociclib. However, it should be noted that the PALOMA-3 was not optimised to detect statistical significance in OS.

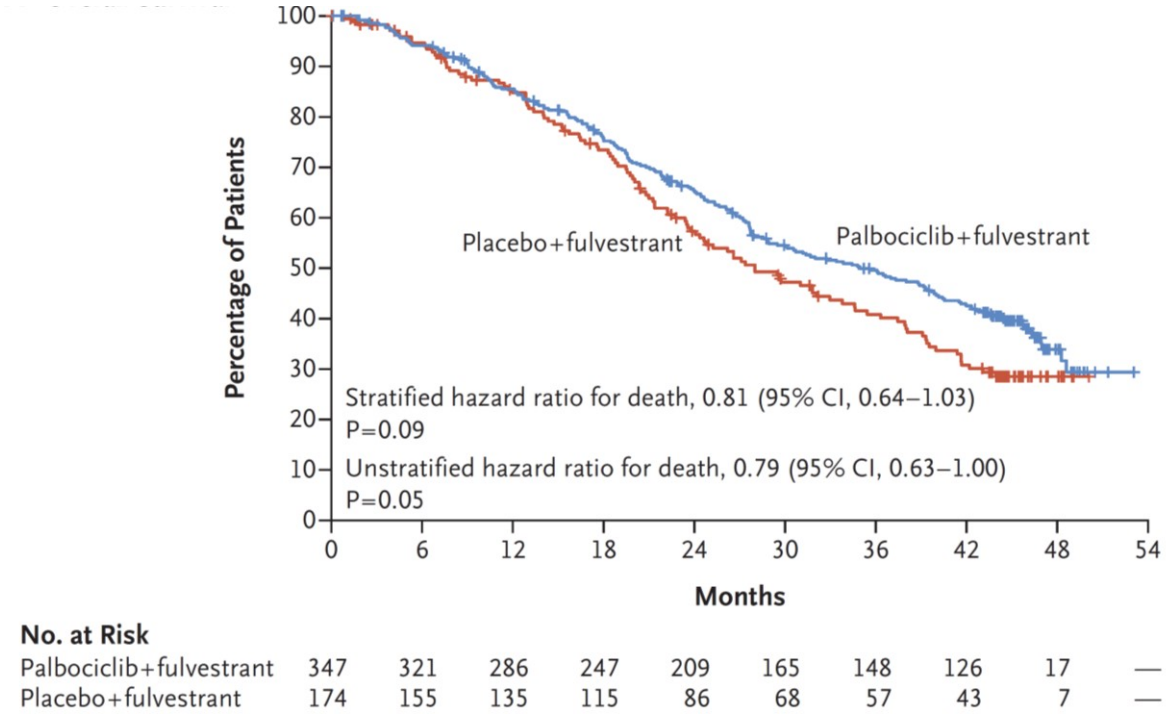
The Kaplan-Meier survival plot in Figure 6 shows a clear and proportional separation between the two arms after 12 months. The increase in observed median OS when adding palbociclib to fulvestrant is highly consistent with the increase observed in median PFS (+6.9 months in median OS and +6.6 months in median PFS).

Table 17. Overall survival analysis in PALOMA-3 using new data cut as at 13 April 2018 - As Treated population[37]

Category	Palbociclib + Fulvestrant (N=347)	Placebo + Fulvestrant (N=174)
Number of Events (%)	201 (57.9)	109 (62.6)
Median OS, months (95%CI)	34.9 (28.8, 40.0)	28.0 (23.6, 34.6)
Stratified HR (95% CI)	0.81 (0.64, 1.03)	
p-value	0.09	
Un-stratified HR (95% CI)	0.79 (0.63, 1.00)	
p-value	0.05	

Abbreviations: CI, confidence interval; HR, hazard ratio; N, total number of patients in population; OS, overall survival.

Figure 6. Kaplan-Meier survival plot for patients in PALOMA-3 as at 13 April 2018[37]



Abbreviations: CI, confidence interval

B.2.6.5 *Time to subsequent chemotherapy*

Delaying chemotherapy and its associated toxicities, and impact of QoL is important to patients and their carers/families. It was discussed in both the NICE and SMC appraisals for palbociclib plus an

aromatise inhibitor in previously untreated HR-positive HER2-negative advanced or metastatic breast cancer.[3,67]

In tandem with the final OS analysis in the data cut of 13 April 2018, an assessment of the time from randomisation to the first use of chemotherapy after disease progression was conducted. In the palbociclib plus fulvestrant arm, the time to chemotherapy was 17.6 months (95% CI, 15.2, 19.7) compared with 8.8 months in the fulvestrant arm (95% CI, 7.3 to 12.7); adding palbociclib statistically significantly delayed the time to chemotherapy (HR=0.58; 95% CI, 0.47 to 0.73; P<0.001).[37]

B.2.6.6 *Patient reported outcomes (PROs)*

Analyses for these outcomes were conducted on the PRO-evaluable population at the time of the Primary Analysis (5 December 2014). A detailed analysis of QLQ-C30 and QLQ-BR23 scores using the 16 March 2015 data cut was presented in Harbeck 2016,[44] and the EQ-5D scores from the 23 October 2015 data cut were analysed and presented in Loibl 2016.[46]

B.2.6.6.1 *EORTC QLQ-C30*

Completion Rates

The percentage of patients completing at least one question on the EORTC QLQ-C30 from baseline through to cycle 24 ranged from [redacted] in the palbociclib and fulvestrant arm. In the placebo plus fulvestrant arm, the percentage of patients completing at least one question on the EORTC QLQ-C30 from baseline to cycle 24 ranged from [redacted].

Global Quality of Life (QOL) and Functional Scales

Baseline mean scores for global QOL were similar for palbociclib plus fulvestrant and placebo plus fulvestrant and were moderately high in both treatment arms (65.9 [95% CI: 63.5, 68.2] vs. 65.3 [95% CI: 61.9,68.6]).

The between-treatment comparison of palbociclib plus fulvestrant versus placebo plus fulvestrant showed a statistically significant difference in global QOL change from baseline scores [redacted] favouring palbociclib). The estimated difference in overall change from baseline score for global QOL was [redacted] (Figure 7) favouring palbociclib.

The overall changes within each treatment arm, based on interpretation from the 95% CIs of the change from baseline analysis, indicated that global QOL was maintained in the palbociclib plus fulvestrant arm and significantly deteriorated in the placebo plus fulvestrant arm.

Forest plots summarising between-treatment differences in the overall change from baseline for the QLQ-C30 functional scales are presented in Figure 7.

The difference between the two PALOMA-3 treatment arms in change from baseline scores for emotional functioning was found to be statistically significant [redacted] favouring palbociclib plus fulvestrant over placebo plus fulvestrant. The estimated difference in overall change from baseline score for emotional functioning was [redacted].

Changes from baseline scores on physical, role, cognitive and social functioning were not found to be statistically significant between the two treatment arms, but the direction of results favoured the palbociclib plus fulvestrant arm.

Figure 7. Comparison between treatments of overall Change from Baseline for EORTC QLQ-C30 Global Health and the QLQ-C30 Functional Scales - PRO Analysis Population[44]

Notes: Graph shows mean between-treatment differences (circles) and 95% CI (lines). Changes from baseline in the patient-reported outcomes analysis population were determined using a repeated-measures mixed-effect model. For functional scores, higher scores indicate higher functioning. Values above zero favour palbociclib.

Abbreviations: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; PRO, patient-reported outcome; QOL, quality of life.

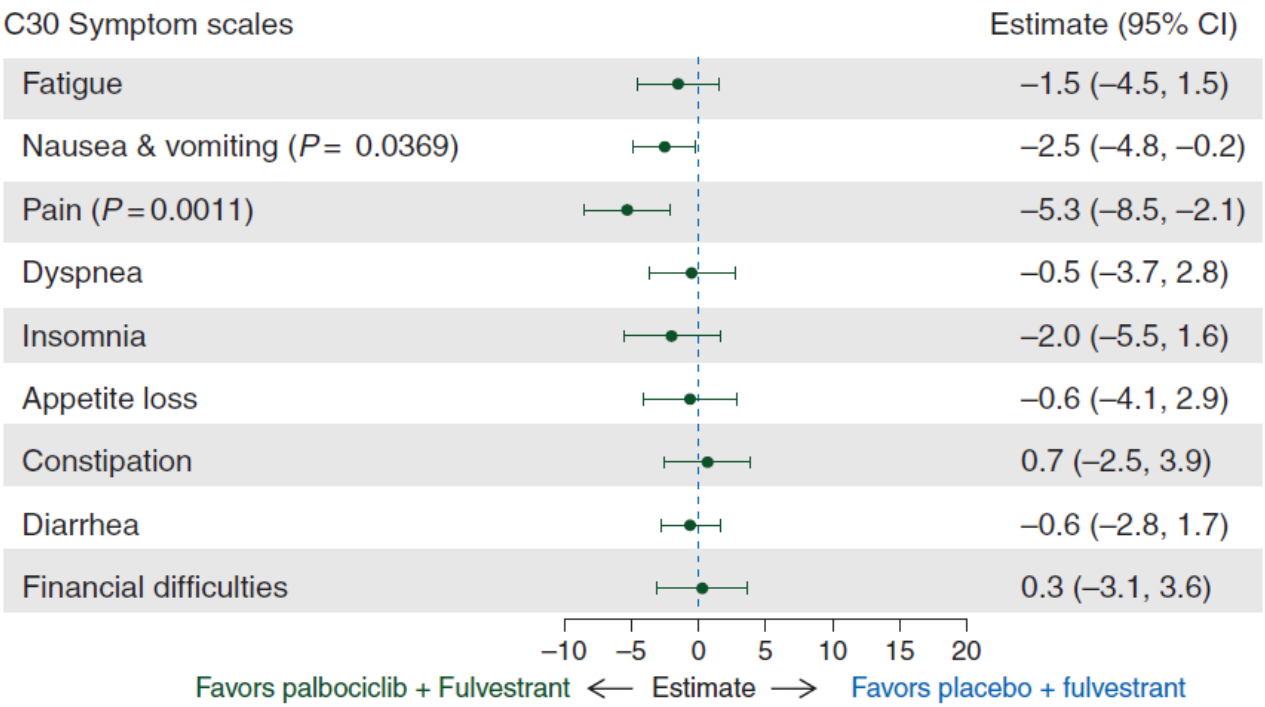
Symptom Scales (QLQ-C30)

Mean baseline scores for the symptoms of the EORTC QLQ-C30 were similar in both PALOMA-3 treatment arms for all symptoms except insomnia (26.3 in the placebo plus fulvestrant arm vs. 32.9 in the placebo plus fulvestrant arm). Baseline scores for the symptoms indicated low symptom severity in both treatment arms.

A statistically significant decrease from baseline in pain was observed with palbociclib plus fulvestrant compared with placebo plus fulvestrant [−3.3 (95% CI −5.1, −1.5) versus 2.0 (95% CI −0.6, 4.6); p = 0.0011] and statistically significant less deterioration from baseline was observed for nausea/vomiting [1.7 (95% CI 0.4, 3.0) versus 4.2 (95% CI 2.3, 6.1); p = 0.0369]. No significant differences between groups were observed in overall change from baseline scores for any other EORTC QLQ-C30 symptoms.

A forest plot showing estimated between-treatment differences in the level of change from baseline for EORTC QLQ-C30 symptoms is displayed in Figure 8.

Figure 8. Comparison between treatments in change from baseline for EORTC QLQC30 Symptoms Scales - PRO Analysis Population[44]

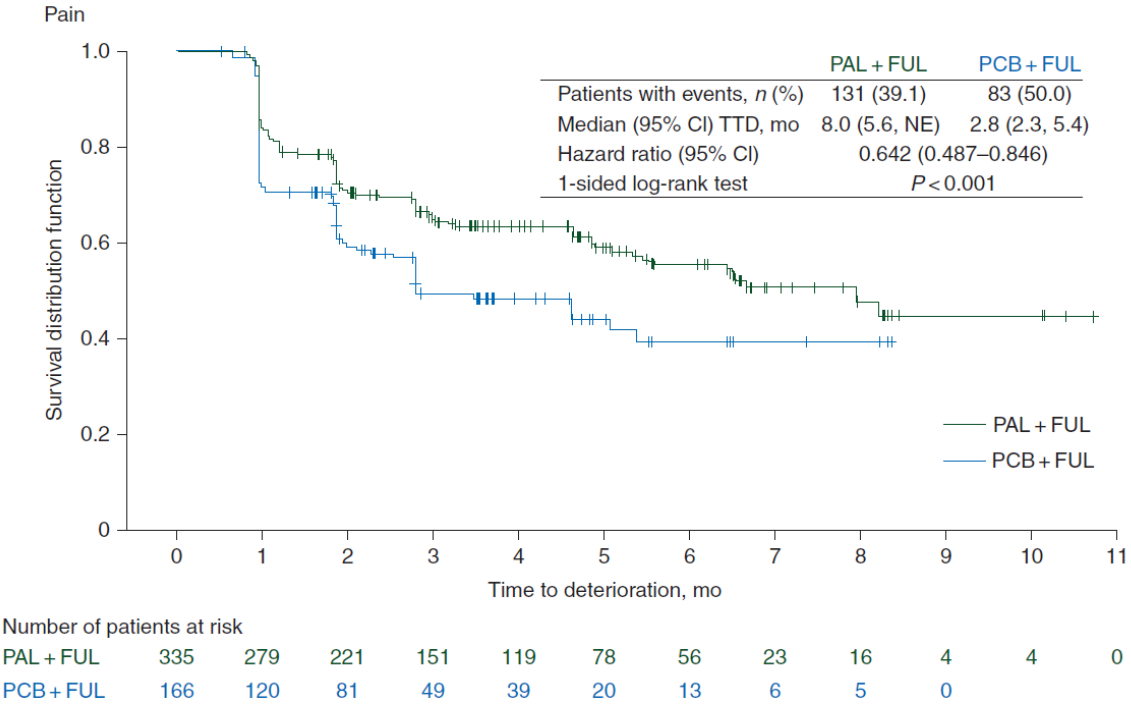


Changes from baseline in the patient-reported outcomes analysis population were determined using a repeated-measures mixed-effect model. P values are shown only if significant between-group differences were observed.
Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items; PRO, patient-reported outcomes

Time to pain deterioration

The median time to deterioration in pain was 8 months (95% CI: 5.6 months, NE) in the palbociclib plus fulvestrant arm compared with 2.8 months (95% CI: 2.3 months, 5.4 months) in the placebo plus fulvestrant arm (Figure 9).[44] Treatment with palbociclib plus fulvestrant significantly extended the time to deterioration in pain symptoms compared with placebo plus fulvestrant (unstratified analysis: HR=0.642; 95% CI: 0.487, 0.846; p < 0.001.[44] This analysis is summarised graphically in Figure 9.

Figure 9. Kaplan-Meier plot of time to deterioration in pain as of 23 October 2015[44]



Abbreviations: NE, not estimable

B.2.6.6.2 *EORTC QLQ-BR23*

Completion rates

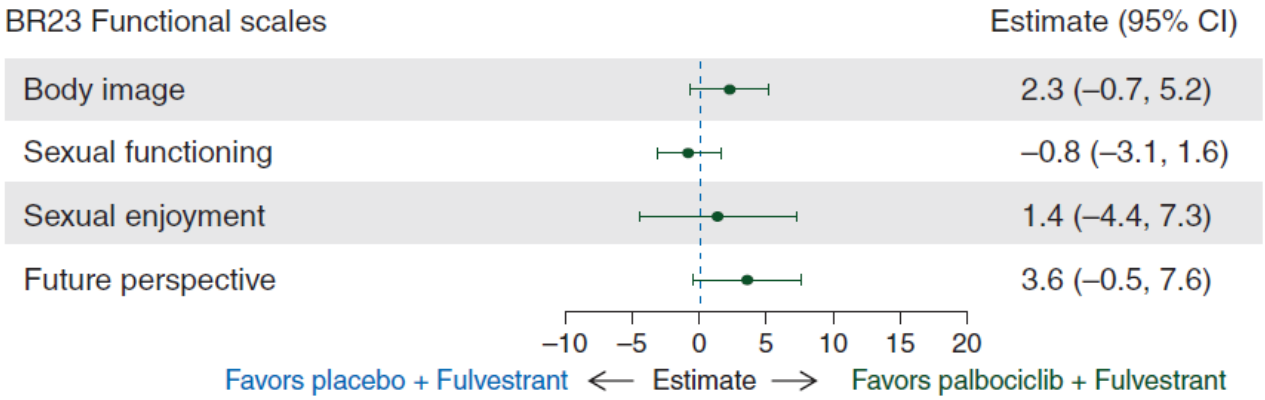
Approximately ≥93.8% of patients in the palbociclib plus fulvestrant group and ≥95.8% in the placebo plus fulvestrant completed ≥1 question on the EORTC QLQ-BR23. [44]

Functional Scale (QLQ-BR23)

Sample sizes for the sexual enjoyment sub-scale were somewhat lower than those for other scales as the question was only completed by women who had stated that they were sexually active. The mean scores on these were generally similar in both treatment groups at baseline.

No statistically significant difference was observed between the palbociclib plus fulvestrant arm and the placebo plus fulvestrant arm in overall change from baseline scores for any of the EORTC QLQ BR23 functional scales (Figure 10). Based on interpretation from the 95% CIs of the overall change from baseline analysis within each treatment group, significant improvement in body image and future perspective was observed in the palbociclib group; significant deterioration in sexual enjoyment was observed in both groups.[44]

Figure 10. Forest plot of EORTC QLQ-B23 Change from Baseline – Functional Scale Scores[44]



Changes from baseline in the patient-reported outcomes analysis population were determined using a repeated-measures mixed-effect model.
Abbreviations: EORTC QLQ-BR23, European Organization for Research and Treatment of Cancer Breast Cancer Module

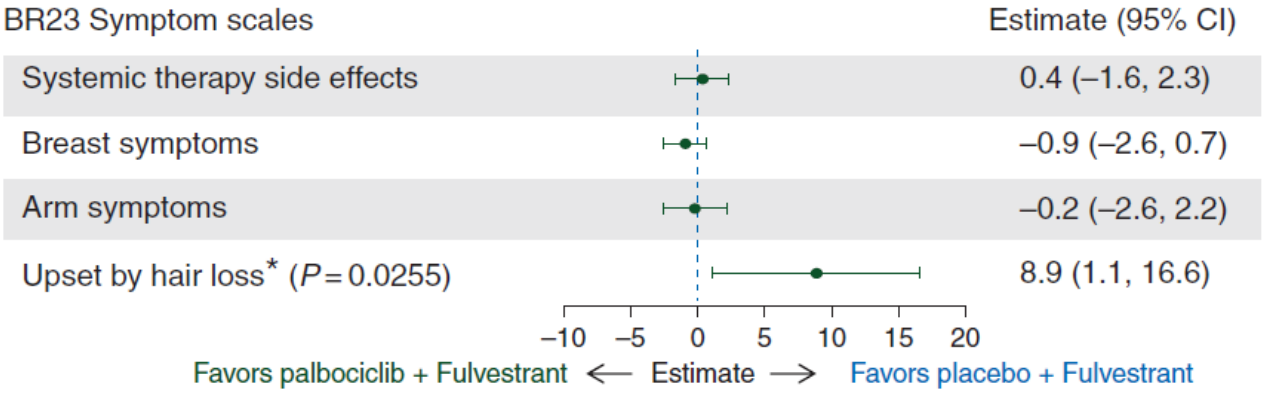
Symptoms Scales (QLQ-BR 23)

The sample sizes for the symptom scale upset by hair loss are much lower than those for the other scales. This is because the question on whether the patient was upset by hair loss was to be answered only if the patient experienced hair loss.

A statistically significant difference between the two treatments was observed in change from baseline score in the symptom scale upset by hair loss ($p = 0.03$) favouring the placebo plus fulvestrant arm over the palbociclib plus fulvestrant arm. The estimated difference in overall change from baseline scores for upset by hair loss was 8.9 (95% CI: 1.1, 16.6).

Between-treatment comparisons of change from baseline on EORTC-QLQ-BR23 symptom scale scores from the repeated measures analyses are presented as a forest plot in Figure 11.

Figure 11. Forest plot of EORTC QLQ-B23 Change from Baseline – Symptom Scale Scores[44]



Changes from baseline in the patient-reported outcomes analysis population were determined using a repeated-measures mixed-effect model. P values are shown only if significant between-group differences were observed. Asterisk denotes that question was only to be answered by patients who stated they had experienced hair loss, resulting in fewer patients responding to this question compared with other questions.

Abbreviations: EORTC QLQ-BR23, European Organization for Research and Treatment of Cancer Breast Cancer Module; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items; PRO, patient-reported outcomes; QoL, quality of life.

EQ-5D

Completion rates

The questionnaire completion rate at baseline was 95% or over in both treatment groups. Completion rates from cycles 2-20 ranged from 90%-99% across both treatment groups. By the end of treatment, around 53% of patients in the palbociclib plus fulvestrant arm and 68% of patients in the placebo plus fulvestrant arm completed one or more EQ-5D questionnaire.[46]

EQ-5D Health State Profile

The proportion of patients reporting the presence of a problem (some problem + extreme problem) at baseline was similar for palbociclib plus fulvestrant and fulvestrant plus placebo, respectively: mobility (28% vs 32%), self-care (9% vs 9%), usual activities (38% vs 45%), pain/discomfort (67% vs 67%), and anxiety/depression (52% vs 61%).[46]

EQ-5D Index and VAS Score results

Baseline mean (SD) EQ-5D index scores and VAS were found to be similar between the palbociclib plus fulvestrant and fulvestrant arms: EQ-5D 0.73 (0.23) vs 0.71 (0.23); VAS 72.9 (17.22) vs 70.3 (19.87).[46]

On treatment, the mean EQ-5D index score for palbociclib plus fulvestrant was significantly higher than for placebo plus fulvestrant (0.74, 95% CI: 0.72, 0.76 versus 0.69, 95% CI: 0.67, 0.72, p=0.0037), indicating that patients on palbociclib plus fulvestrant experienced a higher QoL than patients on fulvestrant monotherapy. The difference on VAS scores was smaller, slightly favouring palbociclib but not attaining statistical significance (71.5, 95% CI: 70.0, 73.0 versus 70.0, 95% CI: 67.8, 72.3, p=0.3005).[46]

The potential impact of neutropenia on EQ-5D scores was analysed, both on the mean on-treatment scores (see Figure 12) as well as on mean change from baseline. No statistically significant differences were observed in the overall EQ-5D index score (Figure 12) and change from baseline

on treatment within the palbociclib plus fulvestrant arm between patients with or without neutropenia. Neutropenia-related changes from baseline per cycle ranged from an improvement of [redacted] (seen at Cycle 20, [redacted] to a decrement of -0.125 (seen at Cycle 22, [redacted]).

Figure 12. Plot of observed means, EQ-5D index - PRO analysis set (based on palbociclib plus fulvestrant patients with and without neutropenia)

Notes: N1, Number of subjects in Palbociclib + Fulvestrant arm with Neutropenia at each assessment time point; N2, Number of subjects in Palbociclib + Fulvestrant arm without Neutropenia at each assessment time point.

Abbreviations: EOT, end of treatment, EQ-5D, EuroQoL five dimensions score; Palbo+Fulv, palbociclib plus fulvestrant; PRO, patient-reported outcome.

B.2.6.6.3 *PRO conclusions*

In conclusion, the PRO results support the positive risk-benefit profile of palbociclib plus fulvestrant, with a significantly higher global QoL maintained on treatment and a significantly greater improvement from baseline in nausea/vomiting, emotional functioning and pain compared to placebo plus fulvestrant. The addition of palbociclib to fulvestrant also resulted in a symptom benefit by significantly delaying time-to-deterioration in pain symptom compared with fulvestrant. A significantly greater deterioration from baseline was observed in the palbociclib plus fulvestrant arm in the symptom scale measuring upset by hair loss compared to placebo plus fulvestrant arm.

B.2.7 **Subgroup analysis**

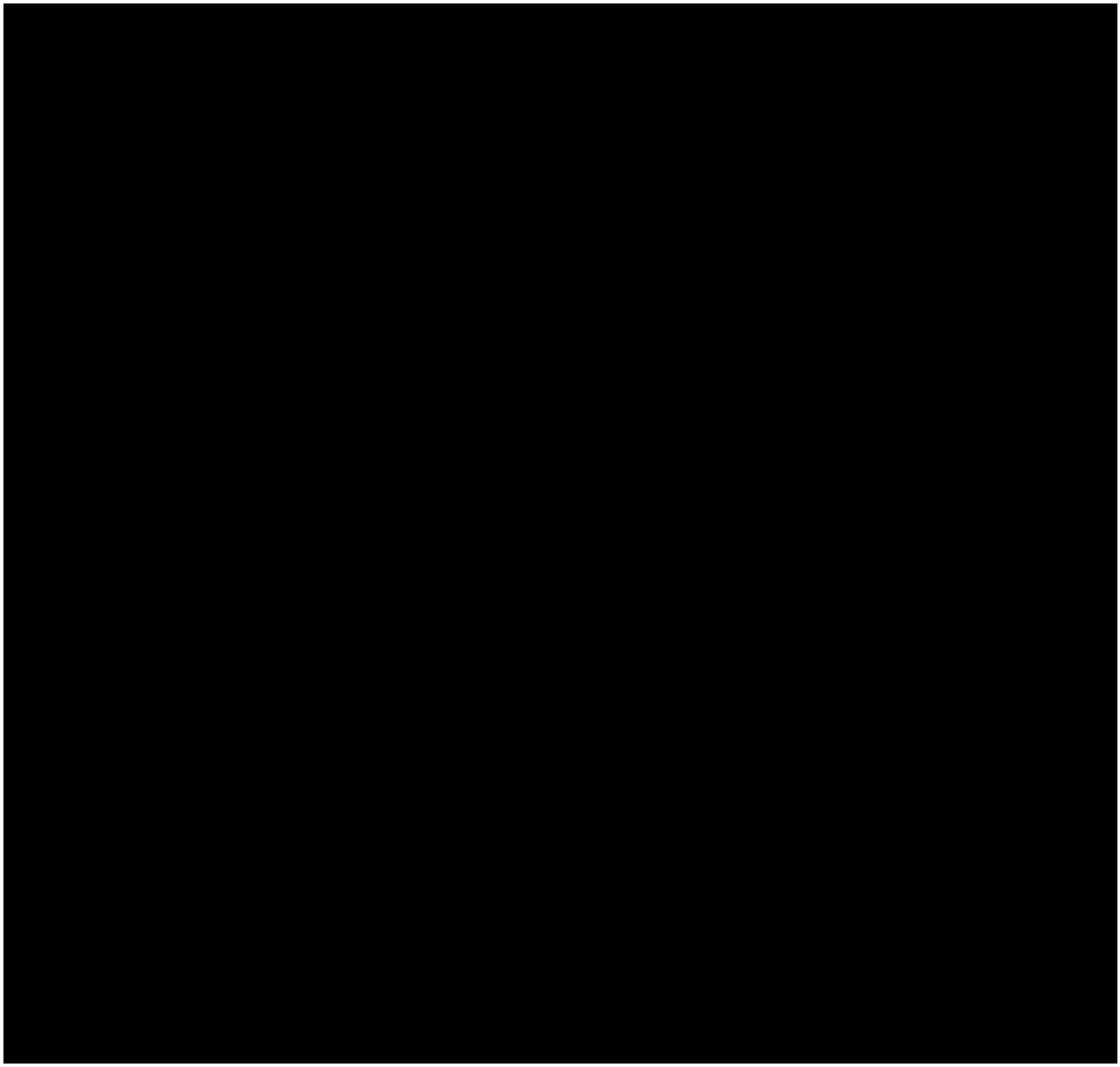
B.2.7.1 *Progression-free survival*

The pre-planned subgroups for PFS analysis were previously listed in Table 8 and the results are summarised in Figure 13. A reduction in the risk of disease progression or death in the palbociclib plus fulvestrant arm was observed in all individual patient subgroups defined by stratification factors and baseline characteristics. For example, this was evident for pre/perimenopausal women [redacted] and postmenopausal women [redacted]. Patients with visceral site of metastatic disease [redacted] and non-visceral site of metastatic disease [redacted] also had similar outcomes. Benefit was observed regardless of lines of prior therapy in the metastatic setting, whether [redacted].[68]

[redacted]The observed heterogeneity of treatment effects is all quantitative, and therefore it would be inappropriate to conclude that one subgroup gains more benefit from the palbociclib regimen than another (older vs. younger patients for an example) because the study was not primarily designed to answer the subgroup questions. The smaller sample size of the subgroups and inability to maintain randomisation for subgroup analyses also prevent us to make such conclusions.

PALOMA-3 excluded patients with advanced or metastatic, symptomatic, visceral spread, who are at risk of life-threatening complications in the short term. This included patients with massive uncontrolled effusions (pleural, pericardial, peritoneal), pulmonary lymphangitis, and over 50% liver involvement.[68] Sixty percent of patients in PALOMA-3 had some form of visceral (not life threatening) involvement in their metastatic disease, as defined by evidence of cancer in the lung, liver, brain, pleura, and/or peritoneum.[55] Figure 13 below provides the PFS analysis separately for the visceral disease subgroup. The PFS for patients with visceral disease was [redacted] for palbociclib plus fulvestrant versus [redacted] for fulvestrant with placebo [redacted]

Figure 13. Investigator-assessed PFS in pre-specified subgroups in PALOMA-3[16]



Notes: 1) Sensitivity to prior hormonal therapy is defined as either: a) documented clinical benefit (i.e., complete response, partial response, or stable disease at 24 weeks) to at least 1 prior hormonal therapy in the metastatic setting or b) at least 24 months of adjuvant hormonal therapy prior to recurrence. 2) Disease-free interval is time from diagnosis of primary breast cancer to first relapse in patients who received adjuvant therapy. 3) Aromatase inhibitor=anastrozole, letrozole, or exemestane; anti-oestrogen=tamoxifen, tamoxifen citrate, toremifene, or toremifene citrate; other=neither an aromatase inhibitor nor an anti-oestrogen. 4) Race=Black and Other. 5) Menopausal status at study entry, Site of metastatic disease, and Sensitivity to prior hormonal therapy data were derived based on the IMPALA randomisation and drug management system.

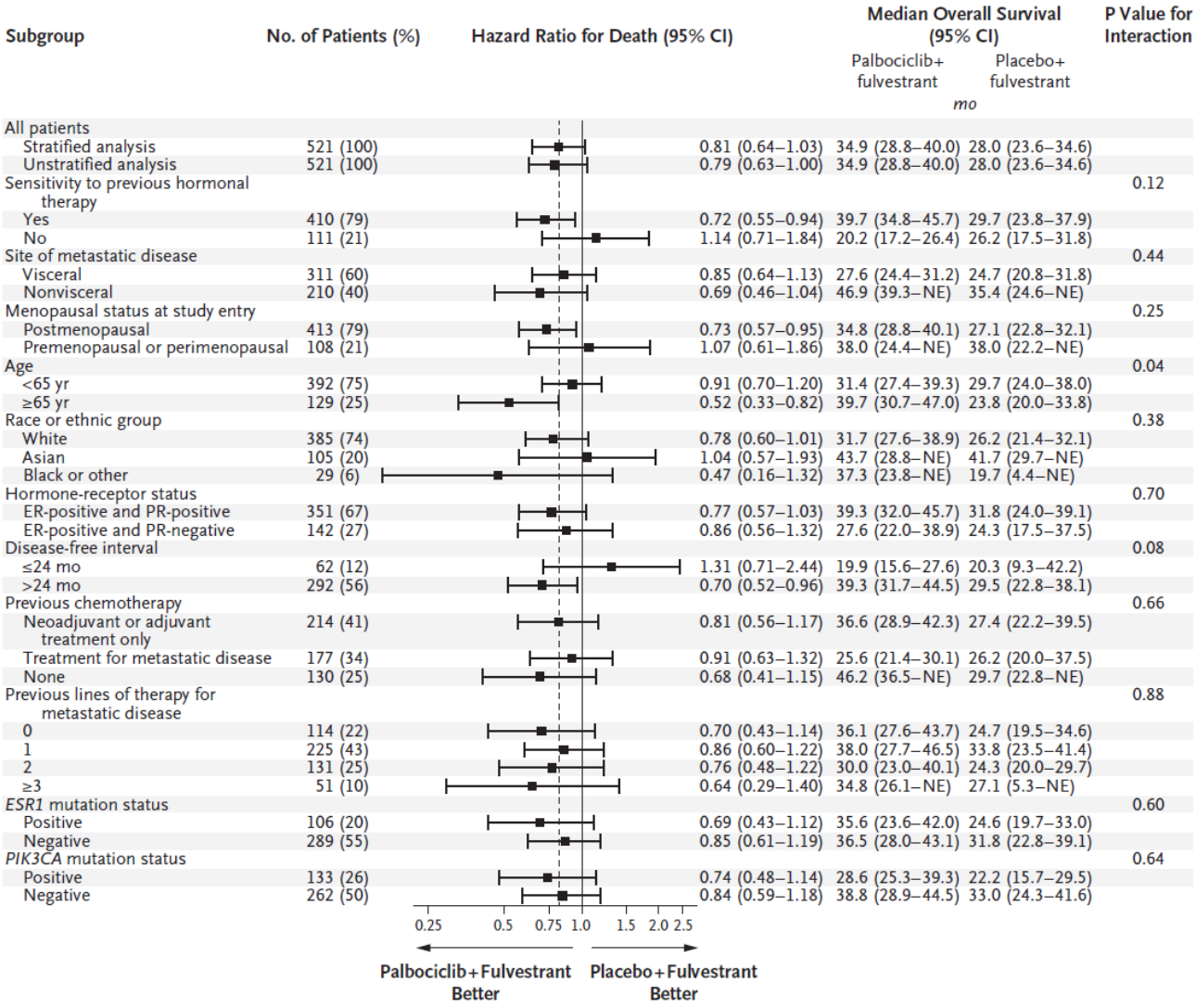
Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; FUL, fulvestrant; ITT, intent-to-treat; n, number of patients meeting pre-specified criteria; PAL, palbociclib; PCB, placebo; PgR, progesterone receptor.

B.2.7.2 *Overall survival*

The results of subgroup analyses of OS assessed by the investigators as of 13 April 2018 are summarised in Figure 14. A reduction in the risk of death in the palbociclib plus fulvestrant arm was observed in all individual patient subgroups defined by stratification factors and baseline characteristics with the exception of those without sensitivity to previous therapy, those with pre/peri-

menopausal status at study entry, disease-free interval of ≤24 months and patients of Asian descent. The three pre-specified stratification factors were the presence or absence of sensitivity to previous endocrine therapy, the presence or absence of visceral metastatic disease, and menopausal status. However, none of these subgroups were associated with significant interactions terms[37] and as noted previously the observed heterogeneity of treatment effects is all quantitative. Therefore, it would be inappropriate to conclude that one subgroup gains more benefit from the palbociclib regimen than another because the study was not optimised sufficiently to answer the subgroup questions. The smaller sample size of the subgroups and inability to maintain randomisation for subgroup analyses also prevent us to make such conclusions.

Figure 14. Investigator-assessed OS in pre-specified subgroups in PALOMA-3[37]



B.2.8 **Meta-analysis**

This section is not applicable for the current submission as no meta-analysis was conducted. PALOMA-3 is the only clinical trial available for palbociclib in the target population.

B.2.9 **Indirect and mixed treatment comparisons**

Given the lack of head-to-head clinical evidence for palbociclib plus fulvestrant versus everolimus plus exemestane, an indirect treatment comparison was carried out as per NICE guidance[69] to inform the PFS and OS parameters.

B.2.9.1 *Identified studies*

Following the RCT SLR update in February 2019, 142 publications for 94 unique studies were included in the review (see Appendix D). Four of these studies (BOLERO-2[9,70], CONFIRM,[71] EFFECT[72]) were identified as relevant to the NMAs. One additional study (SoFEA[73]) that was only included in sensitivity analysis in the Chirila NMA[42] given the low percentage of HER2- patients, was also deemed to be relevant for the NMA given that it had 61% and 57% HER2- patients in the fulvestrant and exemestane arms, respectively.

As part of assessing the trials' eligibility for inclusion in the analyses, details of the following are also provided in Appendix D:

- Risk of bias
- Assessment of heterogeneity in:
    - Baseline patient characteristics
    - Interventions
    - Prior endocrine and chemotherapy treatment
    - HR and HER2 status
    - Blinding of studies
    - Accounting for crossover

B.2.9.2 *Proportional hazards*

Traditional indirect treatment comparison (ITC) techniques rely on the assumption of constant HRs and, if violated, can produce results that are not robust. In cost-effectiveness evaluations based on comparisons of expected survival where the tail of the survival function can have an impact on the expected survival, violations of the constant hazard ratio can lead to biased estimates.[74]

The proportional hazards assumption was assessed using log cumulative hazard plots (parallel line suggested proportional hazards held) and Schoenfeld residual (flat line with no systematic trend suggested proportional hazards held) in PALOMA-3. It was observed that the proportional hazards (PH) assumption may not hold within PALOMA-3 itself for PFS (Appendix D.2.1).[75,76] A traditional Bayesian NMA may thus not be suitable as it relies on a single hazard ratio to be applicable across the observed comparative survival in trials, which relies on proportionality. Hence, the NMA presented in this submission for PFS uses a multi-dimensional treatment effect approach, the fractional polynomial (FP) method[74]. Such an approach has been accepted in previous UK HTA appraisals.[77,78] The methodology of the FP conducted for PFS is presented below in section B.2.9.4.1 and Appendix D.3.1.

Proportional hazards was also assessed for OS and appeared to hold in PALOMA-3 (see tests for proportionality in the OS parameter presented in Appendix D.2.2). Proportional hazards was also appeared to hold in the additional studies included in the NMA for OS (the log-cumulative hazard

plots for OS from SoFEA[73] were not parallel and crossed at many points, however given that the KMs were very similar and showed no separate, proportional hazards was assumed to hold). Therefore, a traditional Bayesian NMA was conducted. Details of the methods used for the Bayesian NMA for OS are presented in section 0 and Appendix D.3.2.

B.2.9.3 *Included studies*

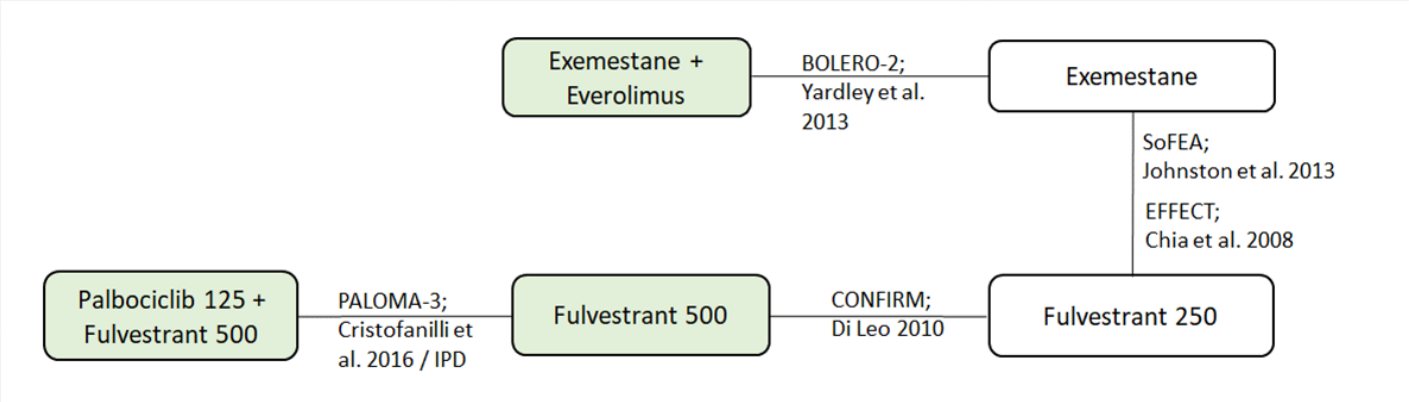
B.2.9.3.1 *PFS*

In addition to the risk of bias and heterogeneity considerations, the selection of studies suitable for inclusion in the fractional polynomial PFS network was based on the following criteria:

- All studies identified in the RCT SLR were examined to ensure Kaplan-Meier data were available for PFS or time to progression (TTP). Any studies that did not contain this data were removed.

On the basis of these criteria, all five studies were eligible for inclusion in the PFS network (Figure 15).

Figure 15. Network diagram for PFS



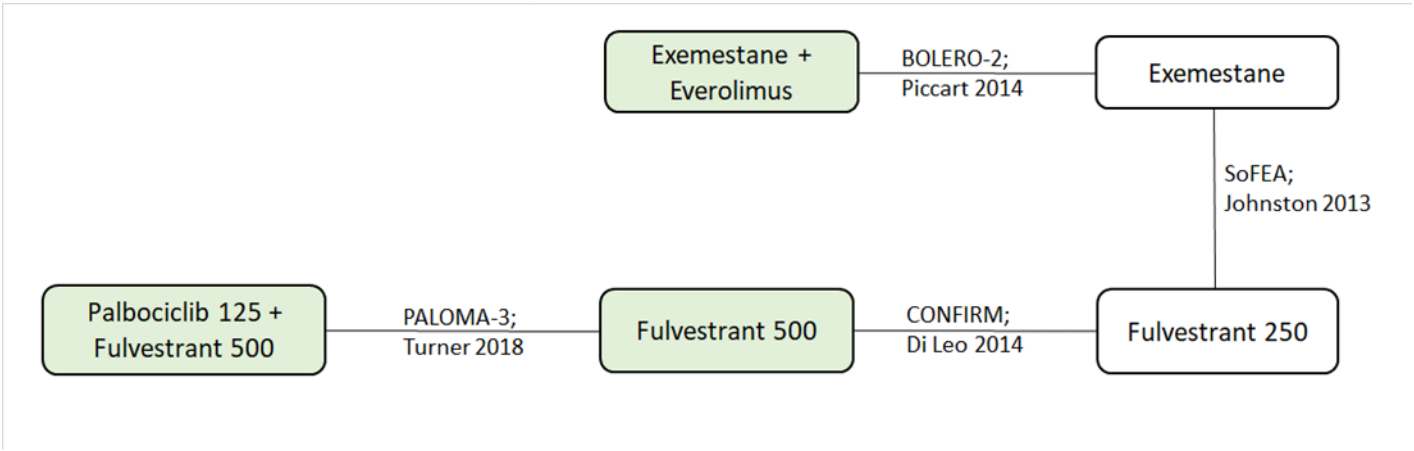
B.2.9.3.2 *OS*

In addition to the risk of bias and heterogeneity considerations, the selection of studies suitable for inclusion in the OS network was based on the following criteria:

- All studies identified in the RCT SLR were examined to ensure OS HR data were available for OS. Any studies that did not contain this data were removed.

On the basis of these criteria, only four studies were eligible for inclusion in the OS network (Figure 16) given that OS data has not been reported from the EFECT[72] study.

Figure 16. Network diagram for OS



B.2.9.4 *NMA methods and results*

B.2.9.4.1 *PFS FP analysis*

FP modelling was conducted following Jansen (2011)[74] methods. First- and second-order FP fixed-effects models were fitted to the data representing all possible combinations of powers from the following set: -2.0, -1.0, -0.5, 0.0, 0.5, 1.0, 2.0, 3.0. The parameters of the different models were estimated using a Markov Chain Monte Carlo (MCMC) method implemented in the WinBUGS software package.[79] The WinBUGS sampler, using two chains with different initial values, was run for a burn-in period of 500,000 iterations first, then a further 5,000,000 with a thinning of 100 in order to obtain the final results. Convergence of the chains towards sensible posterior distributions was confirmed by visual inspection of history plots, posterior densities, and Gelman-Rubin plots.

The Deviance Information Criterion (DIC) was used to compare the goodness-of-fit of different first and second order FP models with different powers. The model with the lowest DIC was selected as the model providing the "best" fit to the data. Other models with a DIC within 3-5 points of the best one were also considered as possible candidates.[74] Results from these models were plotted to assess by visual inspection the fit and plausibility of the predictions in PFS with each treatment.

Based on DIC and validation against KM data from the relevant trials, the second order model (fixed effects) with powers -1 and -1 was selected as the best fit with the second lowest DIC. The remaining two models predicted implausible hazards in the first cycle so were not applied. However, beyond cycle 1 they provided hazard aligned with the base-case model. A graphical representation of this PFS model is presented in Figure 17.

Additional details on the FP analysis are presented in Appendix D.3.1 including (random effects models, DIC table, hazard ratios over time (tabulated and graphical), plots of additional FP model explored, WinBUGS code)

Figure 17. Progression-free survival- Second-order -1, -1

OS Bayesian NMA

A Bayesian NMA for OS was performed according to well-established methods outlined by the NICE DSU.[80 81] The analysis was carried out on hazard ratios (HRs).

Both fixed effect and random effects NMA models were considered; however, because the network was informed by single-study connections between interventions, the ability to reliably estimate between-study variance was very limited. The random-effect model therefore carried a lot of uncertainty and gave results that are not clinically plausible (extremely wide CrI). The fixed-effect model was therefore the chosen one for this analysis.

The NMAs were implemented in WinBUGS (version 1.4.3), using 3 chains, a burn-in sample of 20,000 iterations and 50,000 subsequent sampling iterations with a thinning of 10. To assess whether the models adequately fit the data, the total residual deviance from the NMA was compared to the corresponding number of data points (approximately equal if fit is adequate). The DIC was also compared between fixed- and random-effects models when applicable.

The OS findings for the comparators of interest from the fixed-effect NMA are presented in Table 18. Palbociclib plus fulvestrant was associated with an improved OS compared to everolimus plus exemestane, but this difference was not significant.

Table 18. Pairwise comparisons from the fixed effect OS NMA using palbociclib plus fulvestrant as the reference treatment

Comparator	Median HR	95% CrI
Everolimus plus exemestane	[redacted]	[redacted]

Abbreviations: CrI, credible interval; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival.

Further details on the description of the methods and results for the Bayesian OS NMA is presented in Appendix D.3.2.

B.2.10 **Adverse reactions**

This section summarises adverse reactions observed in the pivotal phase III PALOMA-3 RCT comparing palbociclib plus fulvestrant to fulvestrant (plus placebo) along with additional evidence on the safety profile of everolimus.

B.2.10.1 *PALOMA-3 safety overview*

Overview

- The safety profile of palbociclib plus fulvestrant was tolerable and manageable. Patients were able to remain on effective study treatment with palbociclib throughout the study, by adjusting dose medication and accompanying standard medical therapy.
- The most common treatment-related treatment-emergent adverse events (TEAEs) (≥[redacted]) observed following treatment with palbociclib and fulvestrant were neutropenia, fatigue, leukopenia, nausea, white blood cell (WBC) count decreased, and anaemia, and the most common TEAEs (≥[redacted]) observed following treatment with placebo plus fulvestrant were fatigue and nausea.
- The most common grade 3 treatment-related TEAEs were neutropenia ([redacted]%) and neutrophil count decrease ([redacted]%), leukopenia ([redacted]%) and white blood cell count decrease ([redacted]%). these AEs are laboratory-based AEs and are not experienced by patients as manifestations of physical side effects as reflected in the QoL data. In addition, despite the relatively high rates of neutropenia, febrile neutropenia was only reported in 0.6% patients receiving palbociclib plus fulvestrant in PALOMA 3.
- Overall, the proportions of patients experiencing treatment-related TEAEs associated with dose reduction and dosing interruption/cycle delay were higher for palbociclib than for placebo.
- Overall, the observed changes in TEAEs/treatment-related AEs associated with permanent or temporary discontinuation from treatment and/or dose reduction were minor and are not considered to be clinically meaningful.
- The safety profile of everolimus was informed by pooled data from 2,672 patients across ten clinical studies. Everolimus was associated with an increased risk of stomatitis, skin rash, and pruritus, and high-grade diarrhoea. Clinical expert opinion indicated everolimus' toxicity profile limits its prescribing in some patients.

B.2.10.2 *PALOMA-3: Exposure to study medicine*[16]

As of 31 July 2015, 347 patients were randomised to the palbociclib plus fulvestrant arm, of whom 345 received treatment, whilst 174 patients were randomised to the placebo plus fulvestrant arm, of whom 172 were treated. A total of [redacted] patient ([redacted]%) in the palbociclib plus fulvestrant arm and [redacted] patients ([redacted]%) in the placebo plus fulvestrant arm were permanently discontinued from treatment. Hence, [redacted] patients ([redacted]%) in the palbociclib plus fulvestrant arm and [redacted] ([redacted]%) in the placebo plus fulvestrant arm were ongoing as of 31 July 2015.

Detailed patient exposure analyses relating to palbociclib, placebo and fulvestrant are provided in Appendix Q. The median duration of palbociclib plus fulvestrant treatment was more than 2-fold longer than that of placebo plus fulvestrant ([redacted] versus [redacted] days respectively). The median relative dose intensity estimated for palbociclib was lower than for placebo ([redacted]% versus [redacted]%).

Duration of fulvestrant treatment was greater in the palbociclib with fulvestrant arm (treatment duration median [redacted] days) than in the placebo with fulvestrant arm (treatment duration median [redacted] days). The proportion of patients who had their fulvestrant dosing interrupted was also greater in the palbociclib with fulvestrant arm ([redacted]%) than in the placebo with fulvestrant arm ([redacted]%). It is worth noting that PALOMA-3 study protocol did not allow for the fulvestrant dose to be reduced, but a single dose of the medicine could be skipped or delayed if required due to fulvestrant-related toxicity.

B.2.10.3 *PALOMA-3: Treatment-related adverse events*[16]

Treatment-related AEs are summarised in Table 19. Most of these treatment-related AEs were of Grade 1/2 severity in either treatment arm, except for neutropenia, neutrophil count decrease, leukopenia and white blood cell count decrease.

A total of 203 patients ([redacted]%) in the palbociclib plus fulvestrant and 8 patients ([redacted]%) in the placebo plus fulvestrant arm experienced treatment-related AEs of Grade 3 maximum severity (Table 19). The Grade 3 treatment-related AEs experienced by more than 2% of patients each in the palbociclib plus fulvestrant arm were neutropenia ([redacted]%) and neutrophil count decrease ([redacted]%), leukopenia ([redacted]%) and white blood cell count decrease ([redacted]%), as well as anaemia ([redacted]%). The only Grade 3 treatment-related AEs reported for more than 1 patient in the placebo plus fulvestrant arm were anaemia and fatigue experienced by 2 patients ([redacted]%) each. Palbociclib is a well-tolerated treatment with a manageable adverse events profile and it should be noted that these AEs are laboratory-based AEs and are not experienced by patients as manifestations of physical side effects as reflected in the QoL data in Section B.2.6.6.3.

Table 19. Summary of Treatment-related TEAEs (all cycles) by MedDRA preferred term and maximum CTCAE grade (all cycles) – experienced by at least 5% of patients 'As Treated' population as of 31 July 2015

	Number (%) of Patients (N=517)											
	Palbociclib + Fulvestrant (N=345)						Placebo + Fulvestrant (N=172)					
MedDRA Preferred Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**All Grades**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**All Grades**
Any treatment-related AE												
Neutropenia												
Fatigue												
WBC count decreased												
Anaemia												
Leukopenia												
Nausea												
Neutrophil count decreased												
Alopecia												
Diarrhoea												
Hot flush												
Thrombocytopenia												
Stomatitis												
Constipation												
Platelet count decreased												
Decreased appetite												
Headache												
Vomiting												
Arthralgia												
Rash												
Injection site pain												
Dry mouth												
Myalgia												

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events (National Cancer Institute); MedDRA, medical dictionary for regulatory activities; WBC, white blood cells.

B.2.10.4 *PALOMA-3: Serious treatment-related AEs[16]*

A total of [redacted] patients ([redacted]%) in the palbociclib plus fulvestrant arm and 2 patients ([redacted]%) in the placebo plus fulvestrant arm experienced treatment-related AEs of Grade 4 severity. The Grade 4 treatment-related AEs experienced by more than [redacted] patient ([redacted]%) each in the palbociclib plus fulvestrant arm were neutropenia ([redacted]%) and neutrophil count decreased ([redacted]%) as well as white blood cell count decrease ([redacted]%). The Grade 4 treatment-related AEs experienced by [redacted] patients ([redacted] patient [[redacted]%] each) in the placebo plus fulvestrant arm were white blood count decrease and cholecystitis.

No treatment-related Grade 5 AEs were experienced by patients in either study arm. Serious adverse events are summarised in Table 20.

Table 20. Summary of treatment-related, treatment-emergent serious adverse events (all cycles) experienced by patients receiving palbociclib plus fulvestrant in PALOMA-3

MedDRA (version 18) Preferred term	Number (%) of patients receiving Palbociclib + Fulvestrant (N=345) with event
Any treatment-related serious adverse event	[redacted]
Neutropenia	[redacted]
Febrile neutropenia	[redacted]
Pharyngitis	[redacted]
Alanine aminotransferase increased	[redacted]
Bacteraemia	[redacted]
Cataract	[redacted]
Deep vein thrombosis	[redacted]
Electrocardiogram QT prolonged	[redacted]
Erysipelas	[redacted]
Hepatic failure	[redacted]
Influenza	[redacted]
Intestinal obstruction	[redacted]
Neutrophil count decreased	[redacted]
Otitis media acute	[redacted]
Pericarditis	[redacted]
Rash maculo-papular	[redacted]
Skin disorder	[redacted]

Notes: Includes data up to 28 days after last dose of study drug.

Abbreviations: MedDRA, medical dictionary for regulatory activities.

B.2.10.5 *Discontinuation, dose reduction or modification due to TEAEs[16]*

B.2.10.5.1 *Permanent discontinuation*

[redacted] patients ([redacted]%) in the palbociclib plus fulvestrant arm who had experienced treatment-related AEs associated with temporary discontinuation from treatment, later were permanently discontinued from treatment because of treatment-related AEs. In the fulvestrant arm, [redacted]% experienced permanent discontinuation due to treatment.

B.2.10.5.2 *Temporary discontinuation*

The overall frequency of TEAEs associated with temporary discontinuation from treatment in the palbociclib plus fulvestrant arm ([redacted]%) was greater than that in the placebo plus fulvestrant arm ([redacted]%).

The most frequently reported treatment-related AEs (i.e., ≥5% of patients) associated with temporary discontinuation from treatment in that arm of the study were neutropenia ([redacted]%) and neutrophil count decreased ([redacted]%) as well as white blood cell count decrease ([redacted]%) and leukopenia ([redacted]%). Most TEAEs of neutropenia ([redacted] patients), neutrophil count decrease ([redacted]) and all TEAEs of white blood cell count decrease and leukopenia in the palbociclib plus fulvestrant arm were considered to be related to treatment.

B.2.10.5.3*Dose reductions or schedule changes*[16]

Most TEAEs associated with palbociclib dose reduction/modification experienced by patients in the palbociclib plus fulvestrant arm were considered to be related to treatment ([redacted] patients [[redacted]%]). [redacted] patients ([redacted]%) in the palbociclib plus fulvestrant arm who had experienced treatment-related AEs associated with dose reduction, were subsequently permanently discontinued from treatment because of treatment-related AEs.

A total of [redacted] patients ([redacted]%) in the palbociclib plus fulvestrant arm had had their palbociclib dose reduced as of 31 July 2015: [redacted] patients ([redacted]%) had their dose reduced from 125mg QD to 100mg QD, and [redacted] patients ([redacted]%) had their dose reduced from 125mg QD to 100mg QD and further to 75mg QD. Palbociclib dose was reduced [redacted] in the palbociclib arm. Finally, [redacted] patients ([redacted]) had their palbociclib dose regimen changed from Schedule 3/1 (three weeks on/one week off) to [redacted]. There were [redacted] patients requiring dose reductions ([redacted]%) in the placebo plus fulvestrant arm.

A summary of tumour response in patients who had received at least one dose reduction ([redacted]% of patients in the palbociclib plus fulvestrant arm, n=[redacted]) is shown in Table 21. An analysis of the median PFS for this group showed the median PFS length to be equal to [redacted]. [16] This is comparable to observations in the wider palbociclib group [redacted] where median PFS was [redacted]. Both analyses show that dose reduction, although a regular occurrence in clinical practice, does not diminish the efficacy of palbociclib in halting tumour progression, nor its efficacy in prolonging PFS.[47] It also reiterates that AEs can be managed effectively with dose reductions without compromising efficacy.

Table 21. Summary of Best Overall Tumour Response by Treatment, Investigator Assessment for Subjects with at Least One Dose Reduction: Palbociclib + Fulvestrant Treated Patients, as of the 23 October 2015 data cut

	Palbociclib + Fulvestrant (N=132) n (%)
Complete response	[redacted]
Partial response	[redacted]
Stable/No response	[redacted]
Objective progression	[redacted]
Indeterminate	[redacted]
Objective Response Rate (CR+PR)	[redacted]
95% Exact CI[a]	[redacted]

Notes: [a] CI was calculated using the exact (Clopper-Pearson) method.

Abbreviations: CI, confidence interval; CR, complete response; PR, partial response.

B.2.10.6 *QTc interval prolongation*[16]

No clinically significant effects on QTc interval were observed during treatment with palbociclib plus fulvestrant, [redacted] Palbociclib therapy was temporarily discontinued in response to these events and was subsequently restarted, although at a reduced dose of 100mg QD; the events did not reoccur thereafter.

B.2.10.7 *Clinical management of neutropenia (and asymptomatic)*[16]

As of 31 July 2015, data from PALOMA-3 indicate that neutropenia occurred less often with increasing treatment cycles: among patients with grade 0-2 neutropenia in the first 2 cycles, only [redacted]% experienced grade ≥3 neutropenia beyond cycle 2; among those with grade 0-2 neutropenia in the first 4 cycles, only [redacted]% experienced grade ≥3 neutropenia beyond cycle 4; and among those with grade 0-2 neutropenia in the first 6 cycles, only [redacted]% experienced grade ≥3 neutropenia beyond cycle 6. Febrile neutropenia of grades 3 or 4 was observed in 3 subjects in the palbociclib plus fulvestrant arm, compared to one subject in the placebo plus fulvestrant arm, as summarised in Table 22.

Table 22. Summary of patients who experienced neutropenia of Grade 3 or Grade 4 maximum severity (all cycles) in PALOMA-3 as of 31 July 2015 - all treated patients

	Number (%) of Patients (N=517)	
Patient category	**Palbociclib plus fulvestrant (N=345)**	**Placebo plus fulvestrant (N=172)**
With maximum Grade 3 Neutropenia	[redacted]	[redacted]
With Febrile neutropenia [a]	[redacted]	[redacted]
With dose reduced/interrupted or cycle delayed due to grade 3 or lower Neutropenia	[redacted]	[redacted]
With permanent discontinuation due to Grade 3 or lower Neutropenia	[redacted]	[redacted]
With maximum Grade 4 Neutropenia	[redacted]	[redacted]
With Febrile neutropenia [a]	[redacted]	[redacted]
With dose reduced/interrupted or cycle delayed due to Grade 4 or lower Neutropenia	[redacted]	[redacted]
With permanent discontinuation due to Grade 4 or lower Neutropenia	[redacted]	[redacted]

Notes: Includes data up to 28 days after last dose of study drug/ Each patient is counted once based on the highest severity grade reported for the event. The cluster term "Neutropenia" includes MedDRA (version 18) PTs "Neutropenia" and "Neutrophil count decreased".

a. Neither Neutropenic sepsis nor Neutropenic infection was reported as of 31 July 2015. A follow-up SAE report was filed for 1 of the patients receiving palbociclib plus fulvestrant on 30 November 2015, providing updated clinical information including 2 additional fatal events of Neutropenic sepsis and Multi-organ failure experienced by this patient. Neither of these SAEs was considered to be related to treatment.

The neutropenia associated with palbociclib-based combination therapy appears to be by a G1/S arrest that is cytostatic and reversible upon dose interruption. This is in contrast to the cytotoxic neutropenia associated with the cytotoxic effects of chemotherapy which causes death of immature progenitor cells by apoptosis.[82, 83] The primary toxicity of asymptomatic neutropenia was effectively managed by dose modification without affecting overall time on treatment or efficacy.[47] In PALOMA-3 median PFS was similar between patients who experienced grade ≥3 neutropenia versus grade

≤2 (11.1 vs 11.0 months; HR 0.98, 95% CI 0.64, 1.51), between patients who experienced 1 versus 0 dose reductions because of neutropenia (9.5 vs 9.5 months; HR 0.87, 95% CI 0.61, 1.25), or between patients who experienced a dose interruption or cycle delay because of neutropenia versus those who did not (9.5 vs 9.9 months, HR 0.84, 95% CI 0.61, 1.17).[47]

Since palbociclib is associated with a greater incidence of neutropenia and leukopenia, patients receiving treatment should undergo full blood count monitoring to assess their absolute neutrophil count (please refer to Appendix C for the SmPC).

B.2.10.8 *Additional evidence on safety from wider evidence network*

B.2.10.8.1 *Palbociclib*

The SLR (up to January 2018) conducted for this submission identified unique safety investigations, conducted as Phase 1 or Phase 2 trials or retrospective/prospective observational studies, investigating palbociclib for the treatment of ER-positive HER2-negative aBC (see Appendix F). This evidence supports the safety and tolerability of palbociclib as observed in PALOMA-3. In addition, a cross-sectional survey in 250 patients with HR-positive HER2-negative aBC aimed to establish patient satisfaction with palbociclib, revealed that over 96% of the 104 patients who received the palbociclib plus fulvestrant regimen reported that the side-effects were as expected or better than expected.[84]

To evaluate the tolerability profiles across the intervention and the comparators, information was taken from the respective SmPCs which included adverse reactions listed according to MedDRA system organ class and frequency category, defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Appendix R reports the very common and common adverse reactions.

The overall safety profile for palbociclib was informed by pooled data from 872 patients who received palbociclib plus endocrine therapy (N=527 plus letrozole and N=345 plus fulvestrant) in randomised clinical studies in HR-positive, HER2-negative advanced or metastatic breast cancer. The most common (≥20%) adverse reactions of any grade were neutropenia, infections, leukopenia, fatigue, nausea, stomatitis, anaemia, alopecia, and diarrhoea. The most common (≥2%) Grade ≥3 adverse reactions associated with palbociclib were neutropenia, leukopenia, anaemia, fatigue, and infections.[56] From the pooled safety data for fulvestrant monotherapy, the most frequently reported adverse reactions were injection site reactions, asthenia, nausea, and increased hepatic enzymes (ALT, AST, ALP).[85]

Since positive CHMP from the EMA on the 15th of September 2016 and last safety report update to the EMA has reported no new safety signals with no additional safety monitoring requirements added to the prescribing of palbociclib.

B.2.10.8.2 *Everolimus*

The safety profile of everolimus was informed by pooled data from 2,672 patients across ten clinical studies. The most common adverse events (incidence ≥1/10) from the pooled safety data were (in decreasing order): stomatitis, rash, fatigue, diarrhoea, infections, nausea, decreased appetite, anaemia, dysgeusia, pneumonitis, oedema peripheral, hyperglycaemia, asthenia, pruritus, weight decreased, hypercholesterolaemia, epistaxis, cough and headache. The most frequent Grade 3-4 adverse reactions (incidence ≥1/100 to <1/10) were stomatitis, anaemia, hyperglycaemia, infections, fatigue, diarrhoea, pneumonitis, asthenia, thrombocytopenia, neutropenia, dyspnoea, proteinuria,

lymphopenia, haemorrhage, hypophosphatemia, rash, hypertension, pneumonia, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased and diabetes mellitus (the grades follow CTCAE Version 3.0 and 4.03).[86]

Several meta-analytic studies have been carried out to ascertain the risk of AEs associated with the use of everolimus in cancer patients. They have demonstrated that everolimus is associated with a significantly increased risk of all-grade stomatitis, skin rash, and pruritus and mouth ulceration;[87] all-grade and high-grade diarrhoea and stomatitis;[88,89] all-grade fatigue, hyperglycaemia, hyperlipidaemia and elevated ALT;[90,91] all-grade and high-grade anemia;[92] high-grade rash;[89] all grade and grade 3–4, hyperglycaemia, hypercholesterolemia, and hypertriglyceridemia;[93] infection;[94] and all grades of pneumonitis, a condition which has a high impact on morbidity and mortality,[95] and often leads to permanent discontinuation.[96]

The issue of optimising everolimus risk-benefit profile is prominent in elderly patients. In a comparative study, frequent discontinuations due to AEs were reported in the ≥70-years subgroup treated with everolimus versus ribociclib or palbociclib.[97] Findings from clinical and safety studies (BOLERO-2, BALLETT) on the less favourable experiences of elderly patients in terms of treatment duration, relative dose intensity, AEs and on-treatment deaths have been also documented in a recent literature review of everolimus studies, including RCTs and RW evidence.[98] In the UK over 25% of new cases of breast cancer occur in patients over the age of 75.[99]

Caution in everolimus prescribing is implicit in the fact that, despite higher PFS and OS for everolimus plus exemestane than fulvestrant, fulvestrant is still preferred despite its variable accessibility in the NHS in the UK. Clinical opinion has stated that the use of fulvestrant, in sacrificing efficacy, is because of tolerability with everolimus. During a recent UK Breast Oncology Advisory Board meeting,[100] clinicians have described everolimus as a “difficult” drug, and have observed that in their experience, patients on the combined palbociclib and fulvestrant regimen are happier than those on everolimus plus exemestane, also taking into account the impact on their ability to work and their productivity and QOL. Clinicians have expressed doubts over the safety of everolimus, particularly regarding pneumonitis and mucositis, and given the data on discrepancies between the number of patients starting and finishing the everolimus regimen, they wonder how many patients actually complete a reasonable number of cycles. These are crucial RW data for which at present no information is available.

B.2.11 **Ongoing studies**

B.2.11.1 *Non-RCT studies*

A systematic literature review of non-RCT evidence was conducted (up to January 2018). This is provided in Appendix D. Since this search was not updated with the RCT SLR, key studies published since January 2018 identified internally have also been extracted.

There have been two non-randomised (three additional identified internally), real-world evidence studies in this setting which are relevant to this submission. The IRIS study is currently being expanded to Ex-US sites and their design and main findings are presented in Table 23 with further details provided in Appendix L.

Table 23. Summary of non-RCT studies

Name and type of study	Population	Country	Study objectives and outcomes measured	Summary of outcomes
Darden et al[84,101] Observational, cross-sectional, web-based survey of patients with HR-positive/HER2–negative aBC/mBC.	The study recruited 250 patients with HR-positive/HER2–negative aBC/mBC from September to November 2017. Median age was 40 years, and approximately 42% (n = 104) of the study population had received palbociclib + fulvestrant. Overall mean (SD) time since diagnosis of aBC/mBC was 16.9 (38.82) months; 72.8% were initially diagnosed with aBC/mBC while the remaining recurred from earlier stages. 86 patients with mBC indicated site(s) of metastases. Of these, 37.2% had visceral metastases.	U.S.	The goal of the study was to assess treatment satisfaction among women receiving palbociclib combination therapies for HR-positive / HER2–negative aBC. Satisfaction was measured using the Cancer Therapy Satisfaction Questionnaire (CTSQ), which assesses three domains: • Expectations of therapy in preventing recurrence or progression or returning to normal life • Feelings about side effects (FSE) • Satisfaction with therapy (SWT)	Mean (SD) SWT scores were high in patients treated with palbociclib + AI (71.04 [12.18]) and in patients treated with palbociclib + fulvestrant (76.17 [9.91]). Mean (SD) expectations of therapy scores were 70.48 (16.11) with palbociclib + AI and 76.39 (15.05) with palbociclib + fulvestrant, respectively. Mean (SD) scores for FSE were 47.69 (14.90) for palbociclib + AI and 40.75 (13.55) for palbociclib + fulvestrant. Satisfaction scores did not differ according to visceral metastasis status. Both patients groups taking palbociclib + AI or palbociclib + fulvestrant reported high satisfaction with treatment scores. Over 30% of patients on palbociclib + AI and over 52% on palbociclib + fulvestrant had satisfaction scores >75.
Ibrance Real World Insights Study (IRIS)[102,103] Retrospective, observational study, drawing data from medical chart reviews	Patients who received palbociclib plus an AI or fulvestrant based on the licensed indication. 65 physicians completed electronic case report forms for 652 patients. Mean age (SD) was 64.8 (10.4) years and 63.5 (11.4) for patients receiving palbociclib plus AI and palbociclib plus fulvestrant respectively.	U.S.	The study objective was to describe real world demographics, clinical characteristics, treatment patterns and clinical outcomes of HR-positive/HER2-negative aBC/mBC patients who have received palbociclib plus an AI or fulvestrant. The following data and outcomes were captured from the chart reviews:	79.5% of palbociclib plus AI patients achieved a partial response or better as best response (68.5% partial response, 11.0% complete response). 74.0% of palbociclib plus fulvestrant patients achieved a partial response or better as best response (65.5% partial, 8.5% complete response). At 12 months the progression-free rate was 84.1% and 64.3% at 24 months for patients receiving palbociclib plus an AI. The survival rate was 95.1% at 12 months and 90.1% at 24 months. For those receiving palbociclib plus fulvestrant, the 6-month progression-free rate was 94.3% and 79.9% at 12 months. The survival rate was 97.2% at 6-months and 87.9% at 12 months.

	For patients receiving palbociclib plus AI, more than half (64.7%) of patients were diagnosed with advanced disease at initial diagnosis and 85.3% of patients had an ECOG status of 0 or 1 at initiation. Over 82% of palbociclib plus fulvestrant patients were diagnosed with early disease at initial diagnosis and at initiation, 79.4% had an ECOG status of 0 or 1.		• Patient demographics and clinical profile • Palbociclib treatment patterns • Tumour response variables (CR, PR) • SD at or after 24 weeks • SD before 24 weeks • PD	Palbociclib dose adjustments occurred in 19.7% and 14.4% of patients receiving palbociclib + AI and palbociclib + fulvestrant respectively. In both kinds of combination therapy, similar proportions (between 76% and 79%) of dose changes were reductions and the remainder were interruptions. The most common reason (in over 96% of cases for both treatment combinations) for dose reduction was side effects / tolerability. The frequency of palbociclib dose reductions was lower in both patient groups compared to the PALOMA RCT data. At the time of data abstraction palbociclib treatment was ongoing for 78.9% of palbociclib plus AI patients (n=284) and 80.1% of palbociclib plus fulvestrant patients (n=234).
Ibrance Real World Insights Study (IRIS)[104] Retrospective, observational study, drawing data from medical chart reviews	Patients who received palbociclib plus an AI or fulvestrant based on the licensed indication.	Argentina	Demographics Treatment patterns Clinical outcomes PFS and OS rate at 6 and 12 months	Progression free survival rate at 6 months 95% and overall survival rate at 6 months 98.2%. There was insufficient data at 12 months to calculate PFS and OS rate at 12 months.
Ibrance Real World Insights Study (IRIS)[102,103] Retrospective, observational study, drawing data from medical chart reviews Sub-groups analysis based on age, performance	A retrospective chart review of HR+/HER2- ABC/MBC patients was conducted between June and October 2017. In total, 65 physicians extracted data for 292 patients who had a mean follow up time of 7.4 months. Physicians extracted data from patient medical records for HR+/HER2- ABC patients who received palbociclib plus fulvestrant following disease progression with endocrine	US	Demographics Clinical characteristics Treatment history/patterns Clinical outcomes. Progression free rates and survival rates at 6 and 12 months were estimated via Kaplan-Meier analysis.	Majority of the patients were >65 years (54%) and had ECOG status of 0 (32%) or 1 (48%). Overall 224 (77%) patients had metastatic disease, of which 93 (42%) had visceral metastases. Across all sub-groups, majority of patients prescribed an initial palbociclib dose of 125mg did not require a change of dose while on treatment. The 6-month and 12-month progression free and survival rates; • Up to 65 n=158 • 6-month PFS rate 95.2% • 12-month PFS rate 81.2% • 6-month OS rate 98.0% • 12-month OS rate 90.0%

status and sites of metastases	based therapy for their advanced disease.			• Over 65 n+134 • 6-month PFS rate 93.2% • 12-month PFS rate 77.8% • 6-month OS rate 96.4% • 12-month OS rate 85.1%
Real world treatment patterns associated with palbociclib combination therapy in Germany: Results from the IRIS Study[105]	A retrospective chart review of HR+/HER2- ABC/ MBC patients who received palbociclib combination therapies was conducted in Germany. Physicians completed electronic case report forms (eCFRs)	Germany	Patient demographics Clinical characteristics Treatment patterns from an index date (60 days after physician's first prescription of palbociclib) until the most recent record available	42 physicians completed 257 eCRFs with 48% representing academic centers. The mean (SD) age of patients at palbociclib initiation was 59.6 (9.4) years (median, 60 years). ECOG status at palbociclib initiation was mostly 0 (48.2%) or 1 (33.5%). Visceral disease was present in 65.6% of patients. Approximately 75% of patients received palbociclib plus aromatase inhibitors (AI) and 25% plus fulvestrant. Overall, 97% patients received palbociclib + AI as 1st line advanced therapy, the remaining having received chemotherapy previously in the advanced setting. Letrozole was the most common AI partner therapy (63.4%) followed by anastrozole (23.2%), and exemestane (13.4%). Palbociclib + fulvestrant was mostly used in first (44.4%) and second (52.4%) lines. The most frequently prescribed starting dose was 125 mg/day (73.2%), followed by 100mg/day (26.1%) and 75 mg/day (0.8%). 76% of palbociclib + AI patients started on 125 mg compared to 65% of palbociclib + fulvestrant patients. Dose reductions occurred in only 28 (10.9%) patients (7.4% of those who started at 125 mg/day) and a cycle delay occurred in 1 (3.4%) patient. Dose reduction rates were 10.8% in palbociclib + AI and 11.1% in palbociclib + fulvestrant.

Abbreviations: aBC, advanced breast cancer; AI, aromatase inhibitor; CR, complete response; CTSQ, Cancer Therapy Satisfaction Questionnaire; ECOG, Eastern Cooperative Oncology Group; FSE, Feelings about side effects; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IRIS, Ibrance Real World Insights Study; mBC, metastatic breast cancer; PD, progressive disease; PR, partial response; RCT, randomised controlled trial; SD, stable disease; SD, standard deviation; SWT, satisfaction with therapy; US, United States.

B.2.12 **Innovation**

B.2.12.1 *A novel therapy, which addresses current clinical unmet need: increasing PFS and delaying the need for chemotherapy*

Progression-free survival (PFS) with endocrine therapies in the scope generally remains less than 8 months in patients with HR-positive HER2-negative aBC.[106-111] Furthermore, significant limitations exist with endocrine therapy with intrinsic resistance in many patients and eventual acquired resistance in initial responders, both of which significantly influence patient morbidity and mortality.[112] A medical record review study showed that patients in the UK on first-line endocrine therapies have a median TTP of 12.17 months. In the second-line, patients have a median TTP of 7.93 months.[102] Furthermore, in a multi-country chart review, physicians in Germany, France, Belgium, the Netherlands, and Spain attributed "endocrine resistance" as the reason for stopping first-line treatment for over 95% of patients who stopped endocrine therapy.[102,113] The ability to prolong PFS, while maintaining QOL, is therefore an important unmet medical need in the ER-positive HER2-negative aBC setting. Therapies to address this would also further benefit patients by postponing subsequent treatment options, such as chemotherapy and the fear of its associated toxicities.[20,21] Palbociclib demonstrates synergistic enhancement of endocrine therapy and in doing so provides unprecedented PFS extension in patients with ER-positive HER2-negative aBC. The delays to chemotherapy identified in the RCT by adding palbociclib to fulvestrant represent meaningful improvements to patients' lives and give vital time to women with this terminal disease.

Table 24. Summary of PALOMA clinical studies of palbociclib plus endocrine therapy in women with ER-positive/HER2-negative aBC

	PALOMA-1[1,114-120]	**PALOMA-2[16,121]**	**PALOMA-3[55]**
Design	Phase 2 Open label	Phase 3 Placebo control	Phase 3 Placebo control
Endocrine partner	Letrozole	Letrozole	Fulvestrant
Patients on study, N	n=165	n=666	n=521
Endocrine sensitivity	Sensitive	Sensitive	Resistant
Menopausal status	Post-menopausal	Post-menopausal	Post-menopausal + Pre/peri-menopausal
Primary efficacy endpoint: Investigator assessed PFS			
HR (95% CI; p value)*	0.49 (0.33-0.75; p=0.0004)	[redacted]	[redacted]
Median PFS, mo (95% CI)*	20.2 (13.8-27.5) vs 10.2 (5.7-12.6)	[redacted]	[redacted]
PFS gain compared to control (months)*	10.0	[redacted]	[redacted]
Most frequent all cause AEs in Palbociclib arm, %			
Neutropenia	75	[redacted]	[redacted]

Company evidence submission template for palbociclib plus fulvestrant for endocrine resistant HR-positive, HER2-negative advanced breast cancer [ID916]

Leucopenia	43	[redacted]	[redacted]
Anaemia	35	[redacted]	[redacted]
Thrombocytopenia	17	[redacted]	[redacted]
Infection	55	[redacted]	[redacted]
Fatigue	41	[redacted]	[redacted]

Abbreviations: aBC, advanced breast cancer; AEs, adverse events; CI, confidence interval; ER, oestrogen receptor; HER2, Human epidermal growth factor receptor; HR, hazard ratio; mo, months; OS, overall survival; PFS, progression-free survival.

B.2.12.2 *An innovative therapy recognised at the regulatory level*

On the basis of its PFS benefit, the US Food and Drug Administration approved palbociclib under its Breakthrough Therapy and Priority Review programs for first-line use plus letrozole for treating postmenopausal women with ER-positive HER2−negative aBC. The Breakthrough Therapy designation is only awarded to drugs that act alone or combination with other drugs to treat a serious or life-threatening disease or condition, and that demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints.[122] Furthermore, in the UK, palbociclib was granted a Promising Innovative Medicine designation by the Medicines & Healthcare Products Regulatory Agency (MHRA) in the UK. This designation is awarded to promising new technologies that show major advantages over existing UK therapies in the treatment, diagnosis or prevention of life-threatening or seriously debilitating conditions with high unmet need, such as because existing therapies have serious limitations.[123]

B.2.12.3 *A first-in-class targeted therapy with a new mechanism of action*

Palbociclib is a small molecule inhibitor of the cyclin dependent kinases (CDK) 4 and 6 that synergistically enhances the effect of endocrine therapy leading to a significant improvement in PFS in patients with ER-positive HER2-negative aBC with a generally manageable adverse event profile.[1,2,7,8] Through its mechanism of action palbociclib enhances the anti-proliferative efficacy of endocrine treatments through inhibition of the ER receptor in breast cancer cells.[7] This synergistic enhancement was demonstrated in the phase III PALOMA-2 clinical trial in which palbociclib plus letrozole demonstrated a PFS of median PFS was 27.6 months for palbociclib–letrozole (n = 444) and 14.5 months for placebo-letrozole (n = 222) (HR 0.563; 1-sided P < 0.0001)). in postmenopausal women with ER-positive HER2-negative aBC who had not received prior therapy for their metastatic disease.[121] In addition, evidence suggests that inhibition of CDK4/6 by palbociclib may overcome ET resistance in breast cancer cells[7, 124,125]. The potential for palbociclib to act synergistically with ET and reverse endocrine resistance was demonstrated in the Phase III PALOMA-3 trial in which the addition of palbociclib to the ER antagonist, fulvestrant more than doubled the PFS from 4.6 months for fulvestrant alone to 11.2 months for fulvestrant plus palbociclib in women whose ER-positive HER2-negative aBC had progressed on or shortly after endocrine therapy.[8]

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

B.2.13.1 *Trial design quality assessment for PALOMA-3*

Blinding and allocation

Randomisation was performed appropriately using a centralised, interactive web-based, voice-based system. Care providers, participants and outcome assessors were blind to treatment allocation.

Measurement and analysis quality

PALOMA-3 used a triple blind design and included a BICR of a random sample of 40% of patients to verify the primary outcome of investigator-assessed PFS.

Efficacy analyses were performed on the ITT population. Safety analyses were performed on all randomised patients who received at least one dose of study treatment.

B.2.13.2 *Impact of trial quality on evidence quality*

The trial quality of PALOMA-3 allowed stratified estimates of PFS gain as well as all major clinical response variables to be carried out with good power in a representative sample of the treatment population. Baseline characteristics of the ITT population were well balanced between the study groups. Robust follow-up data allowed for additional analyses of more mature PFS data and other outcomes data to be carried out.

B.2.13.3 *The value of PFS to patients*

PFS was the primary endpoint in PALOMA-3 with OS analysed as a secondary endpoint. The main outcome considered for demonstrating efficacy in this submission was PFS, in line with the primary endpoint from the PALOMA-3 trial, noting its value to patients' and their lives as a stand-alone outcome, but also noting its acceptance as a valid surrogate endpoints.[126]

Avoiding progression

First and foremost, progression is associated with an increase in symptoms and staying progression-free avoids such symptom onset and is therefore associated with higher quality of life.[126] Patients with aBC often present with general symptoms such as fatigue, difficulty sleeping, depression and pain, as well as symptoms related to the sites of metastatic disease,[127] all of which are detrimental to quality of life. Patients with aBC show lower physical functioning[128] and lower HRQoL than the general population.[129,130] A study by Lloyd (2006)[131] examining the quality of life in a UK cohort of aBC patients found that disease progression has the largest impact on quality of life.

Disease progression is also associated with women stopping work which carries with it a societal cost. According to a recent literature review of indirect costs for post-menopausal women with HR-positive/HER2-negative aBC aimed to explore how these costs are affected by disease progression within the metastatic setting, it was estimated that delaying progression has the potential to save patients and society in the UK an average of £418 to £811 per month in indirect and societal costs, by keeping patients pre-progression.[30] Many HR-positive/HER2-negative women are diagnosed with metastatic disease when they are of working age. A study of 19,496 women with breast cancer found a correlation between disease progression and increased rates of absence from work.[17] UK clinical experts have indicated that when faced with aBC, one of the primary goals of treatment is to allow patients to carry on living a 'normal' life for as long as possible: staying in work can help to maintain this

normality, both in financial terms as well as functionally and symbolically. Research has found that the burden of aBC and potential negative effects of therapy also prevent women from fulfilling roles they may want to continue fulfilling, for example parent, partner, friend, sibling.[25]

Delaying chemotherapy

Recent HTAs including the SMC submission for everolimus,[132] the NICE appraisals for abiraterone[133] and palbociclib[3,134] have acknowledged that the EQ-5D fails to capture a patient's preference for avoiding or delaying future events, including the commencement of chemotherapy.[133] Chemotherapy can pose a psychological burden on patients with aBC and is for many a source of fear.[135,136] With severe toxicity and lower quality of life[21,137-140] it has also been associated with a reduced ability to work.[141,142] A systematic review of anxiety in women with breast cancer (stages 0-IIIA) receiving chemotherapy, radiotherapy or surgery concluded that chemotherapy is associated with the highest anxiety levels[31] and these levels can be persistent.[32] NHSE recommend to exhaust all other lines of endocrine or targeted therapy before attempting chemotherapy.[3] Therefore, any extension to PFS delivered by a new agent is not just clinically significant, it corresponds to a lengthening of the sequence of treatments which will be tried before the treating doctor resorts to chemotherapy.

Most patients in PALOMA-3 (around 75%) had already received chemotherapy at the time they started treatment in the study, and more than 50% have received chemotherapy in the (neo)adjuvant setting rather than for treating metastatic disease. The palbociclib plus fulvestrant regimen has been shown to be effective even after chemotherapy (Figure 13), however there remains a preference to minimise or avoid further chemotherapy. Furthermore, there is an important subset of patients in this setting who will not yet have received chemotherapy at all, because their metastases and disease profile did not indicate it initially, yet their highly active disease progressed whilst on endocrine treatment.

In PALOMA-3, patients in the palbociclib plus fulvestrant arm increased PFS by +6.6 months but also delayed the time to subsequent chemotherapy by an additional +8.8 months (17.6 months vs 8.8 months, P<0.001).[37] UK physicians reported a reluctance to offer HR-positive HER2-negative aBC chemotherapy unless other treatment options have been exhausted[3] because other options are more tolerable, patients' have a preference to avoid chemotherapy, and because often these patients can be perceived as generally well. Not only does palbociclib offer a delay to subsequent chemotherapy versus fulvestrant alone, but it offers a broad option in the face of restricted recommendations elsewhere, such as everolimus being only able to be given in postmenopausal women without symptomatic visceral disease.

B.2.13.4 *Overall survival*

Gains in PFS translated to gains in OS; adding palbociclib to fulvestrant was associated with an increase in OS of 6.9 months (34.9 months versus 28.0 months; p=0.09[37]). This observed increase in OS was highly consistent with the observed increase in PFS (+6.9 months in OS and +6.6 months in PFS). Although non-significant, it should be noted that OS is a secondary endpoint of PALOMA-3 with the trial design not optimised to detect a statistically significant difference in OS and clinical expert opinion has indicated that the observed gain in OS is clinically meaningful.

Whilst the gains in PFS hold to OS, the hazard ratio for OS is closer to 1 than the hazard ratio for PFS (0.81 compared with 0.5). This is expected as the gain in absolute months is proportionally larger to the medians for PFS than the medians for OS. With a hazard ratio closer to 1 comes the higher possibility of confidence intervals overlapping 1, as is seen in the upper interval for OS which just lies just above 1 (1.03). Consulted UK clinical expert opinion has agreed that this can be expected in trials with survival of this length (noting this was also seen in BOLERO-2) so is understandable and does not warrant the observed increase in median OS invalid, despite being categorised as not statistically significant. Further, recent expert opinion for ESMO stated that, despite not being statistically significant, the observed OS gain is supportive of palbociclib's clinical benefit.[143]

A review of 144 studies involving more than 43,000 patients with metastatic breast cancer showed that PFS or TTP correlated strongly with OS.[141,144] Although the modelling may suffer from bias, the evidence supports a general trend that drugs associated with longer PFS than a comparator treatment are highly likely to be associated with longer OS as well.[145, 146] The results in PALOMA-3, showing comparable increases in PFS and OS, align with this literature. The recent final analyses of OS are compelling in demonstrating that the addition of palbociclib to current therapy has a significant impact on PFS which then translate to meaningful impacts on OS.

B.2.13.5 *Tumour response*

CBR, which captures CR, PR and as well as the absence of progression (stable disease) for at least 24 weeks, is regarded as a well-established robust measure of anti-tumour activity that is well suited to measure benefit in breast cancer particularly for breast cancer drugs.[147] In this submission, CBR outcomes are presented alongside ORR outcomes to demonstrate the superior anti-tumour activity of palbociclib compared to standard care. Palbociclib plus fulvestrant demonstrated a consistent, statistically significant benefit over fulvestrant alone, with three-fold greater odds of OR and CBR observed in the 23 October 2015 analysis.

B.2.13.6 *Patient reported outcomes – well-being, pain and HRQoL*

An anonymous, Internet-based survey of 1,072 patients diagnosed with breast cancer[148] showed that the issues most commonly flagged by patients as important to their prognosis involved maintaining quality of life (99% of patients), independence (97%), and normal activities (97%). Specific symptoms among the 10 most-often flagged issues included depression, anxiety, and pain. The PALOMA-3 study results showed that the palbociclib plus fulvestrant combination had significant benefit over fulvestrant alone in avoiding and/or delaying deterioration in global HRQoL and pain, as well as improving emotional functioning and nausea/vomiting symptoms.[44]

Pain is among the most common and most distressing symptom in cancer[127] affecting a majority of patients with metastatic breast cancer when they present at hospital.[149] In PALOMA-3, palbociclib plus fulvestrant was associated with statistically significant improvements in pain scores compared to placebo plus fulvestrant. Pain management is resource-intensive, demanding detailed assessment of its location and history, as well as the mechanism by which the pain is generated (e.g. due to lesion expansion, pathologic fracture or damage to adjacent structures[127]). The analgesics, antidepressants, and anti-inflammatory

drugs prescribed to limit pain must be chosen carefully to suit its origin and nature, but also with regard to potential drug-drug interactions.[127] In PALOMA-3, palbociclib plus fulvestrant statistically significantly extended the median time to deterioration in pain by over five months, a significant benefit to patients with further implications for the saving of resources required for pain management.

Consistent with the findings on PFS, the outcomes from PALOMA-3 demonstrated that palbociclib can help to support clinician's goals in this treatment setting as it shows the delay in progression of disease without detriment to qualify of life, both maintaining patients' quality of life and improving pain. The majority of patients taking palbociclib plus fulvestrant reported that side effects were as expected or better than expected and the majority of patients indicated that the benefits of palbociclib exceeded their expectations.[84]

B.2.13.7 *Adverse events*

The PALOMA-3 study found that neutropenia and leukopenia were the most common AEs associated with adding palbociclib to fulvestrant. The majority of neutropenia and leukopenia cases were severity grade 3 or 4 (78% for neutropenia and 55% leukopenia in the palbociclib arm), but they were managed with dose modifications as per the protocol guidance.

The relatively low number of treatment discontinuations and dose reductions is a good reflection of how well-managed these two AEs were in the study. As such, there were very few episodes of febrile neutropenia (0.6% in each arm) and no deaths attributed to this adverse event. The finding that palbociclib-associated neutropenia is relatively uncomplicated and asymptomatic may be due to the mechanism by which palbociclib causes cell cycle arrest which results in an uncomplicated neutropenia; recovery of neutrophil numbers occurs following dose modification and GSCF is not required, which contrasts with the apoptosis-dominated mechanism associated with chemotherapy-induced neutropenia.[82,83] Reassuringly most dose reductions did not result in a loss of efficacy and PFS was similar for patients who had at least 1 dose reduction in comparison to those who did not.[47]

Results of a post-hoc within-treatment arm analysis (see Section 0) to assess the impact of neutropenia on fatigue and quality of life demonstrated that neutropenia does not have a significant negative impact on fatigue and global quality of life in patients treated with palbociclib plus fulvestrant. In PALOMA-3, 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 (see Figure 12). This finding is also consistent with that observed in the PALOMA-2 study.[150]

B.2.13.8 *External validity and generalisability*

The PALOMA trials have high external validity because they have been designed to capture a representative spread of key patient characteristics that are of clinical relevance when treating aBC. These characteristics included stratification factors – menopausal status, resistance to prior endocrine therapy, prior exposure to chemotherapy (both in a (neo)adjuvant and aBC) and to different types of endocrine treatment – as well as more detailed characterisations of prior treatment history, disease site, and current state of health. Of note, the PALOMA-3 study is the only phase 3 study of CDK 4/6s in the hormone resistant population to include patients who had received prior chemotherapy in the metastatic

setting.[4,8] Reflecting the heterogenous prescribing behaviour of clinicians in the real world in the UK.

All of the characteristics were reasonably balanced between the two arms with no notable differences that could have impacted the efficacy conclusions.

B.2.13.9 *Trial populations*

The PALOMA-3 study, which forms the main evidence base for this submission, included patients across 8 sites from the UK. It is notable that in seeking advice from breast oncologists across the UK, no differences in population demographics have been raised compared to England or Wales, lending further weight to the conclusion that the PALOMA clinical studies population is generalisable to the HR-positive HER2-negative metastatic breast cancer population in the UK.

B.2.13.10 *End-of-life criteria and flexibility in the threshold*

With regards to other aBC submissions to NICE, flexibility has recently been shown in the appraisal of the medicine pertuzumab for women with aBC; in this case, the committee recognised the medicine as offering a step forwards in the treatment paradigm due to its associated OS benefit and thus allowed flexibility in the EoL criteria and employed a higher threshold, despite the trial comparator arm being associated with 40.8 months OS (higher than the typical 24 month EoL cut-off).[151]

(i) Flexibility in the threshold as a result of relative OS gain

Improving survival by 7 months is a result of palbociclib's innovation, compared to the trial comparator that only reached 28 months median OS, is a large relative gain; an increase of 25% (+1/4). In the EoL framework, a medicine is assessed under higher willingness-to-pay threshold if it meets the assumption that it would provide an additional 3 months in life expectancy on top of 24 months; hence EoL can be granted for medicines that increase survival by only 16% (+1/6). Although the PALOMA-3 trial comparator just exceeded the EoL cut-off of 24 months, adding palbociclib produced a greater relative survival gain than is required to meet EoL, an increase in survival of 1/4th versus the minimum of what is required for a higher willingness-to-pay (WTP) threshold of 1/6th. 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.

(ii) Subjective willingness to pay for aBC therapies

NICE did not recommend fulvestrant given cost-effectiveness considerations[5]. However, many CCGs do commission treatment with fulvestrant directly[3] in an endeavour to allow patients access this as an option.

B.3 *Cost effectiveness*

Methodology for the pharmacoeconomic evaluation

- A lifetime partitioned survival cohort state-transition *de novo* model (Microsoft Excel®), from an NHS and PSS perspective, was developed to evaluate the cost-effectiveness of palbociclib plus fulvestrant in the treatment for HR-positive, HER2-negative aBC after resistance to previous endocrine therapy.
- Palbociclib plus fulvestrant is compared against everolimus plus exemestane
- The base-case analysis was informed by an indirect comparison versus everolimus plus exemestane using a fractional polynomial NMA for PFS and a Bayesian NMA for OS.
- Health-state utilities in the progression-free state were elicited from EQ-5D scores collected in the PALOMA-3 phase III trial, specific to palbociclib plus fulvestrant and fulvestrant alone. In the absence of EQ-5D data for everolimus plus exemestane, an assumption was made that utility was the same as fulvestrant. Utilities for the post-progression state were informed by the literature.
- Resource use inputs were derived from clinical guidelines, expert opinion and other sources such as the submission of palbociclib plus letrozole (NICE TA495).
    - The analyses considered the simple patient access scheme (PAS) offered to the NHS for palbociclib. Everolimus is also offered with a simple, confidential PAS. Given the confidentiality, the base-case ICER with the everolimus list price is not informative. Therefore, a threshold analysis varying the everolimus PAS is presented.

B.3.1 **Published cost-effectiveness studies**

To establish a context and background for the economic analysis, a systematic review of economic evaluations of palbociclib for the treatment of HR-positive HER2-negative aBC was conducted in January 2016. No relevant studies were identified. An update to this systematic review was undertaken in February 2018. A total of nine potentially relevant publications reporting on six unique studies were identified. A summary of this review is presented in the Appendix G. Only one study was identified that was potentially relevant to the endocrine resistant population: a discrete event simulation modelling the cost-effectiveness of palbociclib plus fulvestrant. However, this study was subsequently excluded as it was conducted from the US healthcare perspective.[152] Therefore, none of these studies were relevant to the scope of this submission.

B.3.2 **Economic analysis**

B.3.2.1 *Patient population*

The economic analysis focused on the use of palbociclib plus fulvestrant in the HR-positive HER2-negative aBC endocrine resistant population, that is, women with HR-positive HER2-negative aBC who progressed whilst receiving or within 12 months of completing (neo)adjuvant endocrine treatment. It also included patients already with advanced disease who have progressed on the endocrine therapy received in the advanced setting.

B.3.2.2 *Model structure*

A *de novo* lifetime partitioned survival cohort state-transition model (Microsoft Excel®) from the perspective of the NHS and personal social services (PSS) was developed. The model structure was informed by the UK clinical pathway and clinical experts' input, previous models in the same therapeutic area and the nature of the available data. UK clinical experts had indicated that several treatment lines are common in HR-positive HER2-negative aBC and, as a result, the model was structured such that it expanded on a traditional three-state framework of stable disease (following the administration of palbociclib plus fulvestrant or the comparators), progressed disease and death. In the post-progression state patients received further active therapies divided by line of treatment, followed by best supportive care (BSC) (Figure 18). The model health states are described in Table 25.

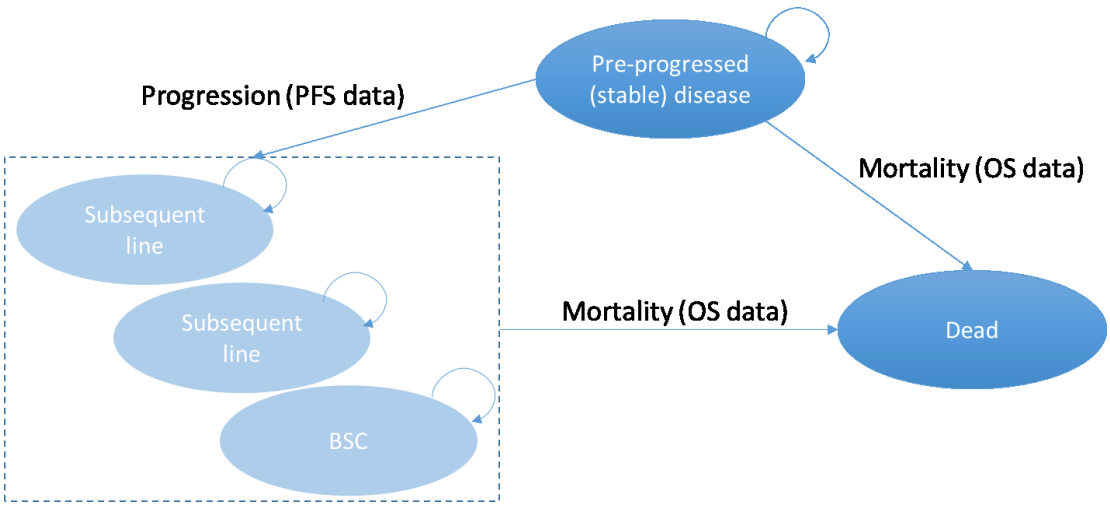
Table 25. Description of the model health states

Health state	Treatment sequence
Pre-progression (stable disease): main comparison of treatments	Pre-progression line (treatments: palbociclib plus fulvestrant, everolimus plus exemestane)
Post-progression: subsequent treatments	First post-progression active therapy* (75%) or BSC** (25%)
	Second post-progression active therapy* (75%) or BSC** (25%)
	BSC (100%)
Death (absorbing state)	Death

Notes: *Active treatment is a treatment which has a potential for modifying or controlling the course of the disease. This is in contrast to BSC, the aims of which is to achieve symptoms management without the use of an active agent and therefore in itself has no effect on modulating the disease time course. UK KOLs have indicated that the following therapies are used post-progression: chemotherapy (capecitabine, paclitaxel, vinorelbine), everolimus plus exemestane, exemestane, fulvestrant, and tamoxifen. For details please see Section B.3.5.5. **It is assumed that 25% of the cohort (assumed CI 0%-50%) move to BSC each time a new treatment sequence starts (progression from previous therapy line) (UK KOL expert opinion).

Abbreviations: BSC, best supportive care.

Figure 18. Model schematic



Abbreviations: BSC, best supportive care; OS, overall survival; PFS, progression-free survival

It was assumed that all patients enter the model in the "pre-progression" state (equivalent to stable disease), receiving treatment. Patients could either remain stable, progress or die. Patients were not assumed to change treatment before disease progression.

Following progression, patients stopped the current treatment and moved to the post-progression state. It was assumed that each post-progression treatment sequence/line lasts for up to six cycles (each cycle being 28 days), drawn from data reported in a study in the UK looking at treatment patterns in ER-positive HER2–negative aBC patients (see Section B.3.5.5 for further details).[113] After completion of up to two additional lines of treatment, patients incurred costs related to best supportive care up to the point of death, with additional terminal care costs included in the last two weeks of life.[19] The probability of death was time-dependent. This was the approach previously accepted in the NICE recommendation for palbociclib plus an aromatase inhibitor (TA495).[3]

Features of the economic model are presented in Table 26 and are compared against previous NICE appraisals for the same indication (TA421[36] for everolimus plus exemestane and TA239[5] for fulvestrant). The model cycle length was 28 days, in line with the administration regimen of palbociclib plus fulvestrant. Half-cycle corrections were included in the model but had minimal impact on the results.

Table 26. Features of the economic analysis

Factor	Previous appraisals		Current appraisal	
	TA421 for everolimus plus exemestane[36,153]	**TA239 for fulvestrant [5,154]**	**Chosen values**	**Justification**
Time horizon	Lifetime defined as: • Initial company submission: 10 years • Following ERG review: 15 years	Life-time (13 years)	Life-time (maximum of 40 years)	To ensure the analysis captures all relevant differences in costs and outcomes between the medicines being compared, as per the NICE reference case[153]
Cycle length	1 month	1 month	28 days	In line with the administration regimens of palbociclib plus fulvestrant
Treatment waning effect?	Not applicable	Not applicable	Not applicable	Not applicable
Source of utilities	Utility values for stable disease were taken from Lloyd et al. 2006[131] and the progressed disease health state was informed by utility values from Launois et al. 1997[155] (company submission) and Lloyd et al. 2006[131] (ERG recommendation).	Utilities values for stable and progressed disease were taken from Lloyd et al. 2006[131] (company submission).	For the pre-progressed health state, PALOMA-3 EQ-5D estimates were derived from patients on treatment and were used to inform the utility values for the palbociclib plus fulvestrant and everolimus plus exemestane. The everolimus plus exemestane pre-progressed utility was assumed to be equal to that of the fulvestrant arm (from PALOMA-3 EQ-5D). For post-progression health states, utility values estimated based on the Lloyd et al. 2006[131] algorithm were used for all three treatment arms.	Values from PALOMA-3 aligned with the NICE reference case[153] Lloyd et al. aligned with values applied in previous aBC appraisals. [5,36]

			See section B.3.4 for source of utilities.	
Source of costs	Publicly available costs included in the model are: drug acquisition (BNF '63), administration (NHS Reference Costs 2010/11),[156] monitoring (PSSRU 2011).[157]	Publicly available costs included in the model are: drug acquisition (MIMS 2010/11), adverse events, administration (NHS Reference Costs 2009/10),[158] monitoring (PSSRU 2010).[159]	Costs included in the model are: drug acquisition, wastage (eMIT; BNF), monitoring, administration, adverse events, miscellaneous (NHS Reference Costs 2017/18; PSSRU 2018). See section B.3.5	To ensure the analysis captures all relevant costs for these treatments and this indication, as per nice reference case.[153]
Discount for utilities and costs	3.5%	3.5%	3.5%	NICE reference case.[153]
Perspective	NHS/PSS	NHS/PSS	NHS/PSS	NICE reference case.[153]

Abbreviations: aBC: advanced breast cancer; BNF, British National Formulary; EQ-5D, 5-dimension EuroQoL questionnaire; ERG, evidence review group; MIMS, Monthly Index of Medical Specialities; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSSRU, Personal Social Services Research Unit; QALYs, quality-adjusted life years; TA, Technology Appraisal

B.3.2.3 *Intervention technology and comparators*

The intervention and the comparator were modelled in line with their respective marketing authorisations. As detailed in Section B.1.1 everolimus in combination with exemestane was considered the relevant comparator. As such, it was included as a comparator in the base-case.

Further details around standard-of-care in UK clinical practice are detailed in Section B.1.3.3.

B.3.3 **Clinical parameters and variables**

B.3.3.1 *Progression-free survival*

Given the lack of direct evidence for palbociclib plus fulvestrant versus everolimus plus exemestane as discussed in Section B.2.8, PFS curves were informed by the results from the FP NMA (Section B.2.9.4.1).

B.3.3.2 *Overall survival*

Given the lack of direct evidence for palbociclib plus fulvestrant versus everolimus plus exemestane, the OS curve of the palbociclib plus fulvestrant arm is informed by the best parametric curve of the PALOMA-3 OS survival analysis (section B.3.3.2.1). The OS curve of the everolimus plus exemestane arm is informed by the Bayesian NMA analysis, anchored on the palbociclib arm OS, as discussed in section B.3.3.2.2.

B.3.3.2.1 *Palbociclib plus fulvestrant*

Six parametric distributions were fitted to the PALOMA-3 OS (13 April 2018 data cut[37]) following guidance from the NICE Decision Support Unit (DSU): the exponential, Weibull, gompertz, log-logistic, log-normal, and generalised gamma.[75]

For OS, the distributions for the base-case and scenario analyses palbociclib plus fulvestrant reference arm were selected following the guidance form the NICE DSU.[75] The model selection process included the following considerations:

- Ranking distributions based on statistical goodness-of-fit to the observed data according to Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC)
- A visual inspection consisting of an analysis of the “Observed vs Predicted” plot. The KM and parametric survival curves were plotted to assess the fit during the trial period, and the long-term extrapolation.
- Comparison of predicted median values and median to mean ratios

The AIC and BIC for all models fit to the PALOMA-3 data are presented in Table 27. The best fitting distributions were the log-logistic, generalised gamma, Weibull and the log-normal. The exponential and gompertz were relatively poor in terms of statistical fit.

The extrapolated PALOMA-3 OS means, medians, and the median to mean ratios are presented in Table 27. Although a good statistical fit, the log-logistic produced the highest

mean OS which suggested it may be less plausible as a result of this extremity due to its long tail. The medians in the observed data were similar between the majority of curves.

Table 27. PALOMA-3 OS survival analysis measures

Treatment arm	Measure	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised Gamma
Palbociclib plus fulvestrant	AIC	1980.2	1957.4	1958.7	1956.2	1966.6	1956.9
	BIC	1984.1	1965.1	1966.4	1963.9	1974.3	1968.5
	Estimated mean (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Estimated median (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Ratio of estimated median to mean (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; OS, overall survival

Observed median for palbociclib plus fulvestrant in PALOMA-3 = 34.9 months

The visual fit of the distributions with respect to the PALOMA-3 Kaplan-Meier data was similar across parametric models (see Figure 19) with the exception of the exponential which provided a poor fit for the first 20 months.

Figure 19. OS parametric distributions compared with Kaplan-Meier curve

Abbreviations: KM, Kaplan-Meier; OS, overall survival

In conclusion, given its plausible predictions and good fit statistically, the preferred base-case distribution was the Weibull distribution for the PALOMA-3 OS data for the palbociclib plus fulvestrant arm. A scenario is also presented for the generalised gamma and log-logistic given their similar statistical fits to the Weibull and the potential slight underestimation from the

Weibull when compared to external data (see Section B.3.10.1). The remaining parametric distribution were not included in sensitivity analysis due to the follow:

- the exponential provided a poor statistical and visual fit,
- the gompetz provided relatively poor statistical fit and provided a clinically implausible extrapolation and
- the log-normal was similar to the log-logistic with a slightly worse statistical fit.

B.3.3.2.2 *Everolimus plus exemestane*

As discussed previously, the PFS for everolimus plus exemestane arm is informed by the Bayesian NMA analysis HR value ([redacted], 95% CI: [redacted]), anchored on the palbociclib arm OS. A graphical representation of the base-case OS for both treatments included in this analysis is presented below (Figure 20).

Appendix D.3.1.6 also presents the plot of the OS curve modelled for everolimus plus exemestane against the observed KM data from its pivotal trial, BOLERO-2; the comparison shows similarity, thus adding external validity to the data used in the model for the everolimus plus exemestane arm.

Figure 20. Comparison of base-case OS for model comparators

Abbreviations: HR, hazard ratio; OS, overall survival

B.3.3.3 *Treatment duration*

Palbociclib plus fulvestrant

Time to treatment discontinuation (TTD) data in PALOMA-3 was used to model treatment duration for the palbociclib plus fulvestrant (Figure 21). In accordance with its marketing authorisations, palbociclib plus fulvestrant was administered until disease progression or until unacceptable toxicity. Using TTD is preferable to using PFS to model treatment duration as using PFS as a proxy can incorrectly estimate true treatment duration as patients may withdraw from treatment for reasons other than disease progression. Further, PFS is an outcome measured from randomisation whilst treatment duration is not. The observed clinical benefit in an RCT is a product of the treatment duration in the arms so TTD should be used to model treatment duration where it is available.

[redacted] patients [redacted] were still on treatment at the PFS data cut-off, meaning TTD was not complete, however the majority of the KM had been observed. Therefore, data were extrapolated by adding an exponential distribution (fitted on the entirety of the KM data) to the end of the observed data. This approach utilised all of the observed data and was only reliant on the exponential extrapolation for a small portion of the curve, thus minimising uncertainty. PALOMA-3 TTD KM plus exponential is presented in Figure 22.

Figure 21. PALOMA-3 TTD Kaplan Meier data, as of 23 October 2015 data-cut

Abbreviations: KM, Kaplan-Meier; TTD, time to treatment discontinuation

Figure 22. Modelled TTD: Kaplan-Meier data followed by exponential (PALOMA-3)

Abbreviations: TTD, time to treatment discontinuation

The KM plus exponential slightly underpredicted expected treatment duration in the longer term compared to the base-case PFS extrapolation given that the exponential did not allow for any reduction in the risk of treatment discontinuation over time. Therefore, to estimate TDT aligned with the extrapolated PFS, a ratio was calculated between the mean TTD and PFS both extrapolated using the KM plus exponential approach ( ). This ratio was then applied as a HR to the base-case PFS to provide a TTD curve that followed the same trend as the base-case PFS (Figure 23). For completeness, two alternative approaches were explored in scenario analyses: i) applying the KM plus exponential TTD (Figure 22); ii) using PFS as a proxy for treatment duration.

Figure 23. Base-case PFS and TTD for palbociclib plus fulvestrant

Abbreviations: PFS, progression-free survival; TTD, time to treatment discontinuation

Everolimus plus exemestane

In the absence of KM TTD data for everolimus plus exemestane PFS was used as a proxy for treatment duration.

B.3.3.4 *Treatment safety*

The adverse event data that informed the economic evaluation for palbociclib plus fulvestrant were taken from the PALOMA-3, as of the 31st July 2015 data cut-off date. [16] The most commonly reported events with severity ≥3 grade were included in the analysis for each treatment arm. For everolimus plus exemestane, the same rule was applied to incorporating events with the data sourced from BOLERO-2.[70] The grade 3+ adverse events incidence included in this analysis for each treatment arm are presented in Table 28.

It was assumed that the probabilities of any grade 3+ event were calculated based on the incidence (see Table 28) and that the risk of an event would only be applied for the first cycle of the model, as per expert opinion (see Section B.3.5.4).

Table 28. Adverse events considered in the economic model

Treatment arm	Palbociclib plus fulvestrant	Everolimus plus exemestane
Number of patients experiencing any grade 3+ adverse event	[redacted]	39*
Total number of patients in trial	[redacted]	482*
Probability of event in trial	[redacted]	8%*#
Source	PALOMA-3 safety data[16]	Yardley et al. 2013[70]

*Yardley et al. did not report any grade 3+ adverse events therefore the most prevalent grade 3+ adverse event incidence was applied

#Yardley et al. report adverse events as percentage values rather than patient numbers. The number of patients experiencing the event was calculated to ensure consistency in the tabular presentation of events.

The model did not show to be sensitive to the inclusion of AEs, therefore other AEs in addition to those listed in Table 28 have not been included. However, we have provided an overview and comparison of AEs across the regimens in Section B.2.10. The review has shown the extent of toxicity and poor tolerability of everolimus with respect to palbociclib and fulvestrant. Caution in everolimus prescribing is implicit in the fact that, despite higher PFS and OS for everolimus plus exemestane than fulvestrant, fulvestrant is still preferred despite its variable accessibility in the NHS in the UK. Clinical opinion has stated that the use of fulvestrant, in sacrificing efficacy, is because of tolerability with everolimus.

B.3.4 **Measurement and valuation of health effects**

EuroQoL five-dimension 3-level (EQ-5D™) data were available directly from the PALOMA-3 trial.[16,46] Estimates were collected:

- At baseline, prior starting the PALOMA-3 trial treatment;
- During primary treatment
- At the time of treatment withdrawal.

To identify further estimates relevant to this submission, a systematic literature review was conducted. This review, described in section B.3.4.3 and Appendix H, yielded several additional studies. One study, Lloyd 2006,[131] has an estimate of post-progression utility which is used in the economic model.

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

The EuroQoL five-dimension questionnaire (EQ-5D™) is one of the PRO measures used in PALOMA-3 clinical trial.

EQ-5D data were collected in the PALOMA-3 RCT and the index scores results are available as of October 2015.[46] PALOMA-3 patients completed self-administered questionnaires at baseline, on day 1 of each treatment cycle until cycle 4, and at every alternate cycle from cycle 6 until end of treatment.[46] Of the 521 patients in the PALOMA-3 ITT population, the percentage of patients completing at least 1 question on the EQ-5D, from baseline to Cycle 14 ranged from [redacted] to [redacted] in the palbociclib and fulvestrant arm, and from [redacted] to [redacted] in the placebo plus fulvestrant arm (except for Cycle 12 in which it was reported to be [redacted] (1 of 2 patients).[55]

The mean scores at baseline were comparable between the two trial arms, 0.73 (95% CI: 0.70, 0.75) for palbociclib plus fulvestrant, and 0.71 (95% CI: 0.67, 0.74) for fulvestrant.[46] Throughout the trial, the overall EQ-5D index scores while on treatment was significantly greater (p-value 0.0037) for palbociclib plus fulvestrant 0.74 (95% CI: 0.72, 0.76) versus fulvestrant 0.69 (95% CI: 0.67, 0.72). The index scores were calculated using a repeated measures mixed-effects model with an intercept term, and treatment, time, treatment-by-time, and baseline as covariates.

No statistically significant difference was found between palbociclib plus fulvestrant and fulvestrant alone in baseline mean overall VAS score (72.9 [SD, 17.22] vs. 70.3 [SD, 19.87]).[46] General health status assessed by VAS on treatment was found to be maintained from baseline, and no significant difference (71.5 vs. 70.0; P = 0.30) in overall VAS scores on treatment was observed between the treatment arms.[46] The overall change from baseline in VAS scores showed a statistically significant (based on 95% CI) deterioration in both treatment arms but the between-treatment comparisons were not statistically significant. [16]

B.3.4.2 *Mapping*

Not applicable since EQ-5D data were available for palbociclib plus fulvestrant from PALOMA-3.[55]

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

A SLR was conducted to identify health state utility value studies in adult patients with locally advanced or metastatic breast cancer on the 16th of January 2016. An updated search was also carried out on the 5th of February 2018. The SLR identified 46 publications meeting the eligibility criteria, corresponding to 40 studies. The updated review has added 11 publications corresponding to nine unique studies. In total, 57 publications for 49 unique studies were included in the systematic review. A PRISMA flow diagram of studies identified in the review along with further details on the HSUV SLR methods results are provided in Appendix H. Of the nine studies identified, only one was used in the submission to inform post-progression utility values.[131]

B.3.4.4 *Adverse reactions*

In the PALOMA-3 trial, the EQ-5D stable disease index scores estimates were derived from patients whilst on treatment. Consequently, these included the negative impact of treatment related adverse events. Therefore, in the base-case no disutility due to adverse events was applied to either of the two arms to avoid double-counting. The inclusion of AE related disutilities was explored in scenario analysis, further details are provided in Section B.3.8.3.

B.3.4.5 *Age-related utility decrement*

Age-related disutility is applied in the base-case, to account for the deterioration in wellbeing as a patient gets older, using the formula from Ara and Brazier (Equation 1).[160] This is applied within the model by use of the baseline age (56.9 years). Within each cycle, age is calculated based upon the baseline mean age plus the time in the model and the baseline gender proportions. Scenario analyses are presented excluding this adjustment.

Equation 1: Age-related disutility

$$\text{General population utility} = 0.9508566 + 0.0212126\text{male} + 0.0002587\text{age} + 0.0000332\text{age}^2$$

B.3.4.6 *Health-related quality-of-life data used in the cost-effectiveness analysis*

In the stable disease health state, the utilities from PALOMA-3 were used to inform the on-treatment PFS utility estimates: 0.74 (95% CI: 0.72, 0.76) for the palbociclib plus fulvestrant arm (as presented in Section B.3.4.1).

There were no published EQ-5D utility data identified from BOLERO-2 to inform the comparison to everolimus plus exemestane, as only EORTC QLQ-C30 data were collected.[161] It is noted that in the NICE submission for everolimus plus exemestane (NICE TA421[36]), quality of life data from Lloyd 2006[131] were used. As noted previously, caution in everolimus prescribing is implicit in the fact that, despite higher PFS and OS for everolimus plus

exemestane than fulvestrant, fulvestrant is still preferred despite its variable accessibility in the NHS in the UK. Hence, it is reasonable to expect that the utility value in the stable disease health state for everolimus plus exemestane should not be higher than that of fulvestrant. Given the EQ-5D data available from PALOMA-3 provides a more recent and preferable source of evidence,[46] and in the absence of EQ-5D data for everolimus, the same on treatment utility as fulvestrant was assumed (0.69).

The baseline utility values for all subsequent post-progression states (two subsequent treatments and BSC) were assumed to be equal, in line with a single post-progression utility estimated from Lloyd (2006).[131] In line with the NICE committee preference in TA421 for everolimus plus exemestane,[36] the values were based on the Lloyd (2006) disease progression decrement applied on the stable disease baseline utility value as explained below:[131]

- Intercept: 0.008871[131]
- Age coefficient: 0.0239[131]
- Disease progression coefficient: -1.1477[131]
- Age in model: 56.9 (mean age from PALOMA-3 trial)[55]
- The utility of the post-progressed health state was calculated using the Lloyd algorithm[131] and the coefficients listed above:

$$Utility_{post-progressed} = 1 + \frac{\exp\left(intercept + age\ coefficient \times Age\ in\ model + disease\ progression\ coefficient\right.}{\exp\left(1 + \exp\left(intercept + age\ coefficient \times Age\ in\ model + disease\ progression\ coefficient\right.\right.} = 0.56$$

The summary of the baseline utility values used in the cost-effectiveness model is presented in Table 29.

Table 29. Summary of utility values for cost-effectiveness analysis

Health state	Palbociclib plus fulvestrant	Everolimus plus exemestane	Source
	Mean value (95% CI)	Mean value (95% CI)	
Stable disease	0.74 (0.72 – 0.76)	0.69 (0.67 – 0.72)	PALOMA-3 EQ-5D analysis (data on file)[46]
Post-progression: all lines	0.56 (0.50 – 0.60)		Based on the algorithm described in Lloyd 2006[131]

Abbreviations: CI, confidence interval

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

B.3.5.1 *Resource identification, measurement and valuation studies*

A de novo systematic review was conducted to identify costs and resource use studies published since 2012 in the patient population with aBC. An updated search was also carried out in the above databases on 5 February 2018.

The original SLR identified 1 relevant study which was conducted in a single centre in West Wales. The systematic review update included 1 study which was conducted in England. In total, 2 publications reporting 2 unique studies were included for review from the original and updated systematic reviews.

A PRISMA flow diagram of studies identified in the review along with further details on the costs and resource use SLR methods results are provided in the Appendix I. Please note that none of these studies were relevant to the scope of this submission.

B.3.5.2 *Intervention and comparators' costs and resource use*

B.3.5.2.1 *Drug acquisition costs*

Drug acquisition costs were sourced from eMIT[162] and BNF[163] and the licensed doses were considered according to the respective marketing authorisations.[164,165] Drug acquisition costs, licensed dose values, and available drug formulations are reported in Table 30. Note that the lowest values reported in BNF for each drug were considered in the cost-effectiveness analysis. The formulations used in the base-case calculations are reported in the table below, for drugs having several available formulations. Due to the confidential nature of the PAS offered to the NHS for everolimus, the base-case cost-effectiveness results should be interpreted with caution.

Table 30. Drug acquisition cost inputs

Technology	Licensed dose (mg)	Package information	Cost (£) per package
Palbociclib	125mg daily (used in the model. 100mg and 75mg also available)	125mg tablets, 21 tablets in pack	£2,950.00[163] [redacted]
Fulvestrant	500mg by slow intra-muscular injection on Days 1, 15, 29, and once monthly thereafter.	250mg/5ml solution in pre-filled syringe, 2 in pack	£522.41[163]
Everolimus	10mg once daily	2.5mg tablets, 30 in pack	£1,200.00[163]
		5mg tablets, 30 in pack	£2,250.00[163]
		10mg tablets, 30 in pack *(used in the model)*	£2,673.00[163] Unknown PAS
Exemestane	25mg once daily after a meal	25mg tablets, 30 in pack	£3.73[162]

Abbreviations: mg, milligrams; ml: millilitres; PAS: patient access scheme

B.3.5.2.2 *Wastage costs*

One pack of palbociclib contains 28 days' treatment (21 days on then 7 days off). It was assumed that once a model cycle was started, the full cost of the pack is incurred and thus, there is no wastage cost for palbociclib.[56]

No wastage was assumed to incur for fulvestrant. For everolimus and exemestane, since the pack sizes contain 30 tablets and the cycle length is 28 days, it was assumed that the two tablets left over from each pack are wasted. As it is expected a new pack would be started every cycle, regardless of whether there are tablets left over, the result in the model was a 30-tablet pack cost applied per 28-day model cycle, a wastage cost of £178.20 per model cycle for everolimus 10mg tablet at list price, and £0.25 for exemestane.

B.3.5.2.3 *Monitoring costs*

Treatment-related monitoring costs related to resource use are included in the model, presented in Table 31 for each treatment. The unit costs for each monitoring resource are listed in Table 32. Telephone interviews with clinical nurse specialists (CNSs) treating aBC from across the UK in 2016 informed the frequency of resource utilisation (Table 31).

Table 31. Monitoring cost assumptions for each drug

Drug	Monitoring resource use assumption	Source
Palbociclib	1 full blood count (FBC) every month for 6 months and then every 3 months. One FBC cost is incurred every 3 model cycles for maintenance.	Palbociclib SmPC[56] in Appendix C
Fulvestrant	No monitoring resource use	Fulvestrant SmPC[85]
Everolimus	1 FBC, 1 liver panel test and 1 chest X-ray every 2 months	Advisory board
Exemestane	No monitoring resource use	Exemestane SmPC[166]

Abbreviations: FBC, full blood count; SmPC: summary of product characteristics.

Table 32. Unit costs of monitoring resources/services

Resource use	Unit cost (£)	Note about unit cost	Source
FBC*	£2.51	DAPS05 Haematology	NHS Reference costs 2017/18[167]
Liver panel test	£2.51	Assume same cost as FBC	
Chest x-ray	£29.78	Direct access Plain Film, DAPF, directly accessed diagnostic services	NHS Reference costs 2017/18[167]

Notes: *This reference cost is assumed to cover all healthcare resource use involved in the FBC laboratory test (i.e. staff time, testing kit costs etc), in addition to the cost of the actual test.

Abbreviations: FBC, full blood count; NHS, National Health Service.

B.3.5.2.4 *Administration costs*

Palbociclib, everolimus, and exemestane are all oral treatments and are self-administered by the patient, therefore no administration costs are incurred.

The administration cost of fulvestrant consisted of 33.3% delivered in the primary care setting and 66.7% delivered in the outpatient setting, details are provided in Table 33. This cost was accepted in TA503.[168]

Table 33. Fulvestrant administration cost

Resource use	Weight	Unit cost (£)	Source
Community nurse specialist 15 minute – Cost per working hour (£45) Band 6	33.3%	£11.25	PSSRU 2018[169]
Non-Consultant Led: Follow up Attendance Non-Admitted Face to Face, Medical oncology Code 370	66.7%	£127.63	NHS Reference costs 2017/18[167]
Total weighted administration cost		£88.84	

Notes: *This reference cost is assumed to cover all healthcare resource use involved in the FBC laboratory test (i.e. staff time, testing kit costs etc), in addition to the cost of the actual test.

B.3.5.3 *Health-state unit costs and resource use*

Resource use was both health-state and treatment-line dependent. Data to inform estimates of resource use for each line of treatment was based upon resource use estimates in the NICE Clinical Guideline 81, first published in 2009 and more recently updated in August 2017.[19]

Additional to treatment-specific resource use, disease-related resource use was guided by 3rd party telephone interviews with clinical nurse specialists (CNSs) treating aBC from across the UK in 2016, based on NICE CG81,[19] to inform the frequency of resource utilisation. Key issues from the CNSs' evaluation were discussed and confirmed with a multi-disciplinary team (included oncologists, a pharmacist, and another clinical nurse specialist) responsible for treating metastatic breast cancer patients at a specialist centre. The findings from these interviews informed the model's resource use and are summarised in Table 34, whilst the unit costs are listed in Table 35.

Terminal care costs are implemented in the model for patients with progressed disease for the last 2 weeks of the patient's life. These consist of time spent at the hospital, hospice, and at home. The proportion of patients distributed to each setting was based on data from the NICE CG81 Package 3: 40% at the hospital, 10% at the hospice, and 50% at home.[19] The resource use and unit costs for terminal care are shown in Table 36.

Table 34. Background health state resource use

Health state	Resource use	Frequency / length of visit	Travel time cost? (i.e. home visit)
Pre-progression (stable disease)	Community nurse home visit	Once every quarter, visit lasting 20 min	Yes
	Consultant visit (oncologist)	Once every 6 months, visit lasting 1 hour	No
	GP contact (surgery visit)	Once every month, visit lasting 9.22 min	No
	Clinical nurse specialist	Once every month, visit lasting 1 hour	No
	Social worker home visit	Once every 2 months, visit lasting 30 min	Yes
	Palliative care (outpatient setting)	Once every 2 months, visit lasting 20 min	No
	CT scan	Once every 3 months	No
Post-progression, first subsequent treatment	Community nurse home visit	Twice as frequent as 2nd line, visit lasting 20 min	Yes
	Consultant visit (oncologist)	Once every 2 months, visit lasting 1 hour	No
	GP contact (surgery visit)	Thrice every 2 months, visit lasting 9.22 min	No
	Clinical nurse specialist	Twice in a month, visit lasting 1 hour	No
	Social worker home visit	Once every 2 months, visit lasting 30 min	Yes
	Palliative care (outpatient setting)	Once every month, visit lasting 20 min	No

Health state	Resource use	Frequency / length of visit	Travel time cost? (i.e. home visit)
	CT scan	Once every 3 months	No
	Occupational therapist	Once every 2 months, visit lasting 30 min	No
	Physiotherapist	Once every 2 months, visit lasting 30 min	No
Post-progression, second subsequent treatment	Community nurse home visit	Once every month, visit lasting 20 min	Yes
	Consultant visit (oncologist)	Once every month, visit lasting 30 minutes	No
	GP contact (surgery visit)	Twice every month, visit lasting 9.22 min	No
	Clinical nurse specialist	Thrice every month, visit lasting 1 hour	No
	Social worker home visit	Once every month, visit lasting 30 min	Yes
	Palliative care (outpatient setting)	Once every month, visit lasting 15 min	No
	CT scan	Twice every 3 months	No
	Occupational therapist	Once every 2 months, visit lasting 30 min	No
	Physiotherapist	Once every month, visit lasting 30 min	No
BSC	Community nurse home visit	Three times every month, visit lasting 20 min	Yes
	GP contact (home visit)	Twice every month, home visit lasting 1 hour	Yes
	Clinical nurse specialist	Three times every month, visit lasting 1 hour	No
	Social worker home visit	Once every month, visit lasting 30 min	No
	Palliative care (outpatient setting)	Three times every month, visit lasting 15 min	No
	Occupational therapist	Once every 2 months, visit lasting 30 min	No
	Physiotherapist	Once every month, visit lasting 30 min	No
	Lymphoedema nurse	Once every month, visit lasting 20 min	Yes

Sources for assumptions as stated in text: NICE GC81, interviews with breast cancer clinical nurse specialists, advisory board with multidisciplinary breast cancer team (including oncologists, pharmacist, nurse), and oncologist consultation.

Abbreviations: BSC, best supportive care; CG, Clinical Guideline; CT, computed tomography; GP, general practitioner; NICE, National Institute for Health and Care Excellence.

Table 35. Unit costs for background health state resource use

Resource use	Unit cost	Note about unit cost	Source
Community nurse visit	£65.36	Average between per hour of patient-related work, without qualifications	Value from PSSRU 2015[170] increased to 2017/2018 using

Resource use	Unit cost	Note about unit cost	Source
		(£60.66) and per hour of patient-related work, with qualifications (£70.07).	inflation indices from PSSRU 2018[169]
Community nurse travel time	£32.68	Assume half of the community nurse visit unit cost to reflect half an hour of travel.	Assumption
Consultant visit (oncologist) – first visit	£187.30	WF01B service code 800 Clinical Oncology (Previously Radiotherapy) Non-Admitted Face to Face Attendance, First	NHS Reference costs 2017/18[167]
Consultant visit (oncologist) – follow-up visit	£132.10	WF01A service code 800 Clinical Oncology (Previously Radiotherapy) Non-Admitted Face to Face Attendance, Follow-up	NHS Reference costs 2017/18[167]
GP contact (surgery visit)	£34.00	9.22 minutes surgery consultation, average between excluding staff time, no qualifications (£31.00) and including direct care staff costs, with qualifications (£37.00)	PSSRU 2018[169]
GP contact (home visit)	£200.00	Average between per hour of patient contact, excluding direct care staff, without qualifications (£181.00) and with qualifications (£219.00). Travel cost is excluded.	PSSRU 2018[169]
GP contact (home visit) – travel cost	£100.00	Assume half of the GP contact (home visit) unit cost to reflect travel time.	Assumption
Nurse (GP practice)	£39.00	Average between per hour cost excluding qualifications (£36.00) and including qualifications (£42.00).	PSSRU 2018[169]
Clinical nurse specialist	£111.00	Assume cost of hospital-based nurse; cost per hour of client contact (band 6)	PSSRU 2018[169]
Social worker visit	£72.50	Average between per hour of client-related work, without qualifications (£61.00) and with qualifications (£84.00)	PSSRU 2018[169]
Social worker travel time	£36.25	Assume half of the social worker visit unit cost to reflect travel time.	Assumption
Palliative care	£65.36	Assume same cost as community nurse.	Assumption
CT scan	£122.22	Weighted average of CT Scan of three areas, with contrast (RD26Z, outpatient) and Computerised Tomography Scan of more than three areas (RD27Z, outpatient)	NHS Reference costs 2017/18[167]
Occupational therapist	£39.50	Average between cost per working hour occupational therapist band 5 (£34.00) and band 6 (£45.00)	PSSRU 2018[169]
Physiotherapist	£39.50	Average between cost per working hour physiotherapist band 5 (£34.00) and band 6 (£45.00)	PSSRU 2018[169]
Lymphoedema nurse	£111.00	Assume cost of hospital-based nurse; cost per hour of client contact (band 6)	PSSRU 2018[169]

Abbreviations: CT, computerised tomography; GP, general practitioner; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

Table 36.Terminal care resource use and unit costs (last 2 weeks of life)

Setting	Percentage cohort in each setting (%)	Source for clinical setting	Unit cost (£)	Source unit cost

Hospital	40%	NICE CG81 Package 3[19]	£5,774.78	NICE CG81 Package 3 unit costs[19] inflated from 2006/07 to 2017/18 values[167]
Hospice	10%		£7,199.46	
Home	50%		£2,979.42	

Abbreviations: CG, Clinical Guideline; NICE, National Institute for Health and Care Excellence.

B.3.5.4 *Adverse reaction unit costs and resource use*

It was assumed that all adverse events occur concomitantly as one cost rather than cumulative costs for each event following expert opinion that indicated AEs are commonly experienced in the early cycles of treatment and so are often treated simultaneously. Therefore, it was assumed that the frequency of any grade 3+ AE for each treatment was multiplied by the cost of treating the most frequent grade 3+ adverse event. For example, neutropenia was the most common event for grade 3+ AE in the palbociclib plus fulvestrant arm of the PALOMA-3 trial and the cost of managing it (1 oncologist visit per event) was used as indicative of the resource use for managing patients with any grade 3+ on palbociclib plus fulvestrant. This approach is line with the palbociclib plus letrozole NICE submission for the 1st line indication.[3] For consistency, the same assumption (i.e. incurring the cost of the most commonly reported grade 3+ adverse events) was applied to the everolimus plus exemestane arms, however the total frequency of grade 3+ AEs was not reported, so the conservative assumption was taken to include the incidence of the most common AE (stomatitis).

Guided by clinical expert opinion that AEs occurring in early cycles, the AE cost was applied in the first model cycle. The AE incidence and the resource use costs associated with the adverse events are listed in Table 37.

Table 37. Resource use assumptions and unit costs for grade >3 adverse events

Treatment arm	Most common AE	Adverse event incidence	Resource use assumption	Unit cost (£)	Note about unit cost	Source
Palbociclib plus fulvestrant	Neutropenia grade 3+	[redacted]% (Any treatment related grade 3+)	1 oncologist visit per event)	£132.10	Consultant Led: WF01A service code 800 Clinical Oncology (Previously Radiotherapy) Non-Admitted Face to Face Attendance, Follow-up	NHS Reference costs 2017/18[167]
Everolimus plus exemestane	Stomatitis grade 3+	[redacted]% (stomatitis)	Assume hospitalisation lasting 3 days on average (expert opinion)	£412.00 per day	Average cost per day, specialist palliative care (adults only)	PSSRU 2018[169]

Abbreviations: NHS, National Health Service; PSSRU, Personal Social Services Research Unit

B.3.5.5 *Subsequent treatment costs*

As described in Section B.3.2.2, subsequent lines were modelled to allow for a more accurate reflection of clinical practice. Progression to subsequent lines was implemented in the model, assuming an average duration for each subsequent treatment.

A targeted literature review identified a cost study which examined the medical records of 41 physicians in the UK (Table 38).[113] In this study the mean number of cycles ranged from 5.8 to 11.1, dependent on line and treatment covering first to third line aBC treatment; no evidence on fourth line was available. For consistency, the duration of time spent in subsequent lines was assumed as 6 cycles per line for all treatment arms considered in the economic evaluation. A range of 5 to 7 cycles was used in sensitivity analyses. The rates of progression from subsequent treatment lines were assumed the same across the two treatment arms.

Table 38. Mean duration (months) by treatment regimen received in Kurosky 2015[113]

	Second line	Third line
Patients initiating therapy line, N (%)	209 (100.0)	116. (55.5)
Endocrine treatment only		
N (%)	113 (54.1)	49 (42.2)
Mean (SD)	9.16 (6.2)	6.17 (7.9)
Chemotherapy only		
N (%)	68 (32.5)	62 (53.5)
Mean (SD)	6.1 (7.5)	6.1 (4.4)
Chemotherapy plus endocrine therapy		
N (%)	11 (5.3)	1 (0.9)
Mean (SD)	8.4 (8.2)	N/A
Chemotherapy followed by endocrine therapy		
N (%)	17 (8.1)	4 (3.5)
Mean (SD)	5.8 (2.7)	11.1 (8.1)

Abbreviations: SD, standard deviation

After each post-progression line, it was assumed in the base-case that 25% of patients would not switch to a subsequent line but would instead receive BSC until death (see Table 25). This

was based on consulted clinical expert opinion and reflects the fact that not all surviving patients continue active treatment (either by choice or being not fit for treatment).[171] Sensitivity analyses were conducted to explore both different treatment durations in these later lines and different proportions of patients remaining on active treatment. After patients had completed subsequent therapies, they incurred costs related to BSC.

Costs related to later lines included drug acquisition (Section B.3.5.2.1 and Appendix T.1), drug wastage (Section B.3.5.2.2 and Appendix T.2), monitoring (Section B.3.5.2.3 and Appendix T.3), and administration (Section B.3.5.2.4 and Appendix T.4) costs related to subsequent therapies and health state management costs. The health state costs were informed through UK clinical expert interviews and the NICE CG81 guidelines (costs detailed in Section B.3.5.3).

Patients were assumed to be on a 'basket' of therapies including: capecitabine, paclitaxel, everolimus plus exemestane, exemestane, fulvestrant, tamoxifen and vinorelbine. The distributions applied in the base-case (Table 39) were informed by clinical experts advising the ERG in a recent appraisal of abemaciclib.[6]

Table 39. Percentage splits of therapies in the first and second post-progression state

Subsequent therapy	% split in first/second subsequent therapy in post-progression state	
	Palbociclib plus fulvestrant	Everolimus plus exemestane
Capecitabine	25%	40%
Paclitaxel	25%	20%
Everolimus plus exemestane	15%	0%
Exemestane	5%	0%
Fulvestrant	0%	10%
Tamoxifen	25%	20%
Vinorelbine	5%	10%

The first and second line post-progression therapy costs per cycle were estimated to be £734.06 and £468.01 for palbociclib plus fulvestrant and everolimus plus exemestane, respectively. These post-progression costs are included in the base-case and are excluded from the analysis in a scenario analysis.

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

B.3.6.1 *Summary of base-case analysis inputs*

A summary of the inputs and variables of the cost-effectiveness analysis is provided in Appendix U.1.

B.3.6.2 *Assumptions*

A list of all assumptions used in the economic model is presented in Appendix U.2.

B.3.7 **Base-case results**

The base-case results are presented in Table 40 (palbociclib with PAS discount). Given the confidentiality of the everolimus PAS, a threshold analysis is presented in Appendix W that varies the everolimus PAS from 5% to 95% at 5% intervals to aid the committee in its decision making. This analysis indicated that the PAS for everolimus would have to exceed [redacted]% for the ICER to be above the £30,000 per QALY threshold.

Table 40. Base-case deterministic results (palbociclib at PAS discount)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Everolimus + exemestane	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Palbociclib + fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

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

The modelled outcomes are aligned with the indirect clinical evidence which show palbociclib has a longer survival than everolimus plus exemestane. Palbociclib was associated with higher total LYs ([redacted]) versus all everolimus plus exemestane ([redacted]) and QALYs ([redacted] versus [redacted]).The breakdown of the total costs is reported in Figure 24 and QALYs in Figure 25.

Figure 24. Breakdown of total costs: palbociclib plus fulvestrant versus fulvestrant (palbociclib at PAS discount)

Abbreviations: AE, adverse event; bckg, background; BSC, best supportive care; PAL_FLV, palbociclib plus fulvestrant; PFS, progression-free survival.

Figure 25. Breakdown of total QALYs: palbociclib plus fulvestrant versus fulvestrant

Abbreviations: EVE_EXE, everolimus plus exemestane; PAL_FLV, palbociclib plus fulvestrant; QALY, quality-adjusted life year; PFS, pre-progressed state; PPS, post-progression state.

Please see Appendix J for clinical outcomes from the model and disaggregated results of the base-case analysis.

B.3.8 **Sensitivity analyses**

B.3.8.1 *Probabilistic sensitivity analysis*

To explore uncertainty around the key model parameters in the base-case, probabilistic sensitivity analysis (PSA) was performed for 1,000 iterations. The mean incremental results obtained from the PSA are presented in Table 41 and the corresponding scatter plot is presented in Figure 26. Appendix U.3 presents the parameters included in the PSA along with their assumed distribution and standard error or range.

Table 41. Base-case probabilistic results (palbociclib at PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Everolimus + exemestane	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Palbociclib + fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; PAS, Patient Access Scheme

The same pattern was observed in the probabilistic analysis. Palbociclib resulted in higher LYs and QALYs compared to everolimus plus exemestane (Figure 26). The cost-effectiveness acceptability curve (Figure 27) indicated that there is an approximately [redacted] chance of palbociclib plus fulvestrant being cost-effective compared to everolimus plus exemestane at the £30,000 per QALY threshold, however this did not account for the everolimus PAS.

Figure 26. Cost-effectiveness plane (palbociclib plus fulvestrant vs. everolimus plus exemestane; palbociclib at PAS discount)

Abbreviations: PAS, Patient Access Scheme; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-years; WTP, willingness-to-pay.

Figure 27. Cost-effectiveness acceptability curve (palbociclib plus fulvestrant vs. everolimus plus exemestane; palbociclib at PAS discount)

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme;

B.3.8.2 *Deterministic sensitivity analysis*

Deterministic sensitivity analyses (DSA) were conducted for all key variables in the model. The mean values and ranges applied are detailed in Appendix U.1.

The tornado diagrams showing the key drivers of cost-effectiveness versus everolimus plus exemestane are presented in One-way sensitivity analysis showed that the inputs that most effect the incremental costs were those related to the health care resource usage, subsequent therapy and administration costs. The model was relatively insensitive to all other parameter explored in the one-way sensitivity analysis.

[redacted] (note, given that palbociclib plus fulvestrant dominates in the base-case, incremental cost and QALYs are presented to demonstrate the impact of each parameter). Results at palbociclib list price are available in Appendix W.

One-way sensitivity analysis showed that the inputs that most effect the incremental costs were those related to the health care resource usage, subsequent therapy and administration costs. The model was relatively insensitive to all other parameter explored in the one-way sensitivity analysis.

Figure 28. Tornado diagram – palbociclib plus fulvestrant vs. everolimus plus exemestane

(palbociclib PAS discount)

Abbreviations: AE, adverse event; BSC, best supportive care; OS, overall survival; PAS, Patient Access Scheme; PFS, progression-free survival; TTD, time to treatment discontinuation

B.3.8.3 *Scenario analysis*

Several additional scenario analyses were considered to explore the uncertainty around various assumptions. A list of the scenarios and results are presented in Table 42. Results at palbociclib list price are available in Appendix W.

Scenarios looking at alternative OS projections and using the KM plus exponential approach to TTD resulted in the most significant changes to incremental costs and QALYs. All other scenario resulted in marginal changes.

Table 42. Scenario analysis results – palbociclib plus fulvestrant vs. everolimus plus exemestane (palbociclib PAS discount)

#	Parameter varied	Incremental costs	Incremental QALYs	Deterministic ICER
	Base-case	[redacted]	[redacted]	***Palbociclib dominates***
1	Generalised gamma for OS, palbociclib plus fulvestrant arm (Section B.3.3.2.1)	[redacted]	[redacted]	Palbociclib dominates
2	Log-logistic for OS, palbociclib plus fulvestrant arm (Section B.3.3.2.1)	[redacted]	[redacted]	£3,046
3	Applying the KM plus exponential TTD for palbociclib	[redacted]	[redacted]	Palbociclib dominates

#	Parameter varied	Incremental costs	Incremental QALYs	Deterministic ICER
	plus fulvestrant (Section B.3.3.3)			
4	Using PFS at a proxy treatment duration (Section B.3.3.3)	[redacted]	[redacted]	Palbociclib dominates
5	Include AE disutility values (double-counting scenario) (Section B.3.4.4)	[redacted]	[redacted]	Palbociclib dominates
6	Exclude age-related utility decrement (Section B.3.4.5)	[redacted]	[redacted]	Palbociclib dominates
7	Exclude post-progression therapy costs (Section B.3.5.5)	[redacted]	[redacted]	Palbociclib dominates
8	Exclude half-cycle correction	[redacted]	[redacted]	Palbociclib dominates
9	Exclude discounting for costs and benefits (discount rates = 0%)	[redacted]	[redacted]	Palbociclib dominates
10	Model horizon: 10 years	[redacted]	[redacted]	Palbociclib dominates
111	Model horizon: 15 years	[redacted]	[redacted]	Palbociclib dominates

Note that the cost values were rounded to the nearest integer.

Abbreviations: AE, adverse event; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year

B.3.9 **Subgroup analysis**

No subgroup analyses were performed.

B.3.10 **Validation**

B.3.10.1 *Validation of cost-effectiveness analysis*

The clinical outcomes from the base-case were compared against clinical trial evidence in Appendix J. The median PFS for palbociclib plus fulvestrant and everolimus plus exemestane derived from the model was similar to that in PALOMA-3 and BOLERO-2, respectively (noting that they will not be exact given the adjustment from the NMAs).

In PALOMA-3 it was observed that patients discontinued treatment prior to or upon progression (Section B.3.3.3). Therefore, given the updated PALOMA-3 TTD (April 2018 OS data cut) that predicts approximately 10% of patients are on treatment with palbociclib plus fulvestrant after 4 years.[37] The long-term PFS from the base-case FP model is plausible and potentially slightly underestimated.

A clinically meaningful gain in OS was observed for palbociclib plus fulvestrant compared to fulvestrant in PALOMA-3 (Section B.2.6.4). In long-term follow-up data from CONFIRM[172] (that informed the NMA), OS for fulvestrant was observed to be approximately 23% at 5 years. Therefore, beyond the observed period the base-case parametric distributions for OS (Weibull) for palbociclib plus fulvestrant can be considered a conservative estimate when compared to this external literature. Given this potential underestimate the generalised gamma and log-logistic were explored in scenario analysis.

Extensive UK clinical expert opinion (multiple experts during interviews, and at an advisory board with a multi-disciplinary breast cancer team) sought to estimate and validate assumptions pertaining to the healthcare resource use inputs, adverse event management, and patient monitoring requirements, as well as using data from UK guidelines for breast cancer. Costing input data was also derived from the most recent UK sources (NHS Reference Costs, PSSRU, eMIT, BNF).

B.3.10.2 *Quality control*

Internal quality control was undertaken by the developers of the model on behalf of the manufacturer.

B.3.11 Interpretation and conclusions of economic evidence

B.3.11.1 *Comparison with published economic literature*

To our knowledge this is the first economic evaluation comparing palbociclib plus fulvestrant to everolimus plus exemestane in patients with HR-positive HER2-negative endocrine resistant aBC patients from the NHS and PSS perspective.

B.3.11.2 *Relevance of the economic analysis to all patients who could potentially use the technology in the decision problem*

This economic evaluation considers all patients identified in the scope of this appraisal.

B.3.11.3 *Generalisability*

As discussed in Section B.2, PALOMA-3 the primary source of clinical data in the evaluation, has high external validity because it was designed to capture a representative spread of key patient characteristics. This was reflected in the broad inclusion criteria around menopausal status, prior use of chemotherapy and extent of pre-treatment (up to 4 treatments). PALOMA-3 also included patients from UK centres.

B.3.11.4 *Strengths of the economic evaluation*

The economic analysis has number of key strengths:

- The model structure was simple and has been applied in previous aBC appraisals, it utilises the available data from the pivotal trial and comparator trial and captures most of the key outcomes of interest in aBC.
- The FP approach utilised in the NMA, is being increasingly utilised in NICE appraisals. The FP method integrated time vary hazard ratios which meant it accounted for the non-proportionality observed in PFS and resulted in clinically plausible extrapolations (Section B.3.10.1).
- EQ-5D was collected in PALOMA-3. This allowed the PF utility to be aligned with the NICE reference case (EQ-5D; measured directly from patients; valued using UK general population tariff). In addition, a repeated measures mixed-effects model was used to calculate utility values which accounted for the correlated between repeated

measures, which avoided patients with longer term follow-up biasing the estimated values.

- All resource usage and costs (administration, PF and PD disease management and terminal care costs) have been validated and accepted in multiple previous NSCLC appraisals, providing an element of certainty in these values.

B.3.11.5 *Limitations of the economic evaluation*

A limitation of the analysis was the lack of head-to-head data. A robust SLR and NMA was undertaken to address this gap in the evidence. There will always be underlying uncertainty within these types of analyses, however the network is aligned with the preferred evidence network in a recent appraisal[6], which provides evidence that the best available evidence has been utilised.

B.3.11.6 *Conclusions from the economic evidence*

The best available evidence informed the economic analysis to assess the cost-effectiveness of palbociclib plus fulvestrant versus everolimus plus exemestane in the treatment of HR-positive HER2-negative endocrine resistant aBC patients from the NHS England perspective. The comparison with everolimus in combination to exemestane was informed by NMAs including both PALOMA-3 and BOLERO-2 in the absence of head-to-head data.

In PALOMA-3 a statistically significant improvement was observed in PFS (Section B.2.6.2) whilst maintaining QoL (Section B.2.6.6), which not only delays progression (impacting patient by avoiding the onset of greater symptom burden, lower QoL and absenteeism) but also time to subsequent chemotherapy (Section B.2.6.5) which can be associated with a substantial psychological burden on patients, not captured by the EQ-5D and thus not taken into account in the cost-effectiveness estimate.

The recently published PALOMA-3 OS data demonstrated gains in PFS translated to gains in OS (OS +6.9 months; PFS +6.6 months) when palbociclib was added to fulvestrant. Expert opinion confirmed that comparative effectiveness in survival is difficult to demonstrate given the prolonged follow-up of patients, the effects of multiple lines of therapy and that statistical significance is applied as a strict binary outcome. However, UK expert opinion confirmed that the observed OS gain in PALOMA-3 by adding palbociclib to fulvestrant (an additional 6.9 months median) is of a magnitude that can be deemed clinically meaningful.

The indirect comparison to everolimus plus exemestane signals that palbociclib plus fulvestrant is expected to be a more clinically effective treatment with respect to PFS and OS. Although everolimus plus exemestane is considered clinically superior to fulvestrant it is not consistently used more than fulvestrant in practice. Consultation with treating clinicians indicated that the reason for this is not because of the restrictions in the licenses, but rather than everolimus has poor tolerability (for example, issues with real-world stomatitis; please see section B.3.3.4 for an overview of toxicity associated with everolimus). These tolerability issues are understood to be impactful enough to prevent some clinicians from using everolimus plus exemestane as their preferred therapy and instead opting for fulvestrant monotherapy, despite its lower efficacy and irregular availability. The safety data from the BOLERO-2 trial have informed the model but may not reflect what it is observed in the real-

world. Hence, the impact of these tolerability issues may not be fully reflected in the cost-effectiveness results.

It is also important to recall that everolimus plus exemestane has a restricted recommendation only in patients who have received prior non-steroidal aromatase inhibitors. However, in practice, it is understood it is used across the endocrine failure population without restriction. In order to provide a comparison of cost-effectiveness relevant to how treatments are used in UK clinical practice and noting the consistency in efficacy observed in palbociclib plus fulvestrant across trial subgroups, data for palbociclib plus fulvestrant representative of the whole endocrine resistant population was used in the economic model.

The clinical benefit demonstrated in the indirect comparison of PFS and OS translated into a QALY gain of +[redacted]. Given the confidentiality of the everolimus PAS, a threshold analysis is presented in Appendix W.2 indicated that the PAS for everolimus would have to exceed [redacted]% for the ICER to be above the £30,000 per QALY threshold. These incremental benefits are in tandem with palbociclib's wide marketing authorisation across the whole of the endocrine resistant population.

Whilst also representing value for money for the NHS, the clinical community and patient association groups have highlighted the need for palbociclib plus fulvestrant to be made available as a treatment option for the endocrine resistant patients. This advocacy for palbociclib comes from the improvement in patient reported outcomes, time to progression and the delay in chemotherapy, which have been repeatedly expressed in NICE meetings as key goals for these patients; the manageable safety profile, whereby neutropenia is a laboratory level, not a clinical sign nor symptom and the clinically meaningful extension to survival.

B.4 *References*

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Palbociclib in combination with fulvestrant for treating metastatic, hormone-receptor positive, HER2-negative breast cancer after endocrine therapy [ID916]

Tuesday 25th June 2019

Company response to ERG clarification questions (received 10th May 2019)

Dear [redacted],

Thank you for the clarification questions and opportunity to provide further detail to aid the evaluation of our evidence submission. Please find below Pfizer's response to the questions. Excel files accompany this document relating to data specifically requested in Excel as are the Clinical Study Reports in question A1.

Sincerely,

[redacted]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Palbociclib in combination with fulvestrant for treating metastatic, hormone-receptor positive, HER2-negative breast cancer after endocrine therapy [ID916]

Clarification questions

June 2019

File name	Version	Contains confidential information	Date
ID916_Palbociclib_ClarificationQs_ Response_29May19(ACiC)	FINAL	Yes	25th June 2019

Notes for company

Highlighting in the template

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

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

Section A: Clarification on effectiveness data

A1. Priority request: Clinical Study Reports

Please provide the Clinical Study Reports for all data cuts of the PALOMA-3 trial; 05 December 2014, 16 March 2015, 23 October 2015 and 13 April 2018.

The Clinical Study Reports for the data cuts from 5th December 2014 (1), 23rd October 2015 (2) and 13th April 2018 (3) have been included in the reference pack. Please note that the information included in the Clinical Study Reports (CSRs) are confidential, unless presented unmarked elsewhere in the submission. There is no associated CSR for the 16th March 2015 data cut, however this exploratory analysis was published in Cristofanilli 2016 (4) which has been included in the reference pack.

A2. Priority request: latest available data for PALOMA-3 trial

Please provide results as per Table 16 (page 47) in the company submission (CS) for the latest data cut (13 April 2018) of the PALOMA-3 trial, if available. Please use the ITT population.

The 13th April 2018 data cut provided overall survival data only. The latest data cut for the progression-free survival is the 2015 data cut which was presented in Table 16 of the company submission.

A3. Priority request: proportional hazards

To further explore the assumption of proportional hazards for progression-free survival (PFS), please provide the log cumulative hazard plots for PFS (for the BOLERO-2, SoFEA, CONFIRM and EFECT trials).

Please test proportional hazards (for both PFS and OS in all of the trials included in the networks) using a statistical significance test, for example, by testing Schoenfeld residuals or testing the significance of a time-varying covariate in a Cox proportional hazards model.

<u>Progression-free survival</u>

The proportional hazards assumption was assessed using log cumulative hazard plots (parallel line suggested proportional hazards held) and Schoenfeld residual (flat

line with no systematic trend suggested proportional hazards held) for all trials included in the network (Figure 1 - Figure 10). The p-values from the proportional hazards test based on the Schoenfeld residuals is presented Table 1.

Based on this analysis, proportional hazards was assumed to hold for the DiLeo 2010 (5), Chia 2008 (6) and Johnston 2013 (7) studies, however it is observed that the assumption may not hold for PALOMA-3 (2) and Yardley 2013 (8).

Figure 1: Log-log plot for PFS from the PALOMA-3 trial

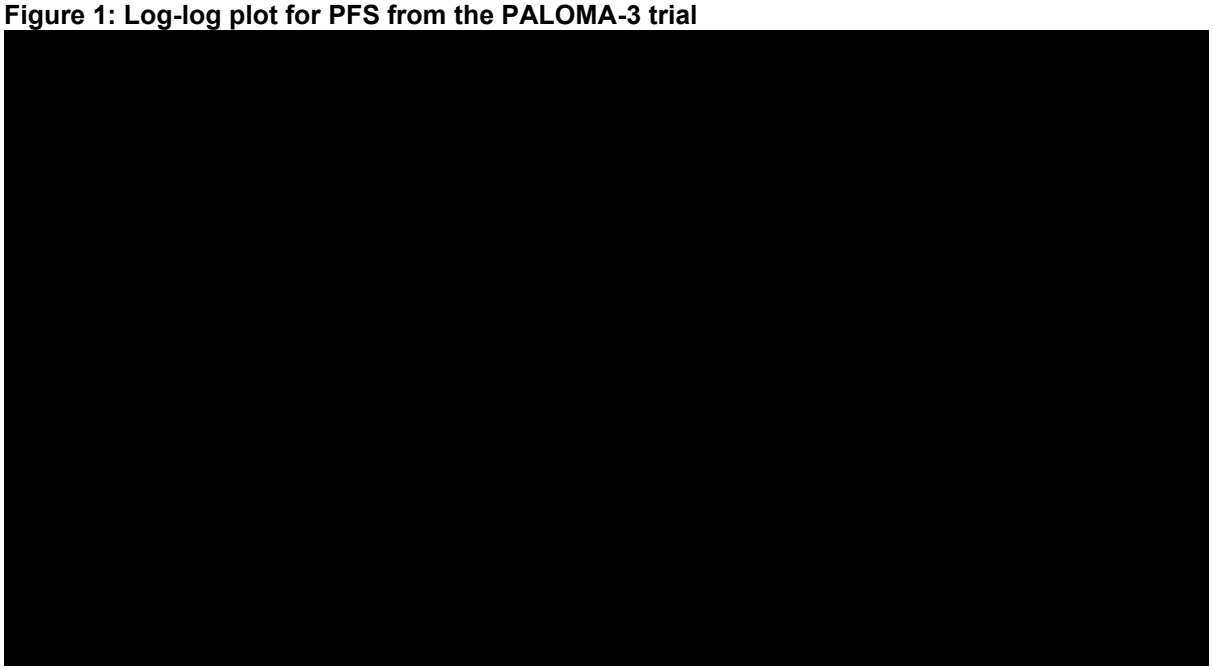

Figure 2: Schoenfeld residuals for PFS from the PALOMA-3 trial

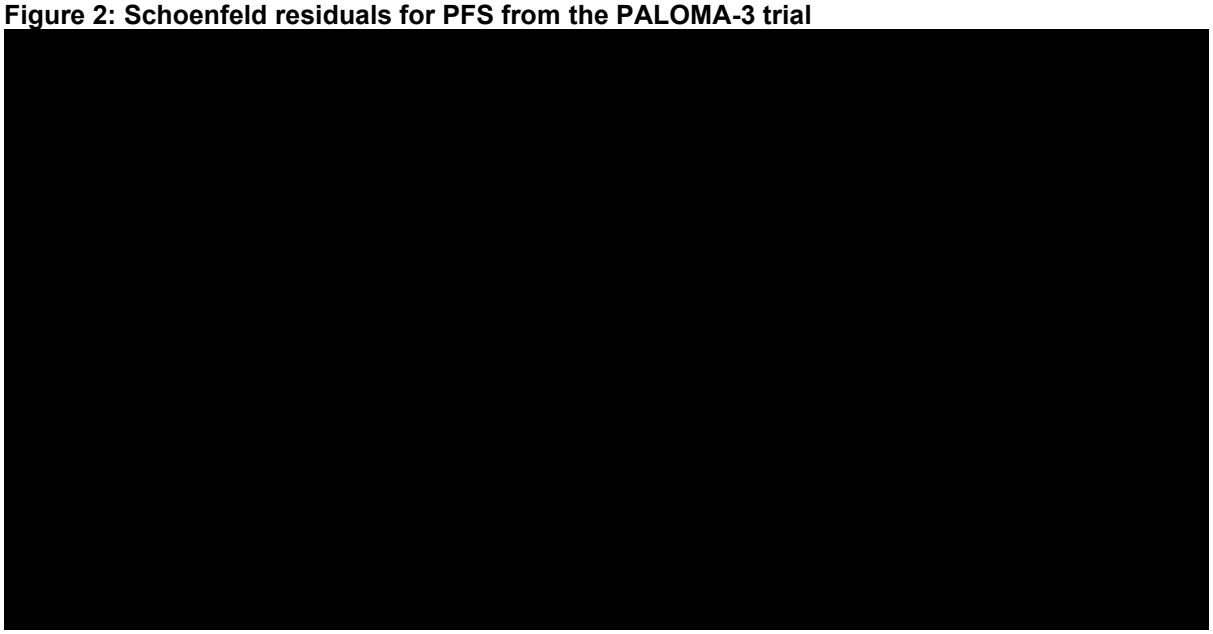

Figure 3: Log-log plot for PFS from DiLeo 2010

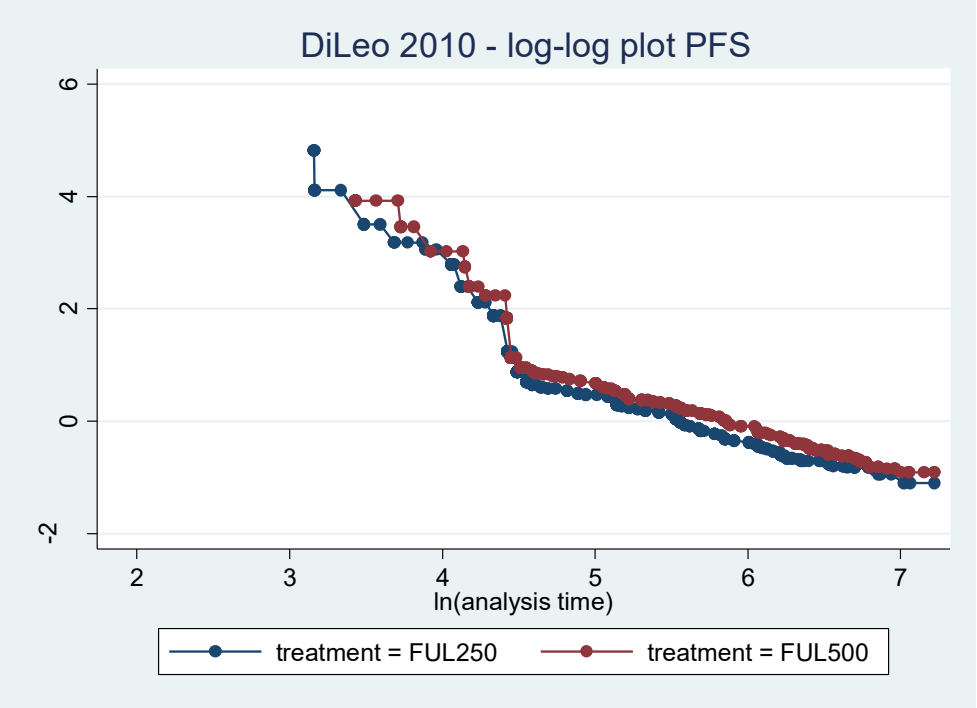

Figure 4: Schoenfeld residuals for PFS from DiLeo 2010

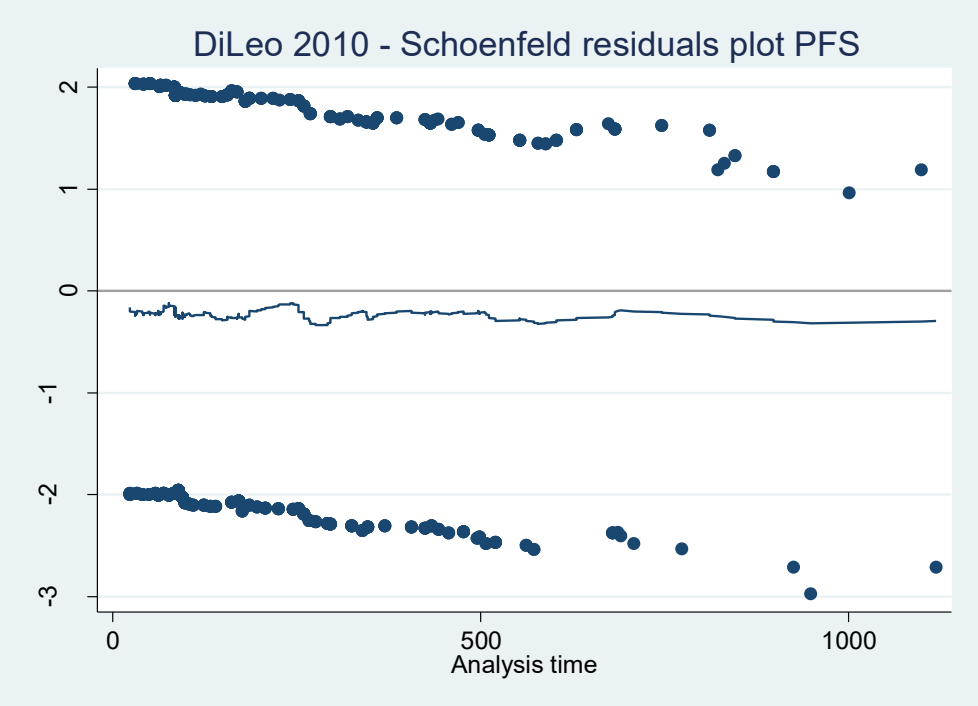

Figure 5: Log-log plot for PFS from Johnston 2013

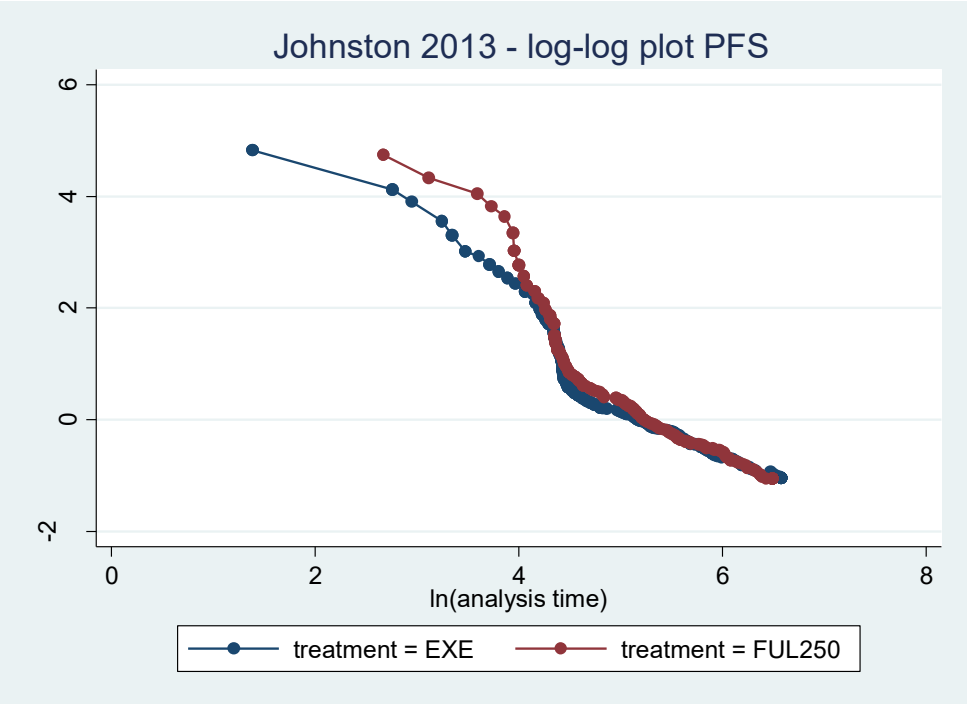

Figure 6: Schoenfeld residuals for PFS from Johnston 2013

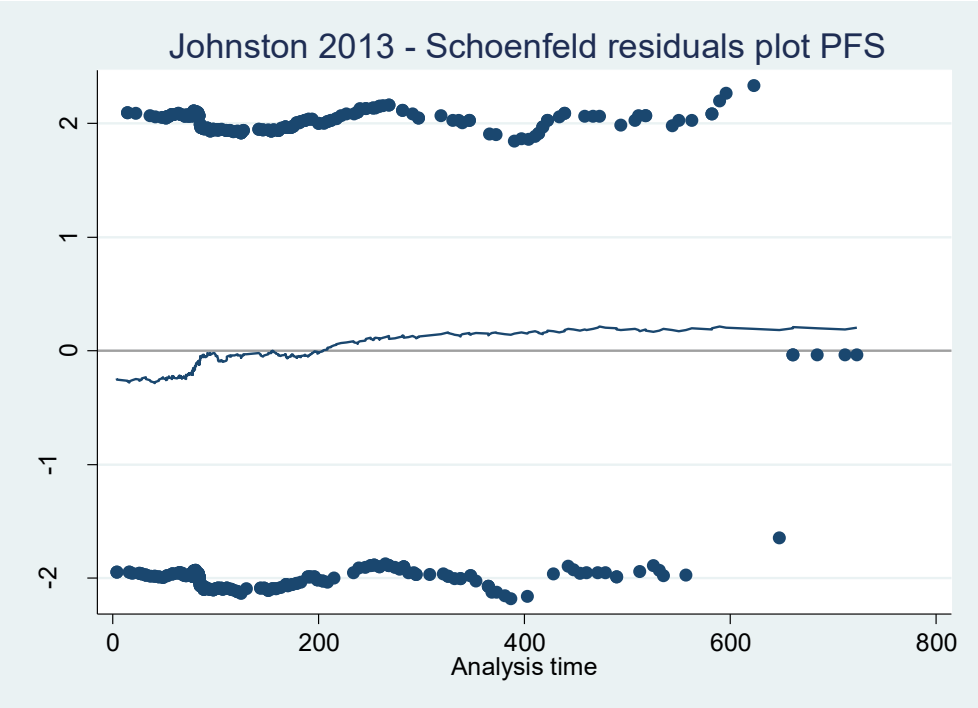

Figure 7: Log-log plot for PFS from Chia 2008

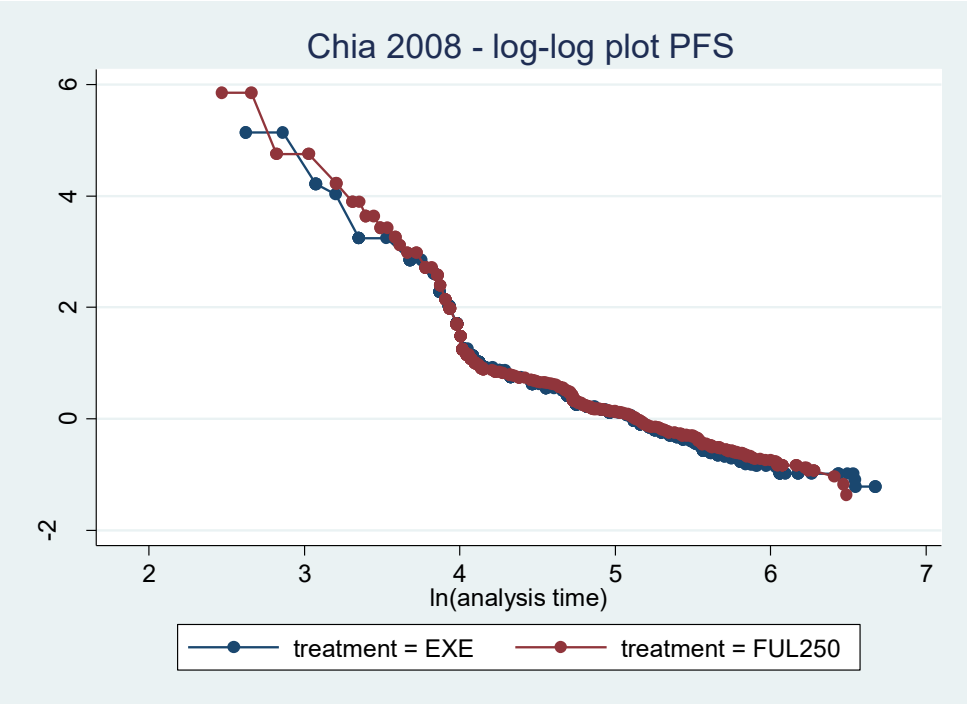

Figure 8: Schoenfeld residuals for PFS from Chia 2008

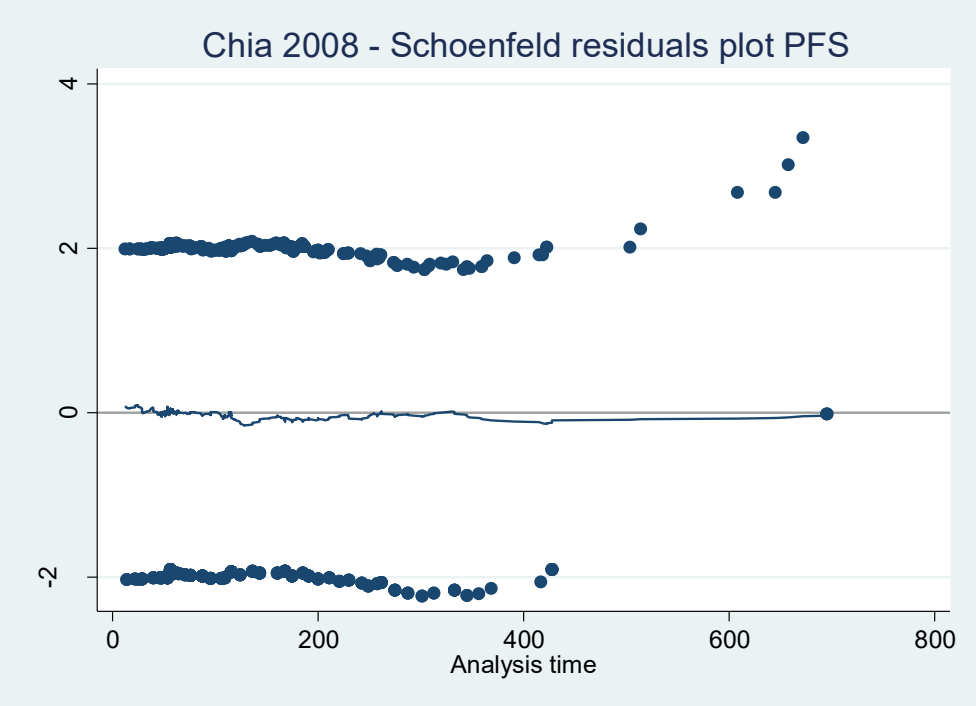

Figure 9: Log-log plot for PFS from Yardley 2013

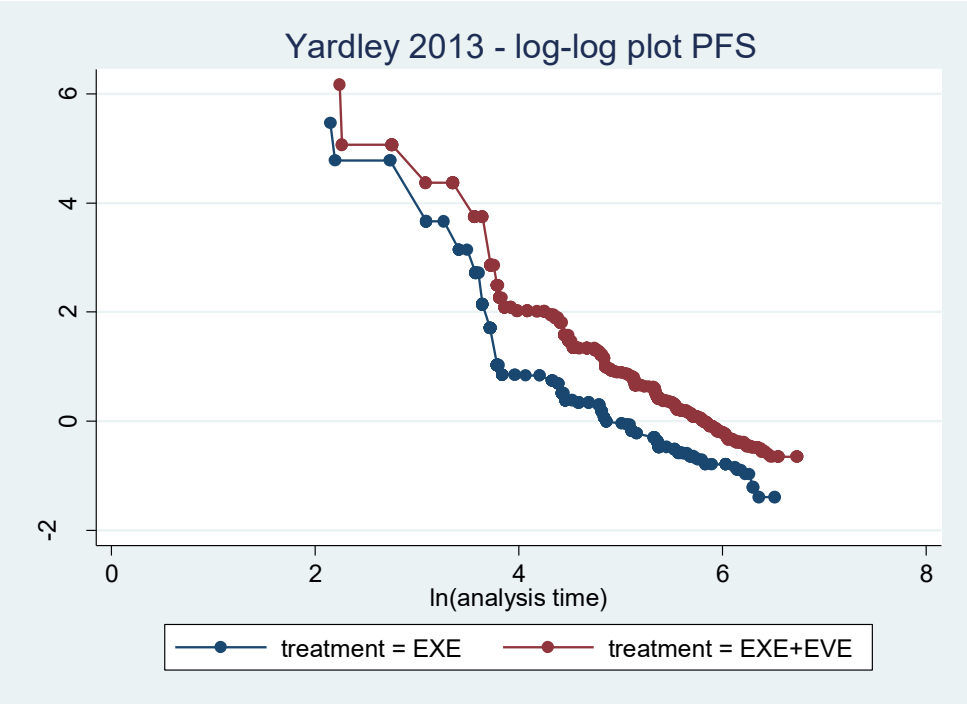

Figure 10: Schoenfeld residuals for PFS from Yardley 2013

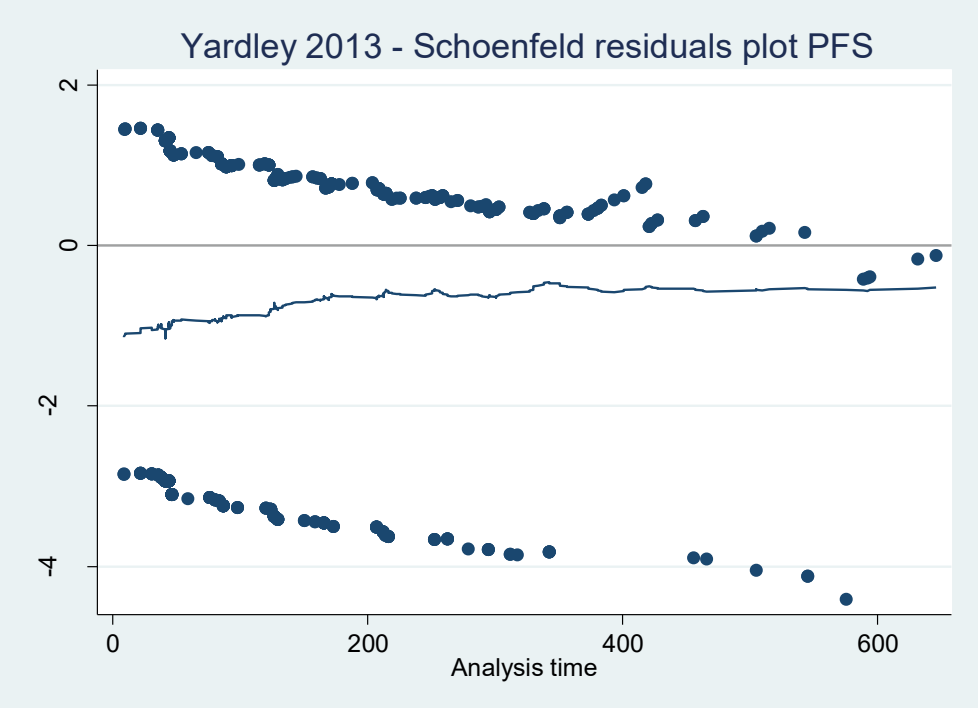

Table 1: Progression-free survival, proportional hazards test - Schoenfeld residuals

Trial	P-values
PALOMA-3	[redacted]
Di Leo 2010	0.543

Johnston 2013	0.080
Chia 2008	0.532
Yardley 2013	0.018

Overall survival

The proportional hazards assumption has been tested for all trials in the network for overall survival. The proportional hazards assumption was tested by visual inspection of the Kaplan-Meier curves and log cumulative hazard plots (Figure 11 - Figure 20) as well as the proportional hazards test based on the Schoenfeld residuals (Table 2).

Based on the analyses, the proportional hazards is assumed to hold for all studies despite some evidence of slight deviations, noting that:

- The p-value from the Schoenfeld residuals is 0.001 for BOLERO-2 (Piccart 2014) (9) which would indicate that the proportional hazards assumption has been violated. However, the variation in the log-log plots appears to occur only at the beginning of the plot and settles to parallel curves in time.

- The proportional hazards assumption appears borderline for SoFEA (Johnston 2013) (7), however, since the Kaplan-Meier curves cross so many times and the observed hazard ration in the trial is close to 1, it can be argued that the two comparators are equivalent.

- The p-value from the Schoenfeld residuals for Chia 2007 (10) is statistically significant. However, the log-log plots indicate that the assumption holds after the first couple of months. Furthermore, the log-log curves overlap continuously indicating that they are proportionally very similar.

Figure 11: Overall Survival PALOMA-3 trial - log-cumulative hazards plot

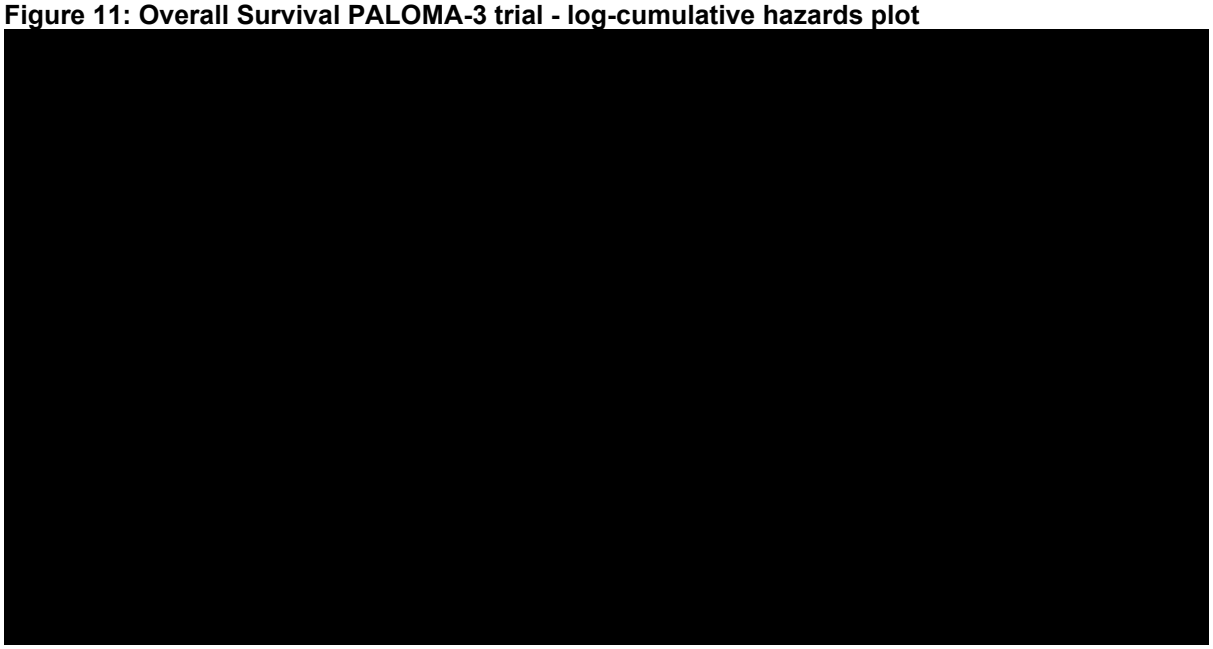

Figure 12: Overall Survival PALOMA-3 – Schoenfeld residuals

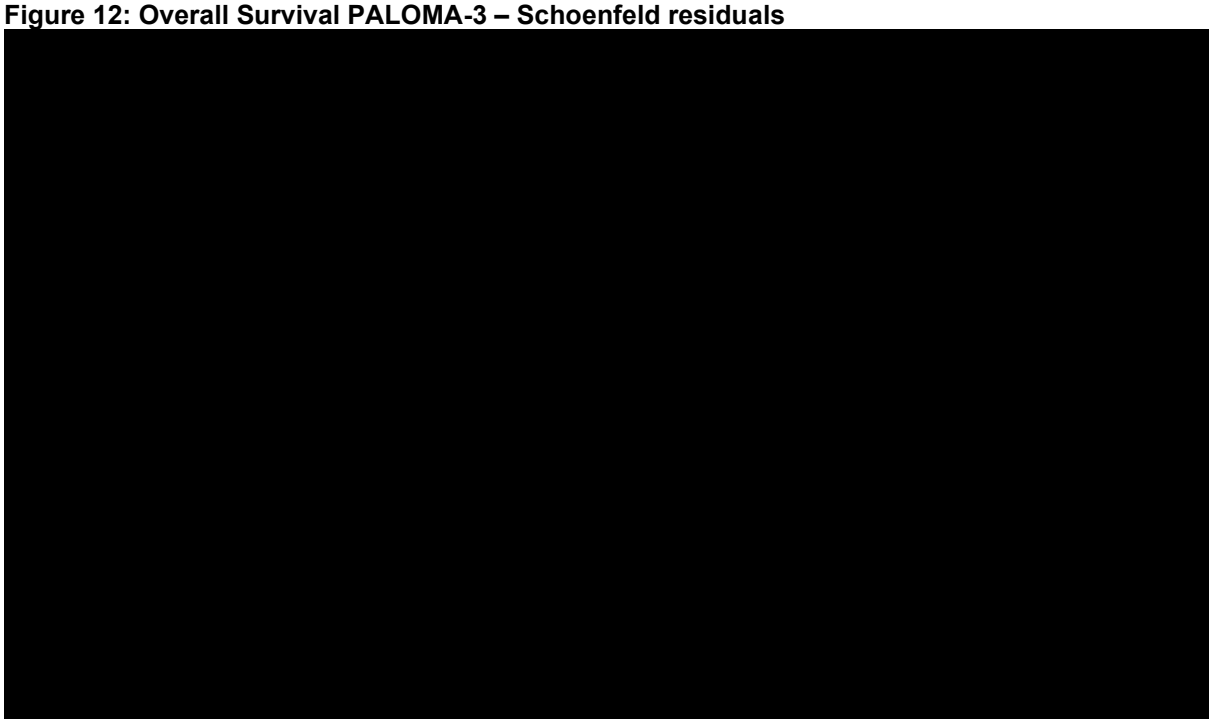

Figure 13: Overall Survival DiLeo 2014 - log-cumulative hazards plot

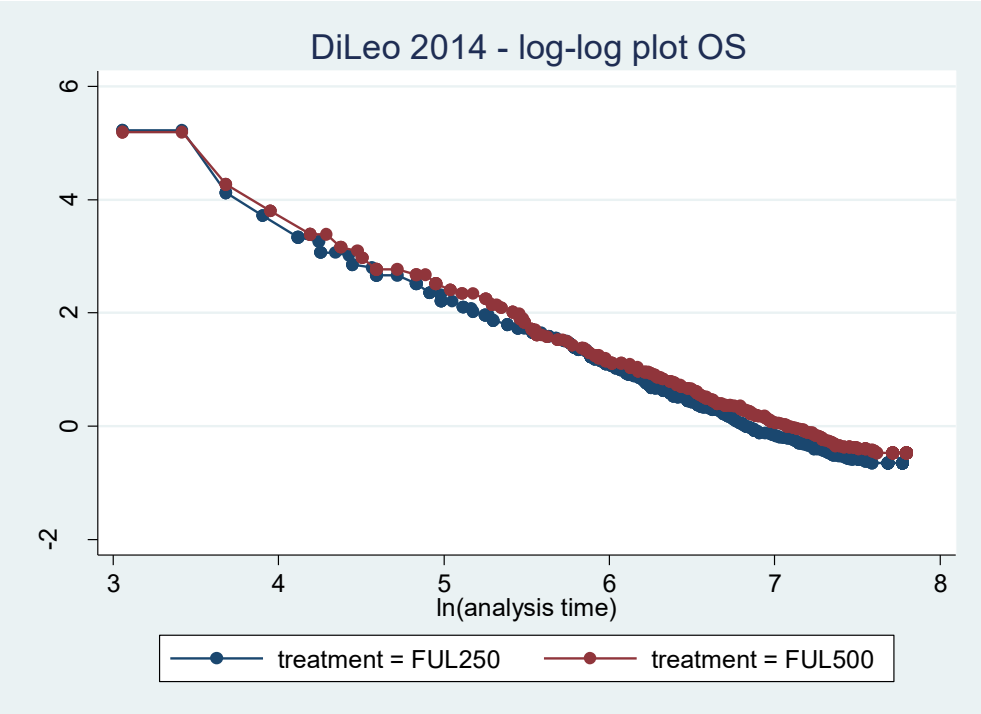

Figure 14: Overall Survival DiLeo 2014– Schoenfeld residuals

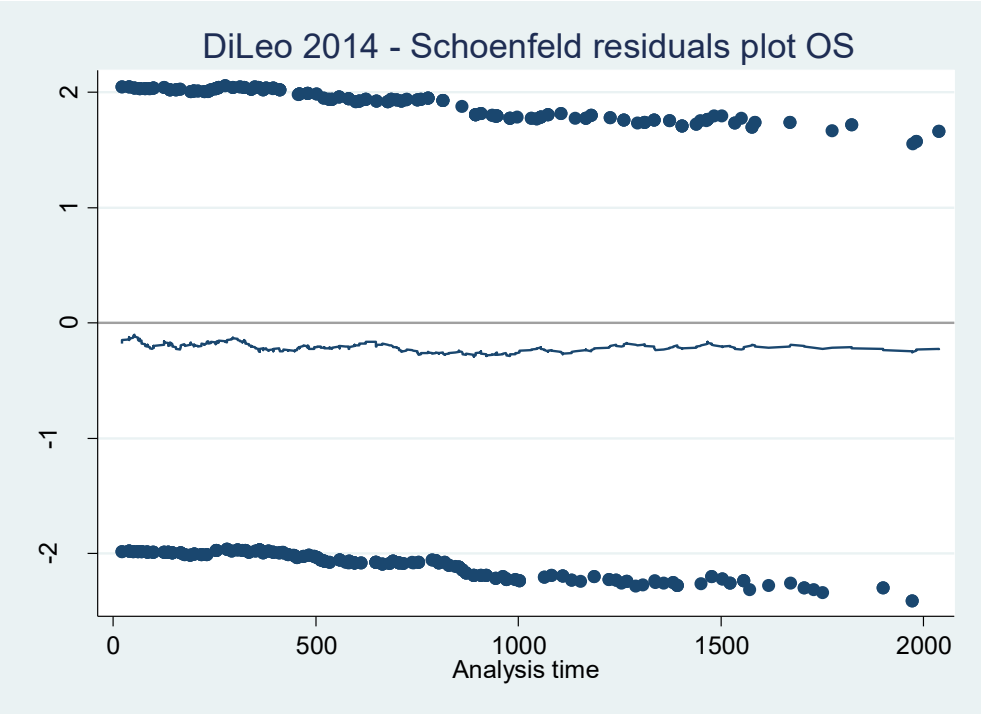

Figure 15: Overall Survival Johnston 2013 - log-cumulative hazards plot

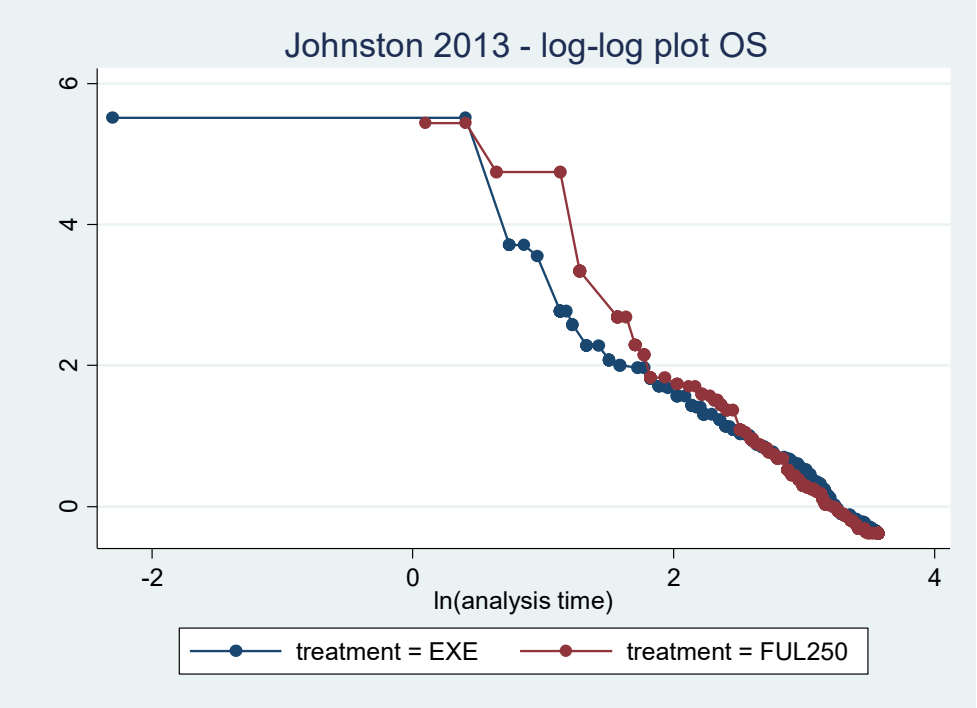

Figure 16: Overall Survival Johnston 2013 – Schoenfeld residuals

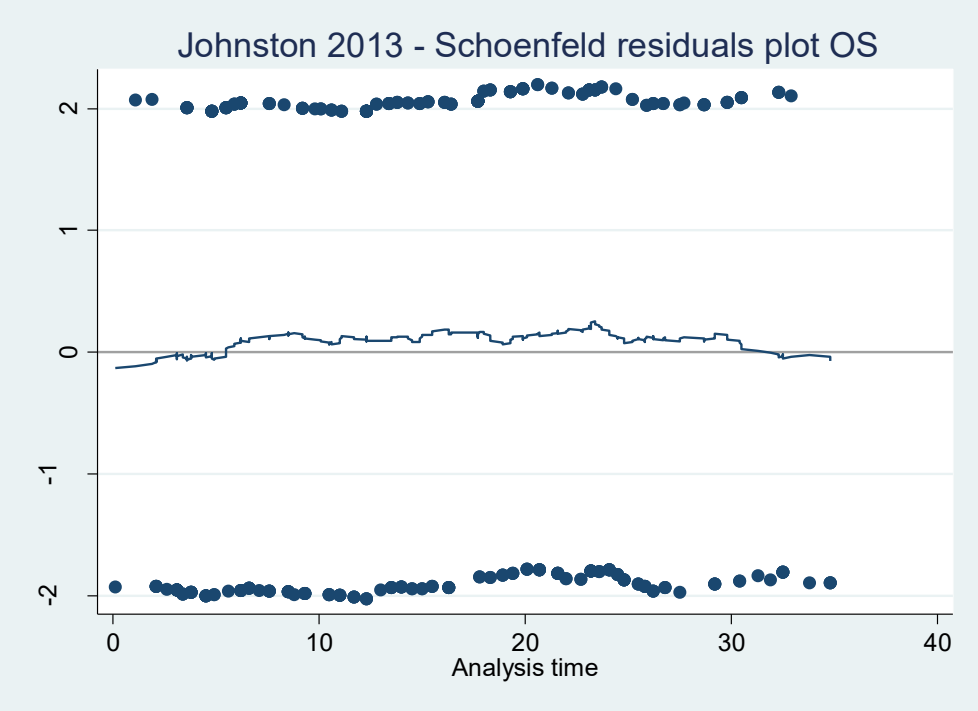

Figure 17: Overall Survival Chia 2007 - log-cumulative hazards plot

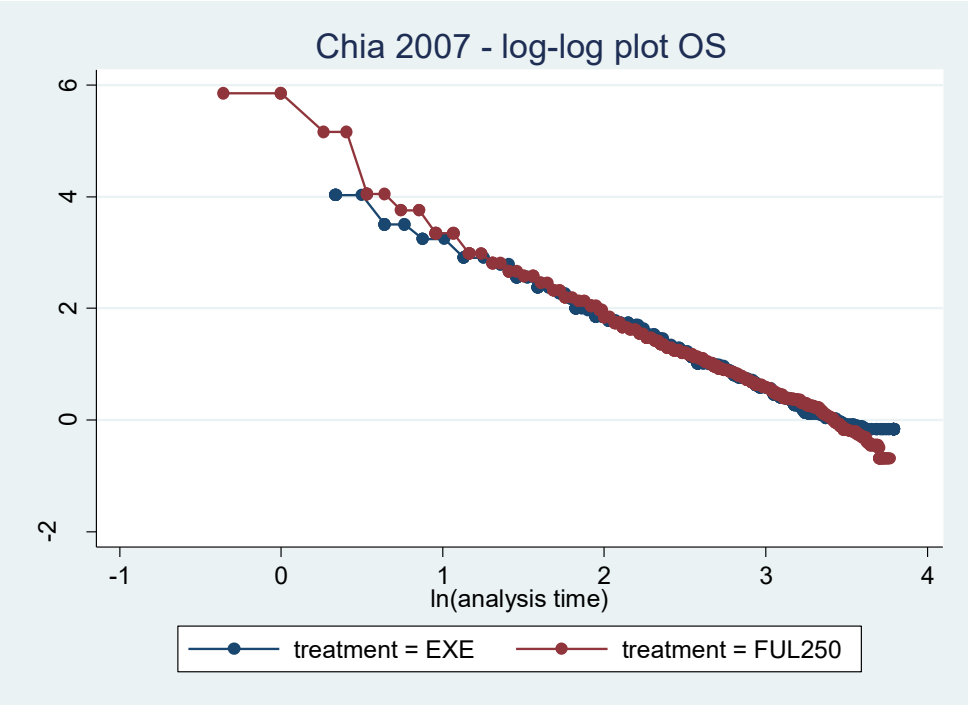

Figure 18: Overall Survival Chia 2007 – Schoenfeld residuals

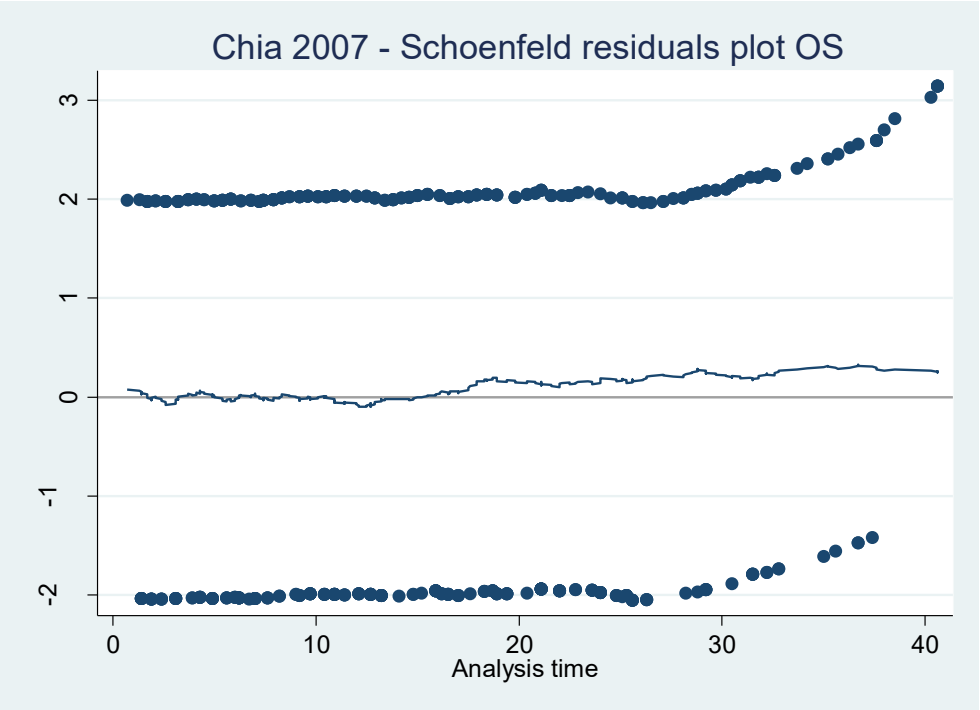

Figure 19: Overall Survival Picart 2014 - log-cumulative hazards plot

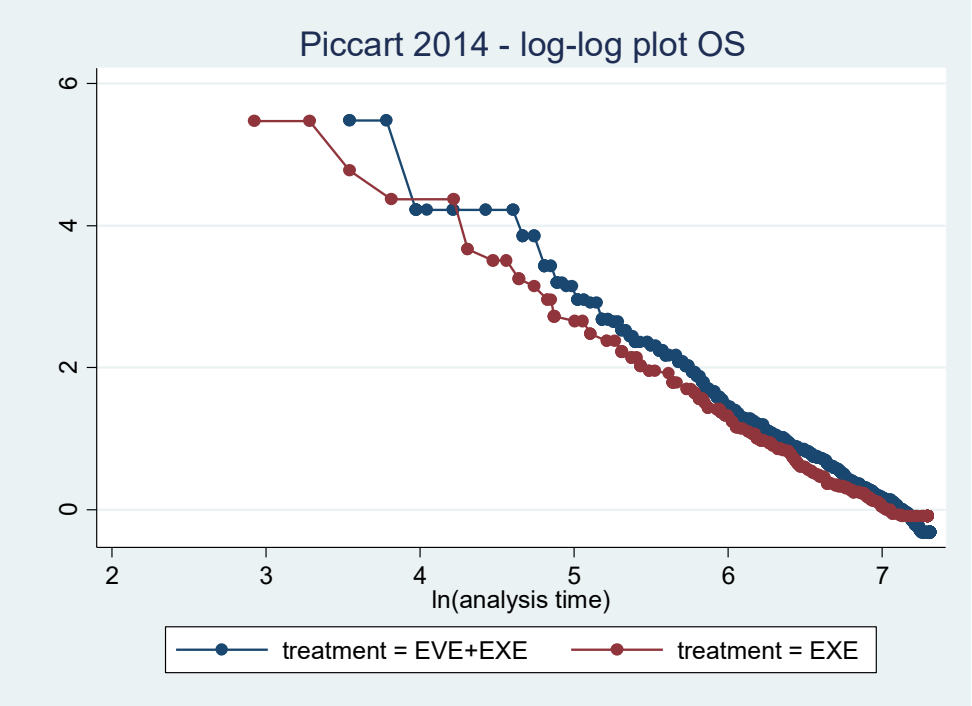

Figure 20: Overall Survival Piccart 2014 – Schoenfeld residuals

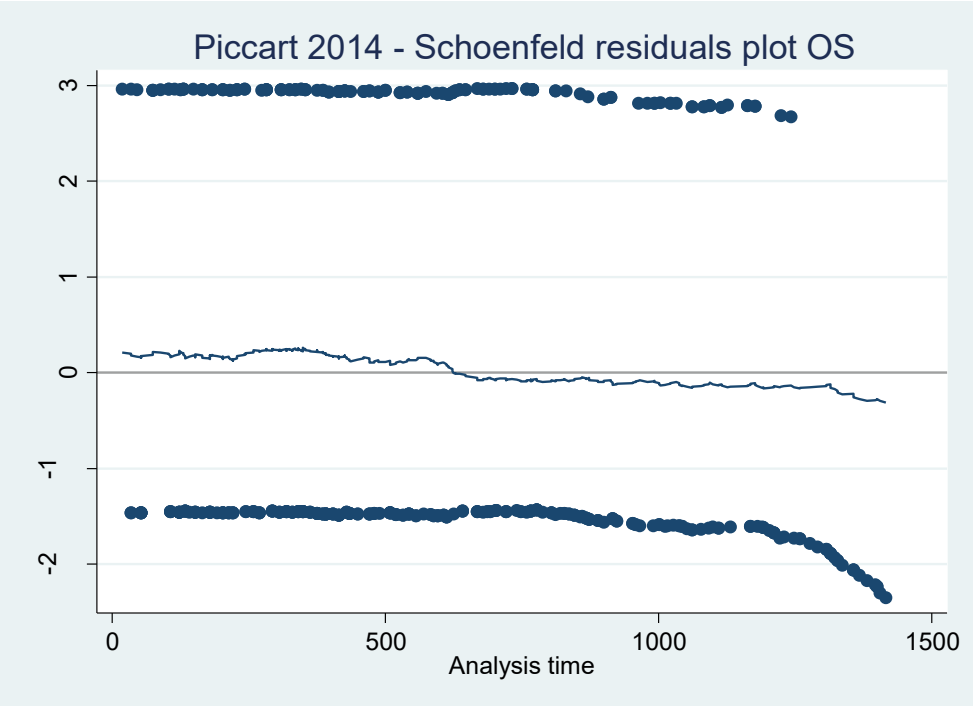

Table 2: Overall survival, proportional hazards test - Schoenfeld residuals

Trial	P-values
PALOMA-3	*****
Di Leo 2010	0.949

Johnston 2013	0.551
Chia 2007	0.007
Piccart 2014	0.001

A4. Network meta-analysis (PFS)

a) Please note that a response to only one option, i) or ii), is required, depending on the outcome of the request made in Question A3.

i) If the additional tests requested in Question A3 show that the proportional hazards assumption has been violated for one or more of the trials included within the NMA for PFS, please provide the median and 95% credible interval values for the beta coefficients of all fixed-effects and random-effects fractional polynomial models which were applied and converged (according to Table 35 of Appendix D).

OR

ii) Priority request: if the additional tests requested in Question A3 show that the proportional hazards assumption has <u>NOT</u> been violated for one or more of the trials included within the NMA for PFS, please provide the median and 95% credible interval values for a hazard ratio from a traditional Bayesian NMA (both fixed-effects and random-effects results).

i) As the proportional hazards assumption does not hold for all the of the studies included in the PFS NMA fixed-effects and random-effects fractional polynomial models were applied and converged. The Deviance Information Criterion (DIC) was used to compare the goodness-of-fit of different first and second order FP models with different powers. The model with the lowest DIC was selected as the model providing the “best” fit to the data. Other models with a DIC within 3-5 points of the best one were also considered as possible candidates.

Error! Not a valid bookmark self-reference. Table 21 present the median and 95% credible interval values for the beta coefficients of all fixed-effects and random-effects fractional polynomial models, presented from the models with smallest DIC to the largest.

Error! Not a valid bookmark self-reference. presents the results for the model used in the company submission. Based on DIC and validation against KM data from the relevant trials, the second order model (fixed effects) with powers -1 and -1 was selected as the best fit with the second lowest DIC.

The remaining two models (Table 4 and Table 5) with a DIC within 3-5 points of the best one were also considered, however they predicted implausible hazards in the first cycle so were not applied. Additional details on the FP analysis are presented in Appendix D.3.1, with Figures 10 and 11 presenting the implausible PFS survival curves. Table 6 - Table 21 present the results for the models which were ruled out based on their DIC values.

Table 3: Second-order model, p1 = -1, p2 = -1

2nd order, p1=-1, p2=-1 DIC=1604.0	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta2	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 4: Second-order model, p1 = -2, p2 = -0.5

2nd order, p1=-2, p2=-0.5 DIC=1603.9	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta2	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 5: Second-order model, p1 = -2, p2 = -1

2nd order, p1=-2, p2=-1 DIC=1607.1	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta2	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 6: Second-order model, p1 = -2, p2 = 0

2nd order, p1=-2, p2=0 DIC=1614.2	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta2	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 7: Second-order model, p1 = -1, p2 = -0.5

2nd order, p1=-1, p2=-0.5 DIC=1622.3	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta2	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 8: Second-order model, p1 = -2, p2 = -2

2nd order, p1=-2, p2=-2 DIC=1628.3	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta2	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 9: Second-order model, p1 = -2, p2 = 0.5

2nd order, p1=-2, p2=0.5 DIC=1635.3	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta2	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 10: Second-order model, p1 = -0.5, p2 = -0.5

2nd order, p1=-0.5, p2=-0.5 DIC=1658.3	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta2	[redacted]	[redacted]	[redacted]	-	-	-

exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 11: Second-order model, p1 = -1, p2 = 0

2nd order, p1=-1, p2=0 DIC=1659.6	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta2	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 12: Second-order model, p1 = -1, p2 = 0.5

2nd order, p1=-1, p2=0.5 DIC=1707.9	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta2	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 13: Second-order model, p1 = -0.5, p2 = 0

2nd order, p1=-0.5, p2=0 DIC=1710.8	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta2	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 14: Second-order model, p1 = -0.5, p2 = 0.5

2nd order, p1=-0.5, p2=0.5 DIC=1775.0	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta2	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 15: Second-order model, p1 = 0, p2 = 0.5

2nd order, p1=0, p2=0.5 DIC=1847.3	Parameter	Absolute effects	Relative to palbociclib - fulvestrant

		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta2	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 16: First-order model, p = -2

1st order, p=-2 DIC=1927.0	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 17: First-order model, p = -1

1st order, p=-1 DIC=2086.6	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 18: First-order model, p = -0.5

1st order, p=-0.5 DIC=2168.9	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 19: First-order model, p = 0 (Weibull PH)

1st order, p=0 and PH assumption (weibull PH) DIC=2225.4	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
Time parameter		[redacted]	[redacted]	[redacted]	-	-	-
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 20: First-order model, p = 0

1st order, p=0 DIC=2217.4	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 21: First-order model, p = 0.5

1st order, p=0.5 DIC=2225.4	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

b) According to the methodology of Jansen 2011, employed by the company, a first order fractional polynomial model with power of 0 corresponds to a Weibull hazard function. However, within Table 35 (Appendix D), the DIC values of the first order model, power 0 and the Weibull model fitted by the company are different, yet these models should be mathematically identical. Please clarify the difference in DIC values.

Two types of Weibull models can be fitted through fractional polynomials. The first order model with power 0 indeed corresponds to a Weibull hazard function. In addition, a proportional hazard assumption can be applied by setting the parameter d_1, which reflects the change in the log hazard ratio over time, to 0, as detailed on page 2 of the Janssen paper (11). Using a Weibull model with a proportional hazard assumption is common practice for cost-effectiveness analysis, as pointed out on page 8 by Janssen (11). In the example presented in the paper, the DIC for the Weibull model in table 2 on page 7 (first order, p=0, DIC=934.6) is indeed different from the DIC for the Weibull PH model on page 8 (DIC=959.1) as these are two different models.

In the company submission, the DIC labelled as “Weibull model” in the DIC table corresponds to the Weibull model with the proportional hazard assumption. It therefore differs from the DIC for the first order model with a power of 0, which corresponds to a Weibull hazard function without any assumption.

A5. Priority request: network meta-analysis (OS)

a) The company states that, “OS data has not been reported for the EFECT study” (CS, page 63). The ERG considers that relevant OS data from the EFECT study is in the public domain [Chia S, Piccart M, Gradishar W, on behalf of the EFECT writing committee. Fulvestrant vs exemestane

following non-steroidal aromatase inhibitor failure: first overall survival data from the EFECT trial. In: Poster presented at the San Antonio Breast Cancer Symposium, Texas, USA, 13-16 December 2007 – see http://www.freecme.net/uptodate/abstract_bct/MEDIA/SABCS_posters/Chia_2091.pdf] and could have been included within the company's OS NMA. Please include these data within the NMA for OS (also see point b) below).

b) Please note that a response to only one of option i) or ii) is required, depending on the outcome of the request made in Question A3.

i) If the additional tests requested in Question A3 show that the proportional hazards assumption has been violated for one or more of the trials included within the NMA for OS, please apply the same first order and second order polynomials as applied to PFS and please provide the median and 95% credible interval values for the beta coefficients of all fixed-effects and random-effects fractional polynomial models which converged (similar to format of Table 35 of Appendix D).

OR

ii) If the additional tests requested in Question A3 show that the proportional hazards assumption has NOT been violated for one or more of the trials included within the NMA for OS, please update the traditional Bayesian NMA with the OS data from the EFECT study (see point a above) and provide both fixed-effects and random-effects results.

a) The preceding systematic literature review that was updated by the company did not capture the Chia 2007 (10) poster which presented the overall survival results from the EFECT trial. This has been included in the OS NMA and the results are presented in part b).

b) Due to the uncertainty around the proportional hazards assumption for overall survival in the Piccart (9) and Chia (10) studies, the Bayesian NMA has been updated and fixed-effects fractional polynomial models have been applied. It was not possible to explore the random-effects fractional polynomial models, given timing restraints but can be provided upon request.

The Bayesian NMA has been updated to include the EFECT OS data presented in Chia 2007 (10).

Table 22: Bayesian NMA results

Comparison	Median HR	95% CrI
PAL+FUL versus EVE+EXE	[redacted]	[redacted]

Table 23 Table 40 present the median and 95% credible interval values for the beta coefficients of all fixed-effects and random-effects fractional polynomial models, presented from the models with smallest DIC to the largest.

Table 23 presents the results for the model used in the company submission and Table 25 presents the results for the model which is within 5 points of the best DIC value. Table 25 Table 40Table 21 present the results for the models which were ruled out based on their DIC values.

Table 23: Second-order model, p1 = 0, p2 = 0.5

2nd order, p1=0, p2=0.5 DIC=2337.5	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta2	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 24: Second-order model, p1 = -0.5, p2 = 0.5

2nd order, p1=-0.5, p2=0.5 DIC=2337.4	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta2	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 25; Second-order model, p1 = -1, p2 = 0.5

2nd order, p1=-1, p2=0.5 DIC=2342.6	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta2	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 26: Second-order model, p1 = -0.5, p2 = 0

2nd order, p1=-0.5, p2=0 DIC=2344.1	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta2	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 27: Second-order model, p1 = -1, p2 = 0

2nd order, p1=-1, p2=0 DIC=2349.3	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta2	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 28: Second-order model, p1 = -0.5, p2 = -0.5

2nd order, p1=-0.5, p2=-0.5 DIC=2350.6	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta2	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 29: Second-order model, p1 = -1, p2 = -0.5

2nd order, p1=-1, p2=-0.5 DIC=2354.0	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta2	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 30: Second-order model, p1 = -2, p2 = 0.5

2nd order, p1=-2, p2=0.5 DIC=2354.0	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%

palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta2	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 31: First-order model, p = -1

1st order, p=-1 DIC=2355.7	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 32: Second-order model, p1 = -2, p2 = 0

2nd order, p1=-2, p2=0 DIC=2356.5	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta2	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 33: Second-order model, p1 = -1, p2 = -1

2nd order, p1=-1, p2=-1 DIC=2359.4	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta2	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 34: Second-order model, p1 = -2, p2 = -0.5

2nd order, p1=-2, p2=-0.5 DIC=2359.6	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta2	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 35: First-order model, p = -0.5

1st order, p=-0.5 DIC=2362.5	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 36: Second-order model, p1 = -2, p2 = -1

2nd order, p1=-2, p2=-1 DIC=2364.1	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta2	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 37: Second-order model, p1 = -2, p2 = -2

2nd order, p1=-2, p2=-2 DIC=2374.5	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta2	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 38: First-order model, p = -2

1st order, p=-2 DIC=2384.7	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 39: First-order model, p = 0

1st order, p=0 DIC=2390.9	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE beta1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 40: First-order model, p = 0 (Weibull PH)

1st order, p=0 and PH assumption (Weibull PH)	Parameter	Absolute effects	Relative to palbociclib - fulvestrant

DIC=2394.3		median	2.5%	97.5%	median	2.5%	97.5%
Time parameter		[redacted]	[redacted]	[redacted]			
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE beta0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A6. Comparison of everolimus plus exemestane and fulvestrant

The company states, "…caution in everolimus prescribing is implicit in the fact that, despite higher PFS and OS for everolimus plus exemestane than fulvestrant, fulvestrant is still preferred…" (CS, page 96-97).

Please provide evidence to support the statement that PFS and OS are higher for everolimus plus exemestane compared to fulvestrant.

If evidence to support this statement is not derived from the company's indirect comparisons of everolimus plus exemestane versus fulvestrant, please provide numerical results of the company's NMAs for everolimus plus exemestane versus fulvestrant.

This statement was not informed by the company's NMA. The clinical community have accepted the clinical superiority of exemestane plus everolimus which has been documented in a published NMA by Bachelot et al. 2014 (12).

Additionally, fulvestrant is not presently reimbursed in England. However, due to the acknowledged significant toxicities and tolerability issues reported in the everolimus and exemestane combination treatment, some trusts have continued to fund fulvestrant single agent treatment despite the clinical community accepting its lower efficacy.

A7. Additional information from the PALOMA-3 trial

i) It is stated in the CS that there are eight UK trial sites. Please provide the number of patients (by arm) that were treated at each UK site.

ii) Please provide information, from the latest data cut, about subsequent therapies received by patients in the PALOMA-3 trial by treatment arm, in a format that is similar to Table 39 in the CS.

iii) If any patient was admitted to hospital during the PALOMA-3 trial, please provide the following information: reason for admittance, duration of stay, and grade/type of adverse event (if appropriate).

i) There are [redacted] UK trial sites in the PALOMA-3 trial and [redacted] We are unable to provide the number of patients by arm as they are still blinded at this time.

ii) Systemic anticancer therapies received as first, second, and third or greater lines of subsequent treatment by more than 10% of the patients in from the PALOMA-3 trial for either trial group who discontinued the intervention is presented in Turner et al. 2018 (13). Table 41 presents a summary of this data in the same format as Table 39 in the company submission as requested.

Table 41: Subsequent lines of treatment from PALOMA-3

Subsequent therapy	% split in first/second subsequent therapy in post-progression state	
	Palbociclib plus fulvestrant	Placebo plus fulvestrant
Eribulin	5%	6%
Paclitaxel	16%	19%
Capecitabine	25%	22%
Doxorubicin	4%	4%
Vinorelbine	3%	5%
Gemcitabine	3%	6%
Cyclophosphamide	5%	5%
Carboplatin	3%	2%
Exemestane	18%	16%
Everolimus	13%	13%
Palbociclib	1%	5%

iii) Tables 16.2.7.2 and 16.2.7.3 in the PALOMA-3 CSR (1) provided in the reference pack present the SAEs for all causality and treatment related SAEs respectively. Reason for admittance grade/outcome and cycle start / stop days are included.

Section B: Clarification on cost-effectiveness data

B1. Priority request: Kaplan-Meier data

Please provide the Kaplan-Meier analyses listed in a to d below to the following specifications:

Requested Kaplan-Meier analyses

ID	Trial data set	Population	Kaplan-Meier data requested
a	*The PALOMA-3 trial, latest data cut*	*Intention-to-treat population*	Time to death from any cause stratified by treatment arm
b			Time to disease progression or death based on investigator assessment, stratified by treatment arm
c			Time from disease progression by investigator assessment to death from any cause (post-progression survival) stratified by treatment arm
d			Time to treatment discontinuation stratified by treatment arm

Sample table: Example of output (SAS) required from specified Kaplan-Meier analyses

- The LIFETEST Procedure

Product-Limit Survival Estimates						
DAYS		**Survival**	**Failure**	**Survival Standard Error**	**Number Failed**	**Number Left**
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58
8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55
10.000		0.8710	0.1290	0.0426	8	54
*****		**	**	**	*	*
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1
999.000		0	1.0000	0	57	0

The life tables from the Kaplan-Meier analyses are provided in Excel in the reference pack. The Kaplan-Meier life tables have been provided for the following:

- Time to death from any cause stratified by treatment arm, from the 13th April 2018 data cut-off.
- Time to disease progression or death based on investigator assessment, stratified by treatment arm, from the 23rd October 2015 data cut-off.
- Time from disease progression by investigator assessment to death from any cause (post-progression survival), stratified by treatment arm, the 23rd October 2015 data cut-off.
- Time to treatment discontinuation, stratified by treatment arm, from the 23rd October 2015 data cut-off which was used in the company submission.

- Time to treatment discontinuation, stratified by treatment arm, from the 13th April 2018 data cut-off.
    - This is the latest data cut for time to treatment discontinuation, however the 23rd October 2015 data cut was used in the submission to be consistent with the PFS data cut.

B2. Health-related quality of life: PALOMA-3 trial

i) Please provide full details and results of the mixed-effects model methods used to calculate 5-dimension EuroQol questionnaire (EQ-5D) utility values for each arm.

ii) Please calculate the mean on study treatment EQ-5D (index) values for palbociclib plus fulvestrant and fulvestrant arms separately.

iii) Please report the statistical significance test results for the EQ-5D (index) values of palbociclib plus fulvestrant versus fulvestrant arms at baseline.

i) EQ-5D general health status and EQ-5D Index scores between treatment arms were compared between the treatment arms using a longitudinal repeated measures mixed model approach adjusting for specified covariates. The longitudinal analysis was pre-specified in the SAP, which detailed that the variables in the model would be treatment, time, treatment-by-time, with baseline used as a covariate. Statistical siginificance of within treatment arm change from baseline was interpreted using the 95% CIs of the average change from baseline score.

Table 42: EQ-5D Index Between Treatment Comparison (Mixed Effects Model) – PRO Analysis Set

	Palbociclib (PD-0332991) + Fulvestrant (N=335)		**Placebo + Fulvestrant (N=166)**		**Palbociclib (PD-0332991) + Fulvestrant - Placebo + Fulvestrant**		
Overall comparison	**Estimated mean**	**95% CI**	**Estimated mean**	**95% CI**	**Estimated mean**	**95% CI**	**P-value**
Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time							[redacted]

Treatment * Time							[redacted]
Baseline							[redacted]

ii)

Table 43: EQ-5D Index Observed means - PRO Analysis Set

	Palbociclib (PD-0332991) + Fulvestrant (N=335)					Placebo + Fulvestrant (N=166)					Palbociclib (PD-0332991) + Fulvestrant - Placebo + Fulvestrant		
	n	Mean (SD)	Median	(Min, Max)	95% CI	n	Mean (SD)	Median	(Min, Max)	95% CI	Mean	95% CI	P-value
Baseline	[redacted]												
Cycle2_Day1													
Cycle3_Day1													
Cycle4_Day1													
Cycle6_Day1													
Cycle8_Day1													
Cycle10_Day1													
Cycle12_Day1													
Cycle14_Day1													
EOT													

iii) At baseline, the statistical significance test results for the EQ-5D (index) values of palbociclib plus fulvestrant versus fulvestrant arm

Table 44: EQ-5D Index Observed means - PRO Analysis Set (statistical significance)

EQ-5D baseline index values	Mean	95% CI	p-value
Palbociclib (PD-0332991) + Fulvestrant - Placebo + Fulvestrant	[redacted]	[redacted]	[redacted]

B3. Cost-effectiveness versus all comparators

Please provide ICERs per QALY gained for palbociclib plus fulvestrant versus each of the comparators listed in the NICE scope, including a fully incremental analysis.

As outlined and discussed in Section B1 of the company submission, the treatment aims in hormone receptor positive breast cancer is to delay chemotherapy until all hormone-based treatments have been utilised or the patient is in visceral crisis, who are ineligible for palbociclib plus fulvestrant. Therefore, chemotherapy is not a comparator as palbociclib and fulvestrant will push chemotherapy use back further.

Single agent fulvestrant is not recommended by NICE and is only variably commissioned by some CCGs across the country, so is not a relevant comparator for the NHS.

Patients should not be prescribed exemestane monotherapy as the first relapse hormone therapy as it makes them ineligible for everolimus plus exemestane as a combination therapy (14). Exemestane monotherapy is used in very small numbers and only in patients who are not suitable for everolimus combination or the other AIs/SERDs are unsuitable.

Tamoxifen is used in minimal numbers as in post-menopausal women, who make up the bulk of patients with mBC would have completed treatment on

AI/SERD/combination therapy and therefore in many patients tamoxifen is used as the last hormone therapy.

These opinions are aligned with the NICE Committee conclusion in the recent appraisal on abemaciclib with fulvestrant for treating HR-positive, HER2-negative aBC after endocrine therapy (15). It was noted that fulvestrant monotherapy was not recommended by NICE, and was available in some parts of the country but not others, so access is variable. The Committee stated that chemotherapy would usually only be used after other less toxic options had been exhausted or if they were not suitable. The Committee agreed that chemotherapy was not a relevant comparator. The Committee also noted that NICE's technology appraisal guidance on everolimus with exemestane for treating advanced breast cancer after endocrine therapy states this is the most clinically effective treatment after endocrine therapy and that it is the only other combination treatment option. The Committee therefore concluded that exemestane plus everolimus was the most relevant comparator for this appraisal.

Furthermore, in the recent appraisal meeting for ribociclib with fulvestrant for treating HR-positive, HER2-negative aBC after endocrine therapy, the Committee also concluded that everolimus and exemestane is the key comparator (16).

Section C: Textual clarification and additional points

C1. Adverse event data from PALOMA-3

i) Please clarify that the data-cut for all adverse event data presented in the company submission are from a data-cut of 31 July 2015.

ii) If so, please clarify whether this data-cut is from the Clinical Study Report for 23 October 2015.

iii) Please clarify that all adverse event data reported in the company submission are academic in confidence, as currently marked.

i) The adverse event data presented in the company submission is from the supplemental New Drug Application (sNDA) 90-Day Safety Update (SU) (17) which provides a comprehensive review of updated cumulative safety data of palbociclib

reported in completed Phase 3 Study A5481023 as of the 31 July 2015 data cut-off date.

ii) This is not the data-cut from the Clinical Study Report for 23 October 2015, it is from the sNDA 90-day safety update as stated in part i).

iii) The adverse event data in the company submission are academic in confidence as marked. There is published adverse event data from the Paloma-3 trial (4) however we have presented the data from the supplemental New Drug Application (sNDA) 90-Day Safety Update because this provides additional detail. This remains academic in confidence as it has not been published, and the publication plan is yet to be decided.

References

1. Pfizer. Clinical study report on trial A5481023: Multicenter, Randomized, Double-Blind, Placebo Controlled, Phase 3 Trial Of Fulvestrant (Faslodex®) With Or Without PD-0332991 (Palbociclib) ± Goserelin In Women With Hormone Receptor-Positive, HER2-Negative Metastatic Breast Cancer Whose Disease Progressed After Prior Endocrine Therapy. Data on file. 2015.

2. Pfizer. A5481023 (PALOMA-3) Progression-Free Survival Update: Palbociclib (IBRANCE®) in Combination With Endocrine Therapy for the Treatment of Women With Hormone Receptor (HR)-Positive, Human Epidermal Growth Factor Receptor 2 (HER2)-Negative Advanced or Metastatic Breast Cancer. Data on file. 2016

3. Pfizer. Clinical study report on trial A5481023: Multicenter, Randomized, Double-Blind, Placebo Controlled, Phase 3 Trial Of Fulvestrant (Faslodex®) With Or Without PD-0332991 (Palbociclib) ± Goserelin In Women With Hormone Receptor-Positive, HER2-Negative Metastatic Breast Cancer Whose Disease Progressed After Prior Endocrine Therapy. Data on file. 2018.

4. Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol. 2016;17(4):425-439.

5. Di Leo A, Jerusalem G, Petruzelka L, et al. Final overall survival: fulvestrant 500 mg vs 250 mg in the randomized CONFIRM trial. J Natl Cancer Inst. 2014;106(1):djt337.

6. Chia S, Gradishar W, Mauriac L, et al. Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFECT. J Clin Oncol. 2008;26(10):1664-1670.

7. Johnston SRD, Kilburn LS, Ellis P, et al. Fulvestrant plus anastrozole or placebo versus exemestane alone after progression on non-steroidal aromatase inhibitors in postmenopausal patients with hormone-receptor-positive locally advanced or metastatic breast cancer (SoFEA): a composite, multicentre, phase 3 randomised trial. Lancet Oncol. 2013;14:989-998.

8. Yardley DA, Noguchi S, Pritchard KI, et al. Everolimus plus exemestane in postmenopausal patients with HR(+) breast cancer: BOLERO-2 final progression-free survival analysis. Adv Ther. 2013;30(10):870-884.

9. Piccart M, Hortobagyi GN, Campone M, et al. Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2. Ann Oncol 2014;25(12):2357-2362.

10. Chia S, Piccart M, Gradishar W, on behalf of the EFECT writing committee. Fulvestrant vs exemestane following non-steroidal aromatase inhibitor failure: first overall survival data from the EFECT trial. In: Poster presented at the San Antonio Breast Cancer Symposium, Texas, USA, 13-16 December 2007

11. Jansen JP. Network meta-analysis of survival data with fractional polynomials. BMC Medical Research Methodology. 2011;11(61).

12. Bachelot T, McCool R, Duffy S, et al. Comparative efficacy of everolimus plus exemestane versus fulvstrant for hormone-receptor-positive advanced breast cancer following progression/recurrence after endocrine therapy: a network meta-analysis. Breast Cancer Res Treat. 2014;143:(125–133).

13. Turner NC, Finn RS, Martin M, et al. Clinical considerations of the role of palbociclib in the management of advanced breast cancer patients with and without visceral metastases. Ann Oncol. 2018;29(3):669-680

14. National Institute for Health and Care Excellence. Everolimus with exemestane for treating advanced breast cancer after endocrine therapy (TA421). 2016.

15. National Institute for Health and Care Excellence. Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy (TA579). 2019.

16. National Institute for Health and Care Excellence. Ribociclib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer [ID1318] - committee papers. 2019.

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Growth Factor Receptor 2 (HER2)-Negative Advanced or Metastatic Breast Cancer. Data on file. 2015.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Palbociclib in combination with fulvestrant for treating advanced, hormone-receptor positive, HER2-negative breast cancer after endocrine therapy [ID916]

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

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

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

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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

About you

1.Your name	[redacted]
2. Name of organisation	Breast Cancer Care and Breast Cancer Now
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	On April 1 2019 Breast Cancer Care and Breast Cancer Now united to create one charity for everyone affected by breast cancer. Our aim is that by 2050, everyone who develops breast cancer will live and be supported to live well. From research to care, our charity has people affected by breast cancer at its heart – providing support for today and hope for the future. We'll find ways to prevent the disease, improve early diagnosis, develop new treatments, campaign for better care and support people with the physical and emotional impact of breast cancer. We're committed to working with the NHS and governments across the UK to ensure that breast cancer services are as good as they can be, and that breast cancer patients benefit from advances in research as quickly as possible. Our main sources of income can be found in our annual reports - http://breastcancernow.org/about-us/what-we-do/annual-report-and-accounts and https://www.breastcancercare.org.uk/home/about-us/what-we-do/our-impact.Our work on access to drugs is independent of any funding we may receive from the pharmaceutical industry and is based on the evidence of the clinical effectiveness of drugs. **Breast Cancer Now and Breast Cancer Care merged on 1 April 2019 and should now be listed as Breast Cancer Care and Breast Cancer Now.**

4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Breast Cancer Care and Breast Cancer Now utilise their various networks of supporters to gather information about patient experience.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Metastatic (also known as advanced, secondary or stage 4) breast cancer is when cancer originating in the breast has spread to other parts of the body; most commonly the lungs, brain, bones or liver. There is no cure for metastatic breast cancer, so treatment aims to control and slow down the spread of the cancer, relieve symptoms and give patients the best quality of life for as long as possible. A patient can be diagnosed with metastatic cancer initially (de novo metastatic), or they can develop the condition years after treatment for their primary breast cancer has ended. Being diagnosed with metastatic breast cancer is extremely difficult to come to terms with both for patients and their family and friends and it can affect patients in different ways. Many people may feel upset and shocked or anxious, as well as angry and alone. These common feelings can have a huge impact on people's mental health.

	As well as the huge emotional toll of living with metastatic breast cancer, patients often have to cope with numerous practical concerns, such as managing their day to day activities, including working, household responsibilities and travelling to and from hospital appointments. Patients are keen to find treatments that will halt progression and extend life for as long as possible. As patients' time is limited, people tell us that quality of life is just as important to take into account as length of life, as this enables them to spend quality time with their loved ones. Therefore, the type and severity of treatment side effects are also important for patients. A patient told us that living with this condition "affects me mentally more than anything as at the moment I am lucky not to experience any pain. I am able to live a normal life on a daily basis but I did cut my work days from full time to three days a week to get a better work life balance. I have had to adjust my finances accordingly. Living with secondary breast cancer feels like you're on a rollercoaster as the treatment never stops and I have scans every three to four months so it is hard mentally. On the positive side, I appreciate my friends and family and don't stress over little things."
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Before April 2019, this patient group would have been offered treatments including exemestane, everolimus in combination with exemestane, tamoxifen, or certain patients may receive chemotherapy. In some parts of England, fulvestrant is available as a second line treatment for women that have already received hormone therapy, although we understand it is not available in the majority of England. In April 2019 NICE published draft guidance recommending abemaciclib with fulvestrant for use on the Cancer Drugs Fund. This now offers an important additional treatment option, providing patients with precious extra time before their disease progresses, and delaying the use of chemotherapy.

8. Is there an unmet need for patients with this condition?	As of April 2019 no CDK 4/6 with fulvestrant has been approved for routine use on the NHS. Whilst abemaciclib with fulvestrant is now recommended by NICE for use on the Cancer Drugs Fund which was welcomed, palbociclib does have a different side effect profile to abemaciclib which may be preferred by some patients. The availability of this treatment could improve patient choice.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	One of the main advantages of palbociclib with fulvestrant is the increase in progression free survival. The PALOMA-3 study demonstrated that palbociclib in combination with fulvestrant improves progression free survival (PFS) compared with fulvestrant alone, with a median PFS of 11.2 months compared to 4.6 months. We know patients value this extra time, as delaying disease progression means more quality time to spend with their relatives and friends. Maintaining a good quality of life for as long as possible is currently the best outcome for this patient group. Delaying progression can also have a positive impact on patients' emotional wellbeing and mental health, as it may mean that the patient can continue doing the activities they enjoy and leading a more or less normal daily life. Increasing the time until a patient's disease progresses is also likely to bring some comfort to their relatives and friends, as this is the best possible outcome for an incurable disease. This in turn could help to reduce any stress the patient is experiencing as a result of worrying about any burden on their friends and family. Importantly, the use of this technology could also delay patients having to start on systemic (non-targeted) chemotherapy. Chemotherapy is traditionally associated with more severe and gruelling side effects which can result in a poorer quality of life for patients and people are often particularly fearful and anxious about starting chemotherapy treatment.

	This treatment option also has a different side effect profile to abemaciclib with fulvestrant which was approved for use on the Cancer Drugs Fund in April 2019. Palbociclib is associated with an increased incidence of neutropenia, whereas abemaciclib tends to increase the likelihood of diarrhoea. The side effect profile of drugs is an important factor for many patients in their treatment decisions and the availability of palbociclib with fulvestrant could provide an alternative treatment option that may be preferred by some patients. Expanding the options available for clinicians to discuss with patients can improve patient choice and enables people to have greater control over their quality of life. Recent trial data has suggested that women taking palbociclib with fulvestrant lived nearly 7 months longer than those who took fulvestrant alone and this improvement appeared to be greater in patients with sensitivity to prior endocrine therapy, reaching 10 months. Although this data (which was a secondary endpoint) did not reach statistical significance, there is a suggestion that there may be a relevant trend between progression free survival translating into overall life-extension. This would be extremely important for this patient group as there is no cure for metastatic breast cancer so the aim of treatment is to extend the length of life, whilst providing a good quality of life. Patients we spoke to are receiving palbociclib with fulvestrant have told us: “The main advantage of this treatment is that it has worked – what more could you ask for?” “This treatment means I can live my life as normal as possible. I have had 17 doses and the side effect I have had (which did upset me but have come to terms with it) is thinning hair. I have also had hot sweats but had had these throughout all my treatments over the last six years. I enjoy having the week off treatment (21 day cycle) as I feel I am on no drugs that week, just like before I had secondary breast cancer.”

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Palbociclib with fulvestrant is associated with some increased side effects, compared to fulvestrant alone. In the PALOMA-3 trial, neutropenia of all grades occurred more frequently in the palbociclib-fulvestrant arm compared to placebo-fulvestrant. Grade 3 or 4 neutropenia occurred in 65% of the palbociclib group, compared to 1% in the placebo arm. It would therefore be important that patients receiving this treatment are given accessible information about neutropenia, including the signs to look out for and when to seek prompt medical advice. The other most common side effects include fatigue, nausea, infections and anaemia. Every treatment for breast cancer has some side effects and each patient's situation will be different, with side effects affecting some patients more than others. Patients' willingness to take treatments will vary, however, as long as all the side effects are clearly discussed with the patient, they will be able to make their own choice with the support of their clinician regarding treatment options. Also as palbociclib is already approved for routine use in a different indication for breast cancer patients, we have heard from patients that it is generally well tolerated and that their day-to-day activities are not heavily impacted. Also, as palbociclib is already in use clinicians are familiar with the side effects associated with this treatment. A patient we spoke to told us "I don't have many side effects. I'm sometimes a bit weary or tired. But it's hard to say whether it's down to the treatment as I'm generally busy with two daughters. I have had mouth ulcers at regular times in the drug cycle. But I can put up with that. I was also constipated on and off for the first month or so, but it got easier." The patient went on to explain "in the first three to six months, my neutrophils were low at the end of the cycle. This meant the next cycle of treatment had to be delayed for a week. There is some monitoring required, but that's minor. I accept that as part of treatment." A patient also told us "my neutrophils are slightly low but this hasn't affected me physically or affected my treatment. Also I've had hair thinning and hot sweats… It took me a while to get used to my thin hair but that is a small price to pay if the treatments are working. I am used to the sweats so I get on with them.

	On a plus note I feel my normal self and have good energy levels. I just hope this works for me for a long time as it's very tolerable." The administration method of a particular treatment can also be important to patients. Whilst palbociclib is taken in tablet form which many patients find particularly convenient, patients would also need to attend hospital or in some places a GP surgery for fulvestrant to be administered, as this is given as an intramuscular injection. There is also some extra monitoring required for patients when taking palbociclib, in the form of regular blood tests. However, for many patients, any inconvenience caused by needing to attend hospital or GP appointments for the administration of fulvestrant or for blood tests, or any discomfort from the injection will be outweighed by an increase in progression free survival. With regards to the administration method of this treatment, one patient explained that "I find the tablet easy to take in the morning. The buttock injection isn't the most pleasant thing but it's not excruciating pain, not even close. I actually don't like needles, but as it's in the buttock I can't see it. And any discomfort is minor in the grand scheme of everything."
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	In the PALOMA-3 trial, patients were excluded if they had received any CDK 4/6 inhibitor, fulvestrant, everolimus or a PI3K inhibitor or had extensive symptomatic visceral metastasis.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None that we are aware of.
Other issues	
13. Are there any other issues that you would like the committee to consider?	N/A.
Key messages	
14. In up to 5 bullet points, please summarise the key messages of your submission: • In the PALOMA-3 trial, palbociclib in combination with fulvestrant improved progression-free survival compared to fulvestrant alone (with a median PFS of 11.2 months, versus 4.6 months respectively). This provided patients with an additional 6.6 months on average before their disease progressed.	

- This delay in disease progression is important as it enables patients to spend quality time with their friends and families as well as being able to continue with their daily activities, which can improve the emotional wellbeing of both patients and their families.
- There are some increased side effects from palbociclib in combination with fulvestrant, compared to fulvestrant alone, however, not all patients will experience side effects. The benefits and risk of a treatment need to be clearly discussed with the patient to make sure they can make a decision that is right for them.
- This treatment would add to the drug options available for patients with this type of breast cancer. It has a different side effect profile compared to abemaciclib with fulvestrant which has been recommended for use on the Cancer Drugs Fund and may therefore be preferred by some patients.
- The use of this technology could delay patients having to start on systemic (non-targeted) chemotherapy. Chemotherapy is traditionally associated with more severe and gruelling side effects which can result in a poorer quality of life for patients and people are often particularly fearful and anxious about being moved onto chemotherapy

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Palbociclib in combination with fulvestrant for treating advanced, hormone-receptor positive, HER2-negative breast cancer after endocrine therapy [ID916]

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

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Nicholas Turner**
2. Name of organisation	**Royal Marsden NHS Foundation Trust**

3. Job title or position	**Consultant Medical Oncologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Advanced hormone receptor positive, HER2 negative, breast cancer is incurable although highly treatable. The condition relevant to this appraisal is patients whose disease has progressed on prior endocrine therapy – either in the advanced disease setting or progressed on adjuvant endocrine therapy. The median survival from diagnosis with endocrine therapy pre-treated advanced disease is approximately 3 years. The aims of treatment are to stop progression and prolong durations of response to therapy, to keep people in as normal a life as possible. The aim is also to keep people alive for longer.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The most effective assessment of treatment efficacy in this disease is 'progression free survival' – the time from randomisation to disease progression (by RECIST criteria) or death, whichever occurs first. Although improving overall survival is the ultimate desired assessment of treatment efficacy, this is in practice a highly challenging endpoint to assess in a disease with a median duration of survival of 3 years.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes there is substantial unmet need. This disease is incurable, and all patients ultimately die of the disease. Treatments that keep people well, for as long as possible, are highly needed. For patients endocrine-based therapy is the standard treatment, but once the cancer no longer responds to endocrine based therapies the alternatives are chemotherapy, which can have substantial side effects, and reduce quality of like. Treatments that are well tolerated, and prolong endocrine based therapy duration, are highly desirable.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Endocrine based therapy or chemotherapy
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Advanced breast cancer: diagnosis and treatment Clinical guideline [CG81] 4th ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4) **Published in 2018** – Ann Oncol (2018); 29: 1634–1657
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Until recently there has been substantial variability in the management of this condition in the NHS (endocrine pre-treated advanced HR positive breast cancer) due to the variable availability of fulvestrant on the NHS. Although fulvestrant is the most effective single agent endocrine therapy for this condition (De Leo JCO 2010), this has not reimbursed widely across the NHS, and has only been available in individual areas. Alternative treatments including tamoxifen, exemestane – everolimus and chemotherapy have been used. This has changed substantially with the approval of abemaciclib and fulvestrant by NICE [TA579], and there is now a rapidly growing use of fulvestrant and abemaciclib for this condition.
• What impact would the technology have on the current pathway of care?	This technology would have a substantial benefit for this condition. CDK4/6 inhibitors in combination with fulvestrant double the duration of response to fulvestrant, and substantially defer the time when chemotherapy must be used to manage the condition. It is also highly likely that the use of CDK4/6 inhibitors, as a class of agents, improve overall survival (Turner NEJM 2018, Im NEJM 2019).
11. Will the technology be used (or is it already used) in	Palbociclib with an aromatase inhibitors is approved for the treatment of advanced HR positive breast cancer that has not relapse on endocrine therapy [TA495]. This is a different patient population to the one

the same way as current care in NHS clinical practice?	under assessment (patients with progression on prior endocrine therapy) A different CDK4/6 inhibitor abemaciclib and fulvestrant by NICE [TA579] is already approved for the treatment of this condition.
• How does healthcare resource use differ between the technology and current care?	No major differences now that abemaciclib and fulvestrant has been approved by NICE [TA579]
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No major investment as abemaciclib and fulvestrant has been approved by NICE [TA579]
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Substantial improvements in progression free survival, time to use of chemotherapy, and highly likely overall survival, compared to treatment without a CDK4/6 inhibitor. Compared to abermacilib and fulvestrant, palbociclib and fulvestrant has a different adverse effect profile, and it would be highly important to have both options available. Palbociclib and fulvestrant has lower rates of fatigue, diarrhoea and deep vein thrombosis than abemacicilib and fulvestrant, which may be clinically important for patients. Conversely palbociclib and fulvestrant has a higher rate of asymptomatic

	neutropenia, although this only rarely results in febrile neutropenia.
• Do you expect the technology to increase length of life more than current care?	Yes, It is highly likely that the use of CDK4/6 inhibitors, as a class of agents, improve overall survival (Turner NEJM 2018, Im NEJM 2019). Definitive assessment of the effect of CDK4/6 inhibitors on overall survival will ultimately require meta-analysis of all trials, and only such a meta-analysis will be able to establish whether the three currently available CDK4/6 inhibitors (palbociclib, abermacicilb, ribociclib) have the same effect on overall survival. All three currently available CDK4/6 inhibitors have the same effect on progression free survival.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, fulvestrant and palbociclib improves quality of life compared to fulvestrant alone (Turner et al NEJM 2015)
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No, all clinical groups appear to have the same overall benefit from fulvestrant and palbociclib.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare	No major differences now that abemaciclib and fulvestrant has been approved by NICE [TA579]. In some regards as listed above, palbociclib causes lower rates of symptomatic adverse effects than abermaciclib.

professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Assessment of disease progression as per standard practice.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year	

(QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	CDK4/6 inhibitors are seen by many experts internationally as the most important treatment development for breast cancer in the last 20 years. This is reflected in the four existing NICE approvals for CDK4/6 inhibitors, and the widespread adoption into evidence based guidelines.
• Is the technology a 'step-change' in the management of the condition?	Yes, reflected in the four existing NICE approvals for CDK4/6 inhibitors.
• Does the use of the technology address any particular unmet need of the patient population?	Yes, reflected in the four existing NICE approvals for CDK4/6 inhibitors.
18. How do any side effects or adverse effects of the technology affect the management of the condition	No major differences now that abemaciclib and fulvestrant has been approved by NICE [TA579]. In some regard palbociclib causes lower rates of symptomatic adverse effects than abermaciclib. Palbociclib and fulvestrant improves quality of life compared to fulvestrant alone.

and the patient's quality of life?	
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Please note prior comment on the lack of availability of fulvestrant in the NHS, prior to TA579. With that important exception, the trial would reflect current UK practice.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Progression free survival is the most important outcome of the trial. Overall survival is a very challenging endpoint in this condition, due to the length of median overall survival.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No

20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA421], [TA239], [TA116]	No, other than TA579
22. How do data on real-world experience compare with the trial data?	Very similar benefits are observed with palbociclib in real world data, reflecting that these drugs are generally well tolerated in routine clinical practice.
Equality	
23a. Are there any potential equality issues that should be taken into account when	No

considering this treatment?	
23b. Consider whether these issues are different from issues with current care and why.	No

Key messages

24. In up to 5 bullet points, please summarise the key messages of your statement.

- Palbociclib and fulvestrant is the new international standard of care for the treatment of advanced HR positive breast cancer that has relapsed or progressed on prior endcocrine therapy, advised by all international guidelines
- Palbociclib and fulvestrant is well tolerated and improves quality of life compared to fulvestrant alone
- Palbociclib and fulvestrant approximately doubles progression free survival compared to fulvestrant alone
- Palbociclib likely improves overall survival, although the assessment of overall survival in this condition is difficult due to the high median overall survival
- Fulvestrant alone is variably, and not widely, reimbursed on the NHS

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient expert statement

Palbociclib in combination with fulvestrant for treating metastatic, hormone-receptor positive, HER2-negative breast cancer after endocrine therapy [ID916]

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

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

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Holly Heath**

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2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ a carer of a patient with the condition? ☒ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	Breast Cancer Care and Breast Cancer Now
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☒ yes

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Stephanie Pollard**
2. Are you (please tick all that	☒ **X** a patient with the condition? ☐ a carer of a patient with the condition?

apply):	☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	Breast Cancer Now
4. Did your nominating organisation submit a submission?	☐ **X** yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ **X** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ **X** I have personal experience of the condition ☐ **X** I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	As I have no symptoms, it is the mental burden of knowing I have secondary breast cancer when I have two daughters who need their mother around that can be difficult at times (they were 10 and 4 when I was first diagnosed nearly 6 years ago). However, I do my best to park those thoughts and get on with my life. It is the medication and treatment which can be intrusive, as they happen regularly, but I try to approach that as something I just have to get on with and incorporate it into my everyday life. I am lucky that I work from home and fit my work around trips to clinics and hospitals, otherwise I would find things very stressful, I 'm sure.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and	The care I have received from the NHS has, on the whole, been fantastic, particularly since the end of 2014 when I transferred my care to the RUH in Bath where I have a consultant who is at the top of his game. My cancer was contained for 3 years with tamoxifen and denosumab, but then it spread to my liver.

care available on the NHS?	At this point my consultant suggested that the best subsequent treatment would be palbociclib with fulvestrant but that I would not be able to access it on the NHS. We were lucky in that we have had help to pay for this, but I feel desperately sorry for those women who are not as fortunate as me and who would, at that point, have had to have further chemotherapy, with all the trauma, stress and cost that can entail. The part of my treatment that I still have on the NHS (denosumab and zoladex injections) continue with no problems.
10. Is there an unmet need for patients with this condition?	I was devastated that I could not have the treatment recommended by my consultant on the NHS, and I can only be thankful that I have had help to finance it as it has been so successful. Other women will not have had access to these benefits.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	At the end of 2017 a scan showed that the cancer had spread to my liver. I started the palbociclib with fulvestrant in January 2018 and a scan I had in April 2018 showed that it had radiologically disappeared from my liver, and my spine showed some signs of healing. That has to be the main advantage, and what you would always hope for as a patient. Other advantages are that it is one pill a day, nice and easy to remember, plus the lack of major side effects. I have not had to alter my lifestyle or cut down on my activities at all while on this treatment.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	At first I suffered from constipation, but that only lasted a few months and was nothing debilitating. Occasionally, my blood tests showed that my neutrophils were too low so I would have to have a second blood test the following week to check they were high enough for me to embark upon the next cycle of treatment. Sometimes in that time (when my neutrophils were low) I suffered from mouth ulcers. This is standard for me when I am a little run down, so I don't regard them as a major problem and they only lasted until my neutrophils had picked up again. The fulvestrant intramuscular injections are not very dignified, but I find them uncomfortable rather than painful, and plenty of exercise afterwards helps avoid any stiffness. The number of needles involved in this treatment is not ideal, but having had six sessions of chemotherapy when I was first diagnosed, I can say that the burden of injections is nowhere near as

	difficult for me as that was
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	I would say that any woman, particularly those with young children, who wishes to continue their life with as little medical intervention as possible, and who can cope with occasional neutropenia would benefit from this treatment.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
15. Are there any other issues that you would like the committee to consider?	

Key messages
16. In up to 5 bullet points, please summarise the key messages of your statement: • this treatment has caused some of my metastases to disappear radiologically • side effects were, if not entirely non existent, negligible • the advantages of the treatment far outweigh the few disadvantages • the treatment has had very little negative impact on my life • the treatment has allowed me to live a full and active life with my children,

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About you	
1. Your name	**Dr Anne Rigg**
2. Name of organisation	**Guys and St Thomas NHS Foundation Trust**

3. Job title or position	**Consultant Medical Oncologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **X**☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**X**☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the	☐ yes

rest of this form will be deleted after submission.)	
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Palbociclib and fulvestrant is a treatment for second line oestrogen receptor positive metastatic breast cancer. The aim of the treatment is to prolong life, delay time to progression and maintain a good quality of life as this is generally a very tolerable regimen.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	In my opinion, a clinically significant treatment response is stabilisation or reduction of tumour volume using a recognised radiological assessment such as RECIST. In addition, symptomatic improvement and a better of quality of life should also be considered clinically significant.
9. In your view, is there an unmet need for patients and	Yes, there is an unmet need. The main additional groups that would benefit are those patients who were given first line cytotoxic chemotherapy because of visceral metastatic disease and those in centres where CDK 4/6 inhibitors are not used routinely at the current time. There is also a small

healthcare professionals in this condition?	population of patients who remain on single agent aromatase inhibitors as they presented with metastatic disease prior to the availability of palbociclib.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Second line treatment for ER+ metastatic breast cancer can be with ribociclib or abemaciclib with fulvestrant via the Cancer Drugs Fund as long as the relevant eligibility criteria are met. There are other cytotoxic chemotherapy options.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are NICE Guidelines for the treatment of advanced breast cancer (Aug 2019). Many centres will also have local therapy guidelines as well.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is some variation between clinicians amongst drugs of choice to be used at different lines of therapy and this variation increases the further the line of therapy.
• What impact would the technology have on the current pathway of care?	If this technology is approved, there are groups of patients that are not able to access ribociclib or abemiciclib who could potentially receive palbociclib and fulvestrant second line.

11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Palbociclib and fulvestrant is not available second line at the current time in NHS clinical practice.
• How does healthcare resource use differ between the technology and current care?	Patients receiving CDK 4/6 inhibitors require closer monitoring for the first 2 months than chemotherapy. This would be the same for all 3 commercially available CDK 4/6 inhibitors.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Prescription by an oncologist only at the current time.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Most oncologists, oncology pharmacists and oncology nurses are already using palbociclib and will be aware of how to supervise this agent.
12. Do you expect the technology to provide clinically	Yes, the results from the PALOMA-3 trial indicate an improvement in progression free survival with palbociclib and fulvestrant and early indications that overall survival may be statistically significant with longer follow up.

meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	As above, I would predict that longer follow up from the PALOMA-3 study will demonstrate an overall survival benefit.
• Do you expect the technology to increase health-related quality of life more than current care?	My experience is that palbociclib and fulvestrant is well tolerated and does not cause many significant side effects. As these patients with metastatic disease cannot be 'cured' extension of life must also be of the best quality. The CDK 4/6 inhibitors have been a very important development for metastatic breast cancer.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	PALOMA-3 trial did examine several pre-specified subgroups including previous sensitivity to endocrine therapy and presence/absence of visceral disease. This is the best evidence base currently available.
The use of the technology	

14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	As ribociclib and abemaciclib are currently available in second line with fulvestrant, adding palbociclib/fulvestrant will not add any additional burden to outpatients, pharmacy teams or laboratory test ordering.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Most oncologists would use radiological tumour progression as the indication to stop treatment with palbociclib and fulvestrant. It is rare for a patient to have to discontinue therapy because of treatment toxicity. No additional testing is required.

16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	I do not think there are any special conditions that need to be considered above and beyond the QALY calculation.
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	The CDK 4/6 inhibitor drugs have made a dramatic difference to the quality of life and longevity for patients with ER+ metastatic breast cancer. As described above, there are specific clinical scenarios where ribociclib/fulvestrant and abemiciclib/fulvestrant are not indicated on the Cancer Drugs Fund and the addition of palbociclib/fulvestrant would enable these patients to access high quality care that they would otherwise not get.
• Is the technology a 'step-change' in the management of the condition?	The major step change was the introduction of CDK 4/6 inhibitors more generally. However, it is essential that as many patients as possible can access this safe and effective treatment.

• Does the use of the technology address any particular unmet need of the patient population?	See above for previous comments.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The main side effects are asymptomatic neutropenia, fatigue, diarrhoea and rash. There is a clearly defined schedule for dose reduction in the event of particular toxicities. Side effects rarely impact on quality of life in a negative way.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes the design of PALOMA-3 reflected the treatment of metastatic breast cancer at the time of the trial. It did pre-date the introduction of CDK 4/6 inhibitors in first line metastatic breast cancer. Only very small numbers of patients were treated with a CDK 4/6 inhibitor in the trial.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Progression free survival was the primary end point as in most metastatic breast cancer clinical trials. This was the case for the PALOMA palbociclib trials.

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	There has been a recent FDA safety report (Sept 2019) that all 3 CDK 4/6 inhibitors can rarely cause pneumonitis or interstitial lung disease.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA421], [TA239], [TA116]	No.

22. How do data on real-world experience compare with the trial data?	I can only comment from my own personal experience that patients for the most part remain well on CDK 4/6 inhibitors and after the initial 2 months do not require many unplanned interventions/clinic attendances.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No.
23b. Consider whether these issues are different from issues with current care and why.	N/A
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your statement.

- The introduction of CDK 4/6 inhibitors has been a ‘game changer’ for the management of metastatic ER+ breast cancer
- Although ribociclib/fulvestrant and abemaciclib/fulvestrant are available via the CDF for second line metastatic breast cancer there are groups of patients who are not able to access it.
- PALOMA-3 clinical trial did include patients who had previously received chemotherapy unlike the other 2 products and also examined the presence of visceral metastases and previous sensitivity to endocrine therapy.
- Palbociclib/fulvestrant is approved via NICE/CDF would meet a small but important unmet need and is for the most part very well tolerated.
- The addition of palbociclib/fulvestrant will not add an additional burden to clinical teams or hospital resources.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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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]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 15/194/11

Completed 26 June 2019
Updated 15 July 2019

CONTAINS [redacted]
AND [redacted] DATA

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]

Produced by: Liverpool Reviews & Implementation Group (LR*i*G)

Authors: Nigel Fleeman, Senior Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

Rachel Houten, Health Economic Modeller, LR*i*G, University of Liverpool

Sarah Nevitt, Research Associate (Medical Statistician), LR*i*G, University of Liverpool

Angela Stainthorpe, Health Economic Modeller, LR*i*G, University of Liverpool

Sophie Beale, Research Associate, LR*i*G, University of Liverpool

Angela Boland, Associate Director, LR*i*G, University of Liverpool

Yenal Dundar, Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

Joanne McEntee, Senior Medicines Information Pharmacist, North West Medicines Information Centre, Liverpool

Ashley Marsden, Senior Medicines Information Pharmacist, North West Medicines Information Centre, Liverpool

Carlo Palmieri, Consultant in Medical Oncology, The Clatterbridge Cancer Centre NHS Foundation Trust, Liverpool

Correspondence to: Nigel Fleeman, Research Fellow, Liverpool Reviews and Implementation Group, University of Liverpool, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool L69 3GB

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Contributions of authors:

Nigel Fleeman	Project lead, critical appraisal of the clinical evidence and supervised the final report
Rachel Houten	Critical appraisal of the economic model
Sarah Nevitt	Critical appraisal of the statistical evidence
Angela Stainthorpe	Critical appraisal of the economic evidence
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
Yenal Dundar	Critical appraisal of the adverse event data
Joanne McEntee	Critical appraisal of the company submission
Ashley Marsden	Critical appraisal of the company submission
Carlo Palmieri	Clinical advice and critical appraisal of the clinical sections of the company submission

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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	Δ costs	Δ 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

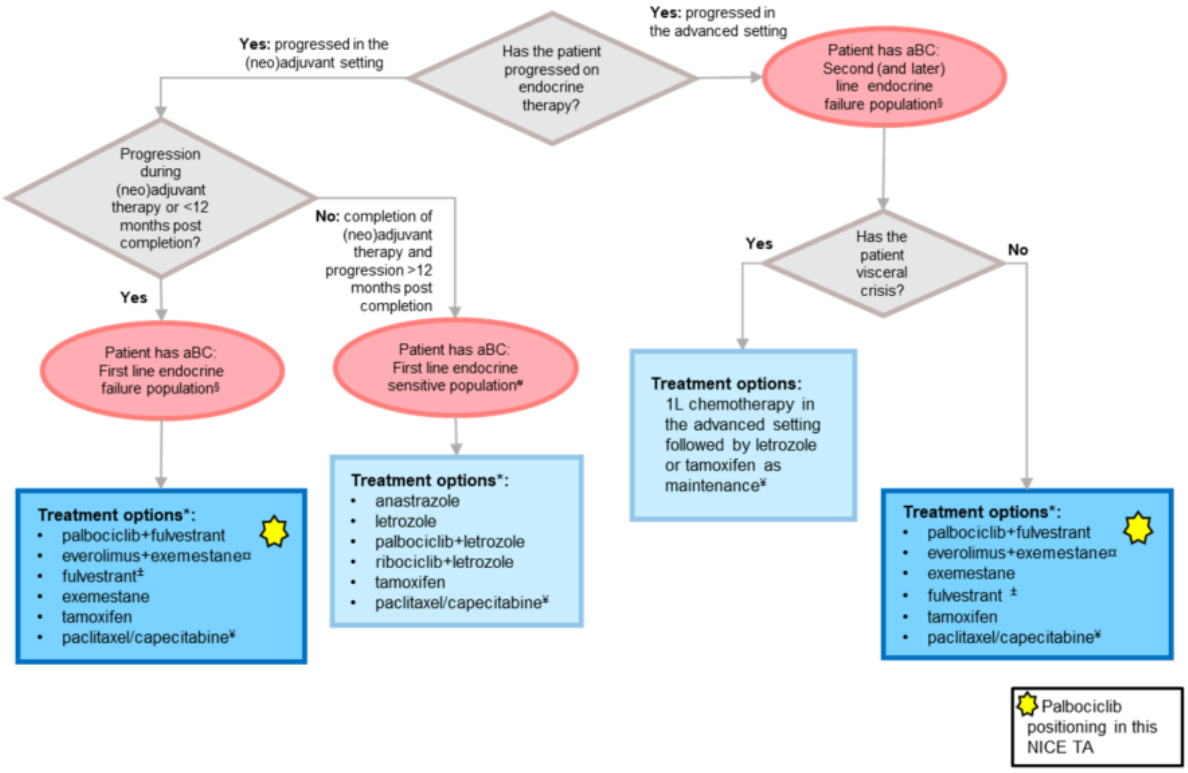
In NICE guidelines it is recommended that: “endocrine therapy is offered as first-line treatment for the majority of patients with ER-positive advanced breast cancer.”[4] For these patients, licensed endocrine therapies include anti-oestrogen therapies (tamoxifen or fulvestrant), non-steroidal aromatase 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.

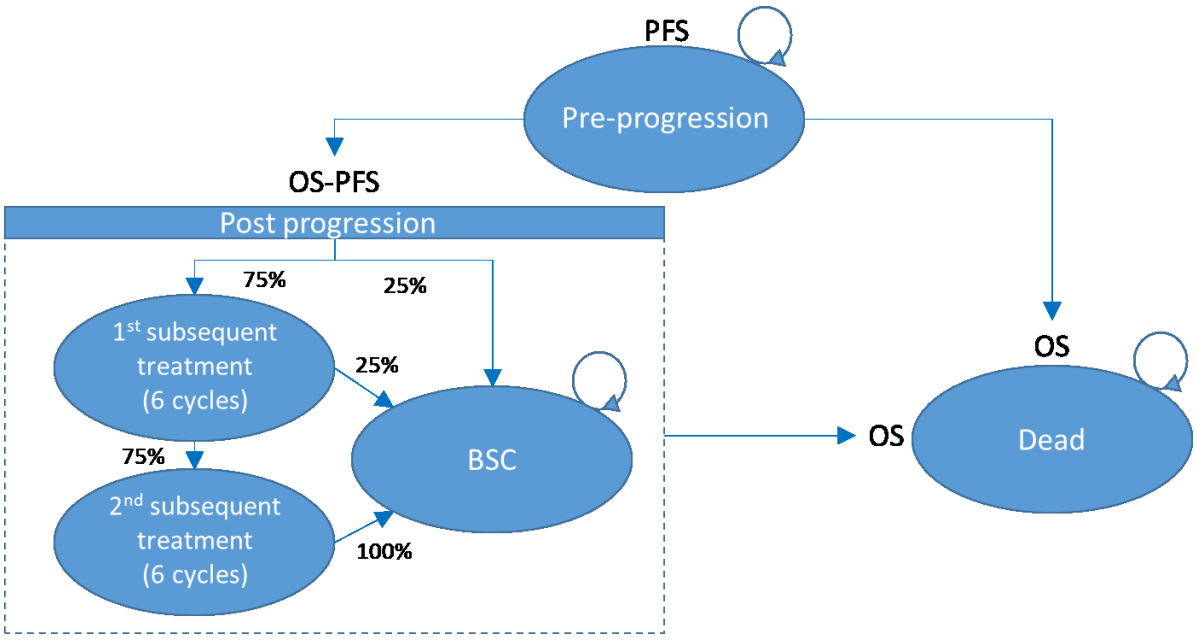


Figure 2 Model schematic

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

[redacted]

[redacted]20[redacted]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

[redacted]

[redacted]21[redacted]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]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]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!$C$13,MIN(F12,M12),MIN(F12,M12),F12,MIN(F12,M12)),(EnginePAL_FLV!E11^(1/TTDAdjPAL))))
		EngineEVE_EXE	AP11	Amend drug costs to use TTD (1st cycle) =IF(mod_C=1,ERG_TTD!E4*AP9,E11*AP9)
			AP12 copy down to AP531	Amend drug costs to use TTD (subsequent cycles) =IF(mod_C=1,ERG_TTD!E5*$AP$10,E12*$AP$10)
			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$9)
			AT11	Amend AEs to use TTD =IF(mod_C=1,ERG_TTD!E4*$AT$9,E11*$AT$9)
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))

ERG ADDENDUM PRE-TECHNICAL REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

ERG STA report addendum pre-technical report

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 15/194/11

Completed 2 August 2019

CONTAINS COMMERCIAL IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 INTRODUCTION

In advance of the preparation of the technical report, the National Institute for Health Care Excellence (NICE) requested clarification of the outcomes of the Evidence Review Group (ERG) remodelling of time to treatment discontinuation (TTD) and additional scenarios using the ERG's amendments to resource use. The clarification and additional scenarios requested are presented in this addendum.

2 MEAN TIME TO TREATMENT DISCONTINUATION

In its original report, the ERG remodelled time to treatment discontinuation (TTD) using data from the PALOMA 3 trial using treatment with placebo plus fulvestrant as a proxy for treatment with everolimus plus exemestane. Using the ERG approach generates mean TTD of [redacted] months for palbociclib plus fulvestrant and [redacted] months for everolimus plus exemestane.

3 ALTERNATIVE RESOURCE USE SCENARIOS

In its original report, the ERG presented three individual amendments to resource use in the company model. The individual amendments are:

- R4) Amend subsequent therapy assumptions
- R5) Remove daily oral drug wastage
- R6) Include monthly oncologist consultation in every health state

NICE requested further analyses using these amendments. The impacts on the incremental cost effectiveness ratio (ICER) per quality adjusted life year (QALY) gained of applying these three amendments in different combinations are shown in Table 1 (using the Patient Access Scheme [PAS] price for palbociclib).

Table 1 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**
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
R4)+R5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates
R4)+R6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates
R5)+R6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates
R4)+R5)+R6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates

ICER=incremental cost effectiveness ratio; OS=overall survival; PAS= Patient Access Scheme; PFS=progression-free survival; QALY=quality adjusted life year

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check

Palbociclib in combination with fulvestrant for treating advanced, hormone-receptor positive, HER2-negative breast cancer after endocrine therapy [ID916]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Friday 5 July 2019** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Dear [redacted],

Pfizer would like to thank Liverpool Reviews and Implementation Group and the NICE technical team for their thorough review of Palbociclib in combination with fulvestrant for treating advanced, hormone-receptor positive, HER2-negative breast cancer after endocrine therapy and welcomes the opportunity to check the ERG report to ensure there are no factual inaccuracies.

Pfizer identified some factual inaccuracies in the ERG report, which are presented in the pages below.

Should the ERG or NICE technical team have further questions please do not hesitate to contact us.

With best wishes,

[redacted]

[redacted]

Issue 1 Additional monitoring for palbociclib + fulvestrant

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 19 – The report notes that "The company states that no additional tests or investigations are required for patients who receive palbociclib plus fulvestrant (CS, Table 2, p15). However, as previously noted by the ERG in TA427,[14,21] additional monitoring is required for patients treated with palbociclib" Pfizer would like to highlight that patients receiving palbociclib plus fulvestrant do not require additional monitoring when compared to everolimus plus exemestane.	No additional tests or investigations are required for patients who receive palbociclib plus fulvestrant.	Factual inaccuracy. Additional monitoring was included in the TA427 in which palbociclib was appraised in combination with an aromatase inhibitor. Additional monitoring was required due to the aromatase inhibitor component. Patients receiving palbociclib plus fulvestrant do not require additional monitoring when compared to everolimus plus exemestane. The previous NICE submission was for palbociclib in combination with an aromatase inhibitor which did require additional monitoring. Fulvestrant is given monthly from hospital clinics due to its commissioning, rather than by GPs as aromatose inhibitors are. Therefore, patients receiving fulvestrant have bloods taken as a course, whereas patients receiving aromatose inhibitors via their GPs are not tested.	The ERG has deleted the text relating to additional investigations from page 19 of the ERG report.

		Additionally, everolimus plus exemestane requires blood tests prior to each cycle too. Furthermore, everolimus requires additional testing including CXR + blood sugar monitoring, as per the SPC (https://www.medicines.org.uk/EMC/medicine/22281/SPC/Afinitor+Tablets/), which palbociclib + fulvestrant does not.	

Issue 2 EFFECT Trial publication

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 25 – The report states that the results from the EFECT study presented in the Chia 2007 poster where not published in a peer reviewed journal. While the overall survival results were not published, the PFS results were published in a peer reviewed journal.	Overall survival results presented in the Chia 2007 poster were not published in a peer reviewed journal. The PFS results were published in a peer reviewed journal (Chia 2008, https://ascopubs.org/doi/pdf/10.1200/JCO.2007.13.5822) as identified by the company in the SLR.	Factual inaccuracy. The EFECT trial results that were reported in a journal was captured by the company in the SLR.	The overall survival (OS) results presented in the poster were not published in the peer reviewed paper by Chia 2008 and have not been subsequently published. However, the ERG recognises that the introduction section of the poster does report some results (including PFS) that were reported in the published paper by Chia 2008. Therefore, the ERG has amended the text slightly for clarity ('It is not clear why the OS results presented in the 2007 poster were not subsequently published in a peer reviewed journal').

Issue 3 .Endocrine resistant definition

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 34 - The ERG considers that it is difficult to draw definitive conclusions about how many patients were 'endocrine resistant' in the five trials but it seems from the information provided, that at trial entry this was 100% in the PALOMA-3 and BOLERO-2 trials[45,46] The company notes that patients who progress on or very shortly after hormone therapy are defined as 'endocrine resistant', therefore it is possible to assume that patients meeting this criteria in the trials are endocrine resistant.	Patients who progress on or very shortly after hormone therapy are defined as 'endocrine resistant'.	Any patient who progresses on or very shortly after hormone therapy is classed as endocrine resistant as they have either progressed through therapy or not maintained response soon after cessation. We therefore can assume anyone who met that criteria across the trials is resistant.	The ERG agrees that patients who progress on or very shortly after hormone therapy are defined as 'endocrine resistant'. This definition is consistent with the definitions used in the PALOMA-3 and BOLERO-2 trials (i.e. 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). Most, if not all, of the CONFIRM trial population also seem to be match this definition. However, the ERG notes that the EFECT trial included a large proportion (62.6%) of patients who are described as having 'AI-sensitive disease'. In the SoFEA trial, information relating to resistance and sensitivity was lacking (although the authors of this trial publication state that the population was similar to that of the BOLERO-2 trial). The ERG has re-worded this paragraph

			(now on page 37) for clarity, as follows: 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.

Issue 4 Overall survival FP models

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 66-67 – The report states that some of the OS FP models suggest an advantage for palbociclib plus fulvestrant over everolimus plus exemestane and others suggest that the opposite is the case. The company notes that the only models which suggest an advantage for everolimus plus exemestane provide a poor fit to the data and can be ruled out based on their DIC values.	The fractional polynomial models within 5 points of best DIC, including the best model, as recommended by the Janssen reference paper on fractional polynomials and the MRC Biostatistics Unit of Cambridge University suggest an advantage for palbociclib plus fulvestrant.	Fractional polynomial models should be assessed on DIC criteria, models which have differences in DIC higher than 10, should be ruled out (MRC Biostatistics Unit of Cambridge University), as they are not an accurate representation of the data.	As described within the ERG report (page 43), 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. Therefore, this is ERG opinion and not a factual error. No changes made to the ERG report.

NICE National Institute for Health and Care Excellence

Technical engagement response form

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

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **9th September 2019**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Anthony Eccleston**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Pfizer**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Questions for engagement

Issue 1: Generalisability of the PALOMA-3 trial results to the endocrine resistant population identified by the company to clinical practice in the NHS	
The company has presented results for palbociclib with fulvestrant for people with 'endocrine resistant' disease only. Is this clinically relevant?	Endocrine resistance population is a sliding scale of a term to describe a group of patients who have progressed on a prior endocrine therapy. This group can be anywhere between failing one line of therapy to all lines of endocrine therapy due to intrinsic mutational changes.
Given that around [redacted] of the trial population included people previously treated with chemotherapy in the advanced setting, is the "endocrine resistant" population identified in PALOMA-3 representative of people in the NHS who would receive palbociclib with fulvestrant? Or would palbociclib with fulvestrant be used earlier in the treatment pathway in order to delay or avoid treatment with chemotherapy?	The aim of a CDK 4/6 inhibitor is to delay chemotherapy. However, in current UK clinical practice many patients receive chemotherapy as their 1st line treatment. Around 40-50% of patients receive chemotherapy as a first line treatment despite only 15% being in visceral crisis. Currently there is an unmet need in this population as they cannot currently access treatment with a CDK4/6 inhibitor. The PALOMA-3 trial study shows that these patients would derive clinical benefit from the use of palbociclib after chemotherapy. The pivotal trials for the other CDK 4/6 inhibitors (abemaciclib and ribociclib) did not include patients who had received prior chemotherapy and therefore the received NICE recommendation excludes these patients. It is important to provide access for patients who have been previously treated with chemotherapy upfront. For example, a patient who correctly received chemotherapy with visceral crisis in the 1st line, who then progresses but is not in visceral crisis should be able to access a CDK 4/6 inhibitor in order to delay a further line of chemotherapy. The recent meta-analysis on CDK 4/6s vs chemotherapy have shown comparable response rates, meaning that even in the second line it is important to delay further lines of chemotherapy (1). It is anticipated that this sub-group of patients will diminish over the next 2-3 years as the number of patients who receive chemotherapy as a 1st line treatment reduces and the use of CDK 4/6 inhibitors is further established as first line standard of care. Consequently, the population in UK clinical practice will match more closely with the chemotherapy-naïve sub-group in the PALMOA-3 trial. Therefore, it is

important to consider the clinical results for the chemotherapy-naïve patients in the PALOMA-3 trial which show better outcomes for both PFS and OS compared to the ITT population, which is to be expected as chemotherapy drives mutational burdens in patients with cancer. Table 1 and Table ***2*** present the PFS and OS results respectively for the ITT and chemotherapy-naïve populations.

Table 1: PALOMA-3 progression-free survival

Progression-free survival - ITT population	**Palbo-fulv (N=347)**	**Placebo-fulv (N=174)**
Median, months	11.2	4.6
CI	9.5 - 12.9	3.5 - 5.6
Hazard ratio (CI)	0.50 (0.40 - 0.662); P<0.0001	
Progression-free survival - No previous chemotherapy	**Palbo-fulv ([redacted])**	**Placebo-fulv ([redacted])**
Median, months	[redacted]	[redacted]
Hazard ratio (CI)	[redacted]	

Table 2: PALOMA-3 overall survival

Overall survival - ITT population	**Palbo-fulv (N=347)**	**Placebo-fulv (N=174)**
Median, months	34.9	28
CI	28.8 - 40.0	23.6 - 34.6
Stratified Hazard ratio (CI)	0.81 (0.64 - 1.03); P=0.09	
Overall survival - No previous chemotherapy	**Palbo-fulv (N=[redacted])**	**Placebo-fulv ([redacted])**
Median, months	[redacted]	[redacted]
CI	[redacted]	[redacted]
Hazard ratio (CI)	[redacted]	

	The company have conducted a cost-effectiveness analysis using outcomes from the chemotherapy-naïve patients from the PALOMA-3 trial. The clinical and cost-effectiveness results for this sub-group are presented in the appendix to the technical engagement response.
Issue 2: Different approaches to estimating the relative clinical effectiveness of treatment with palbociclib plus fulvestrant versus everolimus plus exemestane (NMA versus proxy measure)	
Is the ERG's alternative approach of using fulvestrant monotherapy as a proxy for treatment with everolimus plus exemestane clinically plausible?	The efficacy of everolimus and exemestane vs fulvestrant has never been assessed in head to head studies. The only study to examine both has been the everolimus plus exemestane (EE) plus fulvestrant vs fulvestrant alone which showed superiority of the combination treatment (2). Everolimus and fulvestrant are very different drugs, with different side effect profiles meaning that the clinical profile of patients who go onto either drugs are also very different. It is therefore very difficult without a head to head study to fully state the PFS and OS of the compounds. Moreover, the assumption that the outcomes for EE and fulvestrant would be the same have no basis on clinical assumptions of the way the drugs are used. It is therefore important to conduct an indirect treatment comparison that utilises the clinical data for EE from the BOLERO-2 trial to estimate the relative clinical effectiveness of treatment with palbociclib plus fulvestrant versus EE. Thus, the company conducted an indirect treatment comparison using fractional polynomials.
The company considers that the proportional hazards assumption is not violated for overall survival (OS) and present NMA results using a standard Bayesian method. The ERG considers that proportional hazards do not hold for both progression free survival (PFS) and OS and that only results using a fractional polynomial approach are clinically	The proportional hazards assumption has been tested for all trials in the network for overall survival. The proportional hazards assumption was tested by visual inspection of the Kaplan-Meier curves and log cumulative hazard plots as well as the proportional hazards test based on the Schoenfeld residuals. In the company submission, it was assumed that the proportional hazards assumption holds for all studies despite some evidence of slight deviations. However, upon further analysis after receiving the the ERG

relevant. Both the standard Bayesian and Fractional Polynomial approach for NMAs produce results that are highly uncertain. • The ERG was unable to select a suitable fractional polynomial model for either PFS or OS. In the absence of a suitable FP model for OS, is it appropriate to use the standard Bayesian NMA for OS, and the FP NMA for PFS (company approach) for estimating survival for the comparison of palbociclib and fulvestrant with everolimus with exemestane or is the ERG's approach more appropriate?	report, the company accepts the ERG's view that the proportional hazards assumption is violated, noting that: •The p-value from the Schoenfeld residuals is 0.001 for BOLERO-2 which would indicate that the proportional hazards assumption has been violated (3). •The p-value from the Schoenfeld residuals for Chia 2007 is statistically significant (4). Consequently, the company provided fractionally polynomial analysis for OS. The models have been evaluated via DIC criteria and have been clinically validated. It is the company's opinion that the fractional polynomial models offer the best approach given that the proportionality of the hazards is not verified for all studies in the network.
Issue 3: Impact of company and ERG approaches on progression free survival outputs	
What is the preferred approach to modelling progression free survival? Does the ERG's approach produce more clinically plausible progression free survival estimates than the company's approach using results from the fractional polynomial NMA?	The approach detailed by the ERG, using fulvestrant PFS data from the PALOMA-3 trial, does not use any of the clinical effectiveness data for everolimus plus exemestane and does not attempt to estimate the difference in progression-free survival between palbociclib plus fulvestrant and everolimus plus exemestane. The company has used fractional polynomial analysis as the proportional hazards assumption does not hold for all studies in the network, as recommended by Janssen (5). The models have been evaluated via

DIC criteria and have been clinically validated. The fractional polynomial methodology offers the best approach given the current evidence-base.

Figure 1 presents the Kaplan-Meier PFS plot for everolimus plus exemestane from the BOLERO-2 trial alongside the survival curves produced by the company's fractional polynomial analysis and the ERG's approach.

Figure 1: Everolimus plus exemestane progression-free survival

	Upon visual inspection, the PFS curve produced by the fractional polynomial approach provides a better fit to the Kaplan-Meier data from the BOLERO-2 trial than the ERG's approach, which appears to underestimate the PFS for everolimus plus exemestane.
Issue 4: Impact of company and ERG approaches on overall survival outputs	
What is the preferred approach to modelling overall survival? Does the ERG's approach reduce uncertainty and produce more clinically plausible overall survival estimates than the company's approach using results from the fractional polynomial NMA?	Pooling the survival data from the trial and assuming equivalence based on the lack of overall survival statistically significance is not appropriate. The PALOMA-3 trial was not powered to detect an effect in overall survival, and although the OS results were updated in the April 2018 data-cut, the data is relatively immature with only 58% of events reported in the palbociclib plus fulvestrant arm with median follow-up of 44.8 months. The uncertainty is captured in the model via probabilistic sensitivity analysis. The company has used fractionally polynomial analysis as proportional hazards assumption does not hold, as recommended by Janssen (5). The models have been evaluated via DIC criteria and have been

clinically validated. The fractional polynomial models offer the best approach given the current evidence-base.

Figure 2 shows the Kaplan-Meier OS plot for everolimus plus exemestane from the BOLERO-2 trial alongside the survival curves produced by the company's fractional polynomial analysis and the ERG's approach.

Figure 2: Everolimus plus exemestane overall survival

	Visual inspection of Figure 2 shows that the ERG's approach over estimates overall survival for everolimus + exemestane while the company's fractional polynomial appears to provide a closer fit to the Kaplan-Meier data from the BOLERO-2 trial.
Issue 5: Time-to-treatment discontinuation modelling	
How likely is it in practice for patients to be progression free and yet not continue treatment with palbociclib plus fulvestrant?	It is not unusual for time-on-treatment to be less than PFS as patients can discontinue treatment for a multitude of reasons; adverse event, treatment breaks, and scans are not always in line with the last treatment script. Patients can also continue to derive benefit from treatment whilst off therapy as PFS in a clinical setting is based upon RECIST criteria. In clinical practice, patients could have stopped a treatment for alternative reasons and can have 'stable' disease on a scan and continue to derive benefit from a drug.
Does the ERG's approach of estimating time to treatment discontinuation using Kaplan-Meier 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 produce clinically plausible results?	Table 3 presents the mean and median time to discontinuation produced by the company's and ERG's modelling approaches. The company approach provides a longer average than the ERG modelling approach. The median PFS for everolimus plus exemestane reported in the BOLERO-2 trial is 7.8 months, while the median duration of exposure to treatment was reported as 23.9 weeks (5.98 months) (6). In the SMC advice for everolimus plus exemestane it is reported that the final PFS analysis was conducted at a median follow up of 18 months when the median everolimus treatment duration was 30 weeks (~7.5 months) compared with 14 weeks for placebo (7). Comparing the ERG estimates to the reported medians indicates that the ERG approach underestimates TTD for everolimus plus exemestane. **Table 3: Everolimus plus exemestane time to discontinuation** **Time to discontinuation** / **ERG approach** / **Company CEM** Mean TTD (months) / 8.93 / [redacted]

	Median TTD (months) | 4.60 | [redacted]
What is the preferred approach to modelling time to treatment discontinuation? Does the ERG's approach reduce uncertainty and produce a more clinically plausible time to treatment discontinuation estimates than the company's approach using a ratio of TTD to PFS from PALOMA-3?	Comparing the medians produced by the ERG and company approaches to the reported medians suggests that the company's estimate ([redacted]) provides a more plausible estimate than the ERG's estimate (4.60) which appears to underestimate treatment duration.
Issue 6: Subsequent therapy assumptions	
Is the mean duration that patients in the advanced setting receive subsequent therapies in clinical practice nearer 5 months as stated by the company or 7 months suggested by the ERG?	In the third line setting, patients in the UK are likely to receive everolimus plus exemestane, chemotherapy or tamoxifen. There is no data on the use of everolimus plus exemestane in the post CDK 4/6 inhibitor setting. The median PFS for everolimus plus exemestane reported in the BOLERO-2 trial is 7.8 months (6), however clinical advice suggests that it will be significantly lower in the third-line setting. Patients receiving chemotherapy are likely to receive capecitabine, which has a mean PFS of between 3.5 and 4.7 months (8), or paclitaxel, which is most commonly administered weekly for a total of 12 weeks (alternative 3 weekly is available and most of the studies have been carried out with this does, however in

	clinical practice due to toxicity profile the weekly regimen is significantly more commonly used) with a PFS of around 4-6 months (9,10). There is a lack of data for tamoxifen in the 3rd line setting, however tamoxifen is associated with a PFS of 6 months in the 1st-line setting (11). Clinical advice suggests that the PFS will be significantly lower in the 3rd-line setting. A targeted literature review identified a cost study which examined the medical records of 41 physicians in the UK (12). In this study the mean number of cycles ranged from 5.8 to 11.1, dependent on line and treatment covering first to third line aBC treatment; no evidence on fourth line was available. For consistency, the duration of time spent in subsequent lines was assumed as 6 cycles per line for all treatment arms considered in the economic evaluation. A range of 5 to 7 cycles was used in sensitivity analyses. The rates of progression from subsequent treatment lines were assumed the same across the two treatment arms. It is the company's opinion that 5 months is a more accurate estimate of the mean duration of subsequent therapies and that the assumption by the ERG of a PFS of 7 months is an over estimation.
Is the company's assumption that 75% of patients in clinical practice would proceed to receive best supportive care when the maximum duration of first line subsequent therapy has been reached rather than receive a second line of subsequent therapy, or is the ERG's assumption of 100% more plausible?	After each post-progression line, it was assumed in the base-case that 25% of patients would not switch to a subsequent line but would instead receive BSC until death. This was based on consulted clinical expert opinion and reflects the fact that not all surviving patients continue active treatment (either by choice or being not fit for treatment) (13). It is not clinically plausible for 100% of patients to progress to a 2nd subsequent therapy as there is always a drop off due to a plethora of reasons; drop in performance status, no response, progression of disease, declining further therapy to name a few. In clinical practice there will be a percentage of patients either in visceral crisis, those in whom performance drops during treatment and would not be eligible for further treatment, and those who decline further treatment. These patients instead progress to BSC.
Issue 7: Resource use: number of appointments with a consultant oncologist	

How frequently are people with advanced hormone-receptor positive, HER2-negative breast cancer likely to have appointments with a consultant oncologist?	Endocrine treatments are typically prescribed every 3 months alongside a scan and a meeting with the consultant oncologist. Patients that progress and go on to receive chemotherapy or everolimus plus exemestane will have a consultant oncologist appointment prior to each monthly cycle of treatment. In the end of life stage, patients are transferred to the care of the palliative care team and would not be seen regularly by the oncologist as end of life planning would be taking place. The majority of these patients will be given open OPDs for any emergencies raised by the community palliative care teams. The company have used an estimate of one consultant oncologist appointment once every 2 months which represents an average across subsequent treatments and is supported by CNS interviews conducted.
Issue 8: End of life	
What is the current life expectancy of the relevant patient population?	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). In the BOLERO-2 trial, the median OS for patients who received everolimus plus exemestane was 31.0 months (95% CI: 28.0 to 34.6 months). The gain in median OS in the PALOMA-3 trial for palbociclib plus fulvestrant versus placebo plus fulvestrant was 6.9 months. Improving survival by 7 months is a result of palbociclib's innovation, compared to the trial comparator that only reached 28 months median OS, is a large relative gain; an increase of 25% (+1/4). The gain in median OS in the "Chemotherapy naïve" sub-group in the PALOMA-3 trial for palbociclib plus fulvestrant versus placebo plus fulvestrant was 16.5 months.
How robust are the current estimates of survival benefit?	There have been 3 data cuts of the PALOMA-3 trial, with associated Clinical Study Reports from 5th December 2014 (15), 23rd October 2015 (16), and 13th April 2018 (17). There was also an exploratory analysis from the 16th March 2015 which was published in Cristofanilli 2016 (18). However, PFS results were not updated in the April 2018 data-cut and is therefore relatively immature with only 58% of events reported in the palbociclib plus fulvestrant arm with median follow-up only 15.8

	months. Overall survival results were updated in the April 2018 data-cut but only 58% of events were reported in the palbociclib plus fulvestrant arm with median follow-up of 44.8 months. The final data-cut of the PALOMA-3 trial is expected in mid-2021 which will provide mature PFS and OS results.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Palbociclib (PD-0332991) in combination with fulvestrant for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer that has become resistant to previous endocrine therapy [ID916]

Appendix

Company evidence submission

September 2019

File name	Version	Contains confidential information	Date
ID916_Palbociclib_ Appendix_18APR19(ACiC)	FINAL	Yes	9th September 2019

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Appendix A Scenario analysis

1. Overall survival – fractional polynomial analysis

The proportional hazards assumption has been tested for all trials in the network for overall survival. The proportional hazards assumption was tested by:

- visual inspection of the Kaplan-Meier curves
- log cumulative hazard plots
- the proportional hazards test based on the Schoenfeld residuals.

In the company submission, it was assumed that the proportional hazards assumption holds for all studies despite some evidence of slight deviations. As such, the company conducted a Bayesian Network Meta-Analysis. However, from the analysis conducted by the ERG, the company accepts the ERG's view that the proportional hazards is violated, noting that:

- The p-value from the Schoenfeld residuals is 0.001 for BOLERO-2 (Piccart 2014) (1) which would indicate that the proportional hazards assumption has been violated.
- The p-value from the Schoenfeld residuals for Chia 2007 (2) is statistically significant.

Consequently, the company provided fractionally polynomial analysis for OS following the Janssen methodology (3). The models have been evaluated via DIC criteria and have been clinically validated. Table 1 presents the results for the fractional polynomial model judged to produce the best fit to the data.

Table 1: Second-order model, p1 = 0, p2 = 0.5

2nd order, p1=0, p2=0.5 DIC=2337.5	Parameter	Absolute effects			Relative to palbociclib - fulvestrant		
		median	2.5%	97.5%	median	2.5%	97.5%
palbociclib - fulvestrant	PAL+FUL beta0	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta1	[redacted]	[redacted]	[redacted]	-	-	-
	PAL+FUL beta2	[redacted]	[redacted]	[redacted]	-	-	-
exemestane - everolimus	EXE +EVE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE +EVE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 1 presents the survival curves for palbociclib plus fulvestrant and everolimus plus exemestane produced by the selected fractional polynomial model alongside the Kaplan-Meier curves for each treatment.

Figure 1: Fractional polynomial overall survival curves

The company cost-effectiveness model was adapted to include the fractional polynomial results for overall survival, the results for this scenario analysis are presented in Table 2.

Table 2: Scenario analysis – overall survival fractional polynomial analysis (palbociclib at PAS discount)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Everolimus + exemestane	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Palbociclib + fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,176

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

2. Subsequent treatment costs

In the company base case analysis, the maximum duration of treatment for each line of subsequent treatment was set to six cycles, patients spend approximately 5 months in total receiving subsequent treatments, and 16 to 18 months in the BSC health state. The ERG considered that the mean time spent receiving subsequent therapies is an underestimate and that the mean time spent in BSC is an overestimate. There is uncertainty around the percentage of patients who receive subsequent treatments versus BSC and the duration of subsequent treatments.

A targeted literature review identified a cost study which examined the medical records of 41 physicians in the UK (4). In this study the mean number of cycles ranged from 5.8 to 11.1, dependent on line and treatment covering first to third line aBC treatment; no evidence on fourth line was available. For consistency, the duration of time spent in subsequent lines was assumed as 6 cycles per line for all treatment arms considered in the economic evaluation

and the rates of progression from subsequent treatment lines were assumed the same across the two treatment arms.

In the company base case, 15% of patients could receive everolimus plus exemestane post palbociclib plus fulvestrant as presented in Table 3 which was based upon clinical guidance to the ERG in a recent appraisal of abemaciclib.

During the technical engagement a scenario was discussed whereby the same subsequent treatments were modelled for both treatment arms. As part of this scenario anaylsis, the subsequent treatment split used for the everolimus plus exemestane arm was applied to the palbociclib plus fulvestrant arm (Table 4). This results in the same subsequent treatment cost per patient being applied to both treatment arms.

Table 3: Company base case - Therapies in post-progression bundle and their splits by treatment arm

Therapy	PALBO+FUL	EVE+EXE
Capecitabine	25.00%	40.00%
Paclitaxel	25.00%	20.00%
Everolimus + exemestane	15.00%	0.00%
Fulvestrant	0.00%	10.00%
Tamoxifen	25.00%	20.00%
Exemestane	5.00%	0.00%
Vinorelbine	5.00%	10.00%

Table 4: Scenario - Therapies in post-progression bundle and their splits by treatment arm

Therapy	PALBO+FUL	EVE+EXE
Capecitabine	40.00%	40.00%
Paclitaxel	20.00%	20.00%
Everolimus + exemestane	0.00%	0.00%
Fulvestrant	10.00%	10.00%
Tamoxifen	20.00%	20.00%
Exemestane	0.00%	0.00%
Vinorelbine	10.00%	10.00%

Table 5 presents the cost-effectiveness results for this subsequent therapy scenario. The total incremental cost saving associated with palbociclib plus fulvestrant shows a minor decrease to [redacted] from the base case results. This scenario demonstrates that the subsequent treatment costs do not have a large impact on the ICER and assuming equivalent susbsequent treatment costs and efficacy for both arms results in palbociclib plus

fulvestrant to be the dominant ICER strategy.

Table 5: Scenario analysis – subsequent treatment results (palbociclib at PAS discount)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Everolimus + exemestane	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Palbociclib + fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

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

3. Chemotherapy-naïve patients

The aim of a CDK 4/6 inhibitor is to delay chemotherapy. However, in current UK clinical practice many patients receive chemotherapy as their 1st line treatment. Around 40-50% of patients receive chemotherapy as a first line treatment despite only 15% being in visceral crisis. Currently there is an unmet need in this population as they cannot currently access treatment with a CDK4/6 inhibitor.

The PALOMA-3 trial study shows that these patients would derive clinical benefit from the use of palbociclib after chemotherapy. The pivotal trials for the other CDK 4/6 inhibitors (abemaciclib and ribociclib) did not include patients who had received prior chemotherapy and therefore the received NICE recommendation excludes these patients.

It is important to provide access for patients who have been previously treated with chemotherapy upfront. For example, a patient who correctly received chemotherapy with visceral crisis in the 1st line, who then progresses but is not in visceral crisis should be able to access a CDK 4/6 inhibitor in order to delay a further line of chemotherapy. The recent meta-analysis on CDK 4/6s vs chemotherapy have shown comparable response rates, meaning that even in the second line it is important to delay further lines of chemotherapy (5).

It is anticipated that this sub-group of patients will diminish over the next 2-3 years as the number of patients who receive chemotherapy as a 1st line treatment reduces and the use of CDK 4/6 inhibitors is further established as first line standard of care. Consequently, the population in UK clinical practice will match more closely with the chemotherapy-naïve sub-group in the PALMOA-3 trial. Therefore, it is important to consider the clinical results for the chemotherapy-naïve patients in the PALOMA-3 trial which show better outcomes for both PFS and OS compared to the ITT population, which is to be expected as chemotherapy drives mutational burdens in patients with cancer.

Progression-free survival

The chemotherapy-naïve sub-group in the PALOMA-3 trial was prespecified and both PFS and OS data were reported at each data cut. Progression-free survival data for the chemotherapy-naïve sub-population was taken from the October 2015 data cut of the PALOMA-3 trial. Table 6 presents the median PFS duration and the hazard ratio associated with palbociclib plus fulvestrant vs placebo plus fulvestrant from the PALOMA-3 trials for both the ITT populaiton and chemotherapy-naïve sub-group. The results demonstrate that there is an increased benefit from palbociclib plus fulvestrant in the chemotherapy-naïve population versus placebo plus fulvestrant.

Table 6: Progression-free survival – ITT and chemotherapy naïve populations

Progression-free survival - ITT population	**Palbo-fulv (N=347)**	**Placebo-fulv (N=174)**
Median, months	11.2	4.6
CI	9.5 - 12.9	3.5 - 5.6
Hazard ratio (CI)	0.50 (0.40 - 0.662); P<0.0001	
Progression-free survival - No previous chemotherapy	**Palbo-fulv ([redacted])**	**Placebo-fulv ([redacted])**
Median, months	[redacted]	[redacted]
Hazard ratio (CI)	[redacted]	

Figure 2 presents the PFS Kaplan-Meier curves for the chemotherapy-naïve sub-group.

Figure 2: Progression-free survival KM curves for chemotherapy-naive patients

[redacted]

We were unable to perform additional fractional polynomial analysis for the chemotherapy-naïve sub-group from the PALOMA-3 trial to present in this response. Instead, the company have implemented the modelling approach used by the ERG in order to provide cost-effectiveness results for this population.

In this scenario, for palbociclib plus fulvestrant, the company have modelled the PFS K-M data from the October 2015 data cut of the PALOMA-3 trial directly until [redacted] months, at which point there was increased censoring, and then appended an exponential distribution to extrapolate to the life-time horizon.

Similarly, when modelling PFS for patients treated with everolimus plus exemestane, the company has used the PALOMA-3 trial data for placebo plus fulvestrant for [redacted] months and then appended an exponential distribution. This approach was validated through examination of the cumulative hazard plot for PFS from the PALOMA-3 trial which indicated that a constant hazard trend is present from 2 months for both treatment arms.

Using this approach the mean length of PFS for palbociclib plus fulvestrant is [redacted] months and [redacted] months for placebo plus fulvestrant.

Overall Survival

Overall survival data for the chemotherapy-naïve sub-population was derived from the April 2018 data cut of the PALOMA-3 trial. Table 7 presents the median OS duration and the hazard ratio associated with palbociclib plus fulvestrant vs placebo plus fulvestrant from the PALOMA-3 trials for both the ITT population and chemotherapy-naïve sub-group. The results demonstrate that there is an increased benefit from palbociclib plus fulvestrant in the chemotherapy-naïve population versus placebo plus fulvestrant.

Table 7: Overall survival - ITT and chemotherapy naïve populations

Overall survival - ITT population	**Palbo-fulv (N=347)**	**Placebo-fulv (N=174)**
Median, months	34.9	28
CI	28.8 - 40.0	23.6 - 34.6
Stratified Hazard ratio (CI)	0.81 (0.64 - 1.03); P=0.09	
Overall survival - No previous chemotherapy	**Palbo-fulv ([redacted])**	**Placebo-fulv ([redacted])**
Median, months	[redacted]	[redacted]
CI	[redacted]	[redacted]
Hazard ratio (CI)	[redacted]	

Figure 3: Overall survival KM curves for chemotherapy-naive patients

For palbociclib plus fulvestrant overall survival, the company have modelled the OS K-M data from the October 2015 data cut of the PALOMA-3 trial directly until [redacted] months, at which time point there was increased censoring, and then appended an exponential distribution to extrapolate to the life-time horizon. Similarly, when modelling OS for patients treated with everolimus plus exemestane, the company has used the PALOMA-3 trial data for placebo plus fulvestrant for [redacted] months and then appended an exponential distribution. Appraisal of the cumulative hazard plots for OS for both treatment arms from the PALOMA-3 trial indicate that a constant hazard trend is apparent from about [redacted] months. This indicates that it is appropriate to extrapolate available data using an exponential function.

Using this approach the mean length of OS for palbociclib plus fulvestrant is [redacted] months and [redacted] months for placebo plus fulvestrant.

Time-to-discontinuation

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] months for patients treated with palbociclib plus fulvestrant, meaning it is appropriate to extrapolate trial data using an exponential function. The company, therefore, has used the TTD K-M data from the 4th data cut directly from the PALOMA-3 trial until [redacted] months for both treatment arms, and then appended an exponential function separately to each arm.

Cost-effectiveness

The cost-effectiveness results for chemotherapy naïve patients are presented in Table 8 (palbociclib with PAS discount).

Table 8: Base-case deterministic results (palbociclib at PAS discount)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Everolimus + exemestane	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Palbociclib + fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,093

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

References

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2. Chia S, Piccart M, Gradishar W, on behalf of the EFECT writing committee. Fulvestrant vs exemestane following non-steroidal aromatase inhibitor failure: first overall survival data from the EFECT trial. In: Poster presented at the San Antonio Breast Cancer Symposium, Texas, USA, 13-16 December 2007

3. Jansen JP. Network meta-analysis of survival data with fractional polynomials. BMC Medical Research Methodology. 2011;11(61)

4. Kurosky S, Mitra D, Zanotti G, Kaye JA. Patient characteristics and treatment patterns in ER+/HER2- metastatic breast cancer in the United Kingdom: results from a retrospective medical record review. 18th Annual European Congress of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR); 7-11 November, 2015; Milan, Italy.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Palbociclib (PD-0332991) in combination with fulvestrant for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer that has become resistant to previous endocrine therapy [ID916]

Urgent Information Request

September 2019

File name	Version	Contains confidential information	Date
ID916_Information_ request_response_(ACIC)	FINAL	Yes	26th September 2019

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1. **It is unclear if a revised company base case has been presented. Is this possibly the cost effectiveness estimates presented for scenario analysis in table 2 of the company appendix? If so, can you clarify:**
    a. **Does this scenario contain all the same assumptions as your original base case except for the modelling of OS using a FP NMA?**
    b. **Is the time to treatment discontinuation modelling the same as the previous base- case?**
    c. **Original subsequent therapy and resource use (namely consultant oncologist visits every 2 months) assumptions as your previous base-case?**

The analysis presented in Table 2 of the company appendix does represent the company's revised base case.

a) The scenario analysis presented includes the same assumptions used in the original submission base case, except for the modelling of OS using a FP NMA as the company accepts that the proportional hazards assumption to be violated for the overall survival network.
b) The time to treatment discontinuation was modelled as per the original company base case.
c) The scenario analysis presented includes the original subsequent therapy and resource use assumptions as the original base case.

Therefore, the only change from the original company base case is to the overall survival inputs which were derived from the fractional polynomial analysis.

2. **By extension, do the base case deterministic results in table 8 of the appendix for the chemotherapy naïve subgroup incorporate the same assumptions as your previous base case? We note that you write " Instead, the company have implemented the modelling approach used by the ERG in order to provide cost-effectiveness results for this population". Please clarify whether this included the time to treatment discontinuation modelling, subsequent therapy assumptions and resource use assumptions that were favoured by the ERG as well or only the modelling approach for PFS and OS favoured by the ERG.**

We were unable to perform additional fractional polynomial analysis for the chemotherapy-naïve sub-group from the PALOMA-3 trial to present in the company appendix. Instead, the company have implemented the modelling approach used by the ERG in order to provide cost-effectiveness results for this population.

The results presented in table 8 of the company appendix for the chemotherapy-naïve sub-group analysis use the same subsequent therapy and resource use assumptions as the original company base-case. However, time to treatment discontinuation for both treatment arms were modelled using the same approach employed by the ERG, i.e. the TTD Kaplan-meier data for palbociclib plus fulvestrant and placebo plus fulvestrant were included directly in the CE model with an appended exponential survival function employed to extrapolate.

3. **Please can you provide the outputs of the model in months for the OS FP analysis presented in Figure 1 of your appendix.**

Table 1 presents the median and mean from the fractional polynomial analysis for both palbociclib plus fulvestrant and everolimus plus exemestane which correspond to the survival curves presented in Figure 1.

Figure 1: Fractional polynomial overall survival curves

Table 1: Fractional polynomial overall survival

Fractional polynomial overall survival	Palbo-fulv	Eve-exe
Median, months	[redacted]	[redacted]
Mean, months	[redacted]	[redacted]

4. **In Table 6 of the appendix, there are no confidence intervals reported for PFS for the chemotherapy naïve subgroup.**

The confidence intervals for PFS for the chemotherapy-naïve sub-group are presented in Table 2.

Table 2: Progression-free survival

Progression-free survival - No previous chemotherapy	Palbo-fulv ([redacted])	Placebo-fulv ([redacted])
Median, months	[redacted]	[redacted]
CI	[redacted]	[redacted]
Hazard ratio (CI)	[redacted]	

NICE National Institute for Health and Care Excellence

Technical engagement response form

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

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **9th September 2019**

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- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

- Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted]. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Nicholas Turner**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**I have received advisory board honoraria from Pfizer, Novartis and Lilly and institutional research funding from Pfizer**

Questions for engagement

Issue 1: Generalisability of the PALOMA-3 trial results to the endocrine resistant population identified by the company to clinical practice in the NHS	
The company has presented results for palbociclib with fulvestrant for people with 'endocrine resistant' disease only. Is this clinically relevant?	**Yes, this is a substantial clinically relevant population, that includes patients who relapse on adjuvant endocrine therapy, and those who progress on endocrine therapy alone in the advanced setting.**
Given that around [redacted] of the trial population included people previously treated with chemotherapy in the advanced setting, is the "endocrine resistant" population identified in PALOMA-3 representative of people in the NHS who would receive palbociclib with fulvestrant? Or would palbociclib with fulvestrant be used earlier in the treatment pathway in order to delay or avoid treatment with chemotherapy?	**There is now substantial evidence that the use of CDK4/6 inhibitors improves overall survival, and therefore the use of these drugs first line in the metastatic/advanced setting will increase. For patients who relapse on endocrine therapy or who progress on first line endocrine therapy alone, fulvestrant and CDK4/6 inhibitor will be the standard of care for these patients.**
Issue 2: Different approaches to estimating the relative clinical effectiveness of treatment with palbociclib plus fulvestrant versus everolimus plus exemestane (NMA versus proxy measure)	
Is the ERG's alternative approach of using fulvestrant monotherapy as a proxy for treatment with everolimus plus exemestane clinically plausible?	**It is likely that exemestane and everolimus has slightly longer PFS than fulvestrant monotherapy from cross-study comparisons.** **Fulvestrant monotherapy at the now approved 500mg dose is likely more effective than exemestane monotherapy (cross study comparison of CONFIRM study with EFECT/SOFEA studies). However, the magnitude in improvement in PFS offered by everlimus plus**

	exemestane compared to exemestane monotherapy, is likely larger than the improvement of fulvestrant monotherapy compared to exemestane.
The company considers that the proportional hazards assumption is not violated for overall survival (OS) and present NMA results using a standard Bayesian method. The ERG considers that proportional hazards do not hold for both progression free survival (PFS) and OS and that only results using a fractional polynomial approach are clinically relevant. Both the standard Bayesian and Fractional Polynomial approach for NMAs produce results that are highly uncertain. • The ERG was unable to select a suitable fractional polynomial model for either PFS or OS. In the absence of a suitable FP model for OS, is it appropriate to use the standard Bayesian NMA for OS, and the FP NMA for PFS (company approach) for estimating survival for the comparison of palbociclib and fulvestrant with everolimus with exemestane or is the ERG's approach more appropriate?	**This is a technical question about which I am not qualified to comment.**
Issue 3: Impact of company and ERG approaches on progression free survival outputs	
What is the preferred approach to modelling progression free survival? Does the ERG's approach produce more clinically plausible progression free survival estimates than the company's approach using results from the fractional polynomial NMA?	**The ERG approach would appear to generate more clinically plausible assumptions of PFS.**

Issue 4: Impact of company and ERG approaches on overall survival outputs	
What is the preferred approach to modelling overall survival? Does the ERG's approach reduce uncertainty and produce more clinically plausible overall survival estimates than the company's approach using results from the fractional polynomial NMA?	**It seems unlikely that the approach proposed by ERG is producing clinically plausible results (ie that "Using this approach, the mean OS for patients, irrespective of treatment, is [redacted] months ").** **Across all CDK4/6 inhibitor studies, with palbociclib, ribociclib and abemaciclib, there has been remarkable consistancy in PFS hazard ratios strongly suggesting that the three drugs have similar efficacy. It is now clear that overall survival (OS) is improved by the use of CDK4/6 inhibitors with statistically significant improvements in OS in MONALEESA7 and MONALEESA3 (ribociclib), MOMARCH2 (abemaclciib) and OS improvements in PALOMA3 of overall similar HR but without reaching statistical significance.** **In contrast, exemestane plus everolimus did not statistically, nor convincingly clinically, demonstrate on OS improvement in BOLERO2.** **A model that therefore generates no difference in OS between palbocicilib plus fulvestrant versus everolimus plus exemestane would not appear to be clinically plausible.**
Issue 5: Time-to-treatment discontinuation modelling	
How likely is it in practice for patients to be progression free and yet not continue treatment with palbociclib plus fulvestrant?	**This is unlikely, the substantial majority of patients on palbociclib plus fulvestrant can continue therapy until disease progression.**
Does the ERG's approach of estimating time to treatment discontinuation using Kaplan-Meier 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 produce clinically plausible results?	**This is unlikely to be clinically plausible. Everolimus has relatively substantial toxicity, compared to palbociclib. In routine clinical practice everolimus plus exemestane is likely discontinued more frequently than fulvestrant monotherapy prior to progression. However,**

	if this is correct it would also likely imply that in routine clinical practice everolimus plus exemestane may be less effective than in BOLERO2. **Therefore, I would advise that the ERG approach is a fair model**
What is the preferred approach to modelling time to treatment discontinuation? Does the ERG's approach reduce uncertainty and produce a more clinically plausible time to treatment discontinuation estimates than the company's approach using a ratio of TTD to PFS from PALOMA-3?	**Both appear reasonable assumptions, although the ERG is potentially more plausible.**
Issue 6: Subsequent therapy assumptions	
Is the mean duration that patients in the advanced setting receive subsequent therapies in clinical practice nearer [redacted] as stated by the company or [redacted] suggested by the ERG?	**It is likely that neither of these estimates is correct, and that in routine clinical practice patients receive subsequent treatments for longer than both these estimates.**
Is the company's assumption that 75% of patients in clinical practice would proceed to receive best supportive care when the maximum duration of first line subsequent therapy has been reached rather than receive a second line of subsequent therapy, or is the ERG's assumption of 100% more plausible?	**Many patients will received multiple subsequent therapies in routine clinical practice.**
Issue 7: Resource use: number of appointments with a consultant oncologist	

How frequently are people with advanced hormone-receptor positive, HER2-negative breast cancer likely to have appointments with a consultant oncologist?	**Once established on palbociclib plus fulvestrant, (after the first 2-3 months on therapy) patients see a consultant oncologist every 2 or 3 months, as patients can be seen substantially less frequently than in the PALOMA3 trial.**
Issue 8: End of life	
What is the current life expectancy of the relevant patient population?	**The life expectancy of the control arm in PALOMA3 is appropriate for the population.** **It should be noted that it is not possible to compare absolute median survival estimates between trials, as difference in the patient populations can have substantial effects on overall survival.**
How robust are the current estimates of survival benefit?	**The point estimates of overall survival improvement in PALOMA3 are relatively inaccurately held, as the study was not powered for overall survival.** **Across all CDK4/6 inhibitor studies, with palbociclib, ribociclib and abemaciclib, there has been remarkable consistency in PFS hazard ratios strongly suggesting that the three drugs have similar efficacy. It is now clear that overall survival (OS) is improved by the use of CDK4/6 inhibitors with statistically significant improvements in OS in Monaleesa7 and Monaleesa3 (ribociclib), Monarch2 (abemaclciib) and OS improvements in PALOMA3 of overall similar HR but without reaching statistical significance. Such variation in that statistical significance of OS survival results is to be anticipated, as none of the studies were powered for OS.**

	It would therefore seem most appropriate that there should be consistency in assumption between the NICE assessments of abemaciclib plus fulvestrant, ribociclib plus fulvestrant, and palbociclib plus fulvestrant.

NICE National Institute for Health and Care Excellence

Technical engagement response form

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

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- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**NHS England & Improvement**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Generalisability of the PALOMA-3 trial results to the endocrine resistant population identified by the company to clinical practice in the NHS	
The company has presented results for palbociclib with fulvestrant for people with 'endocrine resistant' disease only. Is this clinically relevant?	**Yes, the population aimed for in the company submission is correct.** **The 3 CDK 4/6 inhibitors in combination with an aromatase inhibitor are all recommended by NICE for the population of patients who are either completely naïve to hormone therapy or have received neoadjuvant/adjuvant hormone treatment in the past but have relapsed 12 months or more after completing such treatment.** **The CDK4/6 inhibitors in combination with fulvestrant have therefore filled the gap in the treatment pathway for those patients who have already received one line of endocrine treatment for advanced/metastatic disease or who have relapsed during or within 12 months of completing neoadjuvant/adjuvant hormone therapy. The combinations of abemaciclib plus fulvestrant and ribociclib plus fulvestrant are in the CDF for this same indication as the one submitted for palbociclib plus fulvestrant.** **It is therefore correct for the company to have focussed their submission on the populations of patients as outlined in the immediately preceding paragraph.**
Given that around [redacted] of the trial population included people previously treated with chemotherapy in the advanced setting, is the "endocrine resistant" population identified in PALOMA-3 representative of people in the NHS who would receive palbociclib with fulvestrant? Or would palbociclib with fulvestrant be used earlier in the	**In the past, some clinicians have been reluctant to use upfront hormone therapy in patients who are hormone receptor positive with visceral metastases (particularly those in the liver) and who do not require an urgent response to treatment: in such circumstances, patients have been treated with chemotherapy first and then hormone therapy has been started after completion of chemotherapy. The entrance criteria of PALOMA-3 reflect this treatment**

treatment pathway in order to delay or avoid treatment with chemotherapy?	**policy of some oncologists at the time of design of the trial and as a consequence [redacted] of patients in PALOMA-3 had prior chemotherapy for advanced disease.** **The data for the use of CDK4/6 inhibitors in combination with aromatase inhibitors has changed practice such that chemotherapy is used less and less in hormone receptor positive HER2 negative patients with visceral metastases who do not require an urgent response to treatment. One of the main aims of CDK4/6 inhibitors in combination with fulvestrant is therefore to delay the need for consideration of chemotherapy and clinicians have been influenced by the high response rates to CDK4/6 inhibitors in combination with hormone therapy, the clinically relevant durations of response and the observed delays in chemotherapy. As a consequence, there has been a change in practice to use CDK4/6 inhibitors plus hormone therapy before chemotherapy as long as an urgent response to treatment is not required.** **That the patients in the PALOMA-3 trial were different to those in the trials of abemaciclib/ribociclib in combination with fulvestrant is shown by the median progression free survivals in the control (fulvestrant) arms: 9.3 mo in the abemaciclib trial,12.8 mo in the ribociclib trial whereas the figure is 4.6 mo in the palbociclib study. The two main explanations for these differences in PFS are the impact of the [redacted] of patients in PALOMA-3 who had prior chemotherapy and also the [redacted] of patients who had 2 or more prior systemic treatments (and it is relevant to note that [redacted] of the 2 prior systemic treatments applied to patients with advanced disease). The PALOMA-3 trial patients were thus generally more heavily pre-treated with both chemotherapy and hormone therapy than in the abemaciclib/ribociclib trials.** **To make any simple comparison between the 3 CDK4/6 inhibitors in combination with fulvestrant would at least require the exclusion of the [redacted] of patients in the PALOMA-3 trial who had already received chemotherapy for their advanced breast cancer and those patients who had failed 2 or more hormonal therapies used to treat advanced disease.**

	Such an analysis would greatly reduce the numbers of patients available and suffers all the disadvantages of post hoc manipulations of data. **If recommended by NICE, NHS E&I would ensure that palbociclib plus fulvestrant would be used in the clinical pathway in those patients who had progressed on one line of hormone therapy for advanced disease or had relapsed during or within 12 months of completing neoadjuvant/adjuvant hormone therapy ie in line with the current use in NHS England of abemaciclib/ribociclib plus fulvestrant. As a consequence of such planned practice in NHS England patients, the results of the PALOMA-3 trial should be regarded as underestimating the benefits of palbociclib plus fulvestrant for the reasons outlined above.** **In terms of clinical efficacy (but not toxicity), the 3 CDK4/6 inhibitors are regarded as being equivalent, a decision that the NICE Technology Appraisal Committee also came to when considering these drugs when in combination with an aromatase inhibitor. A recent meta-analysis agrees with this conclusion (Breast Cancer Res Treat 2019; 174: 597-604).**
Issue 2: Different approaches to estimating the relative clinical effectiveness of treatment with palbociclib plus fulvestrant versus everolimus plus exemestane (NMA versus proxy measure)	
Is the ERG's alternative approach of using fulvestrant monotherapy as a proxy for treatment with everolimus plus exemestane clinically plausible?	**NHS E&I does not agree with the ERG position of using the outcomes of fulvestrant monotherapy as being a proxy for those of everolimus plus exemestane.** **The populations of patients in the Bolero-2 and PALOMA-3 trials were broadly similar. In the Bolero-2 study, patients treated with everolimus and exemestane had median PFS durations of 7.8 mo (investigator assessment) and 11.0 mo (independent review). These are different to the 4.6 mo seen in the fulvestrant monotherapy control arm of PALOMA-3. As a consequence, clinicians consider that the combination of everolimus plus exemestane is more efficacious than fulvestrant monotherapy and this conclusion has been supported by a meta-analysis (Breast Cancer Res Treat 2014; 143: 125-133).**

The company considers that the proportional hazards assumption is not violated for overall survival (OS) and present NMA results using a standard Bayesian method. The ERG considers that proportional hazards do not hold for both progression free survival (PFS) and OS and that only results using a fractional polynomial approach are clinically relevant. Both the standard Bayesian and Fractional Polynomial approach for NMAs produce results that are highly uncertain. • The ERG was unable to select a suitable fractional polynomial model for either PFS or OS. In the absence of a suitable FP model for OS, is it appropriate to use the standard Bayesian NMA for OS, and the FP NMA for PFS (company approach) for estimating survival for the comparison of palbociclib and fulvestrant with everolimus with exemestane or is the ERG's approach more appropriate?	**NHS E & I recognises the uncertainties in the use of fractional polynomials to determine the relative clinical effectiveness of palbociclib plus fulvestrant versus everolimus plus exemestane.** **NHS E&I notes that the ERG pooled the survival outcomes of both arms in the PALOMA-3 trial as there was no statistical difference (34.9 mo for P+F vs 28.0 mo for F, HR 0.81, 95% CI 0.64-1.03) and used this pooled figure to compare with survival of patients treated with everolimus plus exemestane.** **NHS E&I considers that it is likely that there is an overall survival advantage for patients treated with palbociclib plus fulvestrant vs fulvestrant although recognises that PALOMA-3 was not designed to test for an overall survival benefit. Its reasons for concluding this are based on recently reported results which showed statistically significant increases in survival in 2 CDK4/6 inhibitor trials. The first was the MONALEESA-7 trial, the longer term follow up results of which were reported at ASCO June 2019. The trial demonstrated a survival advantage for ribociclib plus endocrine therapy vs endocrine therapy (median OS not reached vs 41 mo, HR 0.71, p=0.001). The second has more direct relevance to this appraisal as the MONARCH 2 trial compared abemaciclib plus fulvestrant with fulvestrant. It was reported at ESMO in September 2019 and using a pre-specified interim analysis of 77% events for overall survival, the median survival durations were 46.7 vs 37.3 mo (HR 0.76, 95% CI 0.61-0.95).** **The ERG's approach of pooling the survival outcomes of the 2 arms of PALOMA-3 when comparing this with survival for exemestane and everolimus is therefore likely to underestimate the incremental survival of palbociclib plus fulvestrant over everolimus plus exemestane.**
Issue 3: Impact of company and ERG approaches on progression free survival outputs	
What is the preferred approach to modelling progression free survival? Does the ERG's approach produce more clinically plausible progression free	**It is difficult for NHS E&I to comment on which is the preferred approach for modelling PFS given the uncertainties in this comparison of palbociclib plus fulvestrant versus**

survival estimates than the company's approach using results from the fractional polynomial NMA?	**everolimus plus exemstane. What is clear is that the ERG's mean PFS for everolimus plus exemestane (ie the mean PFS of the fulvestrant arm in PALOMA-3) is [redacted] mo yet the Bolero-2 trial reported median PFS outcomes of 7.8 mo (investigator-assessed) and 11.0 mo (independent review). It is highly likely that the mean PFS in Bolero-2 is significantly longer than the median PFS and so the ERG's figure of a mean of [redacted] mo is conservative.** **NHS E&I notes that both the company and the ERG show a clinically relevant superiority of palbociclib plus fulvestrant over everolimus plus exemestane in their indirect comparisons. NHS E&I agrees with this conclusion.**
Issue 4: Impact of company and ERG approaches on overall survival outputs	
What is the preferred approach to modelling overall survival? Does the ERG's approach reduce uncertainty and produce more clinically plausible overall survival estimates than the company's approach using results from the fractional polynomial NMA?	**NHS E&I notes the differing methodologies used by the company and the ERG in modelling overall survival. In the company's model, an incremental [redacted] mo in mean PFS for palbociclib over everolimus plus exemestane translates into an incremental mean overall survival difference of [redacted] mo. The ERG considers there to be no survival increment with palbociclib plus fulvestrant because as yet there has been no proven survival advantage for palbociclib plus fulvestrant demonstrated in the PALOMA-3 trial.** **NHS E&I considers that it is plausible that a difference in PFS will lead to a difference in overall survival. As the Appraisal Committee is fully aware, the relationship between PFS and OS is a complex one especially in a disease where there are multiple lines of both hormonal therapy and chemotherapy. Nevertheless and in view of the evidence quoted above for the overall survival advantages for the other 2 CDK4/6 inhibitors, NHS E&I considers it very likely that there will be an advantage to overall survival with palbociclib plus fulvestrant in PALOMA-3 had the trial been powered for survival. In addition, NHS E&I notes that the latest OS analysis in PALOMA-3 shows a HR of 0.81 with 95% CI of 0.64-1.03**

	ie the survival analysis is close to statistical significance and notes that a further planned interim analysis is due in [redacted] and the final analysis is due in [redacted]. The final analysis time in [redacted] is one reason why NHS E&I considers that palbociclib plus fulvestrant is a good candidate for the CDF (as the other 2 CDK4/6 inhibitors also have been in this indication) if the committee considers that there is a plausible ICER on its table. **Whatever the methodologies and assumptions used by the company and the ERG in producing estimates of PFS and OS and when comparing the two, NHS E&I considers that the company's outputs for PFS and OS are more plausible than those of the ERG.**
Issue 5: Time-to-treatment discontinuation modelling	
How likely is it in practice for patients to be progression free and yet not continue treatment with palbociclib plus fulvestrant?	**All cancer treatments have side-effects and so there will always be patients who discontinue treatment whilst yet being progression-free. Everolimus is not a well- tolerated drug and hence there will be a substantial discontinuation rate in the progression free state (although treatment with exemestane would continue). Pfizer has its own figures for time to treatment discontinuation of palbociclib plus fulvestrant but uses the PFS value for everolimus plus exemestane when comparing respective times to discontinuation. This is inappropriate as the cost of everolimus in the modelling is significantly inflated. On the other hand, the ERG has used the fulvestrant treatment duration to model the treatment duration for everolimus and exemestane. This is inappropriate too as everolimus plus exemestane is considered to be more efficacious than fulvestrant monotherapy.** **Scenario analyses of differing treatment durations for everolimus and exemestane could be done by the company. NICE knows the mean treatment duration for everolimus plus**

	exemestane from the appraisal of everolimus plus exemestane and so could use this in its considerations.
Does the ERG's approach of estimating time to treatment discontinuation using Kaplan-Meier 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 produce clinically plausible results?	**See above**
What is the preferred approach to modelling time to treatment discontinuation? Does the ERG's approach reduce uncertainty and produce a more clinically plausible time to treatment discontinuation estimates than the company's approach using a ratio of TTD to PFS from PALOMA-3?	**See above**
Issue 6: Subsequent therapy assumptions	
Is the mean duration that patients in the advanced setting receive subsequent therapies in clinical practice nearer [redacted] as stated by the company or [redacted] suggested by the ERG?	**The possible treatments after palbociclib plus fulvestant or fulvestrant monotherapy or everolimus plus exemestane include further hormonal therapy and various options of chemotherapy. The range of treatment options is wide as are the number of treatment options that patients actually receive. In addition, there is always an attrition rate from one line of treatment to another as the disease takes its toll and the side-effects of treatment take their toll too.** **Most patients will have at least 2 lines of further treatment with some having less but a significant proportion having more. A trial of further therapy to see if it works usually takes**

	at least 2 months of treatment. Palbociclib plus fulvestrant or everolimus plus exemestane are for fitter patients and hence the ERG's figure of a mean of [redacted] months on further treatment is more appropriate than the company's figure of [redacted] months.
Is the company's assumption that 75% of patients in clinical practice would proceed to receive best supportive care when the maximum duration of first line subsequent therapy has been reached rather than receive a second line of subsequent therapy, or is the ERG's assumption of 100% more plausible?	**There is never a 100% move of patients progressing on one therapy onto receiving the next line of active treatment. The rate of attrition of patients from one line of active treatment to another steadily escalates with each line of treatment. As regards the next line of treatment after palbociclib plus fulvestrant or everolimus plus exemestane, the treatment rate for further therapy is likely to be between 75% and 100% with steady falls following each line of therapy. NHS E&I notes that with the current data for the PALOMA-3 patients, [redacted] had 3 or more subsequent lines of treatment in the palbociclib plus fulvestrant arm and the figure for the fulvestrant arm was [redacted].**
Issue 7: Resource use: number of appointments with a consultant oncologist	
How frequently are people with advanced hormone-receptor positive, HER2-negative breast cancer likely to have appointments with a consultant oncologist?	**During the active phase of treatment, patients will be observed closely by a consultant oncologist or a member of the breast cancer team. The company's position of being seen by a consultant every 6 months in the PFS state is wrong although being seen in the post progression state every 2 months is reasonable. The ERG's position is that patients are seen monthly in both PFS and post progression states. Whilst this is reasonable whilst patients are on active therapy, it is inappropriate in the best supportive care period as there is ever greater input into care from the palliative care team.**

Issue 8: End of life	
What is the current life expectancy of the relevant patient population?	**The mean survival duration for patients who are hormone receptor positive with advanced breast cancer is clearly in excess of 2 years.**
How robust are the current estimates of survival benefit?	**NHS E&I considers that it is highly likely that there will be a survival benefit with palbociclib plus fulvestrant given the gains in modelled PFS and the recent demonstration of survival benefit with CDK4/6 inhibitors with hormone therapy and notably in the abemaciclib plus fulvestrant MONARCH-2 trial (see above).** **NHS E&I also wishes to make the following points:** **It considers the 3 CDK4/6 inhibitors to be equally efficacious. NICE has recommended for routine commissioning all 3 CDK4/6 inhibitors when used in combination with an aromatase inhibitor. NICE has recommended abemaciclib plus fulvestrant and ribociclib plus fulvestrant to the CDF. NHS E&I considers that there is a strong case for palbociclib plus fulvestrant also being recommended to the CDF (provided the company places a plausibly cost effective ICER on the appraisal table).** **NHS E & I understands that the 3 CDK4/6 inhibitors in combination with fulvestrant undergo 3 different single technology appraisals, have 3 different economic models with differing sets of assumptions, have 3 different ERGs to review the 3 company submissions and thus can have different sets of company and ERG estimates of cost effectiveness despite the clinical view that these 3 drugs have very similar clinical efficacies. Whilst recognising that the company was wrong to request NICE for a delay to this appraisal, NHS**

	E&I hopes that the NICE Appraisal Committee considers taking a pragmatic view in this appraisal of palbociclib plus fulvestrant when considering its previous decision making in this same indication for the other 2 CDK4/6 inhibitors. **For reasons that it cannot understand, NHS E&I notes that the company has not mentioned in its written submissions to NICE as to the possibility of palbociclib plus fulvestrant being considered for entry into the CDF. The company has had dialogue with NHS E&I as to this possibility and has stated to NHS E&I that it is open to what entry to the CDF requires: the need for the Appraisal Committee to conclude that this is appropriate and also to have a plausible ICER on its consideration table.**

NICE National Institute for Health and Care Excellence

Technical engagement response form

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

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **9th September 2019**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Novartis Pharmaceuticals Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Generalisability of the PALOMA-3 trial results to the endocrine resistant population identified by the company to clinical practice in the NHS	
The company has presented results for palbociclib with fulvestrant for people with 'endocrine resistant' disease only. Is this clinically relevant?	Novartis agree that the endocrine resistant population is a clinically relevant population since there is an unmet need for further therapies to delay disease progression and the need for chemotherapy in patients who develop resistance to endocrine therapy.
Given that around [redacted] of the trial population included people previously treated with chemotherapy in the advanced setting, is the "endocrine resistant" population identified in PALOMA-3 representative of people in the NHS who would receive palbociclib with fulvestrant? Or would palbociclib with fulvestrant be used earlier in the treatment pathway in order to delay or avoid treatment with chemotherapy?	Please see comment above
Issue 2: Different approaches to estimating the relative clinical effectiveness of treatment with palbociclib plus fulvestrant versus everolimus plus exemestane (NMA versus proxy measure)	
Is the ERG's alternative approach of using fulvestrant monotherapy as a proxy for treatment with everolimus plus exemestane clinically plausible?	No Comment
The company considers that the proportional hazards assumption is not violated for overall survival (OS) and present NMA results using a standard Bayesian method. The ERG considers that	No Comment

proportional hazards do not hold for both progression free survival (PFS) and OS and that only results using a fractional polynomial approach are clinically relevant. Both the standard Bayesian and Fractional Polynomial approach for NMAs produce results that are highly uncertain. • The ERG was unable to select a suitable fractional polynomial model for either PFS or OS. In the absence of a suitable FP model for OS, is it appropriate to use the standard Bayesian NMA for OS, and the FP NMA for PFS (company approach) for estimating survival for the comparison of palbociclib and fulvestrant with everolimus with exemestane or is the ERG's approach more appropriate?	
Issue 3: Impact of company and ERG approaches on progression free survival outputs	
What is the preferred approach to modelling progression free survival? Does the ERG's approach produce more clinically plausible progression free survival estimates than the company's approach using results from the fractional polynomial NMA?	No Comment
Issue 4: Impact of company and ERG approaches on overall survival outputs	
What is the preferred approach to modelling overall survival? Does the ERG's approach reduce uncertainty and produce more clinically plausible overall survival estimates than the company's approach using results from the fractional polynomial NMA?	No Comment

Issue 5: Time-to-treatment discontinuation modelling	
How likely is it in practice for patients to be progression free and yet not continue treatment with palbociclib plus fulvestrant?	
Does the ERG's approach of estimating time to treatment discontinuation using Kaplan-Meier 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 produce clinically plausible results?	No Comment
What is the preferred approach to modelling time to treatment discontinuation? Does the ERG's approach reduce uncertainty and produce a more clinically plausible time to treatment discontinuation estimates than the company's approach using a ratio of TTD to PFS from PALOMA-3?	No Comment
Issue 6: Subsequent therapy assumptions	
Is the mean duration that patients in the advanced setting receive subsequent therapies in clinical practice nearer [redacted] as stated by the company or [redacted] suggested by the ERG?	No Comment
Is the company's assumption that 75% of patients in clinical practice would proceed to receive best supportive care when the maximum duration of first line subsequent therapy has been reached rather than receive a second line of subsequent therapy, or is the ERG's assumption of 100% more plausible?	No Comment

Issue 7: Resource use: number of appointments with a consultant oncologist	
How frequently are people with advanced hormone-receptor positive, HER2-negative breast cancer likely to have appointments with a consultant oncologist?	No Comment
Issue 8: End of life	
What is the current life expectancy of the relevant patient population?	Median overall survival of patients with metastatic breast cancer is approximately 3 years
How robust are the current estimates of survival benefit?	No Comment

NICE National Institute for Health and Care Excellence

Technical engagement response form

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

Questions for engagement

Issue 1a: Generalisability of the PALOMA-3 trial results to the endocrine resistant population identified by the company to clinical practice in the NHS	
The company has presented results for palbociclib with fulvestrant for people with 'endocrine resistant' disease only. Is this clinically relevant?	Endocrine resistance population is a sliding scale of a term to describe a group of patients who have progressed on a prior endocrine therapy. This group can be anywhere between failing one line of therapy to all lines of endocrine therapy due to intrinsic mutational changes.
ERG comment	The Evidence Review Group (ERG) considers that the 'endocrine resistant' population is clinically relevant (ERG report, p.13).

Issue 1b: Generalisability of the PALOMA-3 trial results to the endocrine resistant population identified by the company to clinical practice in the NHS	
Given that around [redacted] of the trial population included people previously treated with chemotherapy in the advanced setting, is the “endocrine resistant” population identified in PALOMA-3 representative of people in the NHS who would receive palbociclib with fulvestrant? Or would palbociclib with fulvestrant be used earlier in the treatment pathway in order to delay or avoid treatment with chemotherapy?	The aim of a CDK 4/6 inhibitor is to delay chemotherapy. However, in current UK clinical practice many patients receive chemotherapy as their 1st line treatment. Around 40-50% of patients receive chemotherapy as a first line treatment despite only 15% being in visceral crisis. Currently there is an unmet need in this population as they cannot currently access treatment with a CDK4/6 inhibitor. The PALOMA-3 trial study shows that these patients would derive clinical benefit from the use of palbociclib after chemotherapy. The pivotal trials for the other CDK 4/6 inhibitors (abemaciclib and ribociclib) did not include patients who had received prior chemotherapy and therefore the received NICE recommendation excludes these patients. It is important to provide access for patients who have been previously treated with chemotherapy upfront. For example, a patient who correctly received chemotherapy with visceral crisis in the 1st line, who then progresses but is not in visceral crisis should be able to access a CDK 4/6 inhibitor in order to delay a further line of chemotherapy. The recent meta-analysis on CDK 4/6s vs chemotherapy have shown comparable response rates, meaning that even in the second line it is important to delay further lines of chemotherapy (1). It is anticipated that this sub-group of patients will diminish over the next 2-3 years as the number of patients who receive chemotherapy as a 1st line treatment reduces and the use of CDK 4/6 inhibitors is further established as first line standard of care. Consequently, the population in UK clinical practice will match more closely with the chemotherapy-naïve sub-group in the PALMOA-3 trial. Therefore, it is important to consider the clinical results for the chemotherapy-naïve patients in the PALOMA-3 trial which show better outcomes for both PFS and OS compared to the ITT population, which is to be expected as

chemotherapy drives mutational burdens in patients with cancer. Table 1 and Table *2* present the PFS and OS results respectively for the ITT and chemotherapy-naïve populations.

Table 1: PALOMA-3 progression-free survival

Progression-free survival - ITT population	Palbo-fulv (N=347)	Placebo-fulv (N=174)
Median, months	11.2	4.6
CI	9.5 - 12.9	3.5 - 5.6
Hazard ratio (CI)	0.50 (0.40 - 0.662); P<0.0001	
Progression-free survival - No previous chemotherapy	Palbo-fulv (N=[redacted])	Placebo-fulv (N=[redacted])
Median, months	[redacted]	[redacted]
Hazard ratio (CI)	[redacted]	

Table 2: PALOMA-3 overall survival

Overall survival - ITT population	Palbo-fulv (N=347)	Placebo-fulv (N=174)
Median, months	34.9	28
CI	28.8 - 40.0	23.6 - 34.6
Stratified Hazard ratio (CI)	0.81 (0.64 - 1.03); P=0.09	
Overall survival - No previous chemotherapy	Palbo-fulv (N=[redacted])	Placebo-fulv (N=[redacted])
Median, months	[redacted]	[redacted]
CI	[redacted]	[redacted]
Hazard ratio (CI)	[redacted]	

	The company have conducted a cost-effectiveness analysis using outcomes from the chemotherapy-naïve patients from the PALOMA-3 trial. The clinical and cost-effectiveness results for this sub-group are presented in the appendix to the technical engagement response.
ERG comment	As highlighted in the ERG report (Table 8), it is not uncommon, in England and Wales, for patients with endocrine resistant disease to receive chemotherapy in the advanced setting (before endocrine therapy). As stated in Section 3.8 of the ERG report, the patient population in the PALOMA-3 trial appears to be representative of the population who are currently likely to be treated with palbociclib plus fulvestrant (PAL+FUL) in clinical practice in England and Wales. The chemotherapy-naïve population is not identified as a sub-group within the final scope issued by NICE. The ERG notes that the chemotherapy-naïve subgroup for whom evidence is presented in the company's response appears to include patients who are chemotherapy-naïve in the (neo)adjuvant and in the advanced setting; the size of this subgroup accounts for just 20% of the patients in the PALOMA-3 trial. In the PALOMA trial [redacted] were chemotherapy-naïve in the advanced setting. Therefore, the subgroup considered in the company response may not be the appropriate subgroup if evidence is only being sought for those not treated in the advanced setting.

Issue 2a: Different approaches to estimating the relative clinical effectiveness of treatment with palbociclib plus fulvestrant versus everolimus plus exemestane (NMA versus proxy measure)	
Is the ERG's alternative approach of using fulvestrant monotherapy as a proxy for treatment with everolimus plus exemestane clinically plausible?	The efficacy of everolimus and exemestane vs fulvestrant has never been assessed in head to head studies. The only study to examine both has been the everolimus plus exemestane (EE) plus fulvestrant vs fulvestrant alone which showed superiority of the combination treatment (2). Everolimus and fulvestrant are very different drugs, with different side effect profiles meaning that the clinical profile of patients who go onto either drugs are also very different. It is therefore very difficult without a head to head study to fully state the PFS and OS of the compounds. Moreover, the assumption that the outcomes for EE and fulvestrant would be the same have no basis on clinical assumptions of the way the drugs are used. It is therefore important to conduct an indirect treatment comparison that utilises the clinical data for EE from the BOLERO-2 trial to estimate the relative clinical effectiveness of treatment with palbociclib plus fulvestrant versus EE. Thus, the company conducted an indirect treatment comparison using fractional polynomials.
ERG comment	The company appears to have misinterpreted the ERG approach to modelling: • The ERG is concerned about the reliability of cost effectiveness estimates generated using results from the company's fractional polynomial (FP) progression-free survival (PFS) and overall survival (OS) network meta-analyses (NMAs); the ERG was unable to confidently select suitable FP models for each NMA (ERG report, Section 3.4.3 and Section 3.4.4). • The ERG used the PFS and OS from the PLA+FUL arm of the PALOMA 3 trial to generate lower bound estimates of the clinical effectiveness of everolimus plus exemestane (E+E). • The ERG does not assume clinical effectiveness is the same for E+E and FUL; the ERG suggests that the clinical effectiveness of E+E is [redacted] than the clinical effectiveness of FUL. The ERG reiterates (ERG report, pp67-68) that no robust evidence has been presented to support the company's claim that E+E is clinically superior to FUL in terms of PFS, and that no evidence has been presented to support the claim that E+E is clinically superior to FUL in terms of OS. The ERG

	acknowledges that E+E is generally considered by clinicians to be more effective than treatment with FUL, but underlines that no trial or real-world evidence has been presented to support this opinion.

Issue 2b: Different approaches to estimating the relative clinical effectiveness of treatment with palbociclib plus fulvestrant versus everolimus plus exemestane (NMA versus proxy measure)	
The company considers that the proportional hazards assumption is not violated for overall survival (OS) and present NMA results using a standard Bayesian method. The ERG considers that proportional hazards do not hold for both progression free survival (PFS) and OS and that only results using a fractional polynomial approach are clinically relevant. Both the standard Bayesian and Fractional Polynomial approach for NMAs produce results that are highly uncertain. • The ERG was unable to select a suitable fractional polynomial model for either PFS or OS. In the absence of a suitable FP model for OS, is it appropriate to use the standard Bayesian NMA for OS, and the FP NMA for PFS (company approach) for estimating survival for the comparison of palbociclib and fulvestrant with everolimus with exemestane or is the ERG's approach more appropriate?	The proportional hazards assumption has been tested for all trials in the network for overall survival. The proportional hazards assumption was tested by visual inspection of the Kaplan-Meier curves and log cumulative hazard plots as well as the proportional hazards test based on the Schoenfeld residuals. In the company submission, it was assumed that the proportional hazards assumption holds for all studies despite some evidence of slight deviations. However, upon further analysis after receiving the the ERG report, the company accepts the ERG's view that the proportional hazards assumption is violated, noting that: •The p-value from the Schoenfeld residuals is 0.001 for BOLERO-2 which would indicate that the proportional hazards assumption has been violated (3). •The p-value from the Schoenfeld residuals for Chia 2007 is statistically significant (4). Consequently, the company provided fractionally polynomial analysis for OS. The models have been evaluated via DIC criteria and have been clinically validated. It is the company's opinion that the fractional polynomial models offer the best approach given that the proportionality of the hazards is not verified for all studies in the network.

ERG comment	The ERG notes that the company and the ERG are now in agreement regarding the violation of the proportional hazard (PH) assumption, for at least one trial included in the company's PFS and OS NMA networks. The ERG considers that when the PH assumption has been violated, taking a FP approach is, in principle, appropriate (ERG report, p43). The deviance information criterion (DIC) is a measure of the statistical fit of a model and should not be used alone to select, or rule out an FP model when model outputs are intended to be used to inform cost-effectiveness analyses (ERG report, p43). The company only 'clinically validated' the top three fitting models according to DIC. Due to the large amount of uncertainty and variability in the results produced by the company's PFS and OS FP NMAs, the ERG was unable to confidently select suitable FP models to inform the estimation of the relative effectiveness of treatment with PAL+FUL versus E+E (ERG report, pp44-46). Due to this uncertainty, to enable some alternative cost effectiveness estimates to be generated, the ERG used PFS and OS data from the FUL arm of the PALOMA-3 trial to generate lower bound estimates of the effectiveness of E+E.

Issue 3: Impact of company and ERG approaches on progression free survival outputs	
What is the preferred approach to modelling progression free survival? Does the ERG's approach produce more clinically plausible progression free survival estimates than the company's approach using results from the fractional polynomial NMA?	The approach detailed by the ERG, using fulvestrant PFS data from the PALOMA-3 trial, does not use any of the clinical effectiveness data for everolimus plus exemestane and does not attempt to estimate the difference in progression-free survival between palbociclib plus fulvestrant and everolimus plus exemestane. The company has used fractional polynomial analysis as the proportional hazards assumption does not hold for all studies in the network, as recommended by Janssen (5). The models have been evaluated via DIC criteria and have been clinically validated. The fractional polynomial methodology offers the best approach given the current evidence-base. Figure 1 presents the Kaplan-Meier PFS plot for everolimus plus exemestane from the BOLERO-2 trial alongside the survival curves produced by the company's fractional polynomial analysis and the ERG's approach. Figure 1: Everolimus plus exemestane progression-free survival

	 Upon visual inspection, the PFS curve produced by the fractional polynomial approach provides a better fit to the Kaplan-Meier data from the BOLERO-2 trial than the ERG's approach, which appears to underestimate the PFS for everolimus plus exemestane.

ERG comment	See ERG response to issue 2b regarding DIC. The ERG considers that the FP PFS models with the lowest DIC statistic [redacted] (ERG report, p44) and the ERG cannot select a suitable FP model with any degree of confidence to inform the comparison of the clinical effectiveness of treatment with PAL+FUL versus E+E (ERG report, p45). The main reason for performing an NMA is to avoid breaking randomisation by modelling the relationships between arms of trials in a network and adjusting outcomes accordingly to maintain relative treatment effects. The ERG considers that comparing E+E BOLERO-2 PFS K-M data with company and ERG estimates is, therefore, meaningless.

Issue 4: Impact of company and ERG approaches on overall survival outputs	
What is the preferred approach to modelling overall survival? Does the ERG's approach reduce uncertainty and produce more clinically plausible overall survival estimates than the company's approach using results from the fractional polynomial NMA?	Pooling the survival data from the trial and assuming equivalence based on the lack of overall survival statistically significance is not appropriate. The PALOMA-3 trial was not powered to detect an effect in overall survival, and although the OS results were updated in the April 2018 data-cut, the data is relatively immature with only 58% of events reported in the palbociclib plus fulvestrant arm with median follow-up of 44.8 months. The uncertainty is captured in the model via probabilistic sensitivity analysis. The company has used fractionally polynomial analysis as proportional hazards assumption does not hold, as recommended by Janssen (5). The models have been evaluated via DIC criteria and have been clinically validated. The fractional polynomial models offer the best approach given the current evidence-base. Figure 2 shows the Kaplan-Meier OS plot for everolimus plus exemestane from the BOLERO-2 trial alongside the survival curves produced by the company's fractional polynomial analysis and the ERG's approach. **Figure 2: Everolimus plus exemestane overall survival**

	 Visual inspection of Figure 2 shows that the ERG's approach over estimates overall survival for everolimus + exemestane while the company's fractional polynomial appears to provide a closer fit to the Kaplan-Meier data from the BOLERO-2 trial.

ERG comment	The ERG maintains its position on using DIC to choose the most appropriate FP model as described in issue 2b. 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 (ERG report, p45) and 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 PAL+FUL versus E+E (ERG report, p46). The ERG refers to its response to issue 3 with regards to the comparison of FP NMA survival estimates with those from the BOLERO-2 trial. The ERG considers that comparing E+E BOLERO-2 OS K-M data with company and ERG estimates is, therefore, meaningless.

Issue 5a: Time-to-treatment discontinuation modelling	
How likely is it in practice for patients to be progression free and yet not continue treatment with palbociclib plus fulvestrant?	It is not unusual for time-on-treatment to be less than PFS as patients can discontinue treatment for a multitude of reasons; adverse event, treatment breaks, and scans are not always in line with the last treatment script. Patients can also continue to derive benefit from treatment whilst off therapy as PFS in a clinical setting is based upon RECIST criteria. In clinical practice, patients could have stopped a treatment for alternative reasons and can have 'stable' disease on a scan and continue to derive benefit from a drug.
ERG comment	The ERG agrees with the company that it is not unusual for time-to-treatment discontinuation (TTD) to be less than PFS when treatment is not allowed beyond disease progression.

<table>
<tr><th colspan="2">Issue 5b: Time-to-treatment discontinuation modelling</th></tr>
<tr><td>Does the ERG's approach of estimating time to treatment discontinuation using Kaplan-Meier 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 produce clinically plausible results?</td><td>Table 3 presents the mean and median time to discontinuation produced by the company's and ERG's modelling approaches. The company approach provides a longer average than the ERG modelling approach.
The median PFS for everolimus plus exemestane reported in the BOLERO-2 trial is 7.8 months, while the median duration of exposure to treatment was reported as 23.9 weeks (5.98 months) (6). In the SMC advice for everolimus plus exemestane it is reported that the final PFS analysis was conducted at a median follow up of 18 months when the median everolimus treatment duration was 30 weeks (~7.5 months) compared with 14 weeks for placebo (7). Comparing the ERG estimates to the reported medians indicates that the ERG approach underestimates TTD for everolimus plus exemestane.

Table 3: Everolimus plus exemestane time to discontinuation
<table>
<tr><th>Time to discontinuation</th><th>ERG approach</th><th>Company CEM</th></tr>
<tr><td>Mean TTD (months)</td><td>8.93</td><td>[redacted]</td></tr>
<tr><td>Median TTD (months)</td><td>4.60</td><td>[redacted]</td></tr>
</table></td></tr>
<tr><td>ERG comment</td><td>The ERG reiterates (ERG report, pp72-74) that the company approach to adjusting TTD data from the PAL+FUL of the PALOMA-3 trial appears arbitrary. The ERG considers that using two different approaches to model the same effect is inconsistent (FUL+PAL: use of trial TTD data to model TTD, E+E: use of PFS data to model TTD). The ERG's approach to estimating TTD for E+E is consistent with its general approach to estimating clinical outcomes for E+E using the data and outcomes for FUL from the PALOMA-3 trial. For FUL, TTD in the PALOMA-3 trial is very similar to PFS and, given that FUL should</td></tr>
</table>

	not be given beyond progression, represents the maximum incremental relationship between TTD and PFS for that treatment. The exact overall impact on the ICER per QALY gained of any changes to assumptions regarding PFS and its relationship to TTD for E+E cannot be predicted as it will depend on the magnitude of change and the cost of the drugs.

Issue 5c: Time-to-treatment discontinuation modelling	
What is the preferred approach to modelling time to treatment discontinuation? Does the ERG's approach reduce uncertainty and produce a more clinically plausible time to treatment discontinuation estimates than the company's approach using a ratio of TTD to PFS from PALOMA-3?	Comparing the medians produced by the ERG and company approaches to the reported medians suggests that the company's estimate ([redacted]) provides a more plausible estimate than the ERG's estimate (4.60) which appears to underestimate treatment duration.
ERG comment	The ERG used the results from the FUL arm of the PALOMA-3 trial to estimate TTD for patients treated with E+E.

Issue 6a: Subsequent therapy assumptions	
Is the mean duration that patients in the advanced setting receive subsequent therapies in clinical practice nearer [redacted] as stated by the company or [redacted] suggested by the ERG?	In the third line setting, patients in the UK are likely to receive everolimus plus exemestane, chemotherapy or tamoxifen. There is no data on the use of everolimus plus exemestane in the post CDK 4/6 inhibitor setting. The median PFS for everolimus plus exemestane reported in the BOLERO-2 trial is 7.8 months (6), however clinical advice suggests that it will be significantly lower in the third-line setting. Patients receiving chemotherapy are likely to receive capecitabine, which has a mean PFS of between 3.5 and 4.7 months (8), or paclitaxel, which is most commonly administered weekly for a total of 12 weeks (alternative 3 weekly is available and most of the studies have been carried out with this does, however in clinical practice due to toxicity profile the weekly regimen is significantly more commonly used) with a PFS of around 4-6 months (9,10). There is a lack of data for tamoxifen in the 3rd line setting, however tamoxifen is associated with a PFS of 6 months in the 1st-line setting (11). Clinical advice suggests that the PFS will be significantly lower in the 3rd-line setting. A targeted literature review identified a cost study which examined the medical records of 41 physicians in the UK (12). In this study the mean number of cycles ranged from 5.8 to 11.1, dependent on line and treatment covering first to third line aBC treatment; no evidence on fourth line was available. For consistency, the duration of time spent in subsequent lines was assumed as 6 cycles per line for all treatment arms considered in the economic evaluation. A range of 5 to 7 cycles was used in sensitivity analyses. The rates of progression from subsequent treatment lines were assumed the same across the two treatment arms. It is the company's opinion that [redacted] is a more accurate estimate of the mean duration of subsequent therapies and that the assumption by the ERG of a PFS of [redacted] is an over estimation.
ERG comment	The ERG considers that, in the company base case, the mean time spent receiving subsequent therapies is an underestimate (ERG report, pp75-77). Clinical advice to the ERG is that, in practice, patients will receive many lines of subsequent therapy. In the company model, patients spent approximately [redacted]

	receiving subsequent treatments. However, published evidence from the PALOMA-3 trial shows that the median time patients spent receiving their first subsequent treatment alone was 4.9 months. Therefore, if patients receive more than one line of subsequent therapy (as is assumed in the company model), mean time spent on subsequent therapy should be greater than [redacted]. The ERG also considers that based on clinical advice, mean time spent in the BSC health state ([redacted]) is an overestimate.

Issue 6b: Subsequent therapy assumptions	
Is the company's assumption that 75% of patients in clinical practice would proceed to receive best supportive care when the maximum duration of first line subsequent therapy has been reached rather than receive a second line of subsequent therapy, or is the ERG's assumption of 100% more plausible?	After each post-progression line, it was assumed in the base-case that 25% of patients would not switch to a subsequent line but would instead receive BSC until death. This was based on consulted clinical expert opinion and reflects the fact that not all surviving patients continue active treatment (either by choice or being not fit for treatment) (13). It is not clinically plausible for 100% of patients to progress to a 2nd subsequent therapy as there is always a drop off due to a plethora of reasons; drop in performance status, no response, progression of disease, declining further therapy to name a few. In clinical practice there will be a percentage of patients either in visceral crisis, those in whom performance drops during treatment and would not be eligible for further treatment, and those who decline further treatment. These patients instead progress to BSC.
ERG comment	As stated in the ERG report (pp75-77), clinical advice to the ERG is that in practice patients will receive many lines of subsequent therapy and an estimate of 25% of patients unable to proceed at each subsequent therapy line is too high. As the structure of the model limited the ERG's ability to extend the maximum duration of subsequent therapy (beyond 7 months), the approach taken by the ERG was the only way to further influence of the duration of subsequent therapy on the ICER per QALY gained could be explored.

Issue 7: Resource use: number of appointments with a consultant oncologist	
How frequently are people with advanced hormone-receptor positive, HER2-negative breast cancer likely to have appointments with a consultant oncologist?	Endocrine treatments are typically prescribed every 3 months alongside a scan and a meeting with the consultant oncologist. Patients that progress and go on to receive chemotherapy or everolimus plus exemestane will have a consultant oncologist appointment prior to each monthly cycle of treatment. In the end of life stage, patients are transferred to the care of the palliative care team and would not be seen regularly by the oncologist as end of life planning would be taking place. The majority of these patients will be given open OPDs for any emergencies raised by the community palliative care teams. The company have used an estimate of one consultant oncologist appointment once every 2 months which represents an average across subsequent treatments and is supported by CNS interviews conducted.
ERG comment	Clinical advice to the ERG is that these assumptions do not reflect current NHS clinical practice and that patients have appointments with a consultant oncologist once per month, irrespective of health state (ERG report, p77).

Issue 8a: End of life	
What is the current life expectancy of the relevant patient population?	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). In the BOLERO-2 trial, the median OS for patients who received everolimus plus exemestane was 31.0 months (95% CI: 28.0 to 34.6 months). The gain in median OS in the PALOMA-3 trial for palbociclib plus fulvestrant versus placebo plus fulvestrant was 6.9 months. Improving survival by 7 months is a result of palbociclib's innovation, compared to the trial comparator that only reached 28 months median OS, is a large relative gain; an increase of 25% (+1/4). The gain in median OS in the "Chemotherapy naïve" sub-group in the PALOMA-3 trial for palbociclib plus fulvestrant versus placebo plus fulvestrant was [redacted].
ERG comment	The ERG agrees with the company's estimates of life expectancy. As stated (ERG report, p81), based on the evidence provided by the company, the ERG does not consider the short life expectancy criterion has been met.

Issue 8b: End of life	
How robust are the current estimates of survival benefit?	There have been 3 data cuts of the PALOMA-3 trial, with associated Clinical Study Reports from 5th December 2014 (15), 23rd October 2015 (16), and 13th April 2018 (17). There was also an exploratory analysis from the 16th March 2015 which was published in Cristofanilli 2016 (18). However, PFS results were not updated in the April 2018 data-cut and is therefore relatively immature with only 58% of events reported in the palbociclib plus fulvestrant arm with median follow-up only 15.8 months. Overall survival results were updated in the April 2018 data-cut but only 58% of events were reported in the palbociclib plus fulvestrant arm with median follow-up of 44.8 months. The final data-cut of the PALOMA-3 trial is expected in [redacted] which will provide mature PFS and OS results.
ERG comment	The ERG does not consider that the company has provided any robust evidence of an OS benefit for PAL+FUL versus E+E. The ERG notes (CS [original submission], p49) that "A total of 310 deaths had occurred on the data cut of 13 April 2018, permitting the planned final analysis of OS". The ERG highlights that the company did not state their expectation of a further, final, data-cut in [redacted] in their original submission.

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15. Pfizer. Clinical study report on trial A5481023: Multicenter, Randomized, Double-Blind, Placebo Controlled, Phase 3 Trial Of Fulvestrant (Faslodex®) With Or Without PD-0332991 (Palbociclib) ± Goserelin In Women With Hormone Receptor-Positive, HER2-Negative Metastatic Breast Cancer Whose Disease Progressed After Prior Endocrine Therapy. Data on file. 2015.

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LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

ERG ADDENDUM POST-TECHNICAL ENGAGEMENT

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

ERG STA report addendum post-technical engagement including Patient Access Scheme discount for palbociclib

This report was commissioned by the NIHR HTA Programme as project number 15/194/11

CONTAINS COMMERCIAL IN CONFIDENCE DATA

Completed 3rd October 2019

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 INTRODUCTION

As part of the company's Technical Engagement Response, the company provided three new scenarios:

1. Overall survival (OS) – fractional polynomial (FP) analysis
2. Subsequent treatment costs
3. Chemotherapy-naïve patients.

The ERG has been able to replicate the company's cost effectiveness results for scenario 1 and scenario 2 using the economic model submitted by the company during the technical engagement stage. However, the model provided by the company during the technical engagement stage did not include data to allow the ERG to replicate or update the company cost effectiveness results for scenario 3.

The ERG was notified by NICE during the pre-meeting briefing that the company had revised its base case to include the OS estimates generated by its FP analysis. This document provides a critique of company scenarios 1 (revised base case) and 2. The ERG has also generated cost effectiveness results as requested by NICE. The ICERs per QALY gained in this addendum include the PAS price for palbociclib and the list price for everolimus. The instructions to replicate the ERG's amendments and the company's scenario 2 are provided in Section 4Appendix: ERG revisions to company's revised base case model. The ICERs per QALY gained including the PAS price for everolimus are provided in a separate confidential appendix.

2 ERG CRITIQUE OF COMPANY SCENARIOS

2.1 Overall survival fractional polynomial analysis (scenario 1, new base case)

Technical Engagement Response Form: Issue 4

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. The ERG's position on the company OS FP NMA is described in more detail in its original report (ERG report, p46).

2.2 Subsequent treatment costs (scenario 2)

Technical Engagement Response Form: scenario not included on the form

In the original company base case, subsequent therapy options **differ** between patients treated with palbociclib plus fulvestrant (PAL+FUL) and everolimus plus exemestane (E+E). This is because a proportion of patients who received PAL+FUL are assumed, in the company model, to be able to receive E+E as a later line of treatment.

In the company's scenario 2, patients treated with PAL+FUL are assumed to receive the **same** subsequent therapies as patients treated with E+E, i.e., the proportion of patients who were treated with E+E or exemestane monotherapy as later lines of treatment is now excluded from the model.

Clinical advice to the ERG is that some patients who receive PAL+FUL will receive E+E as a subsequent therapy in clinical practice. Published results from the PALOMA-3 trial[1] also show that patients in the PAL+FUL and in the placebo plus fulvestrant (PLA+FUL) arms of the PALOMA-3 trial received everolimus as a later line of treatment. The ERG therefore considers that assuming subsequent therapy is the same for PAL+FUL and E+E does not reflect clinical practice.

2.3 Chemotherapy-naïve patients (scenario 3)

Technical Engagement Response Form: issue 1b

The company did not provide an economic model for their chemotherapy-naïve patient scenario. Therefore, the ERG cannot verify the company's cost effectiveness results for this scenario.

[1] Turner N, Slamon D, Ro J, Bondarenko I, IM SA, Masuda N*, et al.* Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer. New Eng J Med. 2018; 379:1926-36.

3 COST EFFECTIVENESS RESULTS: REVISED BASE CASE

The ERG has applied its amendments to the revised company base case. These results (generated using the PAS price for palbociclib and the list price for all other drugs) are displayed in Table 1.

The ERG has also explored the effect of applying scenario 2 to the revised company base case (scenario 1). These results (generated using the PAS price for palbociclib and the list price for all other drugs) are displayed in Table 2.

Table 1 ERG adjustments applied to the revised 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 revised base case*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£8,176**
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]	£19,272
R3) Estimating TTD from the PALOMA-3 trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,832
R4) Amend subsequent therapy assumptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£9,831
R5) Remove daily oral drug wastage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,335
R6) Include monthly oncologist consultation in every health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£9,222
ERG preferred modelling of effectiveness R1) +R2) +R3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominates**
Company preferred modelling of effectiveness + ERG amendments R4) + R5) + R6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£13,867**
ERG preferred modelling of effectiveness + ERG amendments R1) to R6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominates**

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; OS=overall survival; PFS=progression-free survival; QALY=quality adjusted life year; TTD=time to treatment discontinuation
*The post-technical engagement revised company base case includes estimates generated by a fractional polynomial model for OS

Table 2 Company scenario 2 applied to the revised 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 revised base case*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£8,176**
Company Scenario 2- same subsequent therapies in both arms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,291

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; OS=overall survival; PFS=progression-free survival; QALY=quality adjusted life year; TTD=time to treatment discontinuation
*The post-technical engagement revised company base case includes estimates generated by a fractional polynomial model for OS

4 APPENDIX: ERG REVISIONS TO COMPANY'S REVISED BASE CASE 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
Company scenario 2	Mod_G	0	Subsequent therapies the same in both arms

Instructions for modifying the company model produced at technical engagement with revised base case (including OS FP)

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))

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
			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))
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!$C$13,MIN(F12,M12),MIN(F12,M12),F12,MIN(F12,M12)),(EnginePAL_FLV!E11^(1/TTDAdjPAL))))
		EngineEVE_EXE	AP11	Amend drug costs to use TTD (1st cycle) =IF(mod_C=1,ERG_TTD!E4*AP9,E11*AP9)
			AP12 copy down to AP531	Amend drug costs to use TTD (subsequent cycles) =IF(mod_C=1,ERG_TTD!E5*$AP$10,E12*$AP$10)
			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$9)
			AT11	Amend AEs to use TTD =IF(mod_C=1,ERG_TTD!E4*$AT$9,E11*$AT$9)
R4) Amend subsequent	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))

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
therapy assumptions			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))
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))
Company scenario 2 - Subsequent	Mod_G	Cost_PPS_subs_therapy	C9	Change % receiving capecitabine after PAL+FUL to match % after E+E =IF(Mod_G=1,D9,25%)

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
therapies the same in both arms			C10	Change % receiving paclitaxel after PAL+FUL to match % after E+E =IF(Mod_G=1,D10,25%)
			C11	Change % receiving everolimus + exemestane after PAL+FUL to match % after E+E =IF(Mod_G=1,D11,15%)
			C12	Change % receiving fulvestrant after PAL+FUL to match % after E+E =IF(Mod_G=1,D12,0%)
			C13	Change % receiving tamoxifen after PAL+FUL to match % after E+E =IF(Mod_G=1,D13,25%)
			C14	Change % receiving exemestane after PAL+FUL to match % after E+E =IF(Mod_G=1,D14,5%)
			C15	Change % receiving vinorelbine after PAL+FUL to match % after E+E =IF(Mod_G=1,D15,5%)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft technical report

Palbociclib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer

This document is the technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

Issue date: October 2019

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

1. Summary of the draft technical report

After technical engagement the technical team has collated the comments received and, if relevant, updated the judgement made by the technical team and rationale. Judgements that have been updated after engagement are highlighted in bold below.

1.1 In summary, the technical team considered the following:

Issue 1 **FOR DISCUSSION: generalisability of the endocrine resistant population identified by the company to clinical practice in the NHS**. The "endocrine resistant" population from PALOMA-3 that the company is focusing on includes around [redacted] of people that had been treated with chemotherapy in the advanced setting prior to starting treatment with palbociclib with fulvestrant. If the aim of palbociclib with fulvestrant is primarily to delay the need for chemotherapy, it is important to know the extent to which the results of the trial are applicable to people with endocrine resistant disease who are likely to receive palbociclib with fulvestrant in clinical practice. The company noted that although currently 40-50% of people in clinical practice receive chemotherapy 1st line, this sub-group is likely to diminish over the next 2-3 years as the use of CDK 4/6 inhibitors is established as first line standard of care. However, the chemotherapy-naïve subgroup analysis provided by the company after technical engagement includes people who have never received chemotherapy

in the adjuvant or neoadjuvant and/or metastatic setting from PALOMA-3. As the subgroup who are chemotherapy naïve in the metastatic setting is potentially the population of interest, for the purpose of decision-making at this point it is unclear whether the overall ITT population or chemotherapy naïve subpopulation should be used in the analyses.

Issue 2 **FOR DISCUSSION: Different approaches to estimating the relative clinical effectiveness of treatment with palbociclib plus fulvestrant versus everolimus plus exemestane (NMA versus proxy measure).** In the absence of direct clinical evidence comparing palbociclib and fulvestrant with everolimus with exemestane, the company presented network meta-analyses (NMAs) to indirectly compare progression free survival (PFS) and overall survival (OS). As the proportional hazards (PH) assumption is violated for at least one trial when considering the PFS NMA, the company presented results using a fractional polynomial (FP) modelling approach which does not assume PH for PFS. After technical engagement, the company presented a FP analysis for OS accepting that PH did not hold for OS as well. The ERG explored FP models for both PFS and OS NMAs and concluded that as there is potentially a large amount of uncertainty around the estimated survival and HR functions generated by 1st and 2nd order FP models, the ERG is unable to 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. Instead of using results from NMAs, the ERG opted to use PFS data from the placebo plus fulvestrant arm of PALOMA-3 as a proxy for people treated with everolimus plus exemestane. The basis of this assumption is clinical advice received by the ERG that treatment with everolimus plus exemestane is generally considered to be more effective than treatment with

fulvestrant. In terms of OS, clinical advice suggested that treatment with everolimus plus exemestane is generally considered to be more effective than treatment with fulvestrant and results from PALOMA-3 show that there is no statistically significant difference between the 2 arms. The ERG therefore pooled the data from both arms of PALOMA-3 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. Both approaches, that is the company's approach using FP NMAs and the ERGs approach using PFS and OS data from the palbociclib plus fulvestrant arm of PALOMA-3 to generate lower bound estimates of the clinical effectiveness of everolimus plus exemestane as a proxy for everolimus with exemestane are unsatisfactory.

Issue 3 **FOR DISCUSSION. Impact of company and ERG approaches on progression free survival outputs**. The company base case progression free survival (PFS) estimates for both the intervention and comparator were calculated using the results of the company's fractional polynomial (FP) NMA. 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 ERG estimated the clinical effectiveness of palbociclib plus fulvestrant compared to everolimus plus exemestane using Kaplan- Meir PFS data from the placebo plus fulvestrant arm of PALOMA-3 as a proxy for people treated with everolimus plus exemestane. Using this approach, mean PFS for people treated with palbociclib plus fulvestrant was [redacted] months and [redacted] months for people treated with everolimus plus exemestane. The company's method of using results of the FP NMA uses the current evidence base whereas the ERG's method of using fulvestrant monotherapy as a proxy for everolimus plus exemestane does not use clinical effectiveness data for everolimus plus exemestane and does not attempt to

estimate the difference in progression-free survival between palbociclib plus fulvestrant and everolimus plus exemestane. Both approaches are uncertain.

Issue 4 **FOR DISCUSION. Impact of company and ERG approaches on overall survival outputs.** In the company's base case, OS estimates for treatment with palbociclib plus fulvestrant were calculated using a Weibull curve fitted to the OS data from PALOMA-3. OS estimates for treatment with everolimus plus exemestane were produced using the FP NMA for OS. 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 ERG used the alternative approach of using pooled data from both arms of PALOMA-3 up until 40 months. This pooled data set was then used as the basis for modelling OS for both people treated with palbociclib plus fulvestrant and everolimus plus exemestane. An exponential projection was then appended to the pooled OS K-M data. Using this approach, the mean OS for patients, irrespective of treatment, is [redacted] months. The clinical expert noted that the ERG approach did not produce clinically plausible results and that PALOMA-3 was not powered to detect differences in OS. Both approaches are uncertain.

Issue 5 **FOR DISCUSSION. Time to treatment discontinuation modelling.** In the company model, time to treatment discontinuation for treatment with palbociclib plus fulvestrant (TTD) was estimated using a ratio of TTD to PFS from PALOMA-3. This produces an estimate of the time that people receiving palbociclib plus fulvestrant spend on treatment and means that the number of people 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 assumes that TTD is equal to the PFS estimated using the results of the company's PFS FP NMA. The

difference in TTD in the company model is 3.8 months. The mean TTD in the company base case is [redacted] months for treatment with palbociclib plus fulvestrant (which is less than the PFS in the palbociclib arm), and [redacted] months with everolimus plus exemestane (which is equal to the PFS). The ERG noted that the company's approach of using TTD data for people treated with palbociclib plus fulvestrant and using PFS data to represent time on treatment for patients receiving everolimus plus exemestane is an unfair comparison and unreliable. The ERG has instead used TTD data from the palbociclib plus fulvestrant and placebo plus fulvestrant arms of PALOMA-3 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. The ERG's approach to modelling TTD produced a mean TTD of [redacted] months for palbociclib plus fulvestrant and [redacted] months for everolimus plus exemestane (difference= [redacted] months). The company's approach uses a ratio of TTD to PFS from PALOMA-3 for the palbociclib plus fulvestrant arm but assumes TTD is equal to PFS for the everolimus plus exemestane which is inconsistent. The ERG approach in contrast may reduce uncertainty and produce more clinically plausible time to treatment discontinuation estimates.

Issue 6 **FOR DISCUSSION. Subsequent therapy assumptions.** In the company base case, patients spend approximately [redacted] months in total receiving subsequent treatments, and [redacted] months in the best supportive care (BSC) health state. The ERG considers that the mean time spent receiving subsequent therapies is an

underestimate and that the mean time spent in BSC is an overestimate in the company's model. Furthermore, the company assumes that 25% of remaining patients proceed to BSC when the maximum duration of first line subsequent therapy has been reached rather than receive a second line of subsequent therapy. The ERG has amended the company model so that mean duration of subsequent therapies is [redacted] months and assumed 100% (rather than 75%) of patients proceed to the next line of therapy in the best supportive care health state. The clinical expert noted that patients will receive multiple subsequent therapies in routine clinical practice and that people will likely receive subsequent treatments for longer than both [redacted] and [redacted] months. A mean duration of [redacted] months for patients in the advanced setting to receive subsequent therapies in clinical practice seems appropriate for decision-making as this is the maximum duration allowed by the economic model. It is uncertain if the company assumption of 75% or the ERG assumption of 100% of patients proceeding to receive BSC when the maximum duration of 1st line subsequent therapy has been reached rather than receive a 2nd line of subsequent therapy is appropriate for decision- making.

Issue 7 **AGREED. Resource use: number of appointments with a consultant oncologist**. In the company model, it is assumed that patients have an appointment with a consultant oncologist every 6 months in the progression-free health state and patients have an appointment with a consultant oncologist every 2 months whilst receiving the first line of subsequent therapy. The ERG considers these estimates are underestimated and patients in the NHS have appointments with a consultant oncologist once per month, irrespective of health state. The clinical expert noted that patients see a consultant oncologist every 2-3 months once established on

palbociclib plus fulvestrant. **Including the cost for an oncologist appointment with a consultant every 2 months in the economic model is preferred for decision making**.

Issue 8 **AGREED. End of Life**: The company noted that a drug is assessed under an End of Life criteria if it meets the assumption that it would provide an additional 3 months in life expectancy on top of 24 months. The ERG noted that based on the evidence provided by the company, median OS for patients who received placebo plus fulvestrant was 28.0 months (95% CI: 23.6 to 34.6 months) in PALOMA-3. In the BOLERO-2 trial, median OS for patients who received everolimus plus exemestane was 31.0 months (95% CI: 28.0 to 34.6 months). In addition, the ERG noted that the company had not provided any robust evidence of an OS gain for palbociclib plus fulvestrant compared to everolimus plus exemestane. The gain in median OS in PALOMA-3 for palbociclib plus fulvestrant versus placebo plus fulvestrant was 6.9 months. However, this gain is not statistically significantly different. The ERG agrees with the company's estimates of life expectancy but notes that short life expectancy criterion for end of life has not been met. Furthermore, no robust evidence of an OS benefit for for palbociclib plus fulvestrant compared to everolimus plus exemestane have been provided. **NICE's End of Life criteria are not met because the estimates of the extension to life are not sufficiently robust and the overall survival in the comparator arm is greater than 2 years**.

1.2 The technical team recognised that the following minor issues remain in the economic model but have little effect on the ICER per QALY gained:

- The utility values used by the company to estimate health related quality of life in the post-progression health state is based on general population preferences of health states of people with metastatic breast cancer described by vignettes which is not in line with the NICE reference case.
- Adverse events in the company model are assumed to to occur only at the beginning of a treatment cycle in the economic model rather than occurring at any time.
- Adverse events for people treated with everolimus plus exemestane are underestimated in comparison to adverse events for people treated with palbociclib plus fulvestrant in the economic model.
- Resource use estimates to manage adverse events may be underestimated for treatment with palbociclib plus fulvestrant and overestimated for treatment with everolimus plus exemestane in the company model.

- Drug monitoring cost of a chest x-ray may be overestimated for treatment with everolimus plus exemestane in the economic model.

1.3 The cost-effectiveness results include a commercial arrangement (patient access scheme) for palbociclib. The ERG's cost-effectiveness results presented in this report include commercial arrangements prices for palbociclib and list prices for fulvestrant, everolimus plus exemestane.

1.4 As there is a comparator PAS for this appraisal (everolimus also has a PAS) the company's base case results, and results from the **ERG's** scenarios, generated using PAS prices for palbociclib and everolimus are provided in a confidential appendix and cannot be presented here.

2. Key issues for consideration

Issue 1 – Generalisability of the PALOMA-3 trial results to clinical practice in the NHS – FOR DISCUSSION

Background/description of issue	The **company** has focused its submission on a subpopulation of the licensed population that they consider to be an "endocrine resistant" population based on advice from clinical experts and to reflect NICE recommendations as well as the treatment pathway in the NHS. The **company** considers that treatment of hormone receptor (HR)-positive HER2-negative advanced breast cancer is not viewed by specific lines of therapy in NHS clinical practice, but rather by whether patients have already received, and become resistant to prior endocrine therapy, that is, whether they are 'endocrine resistant' or 'endocrine sensitive' (although there is no clinical consensus on the definitions of these terms). Palbociclib with fulvestrant is therefore presented as a treatment option for patients with 'endocrine resistant' disease only. There is no formal and standardised definition for endocrine therapy resistance. Recent trials such as PALOMA-3 and BOLERO-2 have defined an 'endocrine resistant' population as "people 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." The **ERG** notes that a high proportion of people had received chemotherapy for their primary diagnosis ([redacted]), either in the (neo)adjuvant setting only ([redacted]) or in the advanced setting ([redacted]) in PALOMA-3. 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%). The **ERG** notes that it is not uncommon for people with endocrine resistant disease to receive chemotherapy for their advanced disease in clinical practice in England and Wales. The **technical team** considers that the aim of treatment with palbociclib with fulvestrant is to avoid/delay chemotherapy, therefore palbociclib with fulvestrant would be used as a treatment option earlier in the treatment pathway before chemotherapy for advanced disease. Therefore, the trial population may potentially represent a population with more advanced disease than people who would receive palbociclib with fulvestrant in clinical practice.

Why this issue is important	The "endocrine resistant" population from PALOMA-3 that the **company** is focusing on includes around [redacted] people that had been treated with chemotherapy in the advanced setting prior to starting treatment with palbociclib with fulvestrant. It is important to know the extent to which the results of the trial are applicable to people who are likely to receive palbociclib with fulvestrant for advanced breast cancer in the NHS. The results may not be generalisable to the NHS if the trial includes people with more advanced disease than people who would receive palbociclib with fulvestrant in clinical practice.
Technical team preliminary judgement and rationale	The **technical team** considers that the "endocrine resistant" population presented by the company is appropriate for decision-making but is unclear the extent to which the trial population in PALOMA-3 is generalisable to clinical practice in the NHS.
Questions for engagement	a) The company has presented results for palbociclib with fulvestrant for people with 'endocrine resistant' disease only. Is this clinically relevant? b) Given that around [redacted] of the trial population included people previously treated with chemotherapy in the advanced setting, is the "endocrine resistant" population identified in PALOMA-3 representative of people in the NHS who would receive palbociclib with fulvestrant? Or would palbociclib with fulvestrant be used earlier in the treatment pathway in order to delay or avoid treatment with chemotherapy?
Summary of comments after technical engagement	**Comments from clinical expert:** • The endocrine resistant population is clinically relevant and includes people who relapse on adjuvant endocrine therapy, and people who progress on endocrine therapy alone in the advanced setting. • Substantial evidence now that CDK4/6 inhibitors improve OS. Therefore, use in the 1st line in the metastatic/advanced setting will increase. For people who relapse on endocrine therapy or who progress on 1st line endocrine therapy alone, fulvestrant and CDK4/6 inhibitor will be the standard of care for these patients. **Comments from comparator company:**

- Agree that the endocrine resistant population is a clinically relevant population since there is an unmet need for further therapies to delay disease progression and the need for chemotherapy in patients who develop resistance to endocrine therapy.

Comments from company:

- 40-50% of patients in clinical practice receive chemotherapy as 1st line treatment in the UK. PALOMA-3 results show clinical benefit for this population with palbociclib plus fulvestrant after chemotherapy. There is a current unmet need for patients previously treated with chemotherapy in the 1st line that cannot access treatment with a CDK4/6 inhibitor to delay further lines of chemotherapy. Trials for the other CDK 4/6 inhibitors (abemaciclib and ribociclib) did not include patients who had received prior chemotherapy, therefore NICE recommendations exclude this population.
- This sub-group is likely to diminish over the next 2-3 years as the number of people who receive chemotherapy 1st line reduces and use of CDK 4/6 inhibitors is established as first line standard of care. NHS population will consequently match more closely with the chemotherapy-naïve sub-group in PALOMA-3. Clinical results for the chemotherapy-naïve patients in PALOMA-3 show better outcomes for both PFS and OS compared to the ITT population (expected as chemotherapy drives mutational burdens in patients with cancer):

Table 1: PALOMA-3 progression-free survival

Progression-free survival - ITT population	**Palbo-fulv (N=347)**	**Placebo-fulv (N=174)**
Median, months	11.2	4.6
CI	9.5 - 12.9	3.5 - 5.6
Hazard ratio (CI)	0.50 (0.40 - 0.662); P<0.0001	
Progression-free survival - No previous chemotherapy	**Palbo-fulv ([redacted])**	**Placebo-fulv ([redacted])**
Median, months	[redacted]	[redacted]
CI	[redacted]	[redacted]
Hazard ratio (CI)	[redacted]	

Table 2: PALOMA-3 overall survival

Overall survival - ITT population	Palbo-fulv (N=347)	Placebo-fulv (N=174)
Median, months	34.9	28
CI	28.8 - 40.0	23.6 - 34.6
Stratified Hazard ratio (CI)	0.81 (0.64 - 1.03); P=0.09	
Overall survival - No previous chemotherapy	**Palbo-fulv ([redacted])**	**Placebo-fulv ([redacted])**
Median, months	[redacted]	[redacted]
CI	[redacted]	[redacted]
Hazard ratio (CI)	[redacted]	

Comments from ERG:

- Patient population in PALOMA-3 is representative of people who are currently likely to be treated with palbociclib plus fulvestrant in clinical practice in England and Wales.
- The chemotherapy-naïve population is not identified as a sub-group in the NICE final scope. This subgroup includes people who are chemotherapy-naïve in the (neo)adjuvant and in the advanced setting (accounting for 20% of the patients in PALOMA-3). [redacted] were chemotherapy-naïve in the advanced setting. Therefore, the subgroup considered in the company response may not be the appropriate subgroup if evidence is only sought for those not treated with chemotherapy in the advanced setting.

Technical team scientific judgement after engagement

The **technical team** considers that the "endocrine resistant" population presented by the **company** is appropriate for decision-making. It would seem that in the future the chemotherapy-naïve subpopulation from PALOMA-3 may be more applicable to clinical practice in the NHS. However, the chemotherapy-naïve subgroup analysis provided by the company after technical engagement includes people who have never received chemotherapy in the adjuvant or neoadjuvant and/or metastatic setting from PALOMA-3. As the subgroup who are chemotherapy naïve in the metastatic setting is potentially the population of

	interest, for the purpose of decision-making at this point it is unclear whether the overall ITT population or chemotherapy naïve subpopulation should be used in the analyses.

Issue 2 – Different approaches to estimating the relative clinical effectiveness of treatment with palbociclib plus fulvestrant versus everolimus plus exemestane (NMA versus proxy estimate)- FOR DISCUSSION

Background/description of issue	In the absence of direct clinical evidence comparing palbociclib and fulvestrant with everolimus with exemestane, the **company** presented network meta-analyses (NMAs) (section B.2.8 and **company's** response to clarification questions) to indirectly estimate PFS and OS. In addition to PALOMA-3 (comparing palbociclib and fulvestrant with placebo and fulvestrant), the **company** identified four relevant trials for inclusion in the NMAs (BOLERO-2, CONFIRM, EFECT and SoFEA). The **company** included RCTs with Kaplan Meier (K-M) data for PFS or time to disease progression (TTP) in the PFS network (assuming equivalence of the two measures) and RCTs with hazard ratio (HR) data available for OS in the OS network. After the clarification process, the NMAs for both PFS and OS included data from all five identified trials. **Proportional Hazards assumption** After visual inspection of log-cumulative hazard plots, the **company** noted that the proportional hazards (PH) assumption for PFS did not hold in PALOMA-3. The assumption was not tested in the other 4 trials due to this violation and the **company** presented an NMA using fractional polynomials (FPs) for PFS which does not rely on the PH assumption. In contrast, the PH assumption was judged to hold for all 5 trials included in the OS NMA based on visual inspection of a log-cumulative hazard plots and the **company** presented a traditional Bayesian NMA approach for OS under the assumption of PH. The **ERG** highlighted that determining the validity of the PH assumption through visual inspection of log-cumulative hazard plots is an inadequate approach on its own as it is subjective. Instead, a statistical test to test this assumption for all 5 trials was requested at clarification by the **ERG** and an NMA using fractional polynomial (FPs) be performed for OS if evidence of violation of the PH assumption was found for any of the 5 trials.

	Plots and Schoenfeld residuals for PFS show that PH seems to be violated for at least one trial (the [redacted]). The company therefore presented results using a fractional polynomial (FP) modelling approach which does not assume PH for PFS. Considering both the log-cumulative hazard plots as well as the plots and a statistical test of Schoenfeld residuals for BOLERO-2 trial and EFECT, the **ERG** judges that the PH assumption has been violated for OS in these trials. The company considered that the PH assumption held for OS although presented FP models at the request for the **ERG** at the clarification stage. The ERG did not think it was 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 timeframe. PH holding in soFEA for also questionable. Therefore, as PH assumption is violated for both PFS and OS, the **ERG** considers that only the NMA results generated from a FP modelling approach to estimate comparative PFS and OS effectiveness are valid. The **ERG** is of the view that the HR produced by the **company's** standard Bayesian NMA for OS is unreliable and cannot be used to provide clinically meaningful results. The **ERG** notes that although the statistical approach taken by the **company** for estimating PFS in the absence of PH is reasonable, 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 goodness-of-fit according to Deviance Information Criterion (DIC). When considering the **company's** three 'best fitting' 2nd order FP models for the PFS FP NMA, the **ERG** considers that the **company's** models [redacted] Although 1st order FP models generated [redacted], the **ERG** concluded that treatment with palbociclib plus fulvestrant may lead to better PFS results than treatment with everolimus plus exemestane. However, the statistical significance and the magnitude of this observed advantage cannot be tested. Please see section 9.2.1 of the ERG report for the graphical results using fixed effects of the PFS FP models considered by the company (figures 10-17, pages 89-93) Similarly, when considering the OS FP models for the OS NMA, the **ERG** noted that some of the FP models suggest [redacted]

	[redacted] Please see section 9.2.2 of the ERG report for the graphical results using fixed effects of the OS FP models considered by the company (figures 18-17, pages 93-96) Overall the **ERG** concluded that there is potentially a large amount of uncertainty around the estimated survival and HR functions generated by 1st and 2nd order FP models for both the PFS and OS NMAs and that all results have been presented using fixed effects. If FP models fitted with random-effects to the NMA had also been presented by the **company**, the uncertainty around survival and HR functions would be even larger. Hence, the **ERG** could not 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. It concluded that the evidence generated by the **company's** FP NMA does not demonstrate that, in terms of OS, treatment with palbociclib plus fulvestrant delivers better results than treatment with everolimus plus exemestane. **ERG approach of using fulvestrant monotherapy as a proxy for treatment with everolimus plus exemestane instead of generating results using NMAs** Due to the ERG being unable to select a suitable FP model with confidence, the **ERG** has opted to use PFS data from the placebo plus fulvestrant arm of PALOMA-3 as a proxy for people treated with everolimus plus exemestane. The **ERG** notes that this is a conservative approach but notes that clinical advice to the ERG is that treatment with everolimus plus exemestane is generally considered to be more effective than treatment with fulvestrant (please see issue 3 for more information). In terms of OS, clinical advice to the ERG suggests that treatment with everolimus plus exemestane is generally considered to be more effective than treatment with fulvestrant and results from PALOMA-3 show that there is no statistically significant difference between the 2 arms. The **ERG** therefore pooled the data from both arms of PALOMA-3 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. The **technical team** would welcome feedback on whether fulvestrant monotherapy is an appropriate proxy for treatment with everolimus plus exemestane.

Why this issue is important	Given the lack of direct evidence, it is important to assess the reliability of the key clinical-effectiveness inputs. The network meta-analyses results are uncertain and could significantly overestimate or underestimate the cost-effectiveness results. The ERG has presented an alternative approach to using results generated from uncertain NMAs and have used fulvestrant monotherapy as a proxy for treatment with everolimus plus exemestane. It is unclear if the ERG's approach is more appropriate and clinically plausible.
Technical team preliminary judgement and rationale	The **technical team** consider that it is unclear which of the 2 approaches i.e. the company's approach using NMAs or the ERGs approach using fulvestrant monotherapy as a proxy for everolimus with exemestane is appropriate.
Questions for engagement	a) Is the ERG's alternative approach of using fulvestrant monotherapy as a proxy for treatment with everolimus plus exemestane clinically plausible? b) The company considers that the proportional hazards assumption is not violated for overall survival (OS) and present NMA results using a standard Bayesian method. The ERG considers that proportional hazards do not hold for both progression free survival (PFS) and OS and that only results using a fractional polynomial approach are clinically relevant. Both the standard Bayesian and Fractional Polynomial approach for NMAs produce results that are highly uncertain. ○ The ERG was unable to select a suitable fractional polynomial model for either PFS or OS. In the absence of a suitable FP model for OS, is it appropriate to use the standard Bayesian NMA for OS, and the FP NMA for PFS (company approach) for estimating survival for the comparison of palbociclib and fulvestrant with everolimus with exemestane or is the ERG's approach more appropriate?
Summary of comments after technical engagement	**Comments from clinical expert:** • Likely that exemestane and everolimus has slightly longer PFS than fulvestrant monotherapy from cross-study comparisons. • Fulvestrant monotherapy is likely more effective than exemestane monotherapy (cross study comparison of CONFIRM study with EFECT/SOFEA studies). However, improvement in PFS by everolimus plus exemestane compared to exemestane monotherapy, is likely larger than the improvement of fulvestrant monotherapy compared to exemestane.

	Comments from company: • Efficacy of everolimus and exemestane with fulvestrant has never been assessed in head to head studies. Only 1 study comparing everolimus with exemestane plus fulvestrant with fulvestrant alone showed superiority of the combination treatment. Without head to head data, PFS and OS outputs are uncertain. • Everolimus and fulvestrant are different drugs, with different side effect profiles. Assumption that outcomes for everolimus with exemestane and fulvestrant would be the same have no basis on clinical assumptions of the way the drugs are used. An ITC using clinical data for everolimus with exemestane from BOLERO-2 to estimate the relative clinical effectiveness of palbociclib plus fulvestrant with everolimus plus exemestane is therefore important. • After technical engagement, the company accepts the ERG's view that the PH assumption is violated for OS and provided a FP analysis to replace their original analysis based on a Bayesian NMA. Results for OS using FP models are presented below: **Figure 3: Fractional polynomial OS curves** 

	Comments from ERG: • Company has misinterpreted ERG approach to modelling: PFS and OS data from the palbociclib plus fulvestrant arm of PALOMA-3 was used to generate lower bound estimates of the clinical effectiveness of everolimus plus exemestane. ERG assumes clinical effectiveness of everolimus plus exemestane is no worse than the clinical effectiveness of fulvestrant which is not the same as assuming clinical equivalency for everolimus plus exemestane and fulvestrant. • No robust evidence to support the company's claim that everolimus plus exemestane is clinically superior to fulvestrant in terms of PFS and OS. ERG acknowledges that everolimus plus exemestane is generally considered to be more effective than treatment with fulvestrant by clinicians, but underlines that no trial or real-world evidence has been presented to support this opinion.
Technical team scientific judgement after engagement	Both approaches, the company's approach using FP NMAs and the ERGs approach using PFS and OS data from the palbociclib plus fulvestrant arm of PALOMA-3 to generate lower bound estimates of the clinical effectiveness of everolimus plus exemestane as a proxy for everolimus with exemestane are unsatisfactory.

Issue 3 – Impact of company and ERG approaches on progression free survival outputs – FOR DISCUSSION

Background/description of issue	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. Some estimates of treatment effectiveness included in the economic model have been produced using results from the **company's** NMAs which the **ERG** considers are unreliable and clinically implausible (see issue 2). The **ERG** noted the **company's** assertion during the clarification stage that PFS is higher for everolimus plus exemestane than fulvestrant montherapy based on the results of a published NMA (Bachelot et al. 2014). However, as the PH assumption in [redacted] was shown not to hold, the **ERG** considers that the

	results of this NMA cannot be used to demonstrate that treatment with palbociclib plus fulvestrant delivers superior PFS results compared with everolimus plus exemestane (see issue 2). Clinical expert advice to the **ERG** suggests that everolimus plus exemestane is generally considered to be more effective than treatment with fulvestrant monotherapy. The **ERG** therefore used PFS data from the placebo plus fulvestrant arm of PALOMA-3 as a proxy for people treated with everolimus plus exemestane but acknowledged that this was a conservative approach. The approach implies that PFS associated with treatment with everolimus plus exemestane is [redacted] than treatment with placebo plus fulvestrant. As the relationship of fulvestrant to palbociclib plus fulvestrant was statistically significantly different in PALOMA-3, the ERG modelled the two arms separately. The assumption that everolimus plus exemestane is no worse than palbociclib plus fulvestrant was then applied to the statistically significantly different relationship of fulvestrant to palbociclib plus fulvestrant. Company base case PFS estimates for both the intervention and comparator were calculated using the results of the company's FP NMA. 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). Amending the **company** base case model, the **ERG** modelled PFS for people treated with palbociclib plus fulvestrant using PFS K-M data from the 4th data cut of the PALOMA-3 trial directly until [redacted] months and then appended an exponential tail. For people treated with everolimus plus exemestane, it used the PALOMA-3 trial placebo plus fulvestrant data for [redacted] 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 [redacted] months for the palbociclib plus fulvestrant arm and from [redacted] months for the placebo plus fulvestrant arm. The **ERG's** revised estimates of PFS alongside the **company** base case estimates are shown graphically below:

	
Why this issue is important	[redacted]
Technical team preliminary judgement and rationale	The **technical team** is unclear which approach to model PFS (i.e. the company's method of using results of the FP NMA or the ERG's method of using fulvestrant monotherapy as a proxy for everolimus plus exemestane) produces clinically plausible results.
Questions for engagement	a) What is the preferred approach to modelling progression free survival? Does the **ERG's** approach produce more clinically plausible progression free survival estimates than the **company's** approach using results from the fractional polynomial NMA?

Summary of comments after technical engagement	**Comments from clinical expert:** • ERG approach appears to generate more clinically plausible assumptions of PFS. **Comments from company:** • ERG approach using fulvestrant PFS data from the PALOMA-3 trial, does not use any of the clinical effectiveness data for everolimus plus exemestane and does not attempt to estimate the difference in progression-free survival between palbociclib plus fulvestrant and everolimus plus exemestane. • Company FP models offer best approach given current evidence base. Kaplan-Meier PFS plot for everolimus plus exemestane from BOLERO-2 alongside survival curves produced by company's FP analysis and the ERG's approach show that the ERG's approach underestimates the PFS for everolimus plus exemestane and that the FP approach is a better fit. **Figure 2: Everolimus plus exemestane PFS** 

	Comments from ERG: • Main reason for performing an NMA is to avoid breaking randomisation by modelling the relationships between arms of trials and adjusting outcomes accordingly to maintain relative treatment effects. Comparing everolimus with exemestane BOLERO-2 PFS K-M data with company and ERG estimates is meaningless.
Technical team scientific judgement after engagement	Both approaches, the company's approach using FP NMAs and the ERGs approach using fulvestrant monotherapy as a proxy for everolimus with exemestane are unsatisfactory.

Issue 4 – Impact of company and ERG approaches on overall survival outputs – FOR DISCUSSION

Background/description of issue	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 expert advice to the **ERG** is that treatment with everolimus plus exemestane is generally considered to be more effective than treatment with fulvestrant. 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. In the **company's** base case, OS estimates for treatment with palbociclib plus fulvestrant were calculated using a Weibull curve fitted to the OS data from PALOMA-3. OS estimates for treatment with everolimus plus exemestane were produced by applying the HR (HR=[redacted]; 95% CI [redacted] to [redacted]) generated by the **company's** Bayesian NMA 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) As the PH assumption did not hold in at least one trial in the OS NMA, the **ERG** considers that the HR produced by this NMA is unreliable. The **ERG** was also unable to choose a single set of results from the range of OS FP NMA results presented by the **company** at clarification due to the uncertainty associated with them. It therefore pooled data from both arms of the PALOMA-3 trial (5th data cut) up until 40 months and used this pooled data set as the basis for modelling OS for both people treated with palbociclib plus fulvestrant and everolimus plus exemestane. Considering the cumulative hazard plot for pooled OS data from PALOMA-3 indicates that a constant hazard trend (a straight line) is apparent from about [redacted] months suggesting 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 pooled OS data from PALOMA-3 suggests better survival than the **company** base case for people treated with everolimus plus exemestane meaning that the magnitude of change in costs and QALYs are greater in this arm than for people treated with palbociclib plus fulvestrant. The **ERG's** revised OS survival curves alongside the **company** base case estimates are shown graphically below: 

Why this issue is important	It is important to select the correct clinical effectiveness data inputs that would generate cost effectiveness results that are reliable and clinically plausible.
Technical team preliminary judgement and rationale	The **technical team** is unclear which approach to model OS (i.e. the **company's** method of using results of the standard Bayesian NMA or the **ERG's** method of using fulvestrant monotherapy as a proxy for everolimus plus exemestane) produces more clinically plausible results.
Questions for engagement	a) What is the preferred approach to modelling overall survival? Does the **ERG's** approach reduce uncertainty and produce more clinically plausible overall survival estimates than the **company's** approach using results from the fractional polynomial NMA?
Summary of comments after technical engagement	**Comments from clinical expert:** • Trials (MONALEESA-7 and MONALEESA-3 (ribociclib), MONARCH-2 (abemaciclib)) show statistically significant improvements in OS for CDK4/6 inhibitors. PALOMA-3 also showed OS improvements for palbociclib plus fulvestrant without reaching statistical significance. In contrast, exemestane plus everolimus did not statistically, nor convincingly clinically, demonstrate an OS improvement in BOLERO-2. • A model that generates no difference in OS between palbociclib plus fulvestrant versus everolimus plus exemestane does not appear clinically plausible (mean OS 46.8 months irrespective of treatment). **Comments from company:** • PALOMA-3 was not powered to detect an effect in OS. Although OS results were updated in the April 2018 data-cut, the data is relatively immature with only 58% of events reported in the palbociclib plus fulvestrant arm with median follow-up of 44.8 months. Pooling survival data from the trial and assuming equivalence based on the lack of OS statistical significance is not appropriate. • After technical engagement, the company conducted a FP analysis instead of the original Bayesian NMA, therefore the OS estimates for everolimus plus exemestane have been updated. The Kaplan-Meier OS plot for everolimus plus exemestane from BOLERO-2 alongside the survival curves produced by the company's fractional polynomial analysis and the ERG's approach shows that the ERG's approach over estimates OS for everolimus + exemestane while the company's FP analysis appears to provide a closer fit to the Kaplan-Meier data from BOLERO-2:

	Figure 3: everolimus plus exemestane OS  **Comments from ERG:**

	• Deviance information criterion (DIC) is the appropriate method to choose FP model. No suitable FP model can be selected based on DIC, therefore FP NMA cannot be used to inform relative comparisons of effectiveness. Due to this uncertainty, to enable alternative cost effectiveness estimates to be generated, PFS and OS data from the fulvestrant arm of PALOMA-3 were used to generate lower bound estimates of the effectiveness of everolimus with exemestane.
Technical team scientific judgement after engagement	Both approaches, the company's approach using FP NMAs and the ERGs approach using OS data from the fulvestrant arm of PALOMA-3 to generate lower bound estimates of the effectiveness of everolimus with exemestaneare unsatisfactory.

Issue 5 – Time-to-treatment discontinuation modelling – FOR DISCUSSION

Background/description of issue	In the **company** model, time to treatment discontinuation (TTD) for treatment with palbociclib plus fulvestrant was estimated by applying a HR to PFS. The **company** states that this is due to the extrapolation of TTD not being in line with their extrapolation of PFS data. To estimate the HR, the company first appended exponential curves to the end of the PFS and TTD K-M data from PALOMA-3, 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. This produces an estimate of the time that people receiving palbociclib plus fulvestrant spend on treatment and means that the number of people 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** assumed that TTD is equal to the PFS estimated using the results of the **company's** PFS FP NMA ([redacted] months) The **ERG** noted that the **company's** approach of calculating TTD data for people treated with palbociclib plus fulvestrant and using PFS data to represent time on treatment for patients receiving everolimus plus exemestane is an unfair comparison. The difference in TTD in the company model is 3.8 months. The mean TTD in the company base case is [redacted] months for treatment with palbociclib plus fulvestrant (which is less than the PFS in the palbociclib arm), and [redacted] months with everolimus plus exemestane (which is equal to the PFS). The **ERG** has instead used TTD data from the palbociclib plus fulvestrant and placebo plus fulvestrant arms of PALOMA-3 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. In the **ERG's** revised modelling of TTD, TTD K-M data taken directly from the 4th data cut of PALOMA-3 until 13 months for both arms of the trial was used and then an exponential function was applied separately to each arm as PH assumption was seen to hold from about [redacted] months for patients treated with palbociclib plus fulvestrant and from [redacted] months for patients treated with placebo plus fulvestrant. The **ERG's** revised TTD estimates also do not include a half-cycle correction included by the **company** as it considered that the cost of the drugs and the other resources associated with the drugs are likely to occur at the beginning of each cycle. Although PFS exceeds TTD for the palbociclib plus fulvestrant arm in PALOMA-3, TTD and PFS are almost identical for the placebo plus fulvestrant arm. However, TTD may be less than PFS by a greater degree for everolimus plus exemestane than for palbociclib plus fulvestrant as treatment discontinuation due to AEs was higher for everolimus plus exemestane in BOLERO-2 (29%) than for palbociclib plus fulvestrant in PALOMA-3 (2.9%). The **ERG** notes that if the use of the fulvestrant plus placebo TTD data from PALOMA-3 overestimates the everolimus plus exemestane drug costs, then the ICER per QALY gained for palbociclib plus fulvestrant versus everolimus plus exemestane would be higher. The **ERG's** approach to modelling TTD produced mean TTD of [redacted] months for palbociclib plus fulvestrant and [redacted] months for everolimus plus exemestane (difference= [redacted] months) The **ERG's** revised estimates of TTD alongside the **company** base case estimates are shown graphically below:

	
Why this issue is important	It is important to select the correct clinical effectiveness data inputs that would generate cost effectiveness results that are reliable and clinically plausible. The **ERG** revisions to modelling TTD have an impact on cost-effectiveness results.
Technical team preliminary judgement and rationale	The **technical team** consider that the company's approach to modelling TTD for palbociclib plus fulvestrant is not clinically plausible as the number of people receiving the treatment is always lower than the number of patients who are progression free.
Questions for engagement	a) How likely is it in practice for patients to be progression free and yet not continue treatment with palbociclib plus fulvestrant? b) Does the **ERG's** approach of estimating time to treatment discontinuation using Kaplan-Meier 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 produce clinically plausible results? c) What is the preferred approach to modelling time to treatment discontinuation? Does the **ERG's** approach reduce uncertainty and produce a more clinically plausible time to treatment discontinuation estimates than the **company's** approach using a ratio of TTD to PFS from PALOMA-3?

Summary of comments after technical engagement

Comments from clinical expert:

- Majority of patients on palbociclib plus fulvestrant continue treatment until disease progression. Everolimus is relatively more toxic compared to palbociclib. In routine clinical practice everolimus plus exemestane is likely discontinued more frequently than fulvestrant monotherapy prior to progression. However, if this is correct it would also likely imply that in routine clinical practice everolimus plus exemestane may be less effective than in BOLERO-2. The ERG approach is a fair model.
- Although both approaches are based on reasonable assumptions, the ERG approach is potentially more plausible.

Comments from company:

- Not unusual for time-on-treatment to be less than PFS as patients can discontinue treatment for a multitude of reasons such as adverse events, treatment breaks. People can continue to derive benefit from treatment whilst off therapy as PFS in a clinical setting is based on RECIST criteria.
- Median PFS for everolimus plus exemestane reported in BOLERO-2 is 7.8 months, while median duration of exposure to treatment reported as 5.98 months. In the SMC advice for everolimus plus exemestane, final PFS analysis was conducted at a median follow up of 18 months when the median everolimus treatment duration was ~7.5 months compared with 14 weeks for placebo. Comparing the ERG estimates to the reported medians indicates that the ERG estimate (4.60 months) underestimates TTD for everolimus plus exemestane and the company's estimate is a better fit to the data from BOLERO-2 and SMC:

Table 4: Everolimus plus exemestane time to discontinuation

Time to discontinuation	ERG approach	Company approach
Mean TTD (months)	8.93	[redacted]
Median TTD (months)	4.60	[redacted]

Comments from ERG:

	Company approach adjusting TTD data from the palbociclib plus fulvestrant of PALOMA-3 is arbitrary. Using two different approaches to model the same effect is inconsistent (for palbociclib plus fulvestrant: trial TTD data used to model TTD, for everolimus plus exemestane: PFS data used to model TTD). Fulvestrant TTD in PALOMA-3 is very similar to PFS and, given that fulvestrant should not be given beyond progression, represents the maximum incremental relationship between TTD and PFS for that treatment. • Exact overall impact on the ICER per QALY gained of any changes to assumptions regarding PFS and its relationship to TTD for everolimus plus exemestane cannot be predicted as it will depend on the magnitude of change and the cost of the drugs
Technical team scientific judgement after engagement	The company's approach uses a ratio of TTD to PFS from PALOMA-3 for the palbociclib plus fulvestrant arm but assumes TTD is equal to PFS for the everolimus plus exemestane which is inconsistent. The **ERG** approach in contrast may reduce uncertainty and produce more clinically plausible time to treatment discontinuation estimates.

Issue 6 – Subsequent therapy assumptions – FOR DISCUSSION

Background/description of issue	In the **company** base case, people can only receive a maximum of 6 cycles of two subsequent lines of treatment. People spend approximately [redacted] months in total receiving subsequent treatments, and [redacted] months in the best supportive care (BSC) health state. Evidence from PALOMA-3 indicates that the median time people spent receiving their first subsequent treatment was 4.9 months. The **ERG** considers that the mean time spent receiving subsequent therapies is an underestimate and that the mean time spent in BSC is an overestimate in the **company's** model. Furthermore, the **company** assumes that 25% of remaining patients proceed to BSC when the maximum duration of first line subsequent therapy has been reached rather than receive a second line of subsequent therapy. No evidence was provided to justify this value and clinical advice to the **ERG** suggests that fewer than 25% of patients will be unfit for, or will refuse, each available subsequent treatment. When the maximum duration of each subsequent treatment is set to 9 model cycles (the maximum allowed by the **company** model), 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.
Why this issue is important	It is important to include the correct costs associated with subsequent therapy assumption as this has an impact on the costs of treatment included in the economic model.
Questions for engagement	a) Is the mean duration that patients in the advanced setting receive subsequent therapies in clinical practice nearer 5 months as stated by the company or 7 months suggested by the ERG? b) Is the company's assumption that 75% of patients in clinical practice would proceed to receive best supportive care when the maximum duration of first line subsequent therapy has been reached rather than receive a second line of subsequent therapy, or is the ERG's assumption of 100% more plausible?
Summary of comments after technical engagement	**Comments from clinical expert:** Neither estimates are likely correct. Patients are likely to receive subsequent treatments for longer than both these estimates in clinical practice • Many patients will receive multiple subsequent therapies in routine clinical practice. **Comments from company:** • In the 3rd line setting, patients in the UK are likely to receive everolimus plus exemestane, chemotherapy or tamoxifen. No data on the use of everolimus plus exemestane in the post CDK 4/6 inhibitor setting is available and median PFS for everolimus plus exemestane is expected to be lower in the 3rd line. • A cost study examining the medical records of 41 physicians in the UK showed that the mean number of cycles ranged from 5.8 to 11.1, depending on line of therapy covering 1st to 3rd line. • For consistency, the duration of time spent in subsequent lines was assumed as 6 cycles per line for all treatment arms. A range of 5 to 7 cycles was used in sensitivity analyses. The rates of progression from subsequent treatment lines were assumed the same across the 2 treatment arms. • 5 months is a more accurate estimate of the mean duration of subsequent therapies and 7 months is an over estimation.

	• In the company base case, it is assumed that after each post-progression line, 25% of patients would not switch to a subsequent line but would instead receive BSC until death based on consulted clinical expert opinion. This reflects that all surviving patients continue active treatment (either by choice or being not fit for treatment) • It is not clinically plausible for 100% of patients to progress to a 2nd subsequent therapy as there is always a drop off due to several reasons such as drop in performance status, no response, progression of disease, declining further therapy. These patients instead progress to BSC. **Comments from ERG:** Clinical advice to the ERG suggests people will receive many lines of subsequent therapy. Published evidence from PALOMA-3 shows that the median time patients spent receiving their first subsequent treatment alone was 4.9 months. Therefore, if people receive more than one line of subsequent therapy (as is assumed in the company model), mean time spent on subsequent therapy should be greater than 5 months. Mean time spent in the BSC health state ([redacted]) is an overestimate. Clinical advice also suggests that an estimate of 25% of patients unable to proceed at each subsequent therapy line is too high. As the structure of the model limited the ERG's ability to extend the maximum duration of subsequent therapy (beyond 7 months), the approach taken by the ERG was the only way to further influence of the duration of subsequent therapy on the ICER per QALY gained could be explored.
Technical team scientific judgement after engagement	A mean duration of 7 months for patients in the advanced setting to receive subsequent therapies in clinical practice is appropriate for decision-making as this is the maximum duration allowed by the economic model and is more plausible than the 5 months proposed by the company. It is uncertain if the company assumption of 75% or the ERG assumption of 100% of patients proceeding to receive BSC when the maximum duration of 1st line subsequent therapy has been reached rather than receive a 2nd line of subsequent therapy is appropriate for decision- making.

Issue 7 – Resource use: number of appointments with a consultant oncologist – AGREED

Background/description of issue	In the **company** model, it is assumed that patients have an appointment with a consultant oncologist every 6 months in the progression-free health state and patients have an appointment with a consultant oncologist every 2 months whilst receiving the first line of subsequent therapy. Clinical advice to the **ERG** suggests that these appointments are underestimates and patients in the NHS have appointments with a consultant oncologist once per month, irrespective of health state. The **ERG** therefore 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 best supportive care).
Why this issue is important	It is important to include the correct number of consultant oncologist meetings annually as this has an impact on the costs of treatment included in the economic model. The technical team is of the opinion that monthly appointments with a consultant oncologist suggested by the ERG may not reflect actual clinical practice in the NHS, but 6 monthly visits as suggested by the company may be an underestimate. Clinical expert opinion on the actual number of appointments people in different health states would have with a consultant oncologist is sought.
Technical team preliminary scientific judgement and rationale	The **technical team** consider that the number of hospital appointments with a consultant oncologist that patients in the NHS will have is unclear.
Questions for engagement	a) How frequently are people with advanced hormone-receptor positive, HER2-negative breast cancer likely to have appointments with a consultant oncologist?
Summary of comments after technical engagement	**Comments from clinical expert:** Patients see a consultant oncologist every 2-3 months once established on palbociclib plus fulvestrant, as patients can be seen substantially less frequently than in PALOMA-3. **Comments from company:** • An estimate of 1 consultant oncologist appointment once every 2 months representing an average across subsequent treatments is used by company supported by CNS interviews conducted**.**

	Comments from ERG: Company assumptions do not reflect current NHS clinical practice and patients have appointments with a consultant oncologist once per month, irrespective of health state
Technical team scientific judgement after engagement	Including the cost for an oncologist appointment with a consultant every 2 months in the economic model is suitable for decision making.

Issue 8 – End of life – AGREED

Background/description of issue	If the technology is deemed to be life-extending compared to current treatments, ICERs greater than what is usually considered a cost- effective use of NHS resources can be considered, provided that all of the following criteria have been met: • the treatment is indicated for patients with a short life expectancy, normally less than 24 months and; • there is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared with current NHS treatment. • the estimates of the extension to life are sufficiently robust and • the assumptions used in the reference case economic modelling are plausible, objective and robust. The **ERG** did not consider that palbociclib in combination with fulvestrant met these criteria. The **ERG** notes that based on the evidence provided by the **company**, median OS for patients who received placebo plus fulvestrant was 28.0 months (95% CI: 23.6 to 34.6 months) in PALOMA-3. In the BOLERO-2 trial, median OS for patients who received everolimus plus exemestane was 31.0 months (95% CI: 28.0 to 34.6 months) therefore the first criteria is not met. The **ERG** considers that the **company** has not provided any robust evidence of an OS gain for palbociclib plus fulvestrant compared to everolimus plus exemestane. The gain in median OS in PALOMA-3 for

	palbociclib plus fulvestrant versus placebo plus fulvestrant was 6.9 months. However, this gain is not statistically significantly different. Although the **company** has not made a formal case for EoL in its company submission, it has noted that adding palbociclib produced a greater relative survival gain than is required to meet EoL, however overall survival in the standard of care arms in the trials for palbociclib plus fulvestrant and everolimus and exemestane is over 24 months.
Why this issue is important	If the technology is deemed to meet the NICE criteria for special consideration, ICERs greater than what is usually considered a cost -effective use of NHS resources can be considered.
Technical team preliminary scientific judgement and rationale	The **technical team** consider that NICE's End of Life criteria are not met because the estimates of the extension to life are not sufficiently robust and the overall survival in the comparator arm is greater than 2 years.
Questions for engagement	a) What is the current life expectancy of the relevant patient population? b) How robust are the current estimates of survival benefit?
Summary of comments after technical engagement	**Comments from clinical expert:** Life expectancy of the control arm in PALOMA-3 is appropriate for the population. It should be noted that it is not possible to compare absolute median survival estimates between trials, as difference in patient populations can have substantial effects on OS**.** CDK4/6 inhibitor studies have shown consistency in PFS HRs strongly suggesting that the CDK4/6's have a class effect and have similar efficacy. OS is improved using CDK4/6 inhibitors with statistically significant improvements shown in MONALEESA-7 and MONALEESA-3 for ribociclib, MONARCH-2 for abemaciclib and OS improvements not reaching statistical significance in PALOMA-3 for palbociclib. This could be because PALOMA-3 was not powered to detect differences in OS. It would therefore seem appropriate that there should be consistency in assumption between the NICE appraisals of CDK4/6's. **Comments from comparator:** • Median overall survival of patients with metastatic breast cancer is approximately 3 years

	Comments from company: The gain in median OS in PALOMA-3 for palbociclib plus fulvestrant when compared with placebo plus fulvestrant was 6.9 months. Improving survival by 7 months is a result of palbociclib's innovation, compared to the trial comparator that only reached 28 months median OS, is a large relative gain; an increase of 25%. The gain in median OS in the "Chemotherapy naïve" sub-group in PALOMA-3 for palbociclib plus fulvestrant compared with placebo plus fulvestrant was [redacted]. PFS results are relatively immature with only 58% of events reported in the palbociclib plus fulvestrant arm with median follow-up only 15.8 months and were not updated in the latest data-cut in April 2018. OS results were updated in the April 2018 data-cut but only 58% of events were reported in the palbociclib plus fulvestrant arm with median follow-up of 44.8 months. Final data-cut from PALOMA-3 expected in [redacted] which will provide mature PFS and OS results. **Comments from ERG**: Agree with the company's estimates of life expectancy but short life expectancy criterion for end of life has not been met. No robust evidence of an OS benefit for for palbociclib plus fulvestrant compared to everolimus plus exemestane. Company did not state their expectation of a further, final, data-cut in [redacted] in original submission.
Technical team scientific judgement after engagement	NICE's End of Life criteria are not met because the estimates of the extension to life are not sufficiently robust and the overall survival in the comparator arm is greater than 2 years.

3. Issues for information

Tables 1 to 4 are provided to stakeholders for information only and not included in the technical report comments table provided.

Table 1: ERG's amendments to company base-case and impact on the cost-effectiveness estimate before technical engagement. These estimates do not include the PAS for everolimus, which is confidential and therefore the actual cost-effectiveness estimates cannot be presented here.

Alteration	ICER
Company base case before technical engagement	Dominates
Revised company base-case (amended by ERG) before technical engagement	Dominates
R1 Estimating PFS using data from the placebo plus fulvestrant arm of PALOMA-3 as a proxy for everolimus plus exemestane instead of using FP NMA results	£8,180
R2 Estimating OS using (pooled) OS data from PALOMA-3 to represent people treated with palbociclib plus fulvestrant and everolimus plus exemestane instead of the standard Bayesian OS NMA results.	Dominates
R3 Estimating TTD using data from the placebo plus fulvestrant arm of PALOMA-3 as a proxy for treatment with everolimus plus exemestane.	£8,731
R4 Amend subsequent therapy assumptions	Dominates
R5 Removing daily oral drug wastage*	Dominates
R6 Include monthly oncologist consultation in every health state	Dominates
Cumulative impact of the ERG's revisions on the cost-effectiveness estimate (R1-R6)	Dominates
Impact of ERG's revisions (R4-R6) on company's revised cost-effectiveness estimate	Dominates

- *The company model assumes drugs dispensed in 30 days packs will mean that two tablets per month are wasted each cycle. The ERG has amended this to remove drug wastage.

Table 2: Impact of key issues assumptions on the cost-effectiveness estimate after technical engagement

Alteration	ICER
Company revised base case post technical engagement (scenario 1 in company's response to TE)*	**£8,176**
R1) Estimating OS (pooled) from the PALOMA-3 trial	Dominates
R2) Estimating PFS from the PALOMA-3 trial	£19,272
R3) Estimating TTD from the PALOMA-3 trial	£19,832
R4) Amend subsequent therapy assumptions	£9,831
R5) Removing daily oral drug wastage	£11,335
R6) Include monthly oncologist consultation in every health state	£9,222
ERG preferred modelling of effectiveness **R1) +R2) +R3)**	**Dominates**

Company preferred modelling of effectiveness + ERG amendments R4) + R5) + R6)	**£13,867**
ERG preferred modelling of effectiveness + ERG amendments R1) to R6)	**Dominates**
A. Company revised base case*	**£8,176**
Company revised base case (company scenario 1 + company scenario 2- same subsequent therapies in both arms)	**£6,291**

*The post-technical engagement revised company base case includes estimates generated by a fractional polynomial model for OS

Table 3: Other issues for information

Issue	Comments
Relevant comparators for the endocrine resistant population	As the focus of the **company's** submission is on the "endocrine resistant" population, results are only presented for the comparison of palbociclib with fulvestrant against everolimus with exemestane. Despite the **ERG** questioning the validity of restricting the comparison to only this combination, the **company** maintained their position that everolimus with exemestane is the most relevant comparator in the endocrine resistant population. The **ERG** notes that clinical opinion they have received from their experts suggests that everolimus plus exemestane is probably the most relevant comparator for the endocrine resistant population, as concluded by the NICE Appraisal Committee's for abemaciclib with fulvestrant and ribociclib with fulvestrant. Other comparators specified in the NICE final scope are also all used in clinical practice but to a lesser extent than everolimus plus exemestane in most NHS centres. Fulvestrant is only available in a limited number of NHS Trusts.
Innovation	Palbociclib is the 3rd drug to be appraised by NICE that falls in the same class category as abemaciclib and ribociclib. Both these drugs have been recommended for use within the

Issue	Comments
	Cancer Drugs Fund as an option for treating hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer in people who have had previous endocrine therapy.
Suitability for Cancer Drug Fund (CDF)	Palbociclib in combination with fulvestrant could be a suitable candidate for the Cancer Drugs Fund despite fulvestrant receiving negative NICE guidance for patients with untreated (TA503) and previously treated (TA239) metastatic breast cancer. The company has however confirmed that a final data-cut of PALOMA-3 is expected in [redacted] which will provide mature PFS and OS results.
Equality considerations	No equalities issues were identified.

Table 4: Minor issues in the economic model that have little effect on the ICER per QALY gained:

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Utility values used in the post-progression health state of the model	The **company** calculated the utility values used to estimate health related quality of life (HRQoL) in the post-progression health state of the **company** model using an algorithm and coefficients published in a paper by Lloyd et al, 2006. The same value is used for patients treated with palbociclib plus fulvestrant and everolimus plus exemestane. The **ERG** notes that, the Lloyd et al. paper 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	Minor impact on the cost-effectiveness estimates

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
	general population preference, as is preferred in the NICE Reference Case.	
Adverse events assumed to occur at the beginning of treatment only	In the **company** 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 on the ICER will be neligible	Minor impact on the cost-effectiveness estimates
Proportion of everolimus plus exemestane AEs	In the **company** model, total number of Grade ≥3 events in the PALOMA-3 trial (69.9%) were modelled for treatment with palbociclib plus fulvestrant. However, only Grade ≥3 stomatitis event (8%) were included for everolimus plus exemestane. The **ERG** noted that BOLERO-2 reported people receiving everolimus plus exemestane who experienced Grade ≥3 AEs to be 55% which means that the AEs for everolimus plus exemestane are underestimated in comparison to the palbociclib plus fulvestrant AEs.	Minor impact on the cost-effectiveness estimates

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Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
AE resource use	The **company** estimated resource use for AEs in its model from the most frequent Grade ≥3 AEs from the palbociclib plus fulvestrant arm of PALOMA-3 and the everolimus plus exemestane arm of BOLERO-2 Clinical advice to the **ERG** suggests 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	Minor impact on the cost-effectiveness estimates
Drug monitoring	The **company's** model assumes that a chest x ray is 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.	Minor impact on the cost-effectiveness estimates

Authors

Jane Adam

Appraisal committee chair

Sana Khan

Technical lead

Joanna Richardson

Technical adviser

Janet Robertson

Associate director

With input from the lead team:

Ellen Rule

Lead team member

Paul Robinson

Lead team member

Pamela Rees

Lead team member

List of abbreviations

AEs, adverse events

ERG, evidence review group

ICERs, incremental cost-effectiveness ratio

PFS, progression free survival

OS, overall survival

QALY, quality adjusted life years

TTD, time-to-treatment discontinuation

Glossary

Adverse events: A toxic reaction relating specifically to drugs or other treatments or interventions that a person is receiving

Dominance: When a new intervention is both clinically superior and cost saving, it is referred to as an economically dominant strategy. The opposite is a "dominated" strategy, that is an intervention is dominated if it has higher costs and worse outcomes than an alternative intervention.

Heterogeneity: Used in meta-analyses and systematic reviews to describe when the results or estimates of effects of a treatment from separate studies seem to be very different (for example, the size of treatment effects may vary across studies, or some studies may indicate beneficial treatment effects whereas others suggest adverse treatment effects). Such difference in results may occur by chance, because of variation in study quality or because of variation in populations, interventions, or methods of outcome measurement in the included studies.

Incremental cost-effectiveness ratio (ICER): The ratio of the difference in the mean costs of a technology compared with the next best alternative to the differences in the mean outcomes.

Meta-analysis: A statistical technique for combining (pooling) the results of a several studies that address the same question and report on the same outcomes to produce a more precise summary estimate of the effect on a particular outcome.

Indirect comparison: An analysis comparing interventions that have not been compared directly within a head-to-head randomised trial

Quality-adjusted life year (QALY): An index of survival that is adjusted to account for the patient's quality of life during this time. QALYs incorporate changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social, and other factors) of life. Used to measure benefits in cost–utility analysis.

Systematic review: Research that summarises the evidence on a clearly formulated question according to a predefined protocol. Systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings are used. Statistical methods for meta-analysis may or may not be appropriate for application to the quantitative results from the different studies.

Utility: A measure of the strength of a person's preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health). Health states can be considered worse than death and thus have a negative value.